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Final Report

The INDEX project

Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU

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Legal notice

Foreword

In the past decades a large number of studies have indicated the presence of different compounds belonging to a variety of chemical classes in indoor environments (buildings, homes). The presence of these chemicals in indoor air is the result of infiltration of polluted outdoor air and of emissions from various indoor sources, including building materials, activities of the occupants, consumer products, smoking etc.

For many of these chemicals, the risk to human health and comfort is almost totally unknown and difficult to predict because of lack of toxicological data and information on the dose-response characteristics in humans or animal models. On the other hand, a full toxicological testing as requested by the "existing chemicals" legislation is difficult to accomplish for these compounds, because it would involve investigation of acute and subacute toxicity, mutagenicity, carcinogenicity and reproductive toxicity according to testing protocols that are complex, time-consuming and expensive. Moreover, the EU policy on limitation of unnecessary animal testing further limits the possibility of advocating a generalized animal testing of these chemicals.

The result of this situation is that there is an objective difficulty in regulating the presence of these substances in indoor air principally because of the absence of adequate hazard and risk assessment. There is therefore an urgent need to develop a strategy for the identification of priorities in testing, assessment and regulation.

In the frame of the INDEX project the existing knowledge worldwide has been assessed on
- type and levels of chemicals in indoor air and
- available toxicological information to allow the assessment of risk to health and comfort.

The collection and evaluation of the aforementioned information within the frame of the INDEX project shall contribute to develop a strategy for prioritization in assessment and regulation of chemicals in indoor environments.

                                                    The Steering Committee

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Executive Summary

Introduction and objectives

The INDEX project (Critical Appraisal of the Setting and Implementation of Indoor exposure Limits in the EU) started in December 2002 and had a duration of two years, until December 2004.The project was financially supported by DG SANCO and it was coordinated and carried out by the JRC in collaboration with a Steering Committee of leading European experts in the area of indoor air pollution. Scope of INDEX was to identify priorities and to assess the needs for a Community strategy and action plan in the area of indoor air pollution by:
- setting up a list of compounds to be regulated in indoor environments with priority on the basis of health impact criteria
- providing suggestions and recommendations on potential exposure limits for these compounds, and
- providing information on links with existing knowledge, ongoing studies, legislation etc. at world scale.

Methodology

The main steps to be followed in the project as they have been defined by the Steering Committee were:
- literature review (step 1)
- setting up criteria to select compounds (step 2)
- review of exposure and dose/response data (step 3)
- risk characterization of the selected compounds (step 4)
- prioritisation of the selected compounds (step 5) and
- recommendations and risk management options on potential exposure limits (step 6)

In the first step the world literature was reviewed to collect background information on exposure concentrations and dose/response data of the chemical pollutants that have strong indoor sources. In the second step, the Steering Committee has defined the criteria for the selection of pollutants for further risk analysis. After careful examination of exposure and toxicological dose response data (step 3), the Steering Committee ended up to a short list of pollutants that were selected for the risk characterization (step 4). The compounds that probably cause the highest health risk in European population according to the risk characterization were prioritized (step 5). Finally, recommendations and risk management options on European exposure limits should be given for a few selected compounds (step 6).

In order to accomplish with the tasks mentioned above the Steering Committee was divided into two working groups, one for exposure assessment and one for dose/response assessment.

Exposure to selected indoor air pollutants was estimated by reviewing exposure data collected from scientific literature, from available databases, and by personal communications. The aim of this work was to summarise prevailing indoor air and personal exposure concentrations of these compounds in Europe and also worldwide. Results from population-based studies have been preferred to be able to generalise the results from studied individuals to larger populations, targeting to assess exposures of all the Europeans. Considering the fact that no new data could be generated in this project, the steering group defined the following criteria to be able to select the chemical compounds to the risk analyses:

1. Only single compounds will be considered
2. The compound should have common indoor sources, which dominate the exposures of at least significant fraction of the population
3. The compound should have known health effects.

It was also decided that compounds, which have been regulated by specific guidelines or regulations would be excluded from theses analyses. For example, radon and tobacco smoke were excluded from the risk assessment process due to these criteria.

In preparing the dose-response assessment fact sheets of the selected chemicals, information were retrieved from scientific literature (mainly by electronic search), comprehending toxicological reviews of leading health organizations, risk evaluation documents and available databases. In addition, Toxline and Medline were searched for relevant scientific communications published up to September 2004.

Nearly all key-studies referred to in the present assessment, establishing effect levels for appropriate toxicological endpoints, are those selected by health organizations for the derivation of health based limits of exposure or among risk

assessment requirements. Although not specifically addressing health hazards and risks associated with indoor air exposure, i.e. not being designed for the expression of effects at lowermost exposure concentrations, nearly all studies were aimed at identifying the most sensitive endpoint considered to be of relevance to humans. Where relevant, studies conducted on susceptible sub-populations (e.g. asthmatics, infants, children, pregnant women etc.) were quoted and taken into consideration in the risk characterization.

In the final step of the general risk assessment process, the incidence of health hazards and risks in the European population, associated with indoor exposure to individual chemicals, was estimated. Limits of exposure (ELs, following short- and long-term exposure) were derived for each chemical after selection of a critical study describing the appropriate toxicological endpoint and by applying the "no-observed-adverse-effect level (NOAEL) / assessment factor (AS)" approach. Where no NOAEL observation was documented, a lowest-observed-adverse-effect level (LOAEL) was taken and an additional assessment factor of 10 used for EL derivation. Only for one compound (benzene) the characterization was based on population cancer risk estimation. Where supported by scientific evidence, susceptible subpopulations were accounted for, in particular: asthmatic individuals, infants, children, individuals with heart diseases, pregnant women, individuals with enzyme deficiencies.

On the basis of the available information and after careful examination of the existing data, the steering committee finally decided to include into a detailed assessment 14 out of initial 41 candidate compounds (phase 4) i.e.: acetaldehyde, alpha-pinene, benzene, carbon monoxide, d-limonene, formaldehyde, meta-and para xylene, ortho-xylene, naphthalene, ammonia, nitrogen dioxide, styrene and toluene.

Risk assessment of the selected compounds

Information from the exposure assessment (Chapters 1-3) and toxicity assessment (Chapters 4-5) were integrated and a risk characterization (Chapter 6) performed on each chemical. Based on the conclusions of the assessments and on the completeness of individual databases, a priority ranking was arranged with the 14 chemicals assigned to three groups as given hereafter.

Group 1: High priority chemicals

Formaldehyde :   Because of its high chemical reactivity, formaldehyde is the most important sensory irritant among the chemicals assessed in the present report. Due to being ubiquitous pollutant in indoor environments and to the increasing evidence indicating that children may be more sensitive to formaldehyde respiratory toxicity than adults it is considered a chemical of concern at levels exceeding 1 $\mu g/m^3$, a concentration more or less corresponding with the background level in rural areas. Results from available exposure data, although limited, confirm that almost the entire population is exposed indoors at levels (Median level±sd: 26±6 $\mu g/m^3$; 90th±sd: 59±7 $\mu g/m^3$; N = 6) higher than this background level, here established as the limit of exposure, with at least 20% of the European population exposed at levels exceeding the no-observed-effect-level (NOAEL: 30 $\mu g/m^3$). Within the concentration range measured, mild irritation of the eyes could be experienced by the general population as well as the odour perceived above 30 $\mu g/m^3$.

Reported formaldehyde concentrations were lower (99th < 150 $\mu g/m^3$) than a presumed threshold for cytotoxic damage to the nasal mucosa (about 1 mg/m^3) and hence considered low enough to avoid any significant risk of upper respiratory tract cancer in humans. The last statement could be subjected to changes due to the current IARC revision of the carcinogenicity of formaldehyde.

Carbon monoxide :   Available exposure data confirm that Carbon Monoxide (CO) sources in EU-residences are contributing to short-term rather than to long-term exposures. Personal exposure outcomes averaged over 1-hour were considered of moderate concern even for the most susceptible subpopulations. Nevertheless, uncertainties resulting from the predictive capabilities of the CFK-model* in individuals exposed at low CO concentrations and its applicability to sensitive subpopulations, suggest that about 10% of the general non-smoking population experience CO levels which could be hazardous for individuals with heart diseases. Increased exposures could be expected for residences in the vicinity of busy city streets.

In addition, there is no evidence that long-term CO exposures in EU residences contribute to carboxyhaemoglobin levels in blood higher than the baseline levels resulting from endogenous production in normal, non-smoking individuals.

On the other hand and in contrast with all other chemicals assessed in the present report, carbon monoxide causes a considerable number of deaths and acute poisonings in the general population (with complications and late sequel). Also, individuals suffering from CO poisoning are often unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression. In indoor environments, these health risks are nearly completely associated with the incorrect use of combustion devices or faulty unvented gas appliances.

* The physiologically based pharmacokinetic (PBPK) model of Coburn, Forster, and Kane (CFK-model) is a reliable method for predicting COHb blood levels for exposure to a given ambient carbon monoxide concentration. This model has been extensively validated over many years. Precision is acceptable, providing that the original conditions of use are rigorously applied.

Nitrogen dioxide :

Reported maximum nitrogen dioxide (NO_2) levels associated with the use of gas appliances in homes (gas cooking and heating) are in the range 180-2500 $\mu g/m^3$. Exposure at these levels could generate effects in the pulmonary function of asthmatics, considered to be the subjects most susceptible to acute NO_2 exposure, with the lower end of the range approximating the WHO guideline (200 $\mu g/m^3$, 1-hour average), established for the protection of asthmatic individuals and the upper end starting to affect health in normal individuals.

For long-term exposures, increased respiratory symptoms and lung function decreases in children were documented to be the most sensitive effect in the general population. Measured background levels in European homes indicate that a remarkable portion of the population is exposed at NO_2 levels higher than current guideline values protecting from respiratory effects in children. In up to 25% of the investigated residences (45% in an Italian study) NO_2 levels exceeded the German indoor-related guideline value (GV II: 60 $\mu g/m^3$, 1-week average), what would have resulted in immediate action i.e. the examination of the situation with regard to a need for control measures.

On the other hand, safe levels in homes, i.e. < 40 $\mu g/m^3$ (following the WHO recommended annual value), are not likely to be achievable everywhere (e.g. in areas with intense automotive traffic) given that ventilation alone may introduce outdoor air containing such concentrations.

Benzene :

Benzene is ubiquitous in the athmosphere, mainly due to anthropogenic sources (90%), with concentrations in the European continental pristine air ranging from 0.6 to 1.9 $\mu g/m^3$. It is a genotoxic carcinogen and hence no safe level of exposure could be recommended. Results from nine monitoring surveys indicate that the European population is experiencing in their homes an increased risk in contracting benzene induced leukaemia, with respect to the estimated background lifetime risk of 7-8 cases per one million people (considering the WHO unit risk factor). Based on the available exposure data (Median levels±sd: 4.2±3.2 $\mu g/m^3$; 90[th]levels±sd: 11.5±11.1 $\mu g/m^3$; N = 9) two main scenarios could be described as follows:

  – People living in highly trafficked urban areas are expected, on average, to experience an estimated 6 to 30-fold increase in contracting benzene induced leukaemia during their life, the benzene levels encountered in these areas not being expected to produce chronic effects other than cancer, in particular haematological effects, nor acute sensory effects such as odour perception (odour threshold: 1.2 mg/m^3) and sensory irritation. Also, a reduced contribution of specific indoor sources is likely to be expected, given that ventilation alone may introduce increased outdoor benzene levels.
  – People living in rural areas or poorly trafficked towns were expected, on average, to experience an estimated 1 to 5-fold increase in contracting benzene induced leukemia during their life, this factor depending principally on the presence of indoor sources.

Naphthalene :

With regard to the general population a long-term exposure limit has been set at 10 $\mu g/m^3$, according to the assumption that nasal effects observed in mice are consistent with the health effects reported among exposed workers. Available exposure data indicate that, on average, the European population is exposed at naphthalene levels 10 times lower than this EL, although an important exception resulted from a survey held in Athens, were levels exceeding the EL were measured in nearly all residences. It is assumed that increased residential exposures originate from the use of naphthalene based moth-repellents, a

widespread use occurring in certain countries of the Mediterranean area.

An important source of uncertainty in establishing safe exposure limits is the potentially greater sensitivity of certain subpopulations to naphthalene toxicity, including infants and neonates, and individuals deficient in glucose-6-phosphate dehydrogenase (G6PD), the prevalence of this inherited deficiency reported to be 2 to 20% in defined Mediterranean subpopulations. In these latter cases manifested effects are hemolytic anemia and its sequel.

In relation to carcinogenicity, naphthalene is not genotoxic in vivo and thus tumour development, observed in rodents, is considered to arise via a non-genotoxic mechanism. Also, the underlying mechanism for the development of nasal tumours in the rat is considered to be the chronic inflammatory damage seen at this site. It follows that prevention of local tissue damage would prevent subsequent development of tumours.

Group 2: Second priority chemicals

Acetaldehyde :

The results from only three indoor air monitoring surveys allow a crude estimate of average acetaldehyde concentrations in European residences. Median concentrations (10-20 $\mu g/m^3$) are one order of magnitude lower than the Exposure Limit set here at 200 $\mu g/m^3$ and are within the same range of concentrations occurring in exhaled breath following its endogenous production in the general population, not taking into account increases resulting from the consumption of alcoholic beverages. Considering that exogenous acetaldehyde peak exposures are mainly associated with tobacco smoke, concentrations in the order of the Exposure Limit could be expected following intense cigarette consumption.

Assuming that the available exposure data are indicative of the population residential exposure it is concluded that people in Europe do not experience increased health hazards associated with acetaldehyde levels in their homes, although additional work should be warranted for a better characterization of exposure and dose response.

Also, measured indoor levels are lower than a presumed threshold for cytotoxic damage to the nasal mucosa, and hence considered low enough to avoid any significant risk of upper respiratory tract cancer in humans.

Toluene :

Human effects on the central nervous system are considered as the most sensitive effect in both short- and long-term inhalatory exposure to toluene. Available exposure data indicate that the European population is not experiencing health effects of concern resulting from the exposure to toluene in their homes. Results from ten monitoring surveys show that toluene levels in the order of the established exposure limit of 300 $\mu g/m^3$ could be reached under worse-case conditions and in a limited number of urban residences. On average, median concentrations (90th percentile) were found to be 16 (5) times lower than the EL. Also, short-term exposures associated with human indoor activities are not expected to exceed the acute EL set here at 15.000 $\mu g/m^3$.

Xylenes :

A chronic exposure limit of 200 $\mu g/m^3$ has been derived based on generally mild adverse effects associated with CNS and increase in the prevalence of eye irritation and sore throat. The results of eight monitoring surveys indicate that background levels of xylenes in European residences are of no concern to human health since median (90th percentile) levels are, on average, 20 (6) times lower than the EL established. Acute exposure data indicate that it is very unlikely that xylenes emissions associated with human indoor activities would generate levels in the order of the proposed short-term EL of 20 mg/m^3, considered protective for irritative effects in the general population.

Although human exposure most likely occurs to the mixture of xylene isomers, animal and human toxicity data suggest that mixed xylenes and the different xylene isomers produce similar effects.

Styrene :

A long-term exposure limit (EL) of 250 $\mu g/m^3$ has been derived based on the assumption that neurological effects are probably the most sensitive indicator of styrene toxicity. When examining the results of eight monitoring surveys it can be concluded that background styrene concentrations in European residences are of no concern to human health since median levels are, on average, two orders of magnitude below the established EL. Although no acute exposure data were available, it is unlikely that styrene emissions associated with human indoor activities would generate levels up to the proposed short-term EL of 2000

$\mu g/m^3$, considered protective for irritative effects in asthmatics.

Although genotoxic effects in humans have been observed at relatively low concentrations, they were not considered as critical endpoints for the derivation of the exposure limit, in view of the equivocal evidence for the carcinogenicity of styrene in humans (WHO).

Group 3: Chemicals requiring further research with regard to human exposure or dose response

Ammonia :
There is a lack of knowledge concerning indoor concentrations and exposures of ammonia. Exposure data are limited on only one monitoring survey describing concentrations of ammonia in Finnish homes with and without known indoor air quality (IAQ) problems. In both cases measured concentrations were within the same order of magnitude with both exposure limits here established for short- and long-term effects (70 and 100 $\mu g/m^3$, respectively), relating on irritative effects and pulmonary functions and taking into account the particular susceptibility of asthmatic subjects. It is assumed that exposure concentrations in the order of the short-term EL could easily be attained during domestic activities making use of ammonia containing household products.

Limonene :
An attempt has been done in deriving an exposure limit (EL) for long-term effects associated with limonene exposure by referring to a study on volunteers exposed at sub-acute (2 hours) inhalation doses. When comparing this EL (450 $\mu g/m^3$) with the results from seven indoor surveys it is concluded that no neurological effects would be expected at background limonene levels encountered in European homes, with median (90th percentile) levels at least 10 (3) times lower than the proposed EL. It is assumed that at 10-fold the level set as the EL, health effects could be expected following acute exposure. Due to its widespread use as a flavouring agent in numerous consumer products, short-term exposures at levels in the order of some mg/m^3 could not be excluded, although significative exposure data are lacking.

An exacerbation of effects (not better defined) could be expected following the concomitant presence in residences of ozone emitting sources, due to the formation of irritant reaction products.

α-Pinene :
An attempt has been done in deriving an exposure limit (EL) for long-term effects associated with α-pinene exposure by referring to a study on volunteers exposed at sub-acute (2 hours) inhalation doses. When comparing this EL (450 $\mu g/m^3$) with the results from six indoor surveys it is concluded that no irritative effects to the eyes, nose and throat would be expected at background α-pinene levels encountered in European homes, with median (90th percentile) levels at least 40 (10) times lower than the proposed EL. It is assumed that at 10-fold the level set as the EL, health effects could be expected following acute exposure. Due to its widespread use as a flavouring agent in numerous consumer products, short-term exposures at levels in the order of some mg/m^3 could not be excluded, although significative exposure data are lacking.

An exacerbation of effects (not better defined) could be expected following the concomitant presence in residences of ozone emitting sources, due to the formation of irritant reaction products.

Risk management tools

The indoor air risk management tools include:

IAQ Standards and guidelines: The huge quantity and privacy of indoor spaces makes enforceable indoor air quality standards impossible. Guideline values for key pollutants, however, are useful when matching potential sources, occupant needs and ventilation rates in the design of new building or renovation of an existing one. Sometimes they can also be applied in judging the acceptability of indoor air quality in a building.

Building codes and ventilation standards apply to every new building, and can therefore be powerful means of preventing or controlling indoor sources and ensuring sufficient contaminant dilution.

Building and household **equipment standards and permits** cover new installations, and can therefore ensure that improper - hazardous or avoidable - emissions are avoided or properly controlled, e.g. exhausted.

Mandatory maintenance and inspections of, e.g., gas appliances or fireplaces & chimneys, help avoid gradual deterioration of the equipment, and accumulation of its risks, and ensure that safe operation requirements are met through their lifetime.

Limits, labelling and reporting of the contents of or releases from building products, furnishing materials, equipment and consumer products can be quite inflexible and heavy instruments when mandated by law, but flexible and effective on voluntary basis, as long as commonly agreed (between consumers, builders, industry and public health authorities), widely published and generally understood criteria are used. Clear product labels guide informed selections of both builders and consumers.

Public awareness raising and information is the key to safe indoor environments, because, due to their sheer numbers, a great majority of potential indoor pollution risks must be identified, assessed and managed by occupants themselves. They are best helped by widespread and general awareness raising information, and easily found and understood sources (leaflets, internet sites) for more specific technical information.

Recommendations and management options

The recommendations and management options proposed protect the general population and most individuals most of the time, but they will not prevent all harm to every individual. Besides, the proposed measures will not prevent health damage from outdoor air pollutants which penetrate indoors. Following general recommendations apply to many indoor air contaminants:

- Restrict tobacco smoking in all indoor spaces.
- Restrict the construction of attached garages, or isolate them from living and working spaces.
- Ensure that ventilation dilutes predictable indoor emissions below the guideline levels.
- Raise public awareness about indoor air risks.

High priority chemicals

The high priority compound list consists of 5 chemicals, with potential of high indoor concentrations, uncontested health impacts, and effective risk management.

Formaldehyde: The non-carcinogenic no-effect level is 30 $\mu g/m^3$. Pending on IARC revision of formaldehyde carcinogenecity, a guideline should be as low as reasonably achievable. Management options are to restrict and avoid the use of formaldehyde containing materials and products in buildings:

Nitrogen Dioxide: Proposed guideline values are 40 $\mu g/m^3$ (1-week) and 200 $\mu g/m^3$ (1-hour). Management options are to connect each indoor combustion device/appliance to chimney or vented hood, and to ensure sufficient local extract ventilation in kitchens with gas stove.

Carbon Monoxide: Proposed guideline values are 10 mg/m^3 (8-hour) and 30 mg/m^3 (1-hour). Management options are to connect each combustion equipment/appliance to chimney or vented hood, to ensure sufficient local extract ventilation in kitchens with gas stove, mandatory inspection and maintenance of indoor combustion devices, and CO alarms.

Benzene: Benzene is a carcinogen, its indoor air concentration should be kept as low as reasonably achievable, and not exceed outdoor concentrations. Management options are to ban benzene sources indoors, and lower the permissible benzene content in any building material and consumer product.

Naphtalene: Proposed long term guideline value is 10 μg/m^3. Management option is to restrict the use of naphthalene containing household products.

Second priority chemicals, which are not considered to urgently require regulatory risk management actions specifically in indoor air are Acetaldehyde, o-, p- and m-Xylene, Toluene and Styrene.

Additional chemicals of interest for indoor air risk management, which are considered to require further research with regard to human exposure or dose response before recommendations can be made, are Ammonia, delta-Limonene, and alpha-Pinene.

1. Introduction

Human exposure to air pollution occurs over 90% indoors, but it depends on both indoor and outdoor air pollution. Outdoor air pollution is important mainly because indoor air is linked to outdoor air via ventilation. The strength of the personal exposure-outdoor air association varies considerably between the individuals, their activities, microenvironments and pollutants. On one hand leisure time exposures of active individuals to various pollutants are mainly associated with outdoor air pollution levels. On the other hand workday exposures, exposures of individuals leading sedentary lifestyles in closed or air conditioned spaces and exposures to pollutants like formaldehyde and radon are essentially independent of outdoor air pollution levels.

Past European Air Quality Directives have not taken population exposure sufficiently into account. They have up to now been mainly oriented on outdoor air pollution. EU legilslation addresses inter alia air quality standards, national emission ceilings and emissions from vehicles and industries. However, the Sixt Environmental Action Plan and the new launched Environmental and Health Strategy are oriented towards the impact of environmental risk factors on human health, and DG SANCO and other relevant DGs are developing proposals for a public health policy. So, in addition to ambient air pollution, the pollution inside confined environments as well as the extent of personal mobility and specific activities all play a significant role in exposure to air pollutants. The relative importance of these pollutants varies greatly depending on the sources, pollutants, and individuals or populations of concern. Concentrations of e.g. volatile organic compounds (VOC), in general, are higher indoors than outdoors, yet for some VOCs outdoor air levels may significantly affect respective indoor levels. For many chemicals occurring indoors the risk for human health and comfort is almost unknown and difficult to predict, in particular, the risk associated with chronic low dose exposures to these compounds because of a quite limited toxicological data and information on dose-response characteristics in human or animal models. Only very recently some few data have been become available, which partly make possible to carry out reliable exposure and risk assessments. Due to the missing risk assessments, it has been difficult to regulate the presence of these chemicals in indoor environments up to now.

It is, therefore, recommended to develop a strategy for indoor air quality assessment and management in Europe and that future clean air policies take into account the total air exposure of European citizens, which will necessarily include exposures to pollutants from both outdoor and indoor sources. This report offers background information for this strategy planning.

2. Objectives

The aim of the project was to create a network of European leading scientists in the area of indoor air pollution and the herewith-associated health impacts in order to identify priorities for a Community strategy and action plan. The key issues that were addressed within the project were:

- to provide information on links with existing knowledge, ongoing studies, legislation etc.,
- the setting up of a list of priority substances to be regulated in indoor environments on the basis of health impact criteria,
- to provide suggestions and recommendations on potential exposure limits or other risk management procedures for these substances, and
- to assess essential research needs for pollutants with high risk potential, but insufficient information for carrying out risk assessment and setting regulatory objectives or selecting regulatory options.

3. Methodology

3.1 Risk Assessment

Risk assessment was based on indoor air quality and exposure data from the scientific literature, databases and directly from the researchers. Similarly, dose/response data was reviewed from scientific literature. Two working groups (WG) of experts from several countries were established to assess these data. Finally, risk characterisation, recommendations for risk management and conclusions were drawn by the scientific steering committee based on the work of the working groups for exposure assessment and dose-response assessment. The main steps of the project are presented in Figure 3.1.1. The risk assessment approach applied to this project is presented in more detail in the following paragraphs.
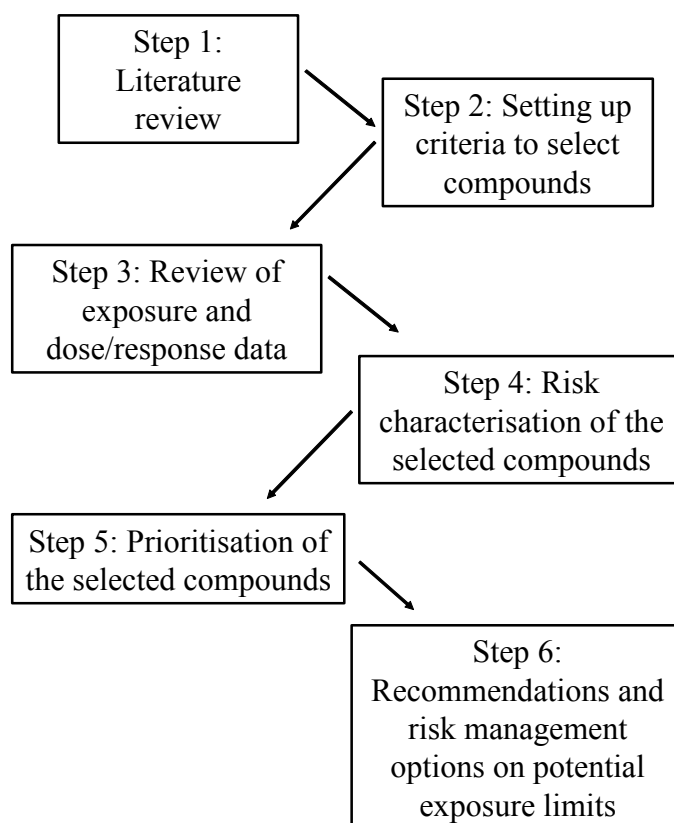
Figure 3.1.1: The main steps of the INDEX project.

3.1.1 Selection of Indoor Air Chemicals for Consideration (Hazard Identification)

The hazard identification of the indoor air pollutants was assessed combining the information of the prevalence of pollutants in European homes with the available knowledge of adverse health effects that these compounds had been linked to in toxicological or epidemiological studies. If a compound was present in the indoor air and it had had adverse health effects, it was considered as a potential hazard to European populations and was thus included in the risk assessment process. The process and the criteria to include or exclude each compound to the risk assessment process in this project are presented in the following paragraphs.

The selection criteria of the compounds to be included in the risk analysis

Considering the time limit of this exercise, and the fact that no new data could be generated in this project, the steering group defined the following criteria to be able to select the chemical compounds to the risk analyses:

1. Only single compounds will be considered
2. The compound should have common indoor sources, which dominate the exposures of at least significant fraction of the population
3. The compound should have known health effects.

It was also decided that compounds, which have been regulated by specific guidelines or regulations would be excluded from this analysis. For example, radon and tobacco smoke were excluded from the risk assessment process due to these criteria.

Phase 1: Literature review

In the first phase, a literature review was carried out to collect information about candidate pollutants to be assessed in the later stages of the project. The scientific literature of the indoor air pollutants was reviewed by using several search engines in the Internet and by searching from the web pages of the relevant journals. In addition to electronic search, numerous study reports concerning indoor air pollutants were reviewed.

The main focus of the review was on recent population-based studies to be able to evaluate current population exposures to selected pollutants in Europe. Only compounds with known indoor sources and known health effects were taken into consideration.

Based on the literature review, a summary table of the concentrations in residential indoor, workplace indoor, residential outdoor and personal exposures was created for the compounds meeting the first criteria (see Annex 1). Simultaneously, some dose/response data were collected for the selected compounds. Also the existing international (i.e. EU and WHO) and national guidelines for those compounds in indoor air were reviewed. Finally, the output of the literature review was used as an input for the next steps of the risk assessment.

Establishment of the working groups

For the evaluation and development of the reviewed literature, two working groups (WG) were established, one for exposure assessment (WG_{ea}) and one for dose/response assessment (WG_{dr}). The following experts were nominated to the working groups:

WG_{ea} on exposure assessment
Members: M. Jantunen (co-ordinator, KTL), Finland, C. Cochet, France, S. Kirchner, France, K. Koistinen, Finland, J. Mc Laughlin, Ireland, S. Kephalopoulos, EU/JRC-Ispra, E. Oliveira-Fernandez, Portugal, B. Seifert, Germany, and

WG_{dr} on dose/response assessment
Members: P. Carrer (co-ordinator, UniMi), Italy, T. Lindvall, Sweden, M. Maroni, Italy, L. Mølhave, Denmark and C. Schlitt, Italy.

Phase 2: The selection of compounds to the further analysis

In the second phase of the selection process, the working groups assessed the reviewed data and collected more detailed information for the previously selected compounds. The aim of the work was to select about 20 compounds for further analyses. In this phase the steering group excluded more compounds using the following criteria:

- no expressed concerns for health at present levels (for example acetone, decane, ethylbenzene, phenol , propylbenzene, trimethylbenzene)
- compound already regulated by use restrictions for indoor materials (pentachlorophenol)
- incomplete or no dose-response data available at present levels (methyl-ethyl-ketone, propionaldehyde)
- the main route/media for the exposure to the compound is other than indoor air (lead, mercury).

After detailed review and discussion of the available information, the working groups selected the 25 compounds presented in Annex 2 to the more detailed analysis.

Phase 3: Compounds selected for a detailed risk assessment

In addition to exposure and dose/response data, also data about odour threshold values were considered important and thus, these data were added to the background information. The standardised human odour threshold values were taken from Devos et al. (1990).

On the basis of the available information and after an extensive discussion on the chemical substances, the steering group decided to conduct detailed assessment of the 14 compounds presented in Figure 3.1.1.1.(phase 3).

Based on the potential/estimated population risk caused by concentrations from indoor sources, toxicological properties including hypersensitivity for allergy and asthma, other known health effects and comfort, the steering group decided to separate the 14 compounds into two groups: 1) compounds to be considered with high priority and 2) compounds that could be included in the final prioritisation after further examination and new published findings of their hazardous potential and the other criteria set within the project.

After a first evaluation the compounds were initially classified as follows:

Group 1 (high priority) Benzene, Acetaldehyde, Formaldehyde, CO and NO_2
Group 2 (further information needed) m&p-Xylenes, o-Xylene, Naphthalene, Styrene, Toluene, a-Pinene, d-Limonene, NH_3.

Flame-retardants were regarded as an emerging issue, which will require further consideration in the future. The compound Tris-(2-chloroethyl) phosphate belongs to this group, but because reliable data on its sources and occurrence in indoor environments, exposure routes and on toxicological properties were lacking, the compound was not included in the evaluation procedure in this project.

Figure 3.1.1.1: The indoor originated compounds that were assessed and considered the most hazardous in the three phases of the hazard identification process.

Phase 1

1-Butanol
2-Buthoxyethanol
2-Ethyl-1-hexanol
2-Methyl-1-propanol
3-Carene
Acetaldehyde
Acetone
Ammonia
a-Pinene
Benzaldehyde
Benzene
Benzo[a]pyrene
Cadmiuim
Carbon monoxide
Decane
Dichloromethane
Diisocyanate
d-Limonene
Ethylbenzene
Formaldehyde
Hexaldehyde
Lead
m&p-Xylene
Mercury
Methyl-ethyl-ketone
Naphtalene
Nitrogen dioxide
Nonane
o-Xylene
Pentachlorophenol
Phenol
Propionaldehyde
Propylbenzene
Styrene
Tetrachloroethylene
Toluene
Trichloroethylene
Trimethylbenzenes
Tris-(2-chloroethyl) phosphate
Undecane

Phase 2

1-Butanol
2-Ethyl-1-hexanol
3-Carene
Acetaldehyde
Ammonia
a-Pinene
Benzaldehyde
Benzene
Cadmiuim
Carbon monoxide
Dichloromethane
Diisocyanate
d-Limonene
Formaldehyde
Hexaldehyde
m&p-Xylene
Naphtalene
Nitrogen dioxide
o-Xylene
Styrene
Tetrachloroethylene
Toluene
Trichloroethylene
Tris-(2-chloroethyl) phosphate

Phase 3

Acetaldehyde
Ammonia
a-Pinene
Benzene
Carbon monoxide
d-Limonene
Formaldehyde
m&p-Xylene
Naphtalene
Nitrogen dioxide
o-Xylene
Styrene
Toluene

1. priority

Formaldehyde
Carbon monoxide
Nitrogen dioxide
Benzene
Naphtalene

3.1.2 Exposure Assessment

Exposure to selected indoor air pollutants was estimated by collecting exposure data from scientific literature, from available databases, and by personal communications. The aim of this work was to summarise prevailing indoor air and personal exposure concentrations of these compounds in Europe and also worldwide. These reviews are mainly focused on indoor air and exposure concentrations measured recently in European population based studies such as EXPOLIS (Jantunen et al 1998), German Environmental Surveys, GerES, (Seifert et al 2000), the German study on Indoor Factors and Genetics in Asthma, INGA (Schneider et al 1999 and 2001), and a national survey of air pollutants in English homes (Raw et al 2002). Also some preliminary results of the French National Survey (Golliot et al 2003, Kirchner 2004) were available during this project. Some comparisons have been also done to the TEAM (Wallace et al 1991) and the NHEXAS (Sexton et al 1995, Pellizzari et al 1995) studies carried out in the USA. Results from population-based studies have been used to be able to generalise the results from studied individuals to larger populations, targeting to assess exposures of all the Europeans.

Population exposures are typically reported in literature using parameters such as arithmetic or geometric mean and standard deviation. Mean concentrations give us a general picture of the concentration levels, but due to presence of subpopulations that are exposed to much higher concentrations, the whole exposure distribution is needed when linking these exposures to toxicological or epidemiological dose-response data. The distributions presented in this report are drawn using arithmetic or geometric means and respective standard deviations, reported in the literature or extracted from the databases, assuming that the measured data is log-normally distributed, which is a typical shape for the distributions of the naturally occurring pollutants. These parameters taken from the large scale European population based studies are presented in Annexes 4, 5, and 6.

Concentrations have been linked to the main emission sources if possible. Short time concentration peak values are presented in tables and graphs to be used in the assessment of acute health effects.

European Union has recently published risk assessment reports (RAR) for some of the chemicals that are reviewed in this report. Final RARs are available for naphthalene (EU 2003a), styrene (EU 2002a), toluene (EU 2003b) and a draft report for benzene (EU 2002b). These reports were used as a data source in this project, and therefore the contents presented in those reports have not been repeated in this report.

3.1.3 Dose/Response Assessment

In preparing the dose-response assessment fact sheets of 12 chemicals (m,p, and o-xylenes handled together), information were retrieved from scientific literature (mainly by electronic search), comprehending toxicological reviews of leading health organizations, risk evaluation documents and available databases, as outlined in Table 3.1.3.1. In addition, Toxline and Medline were searched for relevant scientific communications published up to September 2004.

Nearly all key-studies referred to in the present assessment, establishing effect levels for appropriate toxicological endpoints, are those selected by health organizations for the derivation of health based limits of exposure (WHO/GV, IRIS/REL, OEHHA/RfC, ATSDR/MRL, HC/TC, UBA/GVII&I) or among risk assessment requirements (ECB). Although not specifically addressing health hazards and risks associated with indoor air exposure, i.e. not being designed for the expression of effects at lowermost exposure concentrations, nearly all studies were aimed at identifying the most sensitive endpoint considered to be of relevance to humans. Summary definitions of exposure limits/guidelines established by these health organisations are given in Table 3.1.3.2. Where relevant, studies conducted on susceptible sub-populations (e.g. asthmatics, infants, children, pregnant women etc.) were quoted and taken into consideration in the risk characterization.

Table 3.1.3.1: Toxicological reviews, risk evaluation documents
and databases consulted and referred to in the dose response assessment

	World Health Organization Air Quality Guidelines for Europe	International Program on Chemical Safety Environmental Health Criteria, Concise International Chemical Assessment Documents and Health and Safety Guides	European Chemicals Bureau - Institute for Health and Consumer Protection European Union Risk Assessment Reports	Agency for Toxic Substances and Disease Registry Toxicological Profiles	U.S.EPA - Integrated Risk Information System	Office of Environmental Health Hazard Assessment of the Californian EPA Acute and Chronic Toxicity Summaries		IARC monographs Summaries and Evaluations
	WHO	IPCS	ECB	ATSDR	IRIS	OEHHA	Others when relevant	IARC
Formaldehyde	2000	EHC 89 1989 CICADS 40 2002		1999	being reassessed	acute & chronic 1999	NIWL 2003 [c]	Vol. 88 1995 2004 in preparation
Acetaldehyde		EHC 167 1995 HSG 90 1995			1991 being reassessed	chronic 1997		Vol. 71 1999
Ammonia		EHC 54 1986 HSG 37 1990		2002 draft	2003	acute & chronic 1999		
Carbon monoxide	2000	EHC 213 1999				acute [a] 1999		
Nitrogen dioxide	2000	EHC 188 1997			1993	acute [a] 1999	UBA 1998	
Benzene	2000	EHC 150 1993	2004 draft	1997	2003 [b]	acute & chronic 1999		Vol. 29 Suppl.7 1987
Toluene	2000	EHC 52 1986	2003	2000	1994 being reassessed	acute & chronic 1999	UBA 1996 [d]	Vol. 71 1999
Xylenes		EHC 190 1997		1995	2003	acute & chronic 1999		Vol. 71 1999
Styrene	2000	EHC 26 1983		1992	1993 being reassessed	acute & chronic 1999		Vol. 82 2002
Naphthalene			2003	2003 draft	1998 being reassessed	chronic 1999	UBA 2004 [e]	Vol. 82 2002
Limonene		CICADS 5 1998			1993		NICNAS 2002	Vol. 73 1999
α-Pinene							UBA 2003 [f] NIEHS 2002 [g]	

[a] including: Evaluation of current California Air Quality Standards with respect to protection of children (2000)
[b] including: EPA-Toxicological review of benzene/noncancer effects (2002) and EPA-Carcinogenic Effects of Benzene: An Update (1998)
[c] National Institute for Working Life - The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards: 132. Formaldehyde - Anton Wibowo
[d] Umweltbundesamt: Bundesgesundheitsblatt 11/96: Richtwerte für die Innenraumluft: Toluol. H.Sagunski,
[e] Umweltbundesamt: Bundesgesundheitsblatt 7 · 2004: Richtwerte für die Innenraumluft: Naphthalin. H.Sagunski, W.Heger

[f] Umweltbundesamt: Bundesgesundheitsblatt 4 · 2003: Richtwerte für die Innenraumluft: Bicyclische Terpene (Leitsubstanz α-Pinen). H.Sagunski, B.Heinzow

[g] National Institute of Environmental Health Sciences, Toxicological Summary For Turpentine, Review of Toxicological Literature, February 2002

Table 3.1.3.2: Exposure limits/guidelines established by health organisations and their summary definitions

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World Health Organization - Air Quality Guidelines for Europe

Guidelines: The term "guidelines", in the context of the WHO - Air Quality Guidelines for Europe, implies not only numerical values (guideline values), but also any kind of guidance given. Accordingly, for some substances the guidelines encompass recommendations of a more general nature that will help to reduce human exposure to harmful levels of air pollutants. For some pollutants no guideline values are recommended, but risk estimates are indicated instead.

The starting point for the derivation of *guideline values* is to define the lowest concentration at which adverse effects are observed. On the basis of the body of scientific evidence and judgements of uncertainty factors, numerical guideline values were established to the extent possible. Compliance with the guideline values does not, however, guarantee the absolute exclusion of undesired effects at levels below the guideline values. It means only that guideline values have been established in the light of current knowledge and that uncertainty factors based on the best scientific judgements have been incorporated, though some uncertainty cannot be avoided. The numerical values for the various air pollutants should be considered in the context of the accompanying scientific documentation giving the derivation and scientific considerations. Any isolated interpretation of numerical data should therefore be avoided, and guideline values should be used and interpreted in conjunction with the information contained in the appropriate sections.

Guidelines based on carcinogenic effects are indicated in terms of incremental unit risks in respect of those carcinogens that are considered to be genotoxic. To allow risk managers to judge the acceptability of risks, this edition of the guidelines has provided concentrations of carcinogenic air pollutants associated with an excess lifetime cancer risk of 1 per 10 000, 1 per 100 000 and 1 per 1 000 000.

Agency for Toxic Substances and Disease Registry (ATSDR)

Minimal Risk Levels (MRLs): During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels. MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure.

U.S.EPA - Integrated Risk Information System (IRIS)

The *inhalation Reference Concentration (RfC)* is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency (OEHHA)

The concentration, at or below which no adverse health effects are anticipated in the general human population, is termed the reference exposure level (REL). RELs are based on the most sensitive relevant adverse health effect reported in the medical and toxicological literature. RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety. Protection against carcinogenicity and against adverse health effects of short-term exposures are not considered in these guidelines. For this reason, chemicals should be evaluated separately for their carcinogenic potential and additional acute health effects that may occur.

Methods for the evaluation of acute and chronic health effects and for the carcinogenic potential of chemicals are provided in the OEHHA documents entitled Air Toxics Hot Spots Program Risk Assessment Guidelines:

Acute Reference Exposure Levels (RELs): three categories of acute severity levels are developed in accordance with criteria established by NRC (1993): the level protective against mild adverse effects, the level protective against severe adverse effects, and the level protective against life threatening effects. Each of these three acute exposure levels is determined for one-hour exposure duration. However, the major focus of this document is in developing acute RELs for the preparation of risk assessments for non-emergency routine releases. Thus, the RELs used in the risk assessment are generally levels protective against mild adverse effects; a few are based on severe effects (e.g., reproductive/developmental).

Chronic Reference Exposure Levels (RELs): Chronic reference exposure levels are concentrations or doses at or below which adverse health effects are not likely to occur. A central assumption is that a population threshold exists below which adverse effects will not occur in a population; however, such a threshold is not observable and can only be estimated. Areas of uncertainty in estimating effects among a diverse human population exposed continuously over a lifetime are addressed using extrapolation and uncertainty factors.

Federal Environmental Agency of Germany (Umweltbundesamt – UBA)

In Germany, an important framework for the setting of indoor-related guideline values is given by the building codes (which are under the jurisdiction of the German States). The building codes demand that there be no health hazard to occupants from the building. Hence the work of the ad-hoc group focused on defining concentration levels at which such hazard would probably occur. The introduction of a safety margin would then allow the definition of a concentration where there would be no more concern for adverse health effects. The following two concentration levels were defined:

- *Guideline Value II (GV II):* GV II is a health-related value based on current toxicological and epidemiological knowledge. If the concentration corresponding to GV II is reached or exceeded immediate action must be taken because permanent stay in a room at this concentration level is likely to represent a threat to health, especially for sensitive people. In this context, taking action means an immediate examination of the situation with regard to a need for control measures. It may include the evacuation of the room in question. If by measurement GV II has been found to be

exceeded, the results should be checked by repetitive measurements carried out immediately under normal conditions of occupancy. If possible and deemed meaningful, biological monitoring of the occupants should be carried out in addition.

- *Guideline Value I (GV I):* GV I is the concentration level at which a substance – taken individually – does not give rise to adverse health effects even at life-long exposure. An exceedance of GV I is linked with an exposure beyond normal which is undesirable from a hygienic viewpoint. Thus, there is also a need for action at concentrations between GV II and GV I. GV I is obtained by dividing GV II by a factor of 10. This factor is a convention. However, for odorous substances GV I must be defined based on the odour threshold ("odour detection") if the odour threshold has a lower numerical value than the concentration derived according to the general scheme. GV I can be used as the level to be reached after control measures have been applied. The level should not be "filled up"; rather, the final concentration should fall below.

Environment Canada - Health Canada (EC-HC)
Different approaches were adopted for assessments of Priority Substances for chemicals for which the critical effect is believed to have a threshold and those for which it is considered not to have a threshold. For substances for which the critical effect is considered to have a threshold (i.e., non-neoplastic effects), Tolerable Daily Intakes (TDIs) or Tolerable Concentrations (TCs) have been developed by dividing effect levels observed in studies in exposed populations or animal species, by uncertainty factors.
Priority Substances are classified into one of 6 categories, based on the weight of evidence of carcinogenicity (see Section 3). For genotoxic carcinogens (i.e., primarily compounds which are considered "carcinogenic to humans" or "probably carcinogenic to humans", Groups I or II of the scheme for classification of carcinogenicity under CEPA), quantitative estimates of the carcinogenic potency within or close to the experimental range have been developed. This approach was adopted for several reasons, one of the most important of which was to avoid expressing risk in precise absolute terms (i.e., predicted excess numbers of cancers per unit of the population) based on uncertain low-dose extrapolation procedures.
Tolerable Concentration (TC): Tolerable concentrations (Section 3a) (often expressed in mg/m3) are generally airborne concentrations to which it is believed that a person can be exposed continuously over a lifetime without deleterious effect. They are based on non-carcinogenic effects.
Tumorigenic Concentration 05 (TC05): The Tumorigenic Concentration 05(TC05) is the concentration generally in air (expressed, for example, in mg/m3) associated with a 5% increase in incidence of, or deaths due to, tumours considered to be associated with exposure, observed in epidemiological studies in human populations or bioassays in experimental animals Values derived based on division of the TC05s by a suitable margin (e.g., 5.000 to 50.000)* can provide a benchmark against which the adequacy of indoor or ambient air can be judged, with respect to potential carcinogenicity.
It should be noted that Health Canada does not necessarily deem as "acceptable" from a societal viewpoint health risks associated with these values and that the Health Protection Branch continues to subscribe to the position that exposure to substances for which the critical effect has no threshold be reduced to the extent possible.
* Since Tumorigenic Concentration05s were computed directly from the curve within or close to the experimental region, division by an additional factor of 2 would equate approximately to the lower 95% confidence limit.

Key-studies were summarised among each chapter treating effects of short- and long-term exposure and itemised in tables at the end of the chapter. One-page fact sheets resuming the most relevant toxicological properties are given at the end of each D/R assessment chapter. In the key-study Tables, subscripts were assigned to effect levels (NOAELs and LOAELs), stating on whether occupational average levels or experimental concentrations are quoted or identifying the extrapolation process applied for the given value. Details on these subscripts are given in Table 3.1.3.3.

Table 3.1.3.3: Subscripts used in summary tables and fact sheets quoting key-studies
and the exposure limit derivation process accounted for by health organisation

Subscript	Description	Details
Study	average concentration	time weighted average concentration with no information on maximum concentrations, in chronic studies generally estimated from numerous intermittent measurements in occupational settings, even over years
EXP	experimental concentration	concentrations artificially generated in inhalation/exposure chambers in animal or volunteer studies
ADJ	concentration adjusted from an intermittent to a continuous exposure	When extrapolating from occupational to population based exposures on a [hour/day and days/7 days] basis (generally: division by 4.2)
1h-ADJ	concentration adjusted to 1-hour exposure duration	For the extrapolation from sub-acute to acute
HEC	human equivalent concentration	Generally a blood-to-air partition coefficient of the chemical for the experimental animal species was used in the HEC derivation of an RfC
MLE	maximum likelihood estimate for 5% response	A statistical best estimate of the value of a parameter from a given data set.
BC05	BC05 is the 95% lower confidence limit of the concentration expected to produce a response rate of 5%	Following a Benchmark (BM) approach, alternative to the traditional NOAEL/LOAEL approach. A Benchmark Concentration (BMC) is a statistical lower confidence limit on the dose producing a predetermined, altered response for an effect.
STAT	lowest statistically significant effect concentration	

3.1.4 Risk Characterization and prioritisation of chemicals

In this final step of the general risk assessment process, the incidence of health hazards and risks in the European population, associated with indoor exposure to individual chemicals, was estimated. It is pointed out that the assessment of risk is a scientific one, which has been kept separate from any consideration regarding the risk management process, including the setting or the proposal of Indoor Exposure Limits. Namely, an important uncertainty, not accounted for in the assessment, is the possibility of antagonistic and synergistic effects arising from the exposure to mixtures of chemicals, little scientific information existing in this area. Multiple contaminants are typically occurring in indoor environments (although at low concentrations) and the resulting uncertainty (uncontrolled factor) should be taken into consideration in the risk management.

Nevertheless, Limits of Exposure (ELs) had to be established in order to perform the risk characterization associated with individual chemicals, following inhalatory exposure in indoor environments, for both short-term (indoor-activity related) and long-term exposures (background indoors).

An EL was derived for each chemical after the identification of key-studies (critical-study) describing the appropriate toxicological endpoints (among those selected by health organizations for the derivation of health based reference concentrations).

Uncertainty factors (here named assessment factors, AF) applied in the present assessment to account for the adequacy of the critical study are the product of the individual factors outlined in Table 3.1.4.1.

Table 3.1.4.1: Elements considered for the derivation of Uncertainty (Assessment) Factors (AS)

Description	Detail	Factor
Extrapolation from a LOAEL to a NOAEL	When in the critical study no NOAEL could be observed	10
Interspecies extrapolation	Critical study = experimental animal study (no human study available or appropriate)	10
Inter-interindividual (intraspecies) variability in humans	Always, unless the critical study was performed on individuals of the sub-population considered susceptible	10
Susceptible population	asthmatic individuals, infants, children, individuals with heart diseases, individuals with (hereditary) enzyme deficiencies, pregnant women	10; 3; 2
Adequacy or quality of toxicological data	Old study	2
Extrapolation from sub-acute to chronic	Deficiencies in toxicological database	10
Extrapolation from sub-acute to acute	Deficiencies in toxicological database	10

For all chemicals a threshold-level of action could be identified, enabling a "no-observed-adverse-effect level (NOAEL)/assessment factor (AF)" approach, i.e. EL derived by dividing the critical effect level by the AF, with the AF based on the available scientific evidence. Where no NOAEL observation was documented, a lowest-observed-adverse-effect level (LOAEL) was taken into consideration and an additional assessment factor of 10 used for EL derivation. For one compound only (benzene) the characterization has been based on population cancer risk estimation rather than on an EL.

In those cases where large differences in sensitivity for different susceptible groups were documented, a bimodal distribution of population responses was supposed to exist and a tenfold difference in sensitivity, usually accepted as higher than the encountered range, taken in account in the AF derivation. Susceptible subpopulations considered in the present characterization are: asthmatic individuals, infants, children, individuals with heart diseases, individuals with (hereditary) enzyme deficiencies, pregnant women.

Information from the exposure assessment (Chapters 1-3) and toxicity assessment (Chapters 4-5) were integrated and a risk characterization performed for each chemical (Chapter 6). Based on the conclusions of the assessments and on the completeness of individual databases a priority ranking of the 14 chemicals was established with the chemicals assigned to one of three groups, and the results of the assessment handed over to Risk Management.
Group 1: High priority chemicals
Group 2: Low priority chemicals
Group 3: Chemicals requiring further research with regard to human exposure or dose response

3.2 Risk Management

Buildings are built for shelters from the cold (or heat), wind and rain of the outdoor air. Typically indoor air contains higher levels of most air pollutants than outdoor air. As long as people feel that they are in control of their own indoor environment, however, there is usually a higher tolerance to poor indoor air quality compared to outdoor air quality - after all one can always go outdoors or open a door or window. This tolerance is greatly decreased if self-control is lacking.

Risk assessment disentangles an identified risk complex (e.g. intoxication from a high indoor CO concentration peak) into its details (e.g. formation of CO in a faulty combustion device, release of CO into room instead of chimney, exposure to CO in the room, absorption to bloodstream in the lung, subsequent reduction of oxygen delivery, and hypoxia), and analyses these details one by one and in relation to each other. Risk management must entangle these details back again into an efficient and enforceable policy to reduce the risk (e.g. building codes requiring combustion devices to be vented to chimneys, regular maintenance & inspections, CO-alarms, etc.).

While risk assessment is a science based exercise, risk management by necessity involves also technical, economic, social and legal realities, as well as need for actions in the face of incomplete information. Risk management decisions concerning a specific risk are based on one hand on risk characterisation, produced by risk assessment, and on the other hand on the political and administrative processes that generate, evaluate, select and implement policies in the society (EU Commission directive 93/67/EEC). The indoor air risk management options include, in principle:

- IAQ Standards and guidelines
- Building codes and ventilation standards
- Equipment standards and permits
- Mandatory maintenance and inspections
- Limits, labelling and reporting of the contents of or releases from building products, furnishing materials, equipment and consumer products
- Public awareness raising and information

These alternatives will be discussed separately for each of the final shortlist components in Chpt. 6.1. The following discussion looks at indoor air risk management in general.

The core of ambient air risk management is in the ambient air quality guidelines and standards. The ambient air concentration limits have questionable applicability for indoor environments, because they are derived for different pollution mixtures and exposure patterns, because comparable monitoring and implementation alternatives do not exist indoors, and because indoor air quality for an individual may depend strongly on the behaviour of the same individual. When ambient air quality standards are applied for indoor air quality (as determined by indoor sources and activities), short term (24 h) measurements of indoor pollutants should in most cases be related to long term (annual) outdoor air guidelines.

The occupational exposure limits (OEL, TLV, MAK, etc.), although derived for indoor environments, are not directly applicable either, because they have been developed for healthy adult populations and more or less controlled 40 h exposure in a 168 h week.

Risk managers can intervene in many points (that lead from the primary source of risk to its materialisation). They can prevent the hazardous process, reduce exposures, modify effects, alter perceptions or valuations through education and public relations or compensate for damage after the fact. (Morgan 1993).

The issue, which is most specific for indoor air risk management, becomes obvious by visualising the millions of indoor environments in just one city, and the daily multitudes of potential hazards in them. A vast majority of both indoor air risk observations (assessments) as well as decisions (management) will remain to be made by occupants themselves - and this is particularly true for the acute effects from short term hazardous exposures. No imaginable public service or professional expert resources can ever cover but a tip of the iceberg of all hazardous IAQ situations. At best there are enforceable governmental regulations, respected industrial/professional standards/practices and/or authoritative examples.

In contrast to ambient air quality management, which relies on air quality standards and monitoring networks, the capabilities of public services and experts to manage most indoor air risks lie crucially on their abilities to establish and maintain public *confidence*, to communicate the risks in a way that the public is able to comprehend, to relate to their own living conditions and willing to accept, and to present practical solutions which are technically, financially and legally feasible, and which sufficiently acknowledge the diversity of the buildings, the occupants, expectations and risks.

The largest investments in the life of most individuals are their homes, and buildings represent in the order of 2/3 of national property in most European countries. This fact sets very concrete requirements for any interventions into the

residential building stock, as well as for the allocation of financial burdens and benefits. The fact that most indoor environments are private property and protected by privacy of the individuals significantly limits the options of public indoor air risk management.

The public services can, however, rely more on standards and regulations in managing risks in rented apartments, hotels, public buildings, workplaces, schools, hospitals, shopping malls etc. These buildings should be ensured to be safe for a great majority of the population (excluding only exceptionally sensitive individuals) by public health, occupational health and building inspection authorities as the last resort. When credible concerns arise they should be addressed promptly and properly for the sake of public health, confidence and liability. One of the most important special tasks for the public services and experts is prediction, identification, assessment and management of the situations where susceptible population groups and risky indoor environments coincide.

Risk - benefit: In managing risks from indoor air pollutants, there is a case for erring on the side of caution and acting to reduce risks if there is any reasonable suspicion that a hazard exists. However:

-   any chemical can be hazardous at sufficient concentration, and yet attempt to reduce all measurable concentrations to zero is not feasible;

-   blind application of precaution may divert resources into irrelevant actions, and thus lead to sub-optimal protection of health and/or the environment. It may also unjustifiably deny the benefits of using products or techniques; and

-   consideration should be given to the fact that limiting the use of one chemical may entail the application of a substitute that may not have lower, but only less well-characterised risks.

Hence, legislation in Europe has moved towards approaches based on overall risk rather than mere hazard identification. Article 10 of the Council Regulation (EEC) 793/93 (Existing Substances Regulation) requires that: "Where such control measures include recommendations for restrictions on the marketing and use of the substance in question the rapporteur" [on behalf of the body carrying out the risk assessment] "shall submit an analysis of the advantages and drawbacks and the availability of replacement substances".

Risk Communication: Risk communication is by far the most important tool for the society to manage indoor air health risks. Successful communication will not raise undue concerns, but suggests behaviour, which reduces avoidable risks, yet restricts nonessential interference into the lives of the individuals or to the alternatives of the enterprises. Poor risk communication may not only fail to produce the wanted risk reduction, it may also unnecessarily limit individuals' options, add public and private costs, and generate new risks due to non-productive public concerns and potentially harmful behavioural changes.

The essence of good risk communication is simple: Learn what people believe and the decisions that they are facing and tailor the language and message to this knowledge. Increased (decreased) trust in the managing organisation of the activity under concern - including indoor air risk management - will lead to lower (higher) levels of perceived risk and thus increase public support (opposition). Understanding the dimensions of trust is essential for developing policy strategies that will gain public acceptance. (Flynn et al. 1992)

Economically and technically sound [indoor air risk management] policies may be doomed if people believe that they distribute benefits and burdens unfairly. Three concepts emerge from the philosophical and cultural basis of risk sharing: parity, in which each individual, group or country is treated equally; priority, or giving the burden to those most deserving of it; and proportionality, or the sharing of burdens according to need or contribution. (IIASA 1993)

4. Risk Assessment of the selected chemicals

The exposure and dose/response data reviewed during the project are presented in this chapter. The summary of the typical concentrations in Europe for the selected compounds are presented in Table 4.0.1. To be able to compare recently published results reviewed in this report to the 'normal' indoor concentrations defined by the Working Group of WHO (WHO 1989), these concentrations are summarised in Table 4.0.2.

Table 4.0.1. Typical European microenvironmental and exposure concentrations ($\mu g/m^3$, except CO in mg/m^3) summarised from population based studies reviewed in this report.

	In[1]	W[1]	Out[1]	P[1]
Aromatics				
Benzene	2-13	4-14	1-21	3-23
Naphthalene	1-90	2-8	1-4	2-46
Styrene	1-6	3-7	1-2	1-5
Toluene	15-74	25-69	3-43	25-130
m&p-Xylenes	4-37	25-121	2-23	25-55
o-Xylene	2-12	7-29	1-8	8-15
Aldehydes				
Acetaldehyde	10-18	3	1-2	8
Formaldehyde	7-79	12	2-4	21-31
Terpenes				
a- Pinene	11-23	1-17	1-7	7-18
Limonene	6-83	11-23	5-9	19-56
Classical pollutants				
CO	0.5-1	1	2	0.8-1.7
NO_2	13-62	27-36	24-61	25-43

[1] In, W, Out, P = Indoor, workplace, outdoor and personal exposure concentrations

Table 4.0.2. 'Normal 'residential indoor air concentrations of selected organic pollutants reviewed by a Working Group of WHO in 1987 (adopted from WHO 1989 and Maroni et al 1995).

Pollutant	Concentration ($\mu g/m^3$)				Sources
	10%	median	90%	AM	
Aromatics					
Benzene	2	10	20	10	fuel component, tobacco
Naphtalene		2	5		solvent moth balls
Styrene	< 1	1	5		fuel component
Toluene	30	65	150	80	fuel component, solvent
m,p-xylene	10	20	40	20	fuel component, solvent
o-xylene	3	5	10	10	fuel component, solvent
Aldehydes					
acetaldehyde		10	30		cigarette smoke
formaldehyde		25	60	40	chipboard, urea-formaldehyde insulation
Terpenes					
a-pinene	2	10	20	10	wax, wood product
limonene	2	15	70	30	odorant, detergent

10% and 90% = ith percentile, AM = arithmetic mean

Formaldehyde

Synonyms:	Formalin, methanal, oxoymethane, oxomethylene, methylene oxide, formic aldehyde, methyl aldehyde
CAS Registry Numbers:	50-00-0
Molecular Formula:	CH_2O

1. Compound Identification

Formaldehyde is a colourless, odorous, highly reactive, flammable and easily polymerised gas at room temperature and pressure. It is formed by oxidation or incomplete combustion of hydrocarbons. Formaldehyde is soluble in water, ethanol and diethyl ether and is used in solution or in polymerised form (paraformaldehyde). In atmosphere formaldehyde is photo-oxidised in sunlight to carbon dioxide. Its half-life in urban air, under the influence of sunlight, is short. In the absence of nitrogen dioxide, the half-life of formaldehyde is approximately 50 minutes during the daytime, but in the presence of nitrogen dioxide, it decreases down to 35 minutes (WHO 1989).

In solution formaldehyde has a wide range of uses: in the manufacture of resins and textiles, as a disinfectant, and as a laboratory fixative or preservative in consumer products, such as food, cosmetics, and household cleaning agents (SIS 2003, EPA/Cal 2003).

Formaldehyde is used commonly in homes as an adhesive resin in pressed wood products. There are two types of formaldehyde resins: urea formaldehyde (UF) and phenol formaldehyde (PF). Products made of urea formaldehyde readily release formaldehyde. Urea-formaldehyde foam is used to insulate buildings. It can continue to emit formaldehyde after installation or constituting a source of persistent emission. Formaldehyde is used also in phenolic and polyacetal plastics, but they are not expected to release formaldehyde (WHO 1989, EPA 2002).

2. Physical and Chemical Properties

Molecular weight (g/mol)	30.03
Melting point (°C)	-118
Boiling point (°C)	-19.2
Density (g/l at 20 °C, 1 atm)	0.815
Relative density (air =1)	1.04
Explosivity range in air (vol %)	7-73

Solubility: Soluble in water, ethanol, ether, and acetone

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 1.248 $\mu g/m^3$
1 $\mu g/m^3$ = 0.815 ppb

Sources: (CRC, 1994, WHO 1989, Verschueren 2001, HSDB 2003,)

3. Indoor Air Exposure Assessment

Emission sources

There are several indoor sources that can result in increased human exposure to formaldehyde including cigarette smoke, insulating materials, particle board or plywood furniture containing formaldehyde-based resins, water based paints, fabrics, household cleaning agents, disinfectants, pesticide formulations, paper products and adhesives containing formaldehyde used for plastic surfaces, parquet, carpets and other building materials containing urea-formaldehyde resins. Also gas cookers and open fireplaces emit formaldehyde to indoor air (WHO 1989, COMEAP 1997, Jurvelin et al 2001, EPA/Cal 2003).

There might be also formaldehyde sinks in indoor environment. Zwiener et al (1999) reported reduction of formaldehyde concentration between 80% and 87% in chamber air in two hours after the test had begun. This reduction is due to chemical reaction of formaldehyde and the wool proteins.

Building age was identified a factor for indoor air formaldehyde concentration in UK (Brown VM et al 2002). Indoor air concentration increased with decreasing age, having highest concentrations in buildings built in 1990's. A source identified in this study was particleboard flooring. These findings show that formaldehyde in indoor air is still an issue in European homes and should not be neglected in the forthcoming indoor air surveys.

Emission rates of 55 diverse materials and consumer products were determined in a chamber study in California (Kelly et al 1999). The tests showed that among dry products highest formaldehyde emissions were found from bare pressed-wood materials made with urea-formaldehyde (UF) resins, and from new permanent press fabrics. An acid-cured floor finish showed the highest emissions from wet products, clearly exceeding those of any dry product.

Puhakka and Karkkainen (1993) studied factors that increased formaldehyde concentrations in indoor air. Their results showed the amount of chipboard and the air exchange efficiency in a room being the dominant factors. Formaldehyde emissions from chipboard could be reduced by painting the surfaces. On the other hand elevated relative humidity increased formaldehyde emissions significantly.

Increased formaldehyde concentrations may be present in hospitals and scientific facilities where formaldehyde is used as a sterilising and preserving agent, and in living spaces, such as schools, kindergartens, and mobile homes or apartments where there may be uncontrolled emissions of formaldehyde from tobacco smoking, building materials, and furniture (WHO 1989).

A French study carried out in 61 recently refurbished flats with no previous history of complaint for odour or specific symptoms, showed that aldehyde levels of formaldehyde, acetaldehyde, pentanal, and hexanal were depend on the age of wall or floor coverings (renovations less than 1 year old), smoking, and ambient parameters such as carbon dioxide levels and temperature. Geometric mean and geometric standard deviation of formaldehyde concentrations in bedrooms were 24.5 $\mu g/m^3$ and 2.0 respectively (Clarisse et al 2003).

Formaldehyde is formed naturally by photochemical reactions in the atmosphere. It is also emitted by fuel combustion such as motor vehicles and by industrial fuel combustion such as power generators, oil refining processes, copper plating, and incinerators (EPA/Cal 2003).

Indoor air and exposure concentrations

A large-scale population based indoor air survey has been carried out in UK (Brown VM et al 2002). Geometric mean and the maximum value of 3-day samples (n=833) were 22.2 $\mu g/m^3$ and 171 $\mu g/m^3$, respectively. In Helsinki, average indoor air concentration of formaldehyde, 41.4 $\mu g/m^3$, was more than tenfold compared to the respective ambient concentration. Average personal exposure, 26.8 $\mu g/m^3$, was slightly lower than the respective residential indoor concentration, but anyway clearly higher than the workplace concentration, 15 $\mu g/m^3$. In Sweden (Gustafson et al 2004) average 24-hour personal exposure (n=24, AM=47 $\mu g/m^3$, std=111) was higher than the respective indoor air (bedroom) concentration, (n= 24, AM= 26 $\mu g/m^3$, std = 14). In another campaign of the same study, average 6-day exposure (n=40, AM=31 $\mu g/m^3$, std=18) was slightly higher than the respective indoor air concentration (n=40, AM=35 $\mu g/m^3$, std=22). Both of these levels were about an order of magnitude higher than respective outdoor air concentration (n=20, AM=3.8 $\mu g/m^3$, std=1.2). These results show the dominating role of residential indoor emissions for population exposure to formaldehyde.

In a German study (GerES IV) weekly mean formaldehyde concentration in residential indoor air in a randomly selected population of children and teenagers was 36 $\mu g/m^3$ (n=58) (Ullrich et al 2002). This level was only slightly lower than the respective concentrations in last few years demonstrating the limitations of the source control actions.

A large-scale population based formaldehyde study was also carried out in Austria (Hutter et al 2002). Formaldehyde concentrations in Austrian homes ranged from 8.8 $\mu g/m^3$ to 115 $\mu g/m^3$ (n= 160, AM= 31.3 $\mu g/m^3$ and median =25 $\mu g/m^3$).

Sakai et al (2004) compared indoor air concentrations of formaldehyde in Swedish and Japanese dwellings, showing higher geometric mean values in Japan than in Sweden being, 17.6 $\mu g/m^3$ (n=37) and 8.3 $\mu g/m^3$ (n=27) respectively. The highest concentration was measured in a detached house with an unvented kerosene heater. In general,

formaldehyde concentrations were higher in newer (< 10 years) dwellings than in older ones, possibly due to less natural ventilation and more emissions from building materials.

In Paris, geometric mean and geometric standard deviation of formaldehyde concentrations in recently refurbished flats in bedrooms were 24.5 $\mu g/m^3$ and 2.0 respectively (Clarisse et al 2003). In a study of 174 homes in UK, the annual mean indoor concentration ranged from 7 $\mu g/m^3$ to 76 $\mu g/m^3$, all of them being clearly higher than the mean annual outdoor concentration of 2 $\mu g/m^3$ (COMEAP 1997). In an Italian study (Cavallo et al 1993), formaldehyde concentrations in schools and office buildings ranged 8 – 210 $\mu g/m^3$ and 1.5 – 71 $\mu g/m^3$ respectively. VOC emissions were related to cleaning materials in schools and to carpeting and furniture in offices. Based on the results of a European survey indoor concentration of formaldehyde in homes and schools ranged from 10 $\mu g/m^3$ to 100 $\mu g/m^3$ (COMEAP 1997). Similar concentration levels of formaldehyde were reported by WHO in conventional homes with no urea-formaldehyde foam insulation ranging from 25 to 60 $\mu g/m^3$ (WHO 2000).

In 1970's and 1980's residential indoor formaldehyde concentrations were high, and therefore formaldehyde in indoor air became an issue. It has been suggested to be due to off-gassing from new materials and decreased ventilation in order to decrease energy consumption of house heating. Maximum formaldehyde concentrations were measured in new mobile homes in 1980's showing formaldehyde concentration of several mg/m^3 (WHO 2000). In the NHEXAS study in Arizona, USA (Gordon et al 1999) median and 90th percentile indoor concentrations, 21 $\mu g/m^3$ and 46 $\mu g/m^3$, were about the same levels than those measured in EXPOLIS in European cities. In a Taiwanese study (Li et al 2002), mean 8-hour formaldehyde concentrations in offices ranged 75 $\mu g/m^3$ – 300 $\mu g/m^3$. Maximum short time concentrations were as high as 1000 $\mu g/m^3$ based on the continuous monitoring. Building materials were identified as the main contributor to these high formaldehyde concentrations. Lee and Wang (2004) studied emissions of incense burning in chamber (18 m^3) tests. They found that six tested incense types caused concentrations exceeding the Recommended Indoor Air Quality Objectives for Office Buildings and Public Places in Hong Kong (HKIAQO) of 100 $\mu g/m^3$ for formaldehyde. Maximum concentration exceeded 250 $\mu g/m^3$ during incense burning.

Brown et al (2002) studied emissions and concentrations caused by unflued gas heaters in a room chamber of 32.4 m^3. In normal conditions formaldehyde concentrations ranged from <10 $\mu g/m^3$ to 180 $\mu g/m^3$. When the gas supply was restricted due to the backpressure, as high as 2100 $\mu g/m^3$ of formaldehyde was measured.

Elevated formaldehyde concentrations, up to 375 $\mu g/m^3$, in manufactured houses in US were related to engineered wood products such as particleboard and plywood bonded with urea-formaldehyde resin in 1970's (Sexton et al 1989). Recently measured formaldehyde concentrations in site-built houses were clearly lower, ranging from 8 – 66 $\mu g/m^3$ and 33 – 81 $\mu g/m^3$ prior to occupancy and five months after occupancy respectively (Lindstrom et al 1995). Similar results were reported by Hodgson et al (2000) showing indoor concentrations in site-built houses in eastern United States, ranging from 17 $\mu g/m^3$ to 73 $\mu g/m^3$. Cabinetry materials, passage doors and plywood subfloor were the predominant sources of formaldehyde in a new manufactured house studied by Hodgson et al (2002).

Studies in Denmark (Granby and Kristensen 1997), Finland (Viskari et al 2000), and Italy (Possanzini et al 1996) showed average (3-8 months periods) ambient concentrations of formaldehyde being 3.3 $\mu g/m^3$, 1.3 – 2.8 $\mu g/m^3$, and 13.7 $\mu g/m^3$, respectively. In the USA ambient concentrations ranged from 3.3 to 3.7 $\mu g/m^3$ (Grosejan et al 1993, CARB 1999). In Chinese studies ambient levels ranged from 4.1 $\mu g/m^3$ to 13.3 $\mu g/m^3$, while the mean indoor concentration of formaldehyde in hotels was more than twofold (Ho et al 2002, Feng et al 2004). Relatively high ambient concentrations were found in Japan, (Satsumabayashi et al 1995), Brazil (Grosejan et al 2002), Greece (Bakeas et al 2003) and in Mexico (Baez et al 1995) 3.1–14 $\mu g/m^3$, 10.8 $\mu g/m^3$, 17.2 $\mu g/m^3$ and 43.5 $\mu g/m^3$, respectively.

Cumulative distributions of the indoor and personal exposure concentrations in Europe are presented in Figure 3.1 and Figure 3.2. Indoor air concentrations of formaldehyde in European countries before 1990 are summarised in Table 3.1 and short time peak concentrations in Table 3.2.

Table 3.1. Indoor air concentrations of formaldehyde measured before 1990 (adopted from ECA 1990).

Country	Environment	Averaging time	Concentration ($\mu g/m^3$) AM	max	Expected source
Denmark	apartments		9.9		
Germany	dwellings	48-hour	56	279	
Greece	dwellings	30-minute	6 - 9	22	
France	nursery school	30-minute	29		
	dwellings	24-hour	22	< 70	
	apartments with complaints		600	2800	Particleboard
	collective sites with complaints			3000	UFFI
Norway	dwellings		< 60	110	Particleboard
Switzerland	dwellings		480	2760	UFFI
	new buildings			840	Particleboard
The Netherlands	50% of the dwellings with complaints		> 120	1000	
	66% of the schools with complaints		> 120	2500	
UK	buildings without UFFI		57		
	buildings with UFFI		114		UFFI

AM = aritmethic mean, max = maximum value, UFFI = urea formaldehyde foam insulation

Table 3.2. Short time formaldehyde concentrations related to specific microenvironments or emission sources.

Environment or emission source		Averaging time	Concentration ($\mu g/m^3$) AM	GM	max	Reference
Unflued gas heater	Room chamber tests					Brown et al 2002
	- normal burning		<10 - 180			
	- gas supply restricted				2100	
Offices	Taiwanese study	8-hour	75 - 300			Li et al 2002
		peak			2000	
Incense burning	chamber tests				250	Lee and Wang 2004
Public buildings	Schools	5-hour	8 - 210			Cavallo et al 1993
	Offices	5-hour	1.5 - 71			
Homes in UK	with UF foam insulation	30 - 60 min	130			Brown et al 1993
	without UF foam insulation	31 - 60 min	70			
Houses in US	manufactured	30-min	26 - 59	45		Hodgson et al 2000
	site-built	30-min	17 - 73	43		
Urban dwellings	Sweden	24-hour		8.3	19	Sakai et al 2004
	Japan	24-hour		18	73	

AM = arithmetic mean, GM = geometric mean
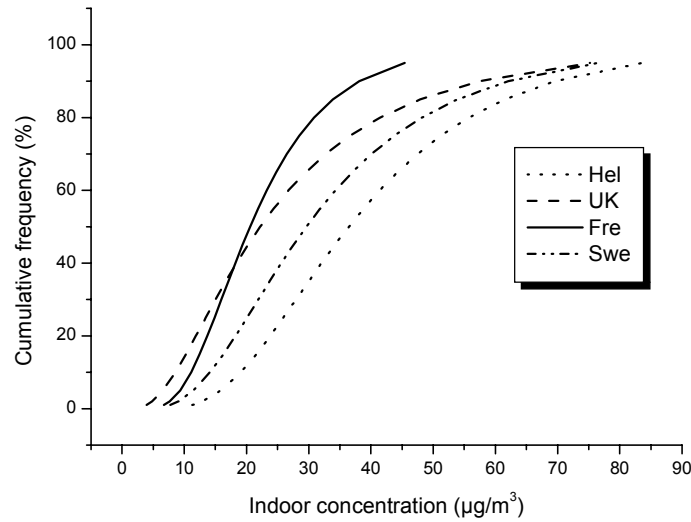
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of formaldehyde in Helsinki (Hel, n=15, Jurvelin et al 2001), in England (UK, n=833, Brown VM et al 2002), in the French Survey (Fre, n=201, Kirchner 2004), and in Sweden (Swe, n=40, Gustafson et al 2004).
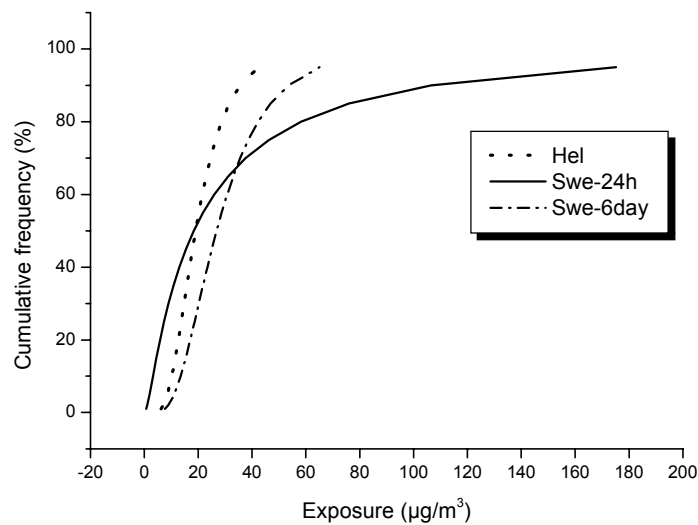
Figure 3.2. Cumulative frequency distribution of personal exposure concentrations of formaldehyde in Helsinki (Hel, 48-hour average, n= 15, Jurvelin et al 2001) and Sweden (Swe-24h = 24-hour average, n=24, and Swe-6day = 6-day average, n=40, Gustafson et al 2004).

4. Toxicokinetics

Absorption

Owing to its solubility in water, formaldehyde is rapidly absorbed in the respiratory and gastrointestinal tracts and metabolized. Over 90% of inhaled formaldehyde gas is absorbed in the upper respiratory tract of rats and monkeys. In rats, it is absorbed in the nasal passages; in monkeys, it is also absorbed in the nasopharynx, trachea and proximal regions of the major bronchi. Although formaldehyde or its metabolites can penetrate human skin – it induces allergic contact dermatitis in humans – dermal absorption appears to be very slight (WHO, 1989; IARC, 1995).

Distribution

Owing to its rapid metabolism, exposure of humans, monkeys or rats to formaldehyde by inhalation does not alter the concentration of endogenous formaldehyde in the blood, which is about 2–3 mg/litre for each of the three species. Intravenous administration of formaldehyde to dogs, cats and monkeys does not result in accumulation of formaldehyde in the blood, because of its rapid conversion to formate. In dogs, orally administered formaldehyde results in a rapid increase in formate levels in the blood. Following a 6-hour inhalation exposure of rats to ^{14}C-formaldehyde, radioactivity was extensively distributed in other tissues, the highest concentration occurring in the oesophagus, followed by the kidneys, liver, intestine and lung, indicating that absorbed ^{14}C-formaldehyde and its metabolites are rapidly removed by the mucosal blood supply and distributed throughout the body (WHO, 1989).

Metabolism and elimination

Formaldehyde reacts virtually instantaneously with primary and secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Formaldehyde acts as an electrophile and can react with macromolecules such as DNA, RNA and protein to form reversible adducts or irreversible cross-links. Absorbed formaldehyde can be oxidized to formate along three different pathways, and can be exhaled as carbon dioxide or incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways. In the body, formaldehyde is produced in small quantities as a normal metabolite and also in the oxidative demethylation of xenobiotics; it may therefore be found in the liver (IARC, 1995). Formaldehyde disappears from the plasma with a half-time of about 1–1.5 minutes, most of it being converted to carbon dioxide and exhaled via the lungs. Smaller amounts are excreted in the urine as formate salts and several other metabolites (WHO, 1987).

5. Health effects

Effects of short-term exposure

Predominant signs of short-term exposure to formaldehyde in humans are irritation of the eyes, nose and throat, together with concentration-dependent discomfort, lachrymation, sneezing, coughing, nausea, dyspnoea and finally death (Table 5.1). Symptoms are often more severe at the start of exposure than after minutes or hours, when they gradually diminish.

Table 5.1: Effects of formaldehyde in humans after short-term exposure

Concentration range or average (mg/m^3)	Time range or average	Health effects in general population
0.03	Repeated exposure	Odour detection threshold (10th percentile) [a]
0.18	Repeated exposure	Odour detection threshold (50th percentile) [a]
0.6	Repeated exposure	Odour detection threshold (90th percentile) [a]
0.1 – 3.1	Single and repeated exposure	Throat and nose irritation threshold
0.6–1.2	Single and repeated exposure	Eye irritation threshold
0.5 – 2	3–5 hours	Decreased nasal mucus flow rate
2.4	40 minutes on 2 successive days with 10 minutes of moderate exercise on second day	Post-exposure (up to 24 hours) headache

2.5 – 3.7	$-b$	Biting sensation in eyes and nose
3.7	Single and repeated exposure	Decreased pulmonary function only at heavy exercise
5 – 6.2	30 minutes	Tolerable for 30 minutes with lachrymation
12 – 25	$-b$	Strong lachrymation, lasting for 1 hour
37 – 60	$-b$	Pulmonary oedema, pneumonia, danger to life
60 – 125	$-b$	Death

[a] Frequency of effect in population.
[b] Time range or average unspecified.
Sources: WHO, 1989; IARC, 1995; WHO, 1987

Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritant effects on the eyes and the upper respiratory tract. Feinman (1988) states that most people cannot tolerate exposures to more than 6 mg/m^3 (5 ppm) formaldehyde in air

A series of pulmonary function studies has been conducted in healthy nonsmokers and asthmatics exposed to formaldehyde vapour; generally, lung function was unaltered. Fifteen healthy nonsmokers and 15 asthmatics were exposed to 2.4 mg/m^3 formaldehyde for 40 minutes to determine whether acute exposures could induce asthmatic symptoms (Schachter et al. 1986; Witek. et al. 1987). No significant airway obstruction, changes in pulmonary function or bronchial hyperreactivity were noted. Similar observations were made on a group of 15 hospital laboratory workers who had been exposed to formaldehyde (Schachter et al. 1987).

Healthy nonsmokers and asthmatics were exposed to 3.7 mg/m^3 formaldehyde for 1 or 3 hours, either at rest or when engaged in intermittent heavy exercise. No significant changes in pulmonary function and nonspecific airway reactivity were observed among asthmatic subjects. Small decreases (< 5%) in pulmonary function were observed in healthy non-smokers exposed to formaldehyde while engaged in heavy exercise. Two normal and two asthmatic subjects had decrements greater than 10% (Sauder et al. 1986; Green et al. 1987).

When 15 asthmatic subjects were exposed for 90 minutes to concentrations of 0.008–0.85 mg/m^3 formaldehyde, no change in pulmonary function was seen, and there was no evidence of an increase in bronchial reactivity (Harving, et al., 1990).

In a study of controlled exposure to formaldehyde, 18 subjects, 9 of whom had complained of adverse effects from urea–formaldehyde foam insulation installed in their homes, were exposed to 1.2 mg/m^3 formaldehyde, or to off-gas products of urea–formaldehyde foam insulation containing 1.5 mg/m^3 formaldehyde, for 90 minutes (Day et al., 1984). No statistically or clinically significant change in pulmonary function was seen either during or 8 hours after exposure, and no evidence was obtained that urea–formaldehyde foam insulation off-gas acts as a lower airway allergen.

Kulle et al. (1987; 1993) exposed 19 healthy subjects to 0, 1.2, and 2.5 mg/m^3 (0, 1.0, and 2.0 ppm) for 3-hour periods and asked them to note symptoms of eye and nose/throat irritation and to rate severity on a 0-3 scale: 0=none; l=mild (present but not annoying); 2=moderate (annoying); and 3=severe debilitating). Ten of the subjects were also exposed to 0.6 mg/m^3 (0.5 ppm) and nine were exposed to 4 mg/m^3 (3 ppm) for 3-hour periods. The frequencies of subjects reporting eye irritation or nose/throat irritation increased with increasing exposure concentration, especially at concentrations ≥ 1.2 mg/m^3. Under nonexposed conditions, 3/19 subjects noted mild nose/throat irritation and l/19 noted mild eye irritation. At 0.6 mg/m^3, l/10 subjects noted mild nose/throat irritation, but none reported eye irritation. Frequencies for subjects with mild or moderate eye irritation were 4/19 at 1.2 mg/m^3 (1 moderate), 10/19 at 2.5 mg/m^3 (4 moderate), and 9/9 at 4 mg/m^3 (4 moderate). The increased frequency for eye irritation (compared with controls) was statistically significant at 2.5 mg/m^3. Frequencies for mild nose/throat irritation were l/19 at 1.2 mg/m^3, 7/19 at 2.5 mg/m^3, and 2/9 at 4 mg/m^3. Compared with control frequency for nose/throat irritation, only the response at 2.5 mg/m^3 was significantly elevated.

Weber-Tschopp et al. (1977) exposed a group of 33 healthy subjects for 35 minutes to concentrations of formaldehyde that increased during the period from 0.04 to 3.9 mg/m^3 (0.03 to 3.2 ppm); another group of 48 healthy subjects was exposed to 0.03, 1.2, 2.1, 2.8, and 4.0 ppm for 1.5 minute intervals. Eye and nose irritation were reported on an l-4 scale (l=none to 4=strong) in both experiments, and eye blinking rate was measured in the second experiment. Average indices of eye and nose irritation were increased in both experiments to a small, but statistically significant at 1.2 ppm compared with indices for nonexposed controlled conditions. The published report of this study graphically showed average severity scores of about 1.3-l.4 for both indices at 1.2 ppm compared with 1.0-l.1 for non exposed conditions. The average severity score was increased to a greater degree at higher concentrations, but was less than about 2.5 at the

highest exposure concentration, 4 ppm. Average rates of eye blinking were not significantly affected at 1.2 ppm, but were statistically significantly increased at 2.1 ppm (about 35 blinks/minute at 2.1 ppm versus about 22 blinks/minutes under nonexposed conditions).

The relation of chronic respiratory symptoms and pulmonary function to formaldehyde (HCHO) in homes was studied in a sample of 298 children (6-15 years of age) and 613 adults. HCHO measurements were made with passive samplers during two 1-week periods. Data on chronic cough and phlegm, wheeze, attacks of breathlessness, and doctor diagnoses of chronic bronchitis and asthma were collected with self-completed questionnaires. Peak expiratory flow rates (PEFR) were obtained during the evenings and mornings for up to 14 consecutive days for each individual. Significantly greater prevalence rates of asthma and chronic bronchitis were found in children from houses with HCHO levels 74-147 $\mu g/m^3$ (60-120 ppb) than in those less exposed, especially in children also exposed to environmental tobacco smoke. In children, levels of PEFR decreased linearly with HCHO exposure, with the estimated decrease due to 74 $\mu g/m^3$ of HCHO equivalent to 22% of PEFR level in nonexposed children. The effects in asthmatic children exposed to HCHO below 61 $\mu g/m^3$ were greater than in healthy ones. The effects in adults were less evident: decrements in PEFR due to HCHO over 49 $\mu g/m^3$ were seen only in the morning, and mainly in smokers (Krzyzanowski et al., 1990).

Studies in children, including the Krzyzanowski study above, indicate adverse health impacts in children at concentrations as low as 37 $\mu g/m^3$ (30 ppb). Wantke et al. (1996) reported that formaldehyde-specific IgE and respiratory symptoms were reduced when children transferred from schools with formaldehyde concentrations of 53 to 92 $\mu g/m^3$ (43 to 75 ppb) to schools with concentrations of 28 to 36 $\mu g/m^3$ (23 to 29 ppb). Garrett et al. (1999) reported increased sensitization associated with the formaldehyde level in children's homes which had a median value of 15.8 $\mu g/m^3$ (12.6 ppb). And Franklin et al. (2000) reported significantly higher exhaled nitric oxide, an indicator of airway inflammation, in the breath of children living in homes with formaldehyde concentrations greater than 61 $\mu g/m^3$ (50 ppb) than in the breath of those children living in homes with formaldehyde levels below 61 $\mu g/m^3$. These human studies are not entirely consistent with each other, and there is potential for confounding in each. Nevertheless, taken together, they suggest that children may be more sensitive to formaldehyde toxicity than adults.

Pulmonary function has been assessed in residents of mobile and conventional homes (Broder et al., 1988) and mobile offices (Main & Hogan, 1983)) exposed to concentrations of 0.007–2.0 mg/m^3. No changes were seen in pulmonary function or airway resistance.

Eleven healthy subjects and nine patients with formalin skin sensitization were exposed to 0.5 mg/m^3 formaldehyde for 2 hours (Pazdrak *et al.*, 1993). Nasal lavage was performed prior to and 5 to 10 minutes, 4 hours, and 18 hours after exposure. Rhinitis was reported and increases in the number and proportion of eosinophils, elevated albumin and increased protein levels were noted in nasal lavage fluid 4 and 18 hours after exposure. No differences were found between patients with skin sensitization and healthy subjects.

Summary of short-term exposure effect levels

Studies of humans under controlled conditions clearly indicate that acute exposures to air concentrations ranging from 0.5 to 3.7 mg/m^3 (0.4 to 3 ppm):
- induce reversible eye, nose, and throat irritation (Andersen and Mølhave 1983; Bender et al. 1983; Day et al. 1984; Gorski et al. 1992; Krakowiak et al. 1998; Kulle 1993; Kulle et al. 1987; Pazdrak et al. 1993; Schachter et al. 1986; Weber-Tschopp et al. 1977; Witek et al. 1986);
- produce changes in nasal lavage fluid contents, indicative of irritation of the nasal epithelium (Gorski et al. 1992; Krakowiak et al. 1998; Pazdrak et al. 1993); and
- do not consistently or markedly affect pulmonary function variables in most individuals (Andersen and Mølhave 1983; Day et al. 1984; Gorski et al. 1992; Green et al. 1987; Harving et al. 1986, 1990; Kulle et al. 1987; Nordman et al. 1985; Sauder et al. 1986; Schachter et al. 1986; Witek et al. 1986).

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
0.6 EXP	1.2 EXP 0.53 BC05 0.94 1h-ADJ-BC05	Mild and moderate eye irritation	Volunteers, 3h	Kulle et al. (1987)	OEHHA 1999; REL: 0.094
	0.5 EXP	Nasal and eye irritation	Volunteers, 2h (potentially sensitive population)	Pazdrak et al. (1993)	ATSDR 1999; MRL: 0.05
	0.24 STAT	Respiratory tract irritation		cited in Sloof et al. (1992)	RIVM 1992
	0.1	Nose and throat irritation	Human, short-term	cited in IPCS/WHO,	WHO 2000

				1989	
	(0.037)	Respiratory symptoms (depending on study)	Children; additional investigation requested	Krzyzanowski et al., (1990); Wantke et al. (1996); Garrett et al. (1999); Franklin et al. (2000)	UCLA 2001

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h\text{-}ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of Acute Reference Exposure Level (for a 1-hour exposure)
Study	Kulle *et al*. (1987)
Study population	19 nonasthmatic, nonsmoking human subjects
Exposure method	0.6- 3.6 mg/m³ (0.5-3.0 ppm)
Critical effects	mild and moderate eye irritation
LOAEL	1.2 mg/m³ (1 ppm)
NOAEL	0.6 mg/m³ (0.5 ppm)
Benchmark concentration	0.44 ppm (BC05)
Exposure duration	3 hours
Extrapolated 1 hour concentration	0.94 mg/m³ [0.76 ppm (0.44^2 ppm* 3 h = C^2 * 1 h)]
LOAEL uncertainty factor	not required in BC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.076 ppm (0.094 mg/m³; 94 μg/m³)

The recommended REL was estimated by a benchmark concentration (BC05) approach, using logprobit analysis (Crump, 1984; Crump and Howe, 1983). The BC05 is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BC05 from this analysis was 0.53 mg/m³ formaldehyde. This value was adjusted to a 1-hour duration using the formula C_n * T = K, where n = 2 (AICE, 1989), resulting in a value of 0.94 mg/m³. An uncertainty factor (UF) of 10 was used to account for individual variation.

Generally an uncertainty factor of 3 would be used with the BC05 for intraindividual variability, since the BC05 accounts for some degree of individual variation. However, information from the literature indicates a wide variability in response to formaldehyde irritancy including reports of irritation (NIOSH HHE reports 1981-1996; Liu et al. 1991; Horvath et al, 1985) or cellular changes associated with irritation and an immune response at levels below the one-hour extrapolated BC05 (Pazdrak et al, 1993; Gorski et al, 1992). For these reasons, we used an uncertainty factor of 10 to account for intraindividual variability in the human population.

ATSDR (1999)
Agency for Toxic Substances and Disease Registry

Derivation of the Minimal Risk Level (MRL):
ATSDR has derived an acute inhalation MRL of 0.05 mg/m³ (0.04 ppm) on the basis of clinical symptoms (increased itching, sneezing, mucosal congestion, transient burning sensation of the eyes and of the nasal passages) and nasal alterations (elevated eosinophil counts and a transient increase in albumin content of nasal lavage fluid) in humans (Pazdrak et al. 1993). This MRL is based on a minimal LOAEL of 0.5 mg/m³ and an uncertainty factor of nine (three for use of a minimal LOAEL and three for human variability).

The Anderson and Mølhave (1983) study identified an apparent effect level at 0.3 mg/m³ (0.2 ppm), based on subjective reports of irritation that is lower than the effect levels at 0.43-0.5 mg/m³ (0.35-0.4 ppm) in the studies by Pazdrak et al. (1993), Krakowiak et al. (1998), and Bender et al. (1983), which used more objective measures of acute irritation (eosinophil counts and protein concentrations in nasal lavage fluid or time to first reporting of irritation). Because of the use of objective measures of toxicity and the general weight of the available data indicating that some people will not experience eye or upper respiratory tract irritation from formaldehyde even at 1.2 mg/m³ (see Day et al. 1984; Kulle et al. 1987, Weber Tschopp et al. 1977, and Witek et al. 1986), the Pazdrak et al. (1993) LOAEL of 0.5 mg/m³ was

considered a minimal LOAEL in a group of potentially sensitive individuals (some subjects had dermal hypersensitivity to formaldehyde) and selected as the basis of the acute MRL.

RIVM (1992)
National Institute of Public Health and the Environment - The Netherlands

Sensory reactions are apparently the most typical effects in the non-industrial indoor environment (Sloof et al., 1992). A large number of observations of people in various settings support a conclusion that the generally observed range over which more than 95 % of people respond is 125-3750 $\mu g/m^3$ (0.10-3.1 ppm). According to the Dutch Health Council (1984) and WHO (1989) the lowest statistically significant effect concentration for respiratory tract irritation is 240 $\mu g/m^3$ (LOAEL) (0.20 ppm) (Sloof et al., 1992).

The Dutch Health Council (1984) recommended the following three limit values (Sloof et al., 1992):
120 $\mu g/m^3$ as ceiling value (based on 30 min. means);
40 $\mu g/m^3$ as 98-percentile value (based on 24 h means);
30 $\mu g/m^3$ as 95-percentile value (based on 24 h means).

WHO (2001)
Air Quality Guidelines for Europe 2000

The lowest concentration that has been associated with nose and throat irritation in humans after short-term exposure is 0.1 mg/m^3, although some individuals can sense the presence of formaldehyde at lower concentrations.
To prevent significant sensory irritation in the general population, an air quality guideline value of 0.1 mg/m^3 as a 30-minute average is recommended. Since this is over one order of magnitude lower than a presumed threshold for cytotoxic damage to the nasal mucosa, this guideline value represents an exposure level at which there is a negligible risk of upper respiratory tract cancer in humans.

Effects of long-term exposure (noncancer)

Long term exposure to elevated levels of formaldehyde in the occupational setting has been shown to result in upper and lower airway irritation and eye irritation in humans; degenerative, inflammatory and hyperplastic changes of the nasal mucosa in humans and animals. The voluminous body of data describing these effects has been briefly summarized below. For the sake of brevity, only the studies that best represent the given effects are presented.

Ritchie and Lehnen (1987) reported a dose-dependent increase in health complaints (eye and throat irritation, and headaches) in 2000 residents living in 397 mobile and 494 conventional homes, that was demonstrated by logistic regression. Complaints of symptoms of irritation were noted at concentrations of 0.12 mg/m^3 formaldehyde or above. Similarly, Liu *et al.* (1991) found that exposure to 0.135 mg/m^3 formaldehyde exacerbated chronic respiratory and allergy problems in residents living in mobile homes.

Employees of mobile day-care centers (66 subjects) reported increased incidence of eye, nose and throat irritation, unnatural thirst, headaches, abnormal tiredness, menstrual disorders, and increased use of analgesics as compared to control workers (Olsen and Dossing, 1982). The mean formaldehyde concentration in these mobile units was 0.43 mg/m^3 (range = 0.24 - 0.55 mg/m3). The exposed workers were exposed in these units a minimum of 3 months. A control group of 26 subjects in different institutions was exposed to a mean concentration of 0.06 mg/m³ formaldehyde.

Occupants of houses insulated with urea-formaldehyde foam insulation (UFFI) (1726 subjects) were compared with control subjects (720 subjects) for subjective measures of irritation, pulmonary function (FVC, FEV1, FEF25-75, FEF50), nasal airway resistance, odour threshold for pyridine, nasal cytology, and hypersensitivity skin-patch testing (Broder *et al.*, 1988). The mean length of time of exposure to UFFI was 4.6 years. The mean concentration of formaldehyde in the UFFI-exposed group was 0.053 mg/m³, compared with 0.043 mg/m³ for the controls. A significant increase in symptoms of eye, nose and throat irritation was observed in subjects from UFFI homes, compared with controls. No other differences from control measurements were observed.

An increase in severity of nasal epithelial histological lesions, including loss of cilia and goblet cell hyperplasia (11%), squamous metaplasia (78%), and mild dysplasia (8%), was observed in 75 wood products workers exposed to between 0.1 and 1.1 mg/m3 formaldehyde for a mean duration of 10.5 years (range = 1 - 39 years), compared to an equal number of control subjects (Edling *et al.*, 1988). Only three exposed men had normal mucosa. A high frequency of symptoms relating to the eyes and upper airways was reported in exposed workers. Nasal symptoms included mostly a runny nose

and crusting. The histological grading showed a significantly higher score for nasal lesions when compared with the referents (2.9 versus 1.8). Exposed smokers had a higher, but non-significant, score than ex-smokers and non-smokers. When relating the histological score to duration of exposure, the mean histological score was about the same regardless of years of employment. In addition, no difference in the histological scores was found between workers exposed only to formaldehyde and those exposed to formaldehyde and wood dust.

Alexandersson and Hedenstierna (1989) evaluated symptoms of irritation, spirometry, and immunoglobulin levels in 34 wood workers exposed to formaldehyde over a 4-year period. Exposure to $0.5 - 0.6$ mg/m³ ($0.4 - 0.5$ ppm) formaldehyde resulted in significant decreases in FVC, FEV_1, and FEF_{25-75}. Removal from exposure for 4 weeks allowed for normalization of lung function in the non-smokers.

Symptoms of irritation were reported by 66 workers exposed for 1 - 36 years (mean = 10 years) to a mean concentration of 0.26 mg/m³ formaldehyde (Wilhelmsson and Holmstrom, 1992). Controls (36 subjects) consisted of office workers in a government office and were exposed to a mean concentration of 0.09 mg/m³ formaldehyde. The significant increase in symptoms of irritation in exposed workers did not correlate with total serum IgE antibody levels. However, 2 exposed workers, who complained of nasal discomfort, had elevated IgE levels. In another occupational health study, 37 workers, who were exposed for an unspecified duration to formaldehyde concentrations in the range of 0.004 to 0.090 mg/m³, reported ocular irritation; however, no significant serum levels of IgE or IgG antibodies to formaldehyde-human serum albumin were detected (Grammer *et al.*, 1990). An epidemiological study of the effects of formaldehyde on 367 textile and shoe manufacturing workers employed for a mean duration of 12 years showed no significant association between formaldehyde exposure, pulmonary function (FVC, FEV_1, and PEF) in normal or asthmatic workers, and occurrence of specific IgE antibodies to formaldehyde (Gorski and Krakowiak, 1991). The concentrations of formaldehyde did not exceed 0.75 mg/m³. Workers (38 total) exposed for a mean duration of 7.8 years to $0.14 - 2.60$ mg/m³ (mean = 0.41 mg/m³) formaldehyde were studied for their symptomatology, lung function, and total IgG and IgE levels in the serum (Alexandersson and Hedenstierna, 1988). The control group consisted of 18 unexposed individuals. Significant decrements in pulmonary function (FVC and FEV_1) were observed, compared with the controls. Eye, nose, and throat irritation was also reported more frequently by the exposed group, compared with the control group. No correlation was found between duration of exposure, or formaldehyde concentration, and the presence of IgE and IgG antibodies.

Holmstrom et al. (1989) examined histological changes in nasal tissue specimens from a group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper, a group of 100 furniture factory workers working with particle board and glue components, and a nonexposed control group of 36 office workers in the same village as the furniture factories. Mean durations of employment in the groups were 10.4 years (SD 7.3, range 1–36 years) for the chemical workers and 9.0 years (SD 6.3, range 1–30 years) for the furniture workers. Estimates of personal breathing zone air concentrations ranged from 0.05 to 0.5 mg/m³ (median 0.29±0.16 ppm) for the chemical workers, from 0.20 to 5 mg/m³ (median 0.25±0.05 ppm) for the furniture workers, and from 0.09 to 0.16 mg/m³ in the late summer for the office workers with a year-round office worker median reported as 0.09 mg/m³ with no standard deviation. The mean wood dust concentration in the furniture factory was reported to have been between 1 and 2 mg/m³. Nasal mucosa specimens were taken from the medial or inferior aspect of the middle turbinate. Histology scores were assigned to each specimen based on a 0–8 scale, identical to the scale used by Edling et al. (1988; described previously). Nasal mucosal biopsy sections for each subject were examined and assigned scores as follows: 0 - normal respiratory epithelium; 1- loss of ciliated epithelium cells; 2 - mixed cuboid/squamous epithelium, metaplasia; 3 - stratified squamous epithelium; 4 - keratosis; 5 - budding of epithelium; 6 - mild or moderate dysplasia; 7 - severe dysplasia; and 8 - carcinoma.

Nasal histology scores ranged from 0 to 4 (mean 2.16; n=62) for the chemical workers, from 0 to 6 (mean 2.07; n=89) for the furniture workers, and from 0 to 4 (mean 1.46; n=32) for the office workers. The mean histological score for the chemical workers, but not the furniture workers, was significantly different from the control score, thus supporting the hypothesis that the development of the nasal lesions is formaldehyde-related and not obligatorily related to possible interaction between formaldehyde and wood dust. The most severe epithelial change found (light or moderate epithelial dysplasia) was found in two furniture workers. Among the chemical workers (not exposed to wood dust), loss of cilia, goblet cell hyperplasia and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently than in the control group of office workers. Within both groups of formaldehyde-exposed workers, no evidence was found for associations between histological score and duration of exposure, index of accumulated dose, or smoking habit.

Summary of long-term exposure effect levels (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
0.09 Study 0.032 ADJ	0.26 Study 0.093 ADJ	Nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, and dysplasia	Occupational, 10y average;	Wilhelmsson and Holmstrom, 1992; supported by Edling et al., 1988	OEHHA 1999; REL: 0.003
	0.3 Study	Mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium	Occupational, 10.4y	Holmstrom et al., 1989	ATSDR 1999; MRL: 0.01
	0.31 STAT	Sensory irritation	for low but significant percentage of exposed workers	Weighting the total body of data	NIWL 2003
	0.12	Symptoms of irritation	LOAEL may be lower only for a very small proportion of the population	well conducted studies	Health Canada 1999; (noTC)

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment

Derivation of Chronic Reference Exposure Level (REL):

Studies	Wilhelmsson and Holmstrom, 1992; supported by Edling *et al.*, 1988
Study population	Human chemical plant workers (66 subjects)
Exposure method	Discontinuous occupational exposure
Critical effects	Nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, and dysplasia
LOAEL	Mean of 0.26 mg/m³ (range = 0.05 to 0.6 mg/m³) (described as exposed group)
NOAEL	Mean of 0.09 mg/m³ (described for control group of office workers)
Exposure continuity	8 hours/day, 5 days/week (assumed)
Exposure duration	10 years (average); range = 1-36 years
Average occupational concentration	0.032 mg/m³ for NOAEL group (0.09 x 10/20 x 5/7)
Human equivalent concentration	0.032 mg/m³
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference level	0.003 mg/m³ (3 μg/m³; 0.002 ppm; 2 ppb)

The Wilhelmsson and Holmstrom study was selected by the Office of Environmental Health Hazard Assessment (OEHHA, reference) for the derivation of the Chronic Reference Exposure Level (REL), because it was a human occupational study that contained a LOAEL and a NOAEL and contained a reasonable number of subjects. The supporting occupational study by Edling *et al.* (1988) noted similar sensory irritation results due to long-term formaldehyde exposure. In addition, nasal biopsies from exposed workers in the Edling et al. (1988) study exhibited nasal epithelial lesions similar to those found in subchronic and chronic animal studies.

For comparison with the proposed REL of 3 μg/m³, we estimated a REL from Edling *et al.* (1988). A median concentration of 0.6 mg/m³ was determined for the LOAEL from the TWA range of 0.1- 1.1 mg/m³. A NOAEL was not reported. The average continuous occupational concentration was 0.2 mg/m³ (0.6 x 10/20 x 5/7) and the exposure duration was 10.5 years (range = 1 – 39 years). Application of a UF of 10 for intraspecies variability and a UF of 10 for estimation of a NOAEL from the LOAEL would result in a REL of 2 μg/m³ (2 ppb).

Data Strengths and Limitations for Development of the REL: The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years and the observation of a NOAEL. In addition, a

number of well conducted animal studies supported the derivation of the REL. The major areas of uncertainty are the uncertainty in estimating exposure in the occupational studies and the potential variability in exposure concentration.

Table 5.2 presents a summary of potential RELs based on chronic and subchronic animal studies. The toxicological endpoint was nasal lesions, consisting principally of rhinitis, squamous metaplasia, and dyplasia of the respiratory epithelium.

Table 5.2: Summary of chronic and subchronic formaldehyde studies in experimental animals

Study	Animal	Exposure Duration	LOAEL/ NOAEL (mg/m³)	HEC adj. (mg/m³)	Cumulative UF	REL (mg/m3)
Woutersen et al., 1989	rat	28 m	9.8 / 1.0	0.06	30	2
Kerns et al., 1983	rat	24 m	2.0 / NA	0.1	300	0.3
Monticello et al., 1996	rat	24 m	6.01 / 2.05	0.1	30	4
Kamata et al., 1997	rat	24-28 m	0.30 / NA	0.02	100	0.2
Appelman et al., 1988	rat	52 w	9.4 / 1.0	0.06	30	2
Rusch et al., 1983	rat	26 w	2.95 / 0.98	0.2	30	7
Kimbell et al., 1997	rat	26 w	6 / 2	0.1	30	3
Wilmer et al., 1989	rat	13 w	4 / 2	0.2	300	0.7
Woutersen et al., 1987	rat	13 w	9.7 / 1.0	0.03	100	0.3
Zwart et al., 1988	rat	13 w	2.98 / 1.01	0.2	300	0.7
Kerns et al., 1983	mouse	24 m	2.0 / NA	0.05	100	0.5
Maronpot et al., 1986	mouse	13 w	10.1 / 4.08	0.09	100	0.9
Rusch et al., 1983	monkey	26 w	2.95 / 0.98	none	300	4

The most striking observation is the similarity of potential RELs among the rat chronic studies (exposures > 26 weeks) that contain a NOAEL. The range of RELs from these animal studies, 2 – 7 mg/m³, is comparable to the proposed REL based on a human study. Another related observation is that the NOAEL and LOAEL are similar among all the studies, regardless of exposure duration. The NOAEL and LOAEL are generally in the range of 1-2 mg/m3 and 2-10 mg/m3, respectively, with the exception of the study by Kamata *et al.* (1997). These results indicate that the formation of formaldehyde-related nasal lesions are more concentration dependent than time, or dose, dependent. A limitation of a majority of the occupational studies is their high reliance on surveys and other methods that focus on sensory irritation. Such sensory irritant results, as exhibited in the Wilhelmsson and Holmstrom (1992) study, may be more related to recurrent acute injury rather than a true chronic injury. The concentration dependent nature of the nasal lesions in the supporting animal studies, and suggested in the supporting human nasal biopsy study, would also imply that the nasal cavity endpoint may be a recurrent acute effect. However, Kerns *et al.* (1983) and Kamata *et al.* (1997) clearly demonstrated that near the LOAEL, increasing exposure durations would result in nasal lesions at lower formaldehyde concentrations. Also, the rat study by Woutersen *et al.* (1989) demonstrated that subchronic exposure to formaldehyde concentrations that produce nasal lesions could result in lifelong changes of the nasal epithelium. These findings substantiate the chronic nature of the nasal/upper airway injury that results from long-term formaldehyde exposure.

ATSDR (1999)
Agency for Toxic Substances and Disease Registry

Derivation of the chronic Minimal Risk Level (MRL).
The chronic inhalation MRL of 0.01 mg/m³ was derived from a LOAEL of 0.3 mg/m³ in humans for nasal effects (Holmstrom et al., 1989). This minmal LOAEL was divided by a total uncertainty factor of 30 (3 for use of a LOAEL and 10 for human variability). The exposure concentration was not adjusted to a continuous exposure basis based on evidence that concentration is more important than the product of concentration and duration of exposure in determining the severity of formaldehyde-induced epithelial damage in the upper respiratory tract (Wilmer et al. 1987).

National Institute for Working Life (NIWL) - Sweden (2003)
Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) and Dutch Expert Committee on Occupational Standards (DECOS)

Summary of the report n°132.Formaldehyde (Scientific basis for an occupational exposure limit):
Inhaled formaldehyde is almost completely absorbed in the upper respiratory tract in rodents. Formaldehyde is a normal metabolite in mammalians and is rapidly metabolised to formate, which may be further oxidised to carbon dioxide. Final elimination occurs via exhalation and via the kidneys. The target organs of formaldehyde vapour are the eyes, nose, and throat. The effects of concern are sensory irritation and cytotoxicity-induced regenerative hyperplasia and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats. Weighting the total body of data 0.31 mg/m^3 (0.25 ppm) formaldehyde is the LOAEL at which sensory irritation may occur in a low but significant percentage of exposed workers. The majority of short- and long-term inhalation animal studies reveal a NOAEL of 1.2-2.5 mg/m^3 (1-2 ppm). However, in a few studies slight histopathological changes of the nasal respiratory epithelium were observed at 0.4-2.5 mg/m^3 (0.3-2 ppm).

Formaldehyde is genotoxic in a variety of experimental systems, including rodents *in vivo.* There is overwhelming evidence that high, cytotoxic formaldehyde vapour concentrations (≥10 ppm) can induce nasal cancer in rats. A large body of data suggests an association between the cytotoxic, genotoxic, and carcinogenic effects of formaldehyde. The crucial role of tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium in formaldehyde carcinogenesis has been demonstrated in a convincing way. Thus, formaldehyde in non-cytotxic concentrations most probably cannot act as a complete carcinogen. However, if human exposure to formaldehyde is accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have carcinogenic potential in man.

Formaldehyde-induced allergic contact dermatitis has been estimated to occur in 3-6% of the population, and skin sensitisation by direct skin contact has been induced with formaldehyde solutions. There is no consistent evidence of formaldehyde being a respiratory sensitiser.

Health Canada (1999)
Canadian Environmental Protection Act (CEPA).

Health Canada did not derive a Tolerable Concentration (TC) for formaldehyde. However, there are considered to be sufficient data from clinical studies and cross-sectional surveys of human populations, as well as supporting observations from experimental studies conducted with laboratory animals, to indicate that the irritant effects of formaldehyde on the eyes, nose and throat occur at lowest concentration. Although individual sensitivity and exposure conditions such as temperature, humidity, duration and co-exposure to other irritants are likely to influence response levels, in well-conducted studies, only a very small proportion of the population experiences symptoms of irritation following exposure to less than or equal to 0.12 mg/m^3 formaldehyde. This is less than the levels that reduce mucociliary clearance in the anterior portion of the nasal cavity in available clinical studies in human volunteers (0.3 mg/m^3) and induce histopathological effects in the nasal epithelium in cross-sectional studies of formaldehyde-exposed workers (Andersen and Mølhave, 1983). Additional investigation of preliminary indication of effects on pulmonary function in children in the residential environment associated with lower concentrations of formaldehyde (0.048-0.072 mg/m^3) (Krzyzanowski et al., 1990) is warranted.

Carcinogenic effects

On June 15, 2004, IARC announced there was sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans and re-classified it as a Group 1, known human carcinogen (previous classification: Group 2A). IARC also reported there was limited evidence that formaldehyde exposure causes nasal cavity and paranasal cavity cancer and "strong but not sufficient" evidence linking formaldehyde exposure to leukemia.

EPA (1991) classified formaldehyde in Group B1 - probable human carcinogen, based on an evaluation of limited human evidence and sufficient laboratory animal evidence. More recently, in a collaborative review and evaluation of the formaldehyde epidemiology studies, EPA and CIIT (CIIT 1998) concluded, "It appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out." Adopting another view, McLaughlin (1994) concluded, "Clearly, the causal criteria used by epidemiologists to evaluate an association, such as strength of the association, consistency, specificity, dose-response, plausibility, and coherence, are not satisfied by the epidemiologic studies in the formaldehyde-cancer research domain". ECETOC (1995) similarly concluded, "After a

careful review of the cytologic, cytogenic and epidemiological studies there is an absence of evidence to support the judgement of an etiologic relationship between formaldehyde and human cancer risk."

Human carcinogenicity data
A series of papers on the cytogenetic effects of formaldehyde in humans has been published (IARC, 1995). The studies mostly concern occupational exposures (plywood makers, makers of wood splinter materials, morticians, paper makers and hospital autopsy service workers) and measure chromosomal anomalies, micronuclei in peripheral lymphocytes, buccal epithelium (Norppa, et al., 1993) or nasal epithelium and sperm abnormalities. Both positive and negative results were obtained, but their interpretation is difficult because of the small number of subjects studied, inconsistencies in the findings, inadequate reporting of the data, and concomitant exposure to other chemicals. No increase in urinary mutagenicity was observed in autopsy workers as compared to controls (Connor, et al. 1985). No data are available on DNA–protein cross-links in humans. The overall conclusion is that adequate data on genetic effects of formaldehyde in humans are not available (IARC, 1995).

The relationship between exposure to formaldehyde and cancer has been investigated in over 25 cohort studies of professionals (pathologists, anatomists and embalmers) and industrial groups (formaldehyde producers, formaldehyde resin makers, plywood and particle board manufacturers, garment workers and workers in the abrasives industry). Relative risks have been estimated as standardized mortality ratios (SMRs), proportionate mortality ratios (PMRs), proportionate cancer mortality ratios (PCMRs) and standardized incidence ratios (SIRs). In some studies, exposure was not assessed but was assumed on the basis of the subject's occupation or industry; in others, it was based on duration of exposure and quantitative estimates of historical exposure levels. Mortality in several of the cohorts was followed beyond the period covered by the original report; only the latest results are reviewed below, unless there were important differences in the analyses performed or changes in the cohort definition (IARC, 1995,).

Recent meta-analyses by Blair et al. (Blair et al. 1990) and Partanen (Partanen, 1993) contain most of the available data. The International Agency for Research on Cancer (IARC) summarized the results of the two meta-analyses in tabular form. IARC (IARC, 1995) also systematically reviewed case-control studies of cancer of the oral cavity, pharynx and respiratory tract. Also, McLaughlin (McLaughlin, 1994) recently published a critical review on formaldehyde and cancer.

Excess numbers of nasopharyngeal cancers were associated with occupational exposure to formaldehyde in two of six cohort studies of industrial or professional groups, in three of four case-control studies and in meta-analyses. In one cohort study performed in 10 plants in the United States, the risk increased with category of increasing cumulative exposure. In the cohort studies that found no excess risk, no deaths were observed from nasopharyngeal cancer. In three of the case-control studies, the risk was highest in people in the highest category of exposure and among people exposed 20–25 years before death. The meta-analyses found a significantly higher risk among people estimated to have had substantial exposure than among those with low/medium or no exposure. The observed associations between exposure to formaldehyde and risk of cancer cannot reasonably be attributed to other occupational agents, including wood dust, or to tobacco smoking. Limitations of the studies include misclassification of exposure and disease and loss to follow-up, but these would tend to diminish the estimated relative risks and dilute exposure–response gradient. Taken together, the epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases in the cohort studies (IARC, 1995).

Of six case-control studies in which the risk for cancer of the nasal cavities and paranasal sinuses in relation to occupational exposure to formaldehyde was evaluated, three provided data on squamous cell tumours and three on unspecified cell types. Of the three studies of squamous cell carcinomas, two (from Denmark and the Netherlands) showed a positive association, after adjustment for exposure to wood dust, and one (from France) showed no association. Of the three studies of unspecified cell types, one (from Connecticut, United States) gave weakly positive results and two (also from the United States) reported no excess risk. The two case-control studies that considered squamous cell tumours and gave positive results involved more exposed cases than the other case-control studies combined. In the studies of occupational cohorts overall, however, fewer cases of cancer of the nasal cavities and paranasal sinuses were observed than were expected. Because of the lack of consistency between the cohort and case-control studies, the epidemiological studies can do no more than suggest a causal role of occupational exposure to formaldehyde in squamous cell carcinoma of the nasal cavities and paranasal sinuses (IARC, 1995).

The cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show low or no risk for lymphatic or haematopoietic cancers, and excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by consistent lack of excess risk for brain cancer in the studies of the industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists (IARC, 1995).

IARC (IARC, 1995) interpreted the above data as limited evidence for the carcinogenicity of formaldehyde in humans, and classified formaldehyde as "probably carcinogenic to humans" (Group 2A).

In a published cohort study (Hansen & Olsen, 1995), a significantly increased relative risk of 3.0 (1.4–5.7; 95% confidence limits) for sinonasal cancer was found among blue-collar workers potentially exposed to formaldehyde, but with no probable exposure to wood dust, the major confounder.

Animal carcinogenicity data

Formaldehyde was tested for carcinogenicity by inhalation in mice, rats and hamsters, by oral administration in drinking-water in rats, by skin application in mice, and by subcutaneous injection in rats. In additional studies in mice, rats and hamsters, modification of the carcinogenicity of known carcinogens was tested by administration of formaldehyde in drinking-water, by application to the skin or by inhalation (IARC, 1995).

Several carcinogenicity studies in which formaldehyde was administered to rats by inhalation produced evidence of carcinogenicity, particularly induction of squamous cell carcinomas of the nasal epithelium, usually only at the highest exposure level which ranged from about 18 to 25 mg/m^3. In one long-term inhalation study, a high incidence of nasal squamous cell carcinomas (15/58) was found in rats exposed to 12.3 mg/m^3, the nasal mucosa of which had been severely damaged by electrocoagulation before the exposure to formaldehyde started. In a comparable group of rats exposed to the same formaldehyde concentration but with an undamaged nasal mucosa, no formaldehyde-related nasal tumours were found (IARC, 1995). In one study in mice, no statistically significantly increase in the incidence of nasal tumours was found after chronic (2-year) exposure to formaldehyde concentrations up to 17.6 mg/m^3. Similar long-term studies in hamsters showed no evidence of carcinogenicity (IARC, 1995).

In rats administered formaldehyde in the drinking-water, increased incidences were seen of forestomach papillomas in one study and of leukaemias and gastrointestinal tract tumours in another; two other studies in which rats were treated through the drinking-water gave negative results. Studies in which formaldehyde was applied to the skin or injected subcutaneously were inadequate for evaluation (IARC, 1995).

In experiments to test the effect of formaldehyde on the carcinogenicity of known carcinogens, oral administration of formaldehyde concomitantly with N-nitrosodimethylamine to mice increased the incidence of tumours at various sites; skin application in addition to 7,12-dimethylbenz[a]anthracene reduced the latency of skin tumours. In rats, concomitant administration of formaldehyde and N-methyl-N´-nitro-N-nitrosoguanidine in the drinking water increased the incidence of adenocarcinoma of the glandular stomach. Exposure of hamsters by inhalation to formaldehyde increased the multiplicity of tracheal tumours induced by subcutaneous injections of N-nitrosodiethylamine (IARC, 1995).

Genotoxic effects

Formaldehyde induces DNA–protein cross-links in mammalian cells in vitro and in vivo (2). The precise nature of these cross-links is unknown. They are removed from normal cells with a half-time of 2–3 hours; the removal rates were similar at nontoxic and toxic concentrations of formaldehyde (Grafström et al., 1984).

DNA–protein cross-links were measured in the mucosa of several regions of the respiratory tract of rats exposed by inhalation to 0.4, 0.9, 2.4, 7.3 or 12.2 mg/m^3 ^{14}C-formaldehyde, and of rhesus monkeys exposed by inhalation (mouth-only) to 0.9, 2.4 or 7.3 mg/m^3 ^{14}C-formaldehyde for 6 hours. The concentration of cross-links increased non-linearly with the airborne concentration in both species. The concentrations of cross-links in the turbinates and anterior nasal mucosa were significantly lower in monkeys than in rats. Cross-links were also formed in the nasopharynx and trachea of monkeys, but they were not detected in the sinus, proximal lung or bone marrow. The investigators suggested that the differences between rats and monkeys with respect to DNA–protein cross-link formation may be due to differences in nasal cavity deposition and in the elimination of absorbed formaldehyde (Casanova et al., 1991; Heck et al., 1989).

In addition to DNA–protein cross-links, formaldehyde induced DNA single-strand breaks, chromosomal aberrations, sister chromatid exchanges and gene mutations in human cells in vitro. It induced cell transformation, chromosomal aberrations, sister chromatid exchanges, DNA strand breaks, DNA–protein cross-links and gene mutations in rodent cells in vitro. Administration of formaldehyde in the diet to Drosophila melanogaster induced lethal and visible mutations, deficiencies, duplications, inversions, translocations and crossing-over in spermatogonia. Formaldehyde induced mutations, gene conversion, DNA strand breaks and DNA–protein cross-links in fungi, and mutations and DNA damage in bacteria. Assays for dominant lethal mutations in rodents in vivo gave inconclusive results. In single studies, formaldehyde induced sperm head abnormalities in rats but not in mice (IARC, 1995).

While there is conflicting evidence that formaldehyde can induce chromosomal anomalies in the bone marrow of rodents exposed by inhalation in vivo, recent studies have shown that it induced cytogenetic damage in the cells of

tissues that are more locally exposed, either by gavage or by inhalation. Rats given 200 mg per kg body weight formaldehyde orally were killed 16, 24 or 30 hours after treatment and examined for the induction of micronuclei and nuclear anomalies in cells of the gastrointestinal epithelium. The frequency of mitotic figures was used as an index of cell proliferation. Treated rats had significant (greater than five-fold) increases in the frequency of micronucleated cells in the stomach, duodenum, ileum and colon; the stomach was the most sensitive, with a 20-fold increase in the frequency of micronucleated cells 30 hours after treatment, and the colon the least sensitive. The frequency of nuclear anomalies was also significantly increased at these sites. These effects were observed in conjunction with signs of severe local irritation (Migliore et al., 1989).

In another experiment, rats were exposed to 0, 0.62, 3.7 or 18.5 mg/m^3 formaldehyde for 6 hours per day on five days per week, for one and eight weeks. There was no significant increase in chromosomal abnormalities in the bone-marrow cells of formaldehyde-exposed rats relative to controls, but there was a significant increase in the frequency of chromosomal aberrations in pulmonary lavage cells (lung alveolar macrophages) from rats that inhaled 18.5 mg/m^3 formaldehyde. Aberrations, which were predominantly chromatid breaks, were seen in 7.6% and 9.2% of the scored pulmonary lavage cells from treated animals, and in 3.5% and 4.8% of the cells from controls, after one and eight weeks, respectively (Dallas et al., 1992).

The spectrum of mutations induced by formaldehyde has been studied in human lymphoblasts in vitro, in Escherichia coli, and in naked pSV2gpt plasmid DNA (IARC, 1995; Crosby et al. 1988). About 50% of formaldehyde-induced tumours of the nasal epithelium of rats appeared to have a point mutation in the p53 tumour suppressor gene (Recio et al., 1992).

Overall, formaldehyde was genotoxic in a variety of experimental systems, ranging from bacteria to rodents, in vivo. Formaldehyde given by inhalation or gavage to rats in vivo induced chromosomal anomalies in lung cells and micronuclei, respectively, in the gastrointestinal tract (IARC, 1995).

Interactions with other chemicals

A group of 24 healthy nonsmokers were exposed while engaged in intermittent heavy exercise for 2 hours to formaldehyde at 3.7 mg/m^3 or to a mixture of formaldehyde and 0.5 mg/m^3 of respirable carbon aerosol, in order to determine whether adsorption of formaldehyde on respirable particles elicits a pulmonary response. Small (<5%) decreases were seen in forced vital capacity and forced expiratory volume, but these effects were not considered to be clinically significant (Green et al. 1989), Risby et al. (1990) and Rothenberg et al. (1989) estimated that the amount of formaldehyde adsorbed on to carbon black or dust particles and delivered to the deep lung by particle inhalation is minuscule in relation to the amount that remains in the vapour phase and is adsorbed in the upper respiratory tract.

The industrial manufacture of furniture, plywood and particle board may entail simultaneous exposure to formaldehyde and wood dust, both being nasal carcinogens, the former in rats and the latter in humans (IARC, 1995). While the epidemiological studies in woodworkers revealed the cancer excess to be attributable to wood dust per se rather than to other exposures in the workplace such as formaldehyde, it is also true that exposure to wood dust is often an important confounder in epidemiological studies on formaldehyde in industrial groups (IARC, 1995), indicating that exposure to formaldehyde may enhance the nasal cancer risk associated with wood dust exposure.

Lam et al. (1985) studied the effects of inhalation co-exposure to acrolein and formaldehyde in male Fischer 344 rats. Rats were exposed for 6 hours to room air (controls), 2 ppm acrolein, 6 ppm formaldehyde, or a combination of 2 ppm acrolein and 6 ppm formaldehyde. The animals were sacrificed immediately after completion of exposure and their nasal tissues were harvested. Exposure to formaldehyde significantly increased the percentage of interfacial DNA (a measure of DNA-protein cross linking) compared to rats exposed to room air only (12.5 versus 8.1%, p<0.05). Co-exposure to acrolein resulted in further increases in the percentage of interfacial DNA (18.6%) which were significantly greater than the effect of formaldehyde alone (p<0.05). The authors concluded that simultaneous exposure to acrolein enhanced formaldehyde-induced DNA-protein cross linking and that depletion of glutathione by acrolein inhibited the metabolism of formaldehyde, thereby increasing formaldehyde-induced DNA-protein cross link formation.

To investigate the possibility of additive or potentiating interactions between inhaled aldehydes, Cassee et al. (1996) compared responses in nasal epithelial histopathology and cell proliferation in groups of male Wistar rats exposed for 3 days (6 hours/day) to 1.0, 3.2, or 6.4 ppm formaldehyde alone; to 0.25, 0.67, or 1.40 ppm acrolein alone; to 750 or 1,500 ppm acetaldehyde alone; or to several mixtures of these aldehydes. At the concentrations tested, the histological and cell proliferation responses measured in the nasal epithelium of rats exposed to the mixture which produced effects (3.2 ppm formaldehyde; 1,500 ppm acetaldehyde; 0.67 ppm acrolein) were attributed by the investigators to the acrolein alone with no additional effects from the formaldehyde or acetaldehyde. The investigators concluded that combined

exposures to these aldehydes at exposure levels in the vicinity of individual no-effect-levels was not associated with a greater hazard than that associated with exposure to the individual chemicals.

Odour perception

Source: WHO (2001)
Formaldehyde has a pungent odour with odour detection thresholds as specified in Table 5.1 ($0.03 - 0.6$ mg/m^3); the odour recognition threshold is not known. Formaldehyde poses nuisance problems in indoor environments owing to its release from building materials or furnishings. Indoor air usually contains other organic compounds which, in combination with formaldehyde or by themselves, may have odorous and irritating properties causing discomfort. It has been reported that some sensitive individuals can sense formaldehyde concentrations of 0.01 mg/m^3 and perhaps even lower as a "warm" feeling on the face (Ahlström et al., 1986).

Source: Devos et al. (1990)
Odour threshold: 35 μg/m^3.

Source: IPCS/WHO (1989)
The absolute odour threshold for formaldehyde is between 0.06 and 0.22 mg/m^3 (a group of observers detected the odour in 50% of the presentations, 10% of an untrained population detected a level of 0.03 mg/m^3). There is a low probability that human beings will be able to detect formaldehyde in air at concentrations below 0.01 mg/m^3.

Source: Moncrieff (1955)
The difference between odour and irritation concentration may be noticeable, but there is no evidence that there is a threshold at which odour is superceded by irritation. However, for most inhaled odorous compounds, the trigeminal nerve has a higher threshold than the olfactory nerve. When the formaldehyde concentration is increased and affects both the eyes and the nostrils, sensory irritation is first experienced in the eyes, then the odour is perceived, and finally nasal irritation occurs.

Summary of Formaldehyde Dose Response Assessment

Exposure other than inhalation: Endogeneous formaldehyde levels in blood: 2-3 mg/litre

Toxicokinetics: Almost completely absorbed (>90%) in the upper respiratory tract; endogenous formaldehyde levels in blood not altered after exposure; does not accumulate, rapid conversion to formate

Health effect levels of short- and long-term exposure (noncancer):

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
0.6 $_{EXP}$	1.2 $_{EXP}$ 0.53 $_{BC05}$ 0.94 $_{1h-ADJ-BC05}$	Mild and moderate eye irritation	Volunteers, 3h	Kulle et al. (1987)	OEHHA 1999; REL: 0.094
	0.5 $_{EXP}$	Nasal and eye irritation	Volunteers, 2h (potentially sensitive population)	Pazdrak et al. (1993)	ATSDR 1999; MRL: 0.05
	0.24 $_{STAT}$	Respiratory tract irritation		cited in Sloof et al. (1992)	RIVM 1992
	0.1	Nose and throat irritation	Human, short-term	cited in IPCS/WHO, 1989	WHO 2000
	(0.037)	Respiratory symptoms (depending on study)	Children; additional investigation requested	Krzyzanowski et al., (1990); Wantke et al. (1996); Garrett et al. (1999); Franklin et al. (2000)	UCLA 2001
Long-term exposure					
0.09 $_{Study}$ 0.032 $_{ADJ}$	0.26 $_{Study}$ 0.093 $_{ADJ}$	Nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, and dysplasia	Occupational, 10y average;	Wilhelmsson and Holmstrom, 1992; supported by Edling et al., 1988	OEHHA 1999; REL: 0.003
	0.3 $_{Study}$	Mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium	Occupational, 10.4y	Holmstrom et al., 1989	ATSDR 1999; MRL: 0.01
	0.31 $_{STAT}$	Sensory irritation	for low but significant percentage of exposed workers	Weighting the total body of data	NIWL 2003
	0.12	Symptoms of irritation	LOAEL may be lower only for a very small proportion of the population	well conducted studies	Health Canada 1999; (noTC)

Carcinogenicity: IARC: 1 (15.06.04); U.S.EPA: B1; Unit risk (EPA-IRIS): 1.3E-5 $(\mu g/m^3)^{-1}$; An association exists between cytotoxic, genotoxic, and carcinogenic effects. Most probably HCHO cannot act as a complete carcinogen at non-cytotoxic concentrations. If exposure is accompanied by recurrent tissue damage at the site of contact, it may be assumed to have carcinogenic potential in humans. Evidence of carcinogenicity in rats: induction of squamous cell carcinoma at > 18 mg/m³.

In June 2004, IARC announced there was sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans and re-classified it as a Group 1, known human carcinogen (previously classified as Group 2A). IARC also reported there was limited evidence that formaldehyde exposure causes nasal cavity and paranasal cavity cancer and strong but not sufficient evidence linking formaldehyde exposure to leukemia.

Genotoxicity: Mutagenic in vitro, in vivo only in tissue of contact at doses adapt to give cytotoxic effects (no primary mutagen)

Odour threshold: range: 0.03 - 0.6 mg/m³ (WHO); 0.035 mg/m³ (Devos); > 6 mg/m³ untolerable to most people

Susceptible population: Wide variability in response to HCHO irritancy; Children seem to bee more sensitive than adults (still additional investigation requested; results would be expected from recent German environmental survey GerES IV); Asthmatics: no significant changes in pulmonary function and non-specific airway reactivity at 3.7 mg/m³; population with allergic contact dermatitis (3-6%) seem not to react differently at 0.5 mg/m³ (Pazdrak, 1993: 9 volunteers with formalin skin sensitization).

Remarks: RD_{50}: 4 mg/m^3; HCHO is a reaction product of ozone and unsaturated VOCs (e.g. limonene, pinene, styrene); neither dose addition nor potentiating interactions occured upon exposure to aldehyde mixtures (formaldehyde, acetaldehyde, acrolein) at exposure levels around the MOEL.

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6. Risk Characterization

Health hazard evaluation

Predominant symptoms of formaldehyde exposure in humans are irritation of the eyes, nose and throat, together with concentration-dependent discomfort, lachrymation, sneezing, coughing, nausea and dyspnoea. Although there is substantial variation in individual responses to formaldehyde in humans, there are sufficient data to indicate that the irritant effects on the nose and throat after short-term exposure occur at concentrations as low as 0.1 mg/m^3 (Health Canada; WHO), set as the LOAEL. A NOAEL of 0.03 mg/m^3 is defined according to the lowest concentration supposed not to give effects in the normal population (OEHHA). This level has been further devided by an assessment factor of 30, taking into account the evidence indicating that children may be more sensitive to formaldehyde respiratory toxicity than adults (3) and intraspecies variation (10) resulting in an Exposure Limit (EL) of 1 µg/m^3. For this chemical the observed acute effects and endpoints are consistent with the pathology seen in long-term studies. Consequently, no distinction has been done between short-term and long-term ELs.

Percentage of population exposed beyond given threshold levels

Table 6.1 Population-based studies		LOAEL [a]	NOAEL [b]	NOAEL 3	NOAEL 30
Description (Study, Year)	N	0.1 mg/m^3	0.03 mg/m^3	0.01 mg/m^3	0.001 mg/m^3
England (BRE)	528	<	35 %	90 %	100 %
England (BRE, 2002)	833	<	35 %	85 %	100 %
Vienna – bedrooms (Hutter, 2001)	160	<	40 %	90 %	100 %
Paris – refurbished flats (Clarisse, 03)	61	<	40 %	90 %	100 %
Helsinki (Expolis, 97)	15	<	65 %	100 %	100 %
French National Survey 7-d TWA (IAQ observatory, 2003-04)	201	<	20 %	90 %	100 %

< out of the evaluation range (i.e. <5% of the environments investigated)
[a] corresponds with 30-min average WHO guideline value
[b] corresponds with lowest odour threshold reported

Cancer risk evaluation

On June 15, 2004, IARC announced there was sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans and re-classified it as a Group 1, known human carcinogen (previous classification: Group 2A). IARC also reported there was limited evidence that formaldehyde exposure causes nasal cavity and paranasal cavity cancer and "strong but not sufficient" evidence linking formaldehyde exposure to leukemia.

Pending the outcome of the current IARC revision, the position taken in the present indoor risk evaluation is as follows: Inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation within the respiratory tract is considered to present a carcinogenic risk to humans. At airborne levels for which the prevalence of sensory irritation is low (i.e., ≤0.1 mg/m^3), risks of respiratory-tract cancers for the general population are exceedingly low.

Comments

Among the available exposure data (see chapter 3), results from a limited number of indoor air surveys enabled the construction of frequency distributions and hence the evaluation of population percentages exposed at given threshold levels (see Table 6.1). When taking into account the whole body of published exposure data, the formaldehyde levels reported in these surveys could be considered as indicative for "indoor air quality non-problem" buildings in the EU.

As summarised in Table 6.1, the results of these measurements indicate that at least more than 20% of the population is exposed at formaldehyde levels higher than the NOAEL. A concentration slightly higher than the established NOAEL has been recently proposed as a LOAEL (37 µg/m^3) for effects on pulmonary functions in children, although additional investigation is required to confirm this level. Concerning childrens' susceptibility, important results are expected from the German environmental survey GerES IV.
An exposure limit of 1 µg/m^3 has been derived, which corresponds more or less with the background outdoor level in rural areas. It could be assessed that indoors almost the entire population in the EU is exposed at levels which are higher than this limit.

For safety check purposes indoor formaldehyde levels are habitually refered to the WHO-air quality guideline value *****
(100 μg/m^3 as a 30-minute average), with the assumption that transient sensory effects would be avoided for most
people. It is here asserted that this level should be regarded as hazardous for susceptible individuals (children) when
evidence exists that concentrations are maintained over prolonged periods.

* WHO-air quality guideline value:
 "The lowest concentration that has been associated with nose and throat irritation in humans after short-term exposure is 0.1 mg/m^3,
although some individuals can sense the presence of formaldehyde at lower concentrations. To prevent significant sensory irritation
in the general population, an air quality guideline value of 0.1 mg/m^3 as a 30-minute average is recommended. Since this is over one
order of magnitude lower than a presumed threshold for cytotoxic damage to the nasal mucosa, this guideline value represents an
exposure level at which there is a negligible risk of upper respiratory tract cancer in humans."

Result

Because of its high chemical reactivity, formaldehyde is the most important sensory irritant among the chemicals
assessed in the present report. Due to its ubiquitousness in indoor environments and to the increasing evidence
indicating that children may be more sensitive to formaldehyde respiratory toxicity than adults, it is considered a
chemical of concern at levels exceeding 1 μg/m^3, a concentration more or less corresponding with background levels in
rural areas. Results from available exposure data, although limited, confirm that almost the entire population is exposed
indoors at levels (Median level±sd: 26±6 μg/m^3; 90th±sd: 59±7 μg/m^3; N = 6) higher than this background level, here
established as the limit of exposure, with more than 20% of the European population exposed at levels exceeding the
no-observed-effect-level (NOAEL: 30 μg/m^3). Within the reported concentration range mild irritation of the eyes could
be experienced by the general population as well as the odour perceived starting from about 30 μg/m^3.

Reported formaldehyde concentrations are lower (99th < 150 μg/m^3) than a presumed threshold for cytotoxic damage to
the nasal mucosa and hence considered low enough to avoid any significant risk of upper respiratory tract cancer in
humans. The last statement could be subjected to changes due to the current IARC revision of the carcinogenicity of
formaldehyde.

Carbon monoxide

Synonyms: Carbon oxide, Carbonic oxide
CAS Registry Number: 630-08-0
Molecular Formula: CO

1. Compound identification

Carbon monoxide is a colourless, practically odourless and tasteless gas that is poorly soluble in water, but it is soluble in alcohol and benzene. It is a product of incomplete combustion of carbon-containing fuels. Carbon monoxide burns with a violet flame and it is classified as an inorganic compound. It has a slightly lower density than air. Anthropogenic emissions are responsible about two-thirds of the CO in the atmosphere and natural emissions account for the remaining one-third Small amounts of carbon monoxide are also produced endogenously (EPA 2000, Alm 1999).

Accidental high exposures to CO can lead to acute health effects that can be fatal. Carbon monoxide exposure causes unintentional and suicidal poisonings, and a large number of deaths annually both in Europe and in the United States. It is estimated that more than half of the 6000 annual deaths from fires in the Unites States is caused by CO poisoning (Raub et al 2000). It is obvious that such homes exist where CO concentrations are high enough to increase chronic health effects, especially among sensitive populations such as pregnant women, the fetus, children, the elderly, and individuals suffering from anemia or other diseases that restrict oxygen transport between blood and cells (IEH 1998). In the human body, CO reacts with haemoglobin to form carboxyhaemoglobin (HbCO). The relationship of CO exposure and the HbCO concentration in blood is presented in Table 1.1.

The scientific literature on carbon monoxide sources, concentrations, and human exposures and health effects in outdoor and indoor environments has been comprehensively reviewed by the US Environmental Protection Agency (EPA) and the health risk assessment has been carried out by WHO (EPA 2000, WHO 1979 and 2000). Raub et al (2000) have also recently reviewed literature about carbon monoxide poisoning from a public health perspective.

Table 1.1. The relationship between carbon monoxide exposure and carboxyhaemoglobin levels in blood (adopted from WHO 1979)

% HbCO	mg/m^3	ppm	% in air
0.87	5.7	5	0.0005
1.73	11.5	10	0.001
3.45	23	20	0.002
5.05	34.5	30	0.003
6.63	46	40	0.004
8.16	57.5	50	0.005
9.63	69	60	0.006
11.08	80	70	0.007
12.46	92	80	0.008
13.8	103	90	0.009
15.11	114.5	100	0.01
16.37	126	110	0.011
17.6	130	120	0.012
18.78	149	130	0.013
19.95	160	140	0.014
21.05	172	150	0.015
22.15	183	160	0.016
23.23	195	170	0.017
24.26	206	180	0.018
25.25	218	190	0.019
26.22	229	200	0.02

2. Physical and Chemical properties

Molecular weight (g/mol)   28.01
Melting point (oC)   -205.1
Boiling point (oC)   -191.5
Density, at 0°C, 1 atm (kg/m^3)   1.250
      at 25°C, 1 atm (kg/m^3)   1.145
Relative density (air =1)   0.967
Solubility in water (at 0°C, 1 atm, ml/100 ml)   3.54
      (at 25°C, 1 atm, ml/100 ml)   2.14
      (at 37°C, 1 atm, ml/100 ml)   1.83

Conversion factors at 20 °C and 760 mm Hg:

1 ppm = 1.164 mg/m^3
1 mg/m^3 = 0.859 ppm

Sources: WHO 1979, 2000a, Verschueren 2001

3. Indoor Air Exposure assessment

Indoor air and exposure concentrations

Residential indoor concentrations of CO were typically lower in Northern Europe than in Central Europe, where they were again lower than in Southern Europe based on the European exposure study, EXPOLIS (Georgoulis et al 2002). Average residential indoor concentration in Helsinki was 1.2 mg/m^3 for non-ETS population. Average 48-hour exposure to CO, being 1.4 mg/m^3, was slightly higher than the respective indoor concentration. In Basle and Prague average exposures to CO were higher than in Helsinki, but lower than in Milan and Athens. The highest geometric mean exposure concentrations were found in a subpopulation of smokers in Athens, being 4.0 mg/m^3 (Georgoulis et al 2002). Average residential indoor CO concentrations in Milan vary from 2.1 to 3.9 mg/m^3. In another Italian study carried out by Maroni et al (1996) an average personal exposure of 2.2 mg/m^3 was reported for office workers. Weekly average CO concentrations in 14 homes in UK ranged from 0.2 to 2.7 mg/m^3 in a study published by Ross (1996). Alm et al (2000) reported mean exposures of 15-min, 1-hour and 8-hour periods for preschool children in Finland, being 8.4 mg/m^3, 6.0 mg/m^3 and 3.3 mg/m^3, respectively.

In UK typical ambient background CO levels range between 0.01 and 0.23 mg/m^3, but in traffic environments, the 8-hour mean concentrations are much higher, but typically less than 20 mg/m^3 (IEH 1998).

The cumulative distributions of the indoor, 48-hour and 1-hour personal exposure concentrations of carbon monoxide in European studies are presented in Figure 3.1, Figure 3.2, Figure 3.3 and Figure 3.4.
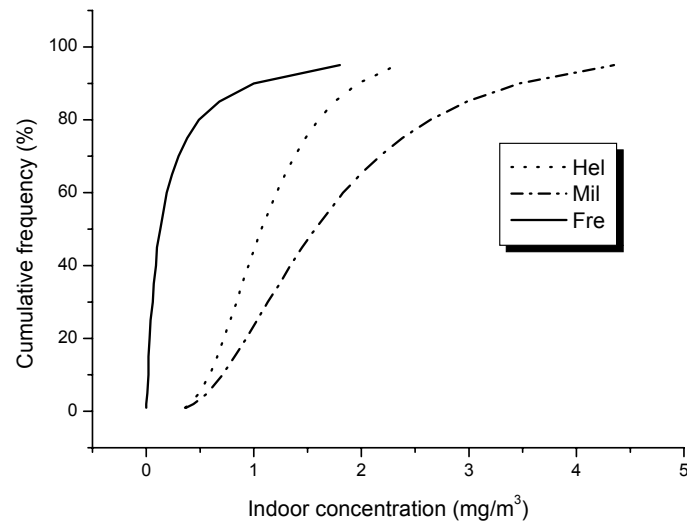
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of carbon monoxide in Helsinki (Hel, n= 258785) for non-ETS population (Scotto di Marco et al 2003), in the French Survey (Fre n= 550666) (Kirchner 2004) and in Milan (Mil, n= 4822) (Bruinen de Bruin et al 2004) for the whole population (sampling periods were 1-min, 15-min, and 5-min in Helsinki, Milan and France, respectively).
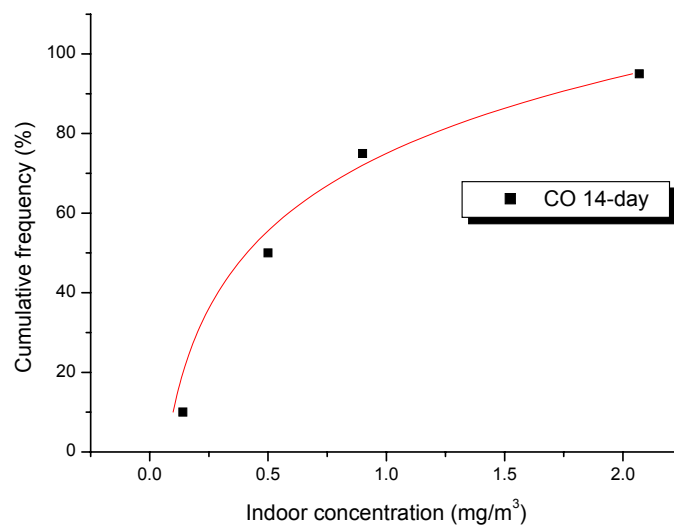
Figure 3.2. Cumulative frequency distribution of 14-day indoor air concentrations of carbon monoxide in the kitchens in England (GM= 0.47 mg/m3, max 4.45 mg/m3, n=830, Raw et al 2002).
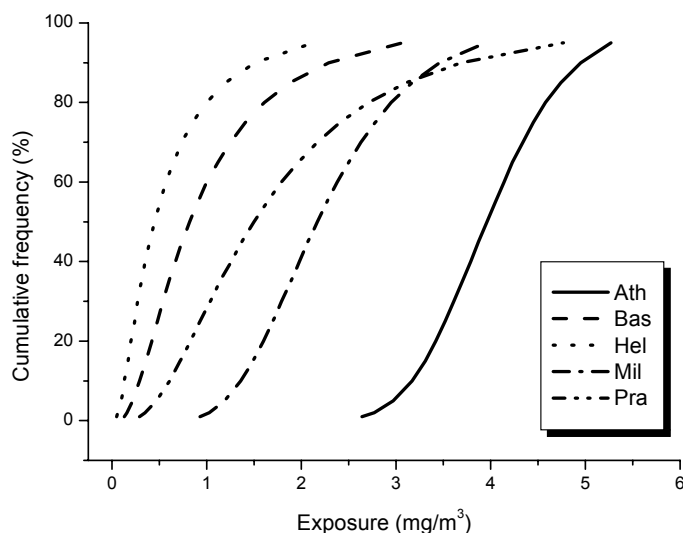
Figure 3.3. Cumulative frequency distributions of 48-hour exposures to carbon monoxide in Athens (Ath), Basel (Bas), and Prague (Pra) (Georgoulis et al 2002), Helsinki (Hel) (EXPOLIS 2002), and Milan (Mil) (Bruinen de Bruin et al 2004).
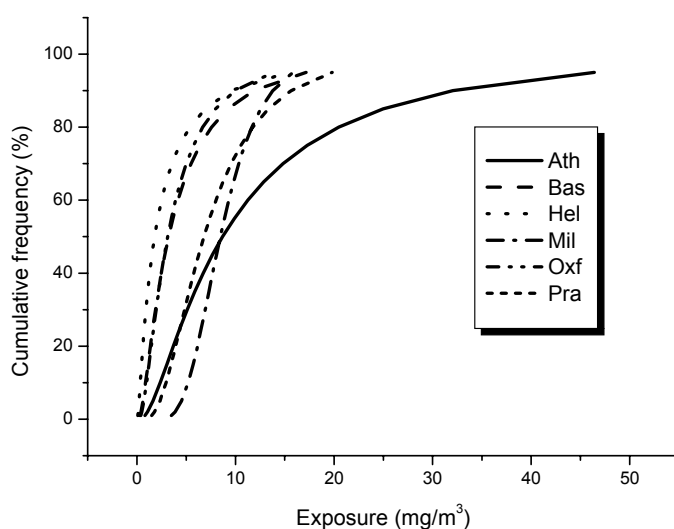
Figure 3.4. Cumulative frequency distributions of 1-hour exposure concentrations of carbon monoxide in Athens (Ath, n=44), Basel (Bas, n=50), Helsinki (Hel, n=195), Milan (Mil, n=45) Oxford (Oxf, n=26) and Prague (Pra, n=23) (Hanninen et al 2004).

Emission sources

The most common cause of high carboxyhaemoglobin concentrations in man is the smoking of tobacco and the inhalation of the products by the smoker. Faulty domestic cooking and heating appliances, inadequately vented to outside air, may cause high indoor concentrations of CO (WHO 1979). Also gas stoves, water heaters, and exhaust from vehicles in attached garages might be important indoor sources (Alm 1999).

The most important source of carbon monoxide in ambient air is the exhaust of gasoline-powered motor vehicles. The emission rate depends on the type of vehicle, its speed, and its mode of operation. Other common ambient sources include heat and power generators, especially when using coal, industrial processes such as the carbonisation of fuel, and the incineration of refuse (WHO 2000).

Based on the EXPOLIS results average residential indoor CO concentrations in Milan were the lowest when no special indoor sources were present and the highest if gas cooking and environmental tobacco smoke (ETS) were present. The highest short-time peak concentration was found during gas cooking, 7.4 mg/m^3. Average 15-min ambient CO concentration, 2.6 mg/m^3, was higher than the respective indoor concentration when no indoor sources were present, but lower if gas cooking or ETS was present. The highest in-transit concentration was measured in cars/taxis being 6.5 mg/m^3 (Bruinen de Bruin et al 2003). Average 1-hour exposures to CO were higher, 8.4 mg/m^3, than the respective ambient concentrations, 5.7 mg/m^3. Instead, average 8-hour and 48-hour ambient concentrations were at the same level than the respective exposures, being 3.8 and 2.4 mg/m^3, respectively.

Short time carbon monoxide concentrations related to some typical indoor sources such as tobacco smoke, gas cooking and commuting in five European cities are presented in Figure 3.5. Much higher concentrations were found in a Finnish study determining personal exposures of preschool children in Helsinki. The highest exposures to carbon monoxide were as high as 80 mg/m^3, 69 mg/m^3 and 28 mg/m^3 for 15-min, 1-hour and 8-hour averages, respectively. Elevated exposures were related to gas stoves, mothers' smoking and living in high rise buildings (Alm et al 2000).

Brown et al (2002) studied emission rates and concentrations caused by unflued gas heaters in a room chamber with a volume of 32.4 m^3. In normal conditions carbon monoxide concentrations ranged from <1.15 mg/m^3 to 4.6 mg/m^3. But when the gas supply was restricted due to the backpressure of 0.02 kPa, concentration of 19.5 mg/m^3 was measured. Even higher concentration, 34.4 mg/m^3, was determined when the researchers caused a slight misalignment of the burner. Because fatal concentrations may occur during malfunction of burning appliances, estimated concentrations caused by burning different fuels in a stove are presented in Table 3.1. Despite of the fact that the assumptions are valid for houses common in developing countries, these estimates may help to assess the concentrations that may be caused by burning these fuels in stoves also in developed countries.

Typical sources and microenvironments where high concentrations of carbon monoxide may occur are reviewed in Table 3.2 based on the recently published studies. The highest maximum values ranging 121 – 182 mg/m^3 were measured in homes when using a gas grill attached to the gas stove (IEH 1998), in the underground parking facilities (El Fadel et al 2001), and in a home with a faulty boiler (Ross 1996). Elevated concentrations were also found in other microenvironments such as motor vehicles, indoor ice arenas, bars and restaurants. Carbon monoxide concentrations in public buildings studied before 1985 are summarised in Table 3.3.

Lately attention is paid to incense burning in homes and other public buildings including stores and shopping malls. Jetter et al (2002) reported emission rates of 23 different types of incense such as incense rope, cones, sticks, rocks, powder etc. that are typically used indoors. The measured emission rates of carbon monoxide ranged 144 - 531 mg/h. The authors estimated a peak concentration of 9.6 mg/m^3 caused by incense burning and, therefore concluded that carbon monoxide concentrations could exceed the US EPA's National Ambient Air Quality Standard (NAAQS) 10 mg/m^3 for an 8-hour average depending on the room volume, ventilation rate and the amount of incense burned. Lee and Wang (2004) reported similar results when studying emissions of incense burning in chamber (18 m^3) tests. They measured maximum carbon monoxide concentrations up to 44 mg/m^3 during burning and concluded that incense burning is an important indoor air pollution source in addition to carbon monoxide also to fine particles and VOCs. Especially, incense burning might be a significant contributor to population exposure in such cultures, where incense is burned frequently, for example in religious rituals.
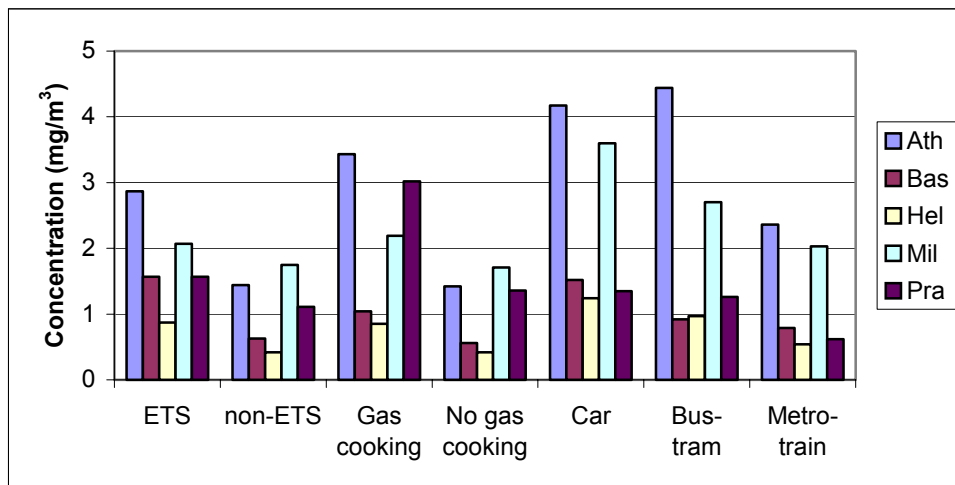
Figure 3.5. Short time (geometric means of the 15-min periods) exposures to carbon monoxide stratified by environmental tobacco smoke (ETS) and gas cooking, and in-vehicle concentrations in European cities Athens (Ath), Basel (Bas), Helsinki (Hel), Milan (Mil) and Prague (Pra) (Georgoulis et al 2002).

Table 3.1. Estimated indoor CO concentrations resulting from burning 1 h of fuel in stove without flues using assumptions relevant in developing countries i.e. fuel consumption equal to the energy used for burning 1.7 kg of fuel wood, ventilation rate of 15 h-1, and room volume of 40 m3 (adopted from Zhang et al 1999).

Fuel	CO concentration (mg/m^3)	
	Avgerage during burning	maximum
Charbiquette	562	603
Charcoal	528	566
Brush wood	511	548
Coal	178	191
Fuel wood	150	161
Kerosene	9.4	10
LPG	4.5	4.8
Biogas	1.6	1.7
Natural gas	0.083	0.089

Table 3.2. Short time CO concentrations related to specific microenvironments or emission sources.

Environment/ emission source	Location	Averaging time		Concentration (mg/m^3)			Reference
				AM	GM	max	
Gas stove with pilot light	UK	peak when using a grill				10-182	IEH 1998
Underground parking facilities	Beirut, Lebanon	30-min		80		26 - 140	El Fadel et al 2001
Home	UK	1-min	faulty boiler gas cooking all-electric homes			121 6 - 49 3.5 - 4	Ross 1996
Undergrounds, car parks, enclosed ice arenas, etc. homes with gas appliances		several hours		>115		60 - 115	WHO 2000
Gas appliances	The Netherlands	max 1-min max 1-hour	kitchen kitchen	5-108 3-56			Lebret et al 1987
Exposure	Helsinki, Finland	max 15-min max 1-hour max 8-hour	pre-school children			80 69 28	Alm et al 2000
Incense burning		peak	chamber tests			44	Lee and Wang 2004
Bars, restaurants	Italy			12 - 23		35	Maroni et al 1995
Indoor ice arenas	Finland	max 1-hour		20-33			Pennanen et al 1997
Exposure	Milan, Italy	max 15-min max 1-hour max 8-hour		12 8.4 3.8	11 8.4 3.8	25 20 9.3	Bruinen de Bruin 2002
Unflued gas heaters	room chamber test	1-min	normal cond. gas supply restricted misaligned burner	<1.2 - 4.6 20 34			Brown et al 2002
Shops and bars	Genoa, Italy	8-hour	shops bars			15 18	Valerio et al 1997
Indoor ice skating rink	Hong Kong, China	15-min 15-min	gasoline-fueled propane-fueled			8-16 5.7	Guo et al 2004
Exposure	Helsinki, Finland	max 15-min max 1-hour max 8-hour	ETS non-ETS ETS non-ETS ETS non-ETS	9.0 7.1 5.7 4.3 2.6 2.0	5.7 5.3 3.7 3.3 2.1 1.8		Scotto di Marco et al 2003
Concert hall	Switzerland	event (5.5 hours)		3.5		5.2	Junker et al 2000
Gas appliances	NY, USA	3-day	gas stove kerosene heater	2.6 3.9			RTI 1990
Public buildings	Athens, Greece	1-hour	Office	3.7			Chaloulakou et al 2003

AM = arithmetic mean, GM = geometric mean, max = maximum value

Table 3.3. Indoor air concentrations of carbon monoxide in selected indoor microenvironments (adopted from Akland et al 1985).

Indoor environment	Mean concentration			
	n	ppm	std	mg/m^3
Public garage	116	13.46	18.14	15.41
Service station/motor vechile repair facility	125	9.17	9.33	10.50
Repair shop	55	5.64	7.67	6.46
Shopping mall	58	4.90	6.50	5.61
Residential garage	66	4.35	7.06	4.98
Restaurant	524	3.71	4.35	4.25
Office	2287	3.59	4.18	4.11
Sport arena, concert hall	100	3.37	4.76	3.86
Store	734	3.23	5.56	3.70
Health care facility	351	2.22	4.25	2.54
Other public buildings	115	2.15	3.26	2.46
Residence	21543	2.04	4.06	2.34
School	426	1.64	2.76	1.88
Church	179	1.56	3.35	1.79

4. Toxicokinetics

Endogenous sources of carbon monoxide:

In addition to inhaled carbon monoxide, humans are also exposed to small amounts of carbon monoxide produced endogenously, conducing in the healthy population to a baseline carboxyhaemoglobin concentration range of 0.4-0.7%. Sources of carbon monoxide in the body include the endogeneous oxidation of halomethanes (e.g. dichloromethane), phenols, flavonoids, as well as the lipid peroxidation of membrane lipids (Rodgers et al., 1994).

Carbon monoxide is a natural degradation product of haemoproteins, mainly haemoglobin* but also myoglobin, cytochromes, peroxidases and catalase. Approximately 0.4 ml/h CO is formed by haemoglobin catabolism, and about 0.1 ml/h originates from non-haemoglobin sources (Coburn et al., 1964). In both males and females, week-to-week variations in carbon monoxide production are greater than day-to-day or within-day variations. In females, carboxyhaemoglobin levels fluctuate with the menstrual cycle; the mean rate of carbon monoxide production in the premenstrual, progesterone phase almost doubles (Deliveria-Papadopoulos et al., 1970; Lynch & Moede, 1972). Neonates and pregnants also showed a significant increase in endogenous carbon monoxide production related to increased breakdown of red blood cells.

Any disturbance leading to increased destruction of red blood cells and accelerated breakdown of other haemoproteins would lead to increased production of carbon monoxide. Haematomas, intravascular haemolysis of red blood cells, blood transfusion and ineffective erythropoiesis will all elevate the carbon monoxide concentration in the blood. Degradation of red blood cells under pathological conditions such as anaemias (haemolytic, sideroblastic, sickle cell), thalassaemia, Gilbert's syndrome with haemolysis and other haematological diseases will also accelerate carbon monoxide production (Berk et al., 1974; Solanki et al., 1988). In patients with haemolytic anaemia, the carbon monoxide production rate was 2–8 times higher and blood carboxyhaemoglobin concentration was 2–3 times higher than in normals (Coburn et al., 1966). As a result, baseline carboxyhaemoglobin levels can be as high as 4%. In subjects with haemoglobin Zürich, where affinity for carbon monoxide is 65 times that of normal haemoglobin, carboxyhaemoglobin levels range from 4% to 7%.

Increased carbon monoxide production rates have been reported after administration of phenobarbital, progesterone (Deliveria-Papadopoulos et al., 1970) and diphenylhydantoin (Coburn, 1970).

* In the process of natural degradation of haemoglobin to bile pigments, in concert with the microsomal reduced nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P-450 reductase, two haem oxygenase isoenzymes, HO-1 and HO-2, catalyse the oxidative breakdown of the *alpha*-methene bridge of the tetrapyrrol ring of haem, leading to the formation of biliverdin and carbon monoxide. The production of haem oxygenase isoenzyme HO-1 is increased by any kind of stress, including heat, light, sound, odors, infection, physical trauma and mental or psychological stress. Chronic stress in any of these pathways thus results in chronic destruction of haem and chronic low-level CO poisoning. Stress-induced HO-1 activity and the relatively constant activity of isozyme HO-2, that does not respond to stress, together account for about 75% of the human body's CO production.

Absorption

After reaching the lungs, inhaled carbon monoxide diffuses rapidly across the alveolar and capillary membranes. It also readily crosses the placental membranes. Carbon monoxide binds reversibly to one of the haem proteins. Approximately 80–90% of the absorbed carbon monoxide binds with haemoglobin, which causes a reduction in the oxygen-carrying capacity of the blood. The affinity of haemoglobin for carbon monoxide is 200–250 times that for oxygen, while the relative affinities of other haem proteins (e.g. myoglobin), cytochrome oxidase and cytochrome P-450 for carbon monoxide are much lower (U.S.EPA, 1991; ACGIH, 1991ab).

When in equilibrium with ambient air, the carboxyhaemoglobin (COHb) content of the blood will depend mainly on the concentrations of inspired carbon monoxide and oxygen. If equilibrium has not been achieved, the COHb concentration will also depend on the duration of exposure, pulmonary ventilation and the COHb originally present before inhalation of the contaminated air.

The absorption and elimination of carbon monoxide have been described in various mathematical models (U.S.EPA, 1991; WHO, 1979). The most important of these models is the Coburn-Foster-Kane exponential equation, which takes into account all known physiological variables affecting carbon monoxide uptake (Coburn et al., 1965). The most important variables determining the COHb level are: baseline COHb level, blood haemoglobin level, minute ventilation, diffusion capacity of the lungs, and mean oxygen tension in pulmonary capillaries. During an exposure to a fixed concentration of carbon monoxide, the COHb concentration increases rapidly at the onset of exposure, starts to level off

after 3 hours, and reaches a steady state after 6–8 hours (see Figure 4.1). At steady state, the carbon monoxide concentrations in alveolar breath and ambient air become practically equal (Peterson, 1970).
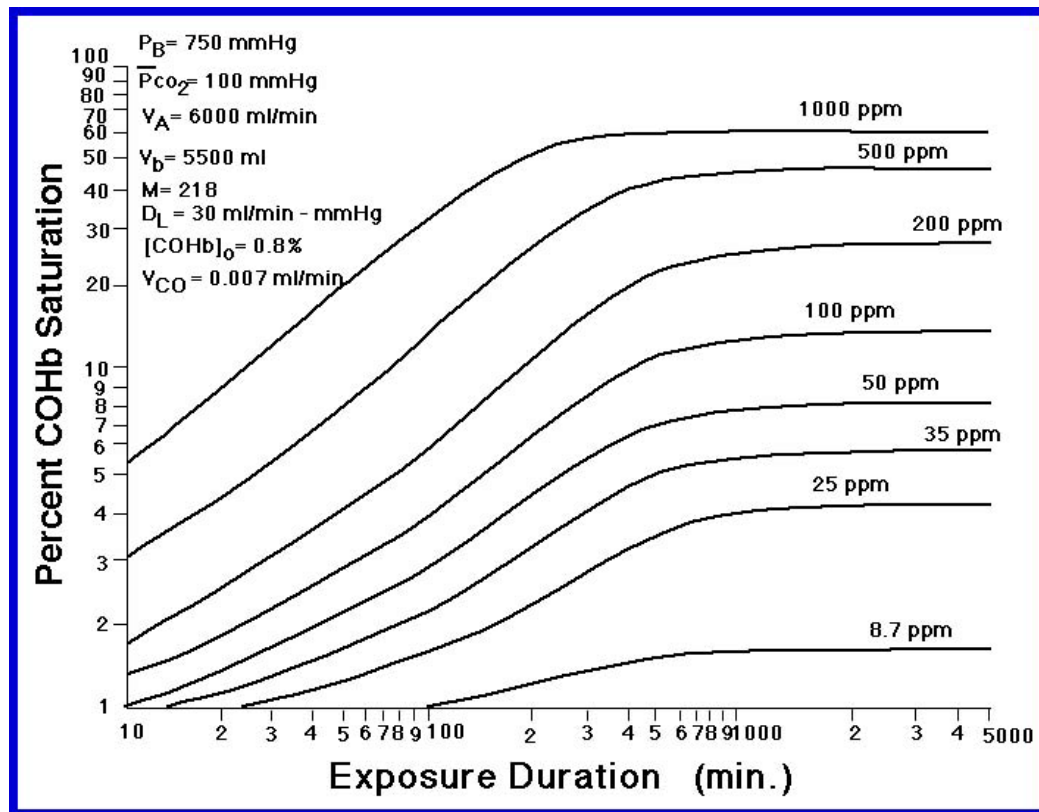
Figure 4.1: Log-log plot of carbon monoxide uptake by humans from
low ambient CO concentrations as computed from the Coburn-Forster-Kane equation.

Abbreviations: Pco2 = mean partial pressure of O2 in lung capillaries, VA = alveolar ventilation rate, Vb = blood volume, M = equilibrium constant, DL = diffusing capacity of lungs, [COHb]0 = value prior to CO exposure, Vco = rate of endogenous CO production. (From: Peterson and Stewart, 1975).

Using an adaptation of the Coburn equation the average 1 and 8 hr ambient concentration required to achieve a COHb level of 2.5% (the target COHb concentration served as a basis for the U.S. air quality standard for CO) for children with different baseline levels of COHb was calculated. As shown in Figure 4.2, as baseline COHb concentration increased, the amount of inhaled CO required to raise the blood level to 2.5% was decreased.
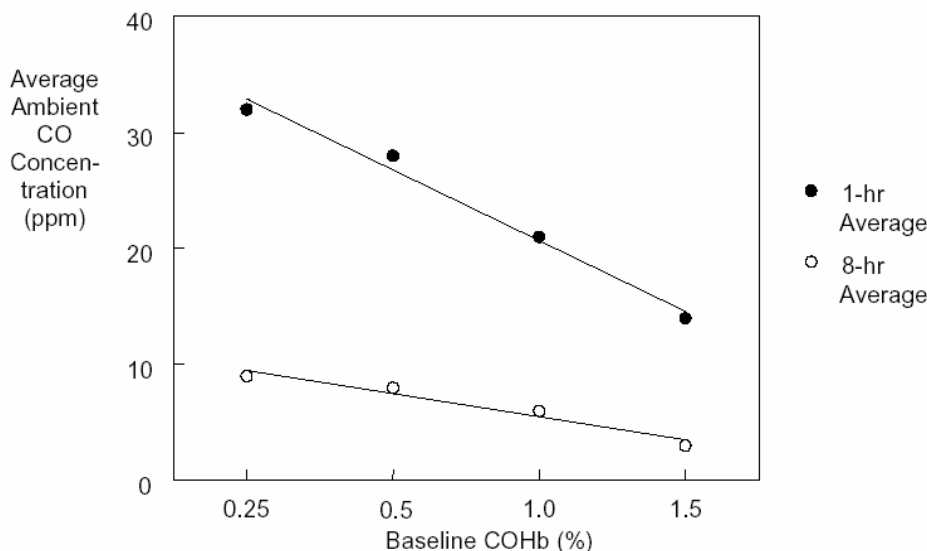
Figure 4.2: Increasing baseline COHb will reduce the time-weighted average
CO concentration required to reach 2.5% COHb after a given exposure. (from OEHHA, 2000)

Elimination

Carbon monoxide is eliminated unchanged via the lungs. The decline in COHb concentration depends on the rate of carbon monoxide release from haem proteins, alveolar ventilation, oxygen concentration in inhaled air, duration of carbon monoxide exposure, and the level of COHb saturation. The formation of COHb is a reversible process, but because of the tight binding of carbon monoxide to haemoglobin, the elimination half-life while breathing room air is 2–6.5 hours depending on the initial COHb level. The elimination half-life of COHb is much longer in the fetus than in the pregnant mother (U.S.EPA, 1991; ACGIH, 1991ab).

5. Health effects

Effects of short-term exposure

CO affects health by interfering with the systemic transport of oxygen to tissues (especially the heart and other muscles and brain tissue) (Costa and Amdur, 1996). The resulting impairment of O_2 delivery cause tissue hypoxia and interferes with cellular respiration. Direct intracellular uptake of CO could permit interactions with haemoproteins such as myoglobin, cytochrome oxidase and cytochrome P-450, and therefore interfere with electron transport processes and energy production at the cellular level (Brown and Piantidosi, 1992). Thus, in addition to observed physiological effects and cardiovascular effects, CO can modify electron transport in nerve cells resulting in behavioral, neurological and developmental toxicological consequences, and may itself play a role in neurotransmission.

The health effects associated with inhaled CO vary with its concentration and duration of exposure. Effects range from subtle cardiovascular and neurobehavioral effects at low concentrations to unconsciousness and death after prolonged exposures or after acute exposures to high concentrations of CO. First signs and symptoms on healthy individuals, such as decreases in work capacity and decrements of neurobehavioral functions start at [COHb] of 5% (WHO, 1999; U.S.EPA, 2000), whereas first signs of CO poisoning appear at [COHb] concentrations of 10% (see Table 5.1). However, the variability within the human population must be considered high. A [COHb] of about 15 % only leads to slight symptoms, such as headache, in healthy adults (Stewart et al., 1970; WHO, 1999). In contrast, the same [COHb] can cause long-lasting defects in the cognitive development and behavioral alterations in children (Klees et al., 1985), or even contribute to death from myocardial infarction in individuals with coronary artery disease (Grace and Platt, 1981; Balraj, 1984).

Table 5.1: Carboxyhaemoglobin levels resulting from steady-state exposure to increasing concentrations of CO in ambient air and associated symptoms in healthy adult humans and susceptible (adapted from U.S.EPA, 2001; Winter and Miller, 1976; Ellenhorn and Barceloux, 1988)

[CO] in atmosphere		[COHb]	Signs and symptoms	
ppm	mg/m^3	%	Healthy adults	Susceptible subpopulations
0	0	0.4 – 0.7	Physiologic background concentration	
10	11.5	2	Asymptomatic	
17	19.5	2.9		during physical exertion reduced time to onset of angina and electrocardiogram signs of myocardial ischaemia in sunjects with coronary artery disease
		5 - 6	Decreases in work capacity and decrements of neurobehavioral function	Increase in cardiac arrythmias in subjects with coronary artery disease
42	48	7		Headache, nausea in children
-	-	3 - 8	Background concentration in smokers	
70	80	10	No appreciable effect, except shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessels.	
		13		Cognitive development deficits in children
		15		Myocardial infarction in subjects with coronary artery disease
120	137	20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples	
		25		syncopes in children - stillbirths
220	252	30	Decided headache; irritable; easily fatigued; judgment disturbed; possible dizziness; dimness of vision	
350 - 520	401 – 595	40 – 50	Headache, confusion; collapse; fainting on exertion	
800 - 1220	916 - 1400	60 – 70	Unconsciousness; intermittent convulsion; respiratory failure, death if exposure is long continued	
1950	2230	80	Rapidly fatal	

At CO levels typically encountered in indoor and outdoor environments, health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO. Subpopulations at increased risk of adverse effects are :

1. Individuals with cardiovascular diseases: COHb levels of 2-6% may impair the delivery of oxygen to the myocardium causing hypoxia and increasing coronary blood flow demand by nearly 30%. When myocardial oxygen demands are increased, as in exercise, the hypoxic effects of CO may exceed the limited coronary reserve producing adverse health effects including earlier onset of myocardial ischaemia, reduced exercise tolerance in persons with stable angina pectoris, increased number and complexity of arrhythmias, and increased hospital admissions for congestive heart failure.
2. Fetuses are more susceptible to CO exposure for several reasons: CO crosses the placenta; fetal Hb has greater affinity for CO than maternal Hb; the half-life of COHb in fetal blood is three times longer than that of maternal blood, and the fetus has high rate of oxygen consumption and lower oxygen tension in the blood than adults. Also, maternal smoking during pregnancy exposes the fetus to greater than normal concentrations of CO leading to a decrease in birth weight.
3. Children develop acute neurotoxic effects (e.g. headaches, nausea), long-lasting neurotoxic effects (e.g. memory deficits) and impaired ability to escape (i.e. syncopes) at lower [COHb] than adults. Children have greater activity levels and smaller body masses than adults and should therefore experience higher levels of CO uptake than will adults for the same average exposure concentration.
4. Pregnant women have increased alveolar ventilation, increasing the rate of CO uptake from inspired air. Also, a pregnant woman produces nearly twice as much endogenous CO.

5. Individuals with chronic obstructive pulmonary disease such as chronic bronchitis, emphysema and chronic obstructive pulmonary disease are more susceptible to CO effects, since their lungs are less efficient at oxygenating the blood.

6. Individuals with reduced blood haemoglobin concentrations, or with abnormal haemoglobin, will have reduced O_2 carrying capacity in blood. In addition, disease processes that result in increased destruction of red blood cells (haemolysis) and accelerated breakdown of haemoproteins accelerate endogenous production of CO, resulting in higher COHb concentrations than in normal individuals. For example, patients with haemolytic anemia have COHb concentrations 2 to 3 times those seen in normal individuals.

7. Certain occupation groups are at risk from ambient CO exposure including those who work on city streets (street repairmen, street cleaners, street vendors, deliverymen, and garage attendants, taxi and bus drivers). Individuals who work in industrial processes including those exposed to other chemical substances (e.g. methylene chloride) that increase endogenous CO formation.

8. Individuals who have not adapted to high altitude and are exposed to a combination of high altitude and CO.

Cardiovascular effects

Numerous controlled human studies have been conducted in healthy subjects and in patients with ischaemic heart disease in order to characterize the effects of low-level carbon monoxide exposures on the cardiorespiratory responses to exercise. In these experiments, the subjects have typically been exposed to clean air and carbon monoxide in a chamber or through a face mask. After the exposure, which has usually been conducted at rest to achieve a predetermined COHb concentration in the blood, the subjects have engaged in an exercise test on a treadmill or cycle ergometer until exhaustion (healthy subjects) or the appearance of angina pectoris or electrocardiographic signs of cardiac ischaemia.

In apparently healthy subjects, the maximal exercise time and the maximal oxygen consumption have decreased at COHb levels as low as 5%. The regression between the percentage decrease in maximal oxygen consumption and the percentage increase in COHb concentration appears to be linear, with approximately a one percentage point fall in oxygen consumption per one point rise in COHb level above 4% (U.S.EPA, 1991; Bascom et al, 1996).

Patients with cardiovascular disease, especially ischaemic heart disease, are expected to be particularly sensitive to carbon monoxide. Atherosclerotic narrowing of the coronary arteries and impaired dilatation mechanisms restrict blood flow to the myocardium and prevent physiological compensation for lowered oxygen delivery caused by elevated levels of COHb. In exercise, these subjects experience myocardial ischaemia, which can impair myocardial contractility, affect cardiac rate and rhythm, and cause angina pectoris (U.S.EPA, 1991; Bascom et al, 1996).

The early studies of Aronow et al. (1972), Aronow & Isbell (1973) and Anderson et al. (1973) have suggested that low-level carbon monoxide exposures resulting in COHb levels of 2.5–3.0% shorten the time to onset of exercise-induced chest pain in patients with angina pectoris. Although the validity of the studies of Aronow and colleagues has been questioned by the US Environmental Protection Agency, subsequent studies by other investigators have actually given similar results (U.S.EPA, 1991; Bascom et al, 1996).

The design and results of the five most important clinical studies (Kleinman et al., 1989; Allred et al.,1989; Sheps et al., 1987; Anderson et al., 1973; Adams et al., 1988) conducted in patients with ischaemic heart disease are summarized in Table 5.2. Despite the obvious differences between these studies, they all show a significant shortening in the time to onset of angina at mean post-exposure COHb levels of 2.9–5.9% (post-exercise COHb levels in Table 5.2 are somewhat lower), which represent mean incremental increases of 1.5–4.4% COHb from the pre-exposure baseline levels (U.S.EPA, 1991).

The potential arrhythmogenic effects associated with low-level carbon monoxide exposures have not been fully resolved at COHb levels of $\leq 5\%$ (U.S.EPA, 1991; ACGIH, 1991b). Hinderliter et al. (1989) reported no effects at 3.5% and 4.9% COHb levels (post-exercise concentrations) on resting and exercise-induced arrhythmias in ten patients with coronary artery disease and no baseline ectopia. In contrast, Sheps et al. (1990) showed in 41 nonsmoking patients with documented coronary artery disease and various levels of baseline ectopia that the frequencies of both single and multiple ventricular depolarizations increased significantly at a mean post-exercise COHb level of 5.0% but not at 3.5%. Dahms et al. (1993) found no additional effect of either 3% or 5% COHb over the exercise-induced increases in single or multiple ectopic beats experienced by patients with myocardial ischaemia and baseline ectopia.

Table 5.2: A summary of results of the five most important double-blind clinical studies on the effects of low-level carbon monoxide exposures on patients with documented ischaemic heart disease and exercise-induced angina

Reference	Exposure		Exposure duration and activity	Subject characteristics	Effects of CO exposure (symptoms, ECG changes, etc.)
	CO (mg/m^3)[a]	COHb (%)[b]			
Anderson et al., 1973	0 57 115	1.3 2.9 4.5	4-hour exposure at rest, post-exposure exercise on a treadmill	10 males, mean age 49.9 years (5 smokers, 5 nonsmokers), repro-ducible angina	Time to onset of angina shortened at COHb 2.9% and 4.5% ($P < 0.005$) and duration of angina prolonged at COHb 4.5% ($P < 0.01$). Deeper ST-segment depressions with CO in 5 subjects.
Kleinman et al., 1989	0 115	1.4 2.8	1-hour exposure at rest, post-exposure incre-mental exercise on a cycle ergometer	24 males, mean age 58.8 years nonsmokers for at least 6 months), reproducible angina	Time to onset of angina shortened by 5.9% ($P = 0.046$), no significant effect on duration of angina, oxygen uptake at angina reduced by 2.2% ($P = 0.04$). Time to 0.1 mV ST-segment depression shortened by 19.1% ($P = 0.044$) in 8 subjects.
Allred et al., 1989	0 134 290	0.6 2.0 3.9	50- to 70-minute exposure at rest, pre- and post-exposure incremental exercise on a treadmill	63 males, mean age 62 years (nonsmokers), reproducible angina	Time to onset of angina shortened by 4.2% ($P = 0.054$) at COHb 2.0% and by 7.1% ($P = 0.004$) at COHb 3.9%. Time to threshold ischaemic ST-segment changes shortened by 5.1% ($P = 0.02$) at COHb 2.0% and by 12.1% ($P < 0.0001$) at COHb 3.9%. Significant dose relationships in the changes of both the onset of angina ($P = 0.02$) and the onset of ST-segment changes ($P < 0.0001$).
Sheps et al., 1987	0 115	1.5 3.6	1-hour exposure at rest, post-exposure incremental exercise on a cycle ergometer	25 males and 5 females, mean age 58.2 years (nonsmokers for at least 2 months), ischaemia in a screening test	No significant changes in time to onset of angina, duration of angina, maximal exercise time, maximal ST-segment depression, time to significant ST-segment depression, or maximal left ventricular ejection fraction. 3 subjects experienced angina only on CO exposure, actuarial analysis including these subjects showed shortening in time to onset of angina in the study group ($P < 0.05$).

[a]Carbon monoxide, 1 mg/m^3 = 0.873 ppm.
[b]Carboxyhaemoglobin concentrations are from venous blood samples taken immediately after exercise; in the study of Anderson et al. *(40)* samples were taken only immediately after carbon monoxide exposure.

According to some epidemiological and clinical data, carbon monoxide from recent smoking and environmental or occupational exposures may contribute to cardiovascular mortality and the early course of myocardial infarction (U.S.EPA, 1991). It is not known whether this contribution is due to arrhythmogenic effects or to some longer-term effects, as suggested by some authors. In patients with severe ischaemic heart disease, carbon monoxide poisonings have been lethal at COHb levels of 10–30%, while usual COHb levels in lethal poisonings are around 50–60% (U.S.EPA, 1991).

A number of recent epidemiological studies reported associations between levels of ambient air pollutants (CO, PM, O3, NOx, SO2) and hospital admissions for cardiovascular diseases (Atkinson et al., 1999; Burnett et al., 1997; Morris et al., 1995; Linn et al., 2000; Le Tertre et al., 2002; Mann et al., 2002; Yang et al., 2004). In all the studies cited a positive association was found between CO ambient concentrations and the daily number of cardiovascular disease hospitalizations. at the local level (Litovitz et al., 1992; Mathieu et al., 1996).

Often, individuals suffering from CO poisoning are unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression (Raub et al., 2000). This may result in a significant number of misdiagnoses by medical professionals (Grace and Platt, 1981; Fisher and Rubin, 1982; Barret et al., 1985; Dolan et al., 1987; Kirkpatrick, 1987; Heckerling et al., 1987, 1988, 1990). Although the precise number of individuals who suffer from CO poisoning is not known, it is certainly much larger than that indicated by mortality figures. Schaplowsky et al. (1974) estimated that more than 10 000 people per year in the United States required medical attention or missed at least 1 day of work in the early 1970s because of sublethal exposures to CO. A recent study (Hampson, 1998) estimated over 40 000 emergency department visits annually for recognized acute CO poisoning in the United States.

Developmental effects

The pregnant mother, the fetus *in utero* and the newborn infant are at high risk of adverse health effects from atmospheric carbon monoxide exposures. During pregnancy, the endogenous production of carbon monoxide can be elevated as much as 3-fold, the concentration of maternal haemoglobin is often reduced, and the mothers have physiological hyperventilation. As a result of these changes, maternal COHb levels are usually about 20% higher than the nonpregnant values. Carbon monoxide diffuses readily across the placental membranes, and the carbon-monoxide-binding affinity of fetal haemoglobin is higher than that of adult haemoglobin. Moreover, carbon monoxide is cleared much more slowly from fetal blood than from maternal blood. At steady state, fetal COHb levels are up to 10–15% higher than maternal COHb levels (U.S.EPA, 1991; Longo, 1977).

There are theoretical reasons and supporting laboratory animal data to suggest that the fetus and the developing organs are especially vulnerable to carbon monoxide. The developing brain seems to have the highest sensitivity of all organs. There is a well established and probably causal relationship between maternal smoking and low birth weight at fetal COHb levels of 2–10%. In addition, maternal smoking seems to be associated with a dose-dependent increase in perinatal deaths and with behavioural effects in infants and young children. Carbon monoxide is probably one of the most important etiological factors for these effects, although there are numerous other toxic pollutants in tobacco smoke (Longo, 1977).

A case-control study of the association between low birthweight infants and maternal CO exposures in approximately 1000 cases in Denver (Alderman et al., 1987) failed to detect a relationship between CO exposure (estimated form fixed-site outdoor monitoring data) during the last 3 months of pregnancy and lower birth weights. Mean CO levels ranged from 0.6 to 4.1 mg/m^3 (0.5 to 3.6 ppm) at 8 monitoring locations in metropolitan Denver. The 5th and 95th percentile concentrations at the site with the highest (4.1 mg/m^3) mean were 1.8 and 5.5 mg/m^3 (1.6 and 4.8 ppm), respectively. The odds ratio at the highest concentration site was 1.1 and the 95% confidence interval was 0.8-1.6. This study did not directly account for unmeasured sources of CO exposure, such as smoking, emissions from gas appliances and exposures to vehicular exhaust, which are limitations of the study design.

A more extensive study of a cohort of 125573 children born to women living in the Los Angeles area (1989-1993) found that exposure to ambient concentrations > 6.3 mg/m^3 (3 mo average) during the last trimester of pregnancy was associated with a significantly increased risk of low birthweight (odds ratio = 1.22; confidence interval =1.03-1.44) after adjustment for potential confounders (Ritz and Yu, 1999). Fetotoxicity has been demonstrated in laboratory animal studies. Altered brain neurochemical development and growth retardation have been demonstrated in rats exposed to CO in utero (Storm and Fechter, 1985; Leichter, 1993).

Neurological and neurobehavioural effects

Central nervous system (CNS) effects in individuals suffering acute CO poisoning cover a wide range, depending on severity of exposure: headache, dizziness, weakness, nausea, vomiting, disorientation, confusion, collapse, and coma. At low concentrations, CNS effects include reduction in visual perception, manual dexterity, learning, driving performance, and attention level. Earlier work is frequently cited to justify the statement that CO exposure sufficient to produce COHb levels of ca. 5% would be sufficient to produce visual sensitivity reduction and various neurobehavioral performance deficits. In a recent literature re-evaluation, however, the best estimate was that [COHb] would have to rise to 15–20% before a 10% reduction in any behavioral or visual measurement could be observed (Raub and Benignus, 2002). This conclusion was based on (1) critical review of the literature on behavioral and sensory effects, (2) review and interpretation of the physiological effects of COHb on the CNS, (3) extrapolation from the effects of hypoxic hypoxia to the effects of CO hypoxia, and (4) extrapolation from rat behavioral effects of CO to humans.

Summary of short-term exposure effect levels

NOAEL % COHb	LOAEL % COHb	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
1.1-1.3	2	aggravation of angina and other cardiovascular diseases	Subjects with angina pectoris, 1h	Aronow, 1981	OEHHA 1999 REL: 23
2.5		- acute ischaemic heart attacks (in documented or latent coronary artery disease) - untoward hypoxic effects in fetuses of nonsmoking pregnants	- Subjects with ischaemic heart disease - Fetuses		WHO 2000 100 (15m) 60 (30m) 30 (1h) 10 (8h)
	2.7	aggravation of angina pectoris, and other symptoms of myocardial ischaemia	Subjects with angina pectoris	Aronow and Isbell, 1973; Aronow et al., 1972; Anderson et al., 1973	U.S.EPA 1994 10.3 (8h) 35 (1h)
	2.9 [a] 2 [b]	cardiorespiratory effects in individuals with ischaemic heart disease.	Subjects with ischaemic heart disease performing	Kleinman et al., 1998; Allred et al.,1989; Sheps et al., 1987;	Health Canada 2003 MDL(1h/8h)=15/6

			light work	Kleinman et al., 1989; Adams et al., 1988	MAL(1h/8h)=35/15 MTC(8h)=20

Health Canada - Recommended National Ambient Air Quality Objectives - MDL(1h/8h): Maximum desirable level (1and 8 hour time weighted average); MAL: Maximum acceptable level; MTC: Maximum tolerable level
[a] as measured by CO-Oximeter - [b] as measured by gas chromatography

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Because angina is a severe effect, there is no level protective against mild adverse effects.

Derivation of Acute Reference Exposure Level (protective against severe adverse effects, for a 1-hour exposure)

Study	Aronow, 1981
Study population	humans
Exposure method	inhalation
Critical effects	aggravation of angina and other cardiovascular diseases
LOAEL	2% carboxyhaemoglobin in blood
NOAEL	1.1%-1.3% carboxyhaemoglobin in blood (corresponds to 20 ppm CO, calculated toxicokinetically)
Exposure duration	1 hour
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	20 ppm (23 mg/m³, 23,000 mg/m³)

WHO Guidelines (2001)

In controlled human studies involving patients with documented coronary artery disease, mean postexposure COHb levels of 2.9–5.9% (corresponding to postexercise COHb levels of 2.0–5.2%) have been associated with a significant shortening in the time to onset of angina, with increased electrocardiographic changes and with impaired left ventricular function during exercise (Anderson et al., 1973; Kleinman et al., 1989; Allred et al., 1989; Sheps et al., 1987; Adams et al., 1988). In addition, ventricular arrhythmias may be increased significantly at the higher range of mean postexercise COHb levels (Sheps et al., 1990; Stern et al., 1988). Epidemiological and clinical data indicate that carbon monoxide from recent smoking and environmental or occupational exposures may contribute to cardiovascular mortality and the early course of myocardial infarction (U.S.EPA, 1991). According to one study there has been a 35% excess risk of death from arteriosclerotic heart disease among smoking and nonsmoking tunnel officers, in whom the long-term mean COHb levels were generally less than 5% (Stern et al., 1988). Current data from epidemiological studies and experimental animal studies indicate that common environmental exposures to carbon monoxide do not have atherogenic effects on humans (U.S.EPA, 1991; Smith and Steichen, 1993).
During pregnancy, endogenous production of carbon monoxide is increased so that maternal COHb levels are usually about 20% higher than the non-pregnant values. At steady state, fetal COHb levels are up to 10–15% higher than maternal COHb levels U.S.EPA, 1991; Longo, 1977). There is a well established and probably causal relationship between maternal smoking and low birth weight at fetal COHb levels of 2–10%. In addition, maternal smoking seems to be associated with a dose-dependent increase in perinatal deaths and with behavioural effects in infants and young children (Longo, 1977).

In order to protect nonsmoking, middle-aged and elderly population groups with documented or latent coronary artery disease from acute ischaemic heart attacks, and to protect the fetuses of nonsmoking pregnant women from untoward hypoxic effects, a COHb level of 2.5% should not be exceeded. The following guidelines are based on the Coburn-Foster-Kane exponential equation, which takes into account all the known physiological variables affecting carbon monoxide uptake (Coburn et al., 1965). The following guideline values (ppm values rounded) and periods of time-weighted average exposures have been determined in such a way that the COHb level of 2.5% is not exceeded, even when a normal subject engages in light or moderate exercise:

100 mg/m^3 (90 ppm) for 15 minutes
60 mg/m^3 (50 ppm) for 30 minutes
30 mg/m^3 (25 ppm) for 1 hour
10 mg/m^3 (10 ppm) for 8 hours.

U.S.EPA (1994)

The National Ambient Air Quality Standards (NAAQS) for CO were promulgated by the Environmental Protection Agency (EPA) in 1971 at levels of 9 ppm (10 mg/m3) for an 8 h average and 35 ppm (40 mg/m3) for a 1 h average, not to be exceeded more than once per year. (Primary and secondary standards were established at identical levels). The 1970 CO criteria document (National Air Pollution Control Administration, 1970) cited as the standard's scientific basis a study which indicated that subjects exposed to low levels of CO, resulting in COHb concentrations of 2 to 3% of saturation exhibited neurobehavioral effects (Beard and Wertheim, 1967). A revised CO criteria document (U.S. Environmental Protection Agency, 1979) concluded that it was unlikely that significant, and repeatable, neurobehavioral effects occurred at COHb concentrations below 5%. However, reports that aggravation of angina pectoris, and other symptoms of myocardial ischaemia, occurred in men with chronic cardiovascular disease, exposed to low levels of CO resulting in COHb concentrations of about 2.7% (Aronow and Isbell, 1973; Aronow et al., 1972; Anderson et al., 1973), lead EPA to retain the 8 h 9 ppm primary standard level and to reduce the 1 h primary standard from 35 to 25 ppm. (EPA also revoked the secondary CO standards because no adverse welfare effects had been reported at nearambient levels). Later, concerns regarding the validity of data on which the proposed reduction in the 1 h standard was based caused EPA to decide to retain the 1 h 35 ppm standard.

Health Canada (2003)

The choice of National Ambient Air Quality Objectives for carbon monoxide is based upon the clinical significance of health effects of concern, the number of people requiring protection, and the relationship between COHb levels, exposure, and ambient carbon monoxide levels.

COHb levels are a biomarker for the toxicity of ambient-level exposures to carbon monoxide and are used as an indicator of carbon monoxide exposure. Although more research is needed to evaluate the predictive capabilities of the CFK model in individuals exposed to low concentrations of carbon monoxide and its applicability to sensitive subpopulation (U.S. EPA, 1991), it is the best model available at present, and it will be used here to estimate appropriate National Ambient Air Quality Objectives for carbon monoxide. However, it must be remembered that models provide estimates based upon small numbers of representative measurements.

Table 5.3: Recommended National Ambient Air Quality Objectives, ppm (mg/m^3) [a]

Averaging Times	Maximum Desirable Level	Maximum Acceptable Level	Maximum Tolerable Level
1 hour	13 (15)	30 (35)	n/a
8 hoursb	5 (b)	13 (15)	17.4 (20)

a 1 ppm = 1.146 mg CO/m^3
b rolling average

The maximum desirable levels are based on the carbon monoxide concentration that will result in a carboxyhaemoglobin (COHb) blood level of less than 1%, or the upper end of the range of baseline COHb levels resulting from endogenous production. Based on the Coburn-Foster-Kane (CFK) equation, a 1-hour exposure of 13 ppm or an 8-hour exposure of 5 ppm would lead to less than 1 % COHB.

The recommended maximum acceptable levels for carbon monoxide are 30 ppm averaged over 1-hour and 13 ppm as an 8-hour rolling average. Results from five recent studies in 3 laboratories were consistent in finding adverse effects of COHb levels ranging from 2.9% to 6% (as measured by CO-Oximeter) or as low as 2% (as measured by gas chromatography) on exercise induced angina and on ECG (electrocardiogram) values. CO levels averaging 13 ppm over 8 hours or 30 ppm over 1 hour resulted in COHb levels at or below 2% for adults performing light work (ventilation rate of 18L/m).

Therefore, the maximum acceptable levels are based on the maintenance of COHb levels of less than 2%, thereby providing a small margin of safety. At levels above these concentrations, action would be required to decrease the probability or severity of effects in sensitive populations. Estimating COHb levels using pNEM indicates that less than 1% of the Toronto study area population will experience COHb levels greater than 2.0% if the ambient air quality is less than or equal to 13 ppm (15 mg/m3) measured over 8 hours.

The recommended maximum tolerable level for an 8 hour exposure could be based on the lowest observed adverse effect level (LOAEL) of 2.9% COHb observed in the same experiments cited previously. This level would be approximately 21 ppm. However, the current tolerable level of 17 ppm is sufficiently close to this value to be retained as the objective.

The recommended maximum tolerable level of 17 ppm averaged over 8 hours will result in a COHb level of about 2.5% as projected by the CFK model. This is still below the COHb levels believed to result in cardiorespiratory effects in the general population. Moreover, it is considered to be slightly more protective in accounting for non-standard conditions and people at the high end of the distribution curve for parameters used in the CFK equation. However, owing to a diminishing margin of safety within the tolerable range, action is recommended without delay when air quality exceeds the highest concentration of this range to protect the health of sensitive subgroups.

The averaging times chosen for the maximum desirable, acceptable, and tolerable ranges of carbon monoxide in ambient air are 1 and 8 hours. The latter averaging time approximates the length of time during which people may be exposed to carbon monoxide continuously in a particular location (e.g., work, sleep). More importantly, most individuals approach equilibrium levels of COHb in the blood after about 8–12 hours of exposure to (Anderson et al., 1973). Owing to the possibility of missing some events (high levels of carbon monoxide exposure) using a continuous averaging time, rolling averages are recommended for the calculation of the 8-hour averages. The 1-hour averaging period is intended to be protective for effects that might occur following short exposures to high concentrations of carbon monoxide.

Effects of long-term exposure

There is not enough reliable information on effects of chronic exposures to low concentrations from either controlled human studies, ambient population-exposure studies, or from occupational studies. For example, current models cannot confidently predict whether reduction in pollution will decrease monthly rates of hospital admissions or mortality, even if they imply a reduction of admissions on days with low pollution. This public-health-related issue cannot be addressed by daily time series analysis, using only admission or mortality counts. In future studies, investigators also could consider time-averaged health effects over, say, 1 or 3 months, in relation to pollution exposure metrics for the corresponding periods (Raub and Benignus, 2002).

Chronic exposures to low CO concentrations may not pose as much a problem as high, acute exposure due to physiological compensation, tolerance, or adaptation. Smokers show an adaptive response to elevated COHb levels, as evidenced by increased red blood cell volumes (through increased haemopoiesis) or reduced plasma volumes (Raub and Benignus, 2002). The major source of total exposure to CO for smokers comes from active tobacco smoking. Baseline COHb concentrations in smokers average 4% (compared to <2% for non-smokers), with a usual range of 3–8%for one to two pack-per-day smokers, reflecting absorption of CO from inhaled smoke. COHb levels as high as 15% have been reported for chain smokers.

The only experimental evidence for short- or long-term compensation to increased COHb levels in the blood from exogenous sources other than smoking is indirect (Raub and Benignus, 2002). Experimental animal data indicate that incremental increases in COHb produce physiological responses that tend to offset the deleterious effects of CO exposure on oxygen delivery to the tissues.

Experimental human data indicate that compensatory cardiovascular responses to submaximal upper and lowerbody exercise (e.g. increased heart rate, cardiac contractility, cardiac output) occur after CO exposures. These changes were highly significant for exposures attaining 20% COHb. Other compensatory responses are increased coronary blood flow, cerebral blood flow, Hb, and oxygen consumption in muscle.

Cardiovascular effects
Kristensen (1989) examined the relationship between cardiovascular diseases and chronic occupational exposures, and concluded that CO exposure increases the acute risk of cardiovascular disease, at least transiently. Stern et al. (1988) investigated the effects of occupational carbon monoxide exposures on deaths from arteriosclerotic heart disease among 5529 New York City bridge and tunnel officers in the period 1952–1981. Among the more exposed tunnel officers there was a 35% excess risk compared with the New York City population, whereas among the less exposed bridge officers the risk was not elevated. The elevated risk among the tunnel officers declined significantly within five years after cessation of the occupational exposure, and there has also been a significant decline since 1970, when the introduction of new ventilation systems lowered the carbon monoxide levels in tunnels and tunnel booths. The 24-hour average carbon monoxide concentrations inside the tunnels were around 57 mg/m^3 (50 ppm) in 1961 and 46 mg/m^3 (40 ppm) in 1968. During rush hour traffic in 1968, carbon monoxide concentrations in tunnel toll booths were as high as 74–189 mg/m^3 (65–165 ppm) and in 1970 the mean concentration over 38 days was 72 mg/m^3 (63 ppm). However, the mean

COHb levels measured among smoking and nonsmoking tunnel officers in 1970 and 1981 were generally lower than 5 %.

Hansen (1989) reported the results of a 10-year follow-up study on mortality among 583 Danish male automobile mechanics between 15 and 74 years of age. The number of deaths expected for the automobile mechanics was compared with those for a similar group of Danish men employed as carpenters, electricians and other skilled workers free from occupational exposure to automobile exhaust, petrochemical products, asbestos and paint pigments. The number of deaths observed among the automobile mechanics exceeded the expected number by 21%. Although the increased mortality was not confined to any single cause of death, the author reported a remarkable excess of deaths attributed to ischaemic heart disease where the standardized mortality ratio was 121 and the 95% confidence interval was 102–145. The only other significant category of death was that due to external causes (SMR = 131; 95% CI = 113–153). No significant differences were found among the automobile mechanics for other diseases except for an increase in pancreatic cancer (SMR = 219; 95% CI = 128–351). Exposure to carbon monoxide and polycyclic aromatic hydrocarbons through the inhalation of automobile exhaust and the handling of solvents and oils may have accounted for the difference in ischaemic heart disease deaths between the automobile mechanics and the comparison group; however, other occupational exposures or other lifestyle factors, as indicated above, may also have contributed to the findings.

The haemodynamic responses to CO have been reviewed by Penney (1988). Chronic CO exposures, at levels sufficient to raise COHb concentrations to greater than 10% can produce increased numbers of red blood cells (polycythemia), increased blood volume, and increased heart size (cardiomegaly). In addition, heart rate, stroke volume, and systolic blood pressure may be increased. Some of these effects have been seen in smokers. Penney and Howley (1991) report that CO can enhance atherosclerosis in individuals with elevated serum cholesterol.

Current data from epidemiological studies and laboratory animal studies do not suggest that common environmental exposures to carbon monoxide have atherogenic effects on humans (U.S.EPA, 1991; Smith and Steichen, 1993).

Effects on pregnancy outcomes
A case-control study of the association between low birthweight infants and maternal CO exposures in approximately 1000 cases in Denver (Alderman et al., 1987) failed to detect a relationship between CO exposure (estimated form fixed-site outdoor monitoring data) during the last 3 months of pregnancy and lower birth weights. Mean CO levels ranged from 0.5 to 3.6 ppm at 8 monitoring locations in metropolitan Denver. The 5th and 95th percentile concentrations at the site with the highest (3.6 ppm) mean were 1.6 and 4.8 ppm, respectively. The odds ratio at the highest concentration site was 1.1 and the 95% confidence interval was 0.8-1.6). This study did not directly account for unmeasured sources of CO exposure, such as smoking, emissions from gas appliances and exposures to vehicular exhaust, which are limitations of the study design. A more extensive study of a cohort of 125,573 children born to women living in the Los Angeles area (1989-1993) found that exposure to ambient concentrations > 5.5 ppm (3 mo average) during the last trimester of pregnancy was associated with a significantly increased risk of low birthweight (odds ratio = 1.22; confidence interval =1.03-1.44) after adjustment for potential confounders (Ritz and Yu, 1999). Fetotoxicity has been demonstrated in laboratory animal studies. Altered brain neurochemical development and growth retardation have been demonstrated in rats exposed to CO in utero (Storm and Fechter, 1985; Leichter, 1993).

Effects on lung function
Individuals exposed to relatively high concentrations of CO in both indoor and outdoor environments may have lung function decreases. In most cases, however, causality is difficult to establish because, in addition to CO, these individuals were also exposed to high concentrations of other combustion products, many of which are respiratory system irritants.

In the study of tunnel and bridge officers, described earlier, lung functions, forced vital capacity (FVC) and forced expiration volume in 1 s (FEV1.0), were slightly reduced in tunnel vs. bridge officers (Evans et al., 1988). Exposures of adults to typical ambient concentrations of CO, both outdoors and indoors, have not been significantly associated with lung function decrements (Lebowitz et al., 1987).

Pollutants related to automotive traffic, especially CO and nitrogen oxides, were associated with the prevalence of asthma in middleschool Taiwanese students (Guo et al., 1999; Lin et al., 1999). Physician consultations in London for lower respiratory diseases were significantly correlated with NO2 and CO levels in children, but not in adults (Hajat et al., 1999). Exposure of children with mild asthma to environmental tobacco smoke resulted in pulmonary function decrements, i.e. reduced FEV1.0 (Magnusen et al., 1993).

Carcinogenic and genotoxic effects

No studies documenting carcinogenic or genotoxic effects of CO in humans were located in the available literature.

No studies documenting carcinogenic or genotoxic effects of CO in humans were located in the available literature.

Summary of Carbon Monoxide Dose Response Assessment

Exposure other than inhalation: Endogenous production of CO due to the catabolism of haemoproteins and membrane lipids results in 0.4-0.7% COHb (healthy subjects), increased to 0.7-2.5% during pregnancy. Increased endogenous production of CO are associated with a series of haematological diseases (e.g.haemolytica anemia) and to the endogenous oxidation of specific pollutants (e.g. halomethanes).

Toxicokinetics: ~80-90% of absorbed dose binds with haemoglobin (COHb; causing a reduction in the oxygen-carrying capacity of the blood). CO affinity for haemoglobin 200-250 times that for O_2. CO is eliminated unchanged via the lungs, with $t_{1/2}$ (COHb) of 2-6.5 hours (while breathing clean air), depending on the initial COHb level. $t_{1/2}$ (COHb) much higher in the fetus than in the pregnant mother.

Health effect levels of short- and long-term exposure

NOAEL % COHb	LOAEL % COHb	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
		SHORT-TERM EXPOSURE			
1.1-1.3	2	aggravation of angina and other cardiovascular diseases	Subjects with angina pectoris, 1h	Aronow, 1981	OEHHA 1999 REL: 23
2.5		- acute ischaemic heart attacks (in documented or latent coronary artery disease) - untoward hypoxic effects in fetuses of nonsmoking pregnants	- Subjects with ischaemic heart disease - Fetuses		WHO 2000 100 (15m-GV) 60 (30m-GV) 30 (1h-GV) 10 (8h-GV)
	2.7	aggravation of angina pectoris, and other symptoms of myocardial ischaemia	Subjects with angina pectoris	Aronow and Isbell, 1973; Aronow et al., 1972; Anderson et al., 1973	U.S.EPA 1994 10.3 (8h) 35 (1h)
	2.9	cardiorespiratory effects in individuals with ischaemic heart disease.	Subjects with ischaemic heart disease	Kleinman et al., 1998; Allred et al.,1989; Sheps et al., 1987; Kleinman et al., 1989; Adams et al., 1988	Health Canada 2003 MDL(1h/8h)=15/6 MAL(1h/8h)=35/15 MTC(8h)=20
		LONG-TERM EXPOSURE (not found in available literature)			

Carcinogenicity: No evidence

Genotoxicity: No evidence

Odour threshold: practically odorless

Susceptible population: Human characteristics increasing risk:
- Individuals with Ischaemic heart disease or coronary artery disease
- Individuals having reduced blood haemoglobin concentrations (e.g.haemolytic anemia) or with abnormal haemoglobin
- Individuals with chronic bronchitis, emphysema and chronic obstructive pulmonary disease (COPD), children with other lung inflammatory problems (e.g.cystic fibrosis)
- Pregnants and fetuses
- Children: physiologically, children have larger metabolic demands and consequently greater oxygen uptake demands than do adults, on a per unit mass basis.

6. Risk Characterization

Health hazard evaluation

Carbon monoxide (CO) is a tasteless, non-irritating, odorless and colorless toxic gas which can cause acute and lethal poisonings with very few and late occurring warning signs. Until very severe symptoms occur (inability to walk) none or only nonspecific symptoms are noted in healthy humans. As a consequence, a large number of deaths occur annually in fires, workplaces and in indoor environments. In the latter instance, poisonings occur because of the incorrect use of combustion devices or due to faulty unvented gas appliances. The associated risk, the evaluation of its impact on the European population as well as the related risk management strategies will be outlined in the following chapter (Risk Management).

The present risk characterization adresses CO exposures experienced by people during their normal daily activities, while changing from one microenvironment to another, the significance of related health effects, as a function of individual susceptibility, and the relationship between carboxyhaemoglobin levels (COHb; the biomarker for CO-exposure and -toxicity), exposure, and indoor carbon monoxide levels.

Currently available evidence suggests that individuals with heart disease (including stable exercise-induced angina, coronary artery disease, and ischaemic heart disease) represent the population at greatest risk from exposure to indoor carbon monoxide levels. In addition, population groups with either increased probability or increased severity of health effects include fetuses, pregnant women, and young infants, individuals with anemia or respiratory disease, the elderly, children, and persons with peripheral vascular disease and chronic obstructive lung disease.

Results from five clinical studies in 3 laboratories were consistent in finding adverse effects of COHb levels as low as 2.9% (as measured by CO-Oximeter) on exercise induced angina and on electrocardiogram values.
Providing a small margin of safety, a COHb level of 2 % will be here considered as the starting point of the present risk characterization, and CO exposures considered acceptable based on the maintenance of COHb levels of less than 2%. These levels are considered protective for the subpopulation sensitive to cardiovascular effects and are expected to provide an adequate margin of safety for the other susceptible subpopulations described above and for the general population with respect to short- and long-term toxicity effects. Additionally, CO exposures are here considered desirable when they result in COHb levels of less than 1%, representing the upper end of the range of baseline COHb levels resulting from endogenous production in normal, non-smoking individuals. This level was chosen taking into consideration uncertainties in the available data and using the most conservative assumptions.

The CO concentrations in inhaled air associated with these threshold COHb levels (see Table 6.1) were estimated using the Coburn-Foster-Kane (CFK) model, considering adults performing light work at a ventilation rate of 18L/min. The CFK model still presents the best model available, although more research is needed to evaluate the predictive capabilities in individuals exposed to low CO concentrations and its applicability to sensitive subpopulation. The averaging times chosen for deriving the CO air concentrations are 1 and 8 hours, the latter approximating the length of time required by most individuals to approach equilibrium levels of COHb in the blood (about 8–12 hours of exposure), or the time during which people may be continuously exposed to carbon monoxide in a particular location. The 1-hour averaging period is intended to evidence short-term exposures related to personal activities generating increased CO levels.

Table 6.1: Carbon monoxide average concentrations in inhaled air derived (CFK-model) from
selected [COHb], considering 1-h and 8-h exposure duration

COHb levels considered	[COHb] %	[CO] in air mg/m^3	
		1 h–avg.	8h–avg.
acceptable	≤ 2	≤ 35	≤ 15
desirable	≤ 1	≤ 15	≤ 6

Percentage of population exposed beyond given threshold CO levels

Table 6.1

Description (Study, Year)	N	acceptable	desirable
Available exposure studies		**1-h averaging period**	
Description (Study, Year)	**N**	**35 mg/m^3**	**15 mg/m^3**
1-h personal exposure (indoors)			
Athens (Expolis, 96-98)	44	10 %	30 %
Basel (Expolis, 96-98)	50	<	< 10 %
Helsinki (Expolis, 96-98)	195	<	5 %
Milan (Expolis, 96-98)	45	<	< 10 %
Oxford (Expolis, 98-00)	26	<	5 %
Prague (Expolis, 96-98)	23	<	10 %
		8-h averaging period	
		15 mg/m^3	**6 mg/m^3**
48-h personal through the day exposure			
Athens (Expolis, 96-98)	44	<	<
Basel (Expolis, 96-98)	50	<	<
Helsinki (Expolis, 96-98)	195	<	<
Milan (Expolis, 96-98)	45	<	<
Prague (Expolis, 96-98)	26	<	<
2-week residential exposure (kitchen and bedroom)			
England (BRE, 97-99)	830	<	<

< out of the evaluation range (i.e. <5% of the environments investigated)

The studies

Expolis study: Within the multi-centre European EXPOLIS study, personal exposure to CO, measured every minute for 48 h, of 401 randomly selected study participants (25–55 yr old; living and working within the metropolitan areas; mainly non-smokers) was monitored in Athens, Basel, Helsinki, Milan and Prague. 1-h average personal exposures were computed in order to assess the influence of specifc sources. Each participant also completed a time-microenvironment-activity diary and an extended questionnaire. In addition, for the same time period, ambient levels of CO from fixed site stations were collected. All measurements were performed between October 1996 and June 1998.
In Georgoulis et al. (2002) both the 48-h and 15-min averaged personal exposures were calculated and compared, the latter corresponding to specific 15-min time periods when different activities (i.e. ''under smoke (ETS) exposure'', ''during use of gas appliances'') were taking place.
Selection bias (Oglesby et al., 2000): In Basel, participants of direct monitoring as compared to non-participants were more likely to live at streets with low traffic volume; although in Helsinki, traffic volume was neither significantly related to participation in direct nor indirect monitoring, the point estimates indicate a tendency to decreased participation with increasing traffic intensity at home.)

BRE, UK: The Building Research Establishment (BRE) has conducted a national survey of air pollutants in 876 homes in England, to increase knowledge of pollutant levels and the factors associated with high concentrations. CO levels were measured, once in each home, using Dräger colorimetric diffusion tubes (passive samplers), as two-week time-weighted averages in the kitchen and main bedroom of each home. All measurements were performed between October 1997 to February 1999.

Comments

Available measurements from the Expolis study are twofold:
- the 48-h data are 'through-the-day' personal average exposures experienced by the working population in European metropolitan areas and, hence, include the contribution of outdoor exposure (commuting). A typical pattern of CO levels as measured (1-min resolution) during a 48-h monitoring cycle is shown in Figure 6.1. As examplified by the Figure, short-term exposures to higher CO levels only marginally affect a 48-h average outcome. The 48-h data are used in the present risk characterization assuming that even 8-h extrapolations from the overall dataset would not be affected by short-term peak exposures. As outlined in the study conclusions (Georgoulis et al., 2002), the 48-h personal CO exposures were highly and consistently associated with urban ambient air concentrations, consistently but less signifcantly associated with exposure to ETS and inconsistently and mostly insignifcantly associated with exposure to the use of gas appliances. Time spent in commuting had an insignifcant effect on the 48-h average CO exposure.

- the 1-h average personal exposure measurements were exclusively taken indoors. As concluded by the study members, the presence of smoking or gas cooking in residences signifcantly increased the short-term CO exposures; the difference with the 48-h averages were explained by the relatively short duration of many activities. The exposure data are here considered indicative for common indoor-activity related short-term exposures experienced by the general population living in (sub-)urban European areas.

Significant differences in both personal exposure and ambient levels (Georgoulis et al., 2002) were found within the five cities, ranging from high values in Milan and Athens to low in Helsinki.

It is noteworthy that, for CO, personal and not microenvironmental samples were drawn in the Expolis study, considering that people experience various CO exposures due to their daily activities and to unhomogeneous CO levels within indoor envornments, and that seasonal effects on CO levels were taken into account, supposed to be largely due to indoor sources.

The BRE study concluded (530 homes; 2-week averaged microenvironmental samples in kitchens and bedrooms) that CO levels were very low for most of the time in the majority of homes in England. Identified factors influencing long-term CO levels were: gas cooking, unflued heaters, smoking and outdoor air (in urban locations). Seasonal effects were largely associated to indoor sources and extract fans were found to have little effect on CO levels in the kitchen.
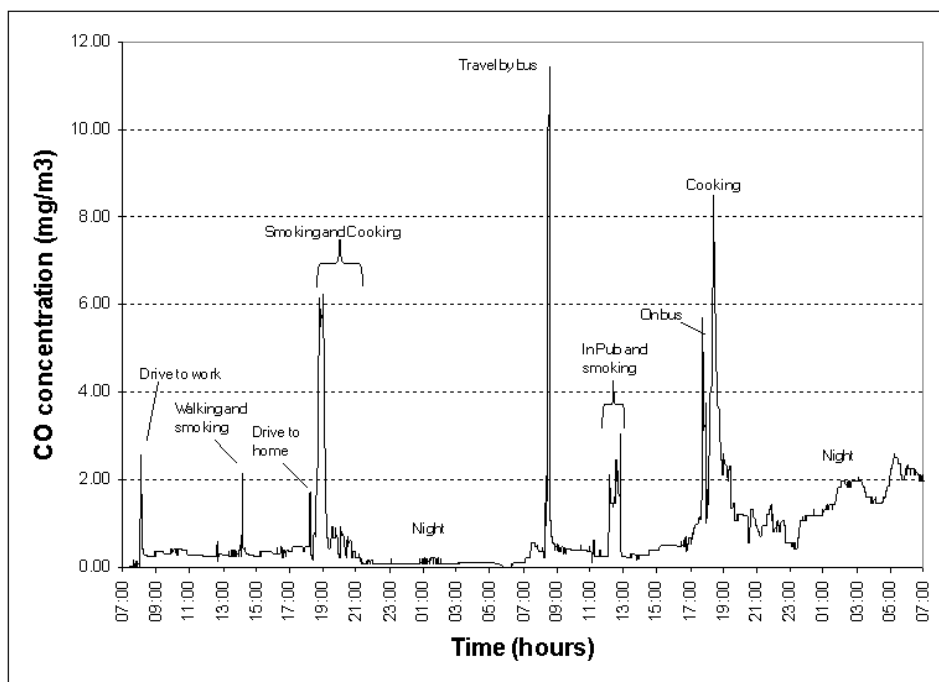
Figure 6.1: Typical result of a 48-h monitoring cycle (1-min resoltution) obtained during the Expolis study

Doubts could be expressed on whether the selected exposure data could be considered as descriptive of the nowadays situation, when considering the recent evolution of ambient CO levels. Current ambient air quality regulations, i.e. those contributing to the reduction of carbon dioxide emissions (the Kyoto Protocol), the EU Limit Value for CO in ambient air and equivalent national regulations in the EU, have shown to be effective with respect to a reduction of CO ambient levels, as examplified in Figure 6.2 for a german metropolitan area, the trend expected to continue in the years to come.
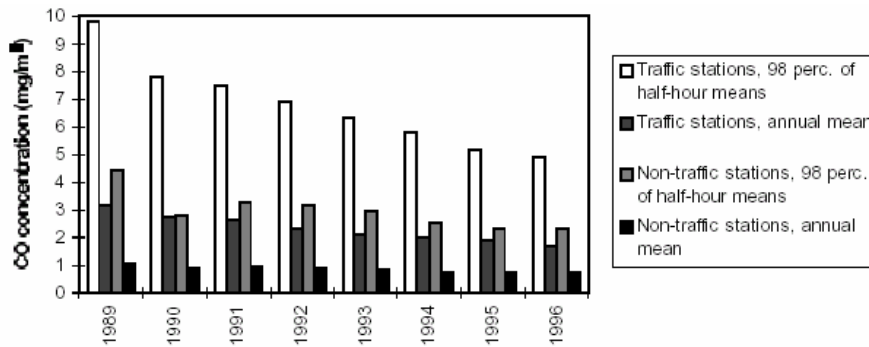
Figure 6.2: CO levels in urban areas - trend in the Ruhr-Rhine region

EU limit value for carbon monoxide in ambient air – Directive 2000/69/EC

Limit value for the protection of human health:
Averaging period: Maximum daily 8-hour mean
Limit value: 10 mg/m^3
Margin of tolerance: 6 mg/m^3 on 13 December, reducing on 1 January 2003 and every 12 months thereafter by 2 mg/m^3 to reach 0 % by 1 January 2005
Date by which limit value is to be met: 1 January 2005

The maximum daily 8-hour mean concentration will be selected by examining 8-hour running averages, calculated from hourly data and updated each hour. Each 8-hour average so calculated will be assigned to the day on which it ends. i.e. the first calculation period for any one day will be the period from 17:00 on the previous day to 01:00 on that day; the last calculation period for any one day will be the period from 16:00 to 24:00 on that day.

Result

Available exposure data confim that Carbon Monoxide (CO) sources in EU-residences are contributing to short-term rather than to long-term exposures. Personal exposure outcomes averaged over 1-hour were considered of moderate concern even for the most susceptible subpopulations. Nevertheless, uncertainties resulting from the predictive capabilities of the CFK-model in individuals exposed to low CO concentrations and its applicability to sensitive subpopulations, suggest that about 10% of the general non-smoking population experience CO levels which could be hazardous for individuals with heart diseases. Increased exposures could be expected for residences in the vicinity of busy city streets.

In addidion, there is no evidence that long-term CO exposures in EU residences contribute to carboxyhaemoglobin levels in blood higher than the baseline levels resulting from endogenous production in normal, non-smoking individuals.

On the other hand and in contrast with all other chemicals assessed in the present report, carbon monoxide causes a considerable number of deaths and acute poisonings in the general population (with complications and late sequelae). Also, individuals suffering from CO poisoning are often unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression. In indoor environments, these health risks are nearly completely associated with the incorrect use of combustion devices or faulty unvented gas appliances.

Nitrogen dioxide

Synonyms: -
CAS Registry Number: 10102-44-0
Molecular Formula: NO_2

1. Compound identification

Nitrogen dioxide is a reddish-brown gas in colour, and a strong oxidant with a characteristic pungent odour. It is soluble in water. A low vapour pressure of 900 mm Hg at 25 °C indicates nitrogen dioxide will exist as a gas in the ambient conditions. It is corrosive and highly oxidising gas. Typically less than 10% by volume of the total emissions of NOx from combustion sources is in the form of NO_2 (WHO 1997). NO is rapidly oxidised to NO_2 by available oxidants, particularly ozone, in ambient conditions. In indoor air, it is generally a much slower process. Photolysis of NO_2 by sunlight is the most important source of ozone (Alm 1999).

Nitrogen dioxide is also an important atmospheric gas, in addition to health effects, also because it absorbs visible solar radiation and, therefore contributes to atmospheric visibility, it could have a role in global climate change, it is with nitric oxide (NO), a main regulator of the oxidising capacity of the free troposphere and ozone (O_3) concentrations in the troposphere (WHO 2000).

There is no clear evidence for a concentration-response relationship for NO_2. Asthmatics and persons with chronic obstructive pulmonary disease (COPD) are the most susceptible populations to acute changes in lung function, airway responsiveness and other respiratory symptoms. (WHO 2000).

2. Physical and Chemical properties

Molecular weight (g/mol)   46.01
Melting point (°C)   -11.2
Boiling point (°C)   21.2
Density (at 20 °C, 1 atm)   1.448
Relative density (air =1)   1.59
Solubility   Soluble in sulphuric and nitric acid

Conversion factors at 20 °C and 760 mm Hg:

1 ppb   = 1.912 µg/m³
1 µg/m³ = 0.523 ppb

Sources: Alm (1999), Verschueren 2001, HSDB (2003)

3. Indoor Air Exposure assessment

Emission sources

The most important indoor sources of NO_2 include gas appliances such as stoves, ovens, space and water heaters, and unflued kerosene heaters. Especially, gas stoves with pilot light have been found strong indoor sources of NO_2. Typically, NO_2 concentrations in homes with gas stoves are 2-5 times higher than in homes with electric stoves. Indoor concentrations of NO_2 are typically higher in winter than in summer, probably due to increased use of gas heating, lower ventilation rates, and higher outdoor concentrations (Alm 1999).

The main ambient sources of nitrogen oxides emissions include intrusion of stratospheric nitrogen oxides, bacterial and volcanic action, and lightning. Fossil fuel power stations, motor vehicles and domestic combustion appliances emit nitric oxide (NO), which is a reactive compound forming rapidly NO_2. Other contributions of nitrogen dioxide to the atmosphere come from specific non-combustion industrial processes, such as the manufacture of nitric acid, the use of explosives and welding. Ambient concentrations of NO_2 in urban areas peak during the morning and evening rush hours due to increased emissions of NO from motor vehicles (COMEAP 1997, WHO 1997, WHO 2000).

Indoor air and exposure concentrations

Indoor concentrations vary widely depending on the presence of special indoor sources of NO_2. Concentrations in homes without NO_2 sources are typically lower than outdoor concentrations and in those cases indoor levels are driven by outdoor sources. In the recently published ECRHS II study, carried out in 21 European cities annual ambient NO_2 concentrations ranged from 4.9 $\mu g/m^3$ in Reykjavik, Iceland to 72 $\mu g/m^3$ in Turin, Italy (Hazenkamph-von Arx et al 2004). The average winter/summer ratio showed considerably higher concentrations in winter than in summer, being 1.5. According to WHO (2000) annual mean ambient concentrations in urban areas throughout the world typically range from 20 to 90 $\mu g/m^3$. Typical indoor air concentrations in homes with gas cooking vary between 25 and 200 $\mu g/m^3$ over a period of several days. Maximum indoor 1-hour peaks may reach up to 2000 (COMEAP 1997, WHO 2000).

In Helsinki and Prague average indoor concentrations were lower than the respective outdoor concentrations that ranged from 24 to 61 $\mu g/m^3$ (Kousa et al 2001). Mean indoor concentrations in Europe ranged from 13 $\mu g/m^3$ in UK to 43 $\mu g/m^3$ in Prague according to the results by Kousa et al (2001) and COMEAP (1997). Average personal exposures were equal or slightly higher.

In an Italian population based study, the highest weekly indoor NO_2 concentrations were measured in a rural area of Po Delta (Simoni et al 2002). Weekly mean indoor concentration in kitchen in winter was higher than the respective concentration in summer, being 62 $\mu g/m^3$ and 38 $\mu g/m^3$. The presence of gas-furnace heating was identified as the determining factor for the elevated NO_2 concentrations.

In a Spanish study of 340 dwellings between 1996 and 1999 (Garcia-Algar et al 2003), average annual indoor concentrations of NO_2 did not vary significantly, ranging only from 12.5 to 14.7 $\mu g/m^3$. Respective outdoor air concentrations were slightly higher in 1996 and 1998 and slightly lower in 1997 and 1999, thus typical indoor-outdoor ratios were close to 1. The principal indoor sources of NO_2 in Spanish homes were the use of gas cooker, the absence of an extractor fan when cooking, the absence of central heating and cigarette smoking.

Levy et al (1998) studied NO_2 concentrations in homes in 18 cities in 15 countries reporting 2-day means ranging from 10 $\mu g/m^3$ to 81 $\mu g/m^3$ and personal exposures from 21 $\mu g/m^3$ to 97 $\mu g/m^3$. Use of a gas stove was found the dominant activity influencing indoor concentrations with an increase in indoor-outdoor ratios from 0.7 to 1.2 for participants using gas stoves. Results showed also the importance of combustion space heaters to elevated NO_2 concentrations. On the contrary, wood-burning appliances were not related to elevated NO_2 concentrations in a Canadian study carried out in 49 houses (Levesque et al 2001).

Brown et al (2002) studied emissions of unflued gas heaters in room chamber (32.4 m^3) tests. NO_2 concentrations in the chamber ranged from 180 $\mu g/m^3$ to 530 $\mu g/m^3$ due to emissions from the gas heaters. Lee and Wang (2004) studied nitrogen dioxide emissions from incense burning also in the chamber (18 m^3) tests. They found that maximum nitrogen dioxide concentrations peaked up to 91 $\mu g/m^3$ during incense burning.

Other studies showed indoor concentrations of NO_2 in homes without gas stoves ranging from 13 $\mu g/m^3$ to 40 $\mu g/m^3$ and with gas stoves from 25 $\mu g/m^3$ to 70 $\mu g/m^3$ in UK (COMEAP 1997). Determinants of NO_2 exposures were studied with preschool children in Finland. Preschool located in down town, gas stoves and parent smoking at home were found the most important factors of the increased NO_2 exposures for those children (Alm 1999).

Emission sources and microenvironments where high concentrations of NO_2 occur are reviewed in Table 3.1. Elevated concentrations were typically related to gas cooking, gas heating, and incense burning. High NO_2 concentrations were also found in some public buildings. The highest maximum values up to 7530 $\mu g/m^3$ were measured in indoor ice arenas (Pennanen et al 1997). Also in kitchens with gas appliances high concentrations, 3808 $\mu g/m^3$, were determined (Lebret et al 1987).

Residential indoor air concentrations of NO_2 in European urban populations are presented in Figure 3.1 and Figure 3.2. Respective exposure concentrations are presented in Figure 3.3.
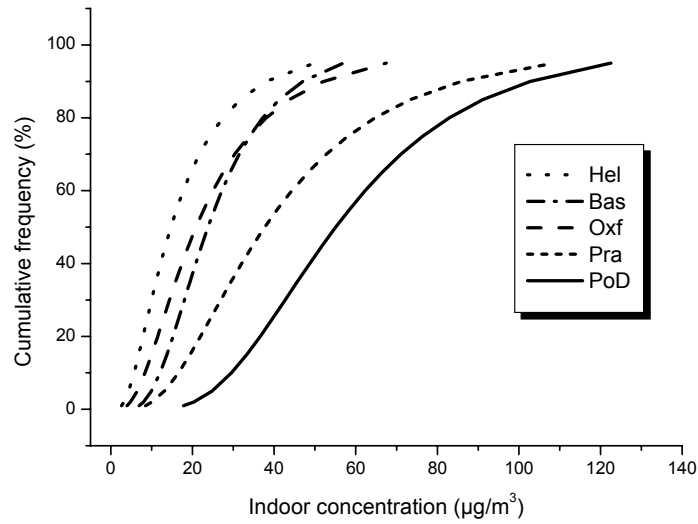
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of nitrogen dioxide in Helsinki (Hel, n= 175), Basel (Bas, n= 50), Prague (Pra, n= 33) (Kousa et al 2001), Oxford (Oxf, n=40) (Hanninen et al 2004, EXPOLIS 2002) and in Po Delta (PoD) (n = 112, AM = 62 µg/m^3, std = 32 µg/m^3) region in Northern Italy (Simoni et al 2002).
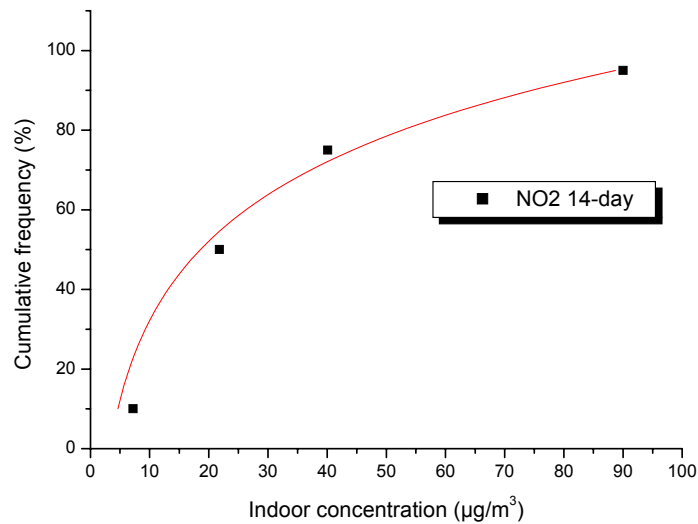
Figure 3.2. Cumulative frequency distribution of 14-day indoor air concentrations of nitrogen dioxide in the kitchens in England (GM= 21.8 µg/m^3, max 620 µg/m^3, n=845, Coward et al 2002).
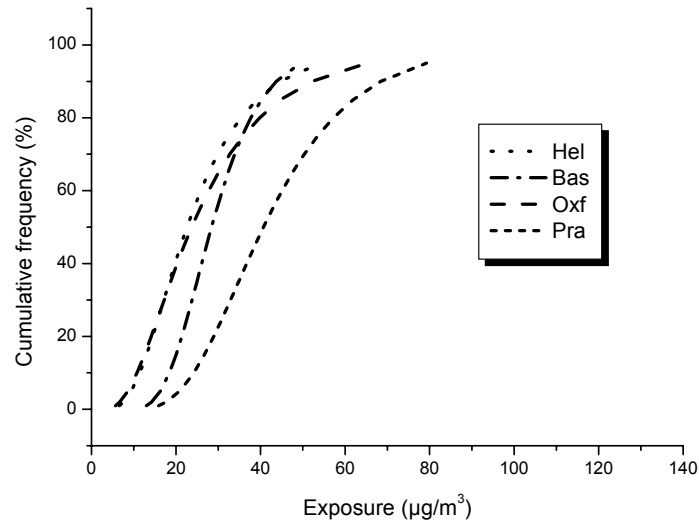
Figure 3.3. Cumulative frequency distributions 48-hour personal exposure concentrations of nitrogen dioxide in Helsinki (Hel, n= 177), Basel (Bas, n= 50), Prague (Pra, n= 35) (Kousa et al 2001) and Oxford (Oxf, n=42) (Hanninen et al 2004, EXPOLIS 2002).

Table 3.1. Short time NO_2 concentrations related to specific microenvironments or emission sources.

Environment/ emission source	Location	Averaging time		Concentration ($\mu g/m^3$)				Reference
				AM	GM	median	max	
Indoor ice arenas	Finland	max 15-min					320 - 7530	Pennanen et al 1997
		max 1-hour					270 - 7440	
Gas appliances	The Netherlands	max 1-min	kitchen				400 - 3808	Lebret et al 1987
		max 1-hour	kitchen				230 - 2055	
		max 24-hour	kitchen				53 - 478	
Gas stoves	The Netherlands		kitchen				2500	Noy et al 1990
Indoor ice arenas	Finland	1-week		2 - 1838				Pennanen et al 1998
		ice resurfacers	propane	396				
			gasoline	283				
			elecrtic	25				
Homes with gas appliances		several hours		200				WHO 2000
		1-hour					2000	
Gas cooking	UK	1-week	gas stove	28 - 107				Ross 1996
		max 1-hour					342 - 1585	
		1-week	electric stove	23 - 26				
		max 1-hour					38 - 55	
Unflued gas heaters	room chamber tests						180 - 530	Brown et al 2002
Homes	Sweden	24-hour	urban dwellings		6.7		11	Sakai et al 2004
	Japan	24-hour	urban dwellings		98		369	
Indoor ice ring	Hong Kong, China	15-min	gasoline-fueled	58 - 91				Guo et al 2004
		15-min	propane-fueled	242				
Homes	15 countries	2-day	indoor	10 - 81				Levy et al 1998
			exposure	21 - 97				
Incense burning	Chamber tests	during burning					17-91	Lee and Wang 2004
Exposure, schoolchildren	Sweden	24-hour	urban			13		Berglund et al 1994
			rural			7		

AM = arithmetic mean, GM = geometric mean, max = maximum value

4. Toxicokinetics

Absorption

Inhaled nitrogen dioxide (NO_2) reaches easily the lower respiratory tract (bronchioli and alveoli of the lungs) and dissolves in lung fluids, hydrating slowly to nitrous (HNO_2) or nitric acid (HNO_3). These acids dissociate into nitrite (NO_2^-) or nitrate (NO_3^-) ions, which are rapidly taken up in the lung epithelium (Goldstein ate al., 1977; Postlethwait and Bidani 1989). NO_2 acts as a strong oxidant and likely reacts with unsaturated lipids and functional proteins in cells either within the lung epithelial lining fluid or in the epithelial cell membrane. This may result in loss of cell permeability and control. Furthermore, the substance activates peroxide detoxification pathways (WHO97).

In Bauer et al. (1986) fifteen asthmatic subjects were exposed to 0.6 mg/m^3 NO_2 via mouthpiece for 20 minutes at rest, followed by 10 minutes of exercise. Expired NO_2 concentrations were measured continuously. NO_2 deposition was 72±2% at rest, increasing to 87±1% with moderate exercise. These findings indicate that the NO_2 dose to the distal airways and alveolar space, and therefore toxic effects in this region, would be substantially increased by exercise.

Mathematical modelling studies show that the deposition of nitrogen dioxide in the tissues of the lower respiratory tract is predicted to be maximal at about the junction of the conducting airways and the gas exchange region of the lungs in humans, rats, guinea pigs and rabbits. Although the actual tissue dose at a similar starting tracheal concentration differs across species, the shape of the deposition curves is roughly equivalent. The region predicted to receive the maximal dose is that where the typical nitrogen-dioxide-induced morphometric lesion is observed in several species of animals. Using this mathematical model, it also can be predicted that, as tidal volume increases in humans (e.g. in exercise), the dose to the tissue of the gas exchange region increases substantially more than the dose to the conducting airways (Miller et al., 1982; Overton, 1984; Overton et al., 1987).

Distribution

After passing the lungs, nitrogen dioxide products are distributed to all parts of the body via the bloodstream. Goldstein et al. (Goldstein ate al., 1977) exposed two female rhesus monkeys to radiolabelled nitrogen dioxide ($^{13}NO_2$) for 6 to 9 minutes through a facemask. The investigators found the radioactive tracer back in the circulation. They also reported that the time-concentration relationship of ^{13}N in arterial blood correlated well with the time-concentration relationship in the lungs. In addition, the investigators showed that the gas was distributed throughout the lungs.

Elimination

No human data have been found. Saul and Archer (1983) observed that nitrogen dioxide or its products (nitrite, nitrate) were excreted as nitrate in the urine of Sprague-Dawley rats. Also, they showed that the amount of urinary nitrate correlated linearly to nitrogen dioxide exposure levels. The urinary values returned to normal after four days.

5. Health effects

Nitrogen dioxide is thought to damage lungs in three ways: (1) it is converted to nitric and nitrous acids in the distal airways, which directly damages certain structural and functional lung cells; (2) it initiates free radical generation, which results in protein oxidation, lipid peroxidation, and cell membrane damage; and (3) it reduces resistance to infection by altering macrophage and immune function.

Effects of short-term exposure

Numerous controlled clinical studies have examined lung function, airway responsiveness to pharmacological, physical (e.g. cold air) or natural (i.e. allergens) bronchoconstrictors and the defence against viral and bacterial airway infections in human subjects exposed to nitrogen dioxide.

Generally, concentrations in excess of 1880 μg/m^3 (1 ppm) are necessary during acute controlled exposures to induce changes in pulmonary function in healthy adults (U.S.EPA, 1993; Berglund et al., 1993; Wagner, 1985). Because these concentrations rarely occur in indoor air, concern about the effects of nitrogen dioxide has been focused on people with

pre-existing lung disease. There have been numerous studies of people with asthma, chronic obstructive pulmonary disease, or chronic bronchitis showing that exposure to low levels of nitrogen dioxide can cause small decrements in forced vital capacity and forced expiratory volume in 1 second (FEV_1) or increases in airway resistance.

The lowest level of nitrogen dioxide exposure reported in more than one laboratory to show a direct effect on pulmonary function in asthmatics was a 30-minute exposure, with intermittent exercise, to 560 $\mu g/m^3$ (0.3 ppm) (Roger at al., 1990; Bauer et al., 1986). Although similar but statistically non significant trends have been observed in other controlled human studies performed at lower concentrations (Bylin et al., 1985; Hazucha et al., 1983; Orehek et al., 1976), the small size of the decrements and questions regarding the statistical significance of some of these results together suggest that caution should be exercised in accepting these findings as demonstrating acute effects.

Orehek and colleagues (Orehek et al., 1976) were the first to report that relatively brief exposures of asthmatics to low-level NO_2 (0.19 mg/m^3) might enhance subsequent responsiveness to challenge with a broncho-constricting drug. Although NO_2 alone caused an increase in airway resistance in only 3 of 20 asthmatics, bronchial responsiveness to carbachol increased in 13 of these 20 subjects. However, this report was challenged because of the retrospective separation of responding from non-responding subjects.

Hazucha and colleagues (Hazucha et al., 1983) failed to confirm these results in a study of 15 asthmatic subjects. Although there were some differences in techniques and patient selection between the Orehek and Hazucha studies, it seems likely that the findings of Orehek and coworkers reflect a retrospective stratification of subjects into "responder" and "non-responder" groups that was not justified a priori.

Other investigators have also been unable to confirm effects of 0.19–0.38 mg/m^3 (0.1-0.2 ppm) NO_2 on lung function in either asthmatic adolescents (Koenig et al., 1985; Koenig et al., 1988) or in mildly asthmatic adults (Koenig et al., 1985; Bauer et al., 1986; Orehek et al., 1976; Bylin et al., 1985; Hazucha et al., 1983; Koenig et al., 1988; Kleinman et al., 1983; Linn et al., 1986; Mohsenin & Gee, 1987; Morrow & Utell, 1989; Roger et al., 1990).

Kleinman and colleagues (Kleinman et al., 1983) evaluated the response of lightly exercising asthmatic subjects to inhalation of 0.38 mg/m^3 NO_2 for 2 hours, during which resting minute ventilation was doubled. Although NO_2 did not cause alterations in flow rates or airways resistance, approximately two-thirds of the subjects experienced increased responsiveness to methacholine after inhalation of NO_2 compared with clean air, as assessed by specific airway resistance.

In view of the inconclusive findings at 0.19 and 0.38 mg/m^3 NO_2, Bauer and colleagues (Bauer et al., 1986) studied the effects of mouthpiece exposure to 0.56 mg/m^3 NO_2 for 30 minutes (20 minutes at rest followed by 10 minutes of exercise at approximately 40 L/min) in 15 asthmatics. At this level, NO_2 inhalation produced significant decrements in forced expiratory flow rates after exercise, but not at rest. Furthermore, after airway function was allowed to return to baseline during a 1-hour recovery period, isocapneic cold-air hyperventilation elicited increased airway responsiveness in the asthmatics who had earlier been exposed to NO_2.

Roger and coworkers (Roger et al., 1990), in a comprehensive, concentration response experiment, were unable to confirm the results of a previous pilot study suggesting airway responses in asthmatic subjects. Twenty-one male asthmatics exposed to NO_2 at 0.28, 0.38, and 1.13 mg/m^3 for 75 minutes did not experience significant effects on lung function or airway responsiveness compared with air exposure. Bylin and coworkers (Bylin et al., 1985) found significantly increased bronchial responsiveness to histamine challenge compared with sham exposure in 8 atopic asthmatics exposed to 0.56 mg/m^3 NO_2 for 20 minutes. Five of 8 asthmatics demonstrated increased reactivity, while 3 subjects showed no change, as assessed by specific airway resistance. Mohsenin (Mohsenin, 1987) reported enhanced responsiveness to methacholine in eight asthmatic subjects exposed to 0.94 mg/m^3 NO_2 at rest for 1 hour; airway responsiveness was measured by partial expiratory flow rates at 40% vital capacity, which may have increased the sensitivity for detecting small changes in airway responsiveness.

Strand et al. (Strand et al., 1996) found increased responsiveness to histamine among 19 asthmatic subjects 5 hours after a 30 minute exposure to 0.49 mg/m^3 NO_2, with intermittent exercise. The inconsistent results of these studies have not been satisfactorily explained. It is evident that a wide range of responses occur among asthmatics exposed to NO_2. This variation may in part reflect differences in subjects and exposure protocols: mouthpiece vs. chamber, obstructed vs. non-obstructed asthmatics, sedentary vs. exercise, and requirements for medication. Identification of factors that predispose to NO_2 responsiveness requires further investigation.

These studies have typically involved volunteers with mild asthma; data are needed from more severely affected asthmatics who may be more susceptible. Overall, there is little convincing evidence that short-term exposures to NO_2 at outdoor ambient concentrations significantly alter lung function or nonspecific airway responsiveness in most people

with mild asthma. However, outdoor levels influence indoor concentrations, which may reach peak levels that are clinically important for some adults and children with asthma.

Effects on Allergen Responsiveness:
The potential for NO_2 exposure to enhance responsiveness to allergen challenge in asthmatics deserves special mention. Several recent studies have reported that low-level exposures to NO_2 ,both at rest and with exercise, enhance the response to specific allergen challenge in mild asthmatics. Tunnicliffe et al. (Tunnicliffe et al., 1994) reported exposures of 8 subjects with asthma to 400 ppb NO_2 for only 1 hour at rest, and found increased responsiveness to a fixed dose of allergen, both during the early and late phases of the response. No significant effect was seen at 100 ppb, but the data suggested an exposure-response relationship. Davies' group from the U.K., in two reports (Devalia et al., 1994; Rusznak et al., 1996), described an effect of exposure to the combination of 400 ppb NO_2 and 200 ppb SO_2, but not either pollutant alone, on subsequent allergen challenge in mild asthmatics.

Strand and colleagues (Strand et al., 1998) from Sweden demonstrated increases in both the early and late phase responses to allergen following 4 daily repeated exposures to 260 ppb NO_2 for 30 minutes, at rest. Finally, Jenkins et al. (Jenkins et al., 1999) exposed asthmatic subjects to NO_2, ozone, and their combination using two different protocols that varied time of exposure and gas concentration, but kept the total exposure constant. All three exposures of the high concentration regimen (200 ppb ozone, 400 ppb NO_2, and the combination for 3 hours), but not the low concentration regimen, enhanced subsequent responsiveness to allergen.

Additional data from both animal exposure and in vitro exposure studies provide support for enhancement of allergen responsiveness by NO_2 exposure. Gilmour (Gilmour, 1995) has reviewed the evidence in animal models. Of particular interest is a rat model of house-dust-mite sensitivity in which a 3-hour exposure to 9.4 mg/m^3 NO_2, after a priming injection and pulmonary challenge with antigen, increased the specific immune response and immune-mediated pulmonary inflammation. NO_2 exposure also enhanced lymphocyte proliferation responses to allergen in both the spleen and mediastinal lymph nodes.

Schierhorn et al. (Schierhorn et al., 1999) observed increased histamine release by cultured human nasal mucosa from surgical resections in response to exposure to NO_2 at 200 and 800 µg/m3 (106 and 424 ppb) for 24 hours. The magnitude of the effect was more pronounced than for ozone.

These recent studies involving allergen challenge appear relatively consistent in demonstrating effects at concentrations that occur indoors, and suggest that NO_2 may enhance both allergen sensitization and its associated inflammatory response. Confirmation of these findings is needed from other centers. However, the rising incidence, prevalence, and mortality from asthma make these observations particularly important and timely. Additional work is needed in understand more completely the exposure-response characteristics, effects of exercise, relationship to severity of asthma, role of asthma medications, and other clinical factors. Animal and in vitro studies are needed to establish the precise mechanisms involved.

Chronic Obstructive Pulmonary Disease:
Few studies have examined responses to NO_2 in subjects with chronic obstructive pulmonary disease (COPD). In a group of 22 subjects with moderate COPD, Linn and associates (Linn et al., 1985a) found no pulmonary effects of 1-hour exposures to 0.94, 1.88, and 3.76 mg/m^3 NO_2. In a study by Morrow and colleagues (Morrow et al., 1992), 20 subjects with COPD were exposed for 4 hours to 0.56 mg/m^3 NO_2 in an environmental chamber, with intermittent exercise. Although progressive decrements in lung function occurred during the exposure, significant decreases were not found for FVC until the end of the exposure. The decrement in lung volume occurred without changes in flow rates. The difference in results between the Linn and Morrow studies may reflect the difference in duration of exposure. It is worth noting that changes in lung function were typical of the "restrictive" pattern seen with ozone rather than the obstructive changes described by some with NO_2 exposure in asthmatics.

Effects on Host Defense:
More recently, investigators have sought to evaluate the effects of nitrogen dioxide on measures other than on pulmonary function. The key studies are summarized here. Analysis of lung lavage from healthy humans indicated that high levels (5640–7520 µg/m^3; 3–4 ppm) reduce the activity of alpha-1-protease inhibitor, a protein that acts to protect the lung from the proteolytic enzyme elastase by inhibiting connective tissue damage. However, 2820 µg/m^3 (1.5 ppm) had no such effect.

Goings et al. (Goings et al., 1989) exposed healthy volunteers to either 1.9-5.6 mg/m^3 NO_2 or to air for 2 hours per day for 3 consecutive days. A live, genetically engineered influenza A vaccine virus was administered intranasally to all subjects after exposure on day 2. Infection was determined by virus recovery from nasal washings, a 4-fold or greater increase in antibody titer, or both. The findings of this study were inconclusive, in part because of limitations in sample

size. In addition, the attenuated, cold-adapted virus used in the study was incapable of infecting the lower respiratory tract, where NO_2 may have its greatest impact on host defense.

Another approach has been to obtain lavaged cells from NO_2-exposed individuals and examine their handling of infectious virus in vitro. Several NO_2 exposure scenarios, including continuous low-level exposure or intermittent peak exposures have been examined (Frampton et al., 1989). Alveolar macrophages obtained by BAL 3 1/2 hours after a 3-hour continuous exposure to 1.1 mg/m^3 NO_2 tended to inactivate influenza in vitro less effectively than cells collected after air exposure. The effect was observed in cells from 4 of the 9 subjects studied; alveolar macrophages from these 4 subjects increased release of interleukin-1 after exposure to NO_2, whereas cells from the remaining 5 subjects decreased release of interleukin-1 following exposure. However, in a subsequent study (Azadniv et al., 1998) involving 3.8 mg/m^3 NO_2 exposures for 6 hours with intermittent exercise, no effect on alveolar macrophage function or inactivation of influenza virus was observed, either immediately or 18 hours after exposure.

Airway Inflammation:
Unlike ozone exposure, NO_2 exposure at near-ambient levels (i.e., less than 3.8 mg/m^3) does not cause a significant influx of polymorphonuclear leukocytes (PMN) into the airways and alveoli (Frampton et al., 1989). NO_2 appears to be much less potent than ozone in eliciting a neutrophilic inflammatory response.

However, prolonged exposure to NO_2 at concentrations only slightly above peak levels occurring indoors can cause mild airway inflammation. Healthy volunteers exposed to 3.8 mg/m^3 NO_2 for 6 hours with intermittent exercise (Azadniv et al., 1998) showed a slight increase in the percentage of PMN obtained in bronchoalveolar lavage fluid 18 hours after exposure (air: 2.2±0.3%; NO_2: 3.1±0.4%). In a separate group of subjects, no effects of this exposure protocol were found on alveolar macrophage phenotype or expression of the adhesion molecule CD11b or receptors for IgG when assessed immediately after exposure (Gavras et al., 1994). Blomberg et al. (Blomberg et al., 1997) reported that 4-hour exposures to 3.8 mg/m^3 NO_2 resulted in an increase in interleukin-8 and PMN in the proximal airways of healthy subjects, although no changes were seen in bronchial biopsies. This group also studied the effects of repeated 4-hour exposures to 3.8 mg/m^3 NO_2 on 4 consecutive days, with BAL, bronchial biopsies, and BAL fluid antioxidant levels assessed 1.5 hours after the last exposure (Blomberg et al., 1999). The bronchial wash fraction of BAL fluid showed a two-fold increase in PMN and a 1.5-fold increase in myeloperoxidase, indicating persistent mild airway inflammation with repeated NO_2 exposure. Interestingly, small but significant decrements in FVC and FEV1 were observed after the first exposure, which returned to baseline following subsequent exposures.

There is evidence from both animal and human studies that exposure to NO_2 may alter lymphocyte subsets in the lung and possibly in the blood. Lymphocytes, particularly cytotoxic T cells and NK cells, play a key role in host defense against respiratory viruses by eliminating infected host cells. Richters and colleagues (Damji & Richters, 1989) (Richters & Damji, 1988; Richters & Richters, 1989; Kuraitis & Richters, 1989) showed that mice exposed to NO_2 at levels as low as 7.5 mg/m^3 for eight hours demonstrate reductions in populations of CD8+ (cytotoxic/suppressor) lymphocytes in the spleen. In humans, Sandstrom et al. (Sandstrom et al., 1991) observed a significant, dose-related increase in lymphocytes and mast cells recovered by BAL 24 hours after a 20-minute exposure to NO_2 at 4.23 – 10.3 mg/m^3. Rubinstein et al. (Rubinstein et al., 1991) found that a series of 4 daily 2- hour exposures to 1.1 mg/m^3 NO_2 resulted in a small increase in NK cells recovered by BAL. In contrast, repeated exposures to 2.8 or 7.5 mg/m^3 NO_2 for 20 minutes every 2nd day on six occasions resulted in decreased CD16+56+ and CD19+ cells in BAL fluid, 24 hours after the final exposure (Sandstrom et al., 1992b; Sandstrom et al., 1992a). No effects were seen on PMN or total lymphocytes. Finally, Azadniv et al. (Azadniv et al., 1998) observed a small but significant reduction in CD8+ T lymphocytes in peripheral blood, but not BAL, 18 hr following single 6 hour exposures to 3.8 mg/m^3 NO_2.

Differing exposure protocols and small numbers of subjects among these studies may explain the varying and conflicting findings. Furthermore, the clinical significance of transient, small changes in lymphocyte subsets is unclear. However, even small changes in susceptibility to respiratory viruses resulting from exposure to NO_2 may have a significant public health impact because of the large number of individuals exposed in the home, both to NO_2 and to respiratory viruses. However, clinical studies provide little evidence for effects on lung function, airway inflammation, or host defense impairment in healthy subjects at outdoor ambient exposure concentrations.

Induction of Emphysema:
Clinical emphysema in humans has been linked with deficient proteinase inhibitor activity in the lung, presumably via inactivation by cigarette smoke. One mechanism by which chronic NO_2 exposure may result in structural lung injury is through inactivation of lung proteinase inhibitors. Animal models involving prolonged exposure to relatively high levels of NO_2 have found pathological changes of emphysema (Evans et al., 1976; Lafuma et al., 1987). Mohsenin and Gee (Mohsenin and Gee, 1987) exposed healthy volunteers to 5.6 or 7.5 mg/m^3 NO_2 for 3 hours and observed a 45% decrease in the functional activity of a1-proteinase inhibitor in BAL fluid. Supplementation with vitamins C and E prior to exposure abrogated the effect of 7.5 mg/m^3 NO_2 on elastase inhibitory capacity of the alveolar lining fluid

(Mohsenin, 1991). In contrast, Johnson et al. (Johnson et al., 1990) found no effect of exposure for 3 hours to continuous 2.8 mg/m^3 or intermittent peaks of 3.8 mg/m^3 NO_2 on either the concentration (immunoassay) or functional activity of a1-proteinase inhibitor in BAL fluid. The absence of an effect in the Johnson study may reflect the lower exposure levels used.

Frampton et al. (Frampton et al., 1989) observed a 47% increase in a2-macroglobulin, a metalloproteinase inhibitor released by alveolar macrophages, in BAL fluid 3 and 1/2 hours following 3-hour exposures to 1.1 mg/m^3 NO_2. This protein may have local immunoregulatory effects as well as provide local protection against proteinases. Its increase following NO_2 exposure suggests a protective response. However, no change in BAL fluid levels of a2-macroglobulin was observed following similar exposures to 2.8 mg/m^3 of NO_2 (Frampton et al., 1989).

Summary of short-term exposure effect levels

NOAEL mg/m^3	LOAEL mg/m^3	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m^3
0.47		increase in airway reactivity	sensitive humans (asthmatics), 1h	Review: California Air Resources Board (CARB), 1992	OEHHA 1999 REL: 0.47
0.19	0.38-0.56	increased responsiveness to bronchoconstrictors	Mild asthmatics, 0.5h		WHO 2000 GV: 0.2 (1h)
	0.96	possible detrimental respiratory effects in both normal and asthmatic subjects	Short-term human clinical studies		Health Canada 1995 ASTER: 0.48 (1h)

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of Acute Reference Exposure Level (protective against mild adverse effects): 0.25 ppm (470 mg/m^3)
California Ambient Air Quality Standard

Study	California Air Resources Board (CARB), 1992
Study population	sensitive humans (asthmatics)
Exposure method	inhalation
Critical effects	increase in airway reactivity
LOAEL	
NOAEL	0.25 ppm
Exposure duration	1 hour
Extrapolated 1 hour concentration	0.25 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	0.25 ppm (0.47 mg/m^3; 470 mg/m^3)

WHO Guidelines (2001)

Despite the large number of acute controlled exposure studies on humans, several of which used multiple concentrations, there is no evidence for a clearly defined concentration–response relationship for nitrogen dioxide exposure. For acute exposures, only very high concentrations (1990 μg/m3; > 1000 ppb) affect healthy people. Asthmatics and patients with chronic obstructive pulmonary disease are clearly more susceptible to acute changes in lung function, airway responsiveness and respiratory symptoms. Given the small changes in lung function (< 5% drop in FEV1 between air and nitrogen dioxide exposure) and changes in airway responsiveness reported in several studies, 375–565 μg/m3 (0.20 to 0.30 ppm) is a clear lowest-observed-effect level. A 50% margin of safety is proposed because of the reported statistically significant increase in response to a bronchoconstrictor (increased airway responsiveness) with exposure to 190 μg/m3 and a meta-analysis suggesting changes in airway responsiveness below 365 μg/m3. (The significance of the response at 190 μg/m3 (100 ppb) has been questioned on the basis of an inappropriate statistical analysis.)
On the basis of these human clinical data, a 1-hour guideline of 200 μg/m^3 is proposed. At double this recommended guideline (400 μg/m3), there is evidence to suggest possible small effects in the pulmonary function of asthmatics. Should the asthmatic be exposed either simultaneously or sequentially to nitrogen dioxide and an aeroallergen, the risk

of an exaggerated response to the allergen is increased. At 50% of the suggested guideline (100 μg/m3, 50 ppb), there have been no studies of acute response in 1 hour.

Effects of long-term exposure

Studies with animals have clearly shown that several weeks to months of exposure to NO_2 concentrations of less than 1880 μg/m^3 (1 ppm) cause a plethora of effects, primarily in the lung but also in other organs such as the spleen, liver and blood. Both reversible and irreversible lung effects have been observed. Structural changes range from a change in cell types in the tracheobronchial and pulmonary regions (lowest reported level 640 μg/m^3) to emphysema-like effects (at concentrations much higher than ambient). Biochemical changes often reflect cellular alterations (lowest reported levels for several studies 380–750 μg/m^3 (0.2–0.4 ppm) but isolated cases of lower effective concentrations). Nitrogen dioxide levels as low as 940 μg/m^3 (0.5 ppm) also increase susceptibility to bacterial and viral infection of the lung.

Several epidemiological studies show significant relationships between ambient (urban) NO_2 levels and health effects, including respiratory symptoms, episodes of respiratory illness, lung function, and even mortality. However, because NO_2 shares sources with other pollutants, one of the difficulties in deriving quantitative estimates of health risks is in separating the relative contributions of NO_2 from those of other major pollutants (ozone, sulfur dioxide, particulate matter, etc.); hence nitrogen dioxide might best be considered as just one indicator of polluted ambient air, especially where it is present in traffic-dominated urban air pollution mixes. Great care is therefore needed in interpreting available outdoor epidemiology studies, so as not to ascribe an undue degree of confidence to reported health associations with nitrogen dioxide concentrations as being specifically due to that compound as compared to the overall ambient air mix.

Indoor studies have compared groups exposed to nitrogen dioxide emitted from the combustion of gas inside buildings to groups in homes without such sources and hence with lower levels of nitrogen dioxide. The limited studies of adults have tended to show no relationship between the use of gas for cooking and respiratory symptoms or lung functions. Thus, the following discussion focuses on children.

Hasselblad et al. (1992) performed a meta-analysis of studies in homes with gas stoves that met several criteria. The endpoint was the presence of lower respiratory symptoms and disease in children aged 5–12 years. Given the nature of the studies evaluated, the goal was to estimate the odds ratio of an increase in nitrogen dioxide concentration of 28.3 μg/m^3 (15 ppb). Although two analytic models (fixed and hierarchical) were used, they gave about the same results. The combined odds ratio was about 1.2, with confidence intervals ranging from about 1.1 to 1.3. Thus, the analysis estimated an increased risk of approximately 20% for respiratory symptoms and disease for each increase of 28.3 μg/m^3 (2-week average), where average weekly bedroom concentrations were between 15 and 122 μg/m^3 (8 and 65 ppb) (Hasselblad et al., 1992). Several uncertainties exist in this analysis, and exposure measurement errors are present in the studies.

A number of additional studies have been published since 1990, with continued mixed results. A prospective cohort study of infants conducted in Albuquerque, New Mexico (Samet et al., 1993) attempted to address many of the issues of previous studies related to sample size and exposure misclassification. Exposures to NO_2 and respiratory illnesses were monitored prospectively from birth to 18 months of age in a cohort of 1205 infants living in homes with gas and electric cooking stoves, without smoking. NO_2 exposures were estimated from serial measurements of bedroom NO_2 concentrations. Respiratory illnesses were quantified from reports of symptoms and illnesses from mothers and validated by home visits. No consistent trends in incidence or duration of illness were observed by level of NO_2 exposure at the time of illness or during the prior month, or by type of stove. However, indoor NO_2 levels were very low in this study.

To further illustrate the indoor epidemiological findings, the study of Neas et al. (1991) is described in further detail here. It was selected because the individual symptom results are consistent with the magnitude of effects found in the British studies and other analyses of the data from six United States cities. The authors evaluated 1286 white children (7–11 years) from the larger six-city study. For the children selected there was complete covariate information and at least one indoor measurement of nitrogen dioxide (Palmes passive diffusion tubes for 2 weeks during the heating season and 2 weeks during the cooling season at three sites: kitchen, activity room and the child's bedroom). Parents completed a questionnaire on symptoms during the previous year. An increase in symptoms was estimated for an additional exposure of 28.3 μg/m3 (15 ppb). A multiple logistic model was used. The odds ratios were as follows: shortness of breath, 1.23 (95% confidence interval (CI), 0.93–1.61); persistent wheeze, 1.16 (CI, 0.89–1.52); chronic cough, 1.18 (CI, 0.87–1.60); chronic phlegm, 1.25 (CI, 0.94–1.66); and bronchitis, 1.05 (CI, 0.75–1.47).When the authors performed a multiple logistic regression of the combined lower respiratory symptom measure (i.e. the presence of any

of the above-mentioned symptoms), they obtained an odds ratio of 1.40 (CI, 1.14–1.72). Table 5.2 shows the adjusted odds ratios for combined lower respiratory symptoms for ordered nitrogen dioxide exposure categories. These findings are consistent with a linear concentration–response relationship.

Table 5.2: Odds ratio and 95% confidence interval for the effect of nitrogen dioxide exposure
on the prevalence of lower respiratory symptoms in children (Neas et al., 1991)

Nitrogen dioxide concentration ($\mu g/m^3$)		Number of children	Odds ratio	95%Confidence interval
Range	Mean			
0–9	7	263	1.00	
9–19	14	360	1.06	0.71–1.58
19–37	27	317	1.36	0.89–2.08
38–147	58	346	1.65	1.03–2.63

More recent studies have utilized personal monitoring methods in an attempt to improve exposure classification. Mukala et al. (Mukala et al., 1999) prospectively studied personal exposure to NO_2 for periods of 13 weeks among 163 preschool children in Helsinki, using individual passive diffusion monitors. Daily diaries of symptoms were kept by the parents, and in a subset of 53 children, peak expiratory flow rates were measured in the morning and evening. Co-variates considered in the model included allergy, education, smoking, stove type, and outdoor pollutant concentrations (NO, NO_2, O_3, SO_2, and total suspended particles). The median personal NO_2 exposure was 21.1 $\mu g/m^3$ (11 ppb), with a maximum of 99 $\mu g/m^3$ (50 ppb). An increased risk of cough was associated with increasing NO_2 exposure (risk ratio = 1.52; 95% confidence interval 1.00-2.31). There were no significant effects on other respiratory symptoms or peak flow.

In Australia, where unvented natural gas cooking and heating are common, Pilotto et al. (Pilotto et al., 1997) queried respiratory symptoms and school absences among 388 children from 6 to 11 years of age, and monitored indoor NO_2 levels at their schools, which were chosen for having either unvented gas heating or electric heating. Classroom monitoring of NO_2 levels was conducted intermittently over several months. A significant increase in sore throat, colds, and absences from school were found for children in environments with hourly peak levels of 150 $\mu g/m^3$, compared with background levels of 38 $\mu g/m^3$. Exposure-response relationships were evident for each outcome. However, no measurements of other pollutants, either indoor or outdoor, were provided. Caution must be used in interpreting the findings from cross-sectional studies, because many factors other than pollutant levels may influence differences between populations.

In the Latrobe Valley of Australia (Garrett et al., 1998), NO_2 levels were monitored in eighty homes, on 5 separate occasions for 4 days each, and health questionnaires administered to the 148 children residing in those homes. 58 of the children were asthmatic, although the diagnostic criteria were not provided. Children underwent allergy prick testing and monitored their peak flow rates for a 2-week period in the winter and spring. The indoor median NO_2 concentration was 11 $\mu g/m^3$ (6.0 ppb), with a maximum of 241 $\mu g/m^3$ (128 ppb). Respiratory symptoms were more common in children exposed to a gas stove (odds ratio 2.3, CI 1.00-5.2), even after adjusting for NO_2 levels (odds ratio 2.2, CI 1.0-4.8). Atopic children tended to have a greater risk than non-atopic children. NO_2 concentration was not a significant risk factor for symptoms. The authors conclude that gas stoves may pose a risk apart from NO_2. However, the relative paucity of NO_2 monitoring data for each home may have provided insufficient statistical power to demonstrate an association. More important weaknesses in the study are the inclusion of homes with cigarette smokers, and the failure to monitor other pollutants, either inside or outside the home. These factors may have confounded the findings.

Jarvis et al. (1996) studied symptoms, lung function, and atopy in 15000 adults aged 20-44 years in Britain, as part of the European Community Respiratory Health Survey. Women, but not men, who reported cooking with gas had an increased risk for symptoms consistent with asthma, such as wheezing (odds ratio (OR) 2.07, CI 1.41- 3.05), waking with shortness of breath (OR 2.32, CI 1.25-4.34), and "asthma attacks" (OR 2.60, CI 1.20-5.65). Lung function was measured in a subset of subjects, and FEV1 was reduced 3.1% of predicted for women cooking with gas compared to those using other means, after adjusting for age, smoking, and town of residence. Total and specific IgE levels were not associated with gas stove use. There was no protective effect associated with use of an exhaust fan. The authors boldly concluded from their estimate of the population attributable risk fraction that "the prevalence of wheeze with breathlessness in young women would be reduced by between 8% and 48% if cooking with gas were abandoned." Although studies such as this are limited by the potential for exposure misclassification and the influence of other environmental and biological factors, the findings are consistent with women spending more time at cooking than men, and with reports of increased responsiveness to allergen challenge following NO_2 exposure (see below).

Taken together, studies of the health effects of exposure to NO_2 indoors fail to make a convincing case for association with respiratory illness in either children or adults. The findings of the Hasselblad meta-analysis (Hasselblad et al., 1992) must be interpreted with caution because the 11 studies used in the analysis employed varying methodologies and study populations. Small sample size, potential for misclassification, inclusion of smokers in many of the studies, and failure to consider potential effects of outdoor pollution, or other indoor pollutants, may bias many of the studies. For example, burning of natural gas in gas stoves emits ultrafine particles in addition to NO_2, and the cooking process is also a source of particles. It is possible that observed health effects associated with gas stove use may represent health effects of particle exposure, or of particles combined with NO_2. This may explain why Garrett et al. (Garrett et al., 1998), found a significant relationship between respiratory symptoms in children and gas stove use, but not indoor NO_2 levels. The Samet et al. study of infants in Albuquerque (Samet et al., 1993) provides convincing evidence that indoor NO_2, at the very low concentrations found in that study, are not associated with respiratory illnesses in children under 18 months of age.

Recently reported time-series analyses of ambient air pollution effects from a European multi-city epidemiology project (Katsouyanni et al., 1996) also found the following very mixed results.

- There was no association with any cause of death for nitrogen dioxide or ozone in Lyon, France, where daily nitrogen dioxide concentrations averaged 70 µg/m^3 (maximum 324 µg/m^3) and both sulfur dioxide and particulate matter were significantly related to mortality from cardiovascular and respiratory causes (Zmirou et al., 1996).

- No relationship between daily nitrogen dioxide levels and daily mortality was found in Cologne, Germany, where the all-year median for daily nitrogen dioxide was 45 µg/m^3 (maximum 176 µg/m^3) and both sulfur dioxide and particulate matter were significantly related to increased mortality risk (Spix and Wichmann, 1996).

- In Paris, there were no significant effects of photo-oxidant pollutants (nitrogen dioxide, ozone) on daily mortality risk, but there was a significantly increased hospital asthma admission relative risk (RR) of 1.175 per 100 µg/m^3 increase in nitrogen dioxide concentration above the reference value. The mean 24-hour nitrogen dioxide concentration averaged 45 µg/m^3 (99th centile 108 µg/m^3) and the mean 1-hour maximum was 74 µg/m^3 (99th centile 203 µg/m^3). Particulate matter and sulfur dioxide significantly increased daily mortality from respiratory causes and hospital admissions for all respiratory disease (Dab et al., 1996).

- Negative (sometimes statistically significant) effects of nitrogen dioxide in decreasing respiratory hospital admissions (RR = 0.86–0.89) were found in Amsterdam for adults (aged 15–64 years) and in chronic obstructive pulmonary disease admissions for all ages (RR = 0.795–0.948), but there were some positive effects on respiratory admissions for the elderly (65+ years) and on asthma admissions (RR = 0.902–1.062). The mean 24-hour nitrogen dioxide concentration averaged 50 µg/m^3 (95th centile 84 µg/m^3) and the mean 1-hour maximum was 75 µg/m^3 (95th centile 127 mg/m^3). In addition, ozone showed nonsignificant positive effects on summer respiratory admissions for the elderly (65+ years) but neither particulate matter nor sulfur dioxide showed any clear effects on hospital admissions (Schouten et al., 1996).

- Rotterdam showed contrasting results, i.e. predominantly positive (albeit few significant at P < 0.05) effects of nitrogen dioxide in terms of relative risk increases for all respiratory admissions for all age groups and increases (mostly significant) for chronic obstructive pulmonary disease admissions for all ages. The mean 24-hour nitrogen dioxide concentration averaged 54 µg/m^3 (95th centile 86 µg/m^3) and the mean 1-hour maximum averaged 82 µg/m^3 (95th centile 138 µg/m^3). Ozone and particulate matter (as black smoke) generally increased the risk of hospital admissions, and sulfur dioxide showed mixed results (Schouten et al., 1996).

- Ambiguities regarding the effects of ambient nitrogen on hospital admissions for asthma were found in Helsinki (daily mean in the range 34–44 µg/m^3). Pönkä & Virtanen (1996) reported asthma admissions for children (aged 0–14 years) to be related to 8-hour ozone levels and for adults (15–64 years) to 24-hour sulfur dioxide levels, but provided no results for nitrogen dioxide. This was in contrast to an earlier report (Pönkä, 1991) of significant associations between hospital admissions for asthma and nitrogen dioxide, sulfur dioxide, ozone and total suspended particulates based on different statistical modelling.

- In London, the effects of nitrogen dioxide and sulfur dioxide on daily mortality were significant but smaller and less consistent than the effects of ozone and particulate matter (as black smoke) on respiratory, cardiovascular and all-cause mortality, the effects being greater in the warm season (April–September) and independent of other pollutants (Anderson et al., 1996).

Summary of long-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
	0.038-0.056	excess of lower respiratory illness	Children 5-12 y old, annual avg conc. , also basing on background level of 0.015 mg/m³	taken from EHC 188	WHO 2000 GV: 0.04 (1y)

WHO Guidelines (2001)

Although there is no particular study or set of studies that clearly support selection of a specific numerical value for an annual average guideline, the database nevertheless indicates a need to protect the public from chronic nitrogen dioxide exposures. For example, indoor air studies with a strong nitrogen dioxide source, such as gas stoves, suggest that an increment of about 30 µg/m3 (2-week average) is associated with a 20% increase in lower respiratory illness in children aged 5–12 years. However, the affected children had a pattern of indoor exposure that included peak exposures higher than those typically encountered outdoors. Thus the results cannot be readily extrapolated quantitatively to the outdoor situation. Outdoor epidemiological studies have found qualitative evidence of ambient exposures being associated with increased respiratory symptoms and lung function decreases in children (most clearly suggestive at annual average concentrations of 50–75 µg/m3 or higher and consistent with findings from indoor studies), although they do not provide clear exposure–response information for nitrogen dioxide. In these epidemiological studies, nitrogen dioxide has appeared to be a good indicator of the pollutant mixture. Furthermore, animal toxicological studies show that prolonged exposures can cause decreases in lung host defences and changes in lung structure. On these grounds, it is proposed that a long-term guideline for nitrogen dioxide be established. Selecting a well-supported value based on the studies reviewed has not been possible, but it has been noted that a prior review conducted for the Environmental Health Criteria document on nitrogen oxides recommended an annual value of 40 µg/m3 (WHO, 1997). In the absence of support for an alternative value, this figure is recognized as an air quality guideline.

Carcinogenic and mutagenic effects

To date, there are no reports that nitrogen dioxide causes malignant tumours or teratogenesis (U.S.EPA, 1993; Berglund et al., 1993; Witschi, 1988). Limited genotoxicity studies have produced mixed results with *in vitro* and high-concentration *in vivo* studies (e.g. 50 000 µg/m^3, 27 ppm) (Victorin, 1994).

Interaction with other chemicals

Environmental exposures to NO_2 do not occur singly, but rather as a complex mixture of pollutants, and failure to consider the presence of other pollutants may confuse interpretation of the observed effects. Recent data suggest exposure to low concentrations of NO_2 at rest may enhance the response to allergen inhalation in subjects with asthma. When considering mixtures of anthropogenic pollutants, It may be impossible to separate the effects of one component from those of other components, particularly with the possibilities of synergistic or antagonistic interactions. In considering the health effects of mixtures, potential causal pathways should be carefully delineated. For example, some reports have suggested that HONO may contribute to the health effects attributed to indoor NO_2 (Spengler et al., 1990).

Efforts have been made to study effects of NO_2-ozone mixtures on pulmonary function. These studies have generally revealed no interactive effects; the observed pulmonary function decrements appear to reflect the ozone component of the mixtures. Hazucha et al., (Hazucha et al., 1994) found that pre-exposure of healthy women to 1.1 mg/m^3 (0.6 ppm) NO_2 for 2 hours enhanced the development of nonspecific airway responsiveness induced by a subsequent 2-hour exposure to 0.6 mg/m^3 (0.3 ppm) ozone, with intermittent exercise.

Relatively high-level, prolonged (6 hours/day, up to 90 days) exposure to NO_2 (27 mg/m^3) and ozone (1.6 mg/m^3) results in a syndrome of progressive pulmonary fibrosis in rats (Rajini et al., 1993), associated with a sustained increase in procollagen gene expression in the central acini (Farman et al., 1999). This does not occur with either gas alone, indicating a true synergistic effect. The relevance of this observation for human ambient exposures is not clear, given the high exposure concentrations used in the study, and absence of evidence for alveolar fibrosis or restrictive lung disease in epidemiological studies.

Bermudez et al. (Bermudez et al., 1999) examined DNA strand breaks in BAL cells from rats exposed to ozone (0.6 mg/m^3), to NO$_2$ (2.3 mg/m^3), and the combination. Ozone and the combination exposure increased DNA strand breaks to a similar degree compared with air exposure, but NO$_2$ alone had no effect.

The effects of NO$_2$ exposure on SO$_2$-induced bronchoconstriction have been examined, but with inconsistent results. Jorres and Magnussen (Jorres & Magnussen, 1991) found an increase in airways responsiveness to SO$_2$ in asthmatic subjects following exposure to 0.47 mg/m^3 NO$_2$ for 30 minutes, yet Rubinstein et al. (Rubinstein et al., 1990) found no change in responsiveness to SO$_2$ inhalation following exposure of asthmatics to 0.56 mg/m^3 NO$_2$ for 30 minutes.

Overall, there are little definitive data suggesting that NO$_2$ interacts with other pollutants in causing human health effects. However, human clinical studies have not systematically addressed the effects of pollutant combinations containing NO$_2$, in part because of the complexity of the experimental design and the difficulty in studying the most susceptible subjects.

Odour perception

Source: Devos et al. 1990
Odour thresholds: 185 μg/m^3

Source: Berglund et al., 1993
Nitrogen dioxide has a stinging, suffocating odour. The odour threshold has been placed by various authors at between 94 μg/m^3 (0.05 ppm) and 410 μg/m^3 (0.22 ppm). Owing to adaptation, however, no odour was perceived during a gradual (15-minute) increase in concentration from 0 to 51 mg/m^3 (0–27 ppm).

Source AIHA, 1989 (Odor thresholds for chemicals with established occupational health standards. American Industrial Hygiene Association, 1989. p. 25, 70-71)
Minimum perceptible value: 207–263 μg/m^3 (0.11-0.14 ppm).

Source: Amoore and Hautala, 1983
Odour thresholds: 733 μg/m^3 (0.39 ppm)

Summary of Nitrogen dioxide Dose Response Assessment

Exposure other than inhalation: Does not exist in water (food), reacting instantaneously to form nitric and nitrous acids

Toxicokinetics: 70-90% absorbed in the respiratory tract (increased during exercise). Oral breathing increases the delivery to the lower respiratory tract. Produces oxidation of either membrane lipids or proteins resulting in the loss of cell permeability control.

Health effect levels of short- and long-term exposure

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
			Short-term exposure		
0.47		increase in airway reactivity	sensitive humans (asthmatics), 1h	Review: California Air Resources Board (CARB), 1992	OEHHA 1999 REL: 0.47
0.19	0.38-0.56	increased responsiveness to bronchoconstrictors	Mild asthmatics, 0.5h		WHO 2000 GV: 0.2 (1h)
	0.96	possible detrimental respiratory effects in both normal and asthmatic subjects	Short-term human clinical studies		Health Canada 1995 ASTER: 0.48 (1h)
			Long-term exposure		
	0.038-0.056	excess of lower respiratory illness	Children 5-12 y old, annual avg conc. , also basing on background level of 0.015 mg/m³	taken from EHC 188	WHO 2000 GV: 0.04 (1y)

Carcinogenicity: No evidence

Genotoxicity: Limited evidence in vitro and in vivo at high concentrations (50 mg/m³)

Odour threshold: Range: 0.09-0.41 mg/m³ (Berglund), 0.185 mg/m³ (Devos), 0.2 mg/m³ (AIHA). Owing to adaptation, however, no odour was perceived during a gradual (15-minute) increase in concentration from 0 to 51 mg/m³

Susceptible population:
- Asthmatic individuals appear to be the most susceptible members of the population. Exposure of asthmatics to NO_2 could increase airway responsiveness to a variety of provocative mediators, including cholinergic and histaminergic chemicals, SO_2 , and cold air.
- Individuals with chronic obstructive pulmonary disease (COPD: emphysema and chronic bronchitis).
- Children are at increased risk for respiratory illness; of concern because repeated lung infections in children can cause lung damage later in life (greater lung surface area/body weight ratios and increased minute volumes/weight ratios; increased exposure of children is finally expected due to higher levels of nitrogen dioxide found nearer to the ground).

Remarks: High uncertainties in exposure-response relationships for both acute (<3-hour) and long-term exposure; high uncertainties in establishing an appropriate margin of protection.

6. Risk characterization

Health hazard evaluation of short- and long-term exposure
[Adopted from WHO, 2000]

Despite the large number of acute controlled exposure studies on humans, several of which used multiple concentrations, there is no evidence for a clearly defined concentration–response relationship for nitrogen dioxide exposure. For acute exposures, only very high concentrations (2000 $\mu g/m^3$) affect healthy people. Asthmatics and patients with chronic obstructive pulmonary disease are clearly more susceptible to acute changes in lung function, airway responsiveness and respiratory symptoms. Given the small changes in lung function (< 5% drop in FEV_1 between air and nitrogen dioxide exposure) and changes in airway responsiveness reported in several studies, 375-565 $\mu g/m^3$ (0.20 to 0.30 ppm) is a clear lowest-observed-effect level. A 50% margin of safety is proposed because of the reported statistically significant increase in response to a bronchoconstrictor (increased airway responsiveness) with exposure to 190 $\mu g/m^3$ and a meta-analysis suggesting changes in airway responsiveness below 0.36 mg/m^3. (The significance of the response at 190 $\mu g/m^3$ (0.1 ppm) has been questioned on the basis of an inappropriate statistical analysis).

On the basis of these human clinical data, a 1-hour exposure limit of 200 $\mu g/m^3$ is proposed. At double this recommended guideline (400 $\mu g/m^3$), there is evidence to suggest possible small effects in the pulmonary function of asthmatics. Should the asthmatic be exposed either simultaneously or sequentially to nitrogen dioxide and an aeroallergen, the risk of an exaggerated response to the allergen is increased. At 50% of the suggested guideline (100 $\mu g/m^3$, 50 ppb), there have been no studies of acute response in 1 hour.

Although there is no particular study or set of studies that clearly support selection of a specific numerical value for an annual average guideline, the database nevertheless indicates a need to protect the public from chronic nitrogen dioxide exposures. For example, indoor air studies with a strong nitrogen dioxide source, such as gas stoves, suggest that an increment of about 30 $\mu g/m^3$ (2-week average) is associated with a 20% increase in lower respiratory illness in children aged 5–12 years. However, the affected children had a pattern of indoor exposure that included peak exposures higher than those typically encountered outdoors. Thus the results cannot be readily extrapolated quantitatively to the outdoor situation. Outdoor epidemiological studies have found qualitative evidence of ambient exposures being associated with increased respiratory symptoms and lung function decreases in children (most clearly suggestive at annual average concentrations of 50–75 $\mu g/m^3$ or higher and consistent with findings from indoor studies), although they do not provide clear exposure–response information for nitrogen dioxide. In these epidemiological studies, nitrogen dioxide has appeared to be a good indicator of the pollutant mixture. Furthermore, animal toxicological studies show that prolonged exposures can cause decreases in lung host defences and changes in lung structure.

On these grounds, it is proposed that a long-term guideline for nitrogen dioxide be established. Selecting a well-supported value based on the studies reviewed has not been possible, but it has been noted that a prior review conducted for the Environmental Health Criteria document on nitrogen oxides recommended an annual value of 40 $\mu g/m^3$. In the absence of support for an alternative value, this figure is recognized as an air quality guideline.

Exposure data of relevance for the European population

Table 6.1: Short-term NO_2 peak levels related to gas appliances (adapted from Chapter 1.3)

Studies based on NO_2 sources	$\mu g/m^3$
Gas appliances in kitchen, 1h-TWA (Lebret. 1987)	230 – 2055
Gas stoves in kitchen, 1h-TWA (Noy, 1990)	2500
Gas cooking, 1h-TWA (Ross, 1996)	342 – 1585
Homes with gas appliances, 1h-TWA (WHO, 2000)	2000
Unflued gas heaters, ?-TWA (Brown, 2002)	180 – 530

Table 6.2: Percentage of population exposed beyond given guideline values for NO_2

Available exposure data Indoor concentrations (48h-PEM)		WHO recommended value 1-y average	German GV II 1-week average
Description (Study, Year)	N	40 µg/m^3 *	60 µg/m^3
Helsinki (Expolis, 96-98)	175	10% (15 %)	<
Basel (Expolis, 96-98)	50	15% (15 %)	5 %
Prague (Expolis, 96-98)	33	50% (50 %)	25 %
Oxford (Expolis, 98-00)	40	20% (20 %)	10 %
Northen Italy-TWA (Simoni, 2002)	112	75%	45 %
England 2-w TWA (BRE, 97-99)	796	25%	20 %

percentages put in parenthesis result from "through the day" 48h-personal exposure monitorings
* also EU annual limit value for the protection of human health (total of NO_2 and oxides of nitrogen) to be met the 01/01/2010 (see margins of tolerance hereafter)
< out of the evaluation range (i.e. <5% of the environments investigated)

Guideline Value II (GV II): GV II is a health-related value based on current toxicological and epidemiological knowledge. If the concentration corresponding to GV II is reached or exceeded immediate action must be taken because permanent stay in a room at this concentration level is likely to represent a threat to health, especially for sensitive people. In this context, taking action means an immediate examination of the situation with regard to a need for control measures. It may include the evacuation of the room in question. If by measurement GV II has been found to be exceeded, the results should be checked by repetitive measurements carried out immediately under normal conditions of occupancy. If possible and deemed meaning ful, biological monitoring of the occupants should be carried out in addition.

EU limit values for nitrogen dioxide NO_2 and oxides of nitrogen NO_X – Directive 1999/30/EC

	Averaging period	Limit value	Margin of tolerance	Date by which limit value is to be met
1. Hourly limit value for the protection of human health	1 hour	200 µg/m^3 NO_2, not to be exceeded more than 18 times a calendar year	50 % on the entry into force of this Directive, reducing on 1 January 2001 and every 12 months thereafter by equal annual percentages to reach 0% by 1 January 2010	1 January 2010
2. Annual limit value for the protection of human health	Calendar year	40 µg/m^3 NO_2	50 % on the entry into force of this Directive, reducing on 1 January 2001 and every 12 months thereafter by equal annual percentages to reach 0% by 1 January 2010	1 January 2010
3. Annual limit value for the protection of vegetation	Calendar year	30 µg/m^3 NO_2	None	19 July 2001

Alert threshold for nitrogen dioxide
400 µg/m3 measured over three consecutive hours at locations representative of air quality over at least 100 km 2 or an entire zone or agglomeration, whichever is the smaller.

Minimum details to be made available to the public when the alert threshold for nitrogen dioxide is exceedeed
Details to be made available to the public should include at least:
- the date, hour and place of the occurrence and the reasons for the occurrence, where known;
- any forecasts of:
- changes in concentrations (improvement, stabilisation, or deterioration), together with the reasons for those changes,
- the geographical area concerned,
- the duration of the occurrence;
- the type of population potentially sensitive to the occurrence;
- the precautions to be taken by the sensitive population concerned

Result

Reported maximum nitrogen dioxide (NO_2) levels associated with the use of gas appliances in homes (gas cooking and heating) are in the range 180-2500 $\mu g/m^3$. Exposure at these levels could generate effects in the pulmonary function of asthmatics, considered to be the subjects most susceptible to acute NO_2 exposure, with the lower end of the range approximating the WHO guideline (200 $\mu g/m^3$, 1-hour average), established for the protection of asthmatic individuals and the upper end starting to affect health in normal individuals.

For long-term exposures, increased respiratory symptoms and lung function decreases in children were shown to be the most sensitive effect in the general population. Measured background levels in European homes indicate that a remarkable portion of the population is exposed at NO_2 levels higher than current guideline values protecting from respiratory effects in children. In up to 25% of the investigated residences (45% in an Italian study) NO_2 levels exceeded the German indoor-related guideline value (GV II: 60 $\mu g/m^3$, 1-week average), what would have resulted in immediate action i.e. the examination of the situation with regard to a need for control measures.

On the other hand, safe levels in homes, i.e. < 40 $\mu g/m^3$ (following the WHO recommended annual value), are not likely to be achievable everywhere (e.g. in areas with intense automotive traffic) given that ventilation alone may introduce outdoor air containing such concentrations.

Benzene

Synonyms:	Annulene, benzine, benzol, benzole, benzol coal naphtha, cyclohexatriene, mineral naphtha, motor benzol, phenyl hydride, pyrobenzol, pyrobenzole
CAS Registry Number:	71-43-2
Molecular Formula:	C_6H_6

1. Compound identification

Benzene is a naturally occurring colourless liquid at room temperature and ambient pressure, and it has a characteristic aromatic odour. It is widely used toxic, volatile, flammable organic solvent. It is used as an industrial solvent for example in paints, varnishes, lacquer thinners and gasoline (1-4%) (IARC, 1989, Holmberg and Lundberg, 1985). Presently it is used as a raw material in the synthesis of styrene, phenol, cyclohexane, aniline, and alkyl benzenes in the manufacture of various plastics, resins, and detergents. Syntheses of many pesticides and pharmaceuticals also involve benzene as a chemical intermediate (HSDB, 2003). The tire industry and shoe factories use benzene extensively in their manufacturing processes. Benzene causes central nervous system damage acutely and bone marrow damage chronically and is carcinogenic. It was formerly used as parasiticide (SIS 2003).

2. Physical and Chemical properties

Molecular weight (g/mol)	78.11
Melting point (°C)	5.5
Boiling point (°C)	80.1
Density (g/l at 20 °C, 1 atm)	0.88
Relative vapour density (air =1)	2.8
Solubility: Water (g/l)	1.8

Miscible in most organic solvents.

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 3.242 $\mu g/m^3$
1 $\mu g/m^3$ = 0.308 ppb

Sources: GDCh (1988), RIVM (1988) and ATSDR (1989), Verschueren 2001, HSDB (2003).

3. Indoor Air Exposure assessment

Emission sources

Probably the most important indoor source is cigarette smoking. Other remarkable indoor sources are emissions from consumer products, including off-gassing from particle board. Similarly, living in the vicinity of hazardous waste sites or industrial facilities may increase exposure to benzene (ATSDR, 1991).

In a German study, being a subject to environmental tobacco smoke together with driving a car and refuelling were found significant determinants of exposure to benzene (Hoffman et al 2000). Similar results were reported in the US TEAM study (Wallace, 1989). It appeared that personal sources (use of products emitting benzene, driving or riding in automobiles), automobile exhaust and smoking (active and passive) were major sources of benzene to the general population. Inhalation exposures accounted for more than 99% of the general population exposure to benzene in US according to Hattemer-Frey et al (1990).

The average daily intake for an adult in Canada was estimated to be about 200 μg/day in total: 14 μg from ambient air, 140 μg from indoor air, 1.4 μg each from food and drinking water and 50 μg from automobile-related activities. The corresponding calculated average daily intake in the USA is 320 μg, with a daily intake from ambient and indoor air ranging between 180 - 1300 μg. Cigarette smoking may add to that as much as 1800 μg/day and passive smoking 50 μg/day. Based on assumptions of spending 2 hours per day in urban ambient air at 7 μg/m³, 21 hours per day in indoor air at 4 μg/m³, and 1 hour per day inside a vehicle at 50 μg/m³ (typical for large roads and heavy traffic), calculated relative uptakes from urban ambient air, indoor air, air inside cars, and intake from food were 9; 53; 30 and 8%, respectively (WHO, 1996).

Indoor air and exposure concentrations

Mean indoor concentrations are typically higher than the respective ambient levels all over Europe. The trend showing increasing ambient concentrations of benzene from northern to southern European cities (Cocheo et al 2000) seems to be similar for the indoor air concentrations (Jantunen et al 1999). In Northern Europe (Helsinki) the mean indoor concentration, 2.1 μg/m³, was slightly higher than the respective outdoor concentration, 1.7 μg/m³, if tobacco smoke was not present indoors (Edwards et al 2001). When tobacco smoke was present in indoor air, indoor concentration of benzene was more than twofold compared to outdoor level. Personal exposures were typically higher than indoor concentrations. The highest mean exposure in Helsinki was found due to active smoking being, 2.4 times higher than the mean indoor concentration in homes without tobacco smoke. In addition to smoking, residential indoor benzene concentration, time spent in a car, workplace concentration and time spent in home workshop determined personal exposures to benzene (Edwards et al 2001, Edwards and Jantunen 2001). Similar pattern between mean indoor, outdoor and personal exposure concentrations could be seen in central and southern European cities, although the concentrations were higher. Mean indoor concentrations ranged between 2.3 and 12 μg/m³ in central European cities such as Basel, Erfurt, Hamburg, Prague and Antwerp (Jantunen et al 1999, Schneider et al 1999 and 2001, Cocheo et al 2000) and between 10 and 13 μg/m³ in southern cities like Milan and Athens (Jantunen et al 1999, Cocheo et al 2000). The mean personal exposures to benzene in central Europe ranged from 6 μg/m³ in Basel, Switzerland (Jantunen et al 1999) to 14 μg/m³ in Germany (Hoffman et al 2000). Carrer et al (2000) studied personal exposures to benzene of 100 office workers in Milan showing an average exposure of 21.1 μg/m³. The highest reviewed mean population exposure to benzene in Southern Europe was measured in Murcia being 23 μg/m³ (Cocheo et al 2000).

In a German population based study of children and teenagers (GerES IV), weekly mean exposure to benzene was higher than the mean residential indoor concentration being 2.5 μg/m³ and 1.6 μg/m³ respectively. The highest exposure and indoor concentrations were 7.7 μg/m³ and 7.0 μg/m³ respectively (Ullrich et al 2002).

Based on these results we can conclude, that in addition to outdoor sources of benzene, there are important indoor sources like smoking, but clearly also emissions from other indoor sources.

Cumulative frequency distributions of the indoor and 48-hour personal exposure concentrations in European studies are presented in Figure 3.1, Figure 3.2, Figure 3.3 and Figure 3.4.

Source related short time concentrations of benzene are presented in Figure 3.5. Lee and Wang (2004) studied emissions of incense burning in chamber (18 m³) tests. They found that all 10 tested incense types caused concentrations exceeding the Recommended Indoor Air Quality Objectives for Office Buildings and Public Places in Hong Kong (HKIAQO) of 16.1 μg/m³. Maximum benzene concentrations peaked up to 117 μg/m³ during incense burning. Brown (2002) studied short time (30-50 min) concentrations of benzene in established and new buildings in Australia, reporting mean concentrations of 7 μg/m³ and <30 μg/m³ respectively. The highest measured indoor concentration was 81 μg/m³. Emission sources of this high concentration could not be identified, but high indoor concentrations (16 – 19 μg/m³) in two other houses were related to attached garages. In general, indoor concentrations of VOCs were much higher in new and recently renovated houses persisting above 'baseline level' for several weeks. Concentration decay rates correlated with molecular volume, indicating the role of diffusion processes for limiting the emissions. Elke at al (1998) measured short time concentrations of benzene inside buildings (60-min average), inside a train and a car (30-min average). Slightly higher concentrations were measured during driving a car than when exposed to tobacco smoke in a smoker compartment of a train or in a smoker day room.

Short time exposure scenarios for potential consumer activities were analysed in European Union Risk Assessment Report (EU 2003). The highest benzene concentration, 150 – 240 μg/m³ were expected to be present in a mainstream tobacco smoke. Exposure of passive smokers to benzene from smoking was assumed to be 7 μg/m³, exposure from painting and from car interior accessories 17 μg/m³ and 12 μg/m³ respectively.
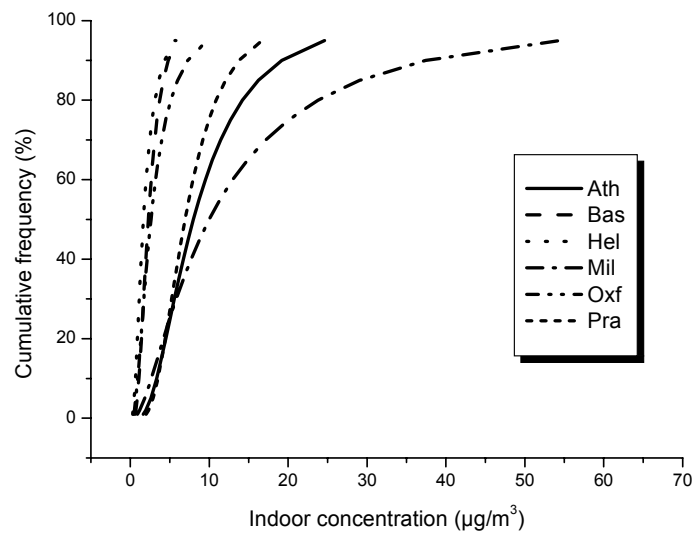
Figure 3.1. Cumulative frequency distributions of 30-hour indoor air concentrations of benzene in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=41) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
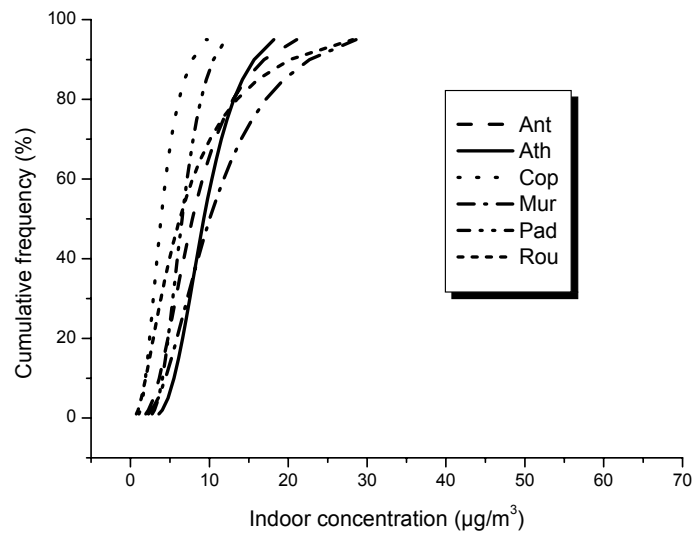
Figure 3.2. Cumulative frequency distributions of 5-day indoor air concentrations of benzene in Antwerp (Ant), Athens (Ath), Copenhagen (Cop), Murcia (Mur), Padova (Pad) and Rouen (Rou) (n= 50 in each city) measured in the MACBETH study (Cocheo et al 2000).
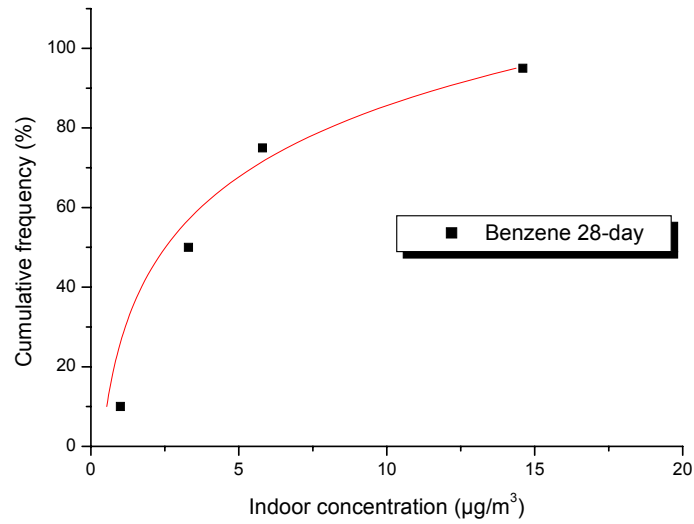
Figure 3.3. Cumulative frequency distribution of 28-day indoor air concentrations of benzene in England (GM= 3.0 µg/m3, max 93.5 µg/m3, n=796, Brown et al 2002).
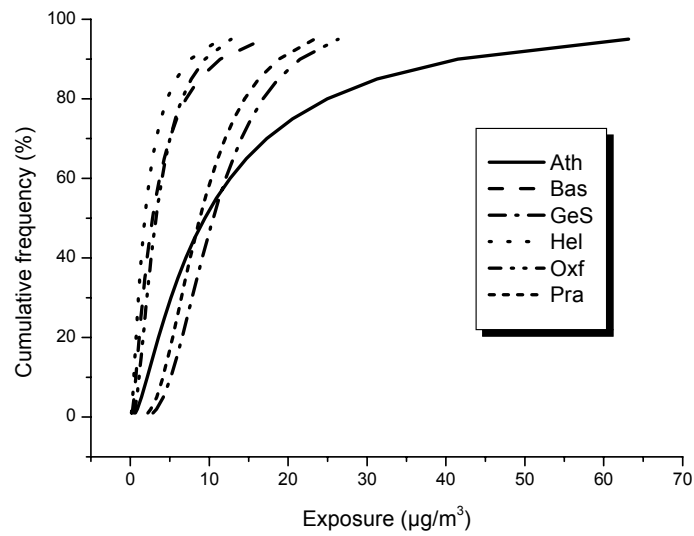
Figure 3.4. Cumulative frequency distributions of 48-hour personal exposure concentrations of benzene in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean concentrations of the German Survey GerES II (Hoffman et al 2000).
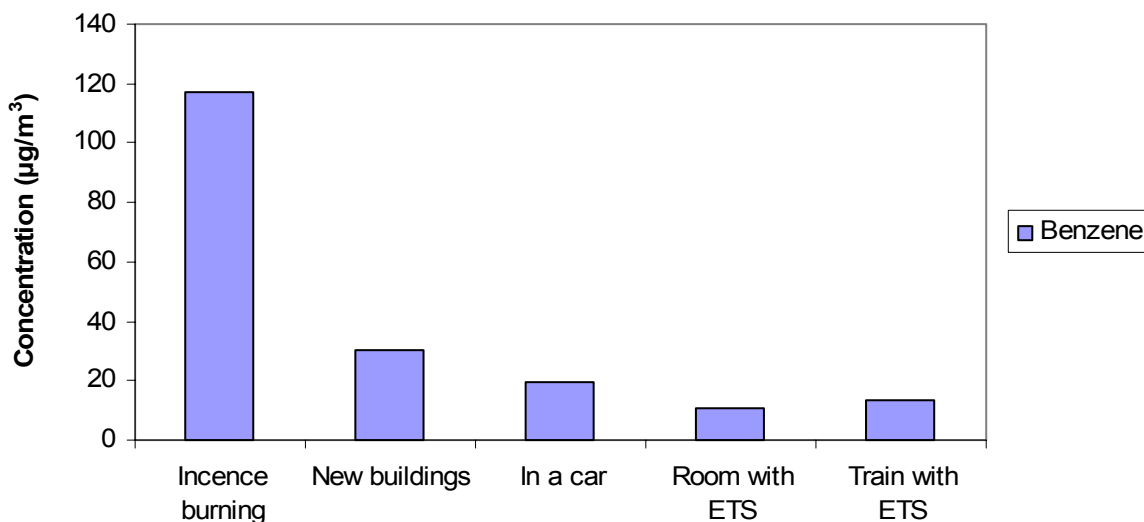
Figure 3.5. Short time benzene concentrations related to specific microenvironments or emission sources. Sampling times of 'New buildings' (Brown 2002), 'In a car', 'Room with ETS', and 'Train with ETS' (Elke at al 1998) were 30-50 min, 30-min, 60-min, 30-min respectively. During incense burning grab samples were obtained (Lee and Wang 2004).

4. Toxicokinetics

Absorption

Benzene is readily absorbed from oral and inhalation exposures. Less than 1% is absorbed through the skin. Pekari et al. (1992) studied respiratory absorption of benzene in three males exposed to 5 and 32 mg/m^3 (1.7 and 10 ppm) benzene for 4 hours each. Absorption of benzene was determined by measuring differences in concentration between inhaled and exhaled air. The average absorption was 52% at the low concentration and 48% at the high concentration.

Most human respiratory absorption studies were conducted at concentrations probably conducing to saturation of the benzene metabolism. The observed decline in absorption with increasing exposure time is apparently due to respiratory excretion of unmetabolized benzene. Animal studies indicate that the metabolism of benzene is saturated at exposure concentrations in excess of 32 mg/m^3. Because absorption at low dose levels is most relevant for derivation of exposure limits, the estimates of 48–52% retention derived by Pekari et al. (1992) are the most relevant values for evaluating absorption in humans. Absorption of benzene through the oral route is complete (100%).

Distribution

Results from test animal studies indicate that absorbed benzene is widely distributed throughout the body, independently of the route of the route of exposure. The parent compound is preferentially stored in the fat, although the relative uptake in tissues also appears to be dependent on the perfusion rate of tissues by blood. Steady-state benzene concentrations in rats exposed via inhalation to 1600 mg/m3 (500 ppm) for 6 hours were blood, 1.2 mg%; bone marrow, 3.8 mg%; and fat, 16.4 mg% (Rickert et al., 1979). Benzene was also found in the kidney, lung, liver, brain, and spleen. Levels of the benzene metabolites phenol, catechol, and hydroquinone were higher in the bone marrow than in blood, with phenol being eliminated more rapidly than catechol or hydroquinone after exposure. Benzene also has been shown to cross the human placenta and has been found in the cord blood in amounts equal to or greater than those in maternal blood (Dowty et al. 1976).

Metabolism and elimination

Despite extensive research, the metabolism of benzene is still not thoroughly understood. It is generally accepted that benzene itself is not directly responsible for causing the toxic effects; however, the metabolic products responsible for the noncancer and carcinogenic effects of benzene exposure have not been clearly defined. The evidence suggests that

several metabolites, as well as interactions between these metabolites, may be necessary to explain the toxic effects of benzene.

Reviews of benzene metabolism are given in ATSDR, 1997; Snyder et al., 1993b; Snyder and Hedli, 1996; Ross, 1996; Witz et al.,1996 (see also Figure 4.1). The liver is the major site of benzene metabolism. Benzene is converted to a number of metabolites (phenol, catechol, hydroquinone, 1,2,4-benzenetriol, benzoquinone and trans,trans-muconaldehyde) by the cytochrome P-450 dependent mixed-function oxidase system. The P-450 enzyme CYP 2E1 appears to exhibit the greatest affinity for benzene and is the most active in benzene metabolism. CYP 2B1 is also capable of hydroxylating benzene, but contributes to the metabolism only at higher concentrations. Oxidative metabolism by CYP 2E1 is required for manifestation of the haematotoxic and genotoxic effects of benzene as confirmed recently by studies on the benzene in vivo metabolism in transgenic CYP 2E1 knockout mice (Valentine et al. 1996).

In the attempt to explain bone marrow toxicity the hypothesis is brought forward that phenol, catechol, and hydroquinone are transported to the bone marrow and converted by peroxidase-mediated reactions to electrophilic compounds. For example, in the bone marrow, phenol is rapidly oxidized by the marrow peroxidases to reactive, protein-binding species such as biphenols and biphenoquinones (Sawahata et al. 1985). Hydroquinone also is oxidized in the marrow via a peroxidase-catalyzed reaction to an extremely short-lived semiquinone radical intermediate. This forms p-benzoquinone, a reactive metabolite, known to cause DNA damage and cytotoxic effects in benzene-exposed animals (Smith et al. 1989). However, trans-trans-muconaldehyde may also play a role (Snyder et al. 1989).

Pharmacokinetic models have been developed for rats and mice and used for risk assessments based on animal cancer data (WHO, 1993; Cox and Ricci, 1992). Physiologically based toxicokinetic models have also been developed using human data (WHO, 1993; Watanabe et al., 1994), but so far these have not been used for risk assessment.

The metabolism of benzene can be inhibited by toluene, leading to decreased toxicity. On the other hand, ethanol can increase the metabolism of benzene, primarily by inducing xenobiotic metabolizing enzymes (Medinsky at al., 1994). The average half-time of benzene in humans is 28 hours (WHO, 1987).

Following inhalation exposure to benzene, the major route of elimination of unmetabolized benzene in humans and animals is in exhaled air. Most benzene is metabolized and the metabolites are excreted after phase-II-conjugation predominantly in the urine. Phenolic metabolites are conjugated with sulfate or glucuronic acid (Henderson et al. 1989). Small amounts of the glucuronides may enter the bile and are found in the feces.

5. Health effects

Effects of short-term exposure

The acute toxicity of benzene is low. In general, acute symptoms are dependent on both the concentration and duration of exposure. Exposure to 24 g/m^3 for 30 min is life-threatening; 5 g/m^3 for 60 min produces significant symptoms; 150-500 mg/m^3 for 5 hr results in headache and weakness; whereas exposure to 80 mg/m^3 or less for 8 hr results in no demonstrable acute effect (Irons, 1992). Exposure at the odor threshold (2.8 mg/m³) for a brief duration has been reported to enhance the electropotential of the brain (Haley, 1977).

Major concerns of systemic benzene toxicity include aplastic anemia and acute myelogenous leukemia (IARC, 1987; Reprotext, 1993). Both of these conditions are typically seen in the chronic and subchronic exposures, but may be of concern following acute exposures as well. Myeloid and erythroid components of the bone-marrow are specific targets of benzene toxicity, which leads to aplastic anemia (IARC, 1982).

The long elimination half-life for benzene (13.1 hours for the longer phase of a 2-compartment model) is due to the formation of catechol, quinone, and hydroquinone in the bone marrow. These reactive metabolites are not readily excreted, and are cytotoxic to the germinal cells in the bone marrow (Greenlee et al., 1981). A 3-compartment model was fitted to human data on benzene disposition and bonemarrow metabolism (Watanabe et al., 1994). The general relationship between cumulative quantity of metabolites produced and inhalation concentration was not linear, but was S-shaped, inflecting upward at low concentrations, and saturating at high concentrations.

Figure 4.1: Benzene Metabolism (taken from OEHHA, 2001)

benzene

P450

glutathione conjugate — benzene oxide — benzene oxide oxepin — oxepin epoxide — muconaldehyde — muconic acid

GST GSH

- H₂O

S-phenylmercapturic acid

epoxide hydrolase

nonenzymatic rearrangement

dihydrodiol dehydrogenase — diol epoxide

P450

1,4-benzoquinone   1,4-semiquinone   hydroquinone   phenol   catechol   1,2-semiquinone   1,2-benzoquinone

P450

sulfate and glucuronide conjugates

1,2,4-trihydroxy-benzene   2-hydroxy-1,4-semiquinone   2-hydroxy-1,4-benzoquinone

Male C57BL/6J mice (7-Wgroup) were exposed to benzene 0, 33, 99, 319 or 961 mg/m³ (0, 10.2, 31, 100 or 301 ppm) in wholebody dynamic inhalation chambers for 6 hours/day for 6 consecutive days (Rozen et al. 1984). Control mice were exposed to filtered, conditioned air only. Erythrocyte counts were depressed in C57BL/6 mice only at 319 and 961 mg/m³. At exposures of 33 and 99 mg/m³, respectively, depressions of the proliferative responses of bone-marrow-derived B-cells and splenic T-cells occurred in C57BL/6J mice without causing a concomitant depression in number of splenic T- or B- cells. Peripheral lymphocyte counts were depressed at all levels. No correlation was made of reduced lymphocytes with general effects. These results demonstrate that short-term inhaled benzene even at low exposure concentrations can cause reduction in certain immune associated processes.

Results from subacute exposures further illustrate the hematotoxic effects of benzene and the potential for immunotoxicity. Inhalation of 334 mg/m³ (103 ppm) benzene for 6 hours/day for 7 days by mice caused decreased spleen and marrow cellularities and decreased spleen weights (Green et al., 1981). Benzene inhalation at concentrations of 0, 32, 96, 319, and 958 mg/m³ (0, 10, 30, 100, and 300 ppm) for 6 hours/day for 5 days resulted in a decreased host-resistance to bacterial infection by Lysteria monocytogenes (Rosenthal and Snyder, 1985). The numbers of L. monocytogenes bacteria isolated from the spleen were increased in a dose-dependent manner on day 4 of infection. The total numbers of T- and B-lymphocytes in the spleen and the proliferative ability of the splenic lymphocytes were decreased in a dose-dependent manner by benzene exposures of 96 mg/m³ or greater. In this study, no decrement in host resistance or immune response was observed at 32 mg/m³ benzene. Later studies in mice have also shown that exposure to 32 mg/m³ for a subacute duration does not significantly alter hematological parameters in blood, spleen, thymus, or bone marrow (Farris et al., 1996; 1997). Farris et al. (1997) reported the hematological consequences of benzene inhalation in B6C3F1 mice exposed to 3.2 , 16, 32, 319 and 639 mg/m³ (1, 5, 10, 100, and 200 ppm) benzene for 6 hr/day, 5 days/week for 1, 2, 4, or 8 weeks and a recovery group. There were no significant effects on hematopoietic parameters from exposure to 10 ppm benzene or less. Thus 32 mg/m³ was a NOAEL for 1 week of exposure (and longer). Exposure to 319 and 639 mg/m³ benzene reduced the number of total bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most blood parameters. Replication of primitive progenitor cells in the bone marrow was increased during the exposure period as a compensation for the cytotoxicity. At 639 mg/m³, the primitive progenitor cells maintained an increased percentage of cells in S-phase through 25 days of recovery compared with controls.

In addition to myelotoxicity, acute exposure to benzene may disrupt erythropoiesis and result in genotoxicity. Erythropoiesis, as measured by uptake of radiolabeled iron in the bone-marrow, has been shown to be inhibited by subcutaneous injection of 10 mmol/kg benzene in mice (Bolcsak and Nerland, 1983). Inhalation of 9.6 mg/m³ benzene for 6 hours by rats resulted in a significant increase over controls in the frequency of sister chromatid exchanges in peripheral blood lymphocytes (Erexson et al., 1986).

Reproductive and developmental effects have been reported following benzene exposure. Coate et al. (1984) exposed groups of 40 female rats to 3.2 , 32, 128, 319 and 639 mg/m³ (0, 1, 10, 40, and 100 ppm) benzene for 6 hours/day during days 6-15 of gestation. In this study, teratologic evaluations and fetotoxic measurements were done on the fetuses. A significant decrease was noted in the body weights of fetuses from dams exposed to 319 mg/m³. No effects were observed at a concentration of 128 mg/m³.

Keller and Snyder (1986) reported that exposure of pregnant mice to concentrations as low as 16 mg/m³ (5 ppm) benzene on days 6-15 of gestation (6 hr/day) resulted in bone-marrow hematopoietic changes in the offspring that persisted into adulthood. However, the hematopoietic effects (e.g., bimodal changes in erythroid colony-forming cells) in the above study were of uncertain clinical significance.

Keller and Snyder (1988) exposed Swiss Webster mice to benzene in utero from day six through day 15 of gestation. Pregnant mice were administered benzene via inhalation at doses of 5, 10 or 20 ppm. On day 16 of gestation, two days after birth and six weeks after birth, offspring were tested for levels of blood haemoglobin and levels of hematopoietic cells in the blood, bone marrow and liver. No adverse effects were observed for fetuses at day 16 of gestation. However, two days after birth, offspring exhibited reduced numbers of circulating erythroid precursor cells (all doses), increased numbers of hematopoietic blast cells in the liver (20 ppm only), increased granulopoietic precursor cells (20 ppm only) and decreased numbers of erythropoietic precursor cells (20 ppm only). Mice examined six weeks after birth also demonstrated increased granulopoiesis in the 20 ppm dose group.

An exposure of 1600 mg/m³ (500 ppm) benzene through days 6-15 of gestation was teratogenic in rats while 160 mg/m³ resulted in reduced fetal weights on day 20 of gestation. No fetal effects were noted at an exposure of 32 mg/m³ (Kuna and Kapp, 1981). An earlier study by Murray et al. (1979) showed that inhalation of 1600 mg/m³ benzene for 7 hours/day on days 6-15 and days 6-18 of gestation in mice and rabbits, respectively, induced minor skeletal variations. Tatrai et al. (1980) demonstrated decreased fetal body weights and elevated liver weights in rats exposed throughout gestation to 150 mg/m³ (47 ppm).

A recent study did not find any increased risk of spontaneous abortion among the wives of 823 male workers occupationally exposed to benzene levels of less than or around 15 mg/m³ *(Strucker et al., 1994)*.

An attempt by Nielsen and Alarie (1982) to determine the inhalation RD_{50} (the concentration of a compound inducing a 40% decrease in respiratory rate in male Swiss-Webster mice) for benzene was not successful. These investigators showed that inhalation of 18,5 g/m³ (5800 ppm) benzene in mice caused an increase in respiratory rate beginning at 5 minutes following onset of exposure. They speculated that the stimulation of respiratory rate resulted from the action of benzene on the central nervous system. In this study, benzene was not irritating to the upper airways of the animals.

Summary of short-term exposure effect levels (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
128_{EXP}	319_{EXP}	Developmental: decreased fetal body weights (severe adverse effect!)	Rats, 6 hours per day during days 5-16 of gestation	Coate *et al.*, 1984; (supported by Kuna and Kapp, 1981; Keller and Snyder, 1988)	OEHHA 1999 REL: 1.3
	16_{EXP}	Developmental: Altered hematopoiesis in offspring (high degree of uncertainty!)	Mice, 6 hours per day during days 5-16 of gestation	Keller and Snyder, 1988	OEHHA 2001 $MADL_{inhal.}$: 1.3 µg/day
	33_{EXP} 8_{ADJ} 47_{HEC}	Haematological: depressed peripheral lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes (less Serious LOAEL) .	Mice, 6 hours per day (for 6 consecutive days)	Rozen et al. 1984	ATSDR 1997 MRL: 0.16

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h-ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5%

response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration; MADL$_{inhal.}$ maximum allowable daily level (OEHHA)

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of Acute Reference Exposure Level (for a 6-hour exposure) (Level Protective Against Severe Adverse Effects):

Study	Coate *et al.*, 1984; (supported by Kuna and Kapp, 1981; Keller and Snyder, 1988)
Study population	pregnant female rats
Exposure method	inhalation of 0, 1, 10, 40, or 100 ppm
Critical effects	decreased fetal body weights
LOAEL	100 ppm
NOAEL	40 ppm
Exposure duration	6 hours per day (for 5 days)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	0.4 ppm (1.3 mg/m³; 1,300 µg/m³)

While benzene exposure results in decreased immune response and hematopoietic effects in laboratory animals following 5 day exposures, it was problematic to extrapolate from these repeated dose studies for these endpoints. Thus, no level protective against mild adverse effects for one-hour is being recommended. The REL is based on developmental toxicity, a severe adverse effect.

Pregnant female rats (40 per group) were exposed for 6 hours/day on days 6-15 of gestation to benzene concentrations of 0, 1, 10, 40, and 100 ppm (0, 3.24, 32.4, 129.6, and 324 mg/m³) (Coate et al., 1984). The mean fetal weights from the females treated with 100 ppm benzene were significantly decreased (p < 0.05) compared to controls. No teratogenic, fetotoxic, or maternally toxic effects were observed in rats exposed to 40 ppm (129.6 mg/m³) benzene or less. The 40 ppm (129.6 mg/m³) concentration is considered a NOAEL for reduced fetal weight. The value of 40 ppm for a 6-hour exposure was extrapolated to a 1-hour exposure using the equation $C^n * T = k$, where $n = 2$. The resulting 100 ppm extrapolated value was used to determine the level protective against severe adverse effects using uncertainty factors of 10 for intraspecies and 10 for interspecies variation. The level protective against severe adverse effects for benzene is therefore 1.0 ppm or 3.24 mg/m³.

Kuna and Kapp (1981) found direct teratogenic effects measured as decreased crown-rump length, exencephaly, and angulated ribs in rats when pregnant females were exposed 6 hours/day during days 6-15 of gestation to a concentration of 500 ppm. In this study, a concentration of 50 ppm during gestation resulted in lower fetal weights measured on day 20 of gestation. No fetal effects were noted at an exposure of 10 ppm (32 mg/m³). Keller and Snyder (1988) reported a NOAEL of 10 ppm for developmental hematopoietic effects in mice. The highest reported NOAEL (i.e., 40 ppm) consistent with reported LOAEL values was chosen for the derivation of the Reference Exposure Level (severe adverse effect level, in this case) for benzene.

OEHHA (2001)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

From all the available animal studies the most sensitive study was a developmental toxicity study in mice using endpoints reflecting altered hematopoiesis (blood cell formation) (Keller and Snyder, 1988). Exposures were by inhalation at 0, 5, 10 and 20 ppm benzene concentrations in air, 6 h/day, during gestation days 6 to 15. The LOEL for developmental hematopoietic effects was 5 ppm based on a significantly reduced relative number of early nucleated red cells in a sample of nucleated cells from the peripheral blood of 2-day old neonates that had been exposed to benzene in utero. Because the Keller and Snyder study provided a LOEL rather than a NOEL, a NOEL for purposes of assessment was calculated by dividing the LOEL of 5 ppm by 10, resulting in a NOEL of 0.5 ppm.
The following calculations were performed to derive the Maximum Allowable Daily Level (MADL) for benzene: Conversion of air concentration in ppm to mg/m³ using a molecular weight for benzene of 78.11 daltons and a partial molar volume of 24.45 at 25°C (=1.6 mg/m³). Conversion of air concentration for 6 hour (h) exposure to a 24 h day

(=0.40 mg/m^3). Calculation of NOEL dose for 30 g mouse with an inhalation rate of 0.063 m^3/day (Bond et al. 1986, Depledge 1985) (=0.84 mg/kg/day). Calculation of NOEL dose for a 58 kg woman (=49 mg/day).
The MADL is derived by dividing the NOEL by one thousand. Thus, the adjusted NOEL was divided by 1000 to obtain the MADL$_{inhalation}$ = 49 μg/day

ATSDR (1997)
Agency for Toxic Substances and Disease Registry

Derivation of the Minimal Risk Level (MRL):
ATSDR derived an acute-duration inhalation MRL of 0.05 ppm for benzene based on a LOAEL of 10 ppm for immunotoxicity (reduced lymphocyte proliferation) following mitogen stimulation in mice (Rozen et al. 1984). The animal LOAEL was converted to a human equivalent concentration (LOAEL$_{HEC}$) of 14.7 ppm and divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) to yield the MRL. The mice were exposed 6 hours/day for 6 days.

Effects noted in the study (Rozen et al. 1984) and corresponding doses: 10.2 ppm: No adverse effect on erythrocytes, depressed peripheral lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes (Less Serious LOAEL). 31 ppm: No adverse effect on erythrocytes, depression of mitogen-induced blastogenesis of splenic T-cells. 100 ppm: Depressed erythrocyte counts. Dose end point used for MRL derivation: 10.2 ppm. Uncertainty factors used in MRL derivation: 300, 10 for use of a LOAEL, 3 for extrapolation from animals to humans, 10 for human variability. The ratio of the blood/gas partition coefficients was assumed to be 1. The concentration was adjusted for intermittent exposure by multiplying the LOAEL (10.2 ppm) by 6/24 to correct for less than a full day of exposure. The resulting number (adjusted LOAEL) is 2.50 ppm.

The human equivalent concentration (HEC) was calculated using Formula 4-l1, from Interim Methods for Development of Inhalation Reference Concentrations, EPA 1990h:

$$LOAEL_{[HEC]} \text{ (mg/m}^3 \text{ or ppm)} = LOAEL \text{ [ADJ] (mg/m}^3 \text{ or ppm)} \times (V_A/BW)_A / (V_A/BW)_H$$

where: LOAEL $_{[HEC]}$ = the LOAEL human equivalent concentration
LOAEL $_{[ADJ]}$ = the LOAEL adjusted for duration (see above)
$(V_A/BW)_A / (V_A/BW)_H$ = the ratio of the alveolar ventilation rate (mL/min or L/hr) divided by Body weight (kg) of the animal species to the same parameters for humans.

Values for this ratio were taken from EPA 1988e, as follows: $(V_A)_A$ = ventilation rate for male B6C3F1 mice, subchronic, 0.053 m^3/day x 1,000 L/m^3 x 1 day/24 hr= 2.208 L/hr = 2.21 L/hr. $(BW)_A$ = body weight for male B6C3F1 mice, subchronic, 0.0316 kg $(V_A)_H$ = ventilation rate for human adult male, 20 m^3/day x 1,000 L/m^3 x 1 day/24 hr= 833.33 L/hr = 833 L/hr. $(BW)_H$ = body weight for human adult male, 70 kg. Resulting in a LOAEL$_{[HEC]}$ given by: 2.50 ppm x (2.21 L/hr / 0.0316 kg) / (833 L/hr / 70 kg) = 14.7 ppm (47 mg/m^3).

Other additional studies or pertinent information that lend support to this MRL: Increased number of MN-PCEs, decreased numbers of granulopoietic stem cells (Toft et al. 1982) lymphopenia (Cronkite et al. 1985), lymphocyte depression, and increased susceptibility to bacterial infection (Rosenthal and Snyder 198.5) are among the adverse hematological and immunological effects observed in several other acute-duration inhalation studies. The study by Rozen et al. (1984) shows benzene immunotoxicity (reduced mitogen-induced lymphocyte proliferation) at a slightly lower exposure level than these other studies. C57BI/6J mice were exposed to 0, 10.2, 31, 100, and 301 ppm benzene for 6 days at 6 hrs/day. Control mice were exposed to filtered, conditioned air only. Lymphocyte counts were depressed at all exposure levels while erythrocyte counts were elevated at 10.2 ppm, equal to controls at 31 ppm and depressed at 100 and 301 ppm. Femoral B-lymphocyte and splenic B-lymphocyte numbers were reduced at 100 ppm. Levels of circulating lymphocytes and mitogeninduced blastogenesis of femoral B-lymphocytes were depressed after exposure to 10.2 ppm benzene for 6 days. Mitogen-induced blastogeneses of splenic T-lymphocytes were depressed after exposure to 31 ppm of benzene for 6 days. In another study, mice exhibited a 50% decrease in the population of erythroid progenitor cells (CFU-E) after exposure to 10 ppm benzene for 5 days, 6 hours per day (Dempster and Snyder 1991). In a study by Wells and Nerland (1991), groups of 4-5 male Swiss-Webster mice were exposed to 0, 3, 25, 55, 105, 199, 303, 527, 1,150, or 2,290 ppm benzene for 6 hours/day for 5 days. The number of leukocytes in peripheral blood and spleen weights were significantly decreased compared with untreated controls at all concentrations ¡Ý25 ppm. Therefore, 3 ppm was the NOAEL and 25 ppm was the LOAEL for these effects. Other endpoints were not monitored in this study. These data support the choice of Rozen et al. (1984) as a critical study.

Effects of long-term exposure (noncancer)

The primary toxicological effects of chronic benzene exposure are on the hematopoeitic system. Neurological and reproductive/developmental toxic effects are also of concern at slightly higher concentrations. Impairment of immune function and/or various anemias may result from the hematotoxicity. The hematologic lesions in the bone marrow can lead to peripheral lymphocytopenia and/or pancytopenia following chronic exposure. Severe benzene exposures can also lead to life-threatening aplastic anemia. These lesions may lead to the development of leukemia years after apparent recovery from the hematologic damage (DeGowin, 1963).

Several types of blood dyscrasia, including pancytopenia, aplastic anaemia, thrombocytopenia, granulocytopenia and lymphocytopenia have been noted following exposure to benzene. As in experimental animals, the primary target organ for benzene that results in haematological changes is the bone marrow. It has been suggested that the cells at highest risk are the rapidly proliferating stem cells *(WHO, 1993)*. Most of these cases were reported several years ago, when benzene was used as a solvent in different workplaces. An increased frequency of anaemia was detected among shoe workers, rotogravure workers and rubber factory workers with prolonged exposure to high benzene concentrations (hundreds of milligrams of benzene per m^3) *(WHO, 1993)*.

Kipen et al. (1988) performed a retrospective longitudinal study on a cohort of 459 rubber workers, examining the correlation of average benzene exposure with total white blood cell counts taken from the workers. These researchers found a significant ($p < 0.016$) negative correlation between average benzene concentrations in the workplace and white blood cell counts in workers from the years 1940-1948. A reanalysis of these data by Cody et al. (1993) showed significant decreases in RBC and WBC counts among a group of 161 workers during the 1946-1949 period compared with their pre-exposure blood cell counts. The decline in blood counts was measured over the course of 12 months following start of exposure. During the course of employment, workers who had low monthly blood cell counts were transferred to other areas with lower benzene exposures, thus potentially creating a bias towards non-significance or removing sensitive subjects from the study population. Since there was a reported 75% rate of job change within the first year of employment, this bias could be highly significant. In addition, there was some indication of blood transfusions used to treat some "anemic" workers, which would cause serious problems in interpreting the RBC data, since RBCs have a long lifespan in the bloodstream. The exposure analysis in this study was performed by Crump and Allen (1984). The range of monthly median exposures was 30-54 ppm throughout the 12-month segment examined. Despite the above-mentioned potential biases, workers exposed above the median concentrations displayed significantly decreased WBC and RBC counts compared with workers exposed to the lower concentrations using a repeated measures analysis of variance.

Tsai et al. (1983) examined the mortality from all cancers and leukemia, in addition to hematologic parameters in male workers exposed to benzene for 1-21 years in a refinery from 1952-1978. The cohort of 454 included maintenance workers and utility men and laborers assigned to benzene units on a "regular basis". Exposures to benzene were determined using personal monitors; the median air concentration was 0.53 ppm in the work areas of greatest exposure to benzene. The average length of employment in the cohort was 7.4 years. The analysis of overall mortality in this population revealed no significant excesses. Mortality from all causes and from diseases of the circulatory system was significantly below expected values based on comparable groups of U.S. males. The authors concluded the presence of a healthy worker effect. An internal comparison group of 823 people, including 10% of the workers who were employed in the same plant in operations not related to benzene, showed relative risks for 0.90 and 1.31 for all causes and cancer at all sites, respectively ($p < 0.28$ and 0.23). A subset of 303 workers was followed for medical surveillance. Up to four hematological tests per year were conducted on these workers. Total and differential white blood cell counts, haemoglobin, hematocrit, red blood cells, platelets and clotting times were found to be within normal (between 5% and 95% percentile) limits in this group. Although the exposure duration averaged only 7.4 years, the study was considered to be chronic since 32% of the workers had been exposed for more than 10 years.

Collins et al. (1997) used routine data from Monsanto's medical/industrial hygiene system to study 387 workers with daily 8-hour time-weighted exposures (TWA) averaging 0.55 ppm benzene (range = 0.01 – 87.69 ppm; based on 4213 personal monitoring samples, less than 5% of which exceeded 2 ppm). Controls were 553 unexposed workers. There was no increase in the prevalence of lymphopenia, an early, sensitive indicator of benzene toxicity, among exposed workers (odds ratio = 0.6; 95% confidence interval = 0.2 to 1.8), taking into account smoking, age, and sex. There also was no increase in risk among workers exposed 5 or more years (odds ratio = 0.6; 95% confidence interval = 0.2 to 1.9). There were no differences between exposed and unexposed workers for other measures of hematotoxicity, including mean corpuscular volume and counts of total white blood cells, red blood cells, haemoglobin, and platelets.

Rothman et al. (1996) compared hematologic outcomes in a cross-sectional study of 44 male and female workers heavily exposed to benzene (median = 31 ppm as an 8-hr TWA) and 44 age and gender-matched unexposed controls from China. Hematologic parameters (total WBC, absolute lymphocyte count, platelets, red blood cells, and hematocrit)

were decreased among exposed workers compared to controls; an exception was the red blood cell mean corpuscular volume (MCV), which was higher among exposed subjects. In a subgroup of 11 workers with a median 8 hr TWA of 7.6 ppm (range = 1-20 ppm) and not exposed to more than 31 ppm on any of 5 sampling days, only the absolute lymphocyte count (ALC) was significantly different between exposed workers and controls (p = 0.03). Among exposed subjects, a dose response relationship with various measures of current benzene exposure (i.e., personal air monitoring, benzene metabolites in urine) was present only for the total WBC count, the absolute lymphocyte count, and the MCV. Their results support the use of the absolute lymphocyte count as the most sensitive indicator of benzene-induced hematotoxicity.

Ward et al. (1985) exposed male and female CD-1 mice and Sprague-Dawley rats to 0, 1, 10, 30 or 300 ppm (0, 3.2, 32, 96 or 960 mg/m3) benzene, 6 hours/day, 5 days/week for 91 days and measured various hematological endpoints. The study identified both a LOAEL of 300 ppm and a NOAEL of 30 ppm. The male mouse appeared to be the most sensitive sex/species in this study. The exposure-response relationships for the different hematological endpoints for the male mouse were modeled using a BMD modeling approach and decreased hematocrit (i.e., volume percentage of erythrocytes in whole blood) was chosen as the critical effect.

An examination of 32 patients, who were chronically exposed to benzene vapors ranging from 150 to 650 ppm for 4 months to 15 years, showed that pancytopenia occurred in 28 cases. Bone marrow punctures revealed variable hematopoeitic lesions, ranging from acellularity to hypercellularity (Aksoy et al., 1972).

In an evaluation of the literature, a WHO Task Group *(WHO, 1993)* drew the conclusion that bone marrow depression or anaemia would not be expected to occur in workers exposed for 10 years to 3.2 mg/m^3 (1 ppm) or less.

Intermediate-duration inhalation and oral exposures to benzene induced neurological effects in animals that included reduced limb grip strength, behavioral disturbances, and changes in brain levels of monoamine transmitters and acetylcholinesterase (Dempster et al. 1984; Frantik et al. 1994; Hsieh et al. 1988; Li et al. 1992).

Older studies on workers exposed to benzene, toluene and xylene have shown decreased levels of agglutinins and IgG and IgA immunoglobulins, and increased levels of IgM.

A loss of leukocytes has been observed in several studies in highly exposed workers as well as reduced numbers of T lymphocytes. In a study of refinery workers exposed to benzene concentrations of less than 32 mg/m^3, no such immunological effects were seen *(WHO, 1993)*.

Summary of long-term exposure effect levels (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
1.7$_{Study}$ 0.60$_{ADJ}$		Haematological effects (total and differential white blood cell counts, haemoglobin, hematocrit, red blood cells, platelets and clotting times)	Occupational, 7.4y	Tsai et al. 1983	OEHHA 1999 REL: 0.06
	44 $_{BMC}$ 23 $_{BMCL}$ 8.2$_{ADJ-BMCL}$	Decreased lymphocyte counts	Occupational, 6.3y (0.7-16y)	Rothman et al. 1996	EPA-IRIS 2003 RfC: 0.03
(3.2)	32 $_{EXP}$	Blood cell depression (lymphocytes)	Mouse, 6-178d NOAEC has been derived, not observed	Dempster and Snyder, 1990, Rozen et al. 1984, Baarson et al., 1984, Green et al., 1981a,b, and other studies	ECB 2003
	2.5 $_{EXP}$ 1.05 $_{HEC}$	Neurological: increased (rapid response time) (Less Serious minimal LOAEL).	Mice, 30d (2h/d, 6d/w)	Li et al. 1992 intermediate duration study !	ATSDR 1997 MRL$_{INT}$: 0.013 (intermediate!)

OEHHA (1999)
Office of Environmental Health Hazard Assessment

Derivation of Chronic Reference Exposure Level (REL)

Study	Tsai *et al.* (1983)
Study population	303 Male refinery workers
Exposure method	Occupational exposures for 1-21 years
Critical effects	Hematological effects
LOAEL	Not observed
NOAEL	0.53 ppm
Exposure continuity	8 hr/day (10 m3 per 20 m3 day), 5 days/week
Exposure duration	7.4 years average (for the full cohort of 454); 32% of the workers were exposed for more than 10 years
Average occupational exposure	0.19 ppm
Human equivalent concentration	0.19 ppm
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level	0.02 ppm (20 ppb; 0.06 mg/m3; 60 μg/m3)

Both the animal and human databases for benzene are excellent. The human data presented by Tsai *et al.* (1983) and associates were selected over animal studies because the collective human data were considered adequate in terms of sample size, exposure duration, and health effects evaluation. Although the study by Tsai *et al.* (1983) is a free-standing NOAEL, the endpoint examined is a known sensitive measure of benzene toxicity in humans. In addition, the LOAEL for the same endpoint in workers reported by Cody *et al.* (1993) help form a dose-response relationship and also yield an REL which is consistent with that derived from Tsai *et al.* (1983). The study by Cody *et al.* (1993), since it failed to identify a NOAEL and was only for a period of 1 year, contained a greater degree of uncertainty in extrapolation to a chronic community Reference Exposure Level. The recent results of Collins *et al.* (1997) that included a NOAEL of 0.55 ppm and of Rothman *et al.* (1996) that included a LOAEL of 7.6 ppm are consistent with those of Tsai *et al.* Therefore the study by Tsai *et al.* (1983) was used as the basis for the chronic REL for benzene.

In the Cody *et al.* (1993) study, significant hematological effects, including reduced RBC and WBC counts, were observed in 161 male rubber workers exposed to median peak concentrations (i.e., only the peak concentrations for any given exposure time were reported) of 30-54 ppm or more for a 12-month period during 1948. The 30 ppm value was considered a 1-year LOAEL for hematological effects. The 30 ppm value is the low end of the range of median values (30-54 ppm) reported by Crump and used in the Kipen *et al.* (1988) and Cody *et al.* (1993) studies. An equivalent continuous exposure of 10.7 ppm can be calculated by assuming that workers inhaled 10 m3 of their total 20 m3 of air per day during their work-shift, and by adjusting for a normal 5 day work week. Application of uncertainty factors for subchronic exposures, estimation of a NOAEL, and for protection of sensitive subpopulations (10 for each) results in an REL of 0.01 ppm (10 ppb; 30 μg/m3). This is comparable to the REL based on Tsai *et al.* (1983).

Ward *et al.* (1996) determined a relationship between occupational exposures to benzene and decreased red and white cell counts. A modeled dose-response relationship indicated a possibility for hematologic effects at concentrations below 5 ppm. However, no specific measures of the actual effects at concentrations below 2 ppm were taken, and the Tsai *et al.* (1983) data were not considered in their analysis. The purpose of this study was to characterize the trend for effects at low concentrations of benzene. A NOAEL or LOAEL was not identified in the study. The selection of a NOAEL of 0.53 ppm is therefore not inconsistent with the results of the Ward *et al.* (1996) study.

For comparison with the REL of 20 ppb based on human data, OEHHA estimated a REL based on the chronic inhalation study in mice by Baarson *et al.* (1984), which showed that bone-marrow progenitor cells were markedly suppressed after intermittent exposures (6 hr/day, 5 days/week) to 10 ppm benzene for 6 months. An extrapolation of this value to an equivalent continuous exposure resulted in a concentration of 1.8 ppm. Application of an RGDR of 1 for a systemic effect and uncertainty factors of 3 and 10 for inter- and intraspecies variability, and 10 for estimation of a NOAEL from the LOAEL would result in an REL of 6 ppb (20 μg/m3). The Farris *et al.* (1997) 8 week study indicated a LOAEL of 100 ppm and a NOAEL of 10 ppm for hematological effects. Application of an RGDR of 1 and UFs of 10 for subchronic, 3 for interspecies and 10 for intraspecies extrapolation (total UF = 300) also resulted in an estimated REL of 6 ppb, in reasonable agreement with the proposed REL of 20 ppb. One could also crudely approximate an inhalation REL from the oral NTP bioassay where a dose of 25 mg/kgday was associated with hematological effects.

The concentration approximately equivalent to a 25 mg/kg dose for a 70 kg human breathing 20 cubic meters per day is 27 ppm. Assuming this is a LOAEL and applying an RGDR of 1 for systemic effects, a 3 fold UF for extrapolation to humans, a 10-fold UF for LOAEL to NOAEL extrapolation and a 10-fold UF for intraspecies extrapolation yields a REL of 90 ppb. There are a number of uncertainties to this approach, yet it comes within a factor of 5 of the proposed REL based on human studies.

IRIS (2003)
Integrated Risk Information System (IRIS) – U.S.EPA

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical effect	Exposures*	UF	MF	RfC
Decreased lymphocyte count (Human occupational inhalation study of Rothman et al., 1996)	BMCL = 8.2 mg/m^3	300	1	0.03 mg/m^3

*Conversion factors: MW = 78.11. BMCL = 7.2 ppm, 8-hour TWA. Assuming 25ºC and 760 mm Hg, BMCL (mg/m^3) = 7.2 ppm x MW/24.45 = 23.0 mg/m^3. BMCL$_{ADJ}$ = 23.0 mg/m^3 x 10 m^3/20 m^3 x 5 days/7days = 8.2 mg/m^3. (The BMC was based on a benchmark response of one standard deviation change from the control mean.)

The RfC is based on BMD modeling of the absolute lymphocyte count (ALC) data from the occupational epidemiologic study of Rothman et al. (1996), in which workers were exposed to benzene by inhalation. A comparison analysis based on BMD modeling of hematological data from the Ward et al. (1985) subchronic experimental animal inhalation study was also conducted. In addition, comparison analyses using the LOAEL from the Rothman et al. (1996) study and the NOAEL from the Ward et al. (1985) study were performed.

BMD modeling of the ALC exposure-response data from Rothman et al. (1996) was done using U.S. EPA's Benchmark Dose Modeling Software (version 1.20). The data are rather supralinear, that is, the change in ALC per unit change in exposure decreases with increasing exposure; therefore, in order to fit the data with one of the available continuous models, the exposure levels were first transformed according to the equation $d' = \ln(d+1)$. Then the exposure-response data were fitted using the continuous linear model, which provided a good fit (p=0.54). A two-degree polynomial and a power model also fit the data, but the linear model was selected because it is the most parsimonious. The parameters were estimated using the method of maximum likelihood. A constant variance model was used.

In the absence of a clear definition for an adverse effect for this continuous endpoint, a default benchmark response of one standard deviation change from the control mean was selected, as suggested in EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000). This default definition of a benchmark response for continuous endpoints corresponds to an excess risk of approximately 10% for the proportion of individuals below the 2nd percentile (or above the 98th percentile) of the control distribution for normally distributed effects (see U.S. EPA, 2000). A 95% lower confidence limit (BMCL) on the resulting BMC was calculated using the likelihood profile method. Transforming the results back to the original exposure scale yields a BMC of 13.7 ppm (8-hr TWA) and a BMCL of 7.2 ppm (8-hr TWA).

As suggested in the draft technical guidance document (U.S. EPA, 2000), the BMCL is chosen as the point of departure for the RfC derivation. An adjusted BMCL is calculated by converting ppm to mg/m3 and adjusting the 8-hour TWA occupational exposure to an equivalent continuous environmental exposure. The BMCL is first converted to mg/m3 using the molecular weight of 78.11 for benzene and assuming 25ºC and 760 mm Hg: 7.2 ppm × 78.11/24.45 = 23.0 mg/m3. The converted value is then adjusted from the 8-hour occupational TWA to a continuous exposure concentration using the default respiration rates (U.S. EPA, 1994): BMCLADJ = 23.0 mg/m3 × (10 m3/20 m3) × 5 days/7 days = 8.2 mg/m3.

The RfC is then derived by dividing the adjusted BMCL by the overall UF of 300: RfC = BMCLADJ/UF = 8.2 mg/m3 ÷ 300 = 3 × 10-2 mg/m3. The overall UF of 300 comprises a UF of 3 for effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies (see Section I.B.3).

For comparison, an RfC was also calculated based on the LOAEL of 7.6 ppm (8-hr TWA) from the Rothman et al. (1996) study. Converting the units and adjusting for continuous exposure as above results in a LOAEL$_{ADJ}$ of 8.7 mg/m3. The LOAEL$_{ADJ}$ is then divided by an overall UF of 1000 to obtain the RfC: 8.7 mg/m3 ÷ 1000 = 9 × 10-3 mg/m3. The combined UF of 1000 represents UFs of 10 to account for the use of a LOAEL because of the lack of an appropriate NOAEL, 10 for intraspecies differences in response (human variability), 3 for subchronic-to-chronic

extrapolation, and 3 for database deficiencies. The value of 9 × 10-3 mg/m3 is in good agreement with the RfC of 3 × 10-2 mg/m3 calculated from the BMC.

ATSDR (1997)
Agency for Toxic Substances and Disease Registry

Derivation of the Minimal Risk Level (MRL):
The intermediate-duration inhalation MRL of 0.004 ppm was derived from a LOAEL value of 0.78 ppm for neurological effects of intermediate-duration inhalation exposure of mice to benzene (Li et al. 1992). The ratio of the blood/gas partition coefficients was assumed to be 1. The dose was adjusted for intermittent exposure by multiplying the LOAEL (0.78 ppm) by 2 hours/24 hours and by 6 days/7 days to adjust to continuous exposure. The resulting adjusted LOAEL 0.056 ppm was then converted to a human equivalent concentration (HEC) by multiplying by the ratio of the mouse ventilation rate (2.21 L/hour) to its body weight (0.0316 kg) divided by the ratio of the human ventilation rate (833 L/hour) to human body weight (70 kg) (formula 4-11, EPA 1990h; ventilation rate and body weight values taken from EPA 1988e). The resulting LOAEL (HEC) of 0.33 ppm was then divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans after adjusting for the human equivalent concentration, and 10 for human variability), yielding the MRL of 0.004 ppm (see Appendix A). ATSDR (1997) did not derive a chronic-duration inhalation MRL for benzene due to lack of suitable data.

ECB (2003)
European Chemical Bureau - Institute for Health and Consumer Protection - European Union Risk Assessment Report

In its recent risk assessment draft report (2003) ECB concludes that chronic benzene exposure leads to depression of white blood and red blood cells. This effect is reversible after long time exposures (years) with low concentrations (reported concentration range: > 32-64 mg/m³ = 10-20 ppm). Exposure to 192 mg/m³ (60 ppm) of benzene for about a week may be associated with an increased proportion of large granular lymphocytes, and not severe narrow effects nor specific cytopenias. At higher concentrations, benzene may lead to aplastic anemia which can be fatal. Jandl's (1977) review suggests a fatal outcome in 13% of the cases (as opposed to 85% for idiopathic aplastic anaemia).

The prevalence of leucopenia correlates with the concentration of benzene as shown by data of Yin et al. (1987) as well as by Kipen et al. (1988, 1989). Taken these data, the LOAEC (lowest observed adverse effect concentration) for leucopenia is in the range between 40 mg/m³ (12.5 ppm) and 64 mg/m³. A higher prevalence for leucopenia is given at concentrations above 320 mg/m³ (100 ppm).

The case control studies presented recently by Rothman et al. (1996a, 1996b) and Dosemeci et al. (1997) have shown, that the most sensitive reaction in humans to chronic benzene exposure is lymphopenia. The data show that a collective of workers exposed to benzene concentrations in a range between 1 and 31 ppm had significantly reduced lymphocyte counts as compared to a cohort of non-exposed workers.

Thus, for blood cell depression an overall LOAEC is suggested to be 32 mg/m³ (10 ppm). For depression of lymphocytes, a NOAEC of 3.2 mg/m³ (1 ppm) has been derived. In conclusion, the NOAEC for effects of benzene is assumed to be 3.2 mg (1 ppm).

Genotoxic effects

WHO (2000) Air Quality Guidelines for Europe 2000
There are numerous studies on chromosomal effects in exposed workers *(2, 22)*. Both structural and numerical chromosome aberrations have been observed. In most cases the benzene exposure has also been high enough to produce haematological effects. The chromosomal effects in these studies are evident at concentrations of around 320 mg/m^3 (100 ppm) or higher, but in some studies effects were reported in workers chronically exposed to levels of around 32 mg/m^3 (10 ppm) *(2, 23, 24)*. Tompa et al. *(25)* reported that the frequency of chromosome aberrations decreased when exposure levels decreased from 3–69 mg/m^3 to 1–18 mg/m^3. In the study by Karacic et al. *(24)*, a decrease in sister chromatid exchanges but not in chromosomal aberrations was noted in a group of female workers when examined with a 5-year interval during which the mean benzene concentration had decreased from 26 to 16 mg/m^3. Smoking did not influence the results *(23, 24, 26)*.

Somatic mutations as an endpoint of benzene-induced genotoxic effects in heavily exposed workers was studied recently by Rothman et al. *(27)*. They used the glycophorin A (GPA) mutation assay. The results suggested that benzene induces gene-duplicating mutations, presumably through recombination mechanisms, but not gene-inactivating mutations due to point mutations or deletions.

RIVM (2001)
National Institute of Public Health and the Environment - The Netherlands
The genotoxicity of benzene has been studied extensively. Benzene appears to have a peculiar genotoxic profile. Benzene is hardly, if at all, able to induce gene mutations in *in vitro* test systems, despite its potent clastogenic properties *in vitro* and *in vivo*. Several studies have demonstrated induction of both numerical and structural chromosomal aberrations, sister chromatid exchanges, and micronuclei in experimental animals and humans after *in vivo* benzene exposure (various routes of exposure). After short-term exposure to benzene levels of 3 to 30 mg/m^3 experimental animals showed chromosomal effects (Vermeirre et al. 1993) and some studies in humans have demosnstrated chromosomal effects at mean workplace exposures as low as 4 to 7 mg/m^3 (EU 1999).

There appears to be a lack of evidence for direct DNA interaction under normal *in vivo* conditions: despite the demonstrated ability of several benzene metabolites to form DNA adducts under *in vitro* conditions, DNA adduct formation in bone marrow cells in experimental animals in vivo could only be demonstrated under quite specific and very high exposure regimes (EU 1999; Health Council of the Netherlands 1997).

IRIS (2000)
Integrated Risk Information System (IRIS) – U.S.EPA
Current evidence indicates that benzene-induced myelotoxicity and genotoxicity result from a synergistic combination of phenol with hydroquinone, muconaldehyde, or catechol. Molecular targets for the action of these metabolites, whether acting alone or in concert, include tubulin, histone proteins, topoisomerase II, and other DNA-associated proteins. Damage to these proteins would potentially cause DNA strand breakage, mitotic recombination, chromosomal translocations, and malsegregation of chromosomes to produce aneuploidy. If these effects took place in stem or early progenitor cells, a leukemic clone with selective advantage to grow could arise as a result of protooncogene activation, gene fusion, and suppressor-gene inactivation. Epigenetic effects of benzene metabolites on the bone marrow stroma, and perhaps the stem cells themselves, could then foster development and survival of a leukemic clone. Since these plausible events have not been conclusively demonstrated, this remains a hypothesis (Smith, 1996).

UK Environment Agency (2003)
Benzene induces both numerical and structural chromosomal changes. Chromosome aberrations and micronuclei have been commonly reported in laboratory animals exposed to benzene either in the atmosphere or by oral administration. Often the positive results are seen throughout the tested dose range (ATSDR, 1997; WHO, 1993). Chromosomal damage has been detected in the peripheral blood of workers by many teams of investigators (ATSDR, 1997), and chromosomal effects have been claimed even at exposures of 4–7 mg m–3 (WHO, 2000).

Chromosomal aberrations may act as predictors of cancer risk, and their role in subsequent leukaemia is thought to involve chromosome numbers 5 and 7, and also possibly numbers 8 and 21 (EBS, 1996; Irons and Stillman, 1996). Aneuploidy may also be a precursor of leukaemogensis (EBS, 1996; Irons and Stillman, 1996). Other indicators of genetic damage are sister chromatid exchange (SCE), DNA crosslinking, DNA adduct formation and DNA repair (reviewed in Paustenbach et al, 1993; Snyder et al, 1993; EBS, 1996). Although benzene is not mutagenic in the Ames test, there are a number of reports of treatment-related mutations in the tissues of mice exposed by inhalation (ATSDR, 1997).

Carcinogenic effects

Both IARC and the US EPA have assigned benzene their highest cancer classification, Group 1 ("is carcinogenic to humans") (IARC, 1987) and Category A ("known human carcinogen") (USEPA, 2002), respectively. A large number of epidemiological studies provide conclusive evidence of a causal association between benzene exposure and leukaemia, acute non-lymphocytic leukaemia (ANLL) certainly, and also possibly chronic non-lymphocytic and chronic lymphocytic leukaemias (USEPA, 2002). There have also been occasional reports of an increased risk in humans of other neoplastic changes in the blood or lymphatics, including Hodgkin's and non-Hodgkin's lymphoma and myelodysplastic syndrome (USEPA, 2002).

The vast majority of the evidence for an association with ANLL derives from occupational epidemiology, where benzene is often a constituent of a complex mixture. These include studies in the shoe-making, printing, petrochemical, chemical, coke production and rubber manufacturing industries (Aksoy et al, 1974; Christie et al, 1991; Decouflé et al, 1983; Hurley et al, 1991; Paxton et al, 1994a; Rushton, 1993; Tsai et al, 1983; Vigliani and Forni, 1976; Yin et al, 1989). Many of the workforces were exposed to benzene at levels markedly higher than those experienced in these industries today.

There have been a number of cohort and nested case control studies that have estimated exposure for each worker. Attempts have been made to develop dose–response relationships using cumulative exposure, which is, assuming a symmetrical contribution of exposure concentration and exposure duration. The cancer mortality seen in the "Pliofilm" cohort, which included workers from three factories manufacturing rubber film in the USA, has been most often used in cancer risk assessment. A wide range of exposures were encountered, with relatively few other chemicals involved, and a clear dose–response was seen between leukaemia risk and benzene exposure. There have been several publications from this cohort giving mortality results (Infante et al, 1977; Paxton et al, 1994a; Rinsky et al, 1981, 1987; Wallace, 1996) and risk assessments using different methods of exposure estimation and different mathematical models (Austin et al, 1988; Brett et al, 1989; Byrd and Barfield, 1989; Crump, 1994, 1996; Crump and Allen, 1984; Paustenbach et al, 1992; Paxton, 1996; Paxton et al, 1994b; Rinsky et al, 1989; Schnatter et al, 1996a,b). For example, the analysis of Paxton et al (1994a), based on 14 cases of leukaemia in the exposed male workers and three previous estimates of worker exposure (Crump and Allen, 1984; Paustenbach et al, 1992; Rinsky et al, 1981), reported standard mortality ratios in the highest exposure group (>1600 mg m^{-3} yr^{-1}) of between 10.3 and 20.

Four other cohort studies have quantified benzene exposures for all workers. Bond et al (1986), in a follow-up of a study by Ott et al (1978) of 956 Dow Chemical workers, found three deaths from leukaemia compared with 1.9 expected. Wong (1987a,b) followed up 7676 chemical workers, 3536 of whom were continuously exposed to benzene. Six leukaemia deaths were reported in the exposed group compared with 4.5 expected. An update of a subgroup of this population has been reported by Ireland et al (1997). There were three cases of leukaemia observed at exposures at or above 6 ppm (19.2 mg m–3) compared with 0.65 expected.

Increased risks of non-haematopoietic cancers have been found in a few studies of occupational cohorts exposed to benzene or mixtures containing benzene. These include bladder, stomach, prostate and lung neoplasms (ATSDR, 1997), although, in general, the risks are only moderately raised; also, in many studies, exposure to multiple chemicals complicates the interpretation of the results.

Benzene has been implicated as a potential risk factor for the development of childhood leukemia (OEHHA, 1997; Ries et al., 1997; Smith and Zhang, 1998; U.S. EPA, 1998).

There are little data on the effects of direct exposure of children to benzene. Because of their small size, increased activity, and increased ventilation rates compared to adults, children may have greater exposure to benzene in the air, on a unit body weight basis (U.S. EPA, 1998). Although no human cancer studies of benzene-exposed children are available, there is good reason to believe that childhood exposure to benzene would also contribute to adult-onset leukemias. Also, there is some evidence to suggest that exposure to benzene is associated with childhood leukemia. Paternal exposure to benzene prior to conception in humans has been associated in some studies with increased childhood leukemia, especially of the acute nonlymphocytic type, findings that are supported by observations in animals of benzene-induced DNA damage to sperm. Maternal exposure to benzene in humans also has been associated with increased incidences of childhood leukemia. These findings are supported by observations in animals of benzene-induced transplacental genotoxicity, altered hematopoiesis, and of carcinogenicity, following exposure in utero and continuing until weaning. It should be noted that other epidemiological studies that represented a large number of cases of various subtypes of leukemia (Kaatsch et al., 1998) or acute lymphocytic leukemia only (Shu et al., 1999) did not find an association with paternal benzene exposure. Thus a casual relationship would be difficult to establish.

Summary of cancer (leukemia) risk values

Risk value	Unit	Risk specific concentration µg/m³ (at an excess lifetime cancer risk of 10⁻⁴)	Risk value name	Study	Source; Ref. Value mg/m³
6 · E-6	$(\mu g/m^3)^{-1}$	17	Unit risk (UR) and guideline value (GV)	Pliofilm cohort Crump, 1994	WHO 1995
2.2 - 7.8 · E-6	$(\mu g/m^3)^{-1}$	13 - 45	UR	Pliofilm cohort multiple: Rinsky et al., 1981, 1987; Paustenbach et al., 1993; Crump and Allen, 1984; Crump, 1992, 1994; U.S. EPA, 1998.	US-EPA 1998
5 · E-8 [a] - 6 · E-6 [b]	$(\mu g/m^3)^{-1}$	20-36	UR [a] lowest plausible estimate [b] highest plausible estimate	multiple: [a] Wong and Raabe (1995) [b] Crump, 1994 (Pliofilm cohort)	EU 1999
1.5 · E+1	mg/m³	30	TC$_{05}$ (Tumorigenic concentration associated with a 5% increase in incidence) - acute myelogenous leukemia	Pliofilm cohort Rinsky et al., 1987	Health Canada 1991

2.4 · E-2	mg/m^3	24		$CR_{inhal.}$ (Lifetime inhalatory excess cancer risk at the 1 in 10^4 level) - haematopoietic system	multiple: Wong and Raabe (1995)	RIVM 1999
0.054	(mg/kg d)$^{-1}$	4.1 using mean children's breathing rate of 0.45m^3/kg-day; 7.9 using mean adult breathing rate of 0.235m^3/kg-day		Inhalation cancer potency	Pliofilm Cohort: Rinsky et al., 1987; Paxton et al., 1994 Chinese Worker Cohort: Hayes et al., 1997	OEHHA 2003
2 · E-5	(ppm)$^{-1}$	16		Lifetime leukemia (AML) risk equivalent	Pliofilm cohort multiple Crump, 1994 USEPA, 1998	NICNAS 2001

WHO (1995)
Air Quality Guidelines for Europe 2000

The WHO derived in 1995 a Unit risk (UR) for leukemia of $6 \cdot 10^{-6}$ (µg/m^3)$^{-1}$ on the basis of risk calculations of Crump (1994). Based on this UR, air quality guidelines corresponding to excess lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6} are 17, 1.7 and 0.17 µg/m^3, respectively (WHO, 2000)

US EPA (1998)

The US EPA is currently in the process of reviewing the evidence relating to the risk of benzene. Their provisional conclusion is that there is insufficient evidence to reject a linear dose-response curve for benzene carcinogenicity at low-dose exposures and that the approach of using a linear dose-response curve is still to be recommended. The US EPA gives a range of risk estimate for leukemia at 1 µg/m^3 from 2.2 10^{-6} to 7.8 10^{-6}.

European Commission (1999)

The EU-Working Group concluded that it is reasonable to assume that benzene-induced effects at low exposure levels differ quantitatively as well as qualitatively from those induced at high occupational exposures. It is not clear whether the underlying mechanism of benzene carcinogenicity is direct DNA interaction. In view of this uncertainty the EU Working Group decided, on precautionary grounds, to hold on to a non-threshold extrapolation method. Though it was not possible to give a precise estimate of the risk associated with benzene it was possible to define a range within which that risk was likely to lie. The UR calculated by the WHO ($6 \cdot 10^{-6}$) was considered to result in the highest plausible estimate of risk. The lowest UR which the EU Working Group felt was likely to be plausible was in the order of $5 \cdot 10^{-8}$, an estimate which is consistent with the Dutch Health Council's analysis of the Wong and Raabe data. This range of URs means that an excess lifetime risk for leukemia of 10^{-6} is associated with annual average concentrations varying between 0.17 and 20 µg/m^3 (EU 1999).

On the basis of this risk estimation the European Commission has adopted an ambient air quality limit value for benzene of 5 µg/m^3 to be met on 1 January 2010 (Directive 2000/69/EC). This limit value has been proposed by the EU working group taking into account practical considerations; 5 µg/m^3 is as low as reasonably achievable in 2010.

Health Canada (1991)

Health Canada based their risk values on the incidence of leukemia in occupationally-exposed humans, resulting in a TC_{05} (Tumorigenic concentration associated with a 5% increase in incidence) of 1.5E+1 mg/m^3. The Health Canada TC_{05} can be divided by 5000 to represent a 1 in 100,000 risk level of $3 \cdot 10^{-3}$ mg/m^3. It should be noted that the Health Canada TC_{05} is computed directly from the dose-response curve within or close to the experimental range.

RIVM (1997)
National Institute of Public Health and the Environment - The Netherlands

The figure of 24 µg/m^3 (risk specific concentration at an excess lifetime cancer risk of 10^{-4}) was derived from the estimate as presented by the Health Council of 12 µg/m^3 being associated with an excess lifetime cancer risk of 10^{-6}. The figure of 12 µg/m^3 was based on the unit risk estimate of the US-EPA of $8.3 \cdot 10^{-6}$ as presented in the Dutch Integrated Criteria Document on benzene (RIVM, 1987) increased with a factor of 100. In combination with the unit risk of the US EPA the 95% upper confidence limit of the cancer risk in the Pliofilm cohort was calculated to be 0.052

(=6234* · 8.3 · 10^{-6}). Linear interpolation between the two points on the dose response curve, i.e. [12 μg/m^3 , 10^{-6}] and [6234 μg/m^3 , 0.052] gives an 10^{-4} excess cancer risk at 24 μg/m^3.

* The average exposure in the Pliofilm cohort was 128 mg/m^3. Converting this value to a continuous lifetime exposure for the general population results in a value of 6234 μg/m^3 (128 mg/m^3 · 10/75 years/lifetime · 5/7 days/week · 48/52 weeks/year · 10/18 inhalation volume/day).

European Commission (1999)

The EU-Working Group concluded that it is reasonable to assume that benzene-induced effects at low exposure levels differ quantitatively as well as qualitatively from those induced at high occupational exposures. It is not clear whether the underlying mechanism of benzene carcinogenicity is direct DNA interaction. In view of this uncertainty the EU Working Group decided, on precautionary grounds, to hold on to a non-threshold extrapolation method. Though it was not possible to give a precise estimate of the risk associated with benzene it was possible to define a range within which that risk was likely to lie. The UR calculated by the WHO (6 · 10^{-6}) was considered to result in the highest plausible estimate of risk. The lowest UR which the EU Working Group felt was likely to be plausible was in the order of 5 10^{-8}, an estimate which is consistent with the Dutch Health Council's analysis of the Wong and Raabe data. This range of URs means that an excess lifetime risk for leukemia of 10–6 is associated with annual average concentrations varying between 0.17 and 20 μg/m^3 (EU 1999).

On the basis of this risk estimation the European Commission has adopted an ambient air quality limit value for benzene of 5 μg/m^3 to be met on 1 January 2010 (Directive 2000/69/EC). This limit value has been proposed by the EU working group taking into account practical considerations; 5 μg/m^3 is as low as reasonably achievable in 2010.

OEHHA (2003)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

The inhalation cancer potency of benzene was estimated from observations of leukemia among U.S. rubber hydrochloride workers exposed to benzene (Pliofilm Cohort) (Rinsky et al., 1987; Paxton et al., 1994) and benzene-exposed workers from various industries in China (Chinese Worker Cohort) (Hayes et al., 1997). In estimating potency, observations were assumed to follow a Poisson distribution. Relative risk was assumed to increase linearly with cumulative exposure, and leukemia onset was assumed unaffected by benzene exposure after 30 years. Cancer potency estimates, obtained from the occupational data, were adjusted using lifetable analyses to those expected for the California population from constant exposure to benzene.

Studies in human volunteers, workers, and animals suggest that humans retain approximately 50 percent of inhaled benzene and absorb 100 percent of ingested benzene at environmentally relevant levels of exposure (OEHHA, 2001a). Based on these differences in absorption of benzene by route of exposure, the oral cancer potency was derived from the inhalation cancer potency.

The evidence regarding the shape of the exposure-response curve for benzene-induced leukemia supports the use of linear risk models to extrapolate to low doses (U.S. EPA, 1998; OEHHA, 2001a,b). Saturation of metabolism and formation of reactive compounds may result in nonlinearity at high exposures.

OEHHA (2001a) reviewed the scientific evidence for associations of benzene and various human cancers. The strongest association is for acute non-lymphocytic leukemia and myelodysplastic syndromes (ANLL/MDS). MDS, if not fatal, often progresses to ANLL. Evidence suggests that benzene causes other forms of leukemia as well. Total leukemia (e.g., all subtypes of leukemia as a related class of diseases) was judged to be appropriate as the basis of risk assessment.

Cancer potency estimates were derived for all exposures and after removal of workers with the highest cumulative exposures. Highly exposed workers were removed from the analysis because of reduced confidence in their exposure assignments or because of observed non-linearity of response at higher exposures.

Upper-bound estimates of cancer potency from Pliofilm Cohort or Chinese Worker Cohort were very similar after removal of the workers with the highest exposures from each cohort. Cancer potency estimates in units of ppm^{-1} were converted to units of (mg/kg-d)$^{-1}$ using default intake parameters of 70 kg body weight and 20 m^3/d for breathing rate:

Potency/(mg/kg-d) = (upper-bound potency/ppm) x (ppm/3.19 mg/m^3) x (70 kg) x (1/20 m^3/d).

Thus, inhalation cancer potency estimates from the Pliofilm Cohort based on the Rinsky et al. or Crump and Allen exposure estimates are 0.048 and 0.049 (mg/kg-day)$^{-1}$, respectively, resulting in a geometric mean of 0.048 (mg/kg-day)$^{-1}$ after rounding. The cancer potency estimate based on the Chinese Worker Cohort is 0.061 (mg/kg-day)$^{-1}$. The geometric mean estimate of these two cohort studies is 0.054 (mg/kg-day)$^{-1}$. Cancer potency estimates from inhalation exposures were converted to those expected from oral exposures by applying a factor of two since 50 percent of inhaled benzene is absorbed and 100 percent of ingested benzene is absorbed (OEHHA, 2001a). The resulting oral cancer potency estimates are 0.11 (mg/kg-day)$^{-1}$ The cancer potency estimates obtained from the Pliofilm Cohort and Chinese Worker Cohort are consistent with estimates obtained from animal cancer bioassays of benzene, other epidemiological studies of benzene-exposed workers, and epidemiological studies of leukemia and cigarette smoke (of which benzene is a constituent) (OEHHA, 2001a).

The NO SIGNIFICANT RISK LEVEL (NSRL) for Proposition 65 is the intake associated with a lifetime cancer risk of 10^{-5}. The cancer potency estimates derived above were used to calculate NSRLs for benzene, which are 13 µg/day for inhalation exposures and 6.4 µg/day for oral exposures.

NICNAS (2001)
National Industrial Chemicals Notification and Assessment Scheme – Australia

NICNAS considered the Pliofilm cohort as the most reliable data set on which to establish the risk estimates. Data from the most recent follow-up of the Pliofilm cohort indicate that the risk for leukaemia is significantly elevated at cumulative exposures >50 ppm-years. However, this finding derives from a single cohort study with insufficient statistical power to rule out the possibility of some increase in leukaemia risk at lower exposures. The additional risk for leukaemia attributable to environmental exposure to benzene can be predicted by low-dose extrapolation of the quantitative estimates for occupational exposure to benzene. Crump (1994) and USEPA (1998a) both predict the number of additional leukaemia cases at two lifetime exposure levels, namely 1 ppm and 1 ppb, however, only the latter is relevant for exposure to benzene in the general environment.

The risk characterisation is based on the most conservative prediction of the Pliofilm cohort (Crump, 1994 and USEPA, 1998a), that is, a lifetime leukaemia (AML) risk equivalent to 2 additional cases of leukaemia per 100,000 population at 1 ppb. By extrapolation, the lifetime leukaemia (AML) risk equivalent for increasing exposure levels can be calculated as follows:
1 ppb $\sim$ 2 additional leukaemia/ 10^5 population
10 ppb $\sim$ 20 additional leukaemia / 10^5 population
20 ppb $\sim$ 40 additional leukaemia / 10^5 population

The NICNAS estimated that the average 24 hour lifetime exposure to benzene, from all sources (including an estimated ambient air component of 11%), of an individual not exposed to environmental tobacco smoke living in an urban area of an Australian city is 5.2 ppb. The predicted excess lifetime risk of leukaemia is therefore 1/10,000, or 1.2% of the lifetime risk of contracting leukaemia of any cause (1 in 118, or 85/10,000 population, based on 1996 incidence figures for Australia (AIHW, 1999).

AIHW. 1999. Cancer in Australia 1996 – incidence and mortality data for 1996 and selected data for1997 and 1998. Bruce, ACT, Australian Institute of Health and Welfare.
NICNAS. 2001. National Industrial Chemicals Notification and Assessment Scheme, Benzene, Priority Existing Chemical Assessment Report No. 21 (2001)

Susceptible population

The potential magnitude or range of susceptibilities cannot be accurately quantified at this time; however, current evidence suggests individual differences in susceptibility may be two or three orders of magnitude.

Benzene's toxicity is intimately tied to its complex metabolism and distribution. Key enzymes involved in the metabolism of benzene, including CYP2E1, the quinone reductase NQO1, and myeloperoxidase are polymorphic. For example, a 7.6-fold difference in benzene-induced hematotoxicity in workers was observed among gene variants of CYP2E1 and NQO1 (Rothman et al., 1997). Thus the expression of genetic polymorphisms may modulate the sensitivity of an individual or ethnic group to the effects of benzene exposure.

Aksoy et al. (1976) suggested familial susceptibility as one of the main factors in the frequency of chronic benzene toxicity. Two patients with pancytopenia associated with chronic exposure to benzene were cousins. One of these two

patients died of aplastic anemia; the son of this patient presented with leukopenia a short time after exposure to this chemical. Genetic polymorphism with regard to the P-450 enzymes that metabolize benzene to its reactive metabolites may render some individuals at higher risk to the toxic effects of benzene (Kato et al. 1995). Although there are possible indications of genetic susceptibility to benzene, it is believed that all humans are susceptible to the pancytopenic effects of this agent.

Children may represent a subpopulation at increased risk due to factors that could increase their susceptibility to effects of benzene exposure (e.g., activity patterns), on key pharmacokinetic processes (e.g., ventilation rates, metabolism rates, and capacities), or on key pharmacodynamic processes (e.g., toxicant-target interactions in the immature hematopoietic system).

There is a possible relationship between thalassemia (abnormal haemoglobins) and exposure to benzene. Aksoy (1989) presented a series of 44 pancytopenic patients, 4 of which had β-thalassemia heterozygotes. Two of these four patients had high levels of fetal haemoglobin, while a third patient had pseudo-Pelger-Huet anomaly. Thus, some forms of β-thalassemia may increase the deleterious effects of benzene on the hematopoietic system.

The occurrence of aplastic anemia in chronic benzene toxicity may be accelerated in individuals with viral hepatitis (Aksoy 1989). Furthermore, children and fetuses may be at increased risk-because their hematopoietic cell populations are expanding and dividing cells are at a greater risk than quiescent cells.

In vitro studies of benzene-caused chromosomal aberrations in human lymphocytes taken from people with different health practices suggests that "unhealthy lifestyles, " including smoking, excessive alcohol consumption, inadequate physical exercise and sleep, excessive stress, and inadequate nutritional balance, could make cells more sensitive to the production of chromosomal aberrations after exposure (Morimoto et al. 1983).

Interactions with other chemicals

It has been reported that high exposures to gasoline (300 to 2000 ppm) which contains benzene may be less hazardous than an equivalent exposure to benzene alone, based on studies in mice and from modeling predictions (Bond et al., 1997). Volatile aromatics in gasoline including toluene, ethylbenzene and xylenes compete with benzene for CYP2E1, thus these co-exposures significantly reduce the overall metabolism of benzene relative to equivalent exposures of pure benzene. However, these experiments employed relatively high concentrations of test material (1) 300 ppm gasoline plus six ppm benzene, and (2) 2000 ppm gasoline plus 40 ppm benzene), levels at which metabolic saturation is expected. At low levels of exposure, competition for the P450 binding sites would be minimal; thus, reduction in benzene toxicity due to co-exposures would also be minimal.

Odour perception

Source: Devos et al. (1990)
Odour threshold: 1.2 mg/m^3.

Source: Haley, 1977
Odour threshold: 2.8 mg/m³

Source: AIHA (1989) - Odor thresholds for chemicals with established occupational health standards.
Detection: 195 mg/m^3 (61 ppm); Recognition 309 mg/m^3 (97 ppm). Reported values range from 2.5 – 510 mg/m^3 (0.78-160 ppm).

Summary of Benzene Dose Response Assessment

Exposure other than inhalation: ingestion of contaminated tap water, potential exposure from dermal contact during showering and bathing (additional inhalatory exposure due to volatilized benzene). Dietary and endogenous sources of phenol, hydroquinone and other primary metabolites of benzene confer potentially large differences in susceptibility to benzene toxicity.

Toxicokinetics: at low levels (<10 ppm) about half of the inhaled dose is retained, the rest being exhaled. Metabolism of benzene occurs largely in the liver, although some metabolism may take place in the bone marrow. Benzene can cross the placenta. Not benzene itself, but several metabolites, as well as interactions between these metabolites, are thought to explain the toxic effects of benzene. The proportion of the putatively toxic metabolites (benzoquinone and muconaldehyde) formed is greater at low doses than at high doses (saturable process at relatively low doses).

Health effect levels of short- and long-term exposure (noncancer):

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
128_{EXP}	319_{EXP}	Developmental: decreased fetal body weights (severe adverse effect!)	Pregnant female rats, 6 hours per day (for 5 days)	Coate et al., 1984; (supported by Kuna and Kapp, 1981; Keller and Snyder, 1988)	OEHHA 1999 REL: 1.3
	16_{EXP}	Developmental: Altered hematopoiesis in offspring (high degree of uncertainty!)	Mice, 6 hours per day during days 5-16 of gestation	Keller and Snyder, 1988	OEHHA 2001 MADL$_{inhal.}$: 1.3 µg/day
	33_{EXP} 8_{ADJ} 47_{HEC}	Haematologica-immunological: depressed peripheral lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes (Less Serious LOAEL) .	Mice, 6 hours per day (for 6 consecutive days)	Rozen et al. 1984	ATSDR 1997 MRL: 0.16
Long-term exposure					
1.7_{Study} 0.60_{ADJ}		Haematological effects (total and differential white blood cell counts, haemoglobin, hematocrit, red blood cells, platelets and clotting times)	Occupational, 7.4y	Tsai et al. 1983	OEHHA 1999 REL: 0.06
	44_{BMC} 23_{BMCL} $8.2_{ADJ-BMCL}$	Decreased lymphocyte counts	Occupational, 6.3y (0.7-16y)	Rothman et al. 1996	EPA-IRIS 2003 RfC: 0.03
(3.2)	32_{EXP}	Blood cell depression (lymphocytes)	Mouse, 6-178d NOAEC has been derived, not observed	Dempster and Snyder, 1990, Rozen et al. 1984, Baarson et al., 1984, Green et al., 1981a,b, and other studies	ECB 2003
	2.5_{EXP} 1.05_{HEC}	Neurological: increased rapid response time (Less Serious minimal LOAEL).	Mice, 30d (2h/d, 6d/w)	Li et al. 1992 intermediate duration study !	ATSDR 1997 MRL$_{INT}$: 0.013 (intermediate!)

Carcinogenicity: IARC: 1 ; U.S.EPA: A ; Genotoxic carcinogen

Unit risks derived from Pliofilm cohort study - leukemia in occupational settings. EPA (1998): $2.2 - 7.8 \cdot 10^{-6}$ (µg/m³)$^{-1}$; WHO(1995): $6.0 \cdot 10^{-6}$ (µg/m³)$^{-1}$; OEHHA(2003; Pliofilm cohort and Chinese worker cohort) with respect to breathing rate: children $24 \cdot 10^{-6}$ (µg/m³)$^{-1}$ and adults $12 \cdot 10^{-6}$ (µg/m³)$^{-1}$

Genotoxicity: Induction of both numerical and structural chromosomal aberrations, sister chromatid exchanges and micronuclei in experimental animals and humans after in vivo benzene exposure (as low as 4-7 mg/m³). Lack of evidence for direct DNA interaction under normal *in vivo* conditions. Genotoxicity may result from a synergistic combination of phenol with hydroquinone, muconaldehyde, or catechol.

Odour threshold: 1.2 mg/m³ (Devos); 2.8 mg/m³ (Haley, 1977)

Susceptible sub-populations: The range of susceptibility to benzene toxicity within the general population could be very large (two or three orders of magnitude). Significant sources of variability are:

- genetic polymorphisms in key enzymes involved in the metabolism of benzene,
- dietary and endogenous sources of primary metabolites of benzene,
- factors such as pre-existing inflammation, radiation exposure, and ethanol consumption can potentiate the toxic effects of exposure to benzene.
- Benzene has been implicated as a potential risk factor for the development of childhood leukemia.

Remarks:

6. Risk Characterization

Cancer risk evaluation

The most severe human responses to benzene exposure are those related to the blood-forming organs. There is a wealth of evidence demonstrating benzene's ability, at high concentrations, to cause bone marrow damage giving rise to clinical outcomes such as various anemias, myelodysplastic syndromes, and leukemia. Additional evidence suggests that benzene may also be associated with increased incidence of childhood leukemia. Benzene is regarded as a genotoxic chemical, causing chromosomal damage and mutations in test systems in vitro, in animals in vivo, and in occupationally exposed humans.

The present risk characterization is adressing benzene-induced leukemia and is supported by an evaluation on haematological effects, considered a promotional condition to tumour development. Since no safe exposure level can be established for genotoxic carcinogens, the quantitative risk estimate is here based on a non-threshold linear extrapolation at low levels using the WHO Unit Risk guideline set as $6 \cdot 10^{-6} \, (\mu g/m^3)^{-1}$ and described as the geometric mean of the range of estimates of the excess lifetime risk of leukemia at an air concentration of $1 \, \mu g/m^3$. This factor, applied to a single exposure value or to a population distribution of exposure values, provides an estimate of the individual risk or the population-based risk, the latter indicating the potential excess cancers among a million people continuously exposed to the given benzene concentration over a 70-year lifetime.

Population cancer risk estimates of benzene-induced leukemia

In Table 6.1 the available exposure data (see cumulative frequency distributions in Chapter 1.3) are listed along with the lifetime cancer risk estimates at three different exposure levels. Indoors, risk estimates are based on the median and the 90th percentile of the cumulative exposure distribution, with the 90th percentile describing a "worse case" scenario among each indoor survey. Both indoor levels were corrected following the assumption that people spend 95% of their time in their homes and resting time outdoors. Additionally, risk estimates are refered to median outdoor concentrations, a scenario describing indoor exposure experienced in the absence of indoor sources of benzene.

Table 6.1 Excess lifetime cancer risks per one million people derived from available exposure data

Population-based studies Description (Study, Year)	N	Median estimate Indoors [a]	90th % estimate Indoors [a]	Median estimate Outdoors [b]
Athens, 30h-TWA (Expolis, 96-98)	42	48	112	45
Basel 30h-TWA (Expolis, 96-98)	47	13	28	8
Helsinki 30h-TWA (Expolis, 96-98)	188	10	25	9
Milan 30h-TWA (Expolis, 96-98)	41	60	216	55
Oxford 30h-TWA (Expolis, 98-00)	40	16[c]	44[c]	n.a.
Prague 30h-TWA (Expolis, 96-98)	46	41	80	28
England 28d-TWA (BRE, 97-99)	796	18[c]	60[c]	n.a.
Germany 4w-TWA (GerES IV pilot study, spring+summer 2001)	44	8	16	7
French National Survey 7d-TWA (IAQ observatory; 2003-04)	109	14[c]	30[c]	n.a.

[a] supposing that people spend 95% of their time at home
[b] supposing outdoor air as the unique source of indoor benzene exposure
[c] not adjusted for outdoor exposure (0.05%)
n.a. data not available

The corresponding benzene concentrations are given in Table 6.2, with an additional column pointing out the percentage of individuals exposed at levels higher than the current (2004) and the finalised (2010) EU-limit value of 10 and 5 $\mu g/m^3$, respectively (1-y average; Directive 2000/69/EC). This limit value has been proposed by the EU working group taking into account the developed risk estimation and practical considerations (5 $\mu g/m^3$ is as low as reasonably considered achievable in 2010). Also, in Figure 6.1 the outcomes of the available indoor surveys are presented together with the results of the MACBETH project.

Table 6.2: Benzene concentrations ($\mu g/m^3$) measured and percentages of population exposed indoors at levels higher than the EU-limit value (1y avg.): 10 $\mu g/m^3$ (current) and 5 $\mu g/m^3$ to be met the 01/01/10

Population-based studies Description (Study, Year)	N	Median Indoors	90th % Indoors	Median Outdoors	10 µg/m³ current	5 µg/m³ 01/01/10
Athens, 30h-TWA (Expolis, 96-98)	42	8,0	19,2	7,5	35%	75%
Basel 30h-TWA (Expolis, 96-98)	47	2,3	4,8	1,3	<	10%
Helsinki 30h-TWA (Expolis, 96-98)	188	1,7	4,3	1,5	<	10%
Milan 30h-TWA (Expolis, 96-98)	41	10,0	37,5	9,1	50%	75%
Oxford 30h-TWA (Expolis, 98-00)	40	2,6	7,3	-	5%	20%
Prague 30h-TWA (Expolis, 96-98)	46	6,9	13,8	4,6	25%	75%
England 28d-TWA (BRE, 97-99)	796	3,0	9,0	-	15%	30%
Germany 4w-TWA (GerES IV pilot study, spring+summer 2001)	44	1,3	2,7	1,1	<	<
French National Survey 7d-TWA (IAQ observatory; 2003-04)	109	2,3	5,0	-	<	10%

n.a. data not available;
< out of the evaluation range (i.e. <5% of the environments investigated)
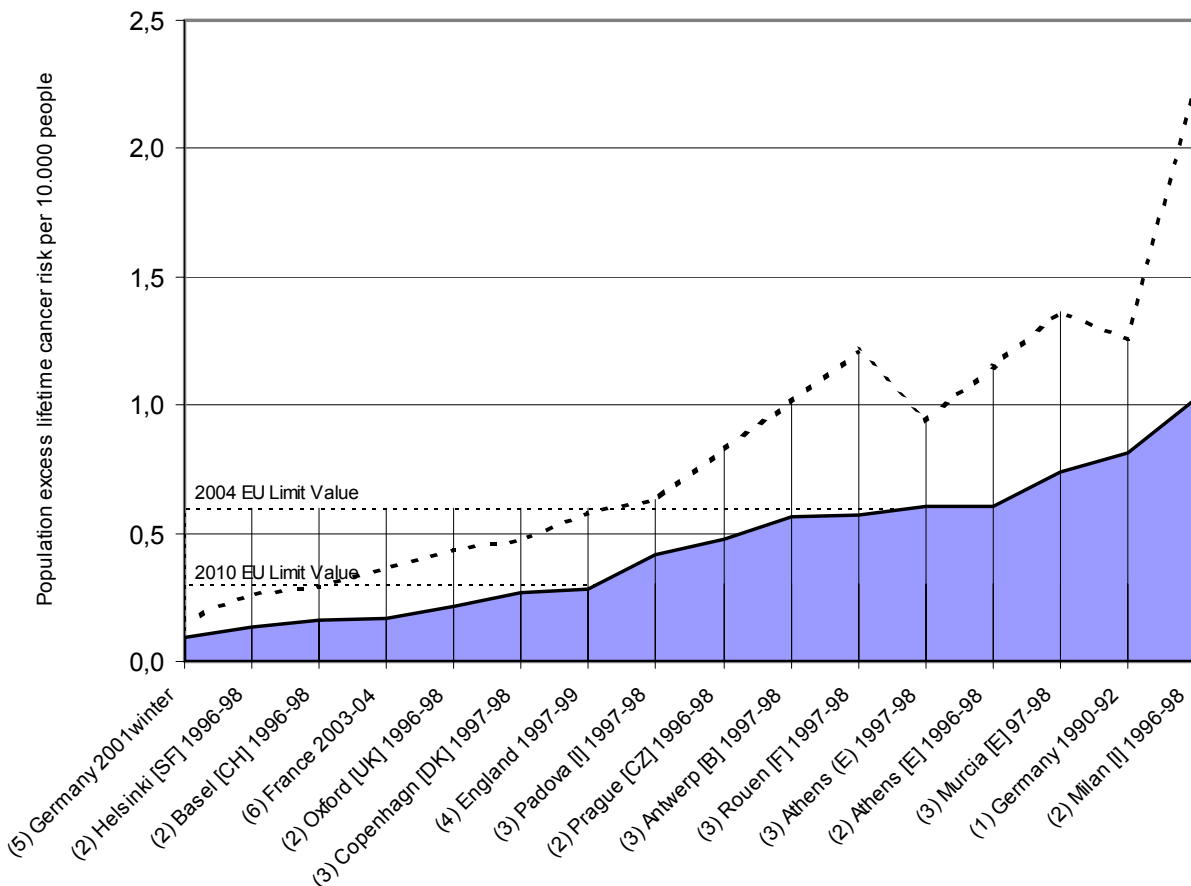
Figure 6.1:Cancer risk estimates of benzene induced leukemia *(last minute implementation)* based on arithmetic mean and 90%ile (---) indoor levels measured among European surveys
(1) GerES II ; (2) EXPOLIS ; (3) MACBETH ; (4) BRE National survey ; (5) GerES IVP ; (6) French National survey

Health hazard evaluation (noncancer)

Both epidemiology and animal experiments show that carcinogenic effects occur at benzene levels also expected to be haematotoxic. Together with the observation that susceptibility to haematotoxicity by benzene evidently predisposes to myelodysplastic syndromes as well as haematopoietic malignancies, this target organ toxicity is considered a promotional condition to tumour development.

A complementary health hazard evaluation is here based on haematological effects (see Table 6.3) with an observed chronic NOAEL of 600 mg/m^3 (OEHHA, corrected for continuous exposure) and an assessment factor of ten for inter-individual variability. In the occupational study refered to, total and differential white blood cell counts, hemoglobin, hematocrit, red blood cells, platelets and clotting times of the population studied were found to be within normal limits (between 5% and 95% percentile) during an exposure duration averaged 7.4 years.

Table 6.3: Haematological effects:
Population exposed beyond given threshold levels (μg/m^3)

Population-based studies Description (Study, Year)	N	NOAEL 600	NOAEL 10 60
Athens, 30h-TWA (Expolis, 96-98)	42	<	<
Basel 30h-TWA (Expolis, 96-98)	47	<	<
Helsinki 30h-TWA (Expolis, 96-98)	188	<	<
Milan 30h-TWA (Expolis, 96-98)	41	<	5%
Oxford 30h-TWA (Expolis, 98-00)	40	<	<
Prague 30h-TWA (Expolis, 96-98)	46	<	<
England 28d-TWA (BRE, 97-99)	796	<	<
Germany 4w-TWA (GerES IV pilot study, spring+summer 01)	44	<	<
French National Survey 7d-TWA (IAQ observatory; 2003-04)	109	<	<

n.a. data not available; < out of the evaluation range (i.e. <5% of the environments investigated)

The studies

The **EXPOLIS study** has been designed to produce direct population based measurements of exposures for major air pollutants, the target population being the adult urban population of Europe (measurements performed from fall 1996 to winter 1997/1998). (Selection bias (Oglesby et al., 2000) In Basel, participants of direct monitoring as compared to non-participants were more likely to live at streets with low traffic volume; although in Helsinki, traffic volume was neither significantly related to participation in direct nor indirect monitoring, the point estimates indicate a tendency to decreased participation with increasing traffic intensity at home.)

The Building Research Establishment (**BRE, UK**) has conducted a national representative survey of air pollutants in 876 homes in England, designed to increase knowledge of baseline pollutant levels and factors associated with high concentrations (17 months, October 1997 to February 1999).

The **GerES IVP** is a one-year pilot study (February 2001 - March 2002) of the German Environmental Survey (GerES), and includes about 560 children/teenagers (0 to 17 years) with a sub collective of 112 for personal, indoor and outdoor air analyses. The aim of the study was to collect information on parameters influencing the response rate and to test the suitability of the different instruments intended to be used for the main study. The here presented benzene exposure data are based on indoor air measurements averaged over 4 weeks.

The **French National Survey**: Study details in
A nationwide survey on indoor air quality has been st up in France in 2003-2004, with the aim of assessing household exposure to indoor pollutants. The target population is the national housing stock of approximately 24 million permanently occupied housing units. For further details refer on Golliot et al., 2003 and Kirchner et al., 2004.

Comments

A widespread characterization of residential exposures to benzene is given by the outcome of the Expolis-study, considered here as indicative of the urban population in Europe. Within this study, a specific bias has been reported (Oglesby et al. 2000) concerning the selection of residences (participants) in Basel and Helsinki, with these data more likely to be collected in lower trafficked areas of the towns.

In two further surveys (BRE and GerES IVP), one-month average benzene levels were measured in randomly distributed residences in England and Germany. With the exception of the GerES IV pilot study, all studies took into account possible seasonal effects on indoor benzene concentration.

Tendency in ambient benzene levels

Since outdoor air is representing a source of indoor benzene levels, the adoption, in most member states, of environmental policies regarding benzene emissions, raises the question on whether the available/selected exposure data could be considered descriptive of the nowadays situation, the comment requiring a brief introduction to the policies adopted and on-going tendencies of benzene ambient levels.

Combustion processes are the largest source of benzene in the atmosphere, with road traffic generally the biggest single source. Especially in urban locations, the emission by vehicles is expected to be the principal cause of increased benzene concentrations. Emissions are resulting from direct emission from the exhausts and from the evaporation of fuels either by car or from fuel distribution and refuelling. These emissions have been declining in recent years, owing to legislation on vehicle emissions, industrial emissions and fuel distribution. In particular, important results were obtained with the introduction of the automobile catalyst converter in the last two decades and the reduction of the benzene content of gasoline more recently. The Air Quality Report of the first Auto-Oil Programme (AOP1) estimated a 56% reduction in urban emissions of benzene between 1990 and 2010. As an example, the control of benzene in gasoline has recently been described as the main reason for the decrease of indoor benzene levels in Germany, together with the reduction of the use of benzene in many consumer products (Seifert, 2002; Schleibinger et al., 2001). Levels decreased by a factor of about 4 over one decade in the Berlin metropolitan area (see Figure). Although an example of a successful application of environmental control measures in Germany, a tendencial decrease is expected to occur in all member states adopting these policies. As a result, both the Expolis and the BRE data, collected more than 5 years ago, are expected to describe a pessimistic picture of the actual situation, with respect to the contribution of ambient benzene levels.

Median Indoor Air Concentrations of Benzene (Berlin Metropolitan Area, 1989 – 1999)

N = 744

Source: Schleibinger et al., 2001

When examining the exposure data (Table 6.2) with respect to the contribution of outdoor air contamination, two exposure scenarios could be depicted as follows:

- In highly trafficked urban areas (outdoor benzene levels >5 $\mu g/m^3$), outdoor air is well contributing to indoor benzene levels, as shown in the case of Milan and Athens, where median indoor-levels exceed outdoor-levels for not more than 9%. In these locations the relative contribution of indoor specific sources (e.g. tobacco smoke) is likely to be impaired.
- At low outdoor levels (benzene <5 $\mu g/m^3$), indoor sources moderately (Basel) or marginally (GerES IVP, Helsinki) contribute to exposure, with median indoor levels not more than three-fold the background benzene concentration (0.6 to 1.9 $\mu g/m^3$ in European continental pristine air, as reported by ECB 2004).

Benzene levels measured in Prague and Oxford (EXPOLIS) and in England (BRE) are expected to fall between the two scenarios described.

As pointed out in Table 6.1, the additional lifetime cancer risk in Europe is expected to range from 8 to $216 \cdot 10^{-6}$ $(\mu g/m^3)^{-1}$, resulting in a 27-fold increase experienced by worse-case residentials in Milan (37 $\mu g/m^3$) with respect to average residentials in Germany (1.3 $\mu g/m^3$), the latter considered as the European background cancer risk estimate, with 7.5 cases of benzene-induced leukemia per one million people. Moreover, almost the entire bulk of data is below the exposure level (60 $\mu g/m^3$) considered safe with respect to haematological effects, the most severe toxicological enpoint other than cancer.

EU limit value for benzene in ambient air – Directive 2000/69/EC

Limit value for the protection of human health: 5 μg/m^3 (averaging period of a calendar year)
Margin of tolerance: 5 μg/m^3 (100 %) on 13 December 2000, reducing on 1 January 2006 and every 12 months thereafter by 1 μg/m^3 to reach 0 % by 1 January 2010
Date by which limit value is to be met: 1 January 2010, except within zones and agglomerations within which a time-limited extension has been agreed in accordance with Article 3(2) of the directive. The limit value for benzene to be granted during conditional extension for a period of up to five years shall, however, not exceed 10 μg/m^3.

Result

Benzene is ubiquitous in the athmosphere, mainly due to anthropogenic sources (90%), with concentrations in the European continental pristine air ranging from 0.6 to 1.9 μg/m^3. It is a genotoxic carcinogen and hence no safe level of exposure could be recommended. Results from nine monitoring surveys indicate that the European population is experiencing in their homes an increased risk in contracting benzene induced leukemia, with respect to the estimated background lifetime risk of 7-8 cases per one million people (considering the WHO unit risk factor). Based on the available exposure data (Median levels±sd: 4.2±3.2 μg/m^3; 90th levels±sd: 11.5±11.1 μg/m^3; N = 9) two main scenarios could be described as follows:

- People living in highly trafficked urban areas are found, on average, to experience an estimated 6 to 30-fold increase in contracting benzene induced leukemia during their life, the benzene levels encountered in these areas not expected to produce chronic effects other than cancer, in particular haematological effects, nor acute sensory effects such as odour perception (odour threshold: 1.2 mg/m^3) and sensory irritation. Also, the contributions of specific indoor sources in these areas are likely to be impaired due to increased background outdoor levels.
- People living in rural areas or poorly trafficked towns were found, on average, to experience an estimated 1 to 5-fold increase in contracting benzene induced leukemia during their life, this factor depending principally on the presence of indoor sources.

Naphthalene

Synonyms:	antimite, naphthalin, naphthaline, naphthene, tar camphor
CAS Registry Numbers:	91-20-3
Molecular Formula:	$C_{10}H_8$

1. Compound identification

Naphthalene is white crystalline powder with aromatic odour (of mothballs). It is a two-ring hydrocarbon isolated from coal tar. It is used as intermediate in chemical synthesis, as insect repellents, fungicides, lubricants, preservatives, and, formerly, as topical antiseptics (EPA/Cal 2003, HSDB 2003). Gasoline and diesel fuels contain naphthalene. Naphthalene is used indoors as a moth repellent, though this use is decreased. It has also been used in the manufacture of phthalic anhydride, phthalic and anthranilic acids, naphthols, naphthylamines, 1-naphthyl-n-methylcarbamate insecticide, beta-naphthol, naphthalene sulfonates, synthetic resins, celluloid, lampblack, smokeless powder, anthraquinone, indigo, perylene, and hydronaphthalenes (EPA/Cal 2003, HSDB 2003).

Naphthalene emissions to atmosphere are mainly originated from fugitive emissions and motor vehicle exhaust. Spills into land and water during the storage, transport and disposal of fuel oil and coal tar are lost and released to atmosphere due to volatilisation, photolysis, adsorption, and biodegradation. Naphthalene has a relatively short half-life, 3-8 hr, in the atmosphere. It is assessed that the primary route of exposure is inhalation, especially in vicinity of heavy traffic, gas stations or refineries. Usual indoor sources of naphthalene are unvented kerosene heaters and tobacco smoke (EPA/Cal 2003, HSDB 2003).

2. Physical and Chemical properties

Molecular weight (g/mol)	128.18
Melting point (°C)	80.5
Boiling point (°C)	218
Density, (g/cm3, at 20 °C, 1 atm)	4.42
Solubility	Soluble in alcohol, acetate

Conversion factors at 20 °C and 760 mm Hg:

1 ppb   = 5.321 $\mu g/m^3$
1 $\mu g/m^3$ = 0.188 ppb

Source: CRC (1995), Verschueren 2001, EPA/Cal (2003)

3. Indoor Air Exposure assessment

Indoor air and exposure concentrations

Average outdoor naphthalene concentrations were low in Europe, ranging from 1 to 4 $\mu g/m^3$ (Table 4.0.1, Jantunen et al 1999). Also residential indoor concentrations were elsewhere low, typically average concentrations below 2 $\mu g/m^3$, but in Athens clearly higher indoor levels were measured, being on average 90 $\mu g/m^3$. Personal exposures to naphthalene ranged from 1 $\mu g/m^3$ to 3 $\mu g/m^3$ elsewhere (Jantunen et al 1999, Hoffman et al 2000), but in Athens average exposure was 46 $\mu g/m^3$. In general we can conclude that exposures to naphthalene were usually low in Europe, but in Athens remarkable indoor sources of naphthalene were present, because personal exposure and workplace concentrations were lower than indoor concentrations (Figure 3.1, Table 4.0.1). Figure 3.2 shows the same distributions as Figure 3.1, but without Athens to be able to see distributions better focused on their scale. Similarly, exposure distributions with and without Athens are presented in Figure 3.3 and Figure 3.4.

Maroni et al (1995) reported typical median and 90th percentile naphthalene concentrations in indoor air being 2 µg/m³ and 5 µg/m³, respectively. Kostiainen et al (1995) detected slightly lower indoor concentrations in Helsinki, Finland, having 0.44 µg/m³ and 1.63 µg/m³ as a mean and maximum concentrations.

Bituminous material, commonly used in UK for damp proofing floors emits naphthalene (Brown et al 1990). Naphthalene concentrations up to 970 µg/m³ were found in homes having an objectionable smell, where the damp proof membrane had been applied, compared with <300 µg/m³ for control homes (EU 2003).

In an Italian study average indoor naphthalene concentration was 11 µg/m³, maximum level being 70 µg/m³ (DeBortoli et al 1986). Similar concentrations were measured in Canada, showing average and maximum concentrations of 14 µg/m³ and 77 µg/m³, respectively (Chan et al 1990).
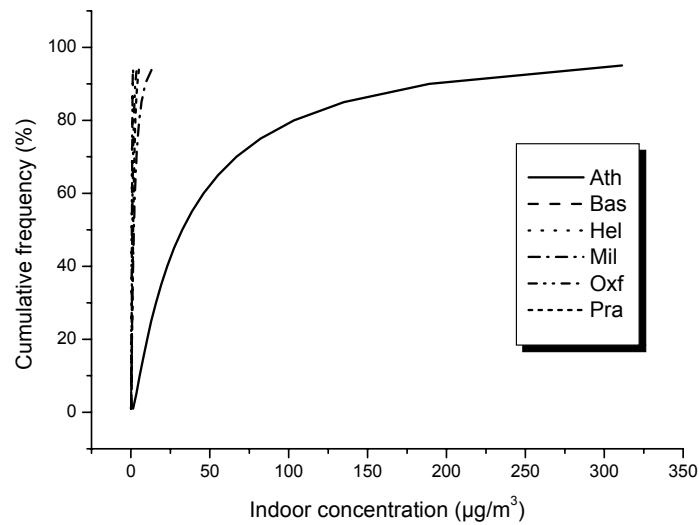
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of naphthalene in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=38) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
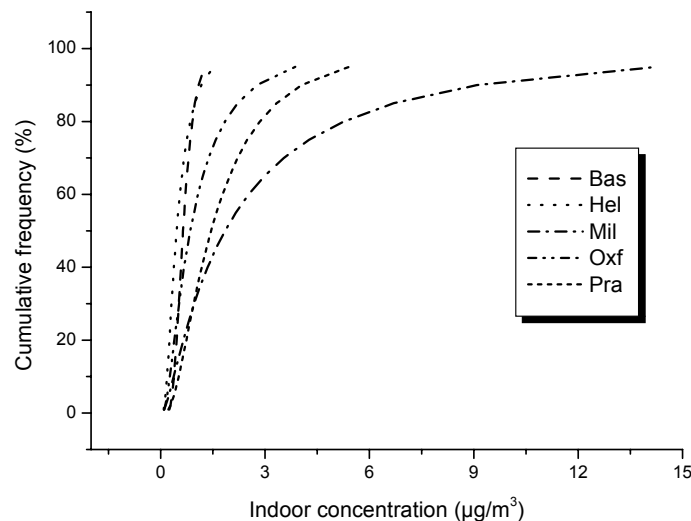
Figure 3.2. Cumulative frequency distributions of indoor air concentrations of naphthalene in Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=38) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
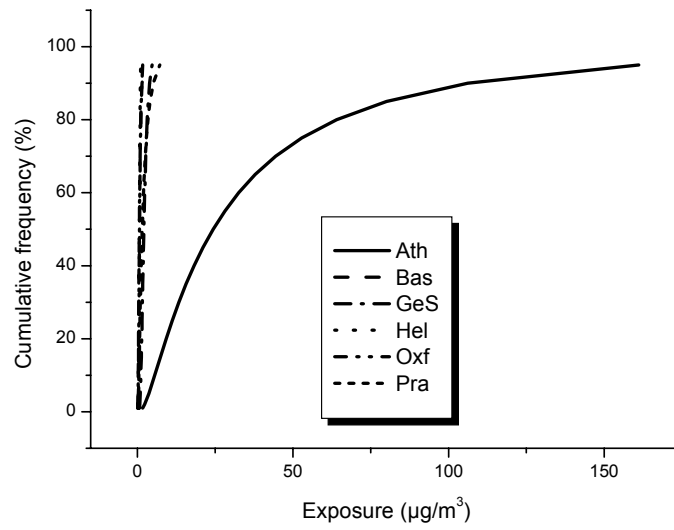
Figure 3.3. Cumulative frequency distributions of 48-hour personal exposure concentrations of naphthalene in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean concentrations of the German Survey GerES II (GeS) (Hoffman et al 2000).
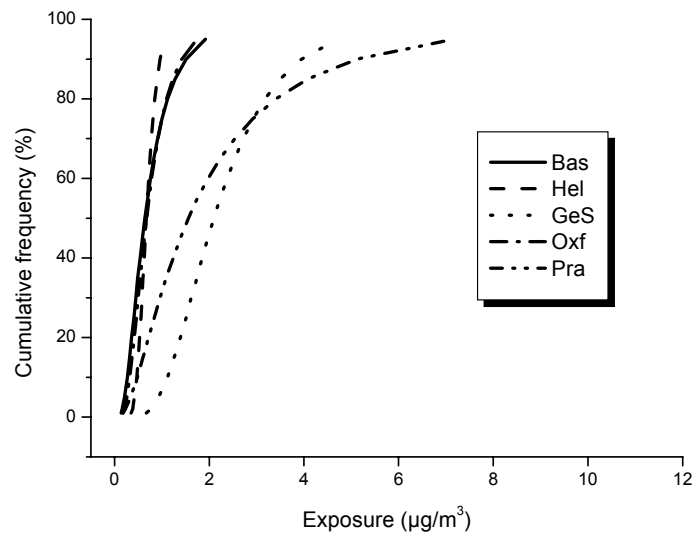
Figure 3.4. Cumulative frequency distributions of 48-hour personal exposure concentrations of naphthalene in Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean concentrations of the German Survey GerES II (GeS) (Hoffman et al 2000).

4. Toxicokinetics

Absorption

No empirical data that describe the rate or extent of naphthalene absorption following inhalation exposure were identified. NTP (2000) developed a physiologically-based pharmacokinetic model to describe the uptake of naphthalene in rats and mice following inhalation exposure. The model was calibrated using blood time course data for naphthalene (parent compound). Results from this model suggest that inhaled naphthalene is absorbed rapidly into the blood (Blood:air partition coefficient of 571). On the basis of estimates of naphthalene metabolism generated by the model, approximately 22% to 31% of inhaled naphthalene is absorbed by rats and 65% to 73% of inhaled naphthalene is absorbed by mice.

Assuming an average ambient concentration level of 5.19 µg/m^3 and an average inhalation rate of 15.2 m^3/day (U.S. EPA, 1996), an average daily dose of 1,127 ng/kgday can be calculated for a 70-kg adult. An estimated average daily dose of 4,5 ng/kg-day can be calculated for a 10-kg child assuming an inhalation rate of 8.7 m^3/day (U.S. EPA, 1996).

Distribution

There are limited data concerning the distribution of naphthalene in human tissues. Naphthalene was present in 40% of the adipose tissue samples that were analyzed as part of the National Human Adipose Tissue Survey (EPA 1986). The maximum concentration observed was 63 ng/g. Naphthalene was also detected in human milk samples (concentration not reported) (Pellizzari et al. 1982). The sources of naphthalene in these milk and body fat samples are not known.

Three reports (Zinkham and Childs, 1958; Anziulewicz et al., 1959; Athanasiou et al., 1997) describe apparent transplacental exposure of a fetus during pregnancy, which resulted in neonatal hemolysis. In the two older cases, unspecified amounts of naphthalene had been ingested by the mother during pregnancy. The more recent report by Athanasiou et al. (1997) documented the occurrence of hemolytic anemia in a neonate whose mother had inhaled naphthalene during the 28th week of pregnancy.

Metabolism and elimination

The *in vivo* and *in vitro* metabolism of naphthalene in mammalian systems has been extensively studied (U.S. EPA 1998). As many as 21 metabolites, including oxidized derivatives and conjugates, have been identified in the urine of animals exposed to naphthalene (Horning et al., 1980; Wells et al., 1989; Kanekal et al., 1990). Factors that potentially influence the relative proportions of individual metabolites include species, tissue type, and tissue concentration of naphthalene (U.S. EPA, 1998). The initial step in naphthalene metabolism is catalyzed by cytochrome P-450 monooxygenases, and results in the formation of the arene epoxide intermediate 1,2-naphthalene oxide (Figure 4.1). 1,2-Naphthalene oxide can undergo spontaneous rearrangement to form naphthols (predominately 1-naphthol). The resulting intermediates may be further metabolized by oxidation reactions, resulting in the formation of di-, tri-, and tetrahydroxylated intermediates (Horning et al., 1980). Some metabolites may undergo conjugation with glutathione, glucuronic acid, or sulfate (ATSDR, 1995; U.S. EPA, 1998). Glutathione conjugates undergo additional reactions to form cysteine derivatives (thioethers). These cysteine derivatives may be further metabolized to mercapturic acids and may be excreted in the bile (U.S. EPA, 1998). Alternative pathway of naphthol metabolism involves enzymatic hydration by epoxide hydrolase (U.S. EPA, 1998).

Bieniek (1994) analyzed the excretion patterns of 1-naphthol in three groups of workers occupationally exposed to naphthalene. The mean excretion rate for these workers was 0.57 mg/hour, with a calculated excretion half-life of approximately 4 hours. The highest urinary levels of 1-naphthol were reported for workers in a naphthalene oil distribution plant. Peak 1-naphthol levels were detected in urine collected one hour after finishing the shift.

Excretion in the feces represents a minor pathway for naphthalene, and the possibility of excretion via exhalation of the unmetabolized compound has not been examined in available studies.

Figure 4.1: Proposed Pathways For Naphthalene Metabolism
Source: U.S. EPA (1998)
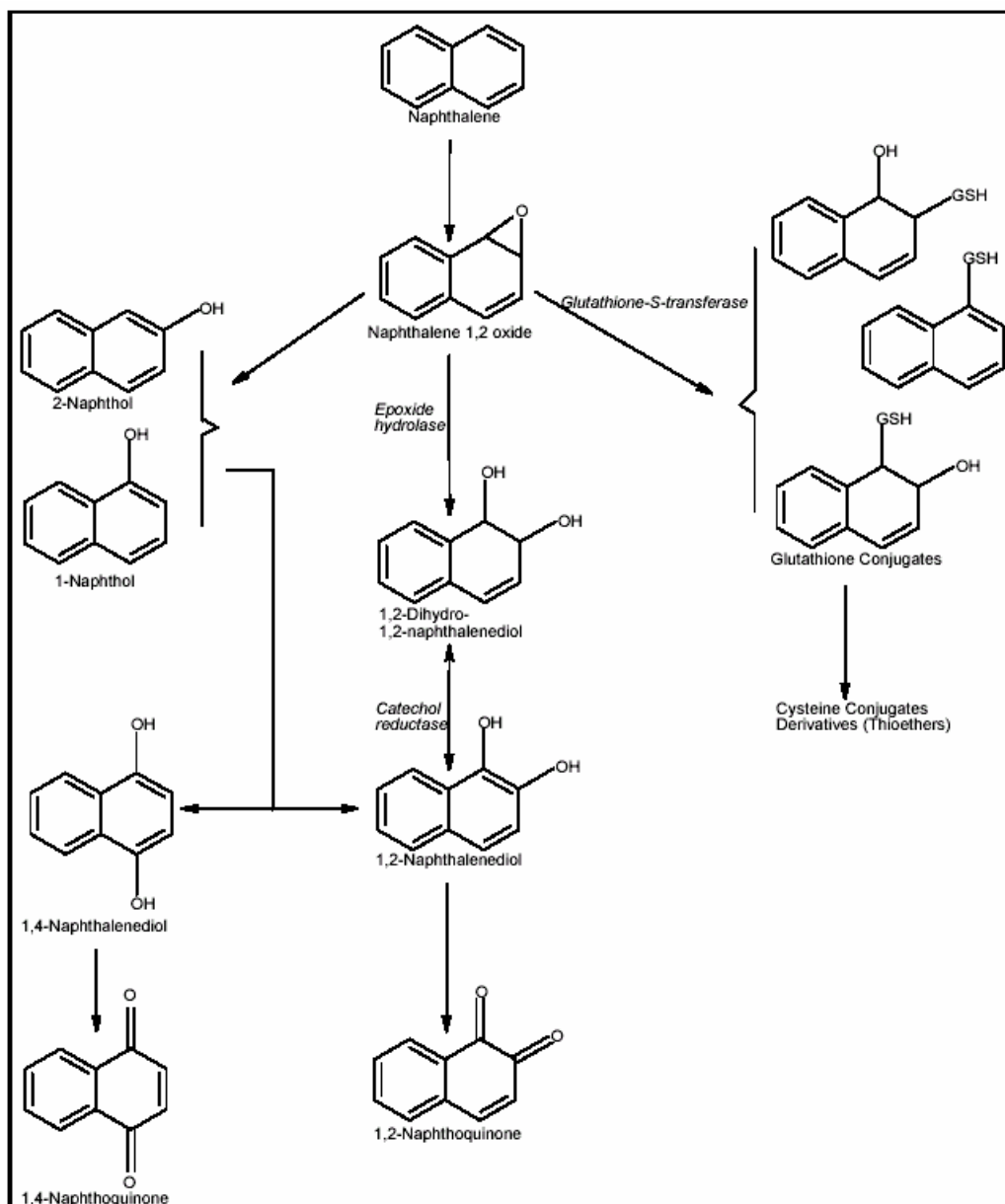
5. Health effects

Information is scarce regarding dose-response relationships for health effects in humans with acute, subchronic, or chronic exposure by any route. Reported health effects associated with indoor exposures to naphthalene are limited to its principal indoor source: mothballs.

Effects of short-term exposure

Reports that establish associations between naphthalene exposure and health effects in humans are restricted to numerous reports of hemolytic anemia or cataracts following acute exposure or occupational exposure to naphthalene, either by ingestion or by inhalation of naphthalene vapors, but these reports have not identified exposure levels associated with these effects. A relationship appears to exist between an inherited deficiency in the enzyme, glucose 6-phosphate dehydrogenase (G6PD), and susceptibility to naphthalene-induced hemolysis. Newborn infants also appear to

be susceptible to naphthalene-induced hemolysis presumably due to a decreased ability to conjugate and excrete naphthalene metabolites.

Individuals with a G6PD genetic defect are prone to hemolysis after exposure to a variety of chemical oxidizing agents including nitrates, nitrites, aniline, phenols (Dean et al. 1992), and naphthalene. Valaes et al. (1963) reported adverse effects in 21 Greek infants exposed to naphthalene from clothing, diapers, blankets, and other items that had been stored in contact with mothballs. Durations of exposure ranged from 1 to 7 days. Inhalation was identified as the primary route of exposure because 19 of the 21 infants did not have dermal contact with the naphthalene-contaminated materials. A total of 21 infants developed hemolytic anemia and two infants died from kernicterus, a severe neurological condition that was thought to be a consequence of massive hemolysis. Ten of the 21 anemic children and 1 of the 2 infants that died from naphthalene exposure had a genetic polymorphism that resulted in a deficiency in glucose-6-phosphate dehydrogenase (G6PD). This enzyme helps to protect red blood cells from oxidative damage, and G6PD deficiency makes the cells more sensitive to a wide variety of toxicants, including naphthalene. Eight adults and one child reported gastrointestinal (nausea, vomiting, abdominal pain) and neurological (headache, malaise, confusion) symptoms after exposure to large numbers of mothballs in their homes (Linick, 1983). The duration of exposure was not specified. Testing at one home following the incident indicated an airborne naphthalene concentration of 105 mg/m^3 (20 ppb). Symptoms abated after removal of the mothballs.

There are no data available on skin or respiratory sensitisation in humans. Acute (4-hour) inhalation exposure to naphthalene induced necrosis of Clara cells in the epithelium of the proximal airways of the lungs of mice at exposure levels as low as 53 mg/m^3 (10 ppm), but did not affect lung tissue in rats at concentrations as high as 526 mg/m^3 (100 ppm) (West et al. 2001). These results, and those from the chronic inhalation studies, show that mice are more susceptible than rats to lung damage from inhaled naphthalene. However, there are no studies that have examined nasal tissues for the development of lesions following acute inhalation exposure. A change to mouth breathing occurred in rats during exposure to 410 mg/m^3 naphthalene, but no other effects on respiration were noted (Fait and Nachreiner 1985).

Hemolytic anaemia (potentially sensitive populations)

Increased sensitivity to naphthalene-induced hemolysis has been associated with reduced levels of glucose-6-phosphate dehydrogenase (G6PD). This enzyme helps to protect red blood cells from oxidative damage, and G6PD enzyme deficiency makes the cells more sensitive to a wide variety of toxicants, including naphthalene. Higher rates of inherited G6PD deficiencies are found more often in defined subpopulations of males from Asian, Arab, Caucasian (of Latin ancestry), African, and African-American ancestry than in other groups (U.S. EPA, 1987). Multiple forms of G6PD deficiency have been identified in these subpopulations. The mildest forms are totally asymptomatic, while moderate forms are associated with an adverse response to chemical stressors, including naphthalene. The most severe forms of G6PD deficiency are associated with hemolytic anemia, even in the absence of external stressors (Beutler, 1991). The overall prevalence of G6PD-deficiency in the United States is reported to be 5.2 to 11.5% (Luzzatto and Mehta, 1989). There is no evidence of haemolytic anaemia in rodents.

Prevalence of G6PD enzyme deficiency in the EU: Polymorphic G6PD variants are those that have achieved a high frequency in some populations. They represent balanced polymorphisms in which the benefit of inheriting the mutation (probably resistance to malaria) counterbalances the disadvantage (susceptibility to hemolysis and neonatal icterus). Generally, each population has its own characteristics mutations, although, as noted below, there are occasional exceptions to this rule.
- Mediterranean Variants: G6PD deficiency is very prevalent in some Mediterranean countries. A gene frequency of about 0.7 has been documented among Kurdish Jews. This is the highest incidence known in any group. Among Greeks, Turks, Sardinians, Sephardic Jews and Italians, G6PD deficiency is also quite prevalent, but more commonly with gene frequencies that range from 0.02 to 0.20. The situation regarding Mediterranean variants is in one respect the reverse of the situation of the African variants. Here several different variants (e.g., G6PD "Sassari" and "Cagliari") were believed to be different on the basis of biochemical characteristics, but all seem to share the same mutation at nt 563. Variants from other parts the world, thought to be unique - G6PD Dallas, Birmingham, and Panama - proved to be G6PD Mediterranean 563T. Other mutations are found in the Mediterranean region as well. G6PD Seattle844T (also described as G6PD Lodi and as G6PD "Modena") and, as noted above, G6PD A- are relatively common.
- African Variants: G6PD deficiency among Africans is relatively mild; red cells contain 10-15% residual enzyme that is electrophoretically rapid. Accordingly it is designated G6PD A- to distinguish its mobility from the normal enzyme, which is designated B. Among Afro- Americans the gene frequency of G6PD A- is about 11%.(11) It is considerably higher in some parts of Africa.(12) Some Africans have an enzyme with the same rapid mobility encountered among deficient individuals, but the activity of the enzyme is normal. This African enzyme is designated

G6PD A+, and it is known to be due to an A®G transition at nt 376 that predicts substitution of a negatively charged aspartic acid for asparagine. Its gene frequency is in the range of 20-30%

Polymorphic G6PD variants that have been characterized at the DNA level have been summarized in Beutler, 1994, Vulliamy et al., 1993 and Beutler et al., 1995.

<u>Summary of short-term exposure effect levels</u>

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
11 $_{EXP}$	53 $_{EXP}$	Respiratory: Clara cell necrosis and decreased Clara cell mass (volume/surface area) in proximal airways	Mouse; 4h	West et al. 2001	ATSDR 2003; no MRL
ECB (2003): In relation to haemolytic anaemia, the available data do not allow the identification of a NOAEL.					

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h-ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

ATSDR (2003)
Agency for Toxic Substances and Disease Registry

Data are inadequate for deriving an acute-duration inhalation MRL for naphthalene. Data are restricted to a 14-day (6 hours/day, 5 days/week) range-finding study in B6C3F1 mice (NTP 1992a), which only examined hematologic end points and did not histologically examine expected critical toxicity targets (lung and nasal cavity epithelial tissue) (NTP 1992a), and a study (West et al. 2001) with Swiss Webster mice and Sprague-Dawley rats, which involved single 4-hour exposure periods. The more recent study, however, only histologically examined the lung and did not examine nasal tissue. A comprehensive inhalation study involving an acute repeated exposure scenario and examining the other critical target (the nose, based on the findings from chronic mouse and rat bioassays) is not currently available. Results from such a study may be useful for deriving an acute-duration inhalation MRL for naphthalene.

Hemolysis is the best documented effect of acute naphthalene exposures in humans, but it has not been observed in studied strains of rats (F344) or mice (CD-1, B6C3F1). Dose-response data for hemolysis from a susceptible animal species (such as dogs or the Jackson Laboratory hemolytic anemia mouse) may be useful to obtain data that could be used for considering changes to the acute-duration oral MRL. Data from both inhalation and oral exposure protocols would be useful.

ECB (2003)
European Chemical Bureau - Institute for Health and Consumer Protection - European Union Risk Assessment Report

In relation to hemolytic anaemia, the available data do not allow the identification of a NOAEL nor the dose-response characteristics for this endpoint. In the absence of such information, any significant body burden is considered to give rise to concerns for human health. Exposure of infants to textiles (clothing/bedding) which have been stored for long periods with naphthalene moth repellent raises significant concern. There is documented evidence for the development of severe hemolytic anaemia resulting from such use, although there is no quantitative information available on the level or duration of exposure to naphthalene in these cases.

Effects of long-term exposure (noncancer)

There are no epidemiological studies on the human health effects of naphthalene, and the only human information available derives from a limited number of early case-reports which provide no quantitative data on the levels or duration of exposure. A principal human health effect is haemolytic anaemia (see previous chapters) which in some cases has been of marked severity in humans exposed by inhalation to naphthalene vapour and by ingestion to solid naphthalene. Dermal exposure to the solid and vapour was also likely in these cases.

Animal studies reveal species differences in response to naphthalene. Haemolytic anaemia was noted in a dog following oral dosing of 220 mg/kg/day for 7 days but not in rodents even with high/prolonged exposures. Cataract formation was the principal effect seen in rats and rabbits following oral exposure to 700 and 1000 mg/kg/day, respectively in studies ranging from 10-180 days, but this effect was not seen in mice with similar exposures. The lack of reliable reports of

cataracts in humans despite the widespread use of naphthalene and high dose accidental exposure, suggests that cataract formation is unlikely to be a significant health effect in humans (ECB, 2003).

The few chronic animal studies that are available for naphthalene were conducted primarily to characterize its carcinogenic potential effects. Noncancer endpoints reported in these studies are summarized below.

Adkins et al. (1986) investigated the impacts of less-than-lifetime inhalation exposures to naphthalene on rats. Groups of 30 female A/J strain rats were exposed to 0, 53, or 158 mg/m^3 (0, 10, or 30 ppm) naphthalene vapors for 6 hours per day, 5 days per week, for 6 months. All animals were sacrificed at the end of the exposure period and their lungs excised and examined for tumors. No adverse noncancer effects on the lung were reported (U.S. EPA, 1998). Other organs were not examined in study.

A chronic inhalation study of naphthalene toxicity was conducted in B6C3F1 mice by NTP (1992a). Naphthalene exposure concentrations in air were 0, 53, or 158 mg/m^3 (0, 10 ppm, or 30 ppm). The concentration of 53 mg/m^3 was chosen because it was equal to the ACGIH TLV® for naphthalene, while the 158 mg/m^3 concentration was chosen because it was one-half the air saturation concentration. The control and low-exposure groups consisted of 75 mice of each sex, while the high-exposure group consisted of 150 mice of each sex. Exposure was for 6 hours per day, 5 days per week, for 2 years. Comprehensive histopathological evaluations were performed on all control and high-exposure mice, and on all low-exposure mice that died or were sacrificed during the first 21 months of exposure. The original study plan called for 50 animals per sex to be exposed for 2 years, and 5 animals per sex to be sacrificed for hematological evaluations at 14 days, 3, 6, 12, and 18 months. However, as a result of excessive mortality in the control males, only the 14-day hematological evaluation was conducted. All of the remaining animals were incorporated into the two-year study.

A statistically significant decrease in survival was noted in the male control group. This phenomenon was attributed to the frequent fighting that occurred among the control group mice. In contrast, the exposed groups tended to huddle together during exposure periods, and fought less. Statistically significant increases were seen in several types of noncancer respiratory tract lesions in both exposed groups. The observed responses included chronic lung inflammation, chronic nasal irritation with hyperplasia of the nasal epithelium, and metaplasia of the olfactory epithelium. The authors of the study described the lung lesions as a chronic inflammatory response with granuloma. These lesions consisted of "focal intra-alveolar mixed inflammatory cell exudates and interstitial fibrosis." The more advanced lesions consisted primarily of "large foamy macrophages sometimes accompanied by giant cells."

No changes in hematological parameters were seen among the exposed animals at 14 days. No cataract formation was observed after 2 years of exposure. Histopathological examination did not reveal treatment-related effects on the liver, gastrointestinal system, reproductive system, brain, or any other organs. The results of this study have been interpreted by U.S. EPA (1998) to support a chronic LOAEL for nasal and respiratory irritation of 53 mg/m^3.

NTP (2000) conducted a chronic inhalation study in F344/N rats. Male and female rats (49/sex/dose) were exposed to naphthalene vapor concentrations of 0, 53, 158, and 316 mg/m^3 (0, 10, 30, and 60 ppm) for 6 hours per day plus T_{90} (the theoretical time to achieve 90% of the target concentration in the vapor chamber: 12 minutes), 5 days per week for 105 weeks. Additional groups of rats were similarly exposed for up to 18 months for evaluation of toxicokinetic parameters. Dose calculations were based upon model estimates of the amount of naphthalene inhaled by rats at the exposure concentrations used in the two-year study, the total amount of naphthalene metabolized following a six-hour exposure period (21% to 31% of inhaled naphthalene), and average weights of 125 grams (male rats) and 100 grams (female rats). Because essentially all of the naphthalene that is absorbed into the bloodstream is metabolized, the total amount of naphthalene metabolized was assumed to represent the internalized dose to rats from the exposure concentrations used in this two-year study. The estimated daily doses determined by this method were 0, 3.6, 10.7, 20.1 mg/kg-day for males, and 0, 3.9, 11.4, and 20.6 mg/kg-day for females.

Rats were clinically examined twice daily and findings were recorded every four weeks beginning at week 4 and every two weeks beginning at week 92. Body weights were recorded at study initiation, every four weeks beginning at week 4, and every two weeks beginning at week 92. Full necropsies and complete histopathologies were performed on all core study animals.

There were no clinical findings related to naphthalene exposure from the two-year inhalation study. The mean body weights all exposed groups of male and female rats were similar to those observed in the appropriate control chamber group. No significant difference in survival rate was observed for any exposed group when compared to the chamber control. The mean body weights of female rats were generally similar to the body weights of the control group, while the mean body weights of naphthalene-exposed male rats were generally less than the chamber control for all exposed groups.

Although naphthalene is a known cataractogen and ocular irritant, no naphthalene-related cataractogenic effects or ocular abnormalities were observed in rats during this study. Treatment-related non-neoplastic lesions were observed in the nose and lungs of male and female rats. The incidence and average severity of nasal lesions (glands, goblet cells, respiratory epithelium and olfactory epithelium) are summarized in Table 5.1. The incidences of these lesions were significantly greater than those in the chamber controls for all male and female exposed groups, with the exception of squamous metaplasia of glands in male and female rats in the 53 mg/m^3 exposure groups (NTP, 2000). In general, the severities of olfactory epithelial and glandular lesions increased with increasing exposure concentrations.

Two noteworthy type of lesions occurred in the lungs of exposed rats: alveolar epithelial hyperplasia and minimal chronic inflammation. Female rats in all exposure groups had increased incidences of alveolar epithelial hyperplasia when compared to the chamber control (chamber control: 4/49, 53 mg/m^3 10ppm: 11/49, 158 mg/m^3: 11/49, 316 mg/m^3: 9/49). This effect reached statistical significance in the 53 and 158 mg/m^3 exposure groups. The incidences of alveolar epithelial hyperplasia in male rats (chamber control: 23/49, 53 mg/m^3: 12/49, 158 mg/m^3: 9/48, 316 mg/m^3: 16/49) were significantly decreased in the 53 and 158 mg/m^3 exposure groups. The incidences of minimal chronic inflammation of the lung were increased in males and females exposed to naphthalene. This lesion is characterized by small focal interstitial and intra-alveolar collections of macrophages, neutrophils, and lymphocytes and minimal interstitial fibrosis. As noted by the NTP study authors, foci of minimal inflammation are common in chamber control rats (as evident in this study). Therefore, this change could not be confidently related to naphthalene exposure.

The study conducted by NTP (2000) identified an estimated inhalation LOAEL of 3.6 mg/kg-day based on the occurrence of nasal lesions in male rats in the 53 mg/m^3 exposure group. A NOAEL was not identified in this study. The 53 mg/m^3 concentration associated with the LOAEL corresponds to the threshold limit value for naphthalene (ACGIH, 2000).

Table 5.1: Nonneoplastic and Neoplastic Lesions of the Nose in Male and Female F344/N Rats
Exposed to Naphthalene 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP, 2000)

Concentration	0 mg/m^3		53 mg/m^3 (10 ppm)		158 mg/m^3 (30 ppm)		316 mg/m^3 (60 ppm)	
Lesion	M	F	M	F	M	F	M	F
Nonneoplastic lesions								
Olfactory epithelium								
Hyperplasia	0/49	0/49	48/49	48/49	45/48	48/49	46/48	43/49
Atrophy	0/49	0/49	49/49	49/49	48/48	49/49	47/48	47/49
Chronic inflammation	0/49	0/49	49/49	47/49	48/48	47/49	48/48	45/49
Hyaline degeneration	0/49	13/49	46/49	46/49	40/48	49/49	38/48	45/49
Respiratory epithelium								
Hyperplasia	0/49	0/49	21/49	18/49	29/48	22/49	29/48	23/49
Squamous metaplasia	0/49	0/49	15/49	21/49	23/48	17/49	18/48	15/49
Hyaline degeneration	0/49	8/49	20/49	33/49	19/48	34/49	19/48	28/49
Goblet cell hyperplasia	0/49	0/49	25/49	16/49	29/48	29/49	26/48	20/49
Gland hyperplasia	0/49	0/49	49/49	48/49	48/48	48/49	48/48	42/49
Gland squamous metaplasia	0/49	0/49	3/49	2/49	14/48	20/49	26/48	20/49
Neoplastic lesions								
Respiratory epithelial adenoma	0/49	0/49	6/49	0/49	8/48	4/49	15/48	2/49
Olfactory epithelial neuroblastoma	0/49	0/49	0/49	2/49	4/48	3/49	3/48	12/49

Source: Adapted from *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene in Rats (Inhalation Studies)*, Table 6 (NTP, 2000) (M=male, F=female)

Naphthalene administered by inhalation at concentrations of 10, 30, or 60 ppm for 6 hours per day, 5 days per week for 105 weeks caused nonneoplastic and neoplastic effects in nasal respiratory and olfactory regions of male and female F344/N rats. Non-neoplastic nasal effects were characterized by an increase in the incidence and severity of a complex group of lesions, including atypical hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and hyperplasia and squamous metaplasia of mucosal glands. Neoplastic effects were characterized by the induction of two types of rare primary nasal tumors, olfactory neuroblastomas and respiratory epithelial adenomas. The incidences of olfactory neuroblastomas in males at 0 ppm, 10 ppm, 30 ppm, and 60 ppm were, respectively, 0%, 0%, 8%, and 6%, whereas in females they were 0%, 4%, 6%, and 24%. The incidences of respiratory epithelial adenomas in

males at 0 ppm, 10 ppm, 30 ppm, and 60 ppm were, respectively, 0%, 12%, 17%, and 31% and in females 0%, 0%, 8%, and 4%. The olfactory neuroblastomas and respiratory epithelial adenomas were considered carcinogenic effects related to naphthalene exposure based on their relatively high incidence in exposed rats, their absence in concurrent control rats and NTP historical controls, and their rare spontaneous occurrence in rats of any strain (Abdo et al., 2001; Long et al., 2003).

In a well conducted unpublished study, groups of 10 male and 10 female rats were exposed nose only for 6 hours/day, 5 days a week for 13 weeks to 0, 11, 53 or 305 mg/m^3 (0, 2, 10 or 58 ppm) vapourised naphthalene (Huntingdon Research Centre, 1993a). A gross pathological examination was carried out on a wide range of tissues and a microscopic examination was carried out on a range of tissues including the lungs, liver, kidneys, adrenals, testes, eyes and optic nerve. Prior to terminal sacrifice, samples of blood were taken from all rats for haematological and clinical chemistry evaluation. In high dose animals body weight gain was reduced by 43% and 34% in males and females, respectively and was associated with reduced food consumption. There were no toxicologically significant haematological or clinical chemistry findings observed. Similarly, no significant changes were noted in organ weight or gross pathology.

Microscopic analysis of the nasal epithelium revealed treatment-related effects at all dose levels. The severity of the effects was dose-related. At the highest exposure level (305 mg/m^3) changes included erosion of the olfactory epithelium, hyperplasia of basal cells in the olfactory epithelium and loss of Bowmans' glands. At the lowest exposure level (11 mg/m^3) changes in olfactory epithelium were less marked but included slight disorganisation, mild erosion (in one rat), minimal atrophy, rosette formation (an attempt at proliferative repair by the olfactory neuroepithelium), occasional degenerate cells, loss of Bowmans' glands and minimal hyperplasia. There were no treatment related effects observed in the lungs or nasal respiratory epithelium at this dose. There were no observed changes in the nasal passages of control animals. In one low dose rat there was evidence of squamous metaplasia of the respiratory epithelium, however as this lesion was not seen in the other rats at higher doses this lesion was not considered toxicologically significant. The effects at 10 mg/m^3 were generally minimal in severity and seen in only small numbers of animals, and therefore appear to represent the low end of the dose-response curve for nasal effects. Overall, signs of damage to the olfactory epithelium were seen at all doses down to 11 mg/m^3 (2 ppm), and a NOAEL cannot be identified for local effects.

In a well conducted unpublished study, groups of 5 male and 5 female rats were exposed nose only for 6 hours/day, 5 days a week for 4 weeks to 0, 5, 16, 53, 153 or 374 mg/m^3 (0, 1, 3, 10, 29 or 71 ppm) vapourised naphthalene (Huntingdon Research Centre, 1993b). Investigations were similar to the 13-week study performed in the same laboratory. Results were similar to those observed in the 13-week study. High dose animals showed approximately a 50% reduction in body weight gain associated with reduced food consumption. There was no evidence of systemic toxicity. Local effects were observed with signs of proliferative repair in the nasal olfactory epithelium changes observed at all doses down to 5 mg/m^3 (1 ppm), and therefore a NOAEL for local effects cannot be identified.

For both the 4 and 13-week studies the mechanism by which the observed effects in the olfactory nasal epithelium arise is unclear, although the effects may be mediated by locally produced metabolite(s) of naphthalene. The relevance of these effects to human health is uncertain, as there may be significant species differences in local metabolism. However, there is no evidence to indicate that these effects are not relevant to human health.

Reproductive and developmental toxicity

No information is available on both the reproductive and developmental effects of naphthalene in humans, although the occurrence of hemolytic anemia in the neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958).

Animal studies involving naphthalene exposure during gestation reported no reproductive effects in rabbits administered doses of up to 120 mg/kg/day by gavage or in rats given doses of up to 450 mg/kg/day, although doses of 150 mg/kg/day and greater were maternally toxic to rats. There was a decrease in the number of live mouse pups per litter with a dose of 300 mg/kg/day given during gestation (Plasterer et al. 1985) and *in vitro* studies of naphthalene embryotoxicity in the presence of liver microsomes support the concept that naphthalene metabolites may be harmful to the developing embryo (Iyer et al. 1991).

No exposure-related lesions in reproductive tissues were found in intermediate-duration oral exposure studies in rats (NTP 1980b) and mice (NTP 1980a) or in chronic inhalation studies in rats (Abdo et al. 2001; NTP 2000) or mice (NTP 1992a). One- or two-generation reproductive toxicity studies evaluating reproductive performance variables in male and female animals exposed to naphthalene are not available.

Studies of the developmental effects of orally administered naphthalene in rats (NTP 1991), mice (Plasterer et al. 1985), and rabbits (NTP 1992b; PRI 1985, 1986) have been negative, except for a slight nonsignificant increase in fused sternebrae in female rabbit pups from a small number of litters at doses of 80 and 120 mg/kg/day (NTP 1992b). No developmental toxicity studies involving inhalation or dermal exposure to naphthalene are available.

Summary of long-term exposure effect levels (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
	53 $_{EXP}$ 9.4 $_{ADJ}$	Respiratory; Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia	Mice, 105w	NTP, 1992a	OEHHA 2000; REL: 0.009; EPA-IRIS 1998 ; RfC: 0.003
	53 $_{EXP}$ 9.4 $_{ADJ}$ 1.2 $_{HEC}$	Respiratory; nonneoplastic lesions in nasal olfactory epithelium and respiratory epithelium in two species	Combined studies: Mice 2y - Rats 105w - Rats 2y	NTP, 1992a; NTP, 2000; Abdo et al., 2001	ATSDR 2003; MRL: 0.004
	5 $_{EXP}$ 0.94 $_{ADJ}$	Respiratory; proliferative repair in the nasal olfactory epithelium	Rats, 4w	Huntingdon Research Centre, 1993b (unpublished)	ECB 2003

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h-ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

OEHHA (2000)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Chronic Reference Exposure Level (REL):
Study	NTP (1992a)
Study population	B6C3F1 mice (75 or 150/group/sex)
Exposure method	Discontinuous whole-body inhalation exposures to 0, 10, or 30 ppm naphthalene vapor
Critical effects	Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia
LOAEL	10 ppm (96% incidence for males and 100% incidence for females)
NOAEL	Not observed
Exposure continuity	6 hours/day for 5 days/week
Average experimental exposure	1.8 ppm (10 ppm x 6/24 x 5/7) for LOAEL group
Exposure duration	104 weeks
Subchronic uncertainty factor	1
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.002 ppm (2 ppb, 0.009 mg/m³, <u>9 μg/m³</u>)

The NTP study was chosen for the REL derivation since it is the only available lifetime animal inhalation bioassay and because no adequate epidemiological studies of long-term human exposure are available. The study was judged to be of adequate study design. The complete lack of nasal effects among control animals and the nearly total effect among animals exposed at 2 different concentrations strongly indicates a causal relationship between naphthalene exposure and nasal effects. The effects seen are consistent with those reported among exposed workers, who developed rhinopharyngolaryngitis or laryngeal carcinoma (Wolf, 1978). However, the hematological effects observed in humans have not been reported in laboratory animals, which raises the possibility that humans may be significantly more sensitive to naphthalene.

The most important limitation of the study is that the lowest concentration tested caused adverse effects in most (≥96%) of the animals tested. Thus the study amply demonstrates the risk of lifetime exposures to 53 mg/m³ (10 ppm), but is uninformative regarding the concentration-response relationship at lower concentrations. Only a general assumption can be drawn on the magnitude of uncertainty factor needed to predict a concentration at which adverse effects would most likely not be observed. Lacking specific guidance or relevant research for this situation, the default 10-fold factor was applied. U.S. EPA also used the NTP study to develop its RfC of 3 mg/m³ with slightly different assumptions and a cumulative uncertainty factor of 3000 (U.S. EPA, 2000). OEHHA followed the U.S. EPA precedent in using an

intraspecies UF of 10 for naphthalene, rather than using the HEC/RGDR approach. According to U.S. EPA (2000), because of its low water solubility and low reactivity, naphthalene-related effects on the nasal epithelium are expected to result following absorption of naphthalene and its metabolism to reactive oxygenated metabolites, not from direct contact. This is supported by data on naphthalene metabolism indicating that toxic effects on the respiratory tract are due to a naphthalene metabolite that may be formed either in the liver or in the respiratory tract. Necrosis of bronchial epithelial (Clara) cells in mice and necrosis of olfactory epithelium in mice, rats, and hamsters occur following intraperitoneal injection of naphthalene. The nasal effects from inhalation exposure to naphthalene were considered to be extra-respiratory effects of a category 3 gas (U.S. EPA, 1994). The assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans; however, it is uncertain that the RfC for naphthalene based on nasal effects will be protective for hemolytic anemia and cataracts, the more well-known effects from naphthalene exposure in humans.

U.S.EPA - IRIS (1998)
Integrated Risk Information System

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical effect	Experimental doses*	UF	MF	RfC
Nasal effects: hyperplasia and metaplasia in respiratory and olfactory epithelium, respectively Chronic mouse inhalation study NTP, 1992a	NOAEL: None LOAEL(HEC): 9.3 mg/m^3	3000	1	0.003 mg/m^3

*Conversion Factors and Assumptions -- Following the Category 3 guidance (U.S. EPA, 1994), experimental exposure concentrations of 0, 10, and 30 ppm were converted to 0, 52, and 157 mg/m^3, respectively; adjusted to a continuous exposure basis in mg/m^3 (6/24 hr × 5/7 days) equals mg/m^3 × 0.1786: 0, 9.3, and 28 mg/m^3. Because the blood:gas (air) coefficients for naphthalene were not available, the default ratio of 1 was used and the values for the LOAEL(HEC) were 0, 9.3, and 28 mg/m^3. Scenario -- The LOAEL human equivalent concentration (HEC) was calculated for an extrarespiratory effect for a category 3 gas. Since the b:a lambda for humans (h) is unknown, a default value of 1.0 is used for this ratio. LOAEL(HEC) × [b:a lambda(animal)/b:a lambda(human)] = 9.3 mg/m^3.

The NTP (1992a) study was given medium confidence because adequate numbers of animals were used, and the severity of nasal effects increased at the higher exposure concentration. However, the study produced high mortality, (< 40% survival in the male control group due to wound trauma and secondary lesions resulting from increased fighting). Also, hematological evaluation was not conducted beyond 14 days. The database was given a low-to-medium confidence rating because there are no chronic or subchronic inhalation studies in other animal species, and there are no reproductive or developmental studies for inhalation exposure. In the absence of human or primate toxicity data, the assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans; **however, it cannot be said with certainty that this RfC for naphthalene based on nasal effects will be protective for hemolytic anemia and cataracts, the more well-known human effect from naphthalene exposure**. Medium confidence in the RfC follows.

Dose conversion: Because of its low water solubility and low reactivity, naphthalene-related effects on the nasal epithelium are expected to result following absorption of naphthalene and metabolism to reactive oxygenated metabolites, rather than being a result of direct contact. This hypothesis is supported by data on naphthalene metabolism indicating that toxic effects on the respiratory tract are due to a naphthalene metabolite that may be formed either in the liver or in the respiratory tract. For example, necrosis of bronchial epithelial (Clara) cells in mice (O'Brien et al., 1985, 1989; Tong et al., 1981) and necrosis of olfactory epithelium in mice, rats, and hamsters (Plopper et al., 1992) occur following intraperitoneal injection of naphthalene. The nasal effects from inhalation exposure to naphthalene were considered to be extra-respiratory effects of a category 3 gas, as defined in the U.S. EPA guidance for deriving RfCs (U.S. EPA, 1994). Following this guidance, experimental exposure concentrations were adjusted to a mg/m^3 basis (0, 52, and 157 mg/m^3), adjusted to a continuous exposure basis (mg/m^3 × 6h/24h × 5d/7d = mg/m^3 × 0.1786: 0, 9.3, and 28 mg/m^3), and converted to human equivalent concentrations (HECs) by multiplying the adjusted concentrations by the ratio of mouse:human blood/gas partition coefficients. Because the blood/gas coefficients for naphthalene were not available, the default ratio of 1 was used.

Dose-response modeling: Whereas the data from the NTP (1992a) study show nasal effects to be the most sensitive effects from chronic inhalation exposure to naphthalene, they provide no indication of the shape of the dose-response curve because the incidence of nasal lesions at the lowest exposure level was 100% in females and nearly 100% in males. In this case, application of a BMD approach, in which quantal mathematical models are fit to the incidence data for nasal effects, does not sensibly assist in extrapolating to a NOAEL, and a NOAEL/LOAEL approach was taken for deriving an RfC for naphthalene.

ATSDR (2003)
Agency for Toxic Substances and Disease Registry

Derivation of the Minimal Risk Level (MRL):
Dose and end point used for MRL derivation: The lowest exposure level in both studies (NTP, 1992a; 2000), 53 mg/m^3 (10 ppm), was a LOAEL in both sexes of both species for nonneoplastic lesions in nasal olfactory epithelium and respiratory epithelium. Applying EPA inhalation dosimetry, a human equivalent LOAEL of 1.2 mg/m^3 (0.2 ppm), based on the rat LOAEL, was selected as the point of departure for the chronic inhalation MRL.

Modifying Factors used in MRL derivation:
       10 for use of a LOAEL
       3 for extrapolation from animals to humans with dosimetric adjustment
       10 for human variability
       Total Uncertainty Factor = 10x3x10=300

Determination of the human equivalent dose:
10 ppm x 6 hours/24 hours x 5 days/7 days x 128.18/24.45 = 9.4 mg/m^3 (duration-adjusted LOAEL for nasal effects in rats or mice)

Following EPA (1994) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry,* equations for a category 1 gas producing nasal effects were used to derive human equivalent concentrations:

HEC=Animal Concentration x $RGDR_{ET}$;
$RGDR_{ET}$= regional gas dose ratio in the extrathoracic (ET) region
      = $(Dose_{ET})A/(Dose_{ET})H$ = [minute volume/ETsurface area]A÷[minute volume/ETsurface area]H;
Reference minute volumes (L/min): 13.8 human, 0.137 rat, 0.0368 mouse;
Reference ET surface area (cm2): 200 human, 15 rat, 3 mouse;
$RGDR_{ET}$(Rat to Human)=[0.137/15]÷[13.8/200]=0.132; $LOAEL_{HEC}$=duration-adjusted LOAEL x 0.132=9.4 mg/m^3 x 0.132=1.2 mg/m^3
$RGDR_{ET}$(Mouse to Human)=[0.0368/3]÷[13.8/200]=0.178; $LOAEL_{HEC}$=duration-adjusted LOAEL x 0.132=9.4 mg/m^3 x 0.178=1.7 mg/m^3
Using public health protection reasoning, the $LOAEL_{HEC}$ based on the rat data was selected as the point of departure for the chronic inhalation MRL.

ECB (2003)
European Chemical Bureau - Institute for Health and Consumer Protection - European Union Risk Assessment Report

The hazardous properties of naphthalene have been evaluated to the extent that the minimum data requirements according to Article 9(2) of Council Regulation EEC No.793/93 have been met. The key health effects of haemolytic anaemia, repeated inhalation toxicity and carcinogenicity have been identified. For haemolytic anaemia, it is not possible to identify a NOAEL from the available data. For repeated inhalation toxicity, the key effect of concern is local damage to the upper respiratory tract. The available data do not allow the identification of a NOAEL; in a 28-day study in rats (Huntingdon Research Centre, 1993b)., damage to nasal olfactory tissue occurred at 5 mg/m^3, the lowest concentration level used. Therefore, the LOAEL of 5 mg/m^3 from this study will be used in the risk characterisation for repeated inhalation toxicity, including carcinogenicity. This experimental exposure concentration has been further adjusted by the authors to a continuous exposure basis: 5 mg/m^3 × 6h/24h × 5d/7d = 0.9 mg/m^3 .

Genotoxicity

Naphthalene has given reproducible negative results in bacterial mutation assays, and was negative in an *in vitro* UDS assay. It was however found to be clastogenic in CHO cells in the presence but not the absence of S9. Two *in vitro* studies using CHO cells and human peripheral lymphocytes were negative for induction of SCE. Naphthalene was found to be negative in two *in vivo* bone-marrow micronucleus tests and an *in vivo* rat liver UDS study. Overall, the balance of evidence indicates that naphthalene is not genotoxic (ECB, 2003).

The available data suggest that genotoxic action by the naphthalene metabolite, 1,2-naphthoquinone, is plausible and that the mutagenic/genotoxic potential of naphthalene and its metabolites may be weak. Assays of possible genotoxic

action in sensitive target tissues of naphthalene in rodents (lung and nasal epithelial tissue), however, are not available (ATSDR, 2003).

Carcinogenic potential

The only studies of cancer in humans exposed to naphthalene are two case series reports of cancer; one report of four laryngeal cancer cases (all of whom were smokers) among workers in a naphthalene purification plant in East Germany, and another report of 23 cases of colorectal carcinoma admitted to a hospital in Nigeria. NTP (2002), EPA (2002), and IARC (2002) concur that these studies provide inadequate evidence of naphthalene carcinogenicity in humans. No cohort mortality or morbidity studies or case-control studies examining possible associations between naphthalene exposure and increased risk of cancer (or other health effects) are available.

There are two comprehensive chronic-duration inhalation toxicology and carcinogenicity studies of naphthalene in animals, one in rats (Abdo et al. 2001; NTP 2000) and one in mice (NTP 1992a). These studies identify respiratory tissues as the most sensitive toxicity targets of chronic-duration exposure to inhaled naphthalene in animals: in particular neuroblastoma of the nasal olfactory epithelium was observed in rats and neoplastic lesions in the lungs of mice. Exposure related lesions in other tissues were not found in these studies. NTP (2002) and IARC (2002) concurred that these studies provide sufficient evidence of naphthalene carcinogenicity in animals. Overall, the proposed mechanism of carcinogenic action IARC (2002) is that the higher rates of metabolism of naphthalene in mice lead to cytotoxic metabolites in the lung, causing increased cell turnover and tumours. The absence of lung tumours in rats is entirely consistent with this mechanism. The maximal rates of metabolism measured in human lung microsomes are about 10–100 times lower than those in mice.

The Office of Environmental Health Hazard Assessment (OEHHA) on march 2004 adopted a unit risk value for naphthalene of 3.4×10^{-5} $(\mu g/m^3)^{-1}$ and slope factor of 1.2×10^{-1} $(mg/kg\text{-}day)^{-1}$. These values are based on data for incidence of nasal respiratory epithelial adenoma and nasal olfactory epithelial neuroblastoma in male rats.

Interactions with other chemicals

Schmeltz et al. (1978) suggested that it is likely that certain naphthalenes compete with benzo[a]pyrene (BaP) for the same enzyme sites, resulting in alteration of the BaP metabolic pathway and decreased production of the active BaP metabolite. This hypothesis is consistent with the observation that benzo(a)pyrene hydroxylase is inhibited by naphthalene (Shopp et al. 1984). Dermal application of the naphthalene mixture did not induce tumors in the absence of BaP. The results of these studies were not analyzed statistically.

Several studies have been conducted to assess factors that influence the toxicity of naphthalene. For the most part, these studies have evaluated the effects of mixed function oxidase activity (MFO) and alterations in glutathione levels on pulmonary and ocular toxicities. The effects of cyclooxygenase activity, antioxidants, and epoxide hydrolase inhibitors on the cataractogenic effect of naphthalene have also been evaluated. The administration of MFO inhibitors (SKF-525A, metyrapone) and antioxidants (caffeic acid and vitamin E) decreased ocular toxicity in mice (Wells et al. 1989). Use of ALO1576, an inhibitor of the enzyme aldose reductase, prevented cataract formation in both *in vivo* and *in vitro* studies (Xu et al. 1992a, 1992b). On the other hand, naphthalene-induced cataracts were enhanced by pretreatment with a MFO inducer (phenobarbital) and a glutathione depletor (diethyl maleate) (Wells et al. 1989). Pulmonary damage was decreased by prior treatment with a MFO inhibitor (piperonyl butoxide), but enhanced by prior treatment with a glutathione depletor (diethyl maleate) (Warren et al. 1982). For the most part, these studies support the role for mixed function oxidase activity and glutathione conjugation in naphthalene-induced pulmonary and ocular lesions.

Odour perception

Source: Amoore and Hautala (1983)
Odour threshold: 0.42 mg/m3 (0.08 ppm)

Source: Devos et al. (1990)
Odour threshold: 7.5 µg/m3

Source: Canadian Centre for Occupational Health and Safety - CCOHS
Odour is perceptible at 1.6 mg/m3 to 4.7 mg/m3 (0.3 to 0.9 ppm)

Source: New Jersey Department of health and senior services - Hazardous Substance Fact Sheets
Odour threshold: 0.2 mg/m3 (0.038 ppm).

Summary of Naphthalene Dose Response Assessment

Exposure other than inhalation: Rapid dermal absorption after skin contact

Toxicokinetics: Rapidly absorbed into the blood. Distributes to adipose tissue, breast milk and fetus.

Health effect levels of short- and long-term exposure (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
11 EXP	53 EXP	Respiratory: Clara cell necrosis and decreased Clara cell mass (volume/surface area) in proximal airways	Mouse; 4h	West et al. 2001	ATSDR 2003; no MRL
Long-term exposure					
	53 EXP 9.4 ADJ	Respiratory; Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia	Mice, 105w	NTP, 1992a	OEHHA 2000; REL: 0.009; EPA-IRIS 1998 ; RfC: 0.003
	53 EXP 9.4 ADJ 1.2 HEC	Respiratory; nonneoplastic lesions in nasal olfactory epithelium and respiratory epithelium in two species	Combined studies: Mice 2y - Rats 105w - Rats 2y	NTP, 1992a; NTP, 2000; Abdo et al., 2001	ATSDR 2003; MRL: 0.004
	5 EXP 0.94 ADJ	Respiratory; proliferative repair in the nasal olfactory epithelium	Rats, 4w	Huntingdon Research Centre, 1993b (unpublished)	ECB 2003

Carcinogenicity: IARC: 2B ; U.S.EPA: C ; ACGIH: A4 ; Inadequate evidence in humans

Genotoxicity: plausible for 1,2-naphthoquinone (naphthalene metabolite)

Odour threshold: 0.0075 mg/m³ (Devos), 0.2 mg/m³ (HSFS), 0.42 mg/m³ (Amoore &Hautala)

Susceptible population:
- Newborn infants susceptible to naphthalene-induced anaemia due to poor metabolism.
- Inherited G6PD enzyme deficiency (with mild, moderate, and severe polymorphic variants). G6PD deficiency is very prevalent in some Mediterranean countries. Among Greeks, Turks, Sardinians, Sephardic Jews and Italians, G6PD deficiency with gene frequencies that range from 0.02 to 0.20.

Remarks: Acute inhalatory exposure seems to be typically associated with wear of naphthalene contaminated clothing.

6. Risk Characterization

Health hazard evaluation of short-term exposure

Case reports of individuals (primarily infants) exposed to naphthalene via inhalation, dermal contact, or a combination of both exposure routes (e.g. textiles which have been stored with naphthalene moth repellent) point to hemolytic anemia and its sequelae as the most commonly manifested effects in humans following exposure at concentrations that exceed average environmental levels. Sensitive populations include individuals deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). Also, newborns and infants are thought to be more susceptible than older people because hepatic enzymes involved in conjugation and excretion of naphthalene metabolites are not well developed after birth. There are no studies that have specifically examined the influence of age on naphthalene toxicokinetic capabilities in humans. Although the availability of such studies may increase the understanding of the specific physiological basis for the apparent susceptibility of newborns, they are unlikely to be conducted. Experiments examining the most sensitive targets in animals are likely surrogates. In addittion, there is no evidence of haemolytic anaemia in rodents. Consequently, in relation to naphthalene induced anaemia, available data do not allow the identification of a NOAEL nor the dose-response characteristics for this endpoint. Naphthalene has a distinct odour of mothbolls or coal tar, with a reported minimum thresholds at 7.5 µg/m³.

Health hazard and cancer risk evaluation of long-term exposure

No reliable human toxicity data were found for subchronic or chronic exposure to naphthalen.
In the NTP study (1992, chosen by U.S.EPA, ATSDR and OEHHA as a key-study for the derivation of exposure limits) mice were exposed discontinuously to whole-body naphthalene inhalation at 0, 53 and 158 mg/m^3. The complete lack of nasal effects among control animals and the nearly total effect among animals exposed at 2 different concentrations strongly indicates a causal relationship between naphthalene exposure and nasal effects. The effects seen (Toxicological endpoint: Respiratory; Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia) are consistent with those reported among exposed workers, who developed rhinopharyngolaryngitis or laryngeal carcinoma and the assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans.

Taking the lower concentration as a LOAEL and adjusting this value in order to allow for conversion from discontinuous to a continuous pattern of exposure a concentration of 10 mg/m^3 is obtained. Incorporating factors of 10 for interspecies variability, 10 for interindividual variation and 10 for use of a LOAEL rather than a NOAEL this results in an Exposure Limit of 0.01 mg/m^3 (see also Table 6.1). However, it cannot be said with certainty that this EL for naphthalene based on nasal effects will be protective for hemolytic anemia, the more well-known human effect from naphthalene exposure.

As stated in the ECB risk assessment report, in relation to carcinogenicity, naphthalene is not genotoxic in vivo and thus the tumours are considered to arise via a non-genotoxic mechanism. The tumours develop only at the sites where non-neoplastic inflammatory changes also occur. Thus, it is considered that the development of the nasal tumours in the rat is a consequence of chronic tissue injury, for which an identifiable threshold of effect will exist, although currently not identified. Given that the underlying mechanism for the development of nasal tumours in the rat is considered to be the chronic inflammatory damage seen at this site, it follows that prevention of local tissue damage would prevent subsequent development of tumours.

Result

With regard to the general population a long-term exposure limit has been set at 10 µg/m^3, according to the assumption that nasal effects observed in mice are consistent with the health effects reported among exposed workers. Available exposure data indicate that, on average, the European population is exposed at naphthalene levels 10 times lower than this EL, although an important exception resulted from a survey held in Athens, were levels exceeding the EL were measured in nearly all residences. It is assumed that increased residential exposures originate from the use of naphthalene based moth-repellents, a widespread use occuring in certain countries of the Mediterranean area.

An important source of uncertainty in establishing safe exposure limits is the potentially greater sensitivity of certain subpopulations to naphthalene toxicity, including infants and children, neonates, fetuses, and individuals deficient in glucose-6-phosphate dehydrogenase (G6PD), the prevalence of this inherited deficiency reported to be 2 to 20% in defined Mediterranean subpopulations. In these latter cases manifested effects are hemolytic anemia and its sequelae.

In relation to carcinogenicity, naphthalene is not genototoxic in vivo and thus tumor development, observed in rodents, is considered to arise via a non-genotoxic mechanism. Also, the underlying mechanism for the development of nasal tumours in the rat is considered to be the chronic inflammatory damage seen at this site. It follows that prevention of local tissue damage would prevent subsequent development of tumours.

Relevance of EU-population exposure to naphthalene

Table 6.1: Percentage of population exposed beyond the established exposure limit (EL) and margins of safety

Population based studies		$LOAEL^a$	$\dfrac{LOAEL}{10}^{b}$	$\dfrac{LOAEL}{100}^{c}$	$\dfrac{LOAEL}{1000}^{d}$ = EL	Margin of safety (MOS)
Description (Study, Year)	N	$10\ mg/m^3$	$1\ mg/m^3$	$0.1\ mg/m^3$	$0.01\ mg/m^3$	$50^{th}\ (90^{th})$
Athens (Expolis, 96-98)	42	<	<	20%	80%	no MOS
Basel (Expolis, 96-98)	47	<	<	<	<	16 (9)
Helsinki (Expolis, 96-98)	188	<	<	<	<	22 (9)
Milan (Expolis, 96-98)	41	<	<	<	5 %	5 (1)
Oxford (Expolis, 98-00)	40	<	<	<	<	12 (4)
Prague (Expolis, 96-98)	46	<	<	<	<	7 (3)
					Avg. MOS: excluding Athens	10 (4)

[a] Animal LOAEL ; [b] not considering a NOAEL (10); [c] interspecies variability (10) ; [d] intraspecies variability (10);
< out of the evaluation range (i.e. <5% of the environments investigated)

Acetaldehyde

Synonyms:	ethanal, acetic aldehyde, ethyl aldehyde, methyl formaldehyde
CAS Registry Number:	75-07-0
Molecular Formula:	C_2H_4O

1. Compound identification

Acetaldehyde is a colourless, volatile liquid and at dilute concentrations has a pungent odour. Acetaldehyde is a highly flammable and reactive compound that is miscible in water and most common organic solvents like alcohol, acetone, gasoline, toluene, xylene, benzene, ether, paraldehyde. It is used in the manufacture of acetic acid, perfumes, and flavours. As a liquid, it is lighter than water but the vapours are heavier than air. It is volatile at ambient temperature and pressure. It is highly reactive and a strong reducing agent. Acetaldehyde can react violently with acid anhydrides, alcohols, ketones, phenols, ammonia, hydrogen cyanide, hydrogen sulfide, halogens, phosphorus, isocyanates, strong alkalis, and amines. It is also an intermediate in the metabolism of alcohol (SIS 2003).

2. Physical and Chemical properties

Molecular weight (g/mol)	44.1
Melting point (°C)	-123.5
Boiling point (°C)	20.2
Density (g/l at 20 °C, 1 atm)	
Relative density (air =1)	1.52
Explosion limits of mixtures (air vol-% acetaldehyde)	4.5-60.5
Solubility: miscible in water and most common solvents	

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 1.829 $\mu g/m^3$
1 $\mu g/m^3$ = 0.547 ppb

Sources: Hagemeyer (1978), IPCS/CEC (1990), Verschueren 2001.

3. Indoor Air Exposure assessment

Contribution of inhalation exposure to total exposure

Acetaldehyde is a metabolic product of sugars and ethanol. On the basis of the assumptions that a standard drink contains 10 g of ethanol and that about 90% of imbibed alcohol is metabolized to acetaldehyde, alcoholic beverages are generally by far the most significant source of exposure to acetaldehyde for the general population (WHO, 1995).

On the basis of the average dietary intake of food groups in different regions of the world and the contents of acetaldehyde in foodstuffs and non-alcoholic beverages in the Netherlands (Maarse & Visscher, 1992), food (particularly fruit juices and vinegar) may be one of the principal sources of exposure to acetaldehyde in the general population. More representative data on mean concentrations in foodstuffs have not been identified, but, on the basis of the ranges of concentrations determined in the Dutch survey, intake in food is estimated to range from just less than 10 to several hundred $\mu g/kg$ body weight per day.

On the basis of a daily inhalation volume for adults of 22 m^3, a mean body weight for males and females of 64 kg, and the assumption that mean concentrations are approximately 5 $\mu g/m^3$ (range: 2 to 8.6 $\mu g/m^3$; Guicheret & Schulting,

1985; Watanabe, 1987; Grosjean, 1991), the mean intake of acetaldehyde from ambient air for the general population is estimated to be 1.7 µg/kg body weight per day (WHO, 1995).

Emission sources

Typically, concentrations are higher indoors than outdoors due to combustion sources such as cigarettes, fireplaces, and woodstoves. Acetaldehyde can also be emitted from cooking hamburgers, coffee roasting and from some building materials such as rigid polyurethane foams, and some consumer products such as adhesives, coatings, lubricants, inks, and nail polish remover. It is also used as a fruit and fish preservative, flavoring agent, a denaturant for alcohol, for hardening gelatin fibers, and as a solvent in the synthetic rubber, paraldehyde, tanning and paper industries, in the manufacture of perfumes, butanol, aniline dyes, plastics, and silvering mirrors (EPA/Cal 2003). Since acetaldehyde is a product of human metabolism and it is found in exhaled air, it is probable that increased indoor concentrations may be, in addition to other sources, related to emissions from humans (Jurvelin 2001).

Residences with smokers have two to eight times higher acetaldehyde concentrations than the outdoor mean concentration (WHO 1995). Based on limited data collected in the US suggest an estimate of an average acetaldehyde concentration inside residences of 5.4 to 27.0 µg/m^3 (3.0 to 15 ppb). The acetaldehyde concentrations in offices and public buildings were similar in magnitude to those inside residences. Average and maximum in-vehicle acetaldehyde concentrations measured in southern California were similar in magnitude to those inside residences (EPA/Cal 2003).

Acetaldehyde is present in vehicle exhaust and in wastes from various industries. Also open burning and incineration of gas, fuel oil, and coal produce acetaldehyde. Similarly, degradation of hydrocarbons, sewage, and solid biological wastes produce acetaldehyde (WHO 1995, EPA/Cal 2003).

Indoor air and exposure concentrations

There is a lack of European population based data for acetaldehyde. In Helsinki average indoor air concentrations of acetaldehyde are clearly higher than ambient concentrations, 18.2 µg/m^3 and 2.7 µg/m^3 respectively. Similarly, indoor concentrations were higher than personal exposures suggesting the presence of considerably strong indoor sources. Cumulative distributions of the indoor and 48-hour personal exposure concentrations in Helsinki are presented in Figure 3.1 and Figure 3.2.

In Paris (Figure 3.1) in recently refurbished flats (a non representative study) indoor concentrations measured in bed rooms were at the same level than in Helsinki (n= 61, GM = 10.2 µg/m^3, GSD = 1.8 (Clarisse et al 2003).

The concentration of acetaldehyde in 14 homes and a small office building in northern Italy ranged from 1 to 48 µg/m^3 with a mean value of 17 µg/m^3 (DeBortoli M et al, 1986). The ratio of the minimum, maximum, mean, and median concentration in indoor versus outdoor air was 0.5, 24, 6.0, and 3.6, respectively. In Sweden Gustafsson et al (2003) reported mean values ranging from 12 µg/m^3 to 14 µg/m^3 in non-smoking homes. In 1986 - 1987, the mean yearly exposure to acetaldehyde from air pollution in Sweden was 1.0 µg/m^3 (Bostrom CE et al 1994).

Lee and Wang (2004) studied emissions of burning ten types of incense in chamber (18 m^3) tests. Acetaldehyde concentrations of the nine incense types ranged from 50 to 150 µg/m^3, one type exceeded a level of 450 µg/m^3. From these results we can conclude that incense burning may increase dramatically indoor air concentrations of acetaldehyde compared to the 'normal' residential levels. Few short time peak concentrations are presented in Table 3.1.

In Denmark (Granby and Kristensen 1997) and Finland (Viskari et al 2000), ambient acetaldehyde showed considerably low average (3-8 months periods) ambient concentrations being 1.8 µg/m^3 and 1.1-3.2 µg/m^3, respectively. In Italy and Greece, much higher average concentrations were measured, being 8.2 µg/m^3 and 15.1 µg/m^3, respectively (Possanzini et al 1996, Bakeas et al 2003).

In the USA ambient concentrations ranged from 2.0 to 5.7 µg/m^3 (Grosejan et al 1993, CARB 1999). The concentration of acetaldehyde measured in EPA headquarters building in Washington, DC ranged from 3.8 to 11.1 µg/m^3 with a median value of 5.2 µg/m^3 (EPA 1990). High concentrations were found in Brazil (Grosejan et al 2002), Japan, (Satsumabayashi et al 1995), and in Mexico (Baez et al 1995), being 10.4 µg/m^3, 2.3-12 µg/m^3, and 28.6 µg/m^3, respectively. In Chinese studies ambient levels ranged from 1.7 µg/m^3 to 7.6 µg/m^3. The mean indoor concentration of acetaldehyde in hotels was tenfold compared to outdoor levels, identified as a consequence of smoking indoors (Ho et al 2002, Feng et al 2004).
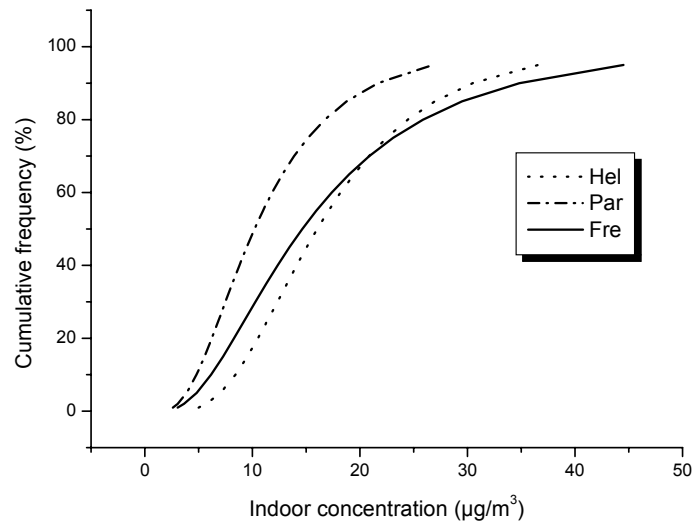
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of acetaldehyde in Helsinki (Hel, n= 15, Jurvelin et al 2001), in the French Survey (Fre, n= 201, Kirchner 2004) and in a non-representative study in Paris (Par) (n= 61, Clarisse et al 2003).
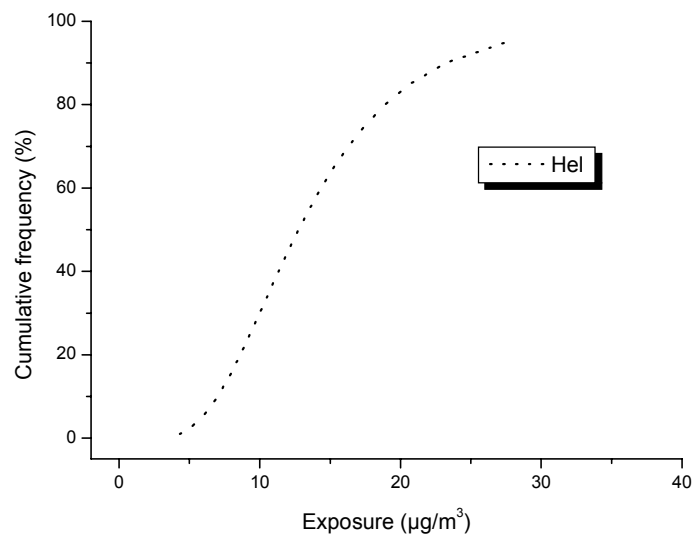
Figure 3.2. Cumulative frequency distribution of 48-hour personal exposure concentrations of acetaldehyde in Helsinki (Hel) (n= 15, Jurvelin et al 2001).

Table 3.1. Short time acetaldehyde concentrations related to specific microenvironments or emission sources.

Environment or emission source		Averaging time	Concentration (µg/m³)			Reference
			AM	GM	max	
Insence burning		during burning	50-450			Lee and Wang 2004
Tavern	tobacco smoke				203	EPA 2003
Houses in US	manufactured	30-min	5 - 34	18		Hodgson et al 2000
	site-built	30-min	21 - 103	36		
Exposure to ETS	non-smoker living with a smoker	1-day	7.6			Nazaroff and Singer (2002)

AM = arithmetic mean, GM = geometric mean

4. Toxicokinetics

Absorption

Consistent with effects being observed primarily at the initial site of exposure following inhalation (i.e., in the respiratory tract), available data indicate that the greatest proportion of inhaled acetaldehyde is retained at the site of contact, becoming rapidly and irreversibly bound to free protein and non-protein sulphydryl groups (notably, cysteine and glutathione). The results of pharmacokinetic studies conducted in humans (Dalhamn et al., 1968; Egle, 1970) and rodents (David and Heck, 1983; Morris, 1997) indicate that the absorption of acetaldehyde into the systemic circulation is likely not extensive following inhalation.

The percentage of acetaldehyde retained by 8 volunteers inhaling acetaldehyde vapour (100-800 mg/m³) from a recording respirometer ranged from 45 to 70%, at different respiratory rates. Total respiratory tract retention was the same whether the vapour was inhaled through the nose or the mouth. A direct relationship was found between the contact time and uptake, independent of rate. Thus, the critical factor in determining acetaldehyde uptake is the duration of the ventilatory cycle (Egle, 1970).

Distribution

Following inhalation by rats, acetaldehyde is distributed to the blood, liver, kidney, spleen, heart, and other muscle tissues (Hobara et al., 1985; Watanabe et al., 1986). Low levels were detected in embryos after maternal intraperitoneal injection of acetaldehyde (mouse) and following maternal exposure to ethanol (mouse and rat) (Blakley and Scott, 1984).

Distribution of acetaldehyde to brain interstitial fluid, but not to brain cells, has been demonstrated following intraperitoneal injection of ethanol in rats. A high affinity, low Michaelis constant ALDH (aldehyde dehydrogenase) may be important in maintaining low levels of acetaldehyde in the brain during the metabolism of ethanol (WHO, 1995). Acetaldehyde is taken up by red blood cells and, following ethanol consumption in humans and in baboons, in vivo, intracellular levels can be 10 times higher than plasma levels (Baraona et al., 1987)

Small amounts of acetaldehyde are produced endogenously during the normal intermediary catabolism of deoxyribose phosphate and various amino acids (Nicholls et al., 1992; Jones, 1995). Consumption of alcoholic beverages is also an important source of acetaldehyde in the body, formed through the metabolism of ethanol by alcohol dehydrogenase.

Studies using the perfused human placental cotyledon indicated that the human placenta has the potential to produce acetaldehyde, which can enter the fetal circulation. Furthermore, partial transfer of acetaldehyde from maternal to fetal blood may occur (Karl et al., 1988).

Metabolism and elimination

Based on the high degree of retention of acetaldehyde in the respiratory tract following inhalation in humans, it is likely that the predominant pathway for the metabolism of acetaldehyde involves conjugation to thiols (i.e., cysteine and

glutathione) at the site of exposure, subsequent formation of hemimercaptal or thiazolidine intermediates, and elimination of thioethers and disulphides in the urine (Sprince et al., 1974; Cederbaum and Rubin, 1976; Hemminiki, 1982; Brien and Loomis, 1983; Nicholls et al., 1992).

Inhaled acetaldehyde is also rapidly oxidized to acetate by aldehyde dehydrogenase (ALDH) in human nasal and lung epithelia (Bogdanffy et al., 1986; Yin et al., 1992; Morris et al., 1996). Acetate enters the citric acid cycle as acetyl-CoA. ALDH activity has been localized in the respiratory tract epithelium (excluding olfactory epithelium) in rats (Bogdanffy et al., 1986), in the renal cortex and tubules in the dog, rat, guinea-pig, and baboon (Michoudet and Baverel, 1987a; 1987b), and in the testes in the mouse (Anderson et al.,1985).

There are several isoenzymes of ALDH with different kinetic and binding parameters that influence acetaldehyde oxidation rates (Marjanen, 1973; Parrilla et al 1974, Teschke et al., 1977). Human liver ALDH consists of at least 4 main isoenzymes, which are also present in many other tissues (Koivula, 1975; Goedde et al., 1979). Subjects homozygous or heterozygous for a point mutation in the mitochondrial ALDH corresponding gene have low activity of this enzyme, metabolize acetaldehyde slowly, and are intolerant of ethanol (Yoshida et al., 1984; Goedde and Agarwal, 1986; Hsu et al., 1978).

Acetaldehyde is metabolized by mouse and rat embryonic tissue in vitro (Priscott and Ford, 1985). Though acetaldehyde is metabolized in a dose-dependent manner in human renal tubules (Michoudet and Baverel, 1987b), the liver is the most important metabolic site. The metabolism of acetaldehyde can be inhibited by crotonaldehyde, dimethylmaleate, phorone, disulfiram, and calcium carbamide (WHO, 1995; IARC 1985).

5. Health effects

Effects of short-term exposure

Humans exposed acutely to moderate concentrations of acetaldehyde experience irritation of the eyes and respiratory tract and altered respiratory function. Animals exposed to moderate to high concentrations exhibit skin and eye irritation and notable cellular alterations in the respiratory epithelium and hyper- keratosis of the forestomach.

A group of 12 human subjects were exposed to acetalclehycle vapour for 15 min while being shown a movie "to divert their attention". Most of the subjects developed eye irritation at 90 mg/m³ (50 ppm), but it took more than 360 mg/m³ (200 ppm) to cause nose or throat irritation in the majority of the subjects (Silverman et al., 1946). Several subjects strenuously objected to the vapor at as low as 45 mg/m³ (25 ppm). Even those who reported no eye irritation at 90 mg/m³ showed erythematous eyelids and bloodshot eyes when exposed to 360 mg/m³ of acetalctehyde (Silverman et al., 1946).

A group of 14 "healthy male" volunteers, aged 18-45 years, were exposed in a 100 m³ chamber to a measured concentration of acetaldehyde vapour of 240 mg/m³ (134 ppm) for 30 min. This concentration was said to be mildly irritating to the upper respiratory tract. No other clinical signs were reported (Sim and Pattle, 1957).

Intravenous infusion of human subjects with 5% acetaldehyde at a rate of 20.6-82.4 mg/min for up to 36 minutes (the lowest dose converts to 10.6 mg/kg over 36 minutes) resulted in an increased heart rate, increased ventilation rates and respiratory dead space, and a decreased alveolar carbon dioxide level (Asmussen et al., 1948; IARC 1985).

Summary of short-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
45 $_{Study}$		Eye irritation	Human volunteers, 15min; poor quality of data	Silverman et al., 1946	WHO 1995; TC: 2
	45 $_{Study}$ 11.5 $_{1h\text{-}ADJ}$	Eye irritation	Human volunteers, 15min; poor quality of data	Silverman et al., 1946	OEHHA 1999; HPC: 0.115
Final statement (UNIMI) : Human LOAEL: 5 mg/m³, Animal NOAEL: 50 mg/m³, no evidence in considering acute and chronic effect levels separately					

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h\text{-}ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

WHO (1995)
International Programme on Chemical Safety - Environmental Health Criteria 167

Approach to risk assessment: The following guidance is provided as a potential basis for derivation of limits of exposure by relevant authorities. Though the principal sources of exposure to acetaldehyde in the general population are through the metabolism of alcohol, in cigarette smoke, and food, air is believed to be the main route of exposure in the occupational environment.
On the basis of data on irritancy in humans, a tolerable concentration can be derived as follows:
Tolerable concentration = 45 mg/m^3 : 20 = 2 mg/m^3 (2000 µg/m^3) where no effects were observed in a limited study on human volunteers at 45 mg/m^3 (Silverman et al., 1946) and 20 is the uncertainty factor (×10 for intraspecies variation and × 2 for the poor quality of the data).

OEHHA (1999b)
Office of Environmental Health Hazard Assessment

Derivation of Health Protective Concentration (draft)
Since adopted health assessment values suitable for assessing potential health impacts from short-term inhalation exposures are not available for acetaldehyde, OEHHA calculated a draft health protective concentration (HPC). In calculating the HPC, OEHHA followed the risk assessment methodology used for developing the acute reference exposure levels (RELs) under the Air Toxics Hot Spots Program risk assessment guidelines process (OEHHA, 1999a). As mandated by state legislation, these guidelines underwent scientific and public peer review, prior to approval by the Scientific Review Panel (Senate Bill 1731, Statutes of 1992, Ch. 1162 of the California Health and Safety Code) and adoption by OEHHA.

Silverman et al. (1946) found that a 15-minute exposure to acetaldehyde induced eye irritation in male and female human volunteers at a concentration of 45 mg/m3 (25 ppm). This concentration was identified as a lowest-observed-adverse-effect level (LOAEL); a no-observed-adverse-effect level (NOAEL) was not observed in this study. Application of "Haber's Law" to extrapolate from a 15 minute exposure to 1 hour results in an adjusted LOAEL of 11.5 mg/m3 (6.5 ppm).

An acute 1-hour draft HPC can be calculated for acetaldehyde using the formula:

Draft HPC = LOAEL / UF = 11.5 mg/m3 / 100 = 115 µg/m3 (65 ppb).
The uncertainty factor (UF) for this calculation is 100, which incorporates uncertainty contributions for extrapolation from a LOAEL to a NOAEL (10) and for potentially sensitive human subpopulations (10).

Effects of long-term exposure

The critical health effects arising from exposure to airborne acetaldehyde are eye and upper respiratory tract irritation with the possibility of chronic tissue damage and inflammation in the respiratory tract following long-term exposure. Such long-term inflammatory changes have been associated with tumour in the nasal passages of experimental animals. The underlying mechanism for tumour formation is considered to be sustained irritation/inflammation accompanied by cellular proliferation. Such a mechanism is consistent with a threshold for tumour formation and thus control to prevent local tissue damage and inflammation would be predicted to control for any risk of tumour formation.

No information is available in humans regarding chronic tissue inflammation, the only data available relate to sensory irritation. The only objective evidence of eye irritation in humans was with a single exposure to 360 mg/m^3. There are reports of subjective irritation symptoms at lower concentrations (down to 45 mg/m^3), although there is uncertainty regarding the reliability of these observations.

In short-term inhalation studies (> 4 weeks) conducted in rodents, degenerative changes (including inflammation, hyperplasia, thinning and disarrangement of epithelial cells, and loss of microvilli and sensory cells) and associated functional effects were observed in the nasal olfactory epithelium in rats exposed (by inhalation) to ≥437 mg/m^3 acetaldehyde, while degenerative changes in the nasal respiratory epithelium, larynx, trachea and lungs were observed at higher concentrations (i.e. ≥1800 mg/m^3) (Appelman et al., 1982, 1986; Saldiva et al., 1985; Cassee et al., 1996).

In the only subchronic inhalation study identified, in which hamsters were exposed to acetaldehyde for 13 weeks (Kruysse et al., 1975), non-neoplastic lesions in the tracheal epithelium (including stratification, keratinization, inflammation, metaplasia and granulation) were observed at ≥2412 mg/m^3 acetaldehyde (considered to be the LOAEL),

while histopathological lesions in the nasal cavities, larynx, bronchi and lungs were observed only at 8208 mg/m^3 acetaldehyde; the NOEL in this study was considered to be 702 mg/m^3 acetaldehyde (Kruysse et al., 1975).

In chronic inhalation studies in which rats were exposed to acetaldehyde for up to 28 months, focal basal cell hyperplasia of the nasal olfactory epithelium was observed at ≥1350 mg/m^3 acetaldehyde (considered to be the LOAEL), while non-neoplastic lesions in the nasal respiratory epithelium (squamous metaplasia, papillomatous hyperplasia, and focal or pseudoepitheliomatous hyperplasia) and larynx (squamous metaplasia and hyperplasia) were observed at concentrations ≥2700 mg/m^3 acetaldehyde (Woutersen et al., 1984, 1986; Feron et al., 1985; Woutersen and Feron, 1987). Similarly, nonneoplastic lesions in the nasal epithelia, larynx and trachea have been observed in hamsters exposed by inhalation to ≥2700 mg/m^3 acetaldehyde for 52 weeks (Feron, 1979; Feron et al., 1982).

The studies that provide best characterization of concentration–response for the critical effects in the most sensitive species (i.e., rats) are the short-term studies of Appelman et al. (1982; 1986). While these studies are short-term in duration, together they establish a concentration-response for lesions after only 4 weeks of exposure. These same types of lesions appear at longer exposure times and higher exposure levels in chronic studies (Wouterson et al., 1986; Wouterson and Feron, 1987; Kruysse et al., 1975). Under other circumstances, studies of short duration may not be considered appropriate, but for acetaldehyde the observed effects are consistent with pathology seen in long-term studies.

Appleman et al. (1986) conducted two inhalation studies on male Wistar rats (10/group) exposing them 6 hours/day, 5 days/week for 4 weeks to 0, 273 and 910 mg/m^3 (0, 150, and 500 ppm respectively). Duration-adjusted concentrations are 0, 48.75, and 162.5 mg/m^3, respectively. One group was exposed without interruption, a second group was interrupted for 1.5 hours between the first and second 3-hour period, and a third group was interrupted as described with a superimposed peak exposure profile of 4 peaks at 6-fold the basic concentration per 3-hour period. The purpose was to test intermittent and peak exposure effects. Urine samples were collected from all rats and lung lavage performed on 4-5 per group at the end of the experiment. Cell density, viability, number of phagocytosing cells, and phagocytic index were determined on the lavage fluid. Microscopic examination was performed on the nasal cavity, larynx, trachea with bifurcation and pulmonary lobes of all rats of all groups.

Continuous and interrupted exposure to 910 mg/m^3 did not induce any visible effect on general condition or behavior, but peak exposures at this level caused irritation. No behavioral differences were noted in the other groups. Mean body weights of the group exposed to 910 mg/m^3 with interruption and with peak exposures were statistically significantly lower than those of the controls. Body weights were similar to controls in the other exposure groups. Mean cell density and cell viability were significantly decreased in the group exposed to 910 mg/m^3 with or without peak exposures. The mean percentage of phagocytosing cells and the phagocytic index were significantly lower than controls in all groups exposed to 910 mg/m^3, especially the group exposed to superimposed peaks. Histopathological changes attributable to exposure were found only in the nasal cavity. Degeneration of the olfactory epithelium was observed in rats exposed to 910 mg/m^3. Interruption of the exposure or interruption combined with peak exposure did not visibly influence this adverse effect. No compound-related effects were observed in rats interruptedly or uninterruptedly exposed to 273 mg/m^3 during the 4-week exposure period; therefore, the NOAEL is 273 mg/m^3.

Appelman et al. (1982) exposed Wistar rats (10/sex/group) for 6 hours/day, 5 days/week for 4 weeks to 0, 728, 1820, 4004 and 9100 mg/m^3 acetaldehyde (0, 400, 1000, 2200, or 5000 ppm, respectively). Duration-adjusted concentrations are 0, 130, 325, 715 and 1625 mg/m^3, respectively. The general condition and behavior of the rats were checked daily. Blood picture (Hb, Hct, RBC, total and differential WBC, and plasma protein) and chemistry were examined at the end of the treatment period. Activities of plasma glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and alkaline phosphatase were also determined. Urine was analyzed for density, volume, pH, protein, glucose, occult blood, ketones, and appearance. The kidneys, lungs, liver, and spleen were weighed. Microscopic examination was performed on the lungs, trachea, larynx, and nasal cavity (3 transverse sections) of all animals and on the kidneys, liver, and spleen of all control and high- concentration groups.

During the first 30 minutes of each exposure at the 9100 mg/m^3 level, rats exhibited severe dyspnea that gradually became less severe during the subsequent exposure period. Two animals died at this level (1 female, 1 male) and one male died at the 4004 mg/m^3 level, but the cause of death could not be determined due to autolysis or cannibalism. Growth was retarded in males at the three highest exposure concentrations and in females at the 9100 mg/m^3 level. The percentage of lymphocytes in the blood was lower and the percentage of neutrophilic leukocytes higher in males and females of the 9100 mg/m^3 group than in controls. There were a few statistically significant differences in several blood chemistry parameters between the exposure groups and the control group but none of them were concentration-related. Statistically significant changes in organ-to-body weight ratios included decreased liver weights in both sexes and increased lung weights in males at the 9100 mg/m^3 level. Males in the 9100 mg/m^3 level produced less urine, but it was of higher density. Compound-related histopathological changes were observed only in the respiratory system. The nasal

cavity was most severely affected and exhibited a concentration-response relationship. At the 728 mg/m^3 level, compound-related changes included: slight to severe degeneration of the nasal olfactory epithelium, without hyper- and metaplasia, and disarrangement of epithelial cells. At the 1820- and 4004 mg/m^3 levels, more severe degenerative changes occurred, with hyperplastic and metaplastic changes in the olfactory and respiratory epithelium of the nasal cavity. Degeneration with hyperplasia/metaplasia also occurred in the laryngeal and tracheal epithelium at these levels. At 9100 mg/m^3 changes included severe degenerative hyperplastic and metaplastic changes of the nasal, laryngeal, and tracheal epithelium. Based on the degenerative changes observed in the olfactory epithelium, the 728 mg/m^3 level is designated as a LOAEL.

Available data are inadequate to assess the potential reproductive, developmental, neurological or immunological effects of direct exposure to acetaldehyde. Based on the limited number of investigations conducted to date, however, reproductive, developmental, neurological and immunological effects have not been observed at concentrations below those that induce damage in the upper respiratory tract (Ortiz et al., 1974; Kruysse et al., 1975; Shiohara et al., 1985; Aranyi et al., 1986; Roumec et al., 1988).

Summary of long-term exposure effect levels

Health Canada and U.S. EPA have evaluated the noncancer inhalation toxicity data for acetaldehyde. Health Canada derived a tolerable concentration of 0.39 mg/m^3. EPA derived a reference concentration (RfC) of 0.009 mg/m^3, which is 40-fold lower than the Health Canada value. Both agencies used the same studies, but differed in their estimation. While EPA used the NOAEL of 273 mg/m^3 from Appleman et al. (1982), Health Canada used the lower 95% confidence limit on a benchmark dose (BMD) for the concentration associated with a 5% increase in the incidence of nasal olfactory epithelial lesions for male rats [from data in the studies by Appleman et al. (1982, 1986)]. Both agencies adjusted for the intermittent exposure in the laboratory, but EPA also adjusted to a Human Equivalent Concentration (HEC) by calculating for a gas:respiratory effect in the extrathoracic region. The agencies also differed in choice of uncertainty factor, with EPA utilizing three factors of ten (intraspecies, use of a subchronic study, and interspecies and database combined for a third ten). Health Canada did not use a factor for limitations in the database due to the fact that a TC that is based on critical effects at the site of entry is likely to be protective for systemic effects. A factor for use of a shorter-term study was not deemed appropriate because there was no indication that severity of the critical effects increases with duration of exposure. Click on the green circle(s) for more information.

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
273$_{EXP}$ 49$_{ADJ}$ 8.7$_{HEC}$	728$_{EXP}$ 130$_{ADJ}$ 16.9$_{HEC}$	Degeneration of olfactory epithelium	Rat, 4w	Appleman et al., 1986;1982	EPA-IRIS 1991; RfC: 0.003
	218$_{BC05}$ 39$_{ADJ}$	Degeneration of olfactory epithelium	Rat, 4w	Appleman et al., 1986;1982	Health Canada 2000; TC: 0.39
-	-	Respiratory system		not specified	OEHHA 1995; REL: 0.009
Although the studies cited establish a concentration-response for lesions after only 4 weeks of exposure, same types of lesions appear at longer exposure times and higher exposure levels, and are consistent with pathology seen in chronic studies. Final statement (UNIMI) : Human LOAEL: 5 mg/m³, Animal NOAEL: 50 mg/m³, no evidence in considering acute and chronic effect levels separately					

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h-ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

U.S.EPA - IRIS (1991)
Integrated Risk Information System

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical effect	Exposures*	UF	MF	RfC
Degenration of olfactory epithelium Short-term Rat	NOAEL: 273 mg/m^3 (150 ppm) NOAEL:(ADJ): 48.75 mg/m^3 NOAEL(HEC): 8.7 mg/m^3	1000	1	0.003 mg/m^3

Inhalation Studies Appleman et al., 1986;1982	LOAEL: 728 mg/m^3 (400 ppm) LOAEL(ADJ): 130 mg/m^3 LOAEL(HEC): 16.9 mg/m^3			

*Conversion Factors -- MW = 44.5. Appleman et al., 1986: Assuming 25C and 760 mmHg, NOAEL(mg/cu.m) = 150 ppm x 44.5/24.45 = 273. NOAEL(ADJ) = 273 mg/cu.m x 6 hours/day x 5 days/7 days = 48.75 mg/cu.m. The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.23 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm, Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.18. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 8.7 mg/cu.m.

Appleman et al., 1982: Assuming 25C and 760 mmHg, LOAEL(mg/cu.m) = 400 ppm x 44.5/24.45 = 130. LOAEL(ADJ) = 728 mg/cu. m x 6 hours/day x 5 days/7days = 130 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.17 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq.cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.13. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 16.9 mg/cu.m.

Two short-term studies conducted by the same research group are the principal studies used. While these studies are short-term in duration, together they establish a concentration-response for lesions after only 4 weeks of exposure. These same types of lesions appear at longer exposure times and higher exposure levels in chronic studies (Wouterson et al., 1986; Wouterson and Feron, 1987; Kruysse et al., 1975). Under other circumstances, studies of short duration may not be considered appropriate, but for this chemical the observed effects are consistent with pathology seen in long-term studies. The 150-ppm exposure level was therefore established as the NOAEL from the Appleman et al. (1986) study and the LOAEL from the Appleman et al. (1982) study.

Uncertainty factors (UF) for the determination of the Inhalation RfC: An uncertainty factor of 10 was applied to account for sensitive human populations. A factor of 10 was applied for both uncertainty in the interspecies extrapolation using dosimetric adjustments and to account for the incompleteness of the data base. A factor of 10 was applied to account for subchronic to chronic extrapolation.

Confidence in the Inhalation RfC: Confidence in the principal studies (Appleman et al., 1982; 1986) is medium since appropriate histopathology was performed on an adequate number of animals and a NOAEL and LOAEL were identified, but the duration was short and only one species was tested. Confidence in the data base is low due to the lack of chronic data establishing NOAELs and due to the lack of reproductive and developmental toxicity data. Low confidence in the RfC results.

Health Canada (2000)
Canadian Environmental Protection Act (CEPA).

Derivation of a Tolerable Concentration (TC):
A tolerable concentration (TC) has been developed on the basis of Benchmark Concentration (BMC) for degeneration in the nasal olfactory epithelium of Wistar rats exposed to acetaldehyde (by inhalation) for four weeks, using combined data from Appelman et al. (1982, 1986).

For many types of effects, studies of short duration are not preferred as the basis for development of a TC. While the data were derived from short-term studies, the incidence of degenerative changes in the olfactory epithelium was not dissimilar to that observed in the same strain of rats in the long-term carcinogenesis bioassay at similar concentrations, conducted by Woutersen et al. (1986). Although group sizes were larger in the long-term bioassay, concentration-response for these lesions was not well characterized because of the small number of dose groups exposed to higher concentrations compared with the short-term study and early mortality among animals at the highest concentration. Data in the Woutersen et al. (1986) study are insufficient to serve as a basis for development of a meaningful BMC for acetaldehyde, even simply for purposes of comparison.

Using the THRESH program (Howe, 1995), the BMC_{05} (the concentration associated with a 5% increase in the incidence of nasal olfactory epithelial lesions) for male Wistar rats is 357 mg/m^3 ; the lower 95% confidence limit for this value ($BMCL_{05}$) is 218 mg/m^3. For female Wistar rats, the BMC_{05} and $BMCL_{05}$ are 445 mg/m^3 and 17 mg/m^3, respectively.

The $BMCL_{05}$ of 218 mg/m^3 was adjusted from an intermittent to a continuous exposure by multiplying the value by 6/24 and 5/7. There are no data that provide direct evidence and few related data to serve as a basis for whether or not such an adjustment is appropriate for acetaldehyde. In short-term studies in the same strain of rats, effects seemed slightly more severe following exposure for eight hours per day (Saldiva et al., 1985) versus six hours per day for four weeks (Appelman et al., 1986). Interruption of daily exposure by 1.5-hour exposure-free periods or by the superimposition of eight five-minute peak exposure periods did not appreciably influence the cytotoxic potency of acetaldehyde in short-term studies in rats compared with uninterrupted exposure to a fixed concentration (Appelman et al., 1986).

An uncertainty factor of 100 was used (10 for interspecies variation, 10 for intraspecies variation). Available data are inadequate to further address toxicokinetic and toxicodynamic aspects of components of uncertainty with data-derived values. The value for interspecies variation is considered to be conservative since, due to greater penetration of inhaled gases into the lower airways of rodents versus humans, the compound is distributed over a larger surface area for the latter; available data are inadequate, however, to quantitatively account for this variation. No additional quantitative element has been included to address limitations of the database such as lack of adequate developmental or reproductive studies by a relevant route of exposure, due to the fact that a TC that is based on critical effects at the site of entry is likely to be protective for systemic effects. Also, in view of the fact that there is no indication that severity of the critical effects increases with duration of exposure, an additional quantitative element to address the use of a shorter-term study as the basis for the TC is considered inappropriate.

The resulting Tolerable Concentration (TC) is 0.39 mg/m^3. This TC is similar to that derived from the NOEL for irritation in the study of Appelman et al. (1986) (TC of 0.49 mg/m^3). On the basis of limited available data in human studies, the TCs derived above (0.39 and 0.49 mg/m^3) are two orders of magnitude lower than the threshold for sensory irritation (i.e., 45 mg/m^3 [25 ppm]) (Silverman et al., 1946).

The degree of confidence in the database on toxicity that serves as the basis for the development of the tolerable concentration (TC) for inhalation is moderate, although there is a relatively high degree of confidence that critical effects occur at the initial site of exposure. Despite differences in the anatomy and physiology of the respiratory tract in rats and humans, respiratory tract defense mechanisms are similar. Thus, it is reasonable to assume that the response of the human respiratory tract mucosa to acetaldehyde will be qualitatively similar to that of experimental species, although the likely site of development of lesions may vary due to oro-nasal breathing patterns in humans, which result in greater potential to deliver acetaldehyde to the lower respiratory tract.

WHO (1995)
Environmental Health Criteria 167

Data suggest that acetaldehyde causes genetic damage to somatic cells *in vivo*. The irritancy of acetaldehyde may also play an important role in the development of tumours in the nose and larynx of rats and hamsters, respectively, exposed by inhalation, though all concentrations of acetaldehyde administered in carcinogenesis bioassays induced both irritancy and nasal tumours. Therefore, two approaches were adopted for the provision of guidance with respect to the potential carcinogenicity of acetaldehyde.

1.) In the first, a tolerable concentration (TC) was derived on the basis of division of an effect level for irritancy in the respiratory tract of rodents by an uncertainty factor, based on the principles outlined in WHO and the assumption that there is a threshold for acetaldehyde-induced cancer of the respiratory tract in rodents exposed via inhalation. There is some support for this approach on the basis of relevant data on the analogues of acetaldehyde, i.e., formaldehyde and glutaraldehyde, which have similar spectra of *in vitro* mutagenic effects, but are clearly not mutagenic *in vivo* (IARC, 1985; WHO, 1989). Thus,

Tolerable concentration = 275 mg/m^3 : 1000 = 0.3 mg/m^3 (300 µg/m3)

where: 275 mg/m^3 was the NOEL for irritation in rats in a 4-week study (Appelman et al., 1986) and 1000 is the uncertainty factor ($\times$10 for interspecies variation, $\times$10 for intraspecies variation and $\times$10 for a less than long-term study and severity of effect, i.e., carcinogenicity associated with irritation).

2.) Since the mechanism of induction of tumours by acetaldehyde has not been well studied, lifetime cancer risk has also been estimated on the basis of a default model (i.e., linearized multistage). However, it is very likely that, since estimated risk is based on tumour incidence at concentrations that induce irritancy in the respiratory tract and no-observed-effect levels for irritancy are well below these concentrations, the true cancer risk is most likely much lower at concentrations generally present in the environment and may, indeed, be zero.

Concentrations associated with a 10^{-5} excess lifetime risk (lower 95% confidence limits) for nasal tumours (adenocarcinomas, squamous cell carcinomas, and carcinomas *in situ)* in male and female rats, in the only carcinogenicity study in which animals were exposed via inhalation to acetaldehyde over the lifetime (Woutersen et al., 1986), calculated on the basis of the linearized multistage model (Global 82), are 11-65 µg/m^3. The high-dose animal groups were excluded in the derivation of these estimates because of early mortality. A body surface area correction was not incorporated.

OEHHA (1993)
Office of Environmental Health Hazard Assessment

A chronic non-cancer Reference Exposure Level (REL) of 9.0 µg/m is listed for acetaldehyde in the California Air Pollution Control Officers Association Air Toxics "Hot Spots" Program, Revised 1992 Risk Assessment Guidelines. The toxicological endpoint considered for chronic toxicity is the respiratory system.

Carcinogenic potential

Acetaldehyde is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (IARC 1985, 1987, 1999). When administered by inhalation, acetaldehyde increased the incidence of squamous cell carcinomas and adenocarcinomas in the nasal mucosa in rats of both sexes and laryngeal carcinomas in hamsters of both sexes. In another inhalation study using a lower exposure level and in an intratracheal instillation study, no increased incidence of tumors in hamsters was observed. When administered by inhalation, acetaldehyde enhanced the incidence of respiratory tract tumors as induced by intratracheal instillation of benzo[a]pyrene in hamsters of both sexes.

There is inadequate evidence for the carcinogenicity of acetaldehyde in humans (IARC 1985, 1987, 1999). A single study of workers in an aldehyde plant reported nine cases of cancer, including five cases of bronchial tumors and two cases of carcinomas of the oral cavity. This study was considered to be inadequate for evaluation because of mixed exposure, the small number of cases, and the poorly defined population. Three case control studies investigated the risk of oral, throat, and esophageal cancers following heavy alcohol intake. These studies consistently showed an increased risk of these cancers in people with genetic polymorphisms; these polymorphisms resulted in higher blood acetaldehyde concentrations after drinking alcohol (IARC 1999). Overall evaluation (IARC 1999): Acetaldehyde is possibly carcinogenic to humans (Group 2B; there is inadequate evidence in humans for the carcinogenicity of acetaldehyde. There is sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde).

Acetaldehyde is considered a probable human carcinogen (Classification: B2; EPA 1998), based on increased incidence of nasal tumors in male and female rats and laryngeal tumors in male and female hamsters after inhalation exposure.

Health Canada (2000) and EPA (1998) each used the same study (Woutersen et al., 1986; Woutersen and Appelman, 1984) and tumors (nasal adenocarcinomas and squamous cell carcinomas) to calculate cancer potency, but their approaches differ in that Health Canada does not do low dose extrapolation. Health Canada calculated a tumorigenic concentration with 5% response (TC_{05}) of 86 mg/m³, with a lower 95% confidence limit (TCL_{05}) of 28 mg/m³. EPA estimated an inhalation unit risk of 2.2 E-6 per µg/m³.

Summary of principal study: The carcinogenicity of acetaldehyde was studied in 420 male and 420 female albino SPF Wistar rats (Woutersen and Appelman, 1984; Woutersen et al., 1985). After an acclimatization period of 3 weeks, these animals were randomly assigned to four groups of 105 males and 105 females each. The animals were then exposed by inhalation to atmospheres containing 0, 1351, 2702, or 5403 mg/m³ (0, 750, 1500, or 3000 ppm) acetaldehydefor 6 hours/day, 5 days/week, for 27 months. The concentration in the highest dose group was gradually reduced from 5403 to 1801 mg/m³ because of severe growth retardation, occasional loss of body weight and early mortality in this group. Interim sacrifices were carried out at 13, 26, and 52 weeks. One tumor was observed in the 52 week sacrifice group and none at earlier times. Exposure toacetaldehyde increased the incidence of tumors in an exposure-related manner in both male and female rats. In addition, there were exposure-related increases in the incidences of multiple respiratory tract tumors. Adenocarcinomas were increased significantly in both male and female rats at all exposure levels, whereas squamous cell carcinomas were increased significantly in male rats at middle and high doses and in female rats only at the high dose. The squamous cell carcinoma incidences showed a clear dose-response relationship. The incidence of adenocarcinoma was highest in the mid-exposure group (2702 mg/m³) in both male and female rats, but this was probably due to the high mortality and competing squamous cell carcinomas at the highest exposure level. In the low-exposure group, the adenocarcinoma incidence was higher in males than in females.

Genotoxicity

Acetaldehyde is genotoxic in vitro, inducing gene mutations, clastogenic effects, and sister-chromatid exchanges (SCEs) in mammalian cells in the absence of exogenous metabolic activation (He and Lambert, 1990; Badr and Hussain, 1977; Obe et al., 1978; 1979; 1985; Veghelyi and Osztovics, 1978; Boehlke, 1983).
The results of in vivo studies suggest that acetaldehyde can react directly with DNA and proteins to form stable adducts. Acetaldehyde produced a concentration-related reduction in the extractability of DNA (suggestive of increased formation of DNA–protein cross-links) from the respiratory nasal mucosa of Fischer 344 rats exposed (whole body) to 1800 or 5400 mg/m³ acetaldehyde for six hours or to 1800 mg/m³ acetaldehyde for six hours per day for five days. Significant reduction in the extractability of DNA in the nasal olfactory epithelia was observed only following exposure

to 1800 mg/m^3 acetaldehyde for six hours per day for five days (Lam et al., 1986). There is indirect evidence from *in vitro* and *in vivo* studies to suggest that acetaldehyde can induce protein-DNA and DNA-DNA cross-links (Lam et al., 1986).

Many of the toxicological effects of acetaldehyde may be due to the saturation of protective cellular mechanisms at the initial site of exposure. As with formaldehyde, the potential for acetaldehyde to react with epithelial DNA (and other cellular components) in the upper respiratory tract may be dependent upon the levels of intracellular thiols (notably glutathione and cysteine), which prevent binding of acetaldehyde with critical sulphydryl groups in proteins, peptides and DNA (Cederbaum and Rubin, 1976; U.S. EPA, 1987; von Wartburg, 1987).

In addition, regional deficiencies in aldehyde dehydrogenase activity in rats correlate with the distribution of nasal lesions in another strain of rats exposed to acetaldehyde in inhalation studies (Bogdanffy et al., 1986). Observed decreases in uptake of acetaldehyde at high concentrations >180 mg/m^3 in a range of species may be a function of exceedance of the metabolic capacity of nasal aldehyde dehydrogenase (Morris, 1997).

The pattern of observed irritancy of acetaldehyde at the site of contact and the results of studies indicating that it can react directly with DNA and proteins to form stable adducts is similar to that for other aldehydes (such as formaldehyde) that have been carcinogenic to the respiratory system in sensitive inhalation bioassays. Although the exact mechanism is unknown, induction of tumours by these aldehydes is considered to be a function of both regenerative proliferative response and DNA–protein cross-linking at the site of contact.

Similarly, it has been proposed that the genotoxicity of acetaldehyde is based principally upon its ability to interact with single-stranded DNA during cell division (Feron et al., 1982, 1984; Woutersen et al., 1986; Roe and Wood, 1992; DECOS, 1993). Thus, a crucial determinant in the carcinogenicity of acetaldehyde in the nasal passages may be the cytotoxicity of this substance at high concentrations (Feron et al., 1982, 1984; Woutersen et al., 1986; Roe and Wood, 1992); cytotoxic concentrations of acetaldehyde cause recurrent tissue damage (and the presence of single-stranded DNA) and possess significant initiating activity. Moreover, the increased cell turnover may strongly enhance the fixation of relevant DNA damage and subsequently increase the progression of pre-cancer (initiated) cells to cancer.

However, the limited available data indicate that the pattern of DNA–protein cross-linking and proliferative response induced by acetaldehyde varies from that of other aldehydes, such as formaldehyde. For acetaldehyde, at concentrations at which tumours are observed 1350 mg/m^3, there are increases in DNA–protein cross-links in the respiratory and olfactory mucosa of rats but no increase in proliferation (Cassee et al., 1996a).

For formaldehyde, at the lower concentrations at which tumours are observed 7.2 mg/m^3, there are increases in DNA–protein cross-links and proliferation in the nasal respiratory (but not olfactory) epithelium (Casanova et al., 1994).

While acetaldehyde is genotoxic in vitro and in vivo, information concerning the potential roles of cytotoxicity, cell proliferation and DNA–protein cross-links in tumour formation is lacking.

Interactions with other chemicals

Acetaldehyde is a highly reactive molecule that can react with many other large or small molecules by addition, condensation, or polymerization. These pathways may have little quantitative significance in acetaldehyde metabolism, but the by-products may have biological significance.

Acetaldehyde can react with various macromolecules in the body, which can lead to marked alterations in the biological function of these molecules, as evidenced by inhibition of enzyme activity, impaired histone-DNA binding, and inhibition of polymerization of tubulin. The best characterized nucleophiles able to form adducts with acetaldehyde are amino groups, notably the alpha-amino terminus of peptides and proteins and the epsilon-amino group on the side-chain of lysine residues.

The toxicity studies with mixtures of aldehydes showed that histopathological changes and cell proliferation of the nasal epithelium induced by mixtures of formaldehyde, acetaldehyde and/or acrolein appeared to be more severe and more extensive, both in the respiratory and the olfactory part of the nose, than those observed after exposure to the individual aldehydes at comparable exposure levels. However the combined effect of the mixtures was at most the sum of the individual effects. Neither dose addition nor potentiating interactions occurred upon exposure to combinations of these aldehydes at exposure levels slightly below or around the minimal-observed-effect level (MOEL) (Flemming, 1995; Cassee, 1996).

Metronidazole or cotrimoxazole (antimicrobial agents) may enhance accumulation of acetaldehyde in blood induced by antialcohol drugs like disulfiram or nitrefazole (Heelon and White, 1998; Cina et al., 1996; Suokas et al., 1985).

Odour perception

Acetaldehyde is a volatile liquid with a pungent, suffocating odour that is fruity in dilute concentrations.

Source: Devos et al.(1990):
Odour threshold: 0.025 mg/m^3,

Source: Amoore and Hautala (1983)
The odour threshold for acetaldehyde is reported to be 0.09 mg/m^3 (0.05 ppm), a geometric average of all available literature data

Source: AIHA (1989)
A wide range of values has been reported: 0.005 to 1800 mg/m^3. An acceptable, critiqued value is 0.12 mg/m^3 (detection)

Source: New Jersey Department of Health and Senior Services
Odour threshold: 0.12 mg/m^3

Summary of Acetaldehyde Dose Response Assessment

Exposure other than inhalation: Acetaldehyde is a metabolic product of ethanol and sugars. Estimate of diatary intake: 10 to several hundred μg/kg bw., one std alc.drink: 100 mg/kg bw., ambient air: 2 μg/kg bw.. Consequently, most toxicological studies in the literature consider systemic effects of acetaldehyde.

Toxicokinetics: The greatest proportion (45-70%) of inhaled acetaldehyde is retained at the site of contact, with irreversible binding to sulphhydryl groups (e.g.cisteine) or oxidation to acetate (acetyl-CoA). No extensive absorption into the systemic circulation. Critical factor determining the uptake is the duration of the ventilation cycle, no difference between nose and mouth breathing.

Health effect levels of short- and long-term exposure (noncancer):

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure						
45 $_{Study}$		Eye irritation	Human volunteers, 15min; poor quality of data	Silverman et al., 1946	WHO 1995; TC: 2
	45 $_{Study}$ 11.5 $_{1h-ADJ}$	Eye irritation	Human volunteers, 15min; poor quality of data	Silverman et al., 1946	OEHHA 1999; HPC: 0.115
Long-term exposure						
273 $_{EXP}$ 49 $_{ADJ}$ 8.7 $_{HEC}$	728 $_{EXP}$ 130 $_{ADJ}$ 16.9 $_{HEC}$	Degeneration of olfactory epithelium	Rat, 4w	Appleman et al., 1986;1982	EPA-IRIS 1991; RfC: 0.003
	218 $_{BC05}$ 39 $_{ADJ}$	Degeneration of olfactory epithelium	Rat, 4w	Appleman et al., 1986;1982	Health Canada 2000; TC: 0.39
-	-	Respiratory system		not specified	OEHHA 1995; REL: 0.009

Remark on Appleman studies: Although the studies cited establish a concentration-response for lesions after only 4 weeks of exposure, same types of lesions appear at longer exposure times and higher exposure levels, and are consistent with pathology seen in chronic studies.

Carcinogenicity: IARC: 2B; U.S.EPA: B2, Unit risk (EPA-IRIS): 2.2E-06 $(\mu g/m^3)^{-1}$; The underlying mechanism for tumour formation is considered to be sustained irritation/inflammation accompanied by cellular proliferation, a mechanism consistent with a threshold for acetaldehyde induced cancer.

Genotoxicity: Genotoxic in vitro and in vivo, though information concerning the potential roles of cytotoxicity, cell proliferation and DNA-protein cross-links in tumour formation is lacking.

Odour threshold: Pungent, suffocating odour that is fruity at dilute concentrations; Detection: 0.12 mg/m^3 (AIHA); geomean: 0.09 mg/m^3 (Amoore and Hautala); 0.025 mg/m^3 (Devos)

Susceptible population: Systemic: Low activities of the aldehyde dehydrogenase enzyme (ALDH), occuring in subjects with point mutations in the corresponding gene, reduce acetaldehyde oxidation rate and conduce to intolerance for ethanol. Acetaldehyde levels in the blood are induced by antialcohol drugs like disulfiram or nitrefazole.

Remarks: RD$_{50}$: 7 g/m^3; neither dose addition nor potentiating interactions occured upon exposure to aldehyde mixtures (formaldehyde, acetaldehyde, acrolein) at exposure levels around the MOEL.

6. Risk Characterization

Cancer risk and health hazard evaluation

Based on short-term and long-term inhalation studies conducted in experimental animals, the upper respiratory tract is the principal target site for effects of inhaled acetaldehyde. In short-term studies acetaldehyde caused degenerative non-neoplastic effects. Although it is genotoxic both in vitro and in vivo, tumours have been observed following inhalation only at concentrations that have produced significant cytotoxicity and it is likely that both the genotoxicity and irritancy of acetaldehyde play a role in its carcinogenicity. At acetaldehyde concentrations for which the prevalence of sensory irritation is low (i.e., < 45 mg/m^3), risks of respiratory-tract cancers for the general population are considered exceedingly low.

An Limit of Exposure (EL) has been here derived for short- and long term effects, based on acute eye irritation observed in human volunteers and on chronic degeneration of the olfactory epithelium observed in rats. No distinction has been done between short- and long-term ELs since the observed acute effects and endpoints are consistent with the pathology seen in long-term studies. Also, two studies were considered for the EL derivation, in order to compensate for the poor quality of the study on volunteers (Silverman et al., 1946). In this study, among 12 volunteers "several" subjects after 15 min of exposure strenuously objected to acetaldehyde vapor at as low as 45 mg/m^3, with this supposed threshold for sensory irritation set here as a LOAEL (eye irritation was developed by most of the subjects at 90 mg/m^3). This level has been devided by an assessment factor of 200, which incorporates uncertainty contributions for extrapolation from a LOAEL to a NOAEL (10), intraspecies variation (10) and the poor quality of the data (2), resulting in an Exposure Limit (EL) of 0.2 mg/m^3. Also, a NOAEL was derived from a subchronic (4 weeks) animal study at 50 mg/m^3, with an exposure limit of 0.5 mg/m^3 (AF=100) resulting from the extrapolation from an animal study (10) and intraspecies variation (10).

In addition to the EL derivation, the present assessment takes into account the possible contribution to inhalatory exposure of the endogenous generation of acetaldehyde in exhaled air. Acetaldehyde is an endogenous metabolite of sugars and could also be locally formed from the microflora inhabiting the upper airways and mouth. Concentrations expelled in breath span from 0.009 to 0.026 mg/m^3, with higher levels observed in smokers and abstinent alcoholics. It is the first metabolite of ethanol with reported breath concentration increasing to 0.22 – 2.2 mg/m^3 in European subjects who drank moderate doses of ethanol (0.4-0.8 g/kg bw) (Jones, 1995).

Percentage of population exposed beyond given threshold levels

Studies available		human LOAEL (acute) 45 mg/m^3	LOAEL 10 4.5 mg/m^3	LOAEL 100 0.45 mg/m^3	LOAEL 200 0.2 mg/m^3
		animal NOAEL (subchronic) 50 mg/m^3	NOAEL 10 5 mg/m^3	NOAEL 100 0.5 mg/m^3	-
Description (Study, Year)	N				
Paris – refurbished flats (Clarisse, 03)	61	<	<	<	<
Helsinki (Expolis, 97)	15	<	<	<	<
French National survey 7-d TWA (IAQ observatory, 2003-04)	201	<	<	<	<

< out of the evaluation range (i.e. <5% of the environments investigated)

Comments

Only three exposure studies were found, enabling the construction of cumulative frequency distributions of indoor exposure to acetaldehyde. Median (90th percentile) indoor concentrations were 0.010 mg/m^3 (0.022) in Paris, 0.016 mg/m^3 (0.030) in Helsinki, and 0.014 mg/m^3 (0.040) in the French National Survey, respectively. Ambient air concentrations over Europe range from 1-3 mg/m^3 in northern countries, up to 8 and 15 mg/m^3 recently measured in Italy and Greece, respectively.

Result

The results from only indoor air monitoring surveys allow a crude estimate of average acetaldehyde concentrations in European residences. Median concentrations (10-20 $\mu g/m^3$) are one order of magnitude lower than the Exposure Limit set here at 200 $\mu g/m^3$ and are within the same range of concentrations occuring in exhaled breath following its endogenous production in the general populaton, not taking into account increases resulting from the consumption of alcoholic beverages. Considering that exogenous acetaldehyde peak exposures are mainly associated with tobacco smoke, concentrations in the order of the Exposure Limit could be expected following intense sigarette consumption.

Assuming that the available exposure data are indicative of the population residential exposure it is concluded that people in Europe do not experience increased health hazards associated with acetaldehyde levels in their homes, although additional work should be warranted for a better characterization of exposure and dose response. Also, measured indoor levels are lower than a presumed threshold for cytotoxic damage to the nasal mucosa, and hence considered low enough to avoid any significant risk of upper respiratory tract cancer in humans.

Toluene

Synonyms: Methyl benzene, methyl benzol, phenyl methane, toluol
CAS Registry Numbers: 108-88-3
Molecular Formula: C_7H_8

1. Compound identification

Toluene is a clear, odorous, colourless, readily volatile liquid at ambient conditions. It is flammable and explosive in air. The technical toluene may contain small amounts of benzene. Toluene will not react with dilute acids or bases and it is not corrosive. It is removed from air by reacting with hydroxyl radicals. It is one of the most prevalent hydrocarbons in the troposphere. The lifetime of toluene range from several days in summer to several months in winter. Toluene is produced in high volume in industrial processes such as catalytic conversion of petroleum and aromatisation of aliphatic hydrocarbons, and coke oven operations. It is used in blending gasoline to enhance octane ratings, in leather tanning and as a common solvent. Occupational exposure to toluene might be high during production and use of toluene-containing products. Toluene is common in many products such as paints, household aerosols, thinners, cleaning agents, coatings, rubber, nail polish and other cosmetics, adhesives, resin and printing products (IARC 1999, WHO 1986, WHO 2000, HSDB 2003)

2. Physical and Chemical properties

Molecular weight (g/mol)   92.14
Melting point (°C)   -94.9
Boiling point (°C)   110.6
Density (g/l at 20 °C, 1 atm)   0.86
Relative density (air =1)   3.2
Solubility: Soluble in ethanol, benzene, diethyl ether, acetone,
                          chloroform, glacial acetic acid and
                          carbon disulfide, insoluble in water

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 3.824 $\mu g/m^3$
1 $\mu g/m^3$ = 0.261 ppb

Sources: WHO (1986), Verschueren 2001, EPA/Cal (2003), HSDB (2003)

3. Indoor Air Exposure assessment

Emission sources

Toluene emissions to the atmosphere result from industrial point sources and gas stations, and from mobile sources such as traffic. Exposure to toluene in indoor environment occurs due to emissions from a variety of toluene-based household products, uses of paints and thinners, together with tobacco smoke (WHO 2000).

Indoor air and exposure concentrations

Average indoor concentrations of toluene were clearly higher than respective outdoor concentrations in all latitudes in Europe (Annex 3). Toluene was the most abundant compound in indoor air accounting for 33-54% of the total sum of

aromatics measured in the European EXPOLIS study (Saarela et al 2003). Average outdoor concentrations ranged from about 6 $\mu g/m^3$ in Helsinki and Basel to 43 $\mu g/m^3$ in Milan (Jantunen et al 1999). Average indoor concentrations ranged from 20 $\mu g/m^3$ in Helsinki to 74 $\mu g/m^3$ in Prague. Personal exposures were clearly higher than indoor concentrations. The highest average personal exposures were measured in German study, being 130 $\mu g/m^3$ (Hoffman et al 2000), and lowest in Helsinki, 25 $\mu g/m^3$. In a German population based study of children and teenagers (GerES IV), weekly mean exposure to toluene was higher than the mean residential indoor concentration being 25 $\mu g/m^3$ and 15 $\mu g/m^3$ respectively. The highest exposure and indoor concentrations were 280 $\mu g/m^3$ and 87 $\mu g/m^3$ respectively. (Ullrich et al 2002). Italian study carried out by Carrer et al (2000) determining 24-hour exposures of office workers in Milan, showed an average of 35 $\mu g/m^3$. Based on these results, it is obvious that at least in Central and Southern Europe the guideline value of 260 $\mu g/m^3$ set by WHO (2000) will be exceeded in certain subpopulations.

Median and 90th percentile indoor concentrations, 10 $\mu g/m^3$ and 49 $\mu g/m^3$, in Arizona, USA (Gordon et al 1999) were clearly lower than the respective concentrations measured in EXPOLIS in European cities.

Ambient air concentrations of toluene in Europe have been measured in several studies (Saeger et al 1995, Ballesta et al 1997, Ballesta et al 1998, Kemp et al., 1998). Typical ambient air concentrations of toluene were in the order of 10 to 30 $\mu g/m^3$. The concentrations of toluene near petrol stations were generally around an order of magnitude higher than the urban air concentrations (EPA 2003).

Ambient toluene concentrations in urban environments in US have been in the same range as in Europe ranging about 17-20 $\mu g/m^3$, the highest level being 62 $\mu g/m^3$ in a metropolitan area. In rural sites levels were typically below 1 $\mu g/m^3$ (Helmig and Arey 1992, WHO 2000).

Residential indoor air concentrations of toluene in European urban populations measured in the EXPOLIS study and the National Survey in England are presented in Figure 3.1 and Figure 3.2. Respective exposure concentrations are presented in Figure 3.3.

Source related short time concentrations of toluene are presented in Figure 3.4. Even higher concentration of toluene, 2.1 mg/m^3 was measured in a kindergarten in Athens in the AIRMEX project (Kotzias 2004). The source of toluene identified in the kindergarten was a spray that was used when preparing Christmas decorations. Lee and Wang (2004) studied emissions of incense burning in chamber (18 m^3) tests. Concentrations ranged from 5 $\mu g/m^3$ to 99 $\mu g/m^3$. Measured concentrations did not exceed the Recommended Indoor Air Quality Objectives for Office Buildings and Public Places in Hong Kong (HKIAQO) of < 1092 $\mu g/m^3$. Brown (2002) studied short time (30-50 min) concentrations of toluene in established and new buildings, reporting mean concentrations of 14 $\mu g/m^3$ and 250 $\mu g/m^3$ respectively. Toluene concentration in a new building decreased to 18 $\mu g/m^3$ and 6.9 $\mu g/m^3$ in 72 and 246 days respectively. Emission sources of toluene were not identified, but VOC emissions in general were related to water-based paints, adhesives and wood-based panels. Elke at al (1998) measured short time concentrations of toluene inside buildings (60-min average), inside a train and a car (30-min average), being at the same level, 55 $\mu g/m^3$, in a train and a car, and 21 $\mu g/m^3$ in a smoker day room.

Short time exposure scenarios for potential consumer activities were analysed in European Union Risk Assessment Report (EU 2003). The highest toluene concentration, 1000 mg/m^3 (note the unit, mg/m^3) were expected during spraying painting. High peak concentrations were also assessed during carpet laying, car polishing and gluing, 195 mg/m^3, 10 mg/m^3 and 7.1 mg/m^3 respectively.
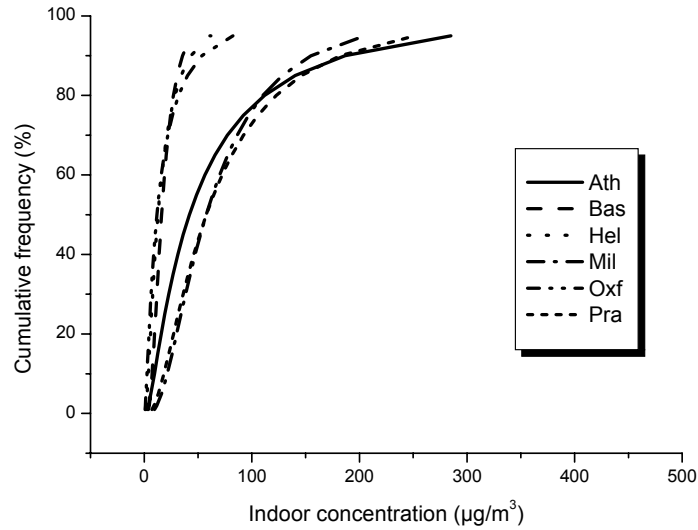
Figure 3.1. Cumulative frequency distributions of 30-hour indoor air concentrations of toluene in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=41) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
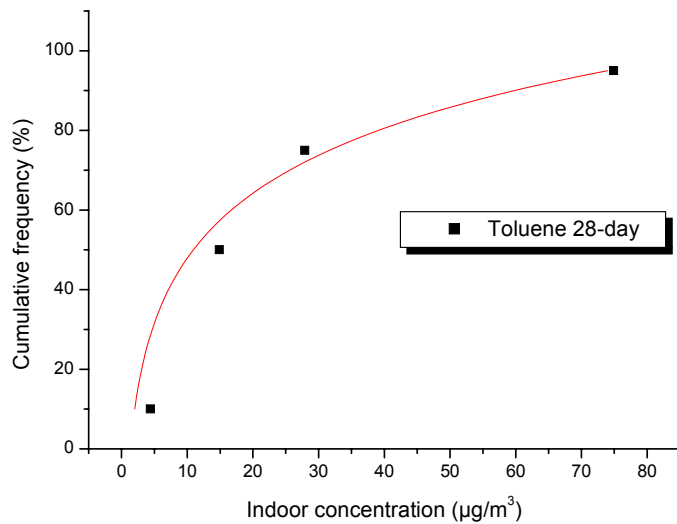
Figure 3.2. Cumulative frequency distribution of 28-day indoor air concentrations of toluene in England (GM= 15.1 $\mu g/m^3$, max 1784 $\mu g/m^3$, n=796, Brown et al 2002).
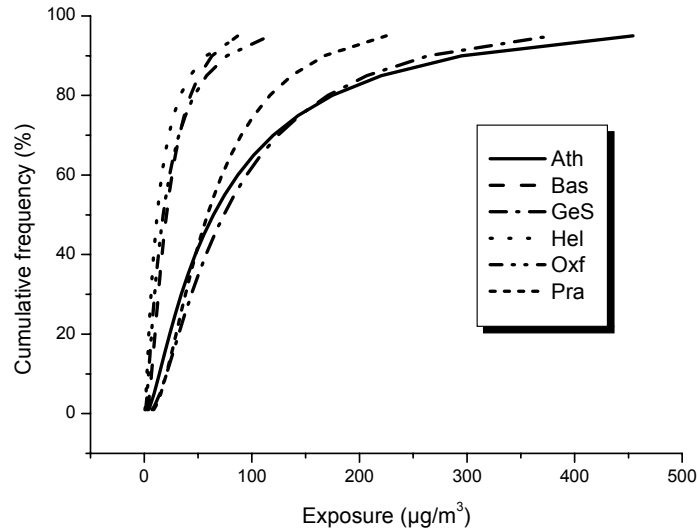
Figure 3.3. Cumulative frequency distributions of 48-hour personal exposure concentrations of toluene in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean concentrations of the German Survey GerES II (GeS) (Hoffman et al 2000).
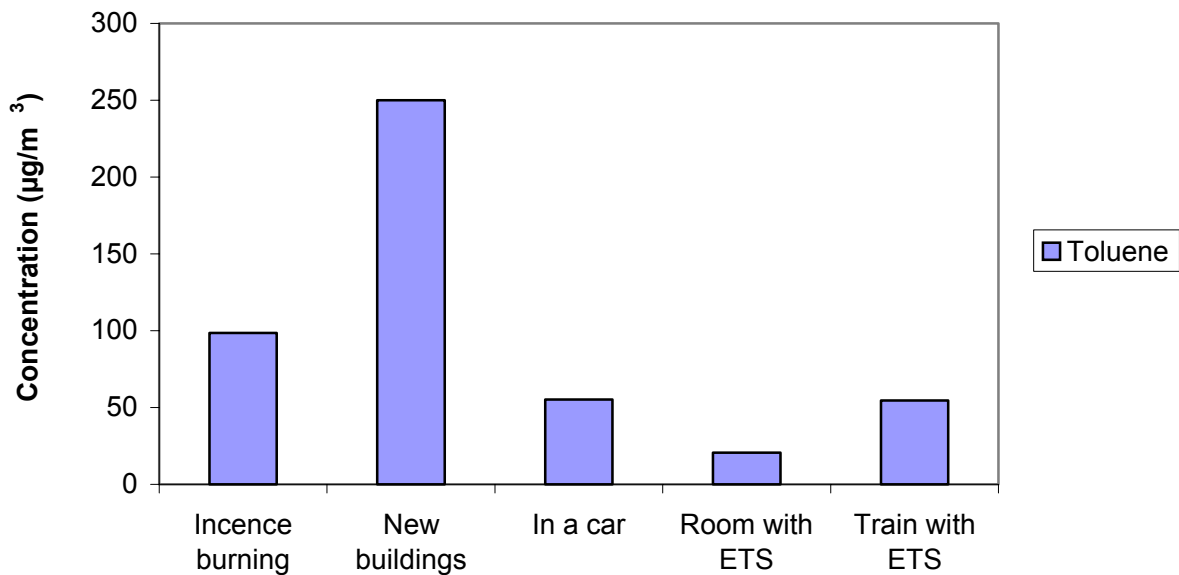
Figure 3.4. Short time toluene concentrations related to specific microenvironments or emission sources. Sampling times of 'New buildings' (Brown 2002), 'In a car', 'Room with ETS', and 'Train with ETS' (Elke at al 1998) were 30-50 min, 30-min, 60-min, 30-min respectively. During incense burning grab samples were obtained (Lee and Wang 2004).

4. Toxicokinetics

Absorption

The major uptake of toluene vapour is through the respiratory system. A number of investigations in humans (Carlsson, 1982; Carlsson and Lindqvist, 1977; Nomiyama and Nomiyama, 1974; Åstrand 1975) have shown that at rest a three-hour exposure to toluene vapour will result in an uptake amounting to approximately 50% of the inhaled toluene.

The blood/air partition coefficient for toluene is 11,2-15,6 at 37°C (Lindqvist, 1977; Sato et al., 1972; Sato and Nakajima, 1977; Sherwood, 1976; Ulfvarson and Övrum, 1976).

The concentration of toluene in alveolar air and in arterial and venous blood rises quickly during the first 10-15 minutes of exposure (Carlsson, 1982; Åstrand et al., 1972). After only 10 seconds of exposure toluene can be detected in blood from brachial arteries (Åstrand et al., 1972).

Data from experimental exposure of voluntary study subjects show that physical work results in increased toluene uptake (Veulemans and Masschelein, 1978b; Carlsson, 1982). Using a 50 W workload, exposure to 300 mg/m^3 (80 ppm) toluene for 2 hours did not result in steady state of the blood concentration of toluene in 12 study subjects. The toluene uptake was 2,4 times higher than the uptake at rest. During the work, lung ventilation was increased 2,8 times. Concentrations of toluene in alveolar air and blood increased with increasing work loads (0-150 W in periods of 30 minutes) (Carlsson, 1982). The amount of toluene absorbed increased with greater amounts of body fat (Carlsson and Ljungquist, 1982).

In nine male volunteers exposed to 200 mg/m^3 (53 ppm) toluene for 2 hours during a workload of 50 W, the total uptake of toluene was 50% of that inhaled (Löf et al., 1993).

Distribution

The distribution of toluene in the body is among other factors dependent on the tissue/blood partition coefficients and the metabolism. In rabbits the following partition coefficients have been found: brain, heart, liver, and intestine: 2,3, muscle tissue: 1,6, adipose tissue: 74,3, bone, connective tissue, and lung tissue: 1,9 (Sato et al., 1974). In rats brain/blood ratios of 1,2 (Kishi et al., 1988) and 1,7 (Zahlsen et al., 1992) have been determined. In humans the adipose tissue/blood partition coefficient for toluene is determined to be 81-83 (Sato et al., 1974; Sherwood, 1976). This high partition coefficient suggests that toluene can be accumulated in adipose tissue.

In mice, the distribution of toluene and its metabolites was investigated using whole body autoradiography after acute inhalation of side chain marked ^{14}C toluene (Bergman, 1979; Bergman, 1983). In adipose tissue, bone marrow, spinal nerves, spinal cord, and in the white parts of the brain, high concentrations of radioactivity occurred as judged from the photographs. In blood, liver, and kidneys, radioactivity was also found. One hour after exposure nerve tissue showed no radioactivity. In adipose tissue nearly all radioactivity had disappeared four hours after exposure, and only traces of non-volatile radioactivity could be found in the liver. After 24 hours all radioactivity had disappeared from the body.

In rats, subcutaneous injection of toluene (100 or 500 mg/kg) resulted in maximum concentrations of blood toluene after 2 hours (Benignus et al., 1984).

Toluene passes the placenta. Two hours following exposure of rats via inhalation to 1375 or 2700 mg/ m^3 (367 or 720 ppm) for 24 hours, foetal blood had a toluene concentration of 74% of that found in the dam's blood. The amniotic liquid contained a toluene concentration of 5% of that in the dam's blood. Four and six hours after exposure, similar relative toluene concentrations were found (Ungváry, 1984; quoted from IPCS 1985).

Groups of four 11, 14 or 17 day pregnant mice were killed 0, 30, 60 and 240 minutes after having inhaled 7500 mg/m^3 (2000 ppm) ^{14}C-toluene for ten minutes. Radioactivity as volatile and non-volatile was measured in lung, liver, kidney, brain, cerebellum, fat, plasma, amniotic fluid, placenta, and foetus. It was shown that toluene immediately after inhalation was taken up in the foetal tissue at a concentration of about 10% of that found in the maternal lungs. At four hours after exposure the toluene radioactivity was decreased to 2% of the original value (Ghantout and Danielsson, 1986).

Toluene has been found in human breast milk. In 12 pooled samples from four urban areas in the United States, toluene was identified qualitatively in at least 7 samples (Pellizzari et al., 1982; quoted from Jensen and Slorach, 1991).

Metabolism and elimination

The major pathway of toluene metabolism in both humans and laboratory animals involves sidechain oxidation by sequential action of cytochrome P-450, alcohol dehydrogenase and aldehyde dehydrogenase leading to benzoic acid which, upon conjugation with glycine, results in hippuric acid, the major urinary metabolite. Minor metabolites include *ortho*- and *para*-cresol. A minor metabolite that is specific for toluene exposure is *S*-benzyl-*N*-acetyl-L-cysteine (Takahashi et al., 1994). *In vitro* evidence suggests that the rate of metabolism in humans is greater than that in rats (Chapman, et al., 1990).

Analysis of blood and urine samples from workers and voluntary study subjects exposed to toluene via inhalation in concentrations ranging from 375 to 2250 mg/m^3 (100-600 ppm) indicate that of the biotransformed toluene, appr. 99% is oxidised via benzyl alcohol and benzaldehyde to benzoic acid. The remaining 1% is oxidised in the aromatic ring, forming ortho-, meta- and para-cresol (Woiwode et al., 1979; Woiwode and Drysch, 1981).

Water solubility of the biooxidation products is achieved through linkage with suitable substances (phase 2 reaction). Benzoic acid is linked to either glycine or glucuronic acid forming either hippuric acid or benzoylglucuronide. Cresols and benzyl alcohol are linked to glucuronic acid or sulphate (IPCS, 1985).

The elimination of toluene from adipose tissue is prolonged according to the findings of Periago et al. (1992), who examined a worker population. The half-time for elimination from adipose tissue was reported to range between 0,5 and 2,7 days, depending on the amount of body fat. Elimination from bone marrow also is prolonged (Chemical and engineering news, 1995; WHO, 1987).

Toluene or its metabolites may be eliminated via the lungs, the kidneys, or the liver.

Data from experimental inhalation exposure of voluntary subjects show that the toluene concentration in expired air decreases rapidly during the first 10 to 20 minutes after cessation of exposure to toluene via inhalation (Veulemans and Masschelein, 1978a; Carlsson, 1982; Echeverria et al., 1989). Two to four hours later, very low toluene concentrations are found in expired air (Carlsson, 1982). Of the toluene absorbed, 15-20% is exhaled during the first few hours after exposure has stopped (Nomiyama and Nomiyama, 1974). The cumulative elimination of toluene via the lungs amounts to 4-8% and 7-14% after 2 and 20 hours, respectively (Carlsson, 1982).

The cumulative elimination (in per cent) of toluene via the lungs appears to increase with increasing amounts of toluene taken up (Carlsson, 1982).

The majority (80-90%) of absorbed toluene is biotransformed and excreted from the body via the kidneys. At an exposure level of 750 mg/m^3 (200 ppm), the excretion is mainly as hippuric acid. About 1% of the biotransformed toluene is excreted as glucuronides or sulphates of o-, m-, or pcresol (IPCS, 1985).

A very small proportion, approximately 0,06% of the toluene absorbed via inhalation, is excreted unchanged in the urine in humans (Williams, 1959).

A good correlation was found between toluene exposure (air concentration multiplied by time) and concentration of hippuric acid in post exposure urine. However, a background level of hippuric acid is present in human urine, as a product of endogenous metabolism, and of metabolism of substances present in food. In the Western part of the world, at exposure levels below 375 mg/m^3 (100 ppm) hippuric acid in post exposure urine cannot be used to separate an exposed person from an unexposed one because the difference between the background level and the toluene-generated level is too small (Lauwerys, 1983). However, hippuric acid background levels in urine vary geographically. In some Third World countries a low urinary hippuric acid background level is found. Thus, in these parts of the world it is possible to use this metabolite as a biological marker for toluene exposure even at exposure levels lower than 375 mg/m^3 (Chang et al., 1996; Vrca et al., 1997a; 1997b).

Data from rats exposed to 3750, 6675, or 11250 mg/m^3 (1000, 1780, or 3000 ppm) of toluene via inhalation for 2 hours showed that elimination could be described by a bi-exponential function with average half-times of 6 and 90 minutes (Rees et al., 1985).

In rats a small proportion, less than 2%, of the absorbed toluene is excreted via the bile to the intestine. The substances excreted are reabsorbed in the intestine. Thus very small amounts are excreted in faeces (Abou-El-Makarem et al., 1967).

5. Health effects

Effects of short-term exposure

Dysfunction of the central nervous system and narcosis are the major effects of acute exposure to toluene (ATSDR, 1989). Irritation of the skin, eye, and respiratory tract can also result. Inhalational abuse of toluene with high level exposure for long periods of time has produced progressive and irreversible changes in brain structure and function (Spencer and Schaumberg, 1985).

Reaction time and perceptual speed were studied in 12 young male subjects exposed by inhalation to toluene concentrations ranging from 400 to 3000 mg/m³ (100 to 700 ppm), each for a 20-minute interval (Gamberale and Hultengren, 1972). Statistically significant impaired reaction time was apparent following exposure to 1100 mg/m³ (300 ppm) toluene. A statistically significant impairment in perceptual speed was observed at 3000 mg/m³ toluene. No effects were observed at 400 mg/m³.

Two groups of middle aged workers, one with previous occupational exposure to solvents and one without, were exposed once to 400 mg/m³ (100 ppm) of toluene for 6,5 hours (Baelum *et al.*, 1985). Fatigue, sleepiness, a feeling of intoxication, and eye, nose and throat irritation were reported. Decrements in manual dexterity, color discrimination, and accuracy in visual perception were also observed. Greater sensitivity to toluene was noted for those subjects with previous solvent exposure.

A random population sample of 32 male and 39 female subjects were allocated into three groups, one exposed to clean air, one exposed to constant toluene at a concentration of 377 mg/m^3 (100 ppm), and one exposed to varying concentrations of toluene (Fourteen 30-minute episodes during the exposure period, each episode starting with an increasing concentration reaching a peak of 1125 mg/m^3 (300 ppm) after 5 min and then decreasing to a stable period of about 15 min at 188 mg/m^3 (50 ppm), giving a TWA of 375 mg/m^3 for the whole exposure period). An exposure period comprised a single day (7 hours). Toluene caused throat and respiratory irritation, headache and dizziness. In performance tests only minimal effects were found, with a tendency towards lower score and more errors but fewer false reactions in the primary task of the vigilance test. The effects were not statistically significant (p<0,1). There was no difference between constant exposure and peak exposure (Bælum et al., 1990).

Nasal mucus flow, lung function, psychometric performance, and subjective responses were studied in 16 young healthy males exposed to toluene concentrations ranging from 38 mg/m³ to 377 mg/m³ (10 to 100 ppm) for 6 hours (Andersen *et al*, 1983). Headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation were reported at 377 mg/m³. The subjects also reported that it became more difficult to participate in the battery of psychometric tests and that their reaction time felt impaired at 377 mg/m³. No significant objective changes compared to control exposures were observed in the performance test results. No symptoms were reported at 38 and 151 mg/m³.

A battery of neurobehavioral and performance tests was conducted among 42 young men and women exposed by inhalation for 7 hours to 0, 283, and 566 mg/m^3 (0, 75, and 150 ppm) toluene (Echeverria *et al.*, 1989). Statistically significant decrements in visual short term memory, visual perception, and psychomotor skills were observed at 560 mg/m³ compared to control exposures. A dose-dependent increase in subjective symptoms of headache and eye irritation was also observed.

Wilson (1943) reported that workers exposed to concentrations of commercial toluene ranging from 200 to 750 mg/m³ (50 to 200 ppm) for periods of 1 to 3 weeks experienced headaches, lassitude, and loss of appetite. At 750 to 2000 mg/m³ (200 to 500 ppm), symptoms of nausea, bad taste in the mouth, slightly impaired coordination and reaction time, and temporary memory loss were also observed. Exposure to 2000 to 5600 mg/m³ (500 to 1500 ppm) resulted in palpitations, extreme weakness, pronounced loss of coordination, and impaired reaction time. Red blood cell counts were decreased and there were 2 cases of aplastic anemia. The hematologic effects were most likely caused by benzene impurities (ACGIH, 1986).

Three volunteer subjects exposed by inhalation to toluene concentrations ranging from 200 to 400 mg/m³ (50 to 100 ppm), 8 hours per day, 2 times per week over 8 weeks experienced fatigue, drowsiness, and headaches (von Oettingen *et al.*, 1942). At 750 to 3000 mg/m³ (200 to 800 ppm), symptoms of muscular weakness, confusion, impaired coordination, paresthesia, and nausea were also reported. After exposure to 3000 mg/m^3, all 3 subjects reported considerable aftereffects (severe nervousness, muscular fatigue, and insomnia) lasting several days.

Summary of short-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
151 EXP 369 1h-ADJ	377 EXP 923 1h-ADJ	CNS-mild, eyes, respiratory; impaired reaction time, headache, dizziness, feeling of intoxication, slight eye and nose irritation	volunteers, 6h	Andersen et al. 1983	OEHHA (1999); REL: 37 ATSDR (2003); MRL: 3.8
151 EXP	283 EXP	CNS; NOAEL: see above LOAEL: visual short term memory, visual perception and psychomotor skills	volunteers, 6-7h	NOAEL: Andersen et al. 1983 LOAEL: Echeverria et al. 1989	ECB (2003)
Final statement (UNIMI) : Human NOAEL = 150 mg/m³					

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Acute Reference Exposure Level (protective against mild adverse effects):
Study   Andersen *et al.*, 1983
Study population   16 young, healthy males
Exposure method   inhalation
Critical effects   impaired reaction time and symptoms of headache, dizziness, a feeling of intoxication and slight eye and nose irritation
LOAEL   100 ppm
NOAEL   40 ppm
Exposure duration   6 hours
Extrapolated 1 hour concentration   98 ppm (40^2ppm* 6 h = C^2 * 1 h)
LOAEL uncertainty factor   1
Interspecies uncertainty factor   1
Intraspecies uncertainty factor   10
Cumulative uncertainty factor   10
Reference Exposure Level   9,8 ppm (37 mg/m³; 37.000 μg/m³)

ECB (2003)
European Chemical Bureau - Institute for Health and Consumer Protection - European Union Risk Assessment Report

In the exposure chamber studies: Echeverria *et al.*, (1989) and Andersen et al., (1983), headache, dizziness, feeling of intoxication, irritation and sleepiness were recorded to occur with significantly increased frequency at exposure levels from 562 mg/m³ (150 ppm) down to 283 mg/m³ (75 ppm). At 151 mg/m³ (40 ppm) and below the effects have not been recorded to occur with increased frequency. For these subjective symptoms a LOAL of 283 mg/m³ (75 ppm) and a NOAEL of 151 mg/m³ (40 ppm) can be established.

With respect to function in performance tests, inhalation of 281 mg/m³ (75 ppm) and 562 mg/m³ (150 ppm) for 7 hours have resulted in significantly worse results in a number of performance tests, indicating a LOAEL of 281 mg/m³ (75 ppm) for function in performance tests while a NOAEL cannot be established.

ATSDR (2003)

Agency for Toxic Substances and Disease Registry
Derivation of the acute Minimal Risk Level (MRL).
There are several human studies for which the central nervous system is the major end point and could have been used to derive an acute inhalation MRL. However, the Andersen et al. (1983) study was chosen as the basis for the MRL because this was the only human study which reported a NOAEL. Baelum et al.(1985) also reported a LOAEL of 377 mg/m³ for neurological effects in humans. In this study, 43 occupationally-exposed subjects and 43 controls were exposed to either clean air or air containing 377 mg/m³ toluene for 6.5 hours in a climate chamber. A battery of ten tests of visuomotor coordination, visual performance, and cortical function were administered during the 6.5 hour period. For

both the controls and toluene exposed subjects, there were complaints of air quality, irritation of the nasal passages, and increased feelings of fatigue and sleepiness. Subjects also complained of headaches and dizziness. Toluene exposure decreased performance on four of the neurobehavioral tests; three of these were tests of visual perseverance. The fourth test affected was the simple peg board test of visuomotor function, where the effect was noted in toluene-exposed workers to a much greater extent than controls. Escheverria et al. (1991) reported a LOAEL of 283 mg/m^3 for neurological effects in humans. In this study, two groups of 42 students were exposed to 0, 75, and 150 ppm toluene for a 7 hour period. A complete battery of 12 tests was administered before and at the end of each exposure. Toluene caused a dose-related impairment of function on digit span pattern recognition, the one hole test, and pattern memory. Rahill et al. (1996) reported a LOAEL of 377 mg/m^3 for neurological effects in humans. In this study, six volunteers were exposed for 6 hours a day to either 377 mg/m^3 toluene or clean air. Three repetitions of two computerized neuropsychological tests were performed, with the composite score on the multitasking test being significantly lower with toluene exposure than with clean air.

Dose endpoint used for MRL derivation: 151 mg/m^3 for neurological effects
Uncertainty factors used in MRL derivation:10 (for human variability)
MRL = 151 mg/m^3 x 5 days/7 days x 8 hours/24 hours ÷10 = 3.8 mg/m^3

Effects of long-term exposure

Most human studies reporting adverse effects due to chronic toluene exposures involve either toluene-containing solvent abuse or occupational exposure to toluene. Solvent abusers are generally exposed to higher levels of toluene than are workers. A continuum of neurotoxic effects ranging from frank brain damage to degraded performance on psychometric tests which roughly track exposure levels has been observed.

An extensive database on human exposure to toluene indicates that dysfunction of the CNS is of primary concern. Deficits in neurobehavioural functioning have been viewed as precursors of more serious indications of CNS toxicity (Chemical and engineering news, 1995; WHO, 1981). Their measurement is generally held to be more reliable than subjective symptoms, which may involve situational factors unrelated to a cause–effect relationship with exposure. Potential confounders such as age, alcohol, drugs and education need to be assessed to ensure correlations of toxicity with exposure.

Solvent workers exposed to 160 mg/m^3 toluene (estimated as a time-weighted average) for an average duration of 6,8 years reported a significantly greater incidence of sore throat, dizziness and headache than controls; the sore throat and headache incidence demonstrated a rough dose-response (Yin et al., 1987).

Orbaek and Nise (1989) examined the neurological effects of toluene on 30 rotogravure printers, 33-61 years of age (mean 50), employed at two Swedish printing shops for 4-43 years (median 29) in 1985. Mean exposure levels at the two printing shops were 43 and 157 mg/m^3 of toluene, respectively; however, before 1980 the exposure levels had exceeded 300 mg/m^3 in both shops. The authors noted that rotogravure printing provides an occupational setting with practically pure toluene exposure. Comparisons were made to a reference group of 72 men aged 27-69 (mean 47). The alcohol consumption of both the workers and referents was also determined (< 200 g/week or > 200 g/week). Neurological function in the workers and referents was evaluated using interviews and psychometric testing; the results from each of the two printing shops were pooled. The printers reported statistically significantly higher occurrences of fatigue (60%), recent short-term memory problems (60%), concentration difficulties (40%), mood lability (27%), and other neurasthenic symptoms. The printers also scored significantly worse than referents in a number of psychometric tests, including synonym, Benton revised visual retention and digit symbol tests, even after adjustment for age. For all comparisons, tests of interaction between the effects of toluene exposure and alcohol consumption were not statistically significant.

A battery of neurobehavioral tests was performed in 30 female workers exposed to toluene vapors in an electronic assembly plant (Foo et al., 1990). The average number of years worked was 5,7 ± 3,2 for the exposed group and 2,5 ± 2,7 years for the controls. Study subjects did not smoke tobacco or drink alcohol, were not taking any medications, and had no prior history of central or peripheral nervous system illness or psychiatric disorders. The exposed group of workers inhaled a time-weighted average (TWA) of 332 mg/m^3 (88 ppm) toluene while the control workers inhaled 49 mg/m^3 (13 ppm). A significant decrease in neurobehavioral performance was observed in the exposed workers in 6 out of 8 tests. Irritant effects were not examined, and concurrent exposures to other chemicals were not addressed. In this study, 332 mg/m^3 was considered a LOAEL for central nervous system effects. However, the workers designated by the authors to be controls did not comprise a true control group, since they were exposed to 49 mg/m^3 toluene. This may have resulted in an underestimation of the effects of exposure to 332 mg/m^3 toluene. Similar effects were noted in a follow-up study by Boey et al. (1997).

Abbate *et al.* (1993) evaluated alterations induced in the auditory nervous system by exposure to toluene in a group of rotogravure workers. A sample of 40 workers of normal hearing ability was selected from a group of 300 workers who were apparently in good health but were professionally exposed to toluene (12 – 14 years exposure, 343 mg/m³ average exposure, exposure assessment not described). They were subjected to an adaptation test utilizing a BAER technique with 11 and 90 stimulus repetitions a second. The results were compared with an age and sex-matched control group not professionally exposed to solvents. A statistically significant alteration in the BAER results was noted in the toluene-exposed workers with both 11 and 90 stimuli repetitions. The authors suggested that these results can be explained as a tolueneinduced effect on physiologic stimulus conduction mechanisms, even in the absence of any clinical sign of neuropathy. Furthermore, this effect could be observed in the responses of the entire auditory system, from peripheral receptors to brainstem nuclei.

A group of 49 printing-press workers occupationally exposed to toluene for approximately 21,6 years was studied by Vrca *et al.* (1997). Toluene exposure levels were determined from blood toluene and urinary hippuric acid levels, and were estimated to range from 151-226 mg/m³. No control group was used. Brain evoked auditory potential (BEAP; similar to BAER) and visual evoked potential (VEP) measurements were performed on a Monday morning after a nonworking weekend. There was a significant increase in the latencies of all the BEAP waves examined, except for P2 waves, as well as in the interpeak latency (IPL) P3-P4, while IPL P4-P5 decreased significantly with the length of exposure. No correlation was noted between the amplitude of BEAP waves and the length of exposure. The amplitude but not the latency of all the VEPs examined decreased significantly with the length of exposure.

The effects of acute and chronic toluene exposure on color vision were studied in a group of eight rotogravure printing workers (Muttray *et al.*, 1999). The workers had been employed as printers for an average of 9,8 years. The color vision acuity of the workers before and after an acute toluene exposure (28– 41 minutes in duration, concentration 1115 – 1358 mg/m³) was evaluated using the Farnsworth panel D-15 test, the Lanthony desaturated panel D-15 test, and the Standard Pseudoisochromatic Plates part 2. A control group of 8 unexposed workers was also tested. Acute toluene exposure had no effect on color vision. Print worker performance prior to acute toluene exposure (chronic effects) was similar to controls on the Farnsworth panel D-15 and Standard Pseudoisochromatic Plates part 2 tests. Print worker performance on the Lanthony desaturated panel D-15 test was worse than that of controls (median scores of 1,18 and 1,05 for exposed and controls (higher number indicates degraded performance), respectively, but not significantly ($p =$ 0,06). The authors noted that the small number of subjects limited the statistical power of the study.

Three groups of Croatian workers were examined by means of interviews, medical examination, and color vision testing using the Lanthony 15 Hue desaturated panel in standard conditions (Zavalic et al., 1998a). Workers were excluded from the study if they met any of the following criteria: less than 6 months employment, congenital color vision loss, a medical condition which can affect color vision, visual acuity below 6/10, use of medications which can affect color vision or a hobby that involved solvent exposure. Alcohol intake and smoking were also assessed for each individual. The first group consisted of 46 workers (43 women and 3 men) employed in manually glueing shoe soles and exposed to median levels of 121 mg/m³ and geometric mean levels of 132 mg/m³ toluene. The second group consisted of 37 workers (34 men and 3 women) employed in a rotogravure printing press and exposed to median levels of 498 mg/m³ and geometric mean levels of 588 mg/m³ toluene. The third group consisted of 90 workers (61 men and 29 women) not occupationally exposed to any solvents or known neurotoxic agents. The study demonstrated a statistically significant impairment of color vision in workers chronically exposed to 588 mg/m³ toluene compared with controls. When the data were adjusted to allow for the confounding effects of alcohol consumption and age, a significant difference due to toluene exposure was also reported for workers exposed to 132 mg/m³ toluene compared with controls.

Zavalic *et al.* (1998b) examined the effects of chronic occupational toluene exposure on color vision using a further group of 45 exposed workers (mean toluene exposure concentration = 452 mg/m³) and 53 controls. Color vision was evaluated using the Lanthony desaturated panel D-15 test; test scores were age and alcohol consumption-adjusted. Color vision was significantly impaired in toluene-exposed workers (p < 0,0001) compared to controls. It was also observed that there was no significant difference between test scores on Monday morning (prework) and Wednesday morning. The authors stated that the effect of toluene on color vision can be chronic and that the possible recovery period is longer than 64 hours.

Effects on kidney and liver

Among 24 toluene abusers examined on the day of admission to hospital, alkaline phosphatase was elevated in 13 patients, while SGOT was elevated in 7. The elevated enzyme levels returned to normal after 2 weeks of abstinence (Fornazzari et al., 1983).

No increase in levels of the enzymes serum aspartate aminotransferase and alanine aminotransferase was found, in 59 men with occupational exposure to toluene (recorded level 375 mg/m^3) for more than one year (1-5 years, 22 men; 6-10 years, 18 men; more than 10 years, 19 men) when compared to an unexposed control group of equal size (Waldron et al., 1982).

In 47 toluene-exposed workers a significant increase in S-ALP (20% relative to referents) compared with a referent group of 46 non-exposed workers was found (Svensson et al., 1992b). The association was still significant when heavy alcohol consumers were excluded from the analysis. The exposure levels were generally below 300 mg/m^3 (80 ppm). Other liver functionrelated enzyme levels were unaffected. There was no association with cumulative exposure.

Sniffing of toluene resulted in reversible kidney damage (O'Brian et al., 1971), haematuria (Massengale et al., 1963), reversible type 1 renal tubular acidosis (Bennett and Forman, 1980; Fischman and Oster, 1979; Kroeger et al., 1980; Moss et al., 1980; Patel and Benjamin, 1986; Reisin et al., 1975; Streicher et al., 1981; Taher et al., 1974; Weinstein et al., 1985; Will and McLaren, 1981) and hypokalaemia (Kelly, 1975; Taher et al., 1974). In some cases sniffing resulted in irreversible damage of the kidneys (Russ et al., 1981).

A workplace accident with massive toluene exposure for 18 hours resulted in renal failure with oligouria probably caused by dehydration and myoglobinuria (Reisin et al., 1975).

Inhalation of 382 mg/m^3 (100 ppm) toluene for 6,5 hours in an exposure chamber resulted in unchanged excretion of albumin and beta-2-microglobulin for 43 printers with occupational exposure to toluene as compared to 43 age-matched controls without occupational exposure to toluene (Nielsen et al., 1985).

No signs of renal damage in 118 painters were found compared with a control group. The painters had an average of 9 years occupational exposure to toluene and xylenes. At the time of investigation, the exposure was approximately 94 mg/m^3 (25 ppm) as determined from metabolites in urine (Franchini et al., 1983).

In 42 printers with an occupational toluene exposure averaging 300 mg/m^3 (80 ppm) (range 100-900 mg/m^3 (30-240 ppm)) compared with 48 unexposed controls, no changes in glomerular filtration rate, renal concentrating ability, beta-2-microglobulin excretion, and excretion of erythrocytes and leukocytes were found (Askergren, 1982).

In conclusion, massive toluene exposure through abuse or workplace accidents has been associated with kidney damage and renal failure. Three occupational studies did not show a relation between toluene exposure and kidney damage.

Developmental, reproductive and teratogenic effects

Abuse of toluene by pregnant women through deliberate inhalation of products such as paint thinners, glues and paints has been associated with a number of developmental and congenital anomalies in infants (Donald et al., 1991). In such reports it is difficult to determine the degree to which other substances may play a role in the development of adverse effects. Effects commonly noted postpartum include low birth weight, growth retardation, microencephaly, CNS dysfunction, renal tubule acidosis, and minor craniofacial and limb abnormalities. Perinatal death has also been reported.

Two studies suggest an increased risk of spontaneous abortions associated with exposure to toluene in the workplace. One of the studies provides no data on exposure levels, while the levels were around 332 mg/m^3 (range 189-566 mg/m^3) in the other study (Ng et al., 1992b). The Ng et al. (1992) study cannot be used to establish definitively a causal relationship between late spontaneous abortions and toluene exposure or the magnitude of the LOAEL To establish a definite relationship, a prospective study including pregnant women exposed to toluene at similar exposure levels with individually monitored data on toluene exposure and fetal loss would be needed. However, based on the current evidence suggesting an increased risk for late spontaneous abortions, exposure of pregnant women to such exposure levels would raise serious ethical concerns. Consequently, the results of the Ng study are used as a basis for the risk characterisation of developmental toxicity in humans.

Menstrual disorders in workers were reported, but the possible presence of other chemicals in the exposure environments and unmatched characteristics of the exposed and control groups make these findings difficult to interpret (WHO, 1987). Possible exposure-related effects upon follicle stimulating hormone and testosterone (Svensson et al.,

1992a), but not serum prolactin levels (Svensson et al., 1992b), have been observed in printers without overt effects of toluene.

Developmental toxicity of toluene has mainly been studied in rats. Rat inhalation studies provide strong evidence of developmental toxicity (lower birth weight and long-lasting developmental neurotoxicity) in the absence of maternal toxicity. The effective dose levels are around or more than 3.77 g/m^3. The NOAEL for lower birth weight and delayed postnatal development is 2.26 g/m^3 (Thiel and Chahoud, 1997). A NOAEL for developmental neurotoxicity cannot be determined from the available studies. The LOAEL for this effect is 4.52 g/m^3 (Hass et al., 1999).

There is no indication that toluene cause malformations in rats, mice or rabbits.

Summary of long-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
151 EXP 27 ADJ	301 EXP 54 ADJ	CNS; decreased brain weight, dopamine receptor binding Supporting study: Neurobehavioral deficits	rats, 4w (supported by occupational, 5.7y)	Hillefors-Berglund et al. 1995; supported by Orbaek and Nise (1989), Foo et al. (1990)	OEHHA (1999); REL: 0.4
	332 EXP 118 ADJ	CNS; neurobehavioural deficits	Occupational, 5.7y	Foo et al. 1990	OEHHA (1999); WHO (2001); GV: 0.26; EPA-IRIS (1992); RfC: 0.4
	2261 EXP 437 ADJ 79 HEC	Respiratory system; nasal epithelium degeneration	rats, 2y	NTP, 1990	EPA-IRIS (1992)
	132 Study 31 ADJ	CNS; color vision impairment	Occupational, >6m	Zavalic et al. (1998a)	ATSDR (2003); MRL: 0.3

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Chronic Reference Exposure Level (REL):
Study	Hillefors-Berglund *et al.* (1995); supported by Orbaek and Nise (1989), Foo *et al.* (1990)
Study population	Male Sprague-Dawley rats
Exposure method	Inhalation
Critical effects	Decreased brain (subcortical limbic area) weight, Altered dopamine receptor (caudate-putamen) binding
LOAEL	80 ppm
NOAEL	40 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	4 weeks, followed by 29-40 days recovery
Average experimental exposure	7 ppm (40 × 6/24 hours × 5/7 days)
Human equivalent concentration	7 ppm (gas with systemic effects, based on RGDR = 1,0 using default assumption that $\lambda a = \lambda h$
Subchronic uncertainty factor	10
Interspecies uncertainty factor	1 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0,07 ppm (70 ppb; 0,3 mg/m³; 300 μg/m³)
Supportive human study	Foo *et al.*, 1990
Study population	30 female workers in an electronic assembly plant
Exposure method	Occupational inhalation
Critical effects	Neurobehavioral deficits in 6 out of 8 tests
LOAEL	88 ppm

NOAEL	Not observed
Exposure continuity	10 m³/day occupational inhalation rate, 5 days/week
Average occupational exposure	31,4 ppm (88 ppm x 10/20 x 5/7)
Exposure duration	5,7 + 3,2 years (exposed group); 2,5 + 2,7 years (controls)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0,1 ppm (100 ppb; 0,4 mg/m³; <u>400 μg/m³</u>)

The critical animal study (Hillefors-Berglund *et al.*, 1995) used to derive a REL for toluene describes adverse neurological effects in rats after a well characterized inhalation exposure to toluene. The study results contain both a LOAEL and a NOAEL. Decreased brain (subcortical limbic area) weight and altered dopamine receptor binding compared to controls were noted at the NOAEL, but the changes were not statistically significant; this suggests that if a threshold for adverse neurological effects exists in this study, it would be at or below the observed NOAEL. The study LOAEL for altered dopamine receptor binding agrees qualitatively with results from similar studies (von Euler *et al.*, 1994).

Additionally, toluene induced neurotoxicity has been described in many studies by a variety of endpoints in both animals and humans (ATSDR, 1999). The adverse neurotoxic effects associated with toluene exposure in the rat study by Hillefors-Berglund *et al.* (1995), decreased brain (subcortical limbic area) weight and altered dopamine receptor binding, occur in areas of the rat brain that are structurally and functionally similar to brain areas (basal ganglia, thalami) of some human toluene abusers that demonstrate MRI alterations (T2 hypointensity). The altered MRI parameters may be the result of the partitioning of toluene into the lipid membranes of brain cells (Unger *et al.*, 1994).

If both human and animal adverse effect data on a chemical are available, OEHHA prefers to use the human data to develop a REL when possible. However, the study by Hillefors-Berglund *et al.* (1995) provides data (decreased brain [subcortical limbic area] weight and altered brain dopamine receptor binding) which are specific and sensitive measures of neurotoxicity that would not be obtainable in human studies. In contrast, the psychometric tests used to generate the neurotoxicity data in the human occupational exposure studies described above tend to be less sensitive and suffer from greater measurement uncertainty. Additionally, the Hillefors-Berglund *et al.* (1995) study has better exposure characterization than the human occupational exposure studies. Nonetheless, the human studies are useful in supporting the derivation of the REL for toluene. Ordinarily, an interspecies uncertainty factor of 3 would be applied, in addition to the human equivalent concentration calculation, to reflect the uncertainty associated with extrapolating from animals to humans. However, in this case the uncertainty in the interspecies extrapolation is reduced by the availability of human epidemiological data with generally consistent effect levels, after appropriate duration corrections. Based on comparison of the data in both animals and humans, it appears that a REL of 271 μg/m³ (rounded to 300 μg/m³ in the final derivation) would protect exposed humans from experiencing chronic neurotoxic effects.

Further studies considered by OEHHA for the derivation of the Reference Exposure are listed in Table 5.1.

Table 5.1: Supporting Neurotoxicity Studies

Study	Duration	Effect	NOAEL mg/m³	NOAEL (TWA) mg/m³	LOAEL mg/m³	LOAEL (TWA) mg/m³
VonEuler *et al. (1994)*	4 weeks	rat: altered brain dopamine receptor binding	n.o.	n.o.	302	54
Orbaek and Nise[b] (1989)	29 years	human: impairment on neuropsychometric tests	n.o.	n.o.	42-155	15-55
Korsak (1992)	6 months	rat: impaired motor function	n.o.	n.o.	377	67

WHO (2001)

Air Quality Guidelines for Europe 2000
The lowest-observed-adverse-effect level for effects on the CNS from occupational studies, is approximately 332 mg/m³ (88 ppm) (Foo *et al.*, 1990). A guideline value of 0.26 mg/m³ is established from these data adjusting for continuous exposure (dividing by a factor of 4,2) and dividing by an uncertainty factor of 300 (10 for interindividual variation, 10 for use of a lowest-observed-adverse-effect level rather than a no-observed-adverse-effect level, and an

additional factor of 3, given the potential effects on the developing CNS). This guideline value should be applied as a weekly average. This guideline value should also be protective for reproductive effects (spontaneous abortions).

The air quality guideline could also be based on the odour threshold. In this case, the peak concentrations of toluene in air should be kept below the odour detection threshold level of 1 mg/m^3 as a 30 minutes average.

U.S.EPA - IRIS (1992)
Integrated Risk Information System

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical effect	Exposures*	UF	MF	RfC
Neurological effects Occupational Study Foo et al., 1990	NOAEL: None LOAEL: 332 mg/m^3 (88 ppm) LOAEL(ADJ): 119 mg/m^3 LOAEL(HEC): 119 mg/m^3	300	1	0,4 mg/m^3
Degeneration of nasal epithelium 2-Year Rat Chronic Inhalation Study NTP, 1990	NOAEL: None LOAEL: 2261 mg/m^3 (600 ppm) LOAEL(ADJ): 437 mg/m^3 LOAEL(HEC): 79 mg/m^3			

*Conversion Factors: MW = 92.15.
Foo et al., 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/m^3) = 88 ppm x 92.15/24.45 = 332 mg/m^3. This is an extrarespiratory effect of a soluble vapor. The LOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 m^3/day, MVh = 20 m^3/day. LOAEL(HEC) = LOAEL(ADJ) = 332 x MVho/MVh x 5 days/7 days = 119 mg/m^3.

NTP, 1990: Assuming 25 C and 760 mmHg, LOAEL (mg/m^3) = 600 ppm x 92.15/24.45 = 2261 mg/m^3. LOAEL(ADJ) = LOAEL (mg/m^3) x 6.5 hours/24 hours x 5 days/7 days = 437 mg/m^3. The LOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa = 0.24 m^3/day, MVh = 20 m^3/day, Sa (ET) = 11.6 sq.cm, Sh (ET) = 177 sq.cm. RGDR = (MVa/Sa) / (MVh/Sh) = 0.18. LOAEL(HEC) = 437 x RGDR = 79 mg/m^3.

In humans, toluene is a known respiratory irritant with central nervous system (CNS) effects. Because available studies could not provide subthreshold (NOAEL) concentrations for either of these effects, the LOAELs for both effects need to be considered in developing the RfC. Consequently, the study of Foo et al. (1990) was used for the CNS effects, and that of the National Toxicology Program (NTP, 1990) for the irritant effects. Because the CNS effect was judged to be a more severe and relevant endpoint, the LOAEL for this effect was used for deriving the RfC. Further, this effect is supported by a number of other occupational studies that show effects around 377 mg/m^3 (100 ppm).

Foo et al. (1990) conducted a cross-sectional study involving 30 exposed female workers employed at an electronic assembly plant where toluene was emitted from glue. Toluene levels reported in the study were from personal sample monitoring and reported as an 8-hour TWA, although the number of samples taken and the actual sampling period were not given. No historical exposure values were given. Co-exposure to other solvents was not addressed in the study. The exposed and control cohorts were matched for age, ethnicity, and use of medications. Members of these cohorts did not use alcohol and were nonsmokers. Medical histories were taken to eliminate any histories of central or peripheral nervous system disorders. The average number of years (+/- SD) worked by the exposed population was 5,7 +/- 3,2 and by the controls was 2,5 +/- 2,7. Exposed workers breathed toluene air levels of 332 mg/m^3 (88 ppm) as a TWA and control workers 49 mg/m^3 (13 ppm) (TWA); both of which are averages of the individual personal samples. A battery of eight neurobehavioral tests were administered to all exposed and control workers. The tests were performed midweek, before the workers reported to their stations for the day. Group means revealed statistically significant differences in 6/8 tests; all tests showed that the exposed workers performed poorly compared with the control cohort. When individual test results were linearly regressed against personal exposure concentrations, poor concentration-response relationships resulted for the six tests, with correlation coefficients ranging from 0,44 to 0,30. Irritation effects were not evaluated in this study, and no clinical signs or symptoms were reported. The paucity of exposure information, coupled with the small size of the cohort, limits the interpretation of this study, although the results were essentially confirmed in a clinical study in which the toluene concentrations were carefully controlled (Echeverria et al., 1989) at levels bracketing 332 mg/m^3 (88 ppm). Although the data in Echeverria et al. (1989) were generated from short- term exposures (3-7 hours over a period of 142 days), the results may be considered relevant to longer-term exposures as several studies indicate the absence of a duration-response relationship in toluene-induced symptomatology. Fornazzari et al. (1983) noted the absence of a duration-effect relationship among toluene abusers when they were segregated into neurologically impaired vs. unimpaired (p = 0,65). The human studies of Iregren (1982), Cherry et al. (1985), Baelum et al. (1985), and the principal study of Foo et al. (1990) all report this lack of a duration-response relationship and

confirm the occurrence of CNS effects. Foo et al. (1990) indicate a LOAEL of 332 mg/m^3 (88 ppm) toluene for neurobehavioral changes from chronic exposure to toluene.

In a 2-year bioassay, Fischer 344 rats (60/sex/group) were exposed to 0, 2261, or 4523 mg/m^3 (0, 600, or 1200 ppm, respectively) toluene vapors, 6,5 hours/day, 5 days/week (duration-adjusted to 0, 437, and 875 mg/m^3, respectively) for 103 weeks (NTP, 1990). To generate toluene vapor, the liquid material was heated, and the vapor diluted with nitrogen and mixed with the chamber ventilation air. An interim sacrifice was carried out at 15 months on control and 4524 mg/m^3 (1200 ppm) groups (10/sex/group) to conduct hematology and histopathology of the brain, liver, and kidney. Body weights were measured throughout the study. Gross necropsy and micropathology examinations were performed at the end of the study on all major organs including the nasal passage tissues (three sections), lungs, and mainstem bronchi. Mean body weights in both exposed groups were not different from controls for either sex. No exposure-related clinical signs were reported, and survival rate was similar for all groups. At the interim sacrifice, there was a mild-to- moderate degeneration in the olfactory and respiratory epithelium of the nasal cavity in 39/40 rats of the 600- and 1200-ppm groups compared with 7/20 controls. At the end of 2 years, there was a significant (p<0,05) increase in the incidence of erosion of the olfactory epithelium (males: 0/50, 3/50, and 8/49; females: 2/49, 11/50, and 10/50; at 0, 600, and 1200 ppm, respectively) and of degeneration of the respiratory epithelium (males: 15/50, 37/50, and 31/49; females: 29/49, 45/50, and 39/50; at 0, 600, and 1200 ppm, respectively) in the exposed animals. The females exposed to 600 and 1200 ppm also exhibited a significant increase in inflammation of the nasal mucosa (27/49, 42/50, and 41/50 at 0, 600, and 1200 ppm, respectively) and respiratory metaplasia of the olfactory epithelium (0/49, 2/50, and 6/50 at 0, 600, and 1200 ppm, respectively). A LOAEL of 2261 mg/m^3 toluene was determined for the concentration-dependent increase in erosion of the olfactory epithelium in male rats and the degeneration of the respiratory epithelium in both sexes. No NOAEL could be derived from this study.

ATSDR (2003)
Agency for Toxic Substances and Disease Registry

Derivation of a Minimal Risk Level (MRL):
Studies (Zavalic et al., 1998a; 1988c) demonstrated a statistically significant impairment of color vision in workers chronically exposed to 588 mg/m^3 (156 ppm) toluene compared with controls. When the data were adjusted to allow for the confounding effects of alcohol consumption and age, a significant difference due to toluene exposure was also reported for workers exposed to 132 mg/m^3 (35 ppm) toluene compared with controls. Uncertainty factors used for MRL derivation: 10 for use of a minimal LOAEL and 10 for human variability
MRL = 132 mg/m^3 x 5 days/7 days x 8 hours/24 hours ÷ 100 = 0.3 mg/m^3

Carcinogenic potential

There is no information from human studies that suggests that toluene has carcinogenic potential. Svensson et al. (1990) examined a cohort of 1020 toluene-exposed workers who had been employed for a minimum period of three months during the period 1925–1985. There were no significant increases in tumours and no cumulative dose–response relationship in workers with an exposure period of at least five years and a latency period of 10 years. Exposure to benzene had taken place up to the 1960s. Toluene has been shown, however, to hyperphosphorylate rat liver p53, a tumour suppressor gene (Dees and Travis, 1994). This observation may be of concern, since a reduced ability of p53 to suppress genetic errors may result in tumour formation.

Genotoxicity

An unequivocal evaluation of the genetic effects of occupational toluene exposure cannot be made because of the small numbers of individuals analysed and insufficient information on possible exposure to other chromosome-damaging agents (WHO, 1985). Recent data indicate that toluene induces clastogenic effects in pokeweed-mitogen-stimulated peripheral blood lymphocytes of printers (Nise et al., 1991). However, variations in exposure history preclude identification of an exposure–response relationship. Toluene exposure of printers was also highly correlated with an excess of chromatid breaks in peripheral lymphocytes compared to controls (Pelclova et al., 1990), although concurrent exposure to printing dyes as a factor cannot be excluded. No effects on sister chromatid exchange, cell cycle delay or cell mortality were observed in peripheral blood lymphocytes in volunteers exposed for three consecutive days to 189 mg/m^3 (50 ppm) (Richer et al., 1993). Previously, Bauchinger et al. (1982) found a significant increase in sister chromatid exchanges and chromosome aberrations in printers (smokers and nonsmokers relative to controls) exposed to toluene for more than 16 years. Even after two years of exposure cessation a higher incidence of aberrations was observed in exposed individuals compared to controls (Dudek et al., 1990).

Interactions with other chemicals

Exposure of volunteers to toluene 189 mg/m^3 and xylene 189 mg/m^3, both being often found together in mixtures such as paint thinners, resulted in decrements in reaction time in one of a battery of psychomotor and cognitive tests administered (Dudek et al., 1990). Toluene alone did not result in deficits in any of the tests. Similar levels of both solvents (189 mg/m^3 xylene, 151 mg/m^3 toluene) did not modify the conversion of either substance to its urinary metabolites (Kawai et al. 1992b; Tardif et al. 1991). At higher concentrations (302 or 566 mg/m^3 xylene, 358 or 566 mg/m^3 toluene), the blood and exhaled air concentrations of both solvents were increased compared to the controls exposed to either solvent alone, indicating that metabolism of both solvents was decreased by the coexposure paradigm (Tardif et al. 1991, 1992).

Ethanol ingestion during exposure of volunteers to a toluene level of 302 mg/m^3 (80 ppm) for 4,5 hours was found not to alter the occurrence or severity of the subjective symptoms associated with toluene alone (Iregren et al., 1986).

A number of studies with laboratory animals have shown that toluene interferes with the metabolism and toxicity of several chemicals, including ethanol, benzene, xylene, hexane and styrene (Chemical and engineering news, 1995; Plappert et al., 1994; Nylen et al., 1995)

Odour perception

Source: WHO, 1986
Odour threshold: 9,4 mg/m3

Source: American Industrial Hygiene Association, 1989
Characteristic : sour, burnt.
Odour Thresholds:
Detection: 6 mg/m3 ; range 0,6-140 mg/m3 (1,6 ppm; range 0,16 - 37 ppm)
Recognition: 41 mg/m3 ; range 7-260 mg/m3 (11 ppm; range 1,9 - 69 ppm)

Source: (Hoshika et al., 1993)
Barely perceptible concentration level of toluene: 3.5/4.2 mg/m^3 (in Japan/The Nederlands, respectively)
International comparison of odor threshold values of several odorants in Japan and in The Netherlands, given as the barely perceptible concentration level revealed striking similarities for hydrogen sulfide (in Japan 0.0005 ppm/in The Netherlands 0.0003 ppm), phenol (0.012/0.010), styrene (0.033/0.016), toluene (0.92/0.99), and tetrachloroethylene (1.8/1.2) but not for m-xylene (0.012/0.12). Such a similarity was not found with any other literature sources.

Summary of Toluene Dose Response Assessment

Exposure other than inhalation: Not relevant

Toxicokinetics: ~50% uptake of the inhaled amount

Health effect levels of short- and long-term exposure

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure						
151 EXP 369 1h-ADJ	377 EXP 923 1h-ADJ	CNS-mild, eyes, respiratory; impaired reaction time, headache, dizziness, feeling of intoxication, slight eye and nose irritation	volunteers, 6h	Andersen et al. 1983	OEHHA (1999); REL: 37 ATSDR (2003); MRL: 3.8
151 EXP	283 EXP	CNS; NOAEL: see above LOAEL: visual short term memory, visual perception and psychomotor skills	volunteers, 6-7h	NOAEL: Andersen et al. 1983 LOAEL: Echeverria et al. 1989	ECB (2003)
Long-term exposure						
151 EXP 27 ADJ	301 EXP 54 ADJ	CNS; decreased brain weight, dopamine receptor binding Supporting study: Neurobehavioral deficits	rats, 4w (supported by occupational, 5.7y)	Hillefors-Berglund et al. 1995; supported by Orbaek and Nise (1989), Foo et al. (1990)	OEHHA (1999); REL: 0.4
	332 EXP 118 ADJ	CNS; neurobehavioural deficits	Occupational, 5.7y	Foo et al. 1990	OEHHA (1999); WHO (2001); GV: 0.26; EPA-IRIS (1992); RfC: 0.4
	2261 EXP 437 ADJ 79 HEC	Respiratory system; nasal epithelium degeneration	rats, 2y	NTP, 1990	EPA-IRIS (1992)
	132 Study 31 ADJ	CNS; color vision impairment	Occupational, >6m	Zavalic et al. (1998a)	ATSDR (2003); MRL: 0.3

Carcinogenicity: IARC: 3 ; U.S.EPA: D ; No indications of carcinogenicity

Genotoxicity: No clear indication of genotoxicity

Odour threshold: Range (detection): 0.6 - 140 mg/m³ , GM: 6 mg/m³ (AIHA); 9.4 mg/m³ (WHO);
Barely perceptible concentration level of toluene: 3.5/4.2 mg/m³ (in Japan/The Nederlands, respectively;Hoshika et al., 1993)

Susceptible population: No evidence

Remarks: RD_{50}: 19 g/m³

6. Risk Characterization

Health hazard evaluation of short- and long-term exposure

Toluene has low acute toxicity. In humans experimentally exposed to toluene, concentrations of 283 mg/m^3 and above caused headache, dizziness, and feeling of intoxication, irritation and sleepiness. Furthermore, toluene causes impaired neuropsychological function, as demonstrated in performance tests (LOAEL: 283 mg/m^3). For acute effects a NOAEL of 150 mg/m^3 has been identified (Andersen et al. 1983) and will be taken forward to the risk characterisation. Dividing by an assessment factor of 10 for interindividual variation, the limit of exposure results in 15 mg/m^3 (see also Table 6.1), applied as a hourly average.

The LOAEL for long-term effects on the CNS from occupational studies is approximately 30 mg/m^3 after adjustment from intermittent to continuous exposure. Dividing by an assessment factor of 100 (10 for interindividual variation, 10 for use of a LOAEL rather than a NOAEL) a limit of exposure of 0.3 mg/m^3 is obtained (to be applied as a weekly average; see also Table 6.1), which should also be protective for reproductive effects (spontaneous abortions).

Limited data in humans indicate an increased risk for late spontaneous abortions at dose levels around 332 mg/m^3. Human data as well as studies in rats and limited data in mice provide evidence of similar developmental effects, i.e. lower birth weight, delayed postnatal development and developmental neurotoxicity. Only very high exposure levels were investigated in humans. In animals, the NOAEL for lower birth weight and delayed postnatal development is 2.3 g/m^3. A NOAEL for developmental neurotoxicity cannot be determined from the available studies. The LOAEL for this effect is 4.5 g/m^3.

There has been no indication that toluene is carcinogenic in bioassays conducted to date and the weight of available evidence indicates that it is not genotoxic.

Table 6.1: Derivation of toluene short- and long-term limits of exposure (EL)

	Effect level - mg/m^3		Assessment factor	EL mg/m^3	Toxicological endpoint
Short-term Exposure Limit	Human NOAEL Volunteers	150	10[b]	15	Impaired reaction time, headache, dizziness, feeling of intoxication, slight eye and nose irritation
Long-term Exposure Limit	Human LOAEL Occupational	30	100[ab]	0.3	CNS: color vision impairment

[a] not considering a NOAEL (10); [b] intraspecies variability (10)

Relevance for the EU-population exposure

Table 6.2: Percentage of population exposed beyond the derived EL and margins of safety

Available exposure data		EL derived	Margins of Safety (MOS)
Description (Study, Year)	N	0.3 mg/m^3	50th (90th)
Athens 30-h TWA (Expolis, 96-98)	42	5%	7 (1)
Basel 30-h TWA (Expolis, 96-98)	47	<	19 (9)
Helsinki 30-h TWA (Expolis, 96-98)	188	<	23 (7)
Milan 30-h TWA (Expolis, 96-98)	38	<	5 (2)
Oxford 30-h TWA (Expolis, 98-00)	40	<	26 (6)
Prague 30-h TWA (Expolis, 96-98)	46	<	5 (2)
England 28d-TWA (BRE, 97-99)	796	<	20 (6)
German Survey 48-h PEM (GerEs II, 1990-92)	113	5 %	4 (1)
Germany 4w-TWA (GerES IV pilot study, spring+summer 2001)	44	<	27 (9)
French National Survey 7d-TWA (IAQ observatory; 2003-04)	110	<	20 (5)
		Avg. MOS:	16 (5)

< out of the evaluation range (i.e. <5% of the environments investigated)

Result

Human effects on the central nervous system are considered as the most sensitive effects in both short- and long-term inhalatory exposure to toluene. Available exposure data indicate that the European population is not experiencing health effects of concern resulting from the exposure to toluene in their homes. Results from ten monitoring surveys show that toluene levels in the order of the established exposure limit of 300 μg/m^3 could be reached under worse-case conditions and in a limited number of urban residences. On average, median concentrations (90th percentile) were found to be 16 (5) times lower than the EL. Also, short-term exposures associated with human indoor activities are not expected to exceed the acute EL set here at 15.000 μg/m^3.

Xylenes (*ortho-*, *meta-* and *para-*)

Synonyms:	o-xylene (1,2-dimethylbenzene or 2-xylene),
	m-xylene (1,3-dimethylbenzene or 3-xylene),
	p-xylene (1,4-dimethylbenzene or 4-xylene, also noted as
	methyltoluene, benzene-dimethyl, dimethylbenzene)

CAS Registry Numbers:	95-47-6 o-xylene,
	108-38-3 m-xylene,
	106-42-3 p-xylene
Molecular Formula:	C_8H_{10}

1. Compound identification

Xylene is an aromatic hydrocarbon, which exists, in three isomeric forms: meta (m-), para (p-) and ortho (o-). Technical grade xylene contains a mixture of the three isomers. Xylenes are widely used in the chemical industry as solvents for products such as paints, inks, dyes, adhesives, pharmaceuticals, and detergents (HSDB, 2003). Approximately 92% of mixed xylenes is blended into gasoline as antiknock agents. It is also used in a variety of solvent applications, particularly in the paint and printing ink industries. Xylene is a colourless liquid at room temperature with an aromatic odour. All three isomers evaporate easily to the air from water. In soil and water, the meta and para isomers are biodegradable, but the ortho isomer is more persistent. p-Xylene is produced in the highest quantities in the U.S. for use in manufacture of plastics and polymer fibers including mylar and dacron (WHO 1997).

Acute (short-term) inhalation exposure to mixed xylenes in humans results in irritation of the eyes, nose, and throat, gastrointestinal effects, eye irritation, and neurological effects. Chronic (long-term) inhalation exposure results primarily in central nervous system (CNS) effects, such as headache, dizziness, fatigue, tremors, and incoordination; respiratory, cardiovascular, and kidney effects have also been reported. EPA has classified mixed xylenes as a Group D, not classifiable as to human carcinogenicity. (EPA 2003)

2. Physical and Chemical properties

	o-Xylene	m-Xylene	p-Xylene
Molecular weight (g/mol)	106.16	106.16	106.16
Melting point (°C; 101.3 kPa)	-25.2	-47.9	13.3
Boiling point (°C; 101.3 kPa)	144.4	139.1	138.3
Relative density (25°/4°C)	0.876	0.860	0.857
Solubility in water (mg/litre)	142	146	185

Conversion factors at 20 °C and 760 mm Hg:

1 ppm = 4.406 mg/m^3
1 mg/m^3 = 0.227 ppm

Sources: WHO 1997, Verschueren 2001, EPA/Cal. 2003.

3. Indoor Air Exposure assessment

Emission sources
The products that contain and may emit xylenes to indoor air are such as perfumes, pesticide formulations, pharmaceuticals, adhesives, paints, printed materials, rubber, plastics, leather, polyester fibres, film and fabricated items (IARC, 1989, ECETOC, 1986; Fishbein, 1988).

Outdoor sources of xylenes are facilities that produce or use xylenes, and exhaust gases from motor vehicles and through volatilisation from their use as solvents (EPA/Cal. 2003).

Indoor air and exposure concentrations

Mean indoor concentrations of m&p-Xylenes were more than twofold in Northern Europe (Helsinki), almost threefold in Central Europe (Basel, Praque) and almost twofold in Southern Europe (Milan), compared to respective ambient concentrations (Annex 3). Xylenes were the second most abundant compounds in indoor air in the EXPOLIS study, accounting for 18-27% of the target aromatics (Saarela et al 2003). The mean indoor concentrations tend to increase from north to south being lowest in Helsinki, 7.8 $\mu g/m^3$, and the highest in Milan, 37 $\mu g/m^3$. Lowest mean exposures to m&p-Xylenes were found in Helsinki, 25 $\mu g/m^3$ and the highest in Germany and Athens, 51 $\mu g/m^3$ and 55 $\mu g/m^3$, respectively. Personal exposures were clearly higher than indoor concentrations. The highest personal/indoor ratios were found in Basel and Helsinki, being over 5 and 3, respectively. Also in all other cities the personal/indoor ratio exceeded 1, suggesting the presence of important personal sources for m&p-xylenes.

Similar patterns were found for o-Xylene including the highest concentrations in exposures and also higher indoor concentrations compared to ambient levels. In general, concentrations of o-Xylene were lower than those of m&p-Xylenes.

TEAM studies carried out in the USA showed maximum 12-hour day time exposures to m&p-Xylenes as high as 1800 $\mu g/m^3$ and 460 $\mu g/m^3$ in New Jersey in 1981 (Wallace et al 1985) and in Los Angeles in 1987 (Wallace et al 1991), respectively. Simultaneous ambient air concentrations were typically 10 to 100 times lower. In California, also residential indoor air concentrations were measured showing a maximum 12-hour concentration of 170 $\mu g/m^3$. Personal exposure concentration in California showed similar values compared to European distributions.

Maximum 12-hour exposure, 160 $\mu g/m^3$, measured in the TEAM study in California (Wallace et al 1991) agreed also with European results (Figure). Instead maximum residential indoor concentration, 68 $\mu g/m^3$, was clearly higher than in European homes. In New Jersey, maximum daytime 12-hour exposure was as high as 830 $\mu g/m^3$ (Wallace et al 1985).

The cumulative distributions of the indoor and 48-hour personal exposure concentrations of m&p- xylenes are presented in Figure 3.1 and Figure 3.2, and source related short time concentrations are presented in Figure 3.3. m&p -Xylene concentrations caused by emissions from incense burning were studied by Lee and Wang (2004). Usually, concentrations caused by incense burning in an 18-m^3 chamber ranged from 0.5 $\mu g/m^3$ to 3.8 $\mu g/m^3$, but one type of incense caused a concentration of 21 $\mu g/m^3$. Brown (2002) studied short time (30-50 min) concentrations of m&p -Xylene in established and new buildings, reporting mean concentrations of 6.9 $\mu g/m^3$ and 30 $\mu g/m^3$ respectively. m&p -Xylene concentration in a new building decreased to 25 $\mu g/m^3$ and 2.8 $\mu g/m^3$ in 72 and 246 days respectively. Expected sources of m&p -Xylene in new buildings were building materials. Elke at al (1998) measured short time concentrations of m&p -Xylene inside buildings (60-min average), inside a train and a car (30-min average). The highest concentrations were found in a car, the second highest in a train and the lowest in a smoker day room.

Source related short time concentrations of o-Xylene are presented in Figure 3.4, and indoor air and personal exposure distributions in Figure 3.5 and Figure 3.6. o-Xylene concentrations caused by incense burning were typically less than 5 $\mu g/m^3$, but one type of incense caused a concentration of 96 $\mu g/m^3$. Short time (30-50 min) concentrations of o-Xylene in established and new buildings were 8.9 $\mu g/m^3$ and 32 $\mu g/m^3$ respectively. Concentration in a car was about the same level with a new building, but lower in a train and in a smoker day room. Due to the similar health outcomes, combined (m-, p-, and o-) indoor air Xylene concentration distributions are presented in Figure 3.7 to be used in the risk characterisation.
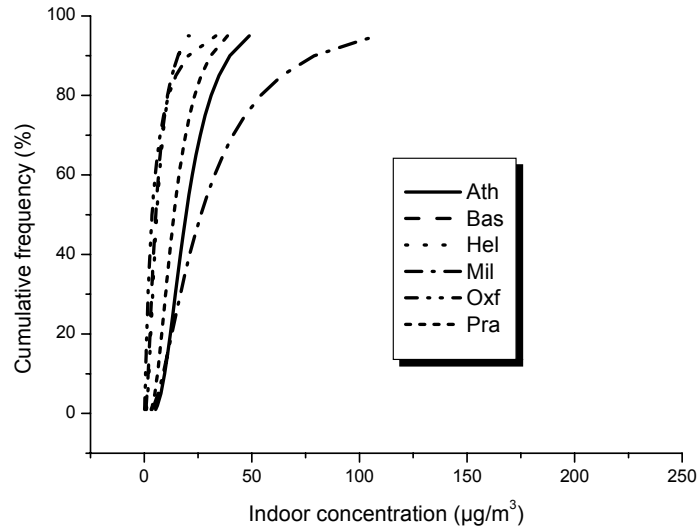
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of m&p – xylenes in Athens (Ath), Basel (Bas), Helsinki (Hel), Milan (Mil) Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002).
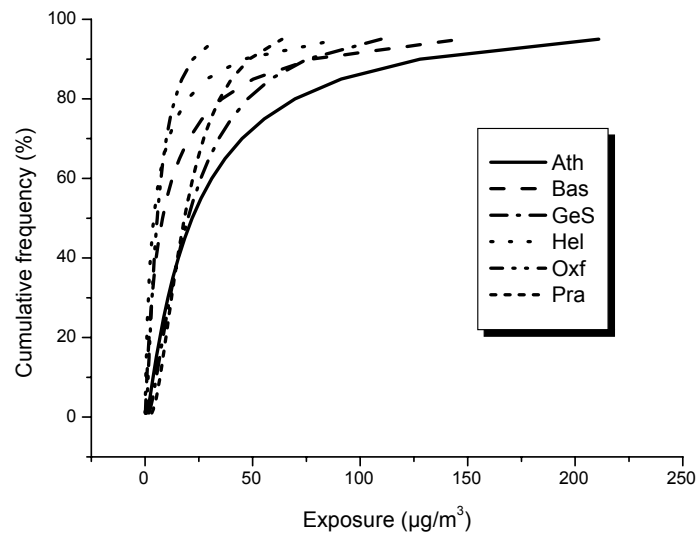
Figure 3.2. Cumulative frequency distributions of 48-hour personal exposure concentrations of m&p – xylenes in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean exposures of the German Survey GerES II (GeS) (Hoffman et al 2000).
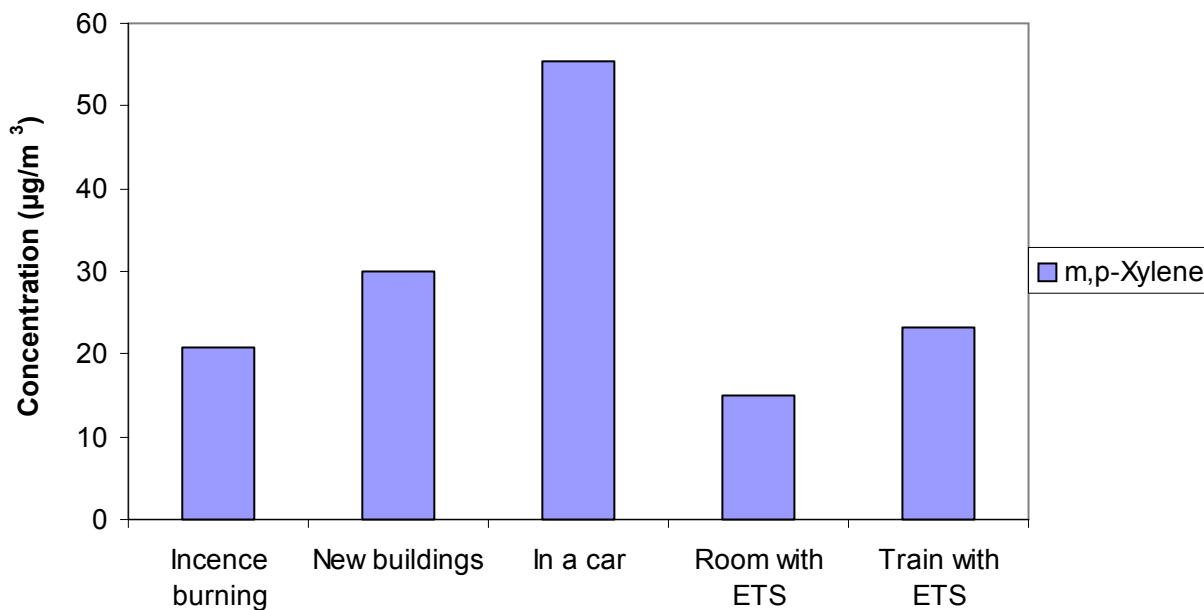
Figure 1. Short time m&p -Xylene concentrations related to specific microenvironments or emission sources.
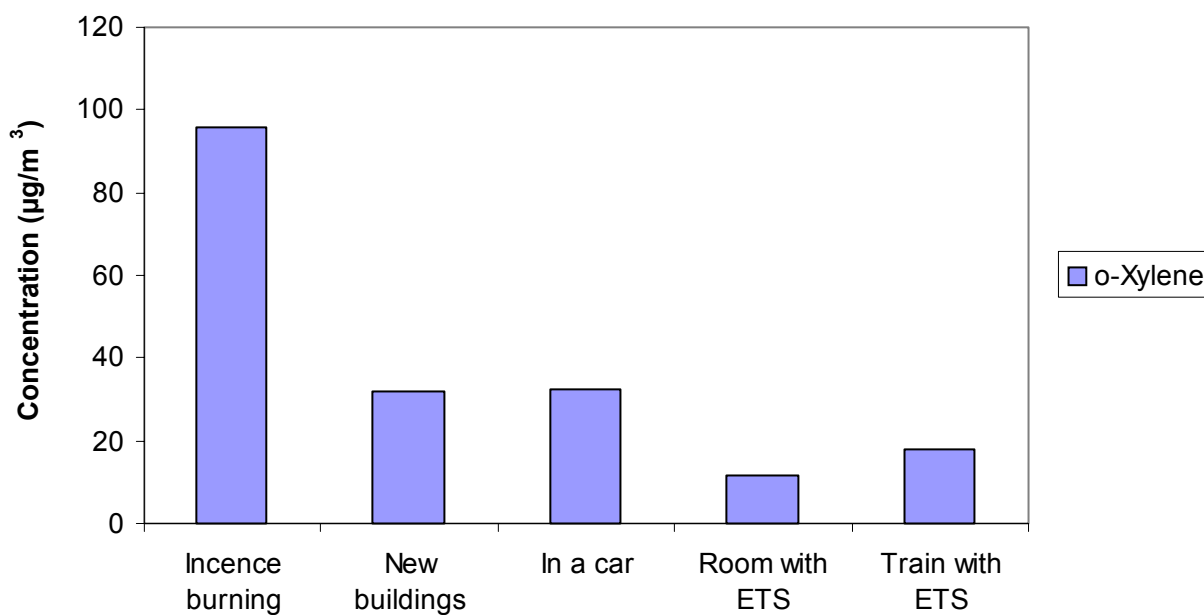
Figure 2. Short time o-Xylene concentrations related to specific microenvironments or emission sources.
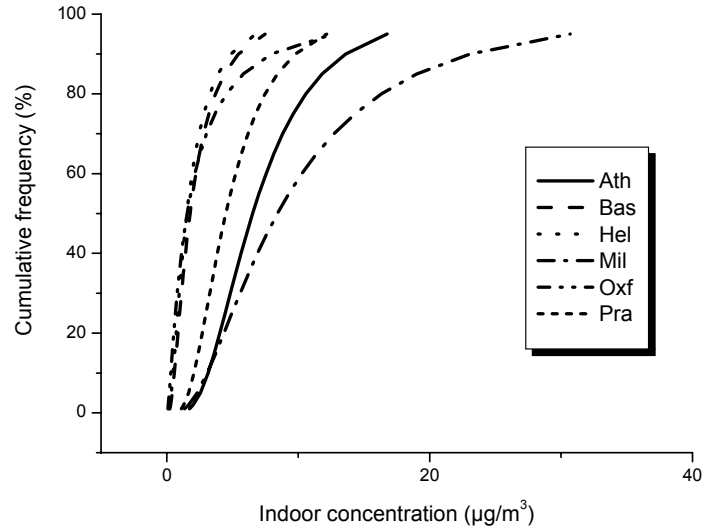
Figure 3.5. Cumulative frequency distributions of indoor air concentrations of o –Xylenes in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=38) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
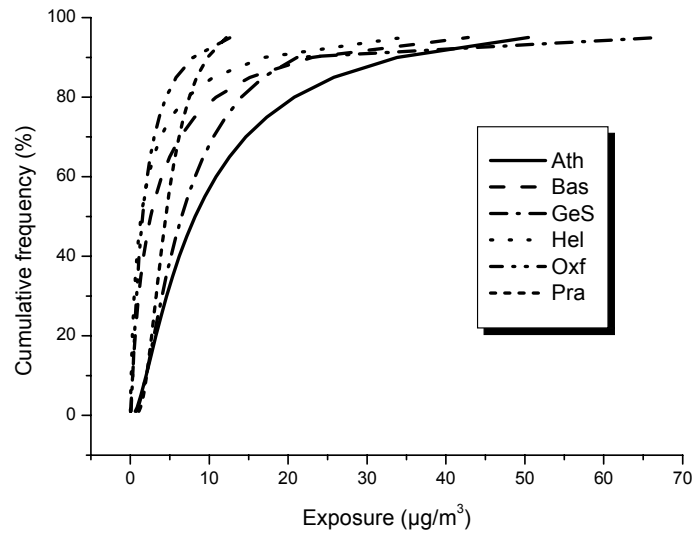
Figure 3.6. Cumulative frequency distributions of 48-hour personal exposure concentrations of o –xylenes in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean exposures of the German Survey GerES II (GeS) (Hoffman et al 2000).
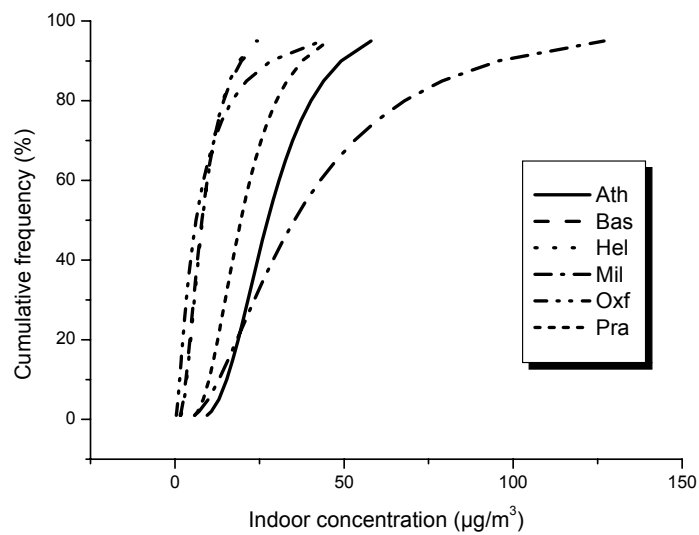
Figure 3.7. Cumulative frequency distributions of indoor air concentrations of m,p and o –Xylenes in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=38) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).

4. Toxicokinetics

Absorption

The blood/air partition coefficient for the three isomers range from 26.4 to 37.6 (Sato and Nakajima, 1979), indicating that xylenes entering the body would be readily absorbed into the blood.

Sedivec and Flek (1976a) made direct measurements of the level of absorption of xylenes by subjecting volunteers to 200 or 400 mg/m^3 of either individual isomers or mixtures of the three isomers of xylenes vapor for 8 hours without interruption and measuring the difference in the concentration of xylenes in the inspired air relative to the amount expired. The amount of the individual isomers absorbed over time was consistent for all three isomers and ranged from 62.4 to 64.2% of the inhaled volume, reflecting a high solubility of xylenes in blood.

Riihimäki and Savolainen (1980) conducted studies on human subjects both at rest and during exercise to measure the kinetics resulting from exposure to mixed xylenes. Healthy male subjects were exposed to xylene for 5 days, 6 hours per day with a 1-hour break at midday and then for an additional 1 to 3 days after a 2-day weekend break. The exposure scenarios included either constant exposure to 434 or 868 mg/m^3 (100 or 200 ppm) or fluctuating exposure with peaks of 868 or 1736 mg/m^3 (200 or 400 ppm) that lasted for 10 minutes. The subjects were either sedentary or exercising on a stationary bike for short periods of time. Regardless of the exposure scenario (constant or fluctuating or with different xylene concentrations), retention consistently remained around 60% (i.e., 60% of the inhaled xylene was retained in the blood and 40% was expired). The results indicate that partitioning of xylene between the tissues and the air occurs, but it is limited by the solubility in the tissue lipids and the rate of passive diffusion through the matrix. Overall, the lowest uptake rate was noted with 434 mg/m^3 exposure during sedentary conditions (22 µmol/min) and the highest uptake was seen with the fluctuating concentrations in which the peaks reached 1.7 mg/m^3 during exercise (266 µmol/min). Given the constant retention values, the two factors that appeared to control the total uptake of xylenes were the ambient concentration of xylene and ventilation rates of the subjects.

Further studies on xylene uptake by inhalation have been conducted by Ogata et al., 1970; Astrand et al., 1978; Senczuk and Orlowski, 1978; David et al., 1979.

Distribution

The K$_{ow}$ (octanol/water distribution coefficient) of xylene indicates that xylene is expected to partition primarily into tissues containing a higher proportion of neutral lipids, such as adipose, liver, and brain tissue.

In their study on the uptake and distribution of ethylbenzene and xylenes, Riihimäki and Savolainen (1980) found that 10–20% of the xylene was distributed to the adipose tissue. Adipose has the highest concentration of neutral fat and the highest affinity for xylene of all tissues. Therefore, once sequestered in adipose tissue, xylene is expected to have the lowest rate of metabolism, the slowest movement to blood, and the longest persistence in the body. The concentration of xylene in gluteal subcutaneous fat was about 10-fold higher than in venous blood following the last day of exposure (5 days exposure + weekend without exposure + 1 day of exposure).

Additional information on the distribution of xylenes in the body is available from Astrand et al. (1978), Engstrom and Bjurstrom (1978) and Kumarathasan et al. (1998).

Metabolism and elimination

Proposed metabolic pathways for o-xylene are shown in Figure 4.1 as a model for all xylene isomers. The principal metabolic fate involves oxidation of one of the methyl groups to a methylbenzoic acid derivative via methylbenzyl alcohol and methylbenzaldehyde intermediates. The methylbenzoic acid derivative is mostly conjugated to glycine, producing methylhippuric acid derivatives that can be excreted in urine. Conjugation to glucuronic acid is a minor pathway. Oxidation of the benzene ring to produce xylenols (i.e., dimethylphenols) is expected to be a negligible metabolic pathway, based on analysis of urinary metabolites. The liver is expected to be the principal site of metabolism for xylenes.

CH₂OH

o-methylbenzyl alcohol

Oxidation

*

o-xylene

expelled unchanged

exhalation (3–5%)
urine (trace amounts)

o-xylene

COOH

o-methyl benzoic acid (o-toluic acid)

glucuronidation (trace amounts)**

glucuronide conjugate of o-methyl benzoic acid

glycine conjugation (95–97%)

CONHCH₂COOH

o-methyl hippuric acid (o-toluric acid)
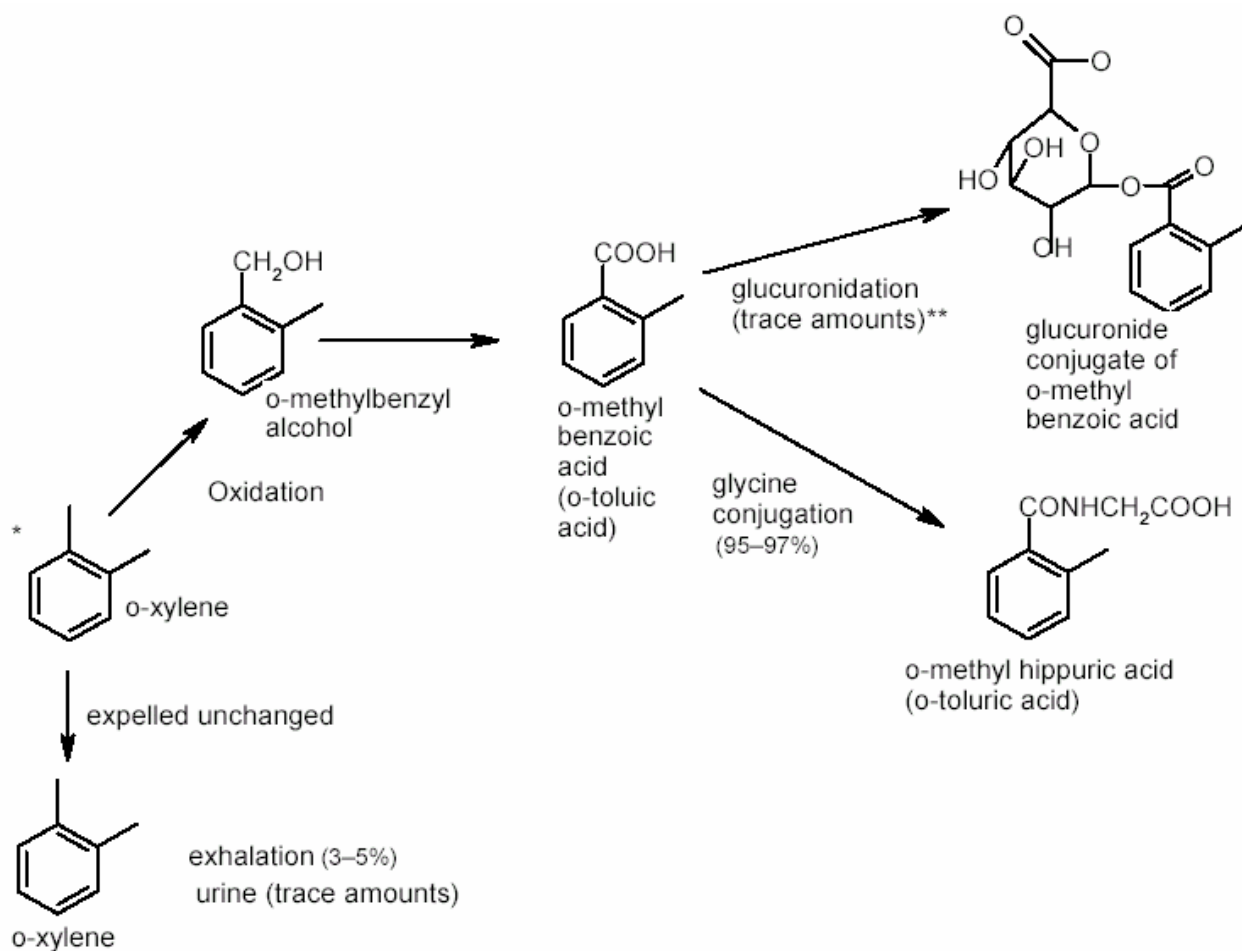
* o-xylene used as a model for all isomers of xylene
** significant production of glucuronic derivative under conditions of high levels of administration

Figure 4.1. Metabolic pathways for xylenes (Source: Adapted from Ogata et al., 1970; Riihimaki and Savolainen, 1980; Riihimaki, 1979; Bray et al., 1949; Sedivec and Flek, 1976a,b; Ogata et al., 1980; Carlsson, 1981; Senszuk and Orlowski, 1978; David et al., 1979)

Riihimäki and Savolainen (1980), in their study of inhalation exposure to xylene by human subjects under sedentary and physically active conditions, found that 95% of the eliminated xylene was in the form of methylhippuric acid, with the remainder lost as unmetabolized xylene in expired air. No deposition sites, such as lipid-rich tissues, were studied. The excretion rate of xylene from the blood followed biphasic, first-order kinetics, with the initial loss of xylene having a half-life in the venous blood of 0.5–1 hour, followed by a second phase with a half-life of 20–30 hours. The authors proposed that the two phases representing the rapid loss of xylene from the blood, mostly through conversion to methylhippuric acid followed by excretion, indicate that well-perfused organs reach equilibrium within minutes and muscles reach equilibrium within a few hours, whereas adipose tissues may require several days of continuous exposure to reach equilibrium.

Riihimäki (1979) evaluated the metabolism and excretion of xylene and toluene derivatives in humans. A volunteer was administered a single dose of 7.4 mmole m-methylbenzoic acid or 7.8 mmole m-methylhippuric acid. Urine was analyzed for 30 hours following administration for the presence of metabolites. All of the administered xylene derivatives appeared in urine as methylhippuric acid, indicating that, under the conditions of this study, once xylene has been oxidized to methylbenzoic acid, the only route of metabolism was as the glycine conjugate.

Following methylbenzoic acid administration, only methylhippuric acid was detected in urine. The rate of loss (i.e, excretion rate) was greater with the methylhippuric acid treatment than with the methylbenzoic acid treatment. This study is limited by the fact that it was conducted on a single individual. The determination that loss of xylene is limited

by the availability of glycine suggests that the rate of utilization of glycine may vary with such factors as age and nutritional status of the individual.

5. Health effects

Differences among individual xylene isomers

Although differences in the toxicity of individual xylene isomers have been detected, no consistent pattern following inhalation exposure has been identified.

In rats exposed by inhalation for 30 minutes, EC_{50}s (the concentrations producing half-maximal decreases in response rate) for effects on an operant behavior test showed a relative toxicity order of o-xylene > p-xylene > m-xylene, whereas EC_{50}s for a motor performance test showed a toxicity order of p-xylene > o-xylene = m-xylene. The range of EC_{50} values among the isomers was not considered large (Moser et al., 1985). In contrast, p-xylene - but not o-xylene or m-xylene - altered audiometric variables in rats exposed to 7800 mg/m³, 6 hours per day, 5 days per week, for 13 weeks (Gagnaire et al., 2001). A different order of toxicity has been described for effects on motor coordination (rotarod performance) in rats following 6 hours exposure to concentrations of 13 g/m³ xylenes: o-xylene > m-xylene > p-xylene (Korsak et al., 1990). All three isomers caused decreased fetal body weights in rats exposed for 24 hours per day on GDs 7–14, but o-xylene caused the effect at a lower concentration (1.5 g/m³) than did either p-xylene or m-xylene (3 g/m³) (Ungváry et al., 1980). No available studies compare the potency of isomers for affecting neurological endpoints following subchronic or chronic inhalation exposure. Other animal studies that have examined the toxicity of individual xylene isomers are: Condie et al. (1988) ; Molnár et al. (1986); Fang et al. (1996).

Humans are most likely exposed to a mixture of xylenes rather than to individual isomers. In commercial mixtures the m-isomer usually predominates (44–70% of the mixture) (Fishbein, 1988; ATSDR, 1995), the exact composition of the isomers depending on the source. In technical product ethylbenzene is commonly present at significant levels. Thus, most of the environmental and occupational exposures and toxicological studies are conducted on this mixture of xylenes containing ethylbenzene. Other minor contaminants of xylenes include toluene and C_9 aromatic fractions.

Effects of short-term exposure

Despite its structural similarity to benzene, xylene does not influence hematopoiesis. Acute controlled exposure studies have identified self-reported symptoms of irritation (e.g., watering eyes and sore throat) or neurological impairment (e.g., mild nausea, headache, altered reaction time, altered balance) as potential effects of xylene following inhalation exposure in humans.

Levels of 434-868 mg/m³ (100-200 ppm) are associated with nausea and headache; 868-2170 mg/m³ (200-500 ppm) with dizziness, irritability, weakness, vomiting, and slowed reaction time; 3480-43000 mg/m³ (800-10000 ppm) with lack of muscle coordination, giddiness, confusion, ringing in the ears, and changes in sense of balance; and 43000 mg/m³ (>10000 ppm) with loss of consciousness (HESIS, 1986). Other documented neurological effects include impaired short term memory, impaired reaction time, performance decrements in numerical ability, and impaired equilibrium (dizziness) and balance (Carpenter et al., 1975; Dudek et al., 1990; Gamberale et al., 1978; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979; Savolainen and Riihimaki 1981; Savolainen et al., 1979b; 1984; 1985b).

Results from subchronic animal studies identify neurological impairment and possible developmental effects as potential health hazards from repeated inhalation exposure. Scattered reports of body weight changes and adaptive liver changes in animals are available, but the results do not consistently identify these effects as potential health hazards.

Nelson et al. (1943) exposed 10 healthy human volunteers for periods of 3 to 5 minutes to estimated concentrations of 434 or 869 mg/m³ (100 or 200 ppm) technical grade xylene. The subjects reported eye, nose, and throat irritation at 869 mg/m³ but not at 434 mg/m³. A significant area of uncertainty arising from the Nelson et al. (1943) study is the use of estimated rather than measured exposure concentrations. Carpenter et al. (1975) evaluated eye irritation in 7 human volunteers exposed for 15 minutes to 460, 1000, 2000, or 3000 mg/m³. One volunteer noted mild throat discomfort at 460 mg/m³, but not at 2000 mg/m³. No subjects reported eye irritation at 460 mg/m³ (106 ppm).

Hastings et al. (1984) exposed 50 healthy individuals to 434, 869, or 1738 mg/m³ (100, 200, or 400 ppm) mixed xylenes for 30 minutes to evaluate eye, nose, and throat irritation. The percent of subjects reporting eye irritation was 56 for

controls (clean air), 60 at 434 mg/m^3, 70 at 869 mg/m^3, and 90 at 1738 mg/m^3. The authors concluded there was no effect on eye irritation at 434 mg/m^3 because the incidence of irritation was as low as the control group. The data from Nelson *et al* (1943), Carpenter *et al.* (1975), and Hastings *et al.* (1984) taken together are consistent with a human NOAEL for eye irritation of about 434 mg/m^3 (100 ppm) for at least a 30-minute exposure.

Exposure of sedentary or exercising subjects to a 10-minute peak concentration of 1736 mg/m³ (400 ppm) resulted in significantly increased uncontrolled body sway in these subjects. Exposure to 868 mg/m³ (200 ppm) xylene for up to 5 hours did not result in CNS disturbances measured by increased body sway (Laine *et al.*, 1993). Riihimaki and Savolainen (1980) reported that a single 5-minute exposure to 1736 mg/m³ xylene (isomeric form unknown) resulted in lightheadedness and inebriation similar to alcohol intoxication. Deleterious effects on EEG, reaction time, body balance, and manual dexterity were found in 8 healthy volunteers following exposure to 434 mg/m³ (100 ppm) m-xylene for 6 hours/day for 6 days (Savolainen *et al.*, 1980a).

Exposure of 15 volunteers to 434 mg/m³ technical xylene mixed with 20% ethylbenzene for 70 minutes, including 30 minutes of exercise, resulted in significant impairments in short-term memory and other CNS performance tests (Gamberale *et al.*, 1978). Because ethylbenzene may have contributed to the CNS effects, definitive conclusions about the effects of xylene cannot be drawn from this study.

Nine healthy male volunteers were exposed to 868 mg/m³ m-xylene 4 hours a day, with or without exercise for 10 minutes at the beginning of each session (Savolainen *et al.*, 1985a). There were no changes in reaction times, but average and maximal body sway were decreased in a concentration dependent manner. Exercise had a sway reducing effect. Male volunteers were exposed to 868 mg/m³ m-xylene vapor for 4 hours a day, either sedentary or with 10 minutes periods of exercise twice a day (Savolainen *et al.*, 1984). The body balance of the subjects was impaired in the anteroposterior direction. Nine healthy male students were exposed to 868 mg/m³ m-xylene for 4 hours per day at 6-day intervals over 6 consecutive weeks (Savolainen *et al.*, 1982a). Body sway tended to decrease with exposure. Only minor electroencephalographic effects were noted on 4 hour exposures to 868 mg/m³ m-xylene exposure, and no other adverse effects were noted (Seppalainen *et al.*, 1991).

Five volunteers were exposed to 174 mg/m³ (40 ppm) xylene for 7 hours/day, 3 consecutive days/week in an inhalation chamber. There was an 11-day break between each 3-day session (Mergler and Beauvais, 1992). Individual differences in olfactory perception thresholds for toluene were noted, but there was no effect of exposure duration.

Summary of short-term exposure effect levels

NOAEL mg/m^3	LOAEL mg/m^3	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m^3
430 Study 215 1h-ADJ	860 Study 430 1h-ADJ	Eye, nose and throat irritation (subjective reports of)	Volunteers, 30min	Hastings *et al.*, 1984 (supp.from other studies)	OEHHA (1999); REL: 22

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Acute Reference Exposure Level
Study	Hastings *et al.*, 1984 (with support from Carpenter et al., 1975; Nelson *et al.*, 1943)
Study population	50 healthy human volunteers
Exposure method	30 minute exposures to 430, 860 or 1720 mg/m^3 xylene (technical grade)
Critical effects	subjective reports of eye, nose, and throat irritation
LOAEL	860 mg/m^3
NOAEL	430 mg/m^3 (100 ppm)
Exposure duration	30 minutes
Equivalent 1 hour concentration	50 ppm (C1 * 60 min = 100 ppm * 30 min)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10

Cumulative uncertainty factor   10
Reference Exposure Level   5 ppm (22 mg/m³, 22,000 μg/m³)

With the possible exception of inconsistently observed developmental endpoints, irritation is the lowest reported human health effect for xylene.

Effects of long-term exposure

Information on the toxicity of xylenes to humans is almost exclusively limited to case reports of acute exposures and studies of occupational exposures in which persons often inhaled a mixture of hydrocarbon solvents 8 hours per day, 5-6 days per week. These studies often have incomplete information on the airborne concentrations of xylene and other hydrocarbons. One study examining chronic effects in humans from inhalation of predominantly mixed xylenes was identified (Uchida *et al.*, 1993) and one 4-week controlled exposure study examining the effects of p-xylene exclusively was identified (Hake *et al.*, 1981).

Xylene exposure has been associated with effects in a number of organ systems including the lungs, skin and eyes; neurological system; heart and gastrointestinal system; kidney; and possibly the reproductive system.

Pulmonary effects have been documented in occupational exposures to undetermined concentrations of mixed xylenes (and other solvents) and include labored breathing and impaired pulmonary function (Hipolito 1980; Roberts *et al.*, 1988). High levels of xylene exposure for short periods are associated with irritation of the skin, eyes, nose and throat (ATSDR, 1995). Chronic exposure to xylenes has been associated with eye and nasal irritation (Uchida *et al.*, 1993).

Although the mechanism by which xylenes exert their toxic effects on the nervous system and developing fetus are not completely understood, some theories exist. The CNS toxicity observed during exposure to high concentrations has been attributed to the liposolubility of xylenes in the neuronal membrane (Desi et al., 1967; Savolainen and Pfaffli, 1980; Tahti, 1992). It has been suggested that xylenes disturb the actions of proteins essential to normal neuronal function. Changes in levels of various neurotransmitters and lipid composition have been observed in several brain areas following acute- and intermediate-duration exposure to xylenes (Andersson et al., 1981; Honma et al., 1983). It is unclear whether these represent direct effects of xylenes or are secondary changes resulting from nonspecific CNS depression. Some authors have also suggested that metabolic intermediates such as arene oxides or methylbenzaldehyde may be responsible for the toxic effects of xylenes (Savolainen and Pfaffli, 1980).

Chronic exposure to xylenes (with other hydrocarbons) has been associated with cardiovascular and gastrointestinal effects. Heart palpitations, chest pain, and abnormal electrocardiogram were noted (Hipolito, 1980; Kilburn *et al.*, 1985) as were effects on the gastrointestinal system producing nausea, vomiting and gastric discomfort in exposed workers (Goldie, 1960; Hipolito, 1980; Uchida *et al.*, 1993; Klaucke *et al.*, 1982; Nersesian *et al.*, 1985).

Results of studies of renal effects of xylene are mixed and come from case reports and occupational studies where multiple chemical exposures are common. The effects from subchronic exposure documented by Hake *et al.* (1981) and from chronic exposure documented by Uchida *et al.* (1993) did not include renal effects. However, Morley *et al.* (1970) found increased BUN and decreased creatinine clearance; Martinez *et al.* (1989) found distal renal tubular acidemia; Franchini *et al.* (1983) found increased levels of urinary β-glucuronidase; and Askergren (1981, 1982) found increased urinary excretion of albumin, erythrocytes, and leukocytes.

Available data (NTP, 1986; Wolfe et al., 1988a, b; Condie et al., 1988) do not consistently identify the kidney and the liver as a sensitive target of xylenes in animals.

Reproductive effects were documented by Taskinen *et al.* (1994) who found increased incidence of spontaneous abortions in 37 pathology and histology workers exposed to xylene and formaldehyde in the work place. The multiple chemical exposures and the small number of subjects in this study limit the conclusions that can be drawn as to reproductive effects of xylene in humans.

No hematological effects have been identified in studies where exposure was to xylene only. Previous studies identifying hematological effects included known or suspected exposure to benzene (ATSDR, 1995; ECETOC, 1986). One series of case reports identified lowered white cell counts in two women with chronic occupational exposure to xylene (Hipolito, 1980; Moszczynsky and Lisiewicz, 1983; 1984), although they may also have had multiple chemical exposures.

Groups of male volunteers (1 to 4 subjects/group) were exposed to p-xylene in a controlled-environment chamber for 7.5, 3, or 1 hr/day, 5 days/week for 4-weeks (Hake *et al*., 1981). The p-xylene concentration was changed on a weekly

basis starting at 434 mg/m^3 (100 ppm) the first week, followed by 87 mg/m^3, 652 mg/m^3, and 434 mg/m^3 (20, 150, and 100 ppm on average, with a range of 50 to 150 ppm) over subsequent weeks. In addition, groups of female volunteers (2 or 3/group) were exposed to 434 mg/m^3 p-xylene for 7.5, 3, or 1 hr/day for 5 days. The volunteers acted as their own controls, with exposure to 0 ppm p-xylene occurring for two days (males) or one day (females) the week before and the week after the xylene exposures. No serious subjective or objective health responses, including neurological tests, cognitive tests and cardiopulmonary function tests were observed. Odor was noted, but the intensity decreased usually within the first hour of exposure. The authors concluded that p-xylene may have a weak irritating effect on the soft tissues starting at 434 mg/m^3, but overall, the small sample size and high variability among the volunteers made all results difficult to interpret.

The Uchida *et al.* (1993) study included a relatively large number of workers studied, exposure for an average of 7 years to xylenes predominately and a comprehensive set of medical examinations to document potential effects. A survey of 994 Chinese workers involved in the production of rubber boots, plastic coated wire and printing processes employing xylene solvents was carried out. The survey consisted of fitting individual workers with diffusive samplers for an 8 hour shift. At the end of the 8 hour shift the samplers were recovered for analysis of solvent exposure, and urine samples were collected for analysis of xylene metabolites. The following day workers answered a questionnaire concerning subjective symptoms, and blood and urine were collected for analysis. Out of this group of xylene-exposed workers, 175 individuals (107 men and 68 women) were selected for further study and analysis based on completion of their health examinations and on results from diffusive samplers showing that xylene constituted 70% or more of that individual's exposure to solvents in the workplace. The control population consisted of 241 (116 men and 125 women) unexposed workers from the same factories or other factories in the same region, of similar age distribution, of similar time in this occupation (average of 7 years), and having a similar distribution of alcohol consumption and cigarette usage. The xylene-exposed and unexposed groups were given health examinations which evaluated hematology (red, white, and platelet cell counts, and hemoglobin concentration), serum biochemistry (albumin concentration, total bilirubin concentration, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, leucine aminopeptidase, lactate dehydrogenase, amylase, blood urea nitrogen, creatinine), and subjective symptoms (survey of symptoms occurring during work and in the previous three months).

Results of analysis of the diffusive samplers showed that workers were exposed to a geometric mean of 61.7 ± 11.3 mg/m^3 (14.2 ± 2.6 ppm) xylene (arithmetic mean of 92.5 ± 93.8 mg/m^3). This was broken down into geometric means of 5.2 mg/m^3 o-xylene, 31.7 mg/m^3 m-xylene, 16.5 mg/m^3 p-xylene, 14.8 mg/m^3 ethyl benzene, and 4.5 mg/m^3 toluene. n-Hexane was rarely present and no benzene was detected. Analysis of data from the health examinations found no statistically significant difference ($p<0.10$) between hematology and serum biochemistry values for xylene-exposed and unexposed populations. The frequency of an elevated ratio of aspartate aminotransferase to alanine transferase and of elevated ratio of alkaline phosphatase to leucine aminopeptidase was significantly ($p<0.01$) higher in exposed men than in the control population of men.

Results of the survey of subjective symptoms found differences in symptoms occurring during work and during a similar analysis over the preceding three month period, apparently related to effects on the central nervous system and to local effects on the eyes, nose and throat. The frequency of five symptoms experienced during work was significantly ($p<0.01$) elevated in either xylene-exposed men or women including: dimmed vision, unusual taste, dizziness, heavy feeling in the head, and headache. The frequency of four symptoms experienced during work were significantly ($p<0.01$) elevated in both men and women including irritation in the eyes, nasal irritation, sore throat, and floating sensation. Ten subjective symptoms occurring in the previous three months were significantly ($p<0.01$) elevated in exposed men and women including nausea, nightmare, anxiety, forgetfulness, inability to concentrate, fainting after suddenly standing up, poor appetite, reduced grasping power, reduced muscle power in the extremities, and rough skin. Dose dependency appeared to exist for 3 subjective symptoms noted during work: irritation in the eyes, sore throat, floating sensation, and for one symptom occurring in the last three months, poor appetite.

Although the human evidence for persistent effects on the nervous system or other persistent effects from repeated inhalation exposure to xylenes is inadequate, results from animal studies more clearly identify potential persistent neurological impairment and possible developmental effects as potential health hazards from repeated inhalation exposure.

A number of subchronic studies in animals provide evidence for neurological effects following repeated inhalation exposure to xylenes (Korsak et al., 1992; Korsak et al., 1994; Gralewicz et al. 1995; Gralewicz and Wiaderna 2001; Pryor et al. 1987; Nylén and Hagman 1994).

The lowest exposure level that produced changes in a number of neurological endpoints was identified in several studies of rats exposed to 434 mg/m^3 (100 ppm) m-xylene, 6 hours per day, 5 days per week, for 3 months. These studies observed statistically significant changes in neurobehavioral tests conducted at least 24 hours following cessation of

exposure: decreased rotarod performance indicative of impaired motor coordination (Korsak et al., 1992, 1994), decreased spontaneous motor activity (Korsak et al., 1992), impaired radial maze performance indicative of a learning deficit (Gralewicz et al., 1995), and decreased latency to paw lick in the hot plate test, indicating increased sensitivity to pain (Korsak et al., 1994).

At a lower exposure level (217 mg/m^3 by the same exposure protocol), rats showed statistically significantly decreased latency in the paw lick response but no statistically significant effects on rotarod performance (Korsak et al., 1994). Rats exposed to 434 mg/m^3 m-xylene by the same daily protocol for a shorter duration (4 weeks) displayed no statistically significant changes in tests of radial maze performance, open-field activity, or active avoidance, but paw lick latency was increased in the hot plate test and step-down time was shortened in 1/6 trials in the passive avoidance test (Gralewicz and Wiaderna, 2001).

There are no available studies on the possible developmental toxicity of inhaled xylenes in humans, but a number of studies have examined standard developmental toxicity endpoints and neurobehavioral endpoints in offspring of animals exposed to mixed xylenes or individual xylene isomers.

The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer doses of 1520 or 3041 mg/m^3 (350 or 700 ppm) 24 hours per day (Ungváry et al., 1980) or at mixed xylenes concentration of 3388 mg/m^3 (780 ppm) 24 hours per day (Ungváry and Tátrai, 1985) and increased abortions in rabbits exposed to 1000 mg/m^3 (230 ppm) 24 hours per day (Ungváry and Tátrai, 1985). These effects, although of concern, occurred at concentrations above those at which neurobehavioral effects were reported in adult animals.

Hass and Jakobsen (1993) exposed groups of 36 pregnant Wistar rats to clean air or 868 mg/m^3 (200 ppm) of xylene for 6 h/day on days 4-20 of gestation. There was no sign of maternal toxicity and no decrease in fetal weights and no increase in soft-tissue or skeletal malformations. A large increase in the incidence of delayed ossification of the *os maxillare* of the skull, however, was observed (53% of experimental fetuses as opposed to 2% of the controls). Potential neurological/muscular changes measured as performance on a rotorod were also noted upon testing of 2-day-old rat pups.

Developmental and reproductive effects

There are no available studies on the possible developmental toxicity of inhaled xylenes in humans, but a number of studies have examined standard developmental toxicity endpoints and neurobehavioral endpoints in offspring of animals exposed to mixed xylenes or individual xylene isomers.

The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer doses of 1500 or 3000 mg/m^3 (350 or 700 ppm) 24 hours per day (Ungváry et al., 1980) or at mixed xylenes concentration of 3400 mg/m^3 (780 ppm) 24 hours per day (Ungváry and Tátrai, 1985) and increased abortions in rabbits exposed to 1000 mg/m^3 24 hours per day (Ungváry and Tátrai, 1985). These effects, although of concern, occurred at concentrations above those at which neurobehavioral effects were reported in adult animals.

Gestational exposure of animals to xylenes has resulted in neurodevelopmental effects (Hass et al., 1995; 1997; Hass and Jakobsen, 1993) and other possible developmental effects (Ungváry et al., 1980; Ungváry and Tátrai, 1985), but only at levels above those at which neurobehavioral effects in adult male rats were reported.

Exposure of pregnant rats for 6 hours/day on days 4-20 of gestation to 870 mg/m³ (200 ppm) technical (mixed) xylene resulted in significantly increased incidence of delayed ossification of the skull in the offspring (Hass and Jakobsen, 1993). The rat pups exposed prenatally to 870 mg/m³ xylene displayed significantly decreased motor performance during adolescence. However, a study using p-xylene showed no significant embryotoxic or developmental effects on the CNS as measured by acoustic startle response in rats following exposure to 7000 mg/m³ throughout gestation (Rosen *et al.*, 1986).

Summary of long-term exposure effect levels

NOAEL	LOAEL	Target system; critical effects	Remarks	Study	Source; Ref.

mg/m³	mg/m³				Value mg/m³
	61.7 Study 22.1 ADJ	Eye irritation, sore throat, floating sensation, poor appetite	Occupational, 7y	Uchida et al. 1993	OEHHA (1999); REL: 0.7 ATSDR (1995); MRL: 0.6
217 EXP 39 HEC	434 EXP 78 HEC	CNS; impaired motor coordination	Rats, 3m	Korsak et al., 1994	EPA-IRIS (2003); RfC: 0.1
	868 EXP	Developmental	Rats	Hass and Jakobsen, 1993	RIVM (1999)
	250 EXP 177 HEC	Developmental	Rats	Ungváry and Tátrai, 1985	Health Canada (1991); TC: 0.18

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Chronic Reference Exposure Level (REL):

Study	Uchida *et al.* (1993)
Study population	175 xylene-exposed factory workers and control population of 241 factory workers
Exposure method	Inhalation
Critical Effects	Dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite.
LOAEL	14.2 ppm (geometric mean of exposure concentrations)
NOAEL	Not applicable
Exposure continuity	8 hr/d (10 m3/day occupational inhalation rate), 5 d/wk
Exposure duration	Occupational exposure for an average of 7 years
Average occupational exposure	5.1 ppm for LOAEL group (14.2 x 10/20 x 5/7)
Human equivalent concentration	5.1 ppm for LOAEL group
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.7 mg/m3; 700 µg/m3) for mixed xylenes or for total of individual isomers

A number of issues are important in considering the uncertainty associated with this REL. For ATSDR (1995), the animal and human toxicity data suggest that mixed xylenes and the different xylene isomers produce similar effects, although different isomers are not equal in potency for producing a given effect. Therefore exposure of workers to a mix of xylenes in the Uchida *et al.* (1993) study would be expected to generate a similar spectrum of responses as exposure to single isomers, however the intensity of particular effects could be different.

The use of a neurological endpoint for derivation of a REL is supported by the large number of inhalation and oral studies, which associate neurological effects with xylene exposure. ATSDR (1995) indicates that neurological effects are a sensitive endpoint. The observation that floating sensation is apparently related to dose, further supports the concept that this subjective symptom related to neurological effects was due to xylene exposure.

A UF of 3, rather than 10, was applied for the LOAEL to NOAEL extrapolation due to the generally mild adverse effects observed and the principally low incidence (<50%) of the effects. A factor of 1 was used for subchronic uncertainty. Although the average occupational exposure was only 7 years, there were 176 xylene-exposed workers of average age 29.7 ± 9.0 years (arithmetic mean ± SD) for whom, according to the report, there had been essentially no change in workplace in their working life. Thus, many workers would likely have been exposed for more than 8.4 years, the cut-off point for chronic human exposure. Another issue is the use of diffusive samplers in the Uchida *et al.* (1993) study. These samplers provide a time weighted average concentration of hydrocarbon and cannot indicate the maximum concentrations a worker is exposed to. It is unknown whether peak concentrations alter the response to xylenes in humans.

For comparison with the proposed REL of 0.7 mg/m³ (200 ppb) based on human studies, (1) the free-standing NOAEL of 339 mg/m³ (78 ppm) o-xylene obtained by Jenkins *et al*. (1970) in rats and guinea pigs continuously exposed for 90

days was used to estimate a REL based on animal data. Use of an RGDR of 1, a subchronic UF of 3, an interspecies UF of 3, and an intraspecies UF of 10 results in a REL of 3.5 mg/m^3 (800 ppb) for o-xylene for systemic effects. (2) Tatrai *et al*. (1981) found a free standing LOAEL of 4761 mg/m^3 (1096 ppm) o-xylene for body weight gain in male rats exposed every day for 8 hours. Time adjustment to continuous exposure and use of an RGDR of 1, a LOAEL UF of 3 for a mild effect, an interspecies UF of 3, and an intraspecies UF of 10 result in a REL of 17.4 mg/m^3 (4000 ppb). (3) Ungváry and Tátrai (1985) exposed mice by inhalation continuously to 521 or 1000 mg/m^3 (120 or 230 ppm) xylene for 24 h/day on days 7-15 of gestation. The LOAEL was 1000 mg/m^3 and the NOAEL was 521 mg/m^3. No time adjustment is needed. Use of an RGDR of 1, a subchronic UF of 1, an interspecies UF of 3, and an intraspecies UF of 10 results in a REL of 17.4 mg/m^3 (4000 ppb) for xylene for developmental effects.

ATSDR (2003)
Agency for Toxic Substances and Disease Registry

Derivation of the Minimal Risk Level (MRL):
Using the most well defined Uchida et al. (1993) study, ATSDR estimated a chronic inhalation MRL of 0.6 mg/m^3 from a LOAEL of 61 mg/m^3 in humans for less serious effects; divided by a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

U.S.EPA - IRIS (2003)
Integrated Risk Information System

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical effect	Experimental doses*	UF	MF	RfC
Impaired motor coordination (decreased rotarod performance) Subchronic inhalation study in male rats (Korsak et al., 1994)	NOAEL: 50 ppm NOAEL$_{(HEC)}$: 39 mg/m^3 LOAEL: 100 ppm LOAEL$_{(HEC)}$: 78 mg/m^3	300	1	0.1 mg/m^3

Conversion Factors and Assumptions - MW = 106.17. Assuming 25°C and 760 mmHg, NOAEL(mg/m^3) = 50 ppm x 106.17/24.45 = 217 mg/m^3. NOAEL$_{[ADJ]}$ = 217 mg/m^3 x 6 hrs/day x 5 days/7 days = 39 mg/m^3. The NOAEL$_{[HEC]}$ was calculated for extrarespiratory effects of a Category 3 gas (U.S. EPA, 1994). Blood/gas partition coefficients: $H(b/g)_{rat}$ = 46.0; $H(b/g)_{human}$=26.4 (Tardif et al., 1995). $(H_{b/g})_{rat}/(H_{b/g})_{human}$ =1.7; value of 1 is used when the ratio is >1 (U.S. EPA, 1994). NOAEL*$_{[HEC]}$ = NOAEL$_{[ADJ]}$ x $(H_{b/g})_{rat}/(H_{b/g})_{human}$ = 39 mg/m^3.

The subchronic rat study by Korsak et al. (1994) was selected as the principal study for derivation of the RfC. A NOAEL of 217 mg/m^3 (50 ppm) and a LOAEL of 434 mg/m^3 (100 ppm) were identified for decreased rotarod performance (impaired motor coordination). This neurologic test was administered 24 hours after termination of the exposure period, when xylenes would be expected to have been eliminated from the body. Other subchronic rat studies provide support for the finding that 434 mg/m^3 exposure produces statistically significant changes in a number of neurological endpoints: decreased rotarod performance (Korsak et al., 1992), decreased spontaneous motor activity (Korsak et al., 1992), and impaired radial maze performance indicative of a learning deficit (Gralewicz et al., 1995).

Additional support for 434 mg/m^3 as an exposure level that may produce mild neurologic deficits comes from the report (Gralewicz and Wiaderna, 2001) that rats exposed to 434 mg/m^3 m-xylene for 4 weeks showed shortened step-down time in 1/6 trials in the passive avoidance test 50 days postexposure. These studies collectively identify 434 mg/m^3 as the lowest reliable subchronic animal LOAEL and 217 mg/m^3 as a NOAEL for deficits in neurologic endpoints.

The NOAEL of 217 mg/m^3 was duration adjusted to 39 mg/m^3, and a NOAEL[HEC] of 39 mg/m^3 was calculated on the basis of species differences in blood/gas partition coefficients. The NOAEL[HEC] of 39 mg/m^3 was divided by a total UF of 300 ($10^{1/2}$ x 10 x $10^{1/2}$ x $10^{1/2}$; 3 for animal-to-human extrapolation using default dosimetric adjustments, 10 for intrahuman variability, 3 for extrapolation from subchronic to chronic duration, and 3 for deficiencies in the data base, including lack of studies in two species [available studies are predominantly in male rats] and a two-generation reproductive toxicity study) to give the RfC of 0.1 mg/m^3. Alternative approaches using available PBPK models to extrapolate rat exposure concentrations to HECs arrived at similar points of departure for the RfC as the NOAEL[HEC] of 39 mg/m^3.

Health Canada (1991)

Determination of a critical effect:

In inhalation studies conducted to date, xylenes have not been teratogenic but have induced fetotoxic effects, sometimes at doses below those that were toxic to the mothers. With the exception of unconfirmed results reported by Mirkova et al. (1983), the lowest concentration of xylenes reported to induce fetotoxic effects in the absence of maternal toxicity in available investigations was 500 mg/m^3. At this concentration, in an incompletely documented study, moderate embryotoxic effects such as retardation of skeletal development and of body weight increase were observed in the offspring of rabbits exposed continuously on days 7 to 20 of gestation to xylenes of unspecified composition (Ungváry and Tátrai, 1985). In rats, maternal toxicity and fetotoxicity were observed following exposure to 250 mg/m^3 on days 7 to 15 of pregnancy, the lowest concentration administered, indicating that rats may be a more sensitive species (Ungváry and Tátrai, 1985).

Derivation of a tolerable concentration (TC):
Inhalation is considered to be the most important route of exposure to xylenes for the general public. A provisional tolerable concentration (TC) for xylenes has been derived on the basis of the results of studies in animal species exposed by inhalation. Based on reported effect levels, developmental toxicity was considered the critical endpoint. The lowest concentration at which fetotoxic effects in the absence of maternal toxicity have been observed following exposure by inhalation to xylenes was 500 mg/m^3 in rabbits in a limited study (Ungváry and Tátrai, 1985); maternal and fetal toxicity were observed in rats at the lowest administered concentration (250 mg/m^3).

A provisional TC of 0.18 mg/m^3 has been derived, therefore, on the basis of the lowest LOEL (250 mg/m^3) for meaningful effects reported in a bioassay of adequate quality (though documentation was incomplete) in the most sensitive species (Ungváry and Tátrai, 1985). This was adjusted for the ratio of inhalation volume to body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg]. An uncertainty factor of 1000 was applied [10 for intraspecies variation, 10 for interspecies variation, 10 for LOEL rather than NOEL (although observed effects at the LOEL were only moderately fetotoxic; documentation was also limited)]. No additional factor was incorporated for the limited period of exposure since fetotoxic effects occur at doses below those which induce adverse effects in subchronic and chronic studies.

The lowest concentration of the individual xylene isomers reported to induce adverse effects in studies in animal species following inhalation is 150 mg/m^3, in which embryo- and fetotoxic effects were observed in the absence of maternal toxicity following continuous exposure of pregnant rats to p-xylene on days 7 to 14 of gestation (Ungváry et al., 1980). This is only slightly less than the LOEL used above in the derivation of a TC for xylenes (177 mg/m^3).

Carcinogenic potential and genotoxicity

Associations between occupational exposure to xylenes and increased risk of leukemia (Arp et al., 1983; Wilcosky et al., 1984), non-Hodgkin's lymphoma (Wilcosky et al., 1984), and cancer of the rectum (Gérin et al., 1998), colon (Gérin et al., 1998), or nervous system (Spirtas et al., 1991) have been reported. However, a number of limitations preclude the usefulness of these data, including small sample sizes, no quantified exposure concentrations, and/or concurrent exposures to other solvents.

Adequate human data on the carcinogenicity of xylenes are not available and the available animal data are inconclusive as to the ability of xylenes to cause a carcinogenic response. Evaluations of the genotoxic effects of xylenes have consistently given negative results.

The genotoxicity of commercial xylenes and all three individual isomers has been studied and the results are, for the most part, negative (IARC, 1989). All studies cited in the GENE-TOX database are negative with the exception of one study for which no conclusion was drawn. Xylenes are not mutagenic in bacterial test systems with Salmonella typhimurium (Bos et al., 1981; Florin et al., 1980; NTP, 1986) and Escherichia coli (McCarroll et al., 1981) or in cultured mouse lymphoma cells (Litton Bionetics, 1978). Xylenes do not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (Anderson et al., 1990) or cultured human lymphocytes (Gerner-Smidt and Friedrich, 1978), chromosomal aberrations in rat bone marrow (Litton Bionetics, 1978), micronuclei in mouse bone marrow (Mohtashamipur et al., 1985), or sperm head abnormalities in rats (Washington et al., 1983). Technical grade xylenes, but not o- and m-xylene, are weakly mutagenic in Drosophila recessive lethal tests (Donner et al., 1980). No increase in the frequency of sister chromatid exchanges was observed in peripheral lymphocytes in individuals exposed to xylenes in an occupational setting (Haglund et al., 1980; Pap and Varga, 1987) or an experimental setting (Richer et al., 1993).

Interactions with other chemicals

The interaction of xylene with alcohol, drugs (aspirin, phenobarbitol), and various solvents (1,l,ltrichlorethane, benzene, toluene, ethylbenzene, methyl ethyl ketone) has been evaluated in experimental studies with humans and animals. Xylene has a high potential to interact with numerous substances because the isomers induce microsomal enzymes in the liver (Blanchard and Morris 1994; Liira et al. 1991), while microsomal enzymes in the lungs are inhibited by xylene exposure (Blanchard and Morris 1994; Elovaara et al. 1987; Pate1 et al. 1978; Silverman and Schatz 1991; Toftgard and Nilsen 1982). Which enzymes will be affected is isomer dependent. For example, m-xylene is a more potent inducer of P-450 2B enzymes than p-xylene (Backes et al. 1993). The isomer differences, as well as organ differences in effects on xenobiotic metabolizing enzymes, make it difficult to predict the interaction of xylene with other substances.

Acute inhalation exposure to a mixture of toluene and xylene resulted in more than additive respiratory and central nervous system toxicity (Korsak et al. 1988, 1992). Elevated blood levels of xylene and toluene and decreased excretion of the major metabolites of xylene and toluene in the urine (Tardif et al. 1992) suggest mutual metabolic inhibition. However, simultaneous exposures in humans indicate that a threshold exists for this interaction (Tardif et al. 1991). No increase in blood levels of these substances was observed during combined exposures to 50 ppm toluene and 40 ppm xylene over 3 consecutive days, whereas increases in blood levels and levels in exhaled air were observed during a combined 4-hour exposure to 95 ppm toluene and 80 ppm xylene. Thus, combined exposures at below threshold level are unlikely to produce greater than additive toxicity (Tardif et al. 1991). A physiologically based toxicokinetic modeling study using rat data suggests that the interaction between toluene and xylene is competitive, with toluene a more potent inhibitor of xylene metabolism than xylene is of toluene metabolism (Tardif et al. 1993a, 1993b).

Exposure to xylene combined with benzene or ethylbenzene may also produce mutual inhibition of the metabolism of both solvents (Engstrom et al. 1984; Nakajima and Sato 1979b). Ethylbenzene is found in commercial xylene. In contrast, ethyl acetate exposure in combination with exposure to m-xylene caused a reduction in blood xylene levels (Freundt et al. 1989).

Possibly because of competition for the enzymes involved in conjugation with glycine during the concurrent metabolism of m-xylene and aspirin by human volunteers, saturation of the conjugation pathway occurred that led to decreases in the metabolism of both aspirin and m-xylene (Campbell et al. 1988). Administration of aspirin to pregnant rats during inhalation exposure to xylene caused greater than additive potentiation of maternal and fetal toxic effects (Ungváry 1985). This was postulated to be due to the interference with metabolism of aspirin by xylene and vice versa.

Inhalation of m-xylene following pretreatment with phenobarbital was associated with both increased pulmonary retention of m-xylene and increased urinary excretion of m-methylbenzoic acid (David et al. 1979). Surprisingly, inhalation of m-xylene and l,l,l-trichloroethane has been associated with slight improvements in certain psychophysiological parameters, including reaction time and equilibrium in humans as compared with pre-exposure measurements (Savolainen et al. 1982a, 1982b), and impairment in others such as visual evoked potentials and equilibrium (Savolainen et al. 1982a; Seppalainen et al. 1983).

Ethanol appears to inhibit the metabolism of xylene, resulting in elevated blood levels of xylene and decreased excretion of methylhippuric acid (Elovaara et al. 1980; Riihimaki et al. 1982a, 1982b; Romer et al. 1986; Savolainen 1980; Savolainen et al. 1978, 1979b, 1980b). A kinetic study in rats (Kaneko et al. 1993) suggests that ethanol inhibition of xylene metabolism occurs only at high concentrations (500 ppm). Paradoxically, ethanol pretreatment causes additive effects with xylene in inducing microsomal enzymes in the liver (Wisniewska-Knypl et al. 1989). This would enhance the metabolic capacity of the liver and modify biological effects of other chemicals that are either detoxified or converted to toxic metabolites by the microsomal enzymes. In summary, it cannot be stated with certainty whether alcohol and xylene would interact to produce synergistic or antagonistic effects in humans and animals because there are reasons why both would occur.

Odour perception

Source: ATSDR (1995)
Odor thresholds in air
Mixture: 4.3 mg/m^3 (1.0 ppm)
m-isomer: 16 mg/m^3 (3.7 ppm)
o-isomer: 0.34-0.74 mg/m^3 (0.08–0.17 ppm)
p-isomer: 2.0 mg/m^3 (0.47 ppm)

Source: Carpenter et al. (1975)
Mixed xylenes: 4.3 mg/m^3 (1 ppm) (detection)

Source: AIHA (1989)
Mixture:: 87 mg/m^3 (20 ppm) (detection);: 174 mg/m^3 (40 ppm) (recognition)
m-Xylene: 1.5 – 4.8 mg/m^3 (0.35 - 1.1 ppm) (detection)
o-Xylene: 23 mg/m^3 (5.4 ppm) (detection)
p-Xylene: 9.1 mg/m^3 (2.1 ppm) (detection)

Summary of Xylenes Dose Response Assessment

Exposure other than inhalation: not relevant

Toxicokinetics: ~60% uptake of the inhaled amount (no difference among isomers); accumulates in adipose tissue of chronically exposed

Health effect levels of short- and long-term exposure

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
430 Study 215 1h-ADJ	860 Study 430 1h-ADJ	Eye, nose and throat irritation (subjective reports of)	Volunteers, 30min	Hastings *et al.*, 1984 (supp.from other studies)	OEHHA (1999); REL: 22
Long-term exposure					
	61.7 Study 22.1 ADJ	Eye irritation, sore throat, floating sensation, poor appetite	Occupational, 7y	Uchida et al. 1993	OEHHA (1999); REL: 0.7 ATSDR (1995); MRL: 0.6
217 EXP 39 HEC	434 EXP 78 HEC	CNS; impaired motor coordination	Rats, 3m	Korsak et al., 1994	EPA-IRIS (2003) ; RfC: 0.1
	868 EXP	Developmental	Rats	Hass and Jakobsen, 1993	RIVM (1999)
	250 EXP 177 HEC	Developmental	Rats	Ungváry and Tátrai, 1985	Health Canada (1991); TC: 0.18

Carcinogenicity: IARC: 3; inadequate evidence in both humans and experimental animals

Genotoxicity: Studies consistently negative

Odour threshold: Mixture of isomers: 4.3 mg/m³ (ATSDR, Carpenter); 0.25 - 0.3 mg/m³ (Devos)

Susceptible population: No evidence

Remarks: RD_{50}: 6.1 g/m³; Although differences in the toxicity of individual xylene isomers have been detected, no consistent pattern following inhalation exposure has been identified; nevertheless, human exposure most likely occurs to the mixture of isomers

6. Risk Characterization

Health hazard evaluation of short- and long-term exposure

Animal and human toxicity data suggest that mixed xylenes and the different xylene isomers produce similar effects, although different isomers are not equal in potency for producing a given effect. Therefore exposure to a mix of xylenes in occupational studies would be expected to generate a similar spectrum of responses as exposure to single isomers, however the intensity of particular effects could be different.

The use of a neurological endpoint for the derivation of an exposure limit EL is supported by the large number of inhalation and oral studies, which associate neurological effects with xylene exposure. The observation that floating sensation is apparently related to dose, further supports the concept that this subjective symptom related to neurological effects was due to xylene exposure.

Using a well defined occupational study (Uchida et al. (1993), a chronic inhalation EL of 0.2 mg/m^3 was derived from a LOAEL of 62 mg/m^3 in humans for generally mild adverse effects observed and principally low incidence (<50%). This LOAEL was adjusted to 22 mg/m^3 accounting for intermittent to continuous exposure and divided by a total assessment factor of 100 (10 for use of a LOAEL and 10 for human variability). The endpoint considered was: dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite.

An acute EL was derived refering on a study on volunteers and subjective reports of eye, nose, and throat irritation as shown in Table 6.1.

Table 6.1: Derivation of short- and long-term exposure limits (EL)

	Effect level - mg/m^3		Assessment factor	EL mg/m^3	Toxicological endpoint
Short-term Exposure Limit	Human NOAEL Volunteers	200	10[b]	20	Eye, nose and throat irritation (subjective reports of)
Long-term Exposure Limit	Human LOAEL Occupational	22	100[ab]	0.2	Dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite

[a] not considering a NOAEL (10); [b] intraspecies variability (10)

Relevance of EU-population exposure to xylenes

Table 6.2: Percentage of population exposed beyond the derived EL and margins of safety

Available exposure data		Xylenes EL	Margins of Safety (MOS)
Description (Study, Year)	N	0.2 mg/m^3	50th (90th)
Athens 30-h TWA (Expolis, 96-98)	42	<	7 (4)
Basel 30-h TWA (Expolis, 96-98)	47	<	25 (10)
Helsinki 30-h TWA (Expolis, 96-98)	188	<	25 (10)
Milan 30-h TWA (Expolis, 96-98)	38	<	6 (2)
Oxford 30-h TWA (Expolis, 98-00)	40	<	32 (7)
Prague 30-h TWA (Expolis, 96-98)	46	<	10 (5)
German Survey 48-h PEM (GerEs II, 1990-1992)	113	<	10 (3)

French National Survey 7d-TWA (IAQ observatory; 2003-04)	102	<	20 (5)
		Avg. MOS:	18 (6)

< out of the evaluation range (i.e. <5% of the environments investigated);

Result

A chronic exposure limit of 200 μg/m^3 has been derived based on generally mild adverse effects associated with CNS and increase in the prevalence of eye irritation and sore throat. The results of eight monitoring surveys indicate that background levels of xylenes in European residences are of no concern to human health since median (90th percentile) levels are, on average, 20 (6) times lower than the EL established. Acute exposure data indicate that it is very unlikely that xylenes emissions associated with human indoor activities would generate levels in the order of the proposed short-term EL of 20 mg/m^3, considered protective for irritative effects in the general population. Although human exposure most likely occurs to the mixture of xylene isomers, animal and human toxicity data suggest that mixed xylenes and the different xylene isomers produce similar effects.

7. Aromatic compounds: Comparison of relevant data

Short-term exposure : derivation of limits of exposure (EL)

	Effect level - mg/m^3		Assessment factor	EL mg/m^3	Toxicological endpoint
Toluene	Human NOAEL Volunteers	150	10[b]	15	Impaired reaction time, headache, dizziness, feeling of intoxication, slight eye and nose irritation
Styrene	Human NOAEL Volunteers	217	100[bc]	2	Eye and throat irritation
Xylenes	Human NOAEL Volunteers	200	10[b]	20	Eye, nose and throat irritation (subjective reports of)

[a] not considering a NOAEL (10); [b] intraspecies variability (10) ; [c] susceptible population (10)

Long-term exposure : derivation of limits of exposure (EL)

	Effect level - mg/m^3		Assessment factor	EL mg/m^3	Toxicological endpoint
Toluene	Human LOAEL Occupational	30	100[ab]	0.3	CNS: color vision impairment
Styrene	Human LOAEL Occupational	25	100[ab]	0.25	CNS; neuropsychological tests: reaction time, s/l term logic memory, s/l term verbal memory, digit-symbol association, block design and figure identification.
Xylenes	Human LOAEL Occupational	22	100[ab]	0.2	Dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite

[a] not considering a NOAEL (10); [b] intraspecies variability (10) ; [c] susceptible population (10)

Percentage of population exposed beyond given threshold limits

EXPOSURE DATA		Toluene EL	Styrene EL	Xylenes EL	Aromatic HC Mixture
Description (Study, Year)	N	0.3 mg/m^3	0.25 mg/m^3	0.2 mg/m^3	refer to text*
Athens 30-h TWA (Expolis, 96-98)	42	5 %	<	<	20%
Basel 30-h TWA (Expolis, 96-98)	47	<	<	<	<
Helsinki 30-h TWA (Expolis, 96-98)	188	<	<	<	<
Milan 30-h TWA (Expolis, 96-98)	38	<	<	<	35%
Oxford 30-h TWA (Expolis, 98-00)	40	<	<	<	5%
Prague 30-h TWA (Expolis, 96-98)	46	<	<	<	15%
England 28-d TWA (BRE, 2002)	796	<	n.a.	n.a.	
German Survey 48-h PEM (GerEs II, 1992-93)	113	5 %	<	<	
French National Survey 7d-TWA (IAQ observatory; 2003-04)	102 - 110	<	<	<	

< out of the evaluation range (i.e. <5% of the environments investigated);
* see reciprocal calculation procedure

The reciprocal calculation approach for mixtures

A further element is included, based on a ACGIH approach commonly used in occupational settings to describe Threshold Limit Values (TLVs) resulting from the exposure to solvent mixtures. Supposing the additivity of substances having similar toxicologic effects, an exposure limit for aromatic hydrocarbons could be defined as follows :

$$[Benzene]/EL_{Benz} + [Toluene]/EL_{Tol} + [Styrene]/EL_{Styr} + [Xylenes]/EL_{Xyls} \leq 1$$

with EL_i= single Exposure Limits considering neurologic endpoints

In order to consider overall neurologic endpoints, the following critical effects and limits were chosen for benzene and the xylenes (toluene and styrene were still classified as neurologic toxicants in the present RA).
Benzene: increased rapid response time, Animal LOAEL: 2.5 mg/m^3, Assessment factor: 100, EL: 0.025
Xylenes: impaired motor coordination, Animal NOAEL: 39 mg/m^3, Assessment factor: 100, EL: 0.4

Figure 6.1: Cumulative frequency distribution of EXPOLIS data, applying the reciprocal calculation approach on a mixture of four aromatic hydrocarbons

Neurological Endpoint:
Animal LOAEL$_{Benz}$= 2.5 mg/m^3 TC = 0.025 mg/m^3
Human LOAEL$_{Tol}$= 31 mg/m^3 GL = 0.3 mg/m^3
Human LOAEL$_{Styr}$= 25 mg/m^3 GL = 0.25 mg/m^3
Animal NOAEL$_{Xyls}$= 39 mg/m^3 TC = 0.4 mg/m^3

TC = tolerable concentration
GL = indoor guideline value proposed
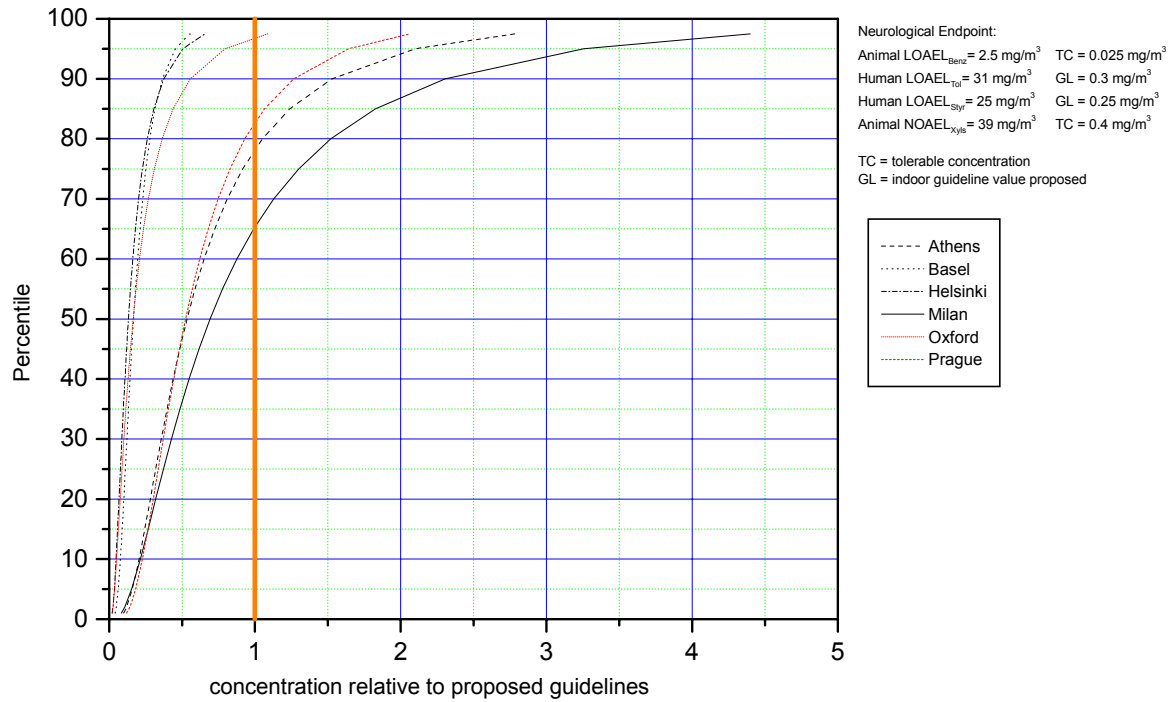
Styrene

Synonyms: phenethylene, phenylethene, phenylethylene, styrol, styrole, styrolene, vinylbenzene, vinylbenzol, cinnamene, cinnamol

CAS Registry Numbers: 100-42-5
Molecular Formula: C_8H_8

1. Compound identification

Styrene is a colourless, viscous liquid with a pungent odour. It is one of the most important monomers, worldwide because of its common use in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and in the reinforced plastics industry. Styrene has been produced since the 1920s by catalytic dehydrogenation of ethylbenzene.

2. Physical and Chemical properties

Molecular weight (g/mol)   104.15
Melting point (°C)   -30.6
Boiling point (°C)   145.2
Density (at 20 °C, 1 atm)   0.91
Relative density (air =1)   3.6
Solubility: slightly soluble in water, soluble in ethanol
                                  and very soluble in benzene and petroleum ether

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 4.323 $\mu g/m^3$
1 $\mu g/m^3$ = 0.231 ppb

Sources: (WHO 1983, WHO 2000, Verschueren 2001, EPA/Cal 2003)

3. Indoor Air Exposure assessment

Emission sources

Styrene exposures, at levels of milligrams per day, have been measured in the manufacture of styrene-based plastics and rubbers and fibre glass-reinforced polyester products and at much higher levels in the glass fibre-reinforced plastics industry. General population is typically exposed to levels of micrograms per day resulted from inhalation of ambient air and cigarette smoke, emissions from newly installed carpets containing a styrene-butadiene rubber latex adhesive, and from intake of food that has been in contact with styrene-containing polymers (WHO, 1983, IARC 1994, IARC 2000, EPA/Cal 2003).

Natural styrene sources are such as cinnamic acid containing plants, e.g. balsamic trees, and a by-production of fungal and microbial metabolism. Ambient air concentration of styrene is relatively low compared with toluene and xylene, because of its reactivity with ozone to yield irritants such as benzaldehyde and peroxides such as peroxybenzyol nitrate, which is a potent eye irritant. (WHO 2000).

Indoor air and exposure concentrations

Usually indoor styrene concentrations were low, but higher than respective outdoor concentrations ranging 1-6 $\mu g/m^3$ and 1-2 $\mu g/m^3$, respectively (Table 4.0.1). Arithmetic mean in Milan was an exception, being as high as 30.3 $\mu g/m^3$ due to few extremely high data points. Indoor concentrations were at the same level or higher in Helsinki and Prague, but less than one half in Athens compared to personal exposures. Probably occupational emissions caused this difference in Athens, because concentrations in workplaces were clearly higher, 7.1 $\mu g/m^3$, than residential indoor concentrations (Annex 3, Jantunen et al 1999).

In Northern America styrene concentrations in outdoor air have been generally <1 $\mu g/m^3$. In an Canadian study, carried out in 1988–1990, the mean concentrations at the ambient 18 sites ranged from 0.09 to 2.35 $\mu g/m^3$. In indoor air the mean concentrations were slightly higher (<1–6 $\mu g/m^3$). Smoking has been found a significant contributor to indoor concentrations of styrene. The styrene content of cigarette smoke has been reported to be 18–48 μg/cigarette (WHO 1983, WHO 2003). Nazaroff and Singer (2002) assessed average daily residential exposures to styrene in ETS for US non-smokers who live with smokers. Using exposure–relevant emission factors and assuming the mean consumption of 20 cigarettes smoked per day, they assessed a concentration of 0.6 $\mu g/m^3$ being caused by ETS.

Lee and Wang (2004) studied styrene emissions from incense burning in the chamber (18 m^3) tests. They found maximum styrene concentrations peaking up to 13 $\mu g/m^3$ during incense burning.

Cumulative distributions of the indoor concentrations of styrene in some European cities are presented in Figure 3.1 and distributions of 48-hour personal exposures in Figure 3.2.
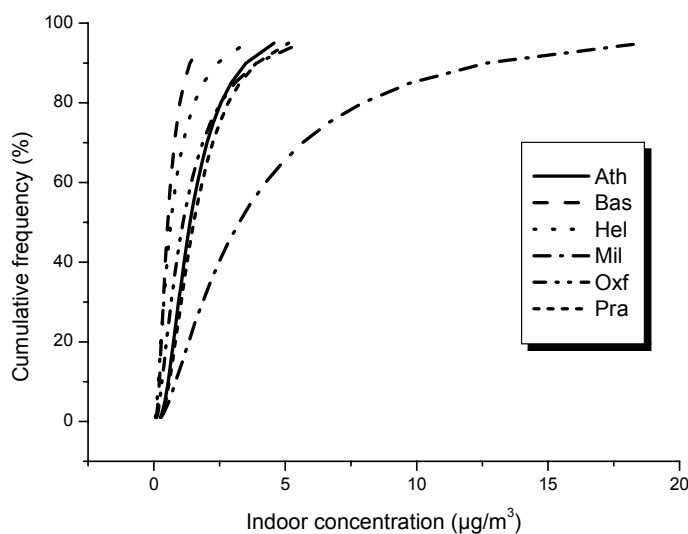
Figure 3.1. Cumulative frequency distributions of 30-hour indoor air concentrations of styrene in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=40) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
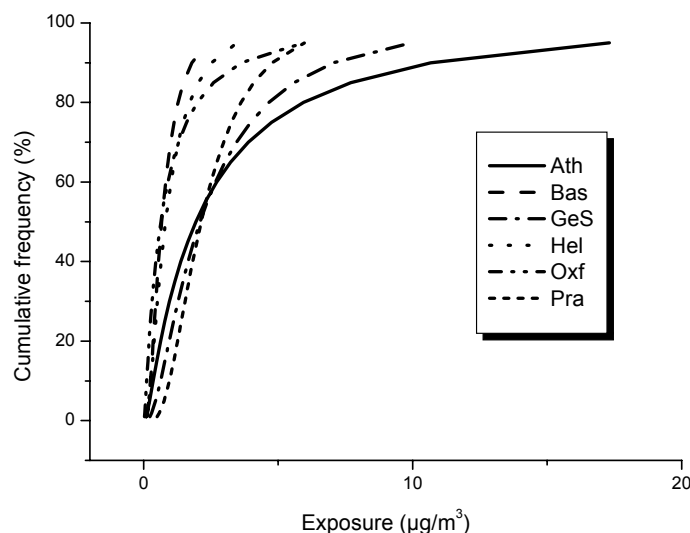
Figure 3.2. Cumulative frequency distributions of 48-hour personal exposure concentrations of styrene in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean concentrations of the German Survey GerES II (Hoffman et al 2000).

4. Toxicokinetics

Absorption

In animal and human controlled studies, the uptake of styrene has been found to be rapid. The principal routes of exposure are pulmonary and, to a lesser extent, dermal. In several studies with workers and volunteers, the pulmonary retention of styrene was 60–70% of the inhaled dose. Styrene in ambient air is absorbed through the skin at 2–5 % of the dose absorbed in the respiratory tract. (IARC, 1994).

Distribution

Styrene is widely distributed throughout the body. The distribution and sequestration of styrene to fat tissue and its subsequent slow elimination indicate a potential for accumulation in situations of repeated daily exposure. However, in a study of workers exposed to 160 mg/m^3 (37 ppm; 8-hour TWA) styrene, no evidence of accumulation was found in monitoring samples during a working week (Pekari et al., 1993).

Metabolism and elimination

Styrene is oxidized to styrene-7,8-oxide by the cytochrome P-450-mediated monooxygenase system. The responsible isozymes are the ethanol-inducible CYP2E1, CYP2B6 and CYP1A2, and additional isozymes with lower activity for styrene may be involved (Nakajima et al., 1994). Styrene can also undergo oxidation by other mechanisms and it can be cooxidized to styrene-7,8-oxide during the lipoxynase-mediated formation of arachidonic acid peroxides (Belvedere, G. et al., 1983). *In vitro*, styrene oxidation to styrene-7,8-oxide has been shown to be mediated by oxyhaemoglobin and myoglobin (Tursi et al., 1983; Ortiz de Montellano and Catalano, 1985).

Enzymatic hydrolysis of styrene-7,8-oxide yields phenylethylene glycol which is further oxidized to mandelic acid and phenylglyoxylic acid, the principal urinary metabolites of styrene in humans (IARC, 1994). Conjugation of styrene-7,8-oxide with glutathione leads to urinary excretion of thioethers or mercapturic acid, quantitatively a minor metabolite in humans. In a field study carried out on workers exposed to 43–311 mg/m^3 of styrene, styrene-7,8-oxide concentration in blood was found to be linearly correlated with ambient styrene (Korn et al. 1994).

The elimination of styrene is linear at lower concentrations of atmospheric styrene. At concentrations of less than 852 mg/m^3 there is a fast elimination phase with a half-life of 0.5–0.7 hours, and a second phase of slow elimination with a half-life of 13 hours (IARC, 1994). Several physiologically-based pharmacokinetic models have been developed *(33,34)* which simulate the behaviour of styrene and styrene-7,8-oxide in the body. Partially saturated metabolism can be predicted by the models at high exposures exceeding 1280 mg/m^3 (300 ppm).

Urinary excretion of mandelic acid and phenylglyoxylic acid is biphasic. After an 8-hour exposure of workers to styrene at concentrations of 26–130 mg/m^3 (6.1–30.5 ppm), both metabolites have a half-life of about 2.5 hour for the first phase and 30 hours for the second (IARC, 1994). These compounds are used in assessing occupational exposure to styrene. According to several studies, an exposure to 80 mg/m^3 (20 ppm) styrene corresponds, the following morning, to a combined mandelic acid and phenylglyoxylic acid level of about 2.9 mmol/litre (Pekari et al., 1993). Coexposure to ethanol inhibits the metabolism of styrene, resulting in a lag in the excretion of mandelic acid (Wilson et al. 1983)*.*

5. Health effects

Effects of short-term exposure

Styrene may irritate the eyes and mucous membranes and may be toxic to the central nervous system (IARC, 1979). Immediate eye and throat irritation, increased nasal mucus secretion, listlessness, impairment of balance, and drowsiness followed by unsteadiness, muscle weakness, and depression were reported in a study of 2 human volunteers exposed to 3408 mg/m^3 (800 ppm) styrene for 4 hours (Carpenter *et al*., 1944). Other symptoms include a feeling of being "lightheaded" or "drunk" (Lorimer *et al*., 1976).

In an exposure chamber study, volunteer subjects complained of an objectionably strong odor when exposed to 852-1704 mg/m^3 (200-400 ppm) styrene; exposure to 256 mg/m³ (60 ppm) resulted in detectable odor but no irritation (Wolf *et al*., 1956). The duration of exposure and number of subjects were not specified. Investigators at a fiberglass plant could not withstand more than 1-2 minute exposure to concentrations of 2130-3410 mg/m^3 (500-800 ppm) styrene (Götell *et al*., 1972). However, workers exposed to this concentration of styrene for hours complained of only mild to moderate complaints of irritation, suggesting that tolerance may have developed.

Stewart *et al*. (1968) found eye and throat irritation in 3 out of 6 volunteers exposed to 422 mg/m^3 (99 ppm) styrene for 20 minutes. No symptoms were reported in 3 subjects after exposure to 217 mg/m^3 for 1 hour. Exposure of these subjects to 1579 mg/m^3 styrene for 25 minutes resulted in nausea, significant discomfort, and an abnormal Romberg test, indicative of cerebellar dysfunction. Significant decrements were noted in 3/5 subjects in other tests of coordination and manual dexterity at 50 minutes. Exposure to 920 mg/m^3 or less for up to 1-hour did not cause measurable impairment of coordination and balance.

The neurotoxic effects mediated by styrene consist of slowing in sensory, but not motor, nerve conduction velocity and CNS depression (Cherry and Gautrin, 1990). Reaction time was significantly impaired in 12 males exposed to 1470 mg/m^3 (350 ppm) styrene for 30 minutes, whereas no significant impairment was observed at 1065 mg/m^3 (250 ppm) or lower (Gamberale and Hultengren, 1974). In this study, no effects on perceptual speed or manual dexterity were detected. In another study of 12 workers exposed during the workday to 111 mg/m³ (26 ppm), Edling and Ekberg (1985) measured reaction time before and after work and found no significant differences. Other non-CNS symptoms were reported in a neuropsychiatric questionnaire completed by the subjects.

The CNS depressant effects of acute exposures to high styrene levels are probably mediated by the direct effect of the lipophilic, unmetabolized styrene on nerve cell membranes.

Abnormal electroencephalograms were correlated with urinary levels of the styrene metabolite, mandelic acid, of 700 mg/l or higher in workers exposed to styrene (Harkonen *et al*., 1978).

Consumption of ethanol has been shown to decrease formation of the metabolites mandelic and phenylglyoxylic acid in human volunteers exposed to 426 mg/m³ (100 ppm) styrene for 8 hours (Cerny *et al*., 1990). Lowered levels of these metabolites have been associated with a reduced risk of CNS disturbances in volunteer workers (Cherry and Gautrin, 1990). Co-exposure to inhaled acetone was reported to alter cytochrome-P450 enzymes as measured by altered urinary steroid metabolites and glucaric acid in workers who consumed moderate amounts of alcohol (Dolara *et al*., 1983). However, the clinical significance of the presence of these compounds in the urine is unknown.

Styrene is bioactivated to styrene 7,8-oxide, a reactive metabolite which binds to tissue proteins, acts as a hapten, and elicits contact allergy in some individuals (Sjoborg *et al*., 1984). Analyses of styrene oxide adducts bound to human serum albumin have been used as biomarkers for exposure to styrene (Rappaport *et al*., 1993). In a study comparing 9

styrene-exposed workers with 24 healthy controls, hematocrit, blood lead levels, and delta-aminolevulinate dehydrase (ALA-D) levels were measured (Fujita *et al*., 1987). The workers were exposed to at least 213 mg/m³ (50 ppm) styrene for 7 days. Styrene oxide was shown to inhibit the formation of ALA-D, an important enzyme in heme biosynthesis, in these workers. Styrene oxide is also known to bind covalently to DNA *in vitro* (Hemminki and Hesso, 1984).

Two subjects with occupational asthma due to prior exposure to styrene were exposed to 64 mg/m³ (15 ppm) styrene in a chamber (Moscato *et al*. 1987). Immediate bronchoconstriction was observed in both subjects while a late rash was also observed in one of the subjects.

Predisposing Conditions for Styrene Toxicity
Medical: Asthmatics may be more sensitive to adverse pulmonary effects from styrene exposure (Moscato *et al*., 1987).
Chemical: Ethanol consumption and acetone inhalation may inhibit the metabolism and clearance of styrene (Cerny *et al*., 1990; Dolara *et al*., 1983; Elovaara *et al*., 1990).

Summary of short-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
217 $_{EXP}$	422 $_{EXP}$	Eye and throat irritation	Volunteers, 1h (NOAEL), 20m (LOAEL)	Stewart *et al*., 1968	OEHHA (1999); REL: 21

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h-ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Acute Reference Exposure Level (protective against mild adverse effects; for a 1-hour exposure)

Study	Stewart *et al*., 1968
Study population	three human volunteers
Exposure method	inhalation
Critical effects	eye and throat irritation
LOAEL	99 ppm (for 20 minutes)
NOAEL	51 ppm
Exposure duration	1 hour
Extrapolated 1 hour concentration	51 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	5.1 ppm (21 mg/m³; 21,000 µg/m³)

ATSDR
Agency for Toxic Substances and Disease Registry

Derivation of the acute Minimal Risk Level (MRL).
The possibility for brief human exposure to high concentrations of styrene exists in occupational settings, and might also exist near major spills. Exposure of the general public to episodic high concentrations of styrene at hazardous waste sites, in the home, or in the general environment is unlikely.

The respiratory tract and central nervous system are the likely target organ systems for inhaled styrene (Alarie 1973; Carpenter et al. 1944; DeCeaurriz et al. 1983; Kankaanpaa et al. 1980; Murray et al. 1978; Spencer et al. 1942; Stewart et al. 1968). The data are not considered sufficient to establish an inhalation acute-duration MRL. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised. However, the potential carcinogenicity of styrene prevents the design of controlled laboratory exposures in humans.

Effects of long-term exposure (noncancer)

Chronic exposures to styrene result in central nervous system (CNS) and peripheral nervous system effects, although the latter are not as pronounced (ATSDR, 1992; Rebert and Hall, 1994; Murata *et al.*, 1991). Irritation or discomfort of the upper respiratory tract resulting from styrene exposure has not been reported in long-term occupational studies (Foureman, 1994). However, sensory irritation and neurological impairment does occur in acute human studies at concentrations above 426 mg/m^3 (Stewart *et al.*, 1968). The evidence for styrene induced hepatic changes is either negative or equivocal (ATSDR, 1992). Evidence for nephrotoxicity due to long-term occupational exposure is also negative or equivocal (ATSDR, 1992; Verplanke and Herber, 1998; Kolstad *et al.,*1995). Some human studies suggest that chronic exposure to styrene results in reproductive effects, but the limited data are difficult to interpret because of the small sample numbers (Brown, 1991; Lindbohm, 1993). Immunologic alterations (e.g., altered phenotypic profiles among lymphocyte subsets, decreased natural killer cell activity, and decreased chemotaxis) have also been observed, but the limited data prevent quantitative interpretation (Bergamaschi *et al.*, 1995; Governa *et al.*, 1994).

The CNS depressant effects of acute exposures to high styrene levels are probably mediated by the direct effect of the lipophilic, unmetabolized styrene on nerve cell membranes. Long-term effects of styrene exposure may result from the action of one or more metabolites of styrene (Savolainen, 1977; Mutti *et al.*, 1988).

One postulated mechanism for the chronic non-cancer toxicity of styrene is the binding of the highly reactive styrene oxide to components of nervous tissue. Another postulated mechanism is an alteration in the levels of circulating catecholamines (e.g., dopamine) due to the binding of PGA to these biogenic amines (Mutti, 1993; Mutti *et al.*, 1984a; Checkoway, 1994) and the subsequent changes in physiological functions that are under biogenic amine control. Although long-term exposures to styrene are associated with decrements in physiological functions, the exact mechanism(s) for these effects have not been clearly established (see reviews by ATSDR, 1992; Mutti, 1993; Rebert and Hall, 1994).

Kolstad *et al.* (1995) estimated excess deaths due to four major non-malignant disease groups for 53847 male workers in the Danish RPI. Low and high styrene exposures were based on companies with less than 50% (low) and those with 50% or more (high) employees involved with reinforced plastics. An internal comparison was made with workers unexposed to styrene to account for more similar activities and lifestyles. Statistically significant (p < 0.05) excess deaths due to pancreatitis and degenerative disorders of the myocardium and non-significant excess deaths due to degenerative diseases of the nervous system were observed. Non-significant excess deaths due to glomerulonephritis were also observed.

Checkoway *et al.* (1994) described a cross-sectional study of 59 male boat plant workers exposed to <4,3 to 613 mg/m^3 mean = 158 mg/m^3 styrene. Monoamine oxidase B (MAO-B) activity in platelets was measured as an indicator of catecholamine metabolism. When the styrene exposed workers were divided into quartile exposures, a dose dependent decrease in MAO-B activity was observed after adjustments were made for age, smoking, alcohol and medication use.

Female workers employed in the reinforced plastics industry (RPI) were studied for levels of substances associated with neuroendocrine function (Mutti *et al.*, 1984a). Serum prolactin, thyroid stimulating hormone, human growth hormone, follicle stimulating hormone, and luteinizing hormone were measured in 30 women who were between the 5th and 15th day of the menstrual cycle. Exposure was based on the nextmorning MA+PGA, and levels of the neuroendocrine substances were measured in venous blood samples taken the next morning before the start of work. On the basis of a relationship (not detailed in the report) between urinary metabolites and styrene air concentration, the authors estimated that the average styrene TWA/8 hr was about 554 mg/m^3 (130 ppm). Controls consisted of women factory workers living in the same area as the styrene-exposed women, but not knowingly exposed to styrene. After controlling for age and exposure time, the increased prolactin and thyroid stimulating hormone levels were correlated with the concentration of next-morning urinary MA+PGA, although only the increased prolactin levels were statistically significant.

Numerous occupational studies have noted CNS disturbances in styrene-exposed workers. Decreased manual dexterity, increased reaction times, and/or abnormal vestibuloocular reflex (ability to track moving objects) were observed by Götell *et al.* (1972), Gamberale *et al.* (1975), Lindstrom *et al.* (1976), Mackay and Kelman (1986), Flodin *et al.* (1989), Moller *et al.* (1990), and Cherry and Gautrin (1990) for air styrene levels of about 51 mg/m^3 (12 ppm) to more than 426 mg/m^3 (100 ppm). However, in each of these studies, there were difficulties in quantifying the effect. The difficulties included small sample size, unknown exposure duration, lack of concurrent control group, lack of dose-response data, and either unknown ethanol consumption or lack of adjustment for ethanol consumption. In the Cherry and Gautrin (1990) investigation, however, the authors determined that accounting for ethanol consumption did not reduce the correlation between increased reaction time and exposure.

Decrements in other CNS functions were observed among workers in the well-controlled studies of Fallas *et al.* (1992), Chia *et al.* (1994), and Mutti *et al.* (1984b). Fallas *et al.* (1992) studied 60 male workers (average age = 29.5 years, average air styrene = 104 mg/m^3). The styrene-exposed population was compared to non-exposed worker controls and matched for age, intellectual level, and ethnic origin. The results from a standardized test battery showed decrements in the aiming response and 22/60 styrene exposed workers exhibited increased reaction times compared to 7/60 controls. Acquired color vision loss (dyschromatopsia) was also observed in the styrene-exposed workers compared to controls. Chia *et al.* (1994) also observed decrements in CNS function as defined by altered visual retention, audio-digit recognition, and digit recognition. However, a dose-response relationship did not exist. These workers also exhibited a statistically nonsignificant dose-dependent dyschromatopsia.

In the most comprehensive occupational study to date on CNS effects of styrene exposure, Mutti *et al.*(1984b) assessed memory and sensory/motor function in a group of 50 male styrene-exposed workers (average exposure = 8.6 years) and a control group of 50 manual workers. In addition to matching for age, sex, and educational level, a vocabulary test was included to match for general intelligence. Eligibility criteria included absence of metabolic, neurologic, or psychiatric disorders, limited ethanol intake, and limited cigarette usage. All subjects were instructed to avoid intake of alcohol and drugs for two days prior to testing. Styrene exposure was assessed from urinary MA+PGA levels the morning after the last workday in the week, followed immediately by participation in a battery of 8 neuropsychological tests designed to measure CNS function. The tests included reaction time, short and long term logic memory, short and long term verbal memory, digit-symbol association (using a reference code), block design (reproducing a displayed design using colored blocks), and embedded figures (timed identification of figures in Rey's table). The mean + 2 SDs of the values found in the control group was set as the normal range limit for each neuropsychological test. The results were expressed as continuous and quantal data. Expressed as continuous data, styrene-exposed workers exhibited significantly poorer performances than controls in all tests, except in the digit-symbol test. Also, urinary metabolite concentration and duration of exposure were found to be significantly correlated with the scores of several tests. As a subgroup, workers with metabolite levels of up to 150 mmoles MA+PGA/mole creatinine (mean = 75 mmoles/mole creatinine + 33 [SD], which is equivalent to a mean styrene concentration of 64 mg/m^3) appeared to have no significant effects. The authors state that this level of urinary metabolites corresponds to a mean daily 8-hour exposure to air styrene of 107 mg/m^3 (25 ppm). Based on greater urinary excretion of styrene metabolites, significantly poorer performances in four or more neuropsychological tests were recorded in the other three subgroups (150-299, 300-450, and > 450 mmoles MA + PGA/mole creatinine).

Mutti *et al.* (1984b) expressed the quantal data as the fraction of tested subjects who responded abnormally to ≥ 1, ≥ 2, and ≥ 3 tests (see Table 5.1). Positive dose-response relationships existed between intensity of styrene exposure (mmoles MA + PGA/mole creatinine) and abnormal scores, whether it was expressed as abnormal responses in at least one, at least two, or at least three neuropsychological tests. The chi-square test and validity calculations were performed by constructing 2 x 2 tables selecting different levels of urinary excretion of MA and PGA as a cut-off point. The highest values for chi-square and predictive validity were found when the cut-off of 150 mmol/mol creatinine was chosen, suggesting that the quantal isolation of the low dose subgroup from the next subgroup is appropriate.

When the quantal data for the low dose subgroup were analyzed by OEHHA using the Fisher's Exact Test, a significant level of abnormal responses were observed for ≥ 1 (p = 0.005) and ≥ 3 (p = 0.04) tests. The abnormal responses for ≥ 2 tests were statistically marginal (p = 0.06). For each of the remaining exposure groups, the p-values were <0.05. Unlike the assumptions made concerning the continuous data, quantal data results suggest that the low dose subgroup represents a LOAEL, and that a NOAEL is not available from the data. Mutti *et al.* (1984b) also expressed the data in a quantal three-way representation including prevalence (number of respondents for at least one, two or three abnormal tests), duration (years at work), and intensity (metabolite level). This representation revealed a positive correlation of neuropsychological deficits with duration as well as intensity.

Table 5.1: Subjects Classified Positive on Neuropsychological Tests as a Function of Styrene Exposure[a].

MA+PGA, mmoles per mole creatinine[b]	Total Subjects	Number of Abnormal Tests		
		≥ 1	≥ 2	≥ 3[c]
Controls	50	4/50	2/50	0/50
< 150 (mean = 75 ± 33)[d]	14	6/14	3/14	2/14
150-299 (mean = 216 ± 45)	9	6/9	5/9	3/9
300 - 450 (mean = 367 ± 49)	14	10/14	7/14	5/14
> 450 (mean = 571 ± 108)	13	11/13	8/13	6/13

[a] Data from Table IV in Mutti *et al.* (1984b).
[b] "Next-morning" styrene urinary metabolites.

In addition to dyschromatopsia observed by Chia *et al.* (1994), Gobba and Cavalleri (1993) and Campagna *et al.* (1995) also reported this visual dysfunction among styrene workers in the reinforced plastics industry. Workers (n=36) exposed to an average of 16 ppm styrene exhibited significantly greater dyschromatopsia than controls, matched for age, ethanol consumption and tobacco smoking (Gobba and Cavalleri, 1993). Among the study population, only 1/36 styrene-exposed workers (compared to 16/36 controls) performed the test with 100 percent accuracy. When a different group of styrene-exposed workers was tested, those exposed to > 50 ppm styrene exhibited greater dyschromatopsia than those exposed to ≤ 50 ppm, and within this group, a subset exhibited a similar decrement after returning from a one month vacation. In the Campagna *et al.* (1995) study, the test for dyschromatopsia was given to 81 reinforced plastics industry workers (79 male and 2 female) exposed to 4.6, 10.1, and 88.8 ppm styrene (first quartile, median, and third quartile, respectively). No control group was used in this study. Statistical analysis revealed a correlation of color vision loss with exposure to styrene (defined as next-morning urinary mandelic acid), age, and ethanol consumption.

Exposure to styrene may affect the peripheral nervous system (PNS). In a case report (Behari *et al.*, 1986), a man working for 5 years with a photostat process that used styrene was diagnosed with peripheral neuropathy. However, in occupational studies, the relationship between exposure to styrene and PNS effects has been inconsistent (Triebig *et al.*, 1985; Cherry and Gautrin, 1990). A major difficulty in understanding the potential for this relationship is the lack of knowledge about the appropriate surrogate for dose that leads to PNS disturbance (Murata *et al.*, 1991). In one study, however, chronic exposure indices were developed which included work method, years at work, time spent laminating (source of high exposure), styrene air concentration, and end-of-shift urinary mandelic acid (Matikainen *et al.* (1993). Numbness in the extremities increased with the exposure index, although statistically the effect was marginally insignificant ($p < 0.1$). The styrene TWA/8 hr was 136 mg/m³ for the 100 study subjects.

Female reproductive toxicity has been inconsistently reported among humans (Brown, 1991; Lindbohm, 1993). These studies are difficult to interpret because of the high background rates of endpoints such as spontaneous abortion and menstrual disorders in combination with confounding exposures. In those studies that showed no reproductive effects due to styrene exposure, the power of the studies was low due to the small numbers of women. Hence the evidence for any adverse effects of exposure to styrene on female reproductive function is inconclusive.

Kishi et al. (1992a, 1992b) reported that Wistar rat offspring exposed to airborne styrene in utero at 256 mg/m³ (60 ppm) for 6 hour/day during days 7 to 21 of gestation, had significantly reduced pup weights at day 1, delayed development of righting reflex and auditory startle reflex, and nonsignificantly decreased levels of serotonin and its metabolites 5-hydroxyindoleacetic acid (5-HT) in the cerebrum. Exposure to 1270 mg/m³ (293 ppm) significantly reduced pup body weight and the levels of serotonin and 5-HT, and induced alterations in a wider range of behavioural measures. Thus, the lowest LOEL for neurotoxic effects in animals following inhalation of styrene in an adequately-conducted study is 260 mg/m³ (60 ppm) in Wistar rats exposed to the compound in utero (Kishi et al., 1992a,b).

Male workers employed in the reinforced plastics industry were examined for effects on sperm chromatin structure and semen quality (Kolstad *et al.*, 1999a) and time to pregnancy (Kolstad et al., 1999b). No indications of an exposure-response relationship were seen when individual changes in semen quality were related to the postshift urinary mandelic acid concentrations among 23 exposed workers. A weak increase in sperm DNA-susceptibility to *in situ* denaturation as a function of mandelic acid concentration was indicated, but was within the interassay variability. No detrimental effect of styrene exposure was observed with regard to male fecundity among 188 exposed workers when compared to 353 unexposed workers.

Immune system alterations were reported in a study conducted by Bergamaschi *et al.* (1995). Reinforced plastics industry workers (n=32 female/39 male, average age = 32 years, average exposure duration = 7 years) were compared with non-styrene exposed factory workers and matched for age, sex, tobacco use and ethanol consumption. Air styrene levels, among the different factories, varied between 43 – 213 mg/m³ (10-50 ppm), and individual worker exposure was measured by urinary metabolites the morning after the last shift (15 hours post-exposure). Among all workers in the study (median exposure = 68 mg/m³ - according to the data of Guillemin *et al.* (1982)), the proportion of 12/18 lymphocyte subsets and the prevalence of abnormal values of immunologic phenotypes for 11/18 subsets were statistically different from the controls ($p < 0.001$ to < 0.05). When the workers were placed into three exposure groups (0, < 107 mg/m³, and > 107 mg/m³ styrene), dose-response relationships were observed for prevalences of abnormal responses for four lymphocyte subsets and, in the case of two subsets, abnormal responses were observed in the group exposed to < 107 mg/m³ styrene. Natural killer cell activity (a lymphocyte function), measured in a different group of

workers in the same study, was decreased compared to unexposed worker controls. The median exposure, given in terms of urinary metabolites, was calculated as 89 mg/m^3 based on the data of Guillemin *et al.* (1982). The data show that exposure of these workers to air styrene levels below 213 mg/m^3, and probably at levels near 107 mg/m^3, resulted in alterations of the immune system.

Governa *et al.* (1994) observed reduced chemotactic responses of polymorphonuclear lymphocytes (PMNs) obtained from 21 styrene-exposed workers. However, the lack of exposure data prevents a quantitative assessment. In the same study, 0.1 - 0.6 mM styrene inhibited the chemotaxis of isolated healthy PMNs.

Reproductive and teratogenic effects
The frequency of spontaneous abortions among women with definite or assumed exposure to styrene has been investigated in a number of studies; the majority do not indicate an increased risk in association with occupational exposure to styrene (IARC, 1994). A study in Canada (McDonald et al., 1988) found an increased risk for spontaneous abortions (18 observed; SMR, 158; 90% CI, 102–235) among women employed in polystyrene manufacture. The expected figures were derived from the experience of 47 316 pregnant women who had worked for 30 hours or more per week at the start of pregnancy. No styrene concentrations were given, and most of these women had mixed exposures. Two studies in Finland found no increase in the frequency of spontaneous abortion or congenital malformation among the wives of men exposed occupationally to styrene (Taskinen et al., 1989; Lindbohm et al., 1991).

The conclusion thus remains that no clear association has been established between occupational exposure of either mothers or fathers to styrene and the frequency of spontaneous abortions or congenital malformations.

Summary of long-term exposure effect levels (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
	64 Study 17 MLE 7.2 BC05 2.6 ADJ	CNS; neuropsychological tests: reaction time, s/l term logic memory, s/l term verbal memory, digit-symbol association, block design and figure identification.	Occupational, 8.6y	Mutti *et al.* 1984b	OEHHA (1999); REL: 0.9
94 95%ICL 34 ADJ	>94 95%ICL	same as above	Occupational, 8.6y;	Mutti *et al.* 1984b	EPA-IRIS (1992); RfC: 1
	107 Study 25 ADJ	same as above	Occupational 8.6y;	Mutti *et al.* 1984b	ATSDR (1992); MRL: 0.25; WHO (2001); GV: 0.26; RIVM (2000)
	260 EXP 65 ADJ 46 HEC	Neurological developmental; body weight, biochemical parameters in the brain and behaviour	Rat offspring	Kishi et al.,1992a,b	Health Canada (1993); TC: 0.092
Final statement (UNIMI) : Human LOAEL: 25 mg/m³					

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration ; 95%ICL lower limit of the 95% confidence interval

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of the Chronic Reference Exposure Level (BMC Approach) :
Study   Mutti *et al.* (1984b)
Study populations   Human (occupational)
Exposure method   Inhalation
Critical effects   Central nervous system
LOAEL   15 ppm
NOAEL   Not established

BMC_{05}	1.7 ppm
Exposure continuity	8 hr/d (10 m^3 per 20 m^3 day), 5 d/wk
Exposure duration	8.6 years (average years at work)
Average occupational exposure	0.61 ppm (1.7 x 10/20 x 5/7)
Human equivalent concentration	0.61 ppm
LOAEL uncertainty factor	Not needed in the BMC approach
Subchronic uncertainty factor	1 (average exposure 12.3% of lifetime)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.9 mg/m3; 900 µg/m^3)

The most relevant chronic noncancer effect due to styrene exposure is neurotoxicity. The Mutti *et al.* (1984b) occupational study presented convincing dose-response information and was well designed and executed in terms of experimental protocol and statistical evaluation, which included tests for false positive and false negative responses. While not all confounders could be ruled out (e.g., compensatory mechanisms, biorhythms, workers who leave because of styrene related illness), careful attention was paid to include eligibility criteria for the control group that correct for confounders unique for this population (e.g., limited ethanol intake, a control work-force not exposed to neurotoxic substances, and a test to allow a match for general intelligence). The use of urinary metabolites to measure exposure dose is based on the observation that the next-morning urinary mandelic acid (MA) and phenylglyoxylic acid (PGA) is directly related to the air level of styrene. The Guillemin *et al.* (1982) study provides the basis for the conversion of urinary MA+PGA levels to styrene exposure levels used by Mutti *et al.* (1984b). The quantal dose-response data by Mutti *et al.* (1984b) is applicable for use in a benchmark concentration (BMC) approach. The quantal grouping of the number of subjects that performed abnormally in >3 tests based on their urinary metabolite concentrations was chosen for a BMC analysis. Basing the BMC on abnormal responses to >3 tests reduces the complexity of multiple test comparisons and the potential for inappropriate comparison of different neuropsychological tests between control and exposure groups for statistical purposes. Also, the potential for false positive responses is reduced due to the zero background level of abnormal responses in the control group when the criteria are >3 abnormal tests. Using a log-normal probit analysis (Tox-Risk, version 3.5; ICF-Kaiser Inc., Ruston, LA) the maximum likelihood estimate (MLE) for a 5% response was 17 mg/m^3 (4.0 ppm). The resulting 95% lower confidence limit at the MLE provided a BMC$_{05}$ of 7.2 mg/m^3 (1.7 ppm). A BMC$_{05}$ is considered to be similar to a NOAEL in estimating a concentration associated with a low level of risk. Following adjustment for exposure continuity (10 m^3 per 20 m^3 day for 5 d/wk) and application of an UF of 3 to account for human intraspecies variability, a REL of 0.9 mg/m^3 (0.2 ppm) was attained. For exposure data that utilizes healthy human subjects, the resulting BMC represents a less than 10% incidence in the general population. When combined with an UF of 3, as carried out above, the resulting REL will be protective of the vast majority of individuals. This analysis of the quantal data is supported by recognizing that, in a population of 50 subjects, individual test-specific effects that occur at low doses may not have been observed. If the criterion for abnormality is expressed in terms of CNS dysfunction, defined by all tests, the sensitivity of the testing procedure is increased and the low dose effects are more easily observed. The quantal data of Mutti *et al.* (1984b), i.e., the proportion of subjects responding abnormally to the tests, therefore provide a more sensitive approach to detecting low dose effects. Collapsing a battery of test data to increase sensitivity may introduce the dilemma of multiple test comparisons, as noted above. However, OEHHA believes that a statistical method to correct for this, known as a Bonferroni correction, is unnecessary. The REL development is based on calculating a statistic of one effect of a complex of responses (or a syndrome) that results from CNS dysfunction, and not based on calculating a statistic for each test within the group of tests. The apparent global nature of the neurological syndrome resulting from long-term styrene exposure, in addition to basing the BMC on abnormal responses to >3 tests, should more than adequately address any concerns that may result from combining neurological test data. Applying NOAEL/LOAEL methodology to the Mutti *et al.* (1984b) quantal data yields an exposure value similar to that attained with the BMC approach. The LOAEL of 64 mg/m^3 (15 ppm) is adjusted to an equivalent continuous exposure of 23 mg/m^3 (64 mg/m^3 x 10/20 m3 x 5/7 d/wk). Use of a LOAEL UF of 3 and an intraspecies UF of 10 resulted in an estimated REL of 0.8 mg/m^3 (0.2 ppm).

The U.S. EPA (1996) calculated a reference concentration (RfC) of 1 mg/m^3 (0.3 ppm), which is slightly higher than the OEHHA-derived chronic REL of 0.9 mg/m^3 (0.2 ppm). The RfC for styrene is also based on the findings of Mutti *et al.* (1984b), but utilized the continuous data for development of the RfC and used standard NOAEL methodology for the RfC derivation. U.S. EPA (1996) established a NOAEL for the lowest exposure group (<150 MA+PGA mmole/mole creatinine; equivalent to < 106 mg/m^3 styrene).

However, OEHHA staff believe that the use of the continuous data to establish a NOAEL overlooks the advantages of using the BMC approach using the quantal data. These advantages are that the BMC$_{05}$ reflects the shape of the dose-response curve and takes into account the number of subjects involved in the study. In addition, OEHHA staff evaluated the quantal data with the Fisher's Exact Test and determined the probabilities of abnormal responses among the exposed

subjects based on the unexposed subjects whose responses were assumed to be normal. At the lowest exposure, the probability that the proportion of subjects responding abnormally to >1 and >3 tests was within the expected range was $p = 0.005$ and $p = 0.04$, respectively, indicating that neuropsychological deficits due to styrene occur in the low dose subgroup. Thus, the quantal data indicate that a NOAEL was not established in this study.

U.S.EPA - IRIS (1992)
Integrated Risk Information System

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC).

Critical effect	Exposures*	UF	MF	RfC
CNS effects Occupational Study Mutti et al. (1984b)	NOAEL: 94 mg/cu.m (25 ppm = 150 mmole urinary styrene metabolites/mole creatinine adjusted to lower 95% confidence limit = 22 ppm) NOAEL(HEC): 34 mg/cu.m LOAEL: >94 mg/cu.m (>22 ppm derived as in NOAEL listing)	30	1	1 mg/m^3

*Conversion Factors: MW = 104.15. Assuming 25 C and 760 mmHg, NOAEL (mg/cu.m) = NOAEL (ppm) x MW/24.45 = 94 mg/cu.m. The NOAEL exposure level is based on a back extrapolation from worker urinary concentration of styrene metabolites reported in the principal study and adjusted to the lower 95% confidence limit listed in Guillemin et al. (1982), which was 88%, 25 ppm x 0.88 = 22 ppm. The NOAEL(HEC) is calculated using an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. NOAEL(HEC) = 94 mg/cu.m x MVho/MVh x 5 days/7 days = 34 mg/cu.m. The feasibility of applying the exposure model of Perbellini et al. (1988) for extrapolation of the values in the principal study is currently being investigated. Application of this model may result in changes in the NOAEL(HEC) value and, therefore, the RfC.

The concentration-response relationship between urinary metabolite concentration (mandelic acid and phenylglyoxylic acid levels normalized to creatinine in "morning-after" urine) and test results indicated a significant effect level in the subgroup whose urine contained 150-299 mmole urinary metabolites/mole creatinine. Workers with metabolite concentrations of up to 150 mmoles/mole appeared to have no significant effects, and this level is therefore designated as the NOAEL in this study. The authors state that this level of urinary metabolites corresponds to a mean daily 8-hour exposure to air styrene of 107 mg/m^3 (25 ppm). Derivation of this air level is from the creatinine-normalized, combined concentration of the styrene metabolites, MA and PGA, in urine collected from the workers on Saturday mornings. Guillemin et al. (1982) demonstrated a logarithmic relationship (r = 0.871) between the summation of urinary metabolites (MA + PGA, next morning) and air concentrations of styrene (ppm x hours). Guillemin calculated the mean combined urinary metabolite concentration (next morning) for an 8-hour exposure to 426 mg/m^3. This relationship was used by both Mutti et al. (1984b) and Guillemin and Berode (1988) in a proportional manner to obtain styrene air levels at lower urinary metabolite concentrations. The 95% confidence interval was also calculated for an 8-hour exposure at 426 mg/m^3, the lower limit of the confidence calculation being 88% of the mean styrene exposure. This factor was applied directly to the NOAEL of 107 mg/m^3 [107 mg/m^3 x 0.88 = 94 mg/m^3]. Due to the construction of the subgroups, designation of a LOAEL was the lower limit of the subgroup in which adverse effects were observed [i.e., greater than the NOAEL of 94 mg/m^3].

Confidence in the Inhalation RfC: The study of Mutti et al. (1984b) documents concentration-response relationships of CNS effects in a relatively small worker population. However, the results of this study are consistent with a number of other studies showing central effects in chronically exposed worker populations, most notably that of Moller et al. (1990). The urinary metabolites, MA and PGA, are direct biological indicators of exposure to styrene. Numerous studies have demonstrated the relationship between urinary metabolites and air levels of styrene to be reliable and quantitative. Physiologically based pharmacological modeling of this exposure methodology demonstrates that it reflects and incorporates at least a portion of intrahuman variability related to pharmacokinetics. The study is therefore assigned a medium confidence level. The data base can be considered medium to high as chronic laboratory animal studies addressing noncancer endpoints are not yet available, but a number of human exposure studies support the choice of critical effect. Preliminary information in mice indicate that styrene is a respiratory tract irritant in mice at concentrations lower than 47.5 mg/cu.m. The RfC is assigned an overall confidence rating of medium.

ATSDR (1992)
Agency for Toxic Substances and Disease Registry

Derivation of the acute Minimal Risk Level (MRL):
Studies in workers exposed to styrene in workplace air suggest that neurological effects are probably the most sensitive indicator of styrene toxicity. Available data do not.provide a clear picture of the NOAEL for neurological effects following acute- or intermediate-duration inhalation exposure, but two chronic studies in workers identify LOAELs of 107 mg/m^3 (25 ppm) (Mutti et al. 1984a) and 132 mg/m^3 (31 ppm) (Harkonen et al. 1978). Based on the lower LOAEL

(25 ppm), a chronic inhalation MRL of 0.25 mg/m^3 (0.06 ppm) has been derived using factors of 8/24 and 5/7 to account for exposure 8 hours/day, 5 days/week, and an uncertainty factor of 100 (10 to account for human variability, and 10 to account for use of a LOAEL).

WHO (2001)
Air Quality Guidelines for Europe, 2000

Although genotoxic effects in humans have been observed at relatively low concentrations, they were not considered as critical endpoints for development of a guideline, in view of the equivocal evidence for the carcinogenicity of styrene.

In occupationally exposed populations, subtle effects such as reductions in visuomotor accuracy and verbal learning skills, and subclinical effects on colour vision have been observed at concentrations as low as 107–213 mg/m^3 (25–50 ppm). Taking the lower number of this range for precautionary reasons and adjusting this value in order to allow for conversion from an occupational to a continuous pattern of exposure (a factor of 4.2), and incorporating a factor of 10 for interindividual variation and 10 for use of a lowest-observed-adverse-effect level (LOAEL) rather than a no-observed-adverse-effect level (NOAEL) this results in a guideline of 0.25 mg/m^3(weekly average). This value should also be protective for the developmental neurological effects observed in animal species.

The air quality guideline could also be based on the odour threshold. In that case, the peak concentration of styrene in air should be kept below the odour detection threshold level of 70 μg/m^3 as a 30-minute average.

Health Canada
Canadian Environmental Protection Act (CEPA).

Derivation of a tolerable concentration (TC):
The available data on nonneoplastic effects (principally neurological) in humans are considered to be inadequate to serve as the basis for the development of a tolerable concentration (TC), due to such factors as the lack of precise exposure data, simultaneous exposures to other chemicals, the short duration of available clinical studies, and the small numbers of subjects in many studies. It should be noted, however, that a TC derived on the basis of neurotoxic effects in cross-sectional epidemiological studies and clinical studies in human volunteers would not vary greatly from that derived below on the basis of studies in animal species.

The lowest reported levels inducing meaningful effects in experimental animals exposed to styrene by inhalation fall within a similar range; indeed, there is no clearly superior critical study and TCs derived on the basis of the lowest effect levels from several studies would be similar. For this assessment, the study by Kishi et al. (1992a,b) has been selected for the derivation of a TC since it leads to the most conservative value and since observed effects included both body weight changes and manifestations of neurotoxicity (including biochemical and behavioral effects).

On the basis of the 260 mg/m^3 (60 ppm) LOEL of the Kishi et al. (1992a,b) studies, a TC of 0.092 mg/cu.m was derived for inhalation exposure. A factor of 6/24 was used to convert from intermittent to continuous exposure. The ratio of inhalation volume to body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 [(12 m^3/day)/27 kg] was applied. An uncertainty factor of 500 (10 for interspecies variation, and 10 for intraspecies variation and 5 for use of a LOEL as the effects observed at this concentration were not clearly adverse).

Limited available data indicate that humans form less of the putative toxic metabolite, styrene-7,8-oxide, and hydrolyze it more quickly than experimental animals; however, available data were insufficient to take these differences into account in the development of the uncertainty factor, and the relevance of this metabolite to developmental and neurotoxic effects is not clear.

This tolerable concentration is within the range of that which would be derived on the basis of neurological effects in occupationally exposed populations.

Macromolecular adducts and genetic toxicity

The genetic toxicology of human styrene exposure and styrene macromolecular binding have been reviewed by several authors (IARC, 1994; Phillips and Farmer, 1994; Barale 1991; Norppa and Sorsa, 1993) and have mostly been studied in the reinforced plastics industry where styrene is the main chemical exposure. Only a few studies are available on other branches of industry, such as styrene production, where exposure to styrene is low. Exposure levels in the studies, evaluated on the basis of urinary styrene metabolites or workplace air samples, have ranged widely.

The levels of the *N*-terminal valine adduct of haemoglobin, *N*-(1-hydroxy-2-phenylethyl)valine, have been found to be four times higher in styrene-exposed workers than in controls. In a Swedish-Finnish study (Christakopoulos et al., 1993), increased levels of adducts to *N*-terminal valine in haemoglobin were seen in reinforced plastics workers (mean 28 pmol $\times$ g^{-1} globin) in relation to control persons (mean $\leq$13 pmol $\times$ g^{-1} globin). This level was low, while a background adduct level was also seen among the controls. A significant correlation of individual adduct levels and free styrene-7,8-oxide and styrene glycol in blood, as well as mandelic acid in urine, was seen in a regression analysis. Extrapolation from the metabolite monitoring data gave an estimate of about 320 mg/m^3 (75 ppm) for the workplace air styrene concentration. In another study, using similar techniques, but at lower exposure levels (30 mg/m^3, 7 ppm), no styrene-7,8-oxide adducts in *N*-terminal valine of haemoglobin were seen (Severi et al., 1994).

The first DNA adducts studies on humans exposed to styrene were published by Liu et al. (1988) who detected styrene-7,8-oxide modified guanine adducts in a single exposed person but none in a single unexposed individual.

Extensive studies on biomonitoring of styrene exposure using DNA adducts have been performed (Canadian Environmental Protection Act, 1993; Vodicka and Hemminki, 1993). Lamination workers from work sites representing high exposures (mean air styrene level 370 mg/m^3, 87 ppm) and moderate exposures (mean air styrene level 210 mg/m^3, 49 ppm) were studied. Using synthetic standards and the ^{32}P-postlabelling technique, O^6-(2-hydroxy-1-phenylethyl)-2'-deoxy-guanosine-3'-monophosphate (O^6-dGMP) adducts were detected among the exposed workers, at 7–16 times higher level than in the controls.

In a further study, where DNA adducts were investigated before and after a 2-week vacation, no decline in adduct levels was seen, indicating a slow removal of the specific O^6-guanine adducts of styrene from DNA (Vodicka et al., 1994). Horvath et al. (1994) studied DNA adducts by postlabelling in mononuclear blood cells of lamination workers and found two types of adducts, one identified as guanine N^2 adduct, to be increased with a significant linear relationship to individual measurements of airborne styrene, but not to SCE frequencies among the same workers. DNA adduct levels were highly elevated among the styrene exposed workers, with a correlation to DNA strand breakage measured by the comet assay, but not to mutant frequencies (hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus) (Vodicka et al., 1995). These results suggest that no simple quantitative relationships exist between the adducts and other parameters of DNA damage in human lymphocytes. In this study, control subjects from the administration of the same plastics factory also showed elevated adduct levels in comparison with unexposed control persons.

In studies on cytogenetic parameters – chromosomal aberrations, SCEs, and micronuclei – in peripheral lymphocytes of workers employed in the reinforced plastics industry (Sorsa et al., 1992; Mäki-Paakkanen et al., 1991; Brenner at al., 1991; Meretoja et al., 1977; Meretoja et al., 1978; Fleig and Thiess, 1978; Thiess and Fleig, 1978; Högstedt et al., 1979; Thiess et al., 1980; Andersson et al., 1980; Watanabe et al., 1981; Watanabe et al., 1983; Högstedt et al., 1983; Camurri et al., 1983; Camurri et al., 1984; Hansteen et al., 1983; Nordenson and Beckman, 1984; Pohlova and Sram, 1985; Mäki-Paakkanen, 1987; Forni et al., 1988; Jablonicka et al., 1988; de Jong et al., 1988; Hagmar et al., 1989; Kelsey et al., 1990; Yager et al., 1990; Yager et al., 1993; Perera et al., 1992; Tomanin et al., 1992; Hallier et al., 1994; Van Hummelen et al., 1994; Artuso et al., 1995; Anwar and Shamy, 1995; Norppa et al., 1981), positive findings have primarily concerned chromosomal aberrations, which have been observed to be increased in the majority of the studies. SCEs and micronuclei were also found to be increased in some studies.

On the basis of rough exposure estimates and observed frequencies of chromosomal aberrations, the NOAEL for long-term styrene exposure has been proposed to be 85–128 mg/m^3 (20–30 ppm) (Knudsen and Sorsa, 1993) or 213 mg/m^3 (50 ppm) (Barale, 1991).

A recent meta-analysis on cytogenetic data from 25 reports on occupational styrene exposure (Bonassi et al., 1996) showed a significant increase in weighed frequency ratio for chromosomal aberrations from studies with median styrene exposure above the chosen dichotomization point, 125 mg/m^3 (30 ppm); results for SCEs and micronuclei were inconclusive. Fleig and Thiess (1978) observed an increase in chromosomal aberrations in a worker group with high exposure to styrene (mean 486 mg/m^3, 114 ppm) but not in two other groups with lower exposure levels (2 and 8 mg/m^3). Anderson et al. (1980) observed an increase in the frequency of chromosomal aberrations with increasing total styrene exposure (expressed as the average concentration in mg/m^3 multiplied by the number of years of employment) in a low-dose group (mean total styrene exposure 137 mg/m^3) but not in a high-dose group (mean 1204 mg/m^3). Forni et al. (1988) found an increase of chromosomal aberrations in workers from a factory where current exposure to styrene was high (41–198 mg/m^3) but not in workers from another factory with low current exposure (1.7–17 mg/m^3); the latter group of workers – who had experienced a high exposure to styrene in the past and had, therefore, a high cumulative exposure – showed an increase in chromosomal aberrations. Mäki-Paakkanen et al. (1991) obtained a significant correlation between the number of cells with chromosomal aberrations and years of exposure. Tomanin et al. (1992) could demonstrate an elevation of chromosomal aberrations in a high-exposure group (115–443 mg/m^3) but not in a

low-exposure group (21–102 mg/m^3). Artuso et al. (1995) obtained a significant styrene-exposure dependent trend for both chromosomal aberrations and SCEs among a high-dose group (gel coaters, laminators, rollers and assemblers; exposure range 85–1389 mg/m^3), a low-dose group (other tasks; exposure range 2–119 mg/m^3), and controls.

Camurri et al. (1984) observed a significant increase in SCEs in workers in reinforced plastics plants with mean airborne styrene levels of more than 200 mg/m^3 but not in plants with mean levels of 30–200 mg/m^3. Yager et al. (1993) obtained a clear relationship among a group of boat manufacturers between SCE frequency and styrene exposure measured either as the concentration of styrene in workroom air (0.9– 234 mg/m^3; mean 64 mg/m^3) or in exhaled air. Hallier et al. (1994) observed an increase in SCEs among laminators exposed to high concentrations of styrene (approximately 170 mg/m^3) but not in formers exposed to much lower levels (43 mg/m^3). When hygienic and technical improvements at the workplace reduced the styrene exposure of the laminators to approximately 85 mg/m^3, a significant reduction in the SCE levels of the laminators was noted, although their values were still higher than in unexposed controls.

The few studies available on DNA strand breakage and *N*-acetylaminofluorene-induced unscheduled DNA synthesis in peripheral leukocytes have given positive results. DNA strand breaks were shown to disappear quickly from the peripheral leukocytes following the exposure, so that blood samples collected before the work shift could be used as control samples (Walles et al., 1993). Reinforced plastics workers showed elevated frequencies of GPA variant erythrocytes – a measure of mutations in the glycophorin A locus – with a significant effect especially among workers belonging to a high-exposure group (breathing zone styrene concentration ≥ 85 mg/m^3, 20ppm) (Bigbee et al., 1996). Another study also suggested an increase in GPA variant frequencies in a high-exposure group (average exposure concentration 136 mg/m^3, 32 ppm) as compared with a low exposure group (average exposure to 5.1 mg/m^3 , 1.2 ppm styrene), but final conclusions were complicated by inadequate matching of the groups (Compton-Quintana et al.,1993). Vodicka et al. (1995) observed a weak elevation in the frequency of HPRT mutations in T-lymphocytes, while another study (Tates et al., 1994) was considered inconclusive.

In summary, genotoxic effects have been observed in the blood cells of reinforced plastics workers for various endpoints at styrene exposure levels of around 85–128 mg/m^3 (20-30 ppm) and above. DNA breakage has been observed at exposure levels below 43 mg/m^3. The role of styrene in generating the genotoxic effects seen in reinforced plastics workers is supported by the elevated levels of styrene-7,8-oxide DNA adducts observed in their peripheral leukocytes. Such adducts appear to be distinguishable following occupational exposures to only a low concentration of styrene.

Genotoxicity assays on styrene in experimental animals have given conflicting results. The findings suggest a weak genotoxic activity for styrene *in vivo*, as revealed by the most sensitive techniques (SCEs and DNA strand breakage), especially in the mouse – the rodent species expected to be more susceptible than the rat or Chinese hamster to styrene.

Carcinogenic potential

IARC has classified styrene as a Group 2B, possibly carcinogenic to humans. EPA does not have a carcinogen classification for styrene; the chemical currently is undergoing an EPA Integrated Risk Information System (IRIS) review to establish such a classification. ATSDR, Health Canada, and RIVM have evaluated the carcinogenicity data for styrene. Health Canada classified styrene as "possibly carcinogenic to humans" (Group III) and also a "possible human germ cell mutagen"(Group III). RIVM concluded that styrene is not a genotoxic compound, and that the carcinogenic potential of styrene is related to the metabolite styrene oxide, but concentration of this metabolite in humans is very low due to rapid biotransformation to styrene glycol. Consequently, RIVM derived risk values based on noncancer endpoints. ATSDR has published a Toxicological Profile for Styrene. Although ATSDR discusses the carcinogenicity data in its Toxicological Profiles, it does not currently assess cancer potency or perform cancer risk assessments.

Cases of leukaemia and lymphoma were identified among workers exposed in the manufacture of styrene and polystyrene, and in the production or manufacture of styrene–butadiene (IARC, 1994).

Epidemiological studies of styrene have been conducted in three types of industry: production of glass-reinforced plastics products, production of styrene monomers and styrene polymerization, and production of styrene–butadiene rubber. The malignancies observed in excess most frequently are of the lymphatic and haematopoietic system.

Reinforced plastics industry

In a European multinational study of more than 40 000 workers in the glass-reinforced plastics industry (660 plants), no overall excess of deaths from lymphatic and haematopoietic cancers was observed in comparison with national controls (Kogevinas et al., 1994). An increased risk for lymphatic and haematopoietic tumours was observed in Poisson

regression models for years since first exposure ($P = 0.012$) and for average exposure ($P = 0.19$) but not for cumulative exposure. Within the models, there was an increasing trend in risk for lymphatic and haematopoietic cancer with average intensity of exposure, culminating in a relative risk (RR) of 3.6 (95% confidence interval (CI), 1.0–13) for the highest category, >852 mg/m^3; for more than 20 years since first employment, the RR was 4.0 (95% CI, 1.3–12). Nonsignificant increases in risk with time since first exposure or cumulative exposure were noted for cancers of the pancreas, kidney, and oesophagus.

A study of cancer incidence in the reinforced plastics industry in Denmark involved 12 800 male workers who had been included within the above study and a further 24 000 workers with a lower probability of exposure to styrene. The mean annual air concentrations of styrene calculated for 128 of the companies studied ranged from 767 mg/m^3 in 1964–1970 to 183 mg/m^3 in 1976–1988. Within this cohort, there were 112 malignancies of the lymphatic and haematopoietic system, with 93.7 expected (standardized incidence ratio (SIR), 1.2; 95% CI, 0.98–1.4). In workers with more than 10 years since first employment, the SIR for leukaemia was 157 (107–222). The excess was concentrated mainly in those workers not previously included in the European study, in short-term workers with at least 10 years since first employment and in those employed before 1970 (Kolstad et al., 1994). The same authors also reported the occurrence of deaths from solid cancers among the 36.610 reinforced plastics workers (Kolstad et al., 1995). An increased incidence rate ratio (IRR) for pancreatic cancer was found (IRR 2.2, 95% CI, 1.1– 4.5).

In a large study on 5826 employees who had worked for at least 6 months between 1948 and 1977 in 30 reinforced plastics plants in the United States, no overall increase in risk for lymphatic and haematopoietic malignancies was observed (Wong, 1990; Wong et al., 1994). The follow-up continued until the year 1989. The overall mortality rate was 108 (95% CI, 103–113), and the mortality rate from all cancers was 116 (95% CI, 105–127). Total lympho-haematopoietic cancers showed no excess. For workers involved in open-mould processing with high exposure to styrene, the standardized mortality ratio (SMR) for lymphatic and haematopoietic cancers was 141 (based on four cases). For the highest cumulative exposure (>426 mg/m^3 × years) and more than 20 years of latency, the SMR was 134 (5–373). Mortality for cancers at a number of sites was increased significantly. These included oesophagus (mortality rate 198; 95% CI, 105–322), bronchus, trachea, and lung (141; 120–164), cervix uteri (284; 136–521), and other female genital organs (202; 107–345). No positive dose–response relationship was found for the lympho-haematopoietic cancers or any other cancer in excess; IARC (1994), however, noted that the possibility that the two exposure variables included in the regression model were correlated may have reduced the likelihood of accurate assessment

A smaller study of 5021 employees in two reinforced plastics boat-building facilities in the United States showed no deaths from leukaemia or lymphomas (1.7 and 2.1 expected, respectively) (Okun et al., 1985). 2060 individuals were considered to have had high exposure to styrene (mean levels of styrene in the air in two facilities, 181 and 305 mg/m^3); 48% of them had worked only for one month to one year and only 5% for more than 5 years. In this group, no lymphatic or haematopoietic cancers were seen (about 1 expected).

A deficit of deaths from lymphatic and haematopoietic malignancies (6 observed, 14.9 expected) was reported in a cohort of 7949 men and women employed during 1947–1984 in eight companies in the United Kingdom manufacturing glass-reinforced plastics involving high exposure to styrene (Coggon et al., 1987). A nonsignificant excess was seen in deaths from cancers of the lung, pleura and mediastinum (SMR, 126; 95% CI, 94–166); this finding particularly related to workers who had had 1–9 years of exposure to styrene, but the risk did not increase with time from the first exposure. Follow-up of this cohort was later extended to 1990 as part of an international collaborative study (Kogevinas *et al., 1994)*. By that time the previous deficit of lymphatic and haematopoietic cancer had largely disappeared (13 deaths; SMR, 88; 95% CI, 47–151) and the excess of lung cancer was less marked (77 deaths; SMR, 106; 95% CI, 84–132).

Styrene manufacture and polymerization
A study of chemical workers in the production of styrene and styrene derivatives in the United States found seven deaths from lymphatic and haematopoietic malignancies (except leukaemias) (SMR, 132; 95% CI, 58–272) and six from leukaemias (SMR 176; 95% CI, 64–383) (Ott et al., 1980). In an update, a total of 28 deaths from lymphatic and haematopoietic cancer were recorded (SMR 144; 95% CI, 95–208) (Bond et al., 1992).

A smaller United Kingdom study of 622 men exposed for at least a year in the production, polymerization and processing of styrene found an excess of deaths from lymphoma (3 observed, 0.56 expected) (Hogdson and Jones, 1985).

Styrene–butadiene rubber production
The large cohorts of styrene–butadiene rubber workers showed increased risks for lymphatic and haematopoietic malignancies, but nested case–control analyses found little evidence for relationship to styrene (Matanoski et al., 1990; Santos-Burgoa et al., 1992; Matanoski et al., 1993). The styrene exposures in these industries are at least one order of magnitude lower than in the reinforced plastics industry.

In summary, several epidemiological studies have suggested that workers exposed to styrene in the reinforced plastics industry have increased risk of lymphatic and haematopoietic tumours. The studies are not, however, fully conclusive because the observed associations are often based on small numbers, and in larger studies, dose relations are somewhat obscure.

Interactions with other chemicals

Styrene metabolism is known to be inhibited by the presence of other chemicals such as toluene, trichloromethylene, and ethyl benzene. The biotransformation of styrene in rats to PGA, MA, and hippuric acid was suppressed by coadministration of toluene (Ikeda et al. 1972). This may be due to competitive inhibition of oxidative mechanisms. Similar results were reported by Ikeda and Hirayama (1978) in rats when styrene metabolism was inhibited by the administration of trichloroethylene. Urinary metabolites of styrene may be markedly reduced when humans or animals are concurrently exposed to organic solvents that inhibit styrene metabolism.

Odour perception

Source: WHO (2001)
The odour threshold for styrene is only 70 $\mu g/m^3$ (0.016 ppm). Its characteristic pungent odour is recognized at concentrations 3–4 times higher than this threshold value. Some individuals can perceive the odour at levels lower than 70 $\mu g/m^3$, but, in general, odour problems are not likely to occur if peak concentrations in the ambient air are kept below this threshold value. When styrene is emitted into the air, its half-time is estimated to be 2 hours. In ambient air it is chemically transformed into benzaldehyde and formaldehyde, both of which are odorous air pollutants (WHO, 1987).

Source: AIHA (1989)
Detection: 72 – 8100 $\mu g/m^3$ (0.017-1.9 ppm)
Recognition: 640 $\mu g/m^3$ (0.15 ppm)

Source: New Jersey department of health and senior services - Hazardous Substance Fact Sheet
Odor threshhold = 85 – 2000 $\mu g/m^3$ (0.02 - 0.47 ppm)

Source: (Hoshika et al., 1993)
Barely perceptible concentration level of styrene: 0.068/0.140 mg/m^3 (in The Nederlands and Japan, respectively)
International comparison of odor threshold values of several odorants in Japan and in The Netherlands, given as the barely perceptible concentration level revealed striking similarities for hydrogen sulfide (in Japan 0.0005 ppm/in The Netherlands 0.0003 ppm), phenol (0.012/0.010), styrene (0.033/0.016), toluene (0.92/0.99), and tetrachloroethylene (1.8/1.2) but not for m-xylene (0.012/0.12). Such a similarity was not found with any other literature sources.

Summary of Styrene Dose Response Assessment

Exposure other than inhalation: Dermal absorption from ambient air <5% of the dose absorbed in the respiratory tract

Toxicokinetics: 60-70% pulmonary retention; widely distributed throughout the body; styrene-oxide in blood linearly correlated with ambient styrene; no evidence of accumulation at occupational levels (160 mg/m^3) due to fast enzymatic oxidation/hydrolysis to MA and PGA and biphasic elimination; MA+PGA used for biological monitoring.

Health effect levels of short- and long-term exposure (noncancer)

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
217 $_{EXP}$	422 $_{EXP}$	Eye and throat irritation	Volunteers, 1h (NOAEL), 20m (LOAEL)	Stewart *et al.*, 1968	OEHHA (1999); REL: 21
Long-term exposure					
	64 $_{Study}$ 17 $_{MLE}$ 7.2 $_{BC05}$ 2.6 $_{ADJ}$	CNS; neuropsychological tests: reaction time, s/l term logic memory, s/l term verbal memory, digit-symbol association, block design and figure identification.	Occupational, 8.6y	Mutti *et al.* 1984b	OEHHA (1999); REL: 0.9
94 $_{95\%lCL}$ 34 $_{ADJ}$	>94$_{95\%lCL}$	see above	Occupational, 8.6y;	Mutti *et al.* 1984b	EPA-IRIS (1992); RfC: 1
	107 $_{Study}$ 25 $_{ADJ}$	see above	Occupational 8.6y;	Mutti *et al.* 1984b	ATSDR (1992); MRL: 0.25; WHO (2001); GV: 0.26; RIVM (2000)
	260 $_{EXP}$ 65 $_{ADJ}$ 46 $_{HEC}$	Neurological developmental; body weight, biochemical parameters in the brain and behaviour	Rat offspring	Kishi et al.,1992a,b	Health Canada (1993); TC: 0.092

Carcinogenicity: IARC: 2B ; ACGIH: A4 ; Little evidence of carcinogenicity in humans (WHO)

Genotoxicity: Genotoxic in vitro and in vivo; increased chromosomal aberrations evidenced in numerous occupational studies; proposed NOAELs based on this endpoint were >85 mg/m^3. Although genotoxic effects in humans have been observed at relatively low concentrations, they were not considered as critical endpoints for development of a guideline, in view of the equivocal evidence for the carcinogenicity of styrene (WHO).

Odour threshold: Range: 0.072 - 8.1 mg/m^3, recognition: 0.64 mg/m^3 (AIHA); Threshold: 0.07 mg/m^3 (WHO); 0.23 (Devos); Barely perceptible concentration levels: 0.140/0.068 mg/m^3 in Japan/The Nederlands, respectively (Hoshika et al., 1993).

Susceptible population: Asthmatics may be more sensitive to adverse pulmonary effects; immediate bronchoconstriction observed in occupational (styrene) asthmatics at 64 mg/m^3.

Remarks: RD$_{50}$: 3.3 g/m^3; styrene toxicity is enhanced (metabolism slowed down, with increase of styrene oxide in blood) by exposure to other solvents (incl.ethanol)

6. Risk Characterization

Health hazard and cancer risk evaluation of short- and long-term exposure
(Adapted from WHO, 2001 - Air Quality Guidelines for Europe)

Potentially critical effects for the derivation of an exposure limit (EL) for styrene are considered to be carcinogenicity/genotoxicity and neurological effects, including effects on development. The value of the available evidence for an association between exposure to styrene and small increases in lymphatic and haemotopoietic cancers observed in workers in some studies is limited by concurrent exposure to other substances, lack of specificity and absence of dose–response. In limited studies in animals, there is little evidence that styrene is carcinogenic. IARC has classified styrene in group 2B.

Styrene was genotoxic in vivo and in vitro following metabolic activation. In cytogenetic studies on peripheral lymphocytes of reinforced plastics workers, there were increased rates of chromosomal aberrations at mean levels of styrene of more than 120 mg/m^3. Elevated levels of single-strand breaks and styrene-7,8-oxide adducts in DNA and haemoglobin have also been observed. Although these genotoxic effects have been observed at relatively low concentrations, they were not considered as critical endpoints for the development of a WHO Air Quality Guideline, in view of the equivocal evidence of carcinogenicity for styrene.

The available data, although limited, indicate that neurotoxicity in the form of neurological developmental impairments, is among the most sensitive of endpoints. In the offspring of rats exposed to styrene at a concentration of 260 mg/m^3, there were effects on biochemical parameters in the brain and behaviour.

Studies in workers exposed to styrene in workplace air suggest that neurological effects are probably the most sensitive indicator of styrene toxicity. Available data do not.provide a clear picture of the NOAEL for neurological effects following acute- or intermediate-duration inhalation exposure. A chronic study in workers (Mutti et al. 1984a) identified subtle effects such as reductions in visuomotor accuracy and verbal learning skills, and subclinical effects on colour vision have been observed at concentrations as low as 107–213 mg/m^3. Taking the lower number of this range as a LOAEL (for precautionary reasons) and adjusting this value in order to allow for conversion from an occupational to a continuous pattern of exposure (dividing by 4.2) a concentration of 25 mg/m^3 is obtained. Incorporating a factor of 10 for interindividual variation and 10 for use of a LOAEL rather than a NOAEL this results in an EL of 0.25 mg/m^3 (to be applied as a weekly average; see also Table 6.1). This value should also be protective for the developmental neurological effects observed in animal species.

Since available data do not.provide a clear picture of the NOAEL for neurological effects following acute exposure, a short-term EL was here derived based on irritation of the eyes and mucous membranes. Stewart *et al*. (1968) found eye and throat irritation in 3 out of 6 volunteers exposed to 422 mg/m^3 styrene for 20 minutes. No symptoms were reported in 3 subjects after exposure to 217 mg/m^3 for 1 hour. A short-term EL is here derived applying an assessment factor of 100 for interindividual variation (10) and the possibility (limited evidence) that asthmatics may be more sensitive to adverse pulmonary effects (10) from styrene exposure (Moscato *et al*., 1987).

The odour threshold for styrene is only 70 µg/m^3. Its characteristic pungent odour is recognized at concentrations 3–4 times higher than this threshold value. Some individuals can perceive the odour at levels lower than 70 µg/m^3, but, in general, odour problems are not likely to occur if peak concentrations in the ambient air are kept below this threshold value.

Table 6.1: Derivation of short- and long-term exposure limits

	Effect level - mg/m^3		Assessment factor	EL mg/m^3	Toxicological endpoint
Short-term Exposure Limit	Human NOAEL Volunteers	217	100[bc]	2	Eye and throat irritation
Long-term Exposure Limit	Human LOAEL Occupational	25	100[ab]	0.25	CNS; neuropsychological tests: reaction time, s/l term logic memory, s/l term verbal memory, digit-symbol association, block design and figure identification.

[a] not considering a NOAEL (10); [b] interindividual variation (10) ; [c] susceptible population (10)

Relevance of EU-population exposure to styrene

Table 6.2: Percentage of population exposed beyond the derived EL and margins of safety

Available exposure data		EL	Margins of Safety (MOS)
Description (Study, Year)	N	0.25* mg/m^3	50th (90th)
Athens 30-h TWA (Expolis, 96-98)	42	<	181 (71)
Basel 30-h TWA (Expolis, 96-98)	47	<	470 (182)
Helsinki 30-h TWA (Expolis, 96-98)	188	<	184 (103)
Milan 30-h TWA (Expolis, 96-98)	38	<	77 (20)
Oxford 30-h TWA (Expolis, 98-00)	40	<	225 (64)
Prague 30-h TWA (Expolis, 96-98)	46	<	164 (64)
German Survey 48-h PEM (GerEs II, 1990-92)	113	<	125 (36)
French National Survey 7d-TWA (IAQ observatory; 2003-04)	109	<	250 (96)
		Avg. MOS:	235 (79)

< out of the evaluation range (i.e. <5% of the environments investigated);
* corresponds with WHO guideline value (weekly average)

Result

A long-term exposure limit of 250 μg/m^3 has been derived based on the assumption that neurological effects are probably the most sensitive indicator of styrene toxicity. When examining the results of eight monitoring surveys (Table 6.2) it can be concluded that background styrene concentrations in European residences are of no concern to human health since median levels are, on average, two orders of magnitude below the established EL. Although no acute exposure data were available, it is unlikely that styrene emissions associated with human indoor activities would generate levels up to the proposed short-term EL of 2000 μg/m^3, considered protective for irritative effects in asthmatics. Although genotoxic effects in humans have been observed at relatively low concentrations, they were not considered as critical endpoints for the derivation of the exposure limit, in view of the equivocal evidence for the carcinogenicity of styrene in humans (WHO).

Ammonia

Synonyms: -
CAS Registry Numbers: 7664-41-7
Molecular Formula: NH_3

1. Compound identification

Ammonia is a colourless gas with a sharp, irritating odour. Ammonia has both natural and anthropogenic sources. It is a key compound in the global nitrogen cycle. It is formed in the body during decomposition of organic materials. The most common natural sources of ammonia include the natural breakdown of manure and dead plants and animals. Majority of all manufactured ammonia is used as fertilizers. It is also released to the atmosphere by leaks during commercial synthesis, production, and transportation, or sewage, burning of coal, wood, and other natural products, and volcanic activity. Ammonia is used to manufacture synthetic fibres, plastics, explosives, and many cleaning products. It is also used as a refrigerant. (WHO 1997, ATSDR, 2002)

Since ammonia occurs naturally in the environment, the general population is exposed to ammonia in air, soil, and water. People are frequently exposed to ammonia while using household products that contain ammonia, such as cleaning solutions, window cleaners, floor waxes, and smelling salts. Household ammonia solutions usually contain 5-10% ammonia in water. Also those who live near farms or cattle feedlots, poultry confinement buildings, or in the vicinity of other areas with high animal populations may be exposed to elevated ammonia levels (ATSDR 2002, EPA/Cal 2003).

Typical environmental ammonia concentrations have not been reported to cause adverse health effects in general population. However, low levels of ammonia may harm some asthmatics and other sensitive individuals (ATSDR 2002).

2. Physical and Chemical properties

Molecular weight (g/mol)   17.03
Melting point (°C)   -77.7
Boiling point (°C)   33.35
Density (g/l at 0 oC, 1 atm)   0.77
Relative density (air =1)   0.59
Solubility: Soluble in water and oxygenated solvents

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 0.707 µg/m3
1 µg/m3 = 1.414 ppb

Source: Verschueren 2001, HSDB 2003.

3. Indoor Air Exposure assessment

Indoor air and exposure concentrations

There is a lack of knowledge and publications about indoor concentrations and exposures of ammonia. Ammonia is studied mostly as an ambient pollutant. Typical ambient background concentrations of ammonia are between 0.71

$\mu g/m^3$ and 3.55 $\mu g/m^3$ (1 and 5 ppb) (ATSDR 2002). Fisher et al (2003) determined indoor and outdoor concentrations of ammonia in an unoccupied residence in Clovis California from October 2000 to January 2001. Monthly mean indoor concentrations ranged from 10.9 $\mu g/m^3$ to 15.1 $\mu g/m^3$, while mean outdoor concentrations were always lower ranging from 8.80 $\mu g/m^3$ to 9.66 $\mu g/m^3$.

Considerably high ammonia concentrations have been measured in new buildings built in 1994–1997 in Finland. Average concentrations exceeded 50 $\mu g/m^3$. Construction materials such as glues, fillers used in floors, walls and ceilings, have been identified as ammonia sources in indoor environments. Ammonia is emitted from these materials by chemical breakdown processes, especially in the presence of moisture.

Puhakka et al (2000) studied reparation methods to reduce ammonia concentrations in 'ammonia problem' buildings. They found the highest indoor air concentrations during preparation and very high levels inside the floor structures up to 15370 $\mu g/m^3$. The reparation of floor did not reduce ammonia concentrations in two months after the reparation, but in other studies indoor concentrations started to decline in 6–8 months after the reparation.

Residential indoor concentrations of ammonia in homes with and without known indoor air quality (IAQ) problems have been monitored in Finland (VTT 2003). Average indoor concentrations of ammonia in homes with and without IAQ problems were 30 $\mu g/m^3$ and 24 $\mu g/m^3$, respectively. Especially, if the building materials became wet due to water damage or poor ventilation of the building structures, elevated ammonia concentrations were usually detected in indoor air. Casein-containing materials were identified a source of ammonia in these cases (Saarela, 2003). Cumulative distributions of ammonia in homes with and without IAQ problems in Finland are presented in Figure 3.1. Short time mean concentrations of ammonia are summarised in Table 3.1.
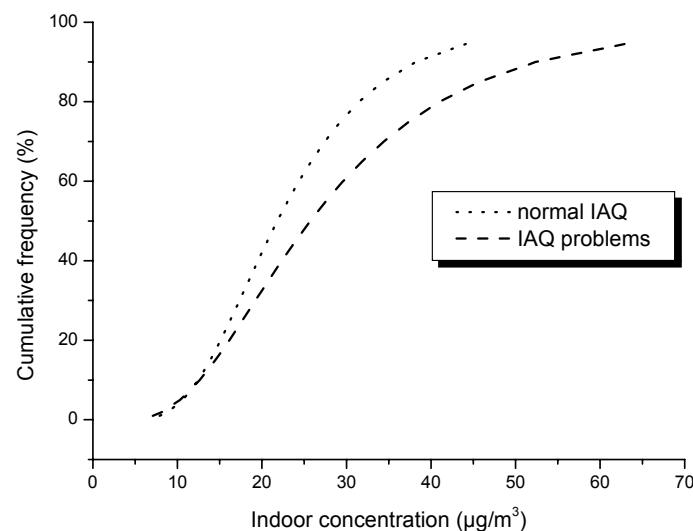
Figure 3.1. Cumulative distributions of residential indoor concentrations of ammonia in Finland in homes without and with indoor air quality (IAQ) problems (VTT 2003).

Table 3.1. Short time ammonia concentrations related to specific microenvironments or emission sources.

Environment or emission source		Averaging time	Concentration ($\mu g/m^3$) AM	range	Reference
Problem buildings	before floor repairs		27 - 79		Puhakka et al 2000
	during repairs		46 - 237		
	2 months after repairs		29 - 99		
	inside the floor structure		3810 - 15370		
Dwellings	empty dwellings	100-min	21	5 - 49	Saarinen et al 2002
	inhabited dwellings	100-min		9 - 90	
New apartments		2-hour		21 - 42	Tuomainen and Pirinen 2002
Toilets	with septic tank	10-minute	1244		Hyung-Suk and Byung-Kee 1993
	traditional vault system		7395		
Homes	kerosene heaters	8 -12-hour	11		Leaderer et al 1993
	gas range	8 -12-hour	8.5		
	no gas appliances	8 -12-hour	7.1		
Archives of the university library	Helsinki downtown		4-12		Raiala et al 1993
	Mikkeli		< 5		

AM = arithmetic mean

4. Toxicokinetics

Absorption

At low concentrations, inhaled ammonia dissolves in the mucous fluid lining of the upper respiratory tract and little reaches the lower airways. At ammonia levels associated with ambient air (i.e., 1 - 200 $\mu g/m^3$), very little, if any, is absorbed through the lungs.

Experiments with volunteers show that ammonia, regardless of its tested concentration in air (range = 40–350 mg/m^3), is almost completely retained in the nasal mucosa (83–92%) during short-term exposure, i.e., up to 120 seconds (Landahl and Herrmann 1950). However, longer-term exposure (10–27 minutes) to a concentration of 350 mg/m^3 resulted in lower retention (4–30%), with 244-279 mg/m^3 eliminated in expired air by the end of the exposure period (Silverman et al. 1949), suggesting an adaptive capability or saturation of the absorptive process. Nasal and pharyngeal irritation, but not tracheal irritation, suggests that ammonia is retained in the upper respiratory tract. Unchanged levels of blood-urea-nitrogen (BUN), non-protein nitrogen, urinary-urea, and urinary-ammonia are evidence of low absorption into the blood.

Distribution

Absorption data from human inhalation exposure suggest that only small amounts of ammonia are absorbed into the systemic circulation (Silverman et al. 1949; WHO 1986). Toxic effects reported from inhalation exposure suggest local damage, or changes resulting from necrotic tissue degradation, rather than the presence of elevated levels of NH_4^+, per se, in tissues other than the respiratory/pharyngeal tissues.

Information on the distribution of endogenously-produced ammonia suggests that any NH_4^+ absorbed through inhalation would be distributed to all body compartments via the blood, where it would be used in protein synthesis or as a buffer, and that excess levels would be reduced to normal by urinary excretion, or converted by the liver to glutamine and urea. If present in quantities that overtax these organs, NH_4^+ is distributed to other tissues and is known to be detoxified in the brain (Takagaki et al. 1961; Warren and Schenker 1964).

Metabolism and elimination

Quantitative data on human metabolism of exogenously introduced ammonia were not located in the available literature.

Ammonia and ammonium ion are metabolized to urea and glutamine mainly in the liver (Fürst et al., 1969; Pitts,1971). However, it can be rapidly converted to glutamine in the brain and other tissues as well (Takagaki et al. 1961; Warren and Schenker 1964).

Studies using low levels of ammonia show that inhaled ammonia is temporarily dissolved in the mucus of the upper respiratory tract, and then a high percentage of it is released back into the expired air.

The quantitative difference between inspired and expired ammonia suggests that small amounts are absorbed across the nasopharyngeal membranes into the systemic circulation. Absorbed ammonia is excreted by the kidneys as urea and urinary ammonium compounds (Gay et al. 1969; Pitts 1971; Richards et al. 1975; Summerskill and Wolpert 1970), as urea in feces (Richards et al. 1975), and as components of sweat (Guyton 1981; Wands 1981), but quantitative data are lacking. Toxic levels do not develop as a result of chronic inhalation exposure because the body has multiple effective mechanisms for detoxifying and excreting it.

5. Health effects

Effects of short-term exposure

The available human and animal data provide strong evidence that acute-duration exposure to ammonia can result in site-of-contact lesions primarily of the eyes and the respiratory tract. Even fairly low airborne concentrations (35 mg/m^3) of ammonia produce rapid onset of eye, nose, and throat irritation, coughing, and narrowing of the bronchi. More severe clinical signs include immediate narrowing of the throat and swelling, causing upper airway obstruction and accumulation of fluid in the lungs. This may result in low blood oxygen levels and an altered mental status. Mucosal burns to the tracheobronchial tree can also occur. Children may be more vulnerable to corrosive agents than adults because of the smaller diameter of their airways.

The eye is especially sensitive to alkali burns. Ammonia combines with moisture in the eyes and mucous membranes to form ammonium hydroxide. Ammonium hydroxide causes saponification and liquefaction of the exposed, moist epithelial surfaces of the eye and can easily penetrate the cornea and damage the iris and the lens (CCOHS, 1988; Way et al., 1992). Damage to the iris may eventually lead to cataracts (CCOHS, 1988).

Silverman and coworkers (1949) exposed 7 volunteers to 348 mg/m³ (500 ppm) ammonia for 30 minutes using an oral-nasal mask. Symptoms due to ammonia inhalation varied widely among the 7 subjects. All seven subjects experienced upper respiratory irritation, which was graded as severe in 2 subjects. Only 2 subjects were able to continue nasal breathing throughout the 30 minute exposure. Reactions included irritation of the nose and throat, hypoesthesia of the exposed skin, and lacrimation. In two subjects, the nasopharyngeal irritation persisted for 24 hours after the exposure. One of the 7 subjects was only exposed to ammonia for 15 minutes rather than the full 30 minutes. The reason for this deviation in the exposure regimen was not given. In a previous experiment, brief exposure to 696 mg/m³ (1000 ppm) reportedly resulted in immediate coughing in human subjects.

Ferguson and coworkers (1977) used six human subjects to demonstrate that a tolerance to ammonia exposure of 70 mg/m³ (100 ppm) can be developed with a two-to-three week inurement period during which volunteers were exposed to lesser concentrations. The results tended to support the belief that persons with no recent history of ammonia exposure are more sensitive to the irritating effects than those who are acclimated to the noxious gas.

Verberk (1977) exposed sixteen volunteers (8 science faculty with knowledge of the effects of ammonia and 8 non-science university students not familiar with ammonia health effects) were exposed, 4 at a time, to 35, 56, 77, 98 mg/m³ (50, 80, 110, and 140 ppm) ammonia for 2 hours. Each group was exposed to each exposure level with 1 week in between exposures. Immediately before and after exposure, respiratory function tests (vital capacity [VC], forced expiratory volume in the first second [FEV$_1$], and forced inspiratory volume in the first second [FIV$_1$]) were done. During exposure, each participant recorded subjective effect levels for smell, taste, irritation of eyes, irritation of nose, irritation of throat, irritation of breast, urge to cough, headache, and general discomfort. The scale used was: 0=no sensation, 1=just perceptible, 2=distinctly perceptible, 3=nuisance, 4=offensive, and 5=unbearable. A (+) or (−) could be used to interpolate between the levels. A few weeks after the experiments, the histamine threshold was determined for 13 of the 16 volunteers as a measure of pre-existing non-specific reactivity of the airways to exogenous stimuli.

None of the participants was hypersusceptible to nonspecific irritants. No participant had a decrease of more than 10% of pre-exposure values for VC, FEV$_1$, or FIV$_1$. There was a difference between the science faculty group (experts) and the students for the subjective scoring. Students consistently scored higher for smell and there was little increase in score with concentration. Score for irritation of the eyes increased with concentration and there was no difference

between groups. Irritation of the throat had a sharp increase in score with concentration and scores were higher for students. All students left the exposure chamber between 0.5 and 1.25 hours in the 98 mg/m³ exposure because of severe irritation. Scores for urge to cough and general discomfort were low in the expert group, but increased with concentration in the student group. All students left the chamber before 2 hours of exposure to 98 mg/m³.

At the end of the initial 30 minutes of the 2-hour exposure period, nuisance level smell, eyes, nose, or throat irritation, or cough urge were reported by 7 of 16 (44%), 9 of 16 (56%), 12 of 16 (75%), or 15 of 16 (94%) individuals at concentrations of 35, 56, 77, 98 mg/m³, respectively.

MacEwen *et al*. (1970) exposed groups of 5 and 6 human subjects to respective ammonia concentrations of 21 and 35 mg/m³ (30 and 50 ppm). The volunteers subjectively rated irritation for the 10-minute exposures. No moderate or higher irritation was discerned by the group at the lower exposure level; however, 4 of the 6 subjects rated the 10 minute exposure at 35 mg/m³ as causing moderate irritation.

The Industrial Bio-Test Laboratories (1973) evaluated ten human subjects for the irritation threshold of ammonia from exposures to ammonia gas at four different concentrations: 22, 35, 50, and 93 mg/m³. Irritation was taken to be any annoyance to the eyes, nose, mouth, throat, or chest which persisted throughout the 5-minute exposure period. At 50 mg/m³ three subjects experienced eye irritation, two had nasal irritation, and three had throat irritation. At 93 mg/m³, five of the ten subjects experienced lacrimation and eye irritation, seven complained of nasal irritation, eight had throat irritation, and one experienced chest irritation. The authors only used 5-minute exposure durations; and it is possible that irritation symptoms could have developed with longer exposure durations at the lower exposures. The authors discounted the significance of nasal dryness reported at the two lowest levels.

Douglas and Coe (1987) determined a lachrymatory threshold of 38 mg/m³ for ammonia following approximately 15 second exposures of volunteers via tight-fitting goggles. The threshold for bronchoconstriction, determined as a 20% increase in airway resistance, was slightly higher at 59 mg/m³ following 10 breaths of ammonia via mouthpiece.

Tolerance appears to develop with repeated exposure (Sekizawa and Tsubone 1994; Verberk 1977). Thus, subjects exposed to 70, but not 35 mg/m³ ammonia 6 hours/day, 5 days/week for 6 weeks experienced nose and throat irritation only during the first week (Ferguson et al. 1977).

Estimates of odor thresholds for ammonia vary from 0.03-72 mg/m³ (Ferguson *et al*., 1977; Henderson and Haggard, 1943; Ruth, 1986). Near the odor threshold, persons exposed to ammonia can experience annoyance and believe the odor to be a nuisance. Exposure to ammonia may result in an exacerbation of preexisting asthma. Shim and Williams (1986) surveyed 60 patients with a history of asthma worsened by certain odors. Nearly 80% of these patients claimed to have an exacerbation of asthma following exposure to household cleaners containing ammonia.

Summary of short-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
	14.0 $_{1h\text{-}ADJ\text{-}MLE}$ 9.5 $_{BC05}$	eye and respiratory irritation	volunteers, 1h-adjusted Benchmark approach	Industrial Biotest Laboratories, 1973; MacEwen *et al*., 1970; Silverman *et al*., 1949; Verberk, 1977	OEHHA 1999; REL: 3.2
	35 $_{EXP}$	irritation to nose and throat; urge to cough	volunteers, 2h	Verberk, 1977	ATSDR 2002; MRL: 1.2
No study with asthmatics! Final statement (UNIMI): Human LOAEL: 35 mg/m³					

$_{Study}$ average concentration ; $_{EXP}$ experimental concentration ; $_{ADJ}$ concentration adjusted from an intermittent to a continuous exposure ; $_{1h\text{-}ADJ}$ concentration adjusted to 1-hour exposure duration ; $_{HEC}$ human equivalent concentration ; $_{MLE}$ maximum likelihood estimate for 5% response ; $_{BC05}$ 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; $_{STAT}$ lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of Acute Reference Exposure Level protective against mild adverse effects (for a 1-hour exposure)
   Study   Industrial Biotest Laboratories, 1973; MacEwen *et al*., 1970;
                            Silverman *et al*., 1949; Verberk, 1977

Study population	humans
Exposure method	inhalation
Critical effects	eye and respiratory irritation
LOAEL	varied (see the text)
NOAEL	varied (see the text)
Exposure duration	varied (see the text)
Extrapolated 1 hour concentration	9.5 mg/m^3 (BC05)
LOAEL uncertainty factor	not needed in BC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Reference Exposure Level	4.5 ppm (3.2 mg/m³; 3200 μg/m³)

The exposure concentrations from the 4 studies were adjusted to 1-hour durations using the formula $C^n \times T = K$ (Table 5.2). The value for the exponent n was empirically derived from the preceding data sets. The value of n (in the formula $C^n \times T = K$) was sequentially varied for the log-normal probit relationship analysis. Using a chi-square analysis, a value of n = 4.6 was found to be the best fit.

The REL was calculated by a benchmark concentration (BC) approach using a log-normal probit analysis (Crump and Howe, 1983; Crump. 1984). The 95% lower confidence limit of the concentration expected to produce a response rate of 5% is defined as the BC05. The maximum likelihood estimate for a 5% response was 14.0 mg/m^3 (20.1 ppm) and the 95% LCL on this value (BC05) for ammonia from this analysis was 9.5 mg/m^3 (13.6 ppm).

Response rate	MLE (mg/m^3)	95% LCL (mg/m^3)
1%	9.3	5.4
5%	14.0	9.5 (BC$_{05}$)

An uncertainty factor (UF) of 3 was used to account for intraspecies variation in the human population.

Table 5.2: Ammonia, Human Irritation, 60 Minute Exposures (adjusted), mg/m^3

Study	Study concentration	Exposure time	60 min adjusted concentration	Response
Industrial Biotest Laboratories, 1973	22	5	13	0/10
MacEwen et al., 1970	21	10	14	0/5
Industrial Biotest Laboratories, 1973	35	5	20	0/10
MacEwen et al., 1970	35	10	24	4/6
Industrial Biotest Laboratories, 1973	50	5	29	3/10
Verberk, 1977	35	120	30	7/16
Verberk, 1977	56	120	48	9/16
Industrial Biotest Laboratories, 1973	93	5	54	8/10
Verberk, 1977	77	60	66	12/16
Verberk, 1977	98	60	84	15/16
Silverman et al., 1949	348	30	299	7/7

Table adapted from: Verberk, 1977; Industrial Biotest Laboratories, 1973; MacEwen et al., 1970; and Silverman et al., 1949. The two lowest concentrations were combined for the log-probit analysis since this improved the fit of the data.

Graphic Representation of Benchmark Concentration Determination
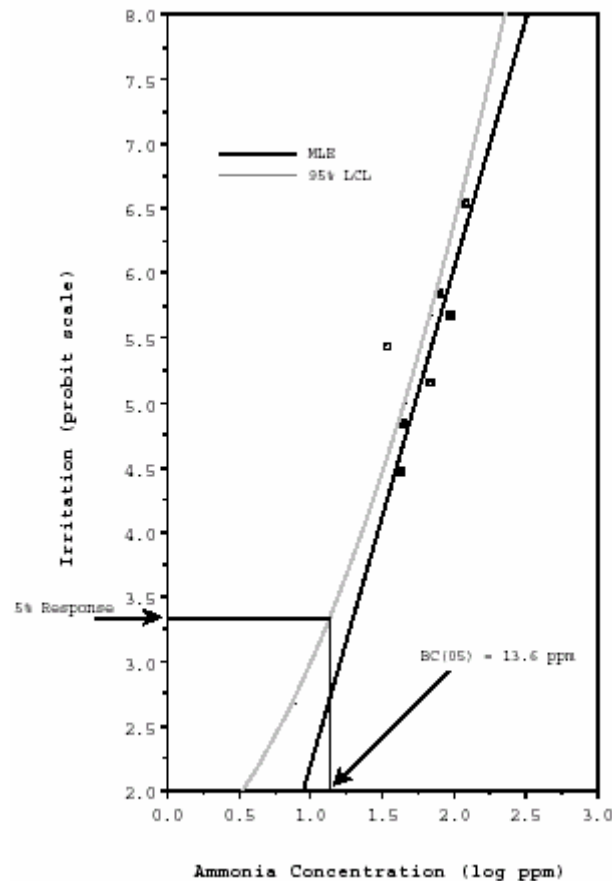
ATSDR (1999)
Agency for Toxic Substances and Disease Registry

Derivation of a Minimal Risk Level (MRL):
An acute inhalation MRL of 1.2 mg/m³ (1.7 ppm) was derived from the Verberk (1977) study. Dose and end point used for MRL derivation are 35 mg/m³ (50 ppm) for mild irritation to the eyes, nose, and throat in humans exposed to ammonia gas for 2 hours. An Uncertainty Factors of 30 was used in MRL derivation: 3 for use of a minimal LOAEL and 10 for human variability
The MRL is supported by other observations of respiratory effects associated with acute- and intermediate-duration exposure including transient irritation of the nose and throat of humans exposed to 70 mg/m³ (Ferguson et al. 1977); nasal discharge in rats at 262 mg/m³ (Coon et al. 1970); nasal lesions in rats at 104 mg/m³ (Broderson et al. 1976); and nasal inflammation and lesions in rats at 348 mg/m³ (Richard et al. 1978). A study of piggerie workers exposed to a mean level of 5.5 mg/m³ ammonia measured lung function change over a workshift; a small but borderline significant decrease in lung function was noted (Heederik et al. 1990). This was not used as a basis for MRL derivation because the workers were also exposed to other potential respiratory toxicants (dust and endotoxins).

Effects of long-term exposure

Several studies have examined the relationship between chronic exposure to ammonia and respiratory effects. Studies of farmers working in enclosed livestock facilities provide evidence that ammonia may contribute to transient respiratory distress (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990, 1991; Melbostad and Eduard 2001; Reynolds et al. 1996; Vogelzang et al. 1997, 2000); however, co-exposure to total dust, respirable dust, carbon dioxide, total endotoxins, respirable endotoxins, fungi, bacteria, and/or molds complicates the interpretation of these studies.

Comparisons were made between 52 workers and 31 control subjects in a soda ash plant for pulmonary function and eye, skin and respiratory symptomatology (Holness *et al.*, 1989). The pulmonary function tests included FVC (forced

vital capacity – the total amount of air the subject can expel during a forced expiration), FEV1 (forced expiratory volume in one second), FEF50 (forced expiratory flow rate at 50% of the FVC) and FEF75 (forced expiratory flow rate at 75% of the FVC). Age, height, and pack-years smoked were treated as covariates for the comparisons. The workers were exposed on average for 12.2 years to mean (time-weighted average) ammonia concentrations of 6.4 ± 1.0 mg/m^3 (9.2 ± 1.4 ppm), while controls were exposed to 0.21 ± 0.7 mg/m^3 (0.3 ± 0.1 ppm). No differences in any endpoints (respiratory or cutaneous symptoms, sense of smell, baseline lung function, or change in lung function over a work shift at the beginning and end of a workweek) were reported between the exposed and control groups.

Groups of human volunteers were exposed to 0, 17, 35, or 70 mg/m^3 (25, 50, or 100 ppm) ammonia 5 days/week for 2, 4, or 6 hours/day, respectively, for 6 weeks (Ferguson *et al.*, 1977). Another group of 2 volunteers was exposed to 35 mg/m^3 ammonia for 6 hours/day for 6 weeks. Pulmonary function tests (respiration rate, FVC and FEV1) were measured in addition to subjective complaints of irritation of the eyes and respiratory tract. The difficulty experienced in performing simple cognitive tasks was also measured, as was pulse rate. There were reports of transient irritation of the nose and throat at 35 or 70 mg/m^3. Acclimation to eye, nose, and throat irritation was seen after two to three weeks (in addition to the short-term subjective adaption). No significant differences between subjects or controls on common biological indicators, in physical exams, or in performance of normal job duties were found. After acclimation, continuous exposure to 70 mg/m^3, with occasional excursions to 139 mg/m^3, was easily tolerated and had no observed effect on general health.

Broderson et al. (1976) exposed groups of F344 rats (6/sex/dose) continuously to 17, 35, 104 or 174 mg/m^3 ammonia (HEC = 1.9, 3.7, 11.2 or 18.6 mg/m^3, respectively) for 7 days prior to inoculation with Mycoplasma pulmonis and from 28-42 days following M. pulmonis exposure. Each treatment group had a corresponding control group exposed only to background ammonia and inoculated with M. pulmonis in order to produce murine respiratory mycoplasmosis (MRM). The following parameters were used to assess toxicity: clinical observations and histopathological examination of nasal passages, middle ear, trachea, lungs, liver and kidneys. All levels of ammonia, whether produced naturally or derived from a purified source, significantly increased the severity of rhinitis, otitis media, tracheitis and pneumonia characteristic of M. pulmonis. Furthermore, there was a significant concentration response between observed respiratory lesions and increasing environmental ammonia concentration for gross and microscopic lesions. All lesions observed were characteristic of MRM. Gross bronchiectasis and/or pulmonary abscesses and the extent of gross atelectasis and consolidation was consistently more prevalent in exposed animals at all concentrations than in their corresponding controls. The severity of the microscopic lesions in the nasal passages, middle ears, tracheas and lungs was significantly greater in all exposed groups compared with controls. Increasing ammonia concentration was not associated with an increasing frequency of M. pulmonis isolations. Additionally, rats not exposed to M. pulmonis and exposed to ammonia at 174 mg/m^3 developed nasal lesions (epithelial thickening and epithelial hyperplasia) unlike those observed in inoculated rats.

The growth of bacteria in the lungs and nasal passages, and the concentration of serum immunoglobulin were significantly increased in rats exposed to 70 mg/m^3 (100 ppm) ammonia over that seen in control rats (Schoeb et al., 1982).

Guinea pigs (10/group) and mice (20/group) were continuously exposed to 14 mg/m^3 (20 ppm) ammonia for up to 6 weeks (Anderson et al., 1964). Separate groups of 6 guinea pigs and 21 chickens were exposed to 35 and 14 mg/m^3 (50 and 20 ppm) ammonia for up to 6 and 12 weeks, respectively. All species displayed pulmonary edema, congestion, and hemorrhage after 6 weeks exposure, whereas no effects were seen after only 2 weeks. Guinea pigs exposed to 35 mg/m^3 ammonia for 6 weeks exhibited enlarged and congested spleens, congested livers and lungs, and pulmonary edema. Chickens exposed to 140 mg/m^3 (200 ppm) for 17-21 days showed liver congestion and slight clouding of the cornea. Anderson and associates also showed that a 72-hour exposure to 14 mg/m^3 ammonia significantly increased the infection rate of chickens exposed to Newcastle disease virus, while the same effect was observed in chickens exposed to 35 mg/m^3 for just 48 hours.

Coon et al. (1970) exposed groups of rats (as well as guinea pigs, rabbits, dogs, and monkeys) continuously to ammonia concentrations ranging from 40 to 470 mg/m^3. There were no signs of toxicity in 15 rats exposed continuously to 40 mg/m^3 for 114 days or in 48 rats exposed continuously to 127 mg/m^3 for 90 days. Among 49 rats exposed continuously to 262 mg/m^3 for 90 days, 25% had mild nasal discharge. At 455 mg/m^3 50 of 51 rats died. Thus 127 mg/m3 (179 ppm) is a subchronic NOAEL for upper respiratory effects in rats. Coon et al. (1970) also found no lung effects in 15 guinea pigs exposed continuously to 40 mg/m^3 (28 ppm) ammonia for 114 days.

No chronic-duration oral or dermal data were located. Studies by these routes of exposure would provide useful information on the identification of target organs especially after low-dose exposure.

Summary of long-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
6.4 Study 2.3 ADJ		Pulmonary function, eye, skin, and respiratory symptoms of irritation	occupational, 12.2y	Holness *et al.*, 1989	OEHHA 1999; REL: 0.2 EPA-IRIS 1991; RfC: 0.1
	17 EXP 1.9 HEC	Increased severity of rhinitis and pneumonia with respiratory lesions	rats, subchronic	Broderson et al., 1976	OEHHA 1999 EPA-IRIS 1991
8.7 Study 2.2 ADJ		Pulmonary function, eye, skin, and respiratory symptoms of irritation, sense of smell	occupational, 12.2y	Holness *et al.*, 1989	ATSDR 2002; MRL: 0.2
Final statement (UNIMI) : Human NOAEL: 2 mg/m³					

Study average concentration ; EXP experimental concentration ; ADJ concentration adjusted from an intermittent to a continuous exposure ; 1h-ADJ concentration adjusted to 1-hour exposure duration ; HEC human equivalent concentration ; MLE maximum likelihood estimate for 5% response ; BC05 95% lower confidence limit of the concentration expected to produce a response rate of 5% (Benchmark concentration approach) ; STAT lowest statistically significant effect concentration

OEHHA (1999)
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency

Derivation of Chronic Reference Exposure Level
Study	Holness *et al.*, 1989 (supported by Broderson *et al.*, 1976)
Study population	52 workers; 31 controls
Exposure method	Occupational inhalation
Critical effects	Pulmonary function, eye, skin, and respiratory symptoms of irritation
LOAEL	25 ppm (Broderson *et al.*, 1976) (rats)
NOAEL	9.2 ppm (Holness *et al.*, 1989)
Exposure continuity	8 hours/day (10 m3/day occupational inhalation rate), 5 days/week
Exposure duration	12.2 years
Average occupational exposure	3 ppm for NOAEL group (9.2 x 10/20 x 5/7)
Human equivalent concentration	3 ppm for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level	0.3 ppm (300 ppb; 0.2 mg/m³; 200 µg/m³)

The Holness *et al.* (1989) study was selected because it was a chronic human study and was published in a respected, peer-reviewed journal. It is also the only chronic study available. The U.S.EPA (1995) based its RfC of 100 µg/m³ on the same study but included a Modifying Factor (MF) of 3 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

For comparison with the proposed REL of 200 µg/m³ based on human data, OEHHA estimated RELs from 2 animal studies. (1) Anderson *et al.* (1964) exposed guinea pigs continuously to 35 mg/m³ (50 ppm) ammonia for 6 weeks and observed pulmonary edema. Use of an RGDR of 0.86 and a cumulative uncertainty factor of 3000 (10 for use of a LOAEL, 10 for subchronic, 3 for interspecies, and 10 for intraspecies) resulted in a REL of 10 µg/m³. Staff note that the nearly maximal total uncertainty factor of 3000 was used in this estimation. (2) Coon *et al.* (1970) exposed rats continuously to 127 mg/m³ ammonia for 90 days and saw no signs of toxicity. Use of an RGDR(ET) of 0.16 for nasal effects (observed in rats exposed to higher levels of ammonia in Broderson *et al.* (1976) and a cumulative uncertainty factor of 100 (3 for subchronic, 3 for interspecies, and 10 for intraspecies) resulted in a REL of 200 µg/m³.

Data Strengths and Limitations for Development of the REL: Significant strengths in the ammonia REL include (1) the availability of long-term human inhalation exposure data (Holness et al., 1989), (2) the demonstration of consistent effects in experimentally exposed human volunteers following short-term exposures (Ferguson et al., 1977), and (3) reasonable consistency with animal data (Coon et al., 1970).

Major areas of uncertainty are: (1) the lack of a NOAEL and LOAEL in a single study, (2) a lack of animal data with chronic exposure and histopathological analyses, and (3) difficulties in estimated human occupational exposures. The overall database for this common chemical is limited.

ATSDR (2002)
Agency for Toxic Substances and Disease Registry

Derivation of the Minimal Risk Level (MRL):
In the Holness et al. (1989) study, the cohort was also divided into groups that were exposed to low (<4.35 mg/m^3), medium (4.35-8.7 mg/m^3), and high (>8.7 mg/m^3) ammonia levels and analyzed for change in lung function. Analysis was performed using each worker's personal exposure and his change in lung function over the workweek. Differences due to number of years of ammonia exposure was also assessed. No statistically significant differences were seen between the level of personal exposure and change in lung function or in lung function between low, medium, and high exposed groups. No association was evident between years of exposure and lung function changes. The dose and end point used for MRL derivation are: 8.7 mg/m^3 (NOAEL) for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (FVC, FEV1, FEV1/FVC, FEF50, and FEF75).

The NOAEL was adjusted for continuous exposure as follows: 8.7 mg/m^3 x 8.4/24 hours x 5/7 days = 2.2 mg/m^3. An Uncertainty Factors of 10 was used in MRL derivation for human variability: MRL = 0.2 mg/m^3 (0.3 ppm).

The MRL is supported by other observations of respiratory effects associated with chronic-duration exposure including an association between exposure to pollutants, including ammonia, in livestock confinement buildings and an increase in respiratory symptoms (such as bronchial reactivity/hyperresponsiveness, inflammation, cough, wheezing, or shortness of breath) and/or a decrease in lung function (such as forced expiratory volume in the first second [FEV1.0], maximum expiratory flow rates [MEF50 and MEF75], and maximal mid-expiratory flow rate [MMEF]) in farmers exposed to ammonia levels of 1.6-14.4 mg/m^3 (Choudat et al. 1994; Cormier et al. 2000; Donham et al. 1995, 2000; Heederik et al. 1990; Reynolds et al. 1996; Vogelzang et al. 1997, 2000). The farmers were also exposed to other possible respiratory toxins, such as dust and endotoxins. A cross-sectional study of male workers at two fertilizer factories in Saudi Arabia showed a significant association between exposure to ammonia gas and respiratory symptoms and bronchial asthma (Ballal et al. 1998). No continuous exposure levels could be calculated for these workers because the number of days worked per week was not provided.

USEPA-IRIS (1991)
Integrated Risk Information System

Determination of the Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical effect	Exposures*	UF	MF	RfC
Lack of evidence of decreased pulmonary function or changes in subjective syptomatology Occupational Study Holness et al., 1989	NOAEL: 6.4 mg/cu.m (9.2 ppm) NOAEL(ADJ): 2.3 mg/cu.m NOAEL(HEC): 2.3 mg/cu.m LOAEL: None	30	1	0.1 mg/m^3
Increased severity of rhinitis and pneumonia with respiratory lesions Rat Subchronic Inhalation Study Broderson et al., 1976	NOAEL: None LOAEL: 17.4 mg/cu.m (25 ppm) LOAEL(ADJ): 17.4 mg/cu.m LOAEL(HEC): 1.9 mg/cu.m			

*Conversion Factors: MW = 17.03 Holness et al., 1989: Assuming 25C and 760 mm Hg, NOAEL (mg/cu.m) = 9.2 ppm x 17.03/24.45 = 6.4 mg/cu.m. The NOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. NOAEL(ADJ) = 6.4 mg/cu.m x (MVho/MVh) x 5 days/7 days = 2.3 mg/cu.m.
Broderson et al., 1976: Assuming 25C and 760 mm Hg, the LOAEL (mg/cu.m) = 25 ppm x 17.03/24.45 = 17.4 mg/cu.m. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq. cm., Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.1068. NOAEL(HEC) = 17.4 x RGDR = 1.9 mg/cu.m.

The use of Holness et al. (1989) as the principal study can only be supported in the context of the data array. It is not surprising that no effects were seen on screening spirometry since the exposure levels were low. Comparing the 9.2 TWA of Holness et al. (1989) with other data on the respiratory effects of ammonia, a trend is observed that at lower concentrations the extrathoracic region of the respiratory system is affected due to the chemical's solubility and reactivity; while at higher concentrations, the lower part of the respiratory system is involved in both experimental animals (Dahlman, 1956; Gamble and Clough, 1976) and humans (Flury et al., 1983). Thus, no effects were observed in the lower respiratory system as reflected by pulmonary function. Pulmonary function may not be a particularly sensitive test because exposure to this type of agent at low concentrations is not expected to result in significant exposure of the lower respiratory region. No objective investigation of the workers' nasal epithelium was performed and the complaint of exacerbated upper respiratory symptoms suggests sensory irritation and supports the extrathoracic region as the critical region for an effect. The possibility of selection bias against atopic predispositions in the population is suggested by the significantly lower prevalence of hay fever in the exposed versus control cohort. Thus, there is a concentration-response in the extrathoracic region in experimental animals beginning at a LOAEL at essentially the same HEC as the NOAEL in Holness et al. (1989) and the NOAEL may be based on a less sensitive endpoint. Also the apparent discrepancy of a lower LOAEL(HEC) from Broderson et al. (1976) and the identified NOAEL(HEC) of the Holness et al. (1989) study may be the result of differences in air flow patterns since rats are obligate nose- breathers and humans breathe oronasally. The use of the NOAEL from Holness et al. (1989) can be supported as marginal in this context due to the symptomatology complaints and because human data engenders less uncertainty than extrapolation from the experimental animal data.

Confidence in the Inhalation RfC: Confidence in the principal study is medium. Although a relatively small sample size (males only) was studied and a free standing NOAEL was determined, mild extrathoracic effects were observed in rats near the same HEC as reported in the Holness study. Additional human subchronic and acute studies support the NOAEL. Confidence in the data base is medium to high. Although developmental, reproductive or chronic toxicity following ammonia exposure has not been adequately tested, pharmacokinetic data suggests systemic distribution at the HEC level is unlikely. Reflecting medium confidence in the principal studies and medium to high confidence in the data base, confidence in the RfD is medium.

Reproductive, mutagenic and carcinogenic effects

Toxicological effects, such as mutagenic, reproductive, or carcinogenic effects, would not be expected from exposures insufficient to cause local effects. There is no evidence that ammonia is carcinogenic, though it can produce inflammatory lesions of the colon and cellular proliferation, which could increase susceptibility to malignant change. There was no evidence that ammonia was responsible for the increased incidence of tumours with increased dietary protein intake. Ammonia did not either cause tumours or increase the spontaneous incidence of tumours in life-time studies on mice.

Interactions with other chemicals

Exposure to substances that would increase the pH of exposed tissues could be expected to enhance the alkalotic effects of ammonia, and vice versa.

Data regarding exposure to mixtures of atmospheric contaminants indicate that, contrary to what might be expected, increased carbon dioxide concentration (up to 5% in air) does not alter the hyperventilatory rate induced by hyperammonemia in dogs (Herrera and Kazemi 1980). Ammonia in expired air may neutralize inhaled acid aerosols (EPA 1979; Larson et al. 1980; Utell et al. 1989).

Odour perception

Odour is characterized as sharp, pungent and intensely irritating.

Source: Devos et al., (1990)
Odour threshold: 1 mg/m^3

Source: Amoore and Hautala (1983)
Odor threshold: 17 mg/m^3 (25 ppm)

Source: Leonardos et al. (1969)
Recognition threshold: 33 mg/m^3 (47 ppm)
The considerable variability in threshold data prompted work by Leonardos et al. (1969), who used a standardized procedure to determine recognition thresholds rather than detection thresholds for 53 chemicals. The odour threshold was defined as the first concentration at which all four panel members (trained odour analysts) were able to recognize the characteristic odour of the chemical. The panel tested only one chemical per day. Concentrations examined were multiples by 10 of 0.7, 1.47, and 3.3 mg/m^3 (1, 2.1, and 4.6 ppm). The recognition threshold for the odour of ammonia was 32.6 mg/m^3 (46.8 ppm) (WHO, 1986).

Source: AIHA (1989)
Reported odour threshold values range from 0.03 to 37.5 mg/m^3 (0.041 to 53 ppm) with a geometric mean of 11.8 mg/m^3 (17 ppm)

Source: WHO (1986)
Estimates of odor thresholds for ammonia vary from 0.04-103 ppm (0.03-73 mg/m³) (Ferguson *et al*., 1977; Henderson and Haggard, 1943; Ruth, 1986). Near the odor threshold, persons exposed to ammonia can experience annoyance and believe the odor to be a nuisance.

Summary of Ammonia Dose Response Assessment

Exposure other than inhalation: Endogenous ammonia (dietary proteins) used for protein synthesis and as a buffer, rapid conversion of excesses to glutamine/urea (liver) and urinary excretion.

Toxicokinetics: At ambient air levels (<350 mg/m^3), almost completely (83-92%) dissolved (NH_4OH) in the upper respiratory tract (nasal and pharyngeal, but not tracheal irritation), reduced absorption at prolonged exposure (>10min, >350 mg/m^3) due to saturation. Low absorption into the blood (systemic circulation), elimination mainly through expired air at the end of exposure. Only small proportion absorbed across the nasopharyngeal membranes.

Health effect levels of short- and long-term exposure

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
	14.0 $_{1h\text{-}ADJ\text{-}MLE}$ 9.5 $_{BC05}$	eye and respiratory irritation	volunteers, 1h-adjusted Benchmark approach	Industrial Biotest Laboratories, 1973; MacEwen *et al.*, 1970; Silverman *et al.*, 1949; Verberk, 1977	OEHHA 1999; REL: 3.2
	35 $_{EXP}$	irritation to nose and throat; urge to cough	volunteers, 2h	Verberk, 1977	ATSDR 2002; MRL: 1.2
General remark: No study with asthmatics!					
Long-term exposure					
6.4 $_{Study}$ 2.3 $_{ADJ}$		Pulmonary function, eye, skin, and respiratory symptoms of irritation	occupational, 12.2y	Holness *et al.*, 1989	OEHHA 1999; REL: 0.2 EPA-IRIS 1991; RfC: 0.1
	17 $_{EXP}$ 1.9 $_{HEC}$	Increased severity of rhinitis and pneumonia with respiratory lesions	rats, subchronic	Broderson et al., 1976	OEHHA 1999 EPA-IRIS 1991
8.7 $_{Study}$ 2.2 $_{ADJ}$		Pulmonary function, eye, skin, and respiratory symptoms of irritation, sense of smell	occupational, 12.2y	Holness *et al.*, 1989	ATSDR 2002; MRL: 0.2

Carcinogenicity: No evidence in life-time studies on mice. Mutagenic or carcinogenic effects would not be expected from exposures insufficient to cause local effects (inflammatory lesions and cell proliferation).

Genotoxicity: No evidence

Odour threshold: Range: 0.03-38 mg/m^3, with geometric mean: 12 mg/m^3 (AIHA) and recognition: 33 mg/m^3; 1 mg/m^3 (Devos); Coughing reflex and lachrymation starting from 35 mg/m^3, immediate coughing at 700 mg/m^3

Susceptible population: Exposure to ammonia result in an exacerbation of preexisting asthma (48/60 asthmatics claimed following exposure to household cleaners containing ammonia). Wide variability of symptoms depending on recent history of ammonia exposure; tolerances up to 70 mg/m^3 after weekly inurement period.

Remarks: RD_{50}: 211 mg/m^3

6. Risk Characterization

Health hazard evaluation of short-term exposure

Toxicological endpoint: Irritation to nose and throat; urge to cough

Derivation of a limit of exposure (EL)			
LOAEL[a]	LOAEL 10 [b]	LOAEL 100 [c]	LOAEL 300 [d]
35 mg/m^3	3.5 mg/m^3	0.35 mg/m^3	0.1 mg/m^3

[a] Human LOAEL ; [b] not considering a NOAEL (10); [c] intraspecies variability (10) ; [d] susceptible population (3)

Odour threshold: Range: 0.03-38 mg/m^3, with geometric mean: 12 mg/m^3 (AIHA) and recognition: 33 mg/m^3; 1 mg/m^3 (Devos); Coughing reflex and lachrymation starting from 35 mg/m^3, immediate coughing at 700 mg/m^3

Health hazard evaluation of long-term exposure

Toxicological endpoint: Pulmonary function, eye, skin, and respiratory symptoms of irritation

Relevance of EU-population exposure to Ammonia

Non population-based study		NOAEL[a]	NOAEL 10 [b]	NOAEL 30 [c]	Margin of safety (MOS)
Description (Study, Year)	N	2 mg/m^3	0.2 mg/m^3	0.07 mg/m^3	50th (90th)
Helsinki (VTT 2003) Homes without known IAQ problems		<	<	<	3.0 (1.8)
Helsinki (VTT 2003) Homes with known IAQ problems		<	<	<	2.6 (1.3)

[a] Occupational LOAEL, adjusted for continuous exposure; [b] intraspecies variability (10); [c] susceptible population;
< out of the evaluation range (i.e. <5% of the environments investigated)

Result

There is a lack of knowledge concerning indoor concentrations and exposures of ammonia. Exposure data are limited on only one non population-based study describing concentrations of ammonia in Finnish homes with and without known indoor air quality (IAQ) problems. In both cases measured concentrations were within the same order of magnitude with both exposure limits here esteblished for short- and long-term effects (70 and 100 μg/m^3, respectively) relating on irritative effects and pulmonary funtions and taking into account the particular susceptibility of asthmatic subjects. It is assumed that exposure concentrations in the order of the short-term EL could easily be attained during domestic activities making use of ammonia containing household products.

Limonene

Synonyms:	1-methyl-4-(1-methylethenyl)cyclohexene
CAS Registry Numbers:	138-86-3
Molecular Formula:	$C_{10}H_{16}$

1. Compound identification

Limonene exists as two optical isomers, d-limonene (pleasing orange scent) and l-limonene (smells piney, turpentine smell; mixture of both isomers: dipentene), and is used as a flavour and fragrance additive in food, household cleaning products and perfumes or could be contained in solvents (e.g. turpentine).

Limonene is both a naturally occurring and a synthetic colourless mobile liquid, which is used in many food products, for its characteristic lemon-like flavour and odour. It is also used as a solvent, wetting agent, in resins, and as a monomer and copolymer. It may be emitted to indoor air also from cats and dogs repellent spray and shampoo, pet sleeping quarters, household dwellings, indoor premises, and human clothing. Limonene emissions have been detected in the industries such as extraction of pine gum, paper and pulp mills, plastics materials-synthetic resins, perfumes, cosmetics and other toilet preparations, organic solvents and lubricating oils and greases (HSDB 2003).

Limonene may be emitted to household environments from furniture polishes and room fresheners. Occupational exposure to limonene may occur by inhalation or dermal contact during its production, formulation, transport or use. The main routes of human exposure to limonene in the general population is assessed to be inhalation of limonene and ingestion of food in which it occurs naturally or to which it has been added as a flavour or fragrance (EPA 1994, HSDB 2003).

2. Physical and Chemical properties

Molecular weight (g/mol)	136.23
Melting point (°C)	-74
Boiling point (°C)	176
Density (at 20 °C, 1 atm)	0.8402
Relative density (air =1)	4.7
Solubility:	Miscible with alcohol and ether

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 5.654 $\mu g/m^3$
1 $\mu g/m^3$ = 0.177 ppb

Sources: Verschueren 2001, HSDB 2003

3. Indoor Air Exposure assessment

Contribution of inhalation exposure to total exposure

Food is the principal source of exposure to limonene (96%), the contribution from ambient air being approximately 4% (WHO, 1998). d-limonene is generally recognized as safe in food by the Food and Drug Administration. Based on daily US consumption of d-limonene per capita, the intake of d-limonene from food for the general population was estimated to be 0.27 mg/kg body weight per day (Flavor and Extract Manufacturers Association, 1991). The intake of limonene from indoor and outdoor air for the general population is estimated to be 10 and 0.1 µg/kg body weight per day,

respectively. This is based on the daily inhalation volume for adults of 22 m^3, a mean body weight for males and females of 64 kg, the assumption that 4 of 24 hours are spent outdoors (IPCS, 1994), and arithmetic mean limonene levels in indoor and outdoor air of 0.04 and 0.002 mg/m^3, respectively, in a study from Los Angeles (Wallace et al., 1991).

Terpene/ozone reaction products

It has been proposed that reactions between unsaturated volatile compounds (e.g. limonene, α-pinene, styrene) and ozone or hydroxyl (OH) radicals produce chemically reactive products more likely to be responsible for eye and airway irritation than the chemically non-reactive VOCs usually measured indoors. Many of the known reaction products are oxygenates (e.g. formaldehyde and other aldehydes, carboxylic acids, peroxides) which may cause irritation at low concentrations or odor annoyance due to their usually low odour thresholds (Weschler and Shields, 1997; Wolkoff et al., 1997; 2000). Ozone enters the indoor environment (<0.3 mg/m3) by infiltration of the outdoor air (<0.6 mg/m3) or could be produced by photocopiers and certain air cleaners.

Indoor air and exposure concentrations

Residential indoor concentrations of limonene were clearly higher than respectively outdoor concentrations in all regions of Europe based on EXPOLIS results (Table 4.0.1, Jantunen et al 1999). Average indoor concentrations were lowest in Central Europe and highest in Athens (Figure 3.1, Annex 1). Personal exposures to limonene, ranging from 19 μg/m^3 to 56 μg/m^{3,} were lower than residential indoor concentrations (Jantunen et al 1999, Hoffman et al 2000). Kostiainen et al (1995) reported clearly lower mean and median indoor concentrations of limonene in Helsinki, Finland, 14.2 μg/m^3 and 8.8 μg/m^3 respectively. Maroni et al (1995) reported typical limonene concentrations in residential indoor environments in Europe and in the United States, being on average 30 μg/m^3. Indoor concentrations measured in offices in Milan, Italy were about half of the residential levels, being on average 17 μg/m^3. Brown (2002) studied limonene concentrations in new and established buildings. Limonene concentrations in a new building increased after construction, being 12 μg/m^3, 15 μg/m^3, and 34 μg/m^3 2, 19, and 72 days after construction respectively. This decreasing trend suggested the dominant source of limonene being human activities, possibly consumer products, rather than building materials.

TEAM study carried out in Los Angeles, the USA showed a maximum 12-hour day time exposure of 990 μg/m^3 to limonene (Wallace et al 1991). Respective residential indoor and outdoor concentrations showed concentrations of 230 μg/m^3 and 10 μg/m^3. Maximum exposure concentration in California showed higher value than in European studies. Maximum residential indoor concentration was in the range with European maximum levels.

WHO (1989) has assessed indoor air concentrations of VOCs in "typical homes" giving median and 90th percentile concentrations of 15 μg/m^3 and 70 μg/m^3 for limonene. Brown et al (1994) calculated weighted geometric mean (WAGM) indoor concentrations for several building types using mean values collected from the studies carried out worldwide. Also they reported lower indoor values, WAGM of 21 μg/m^3 and 90th percentile of 85 μg/m^3 for limonene than found in European population based studies.

Residential indoor air concentrations of limonene in European urban populations measured in the EXPOLIS study and the National Survey in England are presented in Figure 3.1 and Figure 3.2. Respective exposure concentrations are presented in Figure 3.3.
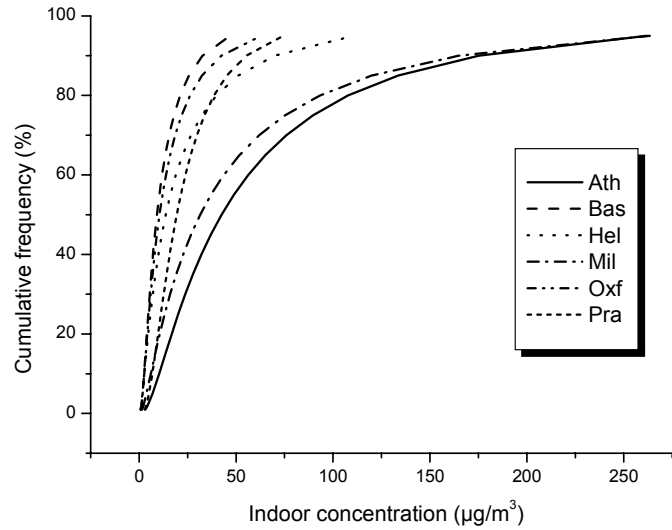
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of limonene in Athens (Ath, n= 42), Basel (Bas, n= 47), Helsinki (Hel, n= 188), Milan (Mil, n= 41) Oxford (Oxf, n= 40) and Prague (Pra, n= 46) (EXPOLIS 2002).

Figure 3.2. Cumulative frequency distribution of 28-day indoor air concentrations of limonene in UK (GM= 6.2 µg/m^3, max 308 µg/m^3, n=796, Brown et al 2002).
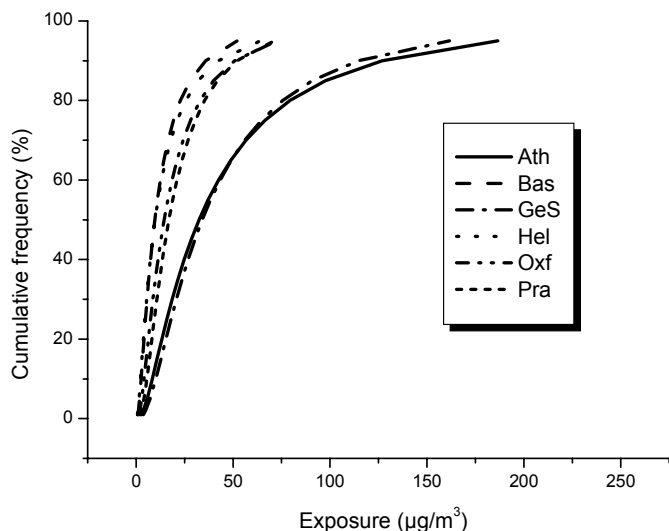
Figure 3.3. Cumulative frequency distributions of 48-hour personal exposure concentrations of limonene in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean exposures of the German Survey GerES II (GeS) (Hoffman et al 2000).

4. Toxicokinetics

Absorption

Limonene has a high partition coefficient between blood and air ($\lambda_{blood/air}$ = 42) and is easily taken up in the blood at the alveolus (Falk et al., 1990). The net uptake of limonene in volunteers exposed to the chemical at concentrations of 450, 225, and 10 mg/m^3 for 2 hours during light physical exercise averaged 65% (Falk Filipsson et al., 1993). Orally administered limonene is rapidly and almost completely taken up from the gastrointestinal tract in humans as well as in animals (Igimi et al., 1974; Kodama et al., 1976).

Distribution

Limonene is rapidly distributed to different tissues in the body and is readily metabolized. Clearance from the blood was 1.1 litre/kg body weight per hour in males exposed for 2 hours to d-limonene at 450 mg/m^3 (Falk Filipsson et al., 1993). A high oil/blood partition coefficient and a long half-life during the slow elimination phase suggest high affinity to adipose tissues (Falk et al., 1990; Falk Filipsson et al., 1993).

In rats, the tissue distribution of radioactivity was initially high in the liver, kidneys, and blood after the oral administration of [^{14}C] d-limonene (Igimi et al., 1974); however, negligible amounts of radioactivity were found after 48 hours. Differences between species regarding the renal disposition and protein binding of d-limonene have been observed.

Metabolism and elimination

The biotransformation of d-limonene has been studied in many species, with several possible pathways of metabolism (see Figure 4.1). Metabolic differences between species have been observed with respect to the metabolites present in both plasma and urine. About 25-30% of an oral dose of d-limonene in humans was found in urine as d-limonene-8,9-diol and its glucuronide; about 7-11% was eliminated as perillic acid (4-(1-methylethenyl)-1-cyclohexene-1-carboxylic acid) and its metabolites (Smith et al., 1969; Kodama et al., 1976). d-Limonene-8,9-diol is probably formed via d-limonene-8,9-epoxide (Kodama et al., 1976; Watabe et al., 1981). In another study, perillic acid was reported to be the principal metabolite in plasma in both rats and humans (Crowell et al., 1992). Other reported pathways of limonene metabolism involve ring hydroxylation and oxidation of the methyl group (Kodama et al., 1976).

Following the inhalation exposure of volunteers to *d*-limonene at 450 mg/m^3 for 2 hours, three phases of elimination were observed in the blood, with half-lives of about 3, 33, and 750 minutes, respectively (Falk Filipsson et al., 1993). About 1% of the amount taken up was eliminated unchanged in exhaled air, whereas about 0.003% was eliminated unchanged in the urine. When male volunteers were administered (per os) 1.6 g [^{14}C] *d*-limonene, 50-80% of the radioactivity was eliminated in the urine within 2 days (Kodama et al., 1976). Limonene has been detected, but not quantified, in breast milk of non-occupationally exposed mothers (Pellizzari et al., 1982).

Figure 4.1: Major pathways for d-limonene metabolism (Source: WHO 1998, from Kodama et al., 1976)
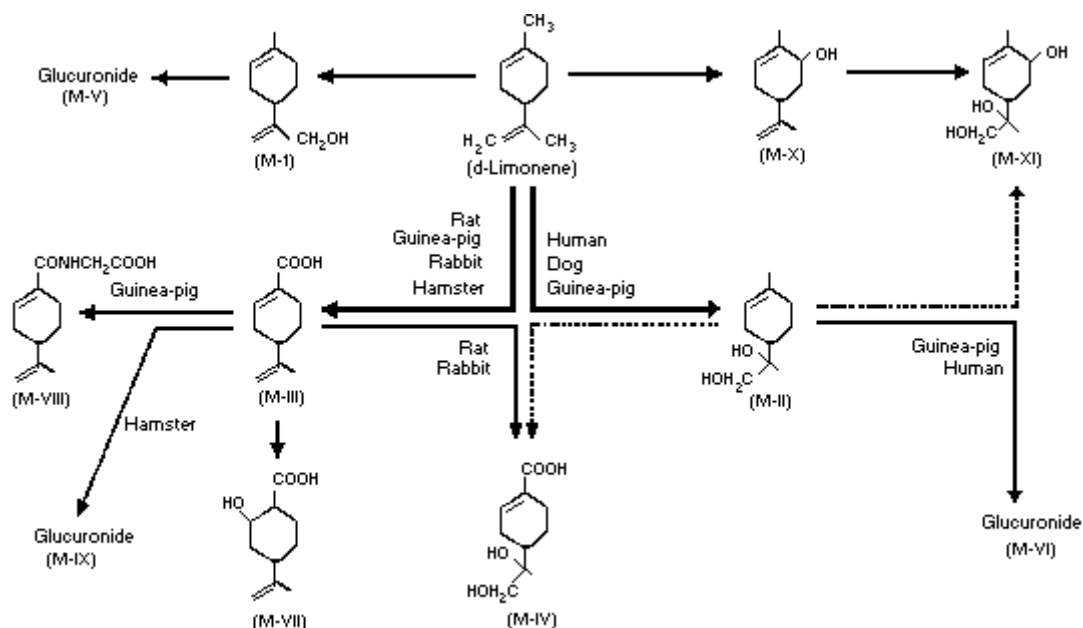
5. Health effects

Effects of short-term exposure

In general, limonene could be considered, with the exception of its irritative (skin, eyes) and sensitizing properties, to be a chemical with fairly low acute toxicity (WHO, 1998). Potential hazard to the general population are skin irritancy and sensitisation from use of consumer products, varying with the concentration of limonene in the product and, for sensitisation, with its oxidation status (addition of oxidised limonene to the list of substances used in allergy testing has been recommended)..

None of eight volunteers reported any discomfort, irritation, or symptoms related to central nervous system effects during a 2-hour inhalation exposure in an exposure chamber (work load 50 W) to *d*-limonene at 10, 225, or 450 mg/m^3; however, a slight decline in vital capacity was observed following exposure to the highest concentration (Falk Filipsson et al., 1993).

Eye irritation of l-limonene was measured using goggles instrumentation and a relatively short exposure time of 2 minutes. The threshold level for irritation in 12 volunteers was 1700-3400 mg/m^3 (Mølhave et al., 2000).

d-Limonene infused directly into the bile system of human volunteers to dissolve gallstones caused pain in the upper abdomen, nausea, vomiting, and diarrhoea, as well as increases in serum aminotransferases and alkaline phosphatase (Igimi et al., 1976, 1991). The oral administration of 20 g *d*-limonene to volunteers resulted in diarrhoea, painful constrictions, and proteinuria, but no biochemical changes (total protein, bilirubin, cholesterol, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase) in the liver (Igimi et al., 1976).

It has recently been proposed that reactions between limonene (or other unsaturated volatile compounds) and ozone or reactive radicals produce chemically reactive products more likely to be responsible for eye and airway irritation than the chemically non-reactive VOCs usually measured indoors (Weschler and Shields, 1997; Wolkoff et al., 1997; 2000).

Reaction mixtures of excess alpha-pinene, limonene and isoprene with ozone considerably below their NOEL concentrations resulted in significant upper airway irritation (Wolkoff et al, 2000). The reduction of the respiratory rate was from 30% to about 50%. Chemical analysis of reaction mixtures by conventional methods showed that readily identified stable products and residual reactants at the concentrations found could not account for the observed reductions of the respiratory rate, assuming additivity of the reaction products. The results suggest that, in addition to known irritants (formaldehyde, acrolein, methacrolein, methyl vinylketone), one or more strong airway irritant(s) of unknown structure(s) were formed (Wolkoff et al, 2000). Effects of variation of reaction time, relative humidity and initial ozone concentration on irritant formation were described by Wilkins et al. (2003).

Kleno and Wolkoff (2004) exposed 8 male subjects for 20 min to limonene oxidation products (LOPs) and measured relative changes in blink frequencies. The subjects were exposed locally in the non-dominant eye and single blind in random order. Blinking was video-recorded and evaluated for full sessions of 36 min while the subjects viewed an educational film. The mean blink frequency increased significantly at lower ppb levels of LOPs, 42% ($P<0.0001$), compared with that at baseline. Neither the residual reactants nor clean air changed the blink frequency significantly. The findings coincided with qualitative reporting of weak eye irritation symptoms (Kleno and Wolkoff, 2004).

Irritative effects in experimental animals exposed to oxidation products of ozone and unsaturated hydrocarbons, including limonene, were recently described in Wolkoff et al. (2000), Clausen et al. (2001), Rohr et al. (2002), Wilkins et al. (2003).

Oxidised Histo-clear solvent (used in some pathology laboratories, containing d-limonene as a replacement for xylene) produced respiratory irritation requiring medical treatment in a hystology technician (NICNAS, 2002). It was considered that the autoxidation products might be the cause of the irritation. An increase in nasal or throat irritation was also reported by 4/12 workers in a facility were a limonene-based cleaner was stored in an uncovered tank (NICNAS, 2002).

The acute toxicity of *d*-limonene in rodents is fairly low after oral, intraperitoneal, subcutaneous, and intravenous administration, based on the magnitude of the LD_{50} values. LD_{50} values were approximately 5 g/kg body weight for the oral administration of *d*-limonene or *d/l*-limonene to rats and for dermal application of *d/l*-limonene to rabbits and 6 g/kg body weight for oral administration to mice (Tsuji et al., 1974, 1975b; Opdyke, 1978).

Effects observed following the acute exposure of rodents to limonene include increased bile flow at 85 mg/kg body weight (Kodama et al., 1976), inhibition of *S*-3-hydroxy-3-methylglutaryl-CoA reductase activity at 409 mg/kg body weight (Clegg et al., 1980), enzyme induction at 600 and 1200 mg/kg body weight (Ariyoshi et al., 1975), and decreased motor activity, hypothermia, and potentiation of hexobarbital-induced sleep at 3 ml/kg body weight (Tsuji et al., 1974).

Studies in guinea-pigs have revealed that air-oxidized *d*-limonene, but not *d*-limonene itself, induced contact allergy (Karlberg et al., 1992).

Summary of short-term exposure effect levels

NOAEL mg/m³	LOAEL mg/m³	Target system; Critical effect studied	Remarks	Study	Source (Organization)
225	450	CNS related symptoms, irritation, Endpoint: decline in vital capacity	Volunteers, 2h - work load 50W	Falk Filipsson et al., 1993	

Effects of long-term exposure

No information is available on the chronic health effects of inhalation exposure to d-limonene in humans, and no long-term inhalation studies have been conducted in laboratory animals. Limonene/ozone reaction products have not yet been submitted to chronic toxicity studies.

In numerous experimental studies on animals, oral exposure (gavage) to limonene has been shown to affect the liver. Exposure affects the amount and activity of liver enzymes, liver weight, cholesterol levels and bile flow. However, no toxic effects on the liver have been reported.The liver effects in animals are thought to be due to physiological adaptation. Owing to a lack of data on *d*-limonene exposure in humans, this organ cannot with certainty be stated as the critical organ in humans. From the data available, it is not possible to identify a NOAEL for these effects.

The only microscopic evidence of compound-related toxicity noted in rats was nephropathy in the males. d-Limonene is one of a diverse group of hydrocarbons that has been shown to induce a unique syndrome of nephropathy in male rats following subchronic or chronic exposure. Based on a review of the literature concerning this effect (U.S. EPA, 1991), EPA's Risk Assessment Forum concluded that nephropathy in male rats that is associated with alpha- 2u-globulin accumulation in hyaline droplets is not an appropriate endpoint to determine noncancer effects potentially occurring in humans (U.S. EPA, 1993).

In two subchronic oral exposure studies in rats, the following effect levels were identified. The NOEL, based upon histopatological examination of the kidneys, was considered to be 5 mg/kg bw/d. The LOEL for increased liver and kidney weight was 75 mg/kg bw/d. For effects in the liver the NOEL was 10 mg/kg bw/d and the LOAEL was 30 mg/kg bw/d (Ariyoshi et al., 1975; Webb et al., 1989).

Based on available data, food is believed to be the principal source of exposure (96%) to limonene; the contribution from ambient air is approximately 4%. To calculate a tolerable intake for humans, the animal study was chosen in which effects on the liver were observed at the lowest exposure level (Webb et al., 1989). In this study, gavage administration of *d*-limonene (5 days/week for 13 weeks) to rats caused increased relative liver weight at 30 and 75 mg/kg body weight per day. The NOEL for the liver was considered to be 10 mg/kg body weight per day. Using uncertainty factors of 10 for intraspecies differences and 10 for interspecies differences, a tolerable intake for ingestion of *d*-limonene by humans of 0.1 mg/kg body weight per day may be calculated from the NOEL. This value is of a similar magnitude as the estimated daily US consumption of *d*-limonene of 0.27 mg/kg body weight per day (Flavor and Extract Manufacturers Association, 1991). U.S. FDA approves d-limonene for use as a food additive.

Matthys et al. (2000) observed that "Myrtol standardized" (Gelomyrtol forte), a phytotherapeutic extract (distillate) consisting mainly of three monoterpenes: d-limonene, (+)alpha-pinene, and 1,8-cineole, is a well-evidenced alternative to antibiotics for acute bronchitis treatment and was considered safe and tolerable in 170 patients at daily doses of 4 x 300 mg for 2 weeks.

Occupational exposure standards for limonene are summarised in Table 5.1. Supporting documentation for the exposure standard adopted by the American Industrial Hygiene Association (AIHA) states that the 167 mg/m^3 (30 ppm) 8-hr TWA was set to protect against liver effects seen in male mice and reduced survival in female rats in a 2-yr NTP study (AIHA, 1993). In Germany no MAK (maximum workplace concentration) has been set for limonene as it was considered that insufficient information was available.

Table 5.1: National occupational exposure standards for limonene

Country	8-h TWA mg/m^3	STEL mg/m^3	Year adopted	Reference
Norway	140	-	1999	RTECS, 2001
Sweden	140	280	1990	Karlberg and Lindell, 1993
Finland	140	280	not known	Finnish Institute of Occupational Health, 2001
AIHA	167	-	1993	AIHA, 1993

TWA: time-weighted average
STEL: short-term (15 min) exposure limit

U.S. EPA deemed the database at the time of review (1993) to be insufficient to derive an inhalation RfC according to the Interim Methods for Development of Inhalation Reference Concentrations (U.S. EPA, 1990).

Carcinogenic and genotoxic effects

There is inadequate evidence in humans for the carcinogenicity of d-limonene.

There is sufficient evidence in experimental animals for the carcinogenicity of d-limonene. Overall evaluation: In making its overall evaluation of the carcinogenicity to humans of d-limonene, the IARC Working Group concluded that d-limonene produces renal tubular tumors in male rats by a non-DNA reactive alpha-2-globulin associated response. Therefore, the mechanism by which d-limonene increases the incidence of renal tubular tumors in male rats is not

relevant to humans. d-Limonene is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1999).

The few available data indicate that d-limonene and its 1,2-epoxide metabolite are not genotoxic. Limonene administered in the diet was not mutagenic in the liver or kidney of male Big Blue rats Turner et. al. (2001).

Interactions with other chemicals

The formation of unidentified strong upper airway irritants in reaction mixtures of terpenes and ozone has been recently reported. Identified products included formaldehyde and other aldehydes, carboxylic acids, peroxides, which may cause irritation at low concentrations or odor annoyance due to their usually low odour thresholds (Weschler and Shields, 1997; Wolkoff et al., 1997; 2000).

Maximum irritation of reaction mixtures of limonene and ozone, measured in mice, was observed at low humidity (<2% RH) and short time (16-30 s) reaction mixtures. Moderate humidity (approximately 32% RH) and longer reaction times (60-90 s) resulted in significantly less irritation, suggesting that some unidentified intermediates react with water vapor to give less irritating products (Wilkins et al., 2003). Irritation measured at four ozone concentrations (1, 2, 4 and 7 mg/m^3) using low humidity/short time reaction conditions for limonene (280 mg/m^3) and isoprene (1400 mg/m^3) revealed that at 1 mg/m^3, irritation was at the same level as that for the pure terpenes, indicating that at 1 mg/m^3 ozone the combined irritant effect was near the no effect level for the product mixture (Wilkins et al., 2003).

Odour perception

Source: Leffingwell & Associates
d-limonene - fresh citrus, orange-like - odour perception : 1.1 mg/m^3 (200 ppb)
l-limonene - harsh, turpentine-like, lemon note - odour perception : 2.8 mg/m^3 (500 ppb)

Summary of Limonene Dose Response Assessment

Exposure other than inhalation: Oral: About 96% of limonene absorbed by humans originate from food. Generally recognized as safe in food by U.S.FDA. Dermal: Potential hazard to the general population may derive from skin irritancy and sensitisation from use of consumer products For contact allergy, air-oxidized limonene seems to play a major role than limonene itself.

Toxicokinetics: ~65% net uptake of the inhaled amount, rapid distribution and high affinity for adipose tissue

Health effect levels of short- and long-term exposure

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
225	450	CNS related symptoms, irritation, Endpoint: decline in vital capacity	Volunteers, 2h - work load 50W	Falk Filipsson et al., 1993	
Long-term exposure (no studies have been found in literature)					

Carcinogenicity: Inadequate evidence in humans; sufficient evidence in animals, with mechanism not relevant to humans.

Genotoxicity: The few available data indicate that d-limonene and its 1,2-epoxide metabolite are not genotoxic.

Odour threshold: 2.15 mg/m³ (Devos); d-limonene (orange-like): 1.1 mg/m³; l-limonene (turpentine-like) : 2.8 mg/m³ (Leffingwell & Associates)

Susceptible population:

Remarks: RD_{50}: 6 g/m³; In addition to known irritant reaction products (formaldehyde, acrolein, methacrolein, methyl vinylketone), one or more strong airway irritant(s) of unknown structure(s) could be formed following the reaction between limonene and ozone or reactive radicals.

6. Risk Characterization

Health hazard evaluation of long-term exposure

	Effect level - mg/m^3		Assessment factor	EL mg/m^3	Toxicological endpoint
Long-term Exposure Limit	Human LOAEL Volunteers	450	1000[abc]	0.45	CNS related symptoms, irritation, Endpoint: decline in vital capacity

[a] extrapolation from subacute to chronic exposure (10); [b] not considering a NOAEL (10) [c] intraspecies variability (10);

Relevance of EU-population exposure to limonene

Population based studies Description (Study, Year)	N	EL derived 0.45 mg/m^3	Margin of safety (MOS) 50th (90th)
Athens (Expolis, 96-98)	42	<	11 (3)
Basel (Expolis, 96-98)	47	<	49 (14)
Helsinki (Expolis, 96-98)	188	<	33 (6)
Milan (Expolis, 96-98)	41	<	14 (3)
Oxford (Expolis, 98-00)	40	<	43 (11)
Prague (Expolis, 96-98)	46	<	23 (8)
England 28d-TWA (BRE, 97-99)	796	<	56 (11)
		Avg MOS:	33 (8)

< out of the evaluation range (i.e. <5% of the environments investigated)

Result

An attempt has been done in deriving an exposure limit (EL) for long-term effects associated with limonene exposure by refering to a study on volunteers exposed at sub-acute (2 hours) inhalation doses. When comparing this EL (450 μg/m^3) with the results from seven indoor surveys it is concluded that no neurologic effects would be expected at background limonene levels encountered in European homes, with median (90th percentile) levels at least 10 (3) times lower than the proposed EL. It is assumed that at 10-fold the level set as the EL, irritation could be expected following acute exposure. Due to its widespread use as a flavouring agent in numerous consumer products, short-term exposures at levels in the order of some mg/m^3 could not be excluded, although significative exposure data are lacking.

alpha-Pinene

Synonyms: 2,6,6-Trimethylbicyclo(3.1.1)-2-hept-2-ene
                                             2,6,6-Trimethylbicyclo(3.1.1)hept-2-ene
                                             2-Pinene
CAS Registry Numbers: 80-56-8
Molecular Formula: $C_{10}H_{16}$

1. Compound identification

Alfa-pinene is a colourless liquid with a characteristic odour of pine. It is a naturally occurring terpene, which is emitted by trees, fruits, grasses, bushes, fungi, herbs, and flowers and it is a constituent of many common oils. Alfa-pinene will exist solely as a vapour in the atmosphere. It is used in aerosol paint concentrates, cleaning and sanitation products, paints and varnish removers, waterproofing compounds solvent, and flavouring. It is also emitted to indoor air from commonly used wooden furniture and waxes (HSDB 2003, Maroni et al 1995).

Alpha and beta pinene ($C_{10}H_{16}$) are principal constituents of turpentine. Turpentine is a thin volatile essential oil ($C_{10}H_{16}$) obtained by steam distillation from the wood or the exudate of pine trees. Main uses of turpentine include as a solvent thinner for paint, varnishes, and lacquer, and as a vehicle for paints (professional painters, private individuals). Turpentine is also used in perfumery, sprays, and deodorizers. The composition of wood turpentine varies with species, location, and season. Steam-distilled (wood) turpentine produced in the United States is made up primarily of alphapinene (75 to 85%) with varying amounts of beta-pinene (up to 3%), camphene (4 to 15%), limonene (dipentene, 5 to 15%), 3-carene, and terpinolene (percentages not provided) (Chinn, 1989). In a Swedish study (Falk Filipsson, 1996) volunteers were exposed to turpentine vapour with a composition measured in air: 54% alpha-pinene, 11% beta-pinene and 35% 3-carene.

Exposure to alpha-pinene in the general population may occur by inhalation, by dermal contact of consumer products and by ingestion of foods.

2. Physical and Chemical properties

Molecular weight (g/mol)   136.23
Melting point (°C)   -55
Boiling point (°C)   156
Density (at 20 oC, 1 atm)   0.859
Relative density (air =1)   4.7
Solubility: Insoluble in water, soluble in alcohol, chloroform,
                                    ether, and glacial acetic acid

Conversion factors at 20 °C and 760 mm Hg:

1 ppb = 5.654 $\mu g/m^3$
1 $\mu g/m^3$ = 0.177 ppb

Sources: Verschueren 2001, HSDB 2003

3. Indoor Air Exposure assessment

Terpene/ozone reaction products

It has been proposed that reactions between unsaturated volatile compounds (e.g. limonene, a-pinene, styrene) and ozone or hydroxyl (OH) radicals produce chemically reactive products more likely to be responsible for eye and airway irritation than the chemically non-reactive VOCs usually measured indoors. Many of the known reaction products are oxygenates (e.g. formaldehyde and other aldehydes, carboxylic acids, peroxides) which may cause irritation at low concentrations or odour annoyance due to their usually low odour thresholds (Weschler and Shields, 1997; Wolkoff et al., 1997; 2000).

Indoor air and exposure concentrations

Exposures to alpha-Pinene in indoor environments did not follow the same increasing trend from north to south as many other VOC compounds do (Figure 3.1). Average indoor concentrations were at about the same level in Northern and Central Europe, being typically 15 – 17 $\mu g/m^3$ (EXPOLIS 2002, Edwards et al 2001)). Slightly lower levels were measured in Southern Europe, being there about 10-17 $\mu g/m^3$. Maroni et al (1995) concluded, as a summary of several studies, a typical mean concentration being 10 $\mu g/m^3$ for alpha-Pinene in indoor air. The results presented by Kostiainen et al (1995) in Helsinki, Finland showed similar mean and median indoor concentrations, 9.3 $\mu g/m^3$ and 7.7 $\mu g/m^3$, respectively. Wolkoff et al (2000) reviewed alpha-Pinene concentrations in major indoor air studies. Mean concentrations ranged from 10 $\mu g/m^3$ to 40 $\mu g/m^3$ and maximum concentrations from 8 $\mu g/m^3$ to 250 $\mu g/m^3$. Rehwagen et al reported 4-week mean concentration of 25 $\mu g/m^3$ and a maximum value of 393 $\mu g/m^3$ in Leipzig, Germany. Interesting detail in this study was the increasing trend of terpenes between 1996 and 1999 on the contrary to other VOCs, which showed a decreasing trend. Explanations to this trend for alpha-Pinene could not be identified.

Average personal exposures to alpha-Pinene ranged from 7 $\mu g/m^3$ to 18 $\mu g/m^3$ (Figure 3.2, Jantunen et al 1999, Hoffman et al 2000). All over Europe average population exposures tend to be lower than respective indoor concentrations, suggesting the presence of remarkable indoor sources of alpha-Pinene. Exposures to alpha-Pinene in Europe were considerably higher than those measured in TEAM studies in the USA, median daytime exposures ranging from 1.0 $\mu g/m^3$ to 2.8 $\mu g/m^3$ (Wallace et al 1996).
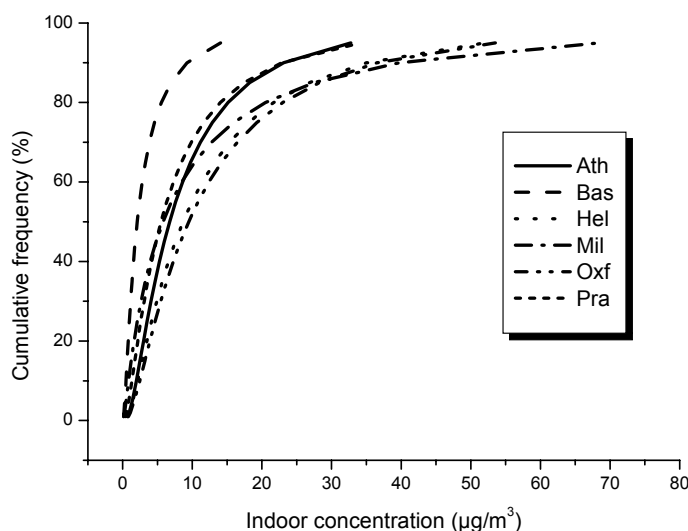
Figure 3.1. Cumulative frequency distributions of indoor air concentrations of alpha-Pinene in Athens (Ath, n=42), Basel (Bas, n=47), Helsinki (Hel, n=188), Milan (Mil, n=41) Oxford (Oxf, n=40) and Prague (Pra, n=46) (EXPOLIS 2002).
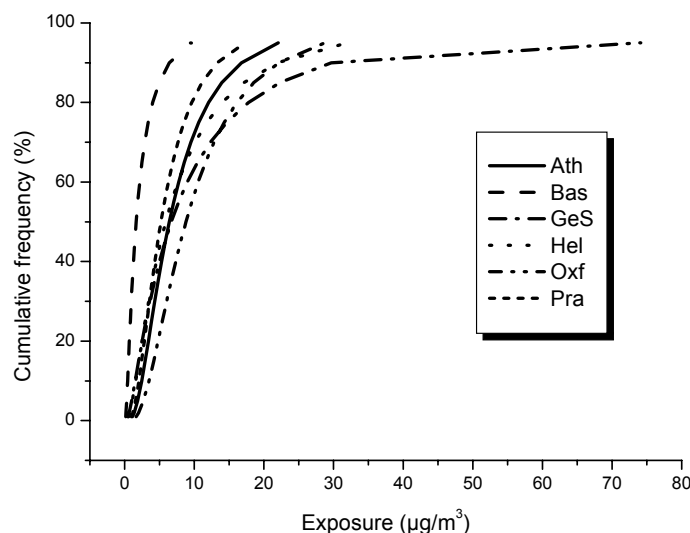
Figure 3.2. Cumulative frequency distributions of 48-hour personal exposure concentrations of alpha-Pinene in Athens (Ath), Basel (Bas), Helsinki (Hel), Oxford (Oxf) and Prague (Pra) (EXPOLIS 2002), and 1-week mean exposures of the German Survey GerES II (GeS) (Hoffman et al 2000).

4. Toxicokinetics

Absorption

The toxicokinetics of alpha-pinene was studied in volunteers experimentally exposed to the vapour of the pure compound and of turpentine with composition in air: 54% alpha-pinene, 11% beta-pinene and 35% 3-carene (Falk et al., 1990a; Falk Filipsson, 1996). In the first study eight healthy males were exposed to 0, 10, 225, or 450 mg/m^3 (+)-alpha-pinene or 450 mg/m^3 (-)-alpha-pinene for 2 hr in an inhalation chamber. During exposure they exercised on a cycle ergometer at the rate 50 watts. Average pulmonary uptake of (+)-alpha-pinene and (-)-alpha-pinene amounted to 59% (62%, 66%, and 68% respectively for turpentine vapour constituents in Falk Filipsson, 1996) of the exposure concentration. The blood:air partition coefficient for alpha-pinene is 15. Absolute uptake increased linearly with concentration. Blood alpha-pinene concentration increased rapidly at first then tapered off. Mean blood concentration at the end of exposure were linearly related to inhaled concentration.

Distribution

The solubility of monoterpenes in olive oil is high; the oil:air partition coefficient for alpha-pinene is 2900. This should imply accumulation in adipose tissue (Falk et al., 1990b). In rats, terpenes accumulate in peripheral fat, kidneys, and the brain (Savolainen and Pfaffli, 1978; Sperling et al. 1967).

Metabolism and elimination

Slow metabolism and renal elimination of monoterpenes were suggested after a patient acutely poisoned by pine oil was studied (Koppel et al., 1981). Up to 4% of the total uptake of alpha-pinene after human exposure by inhalation was eliminated in the urine as cis- and transverbenol (Levin et al. 1992). Both the respiratory elimination of alpha-pinene and the urinary excretion of verbenols after inhalation of alpha-pinene enantiomers were studied (same exposure conditions as in Falk et al., 1990a). Respiratory elimination of both pinene enantiomers was similar; at a concentration of 450 mg/m^3, 7.7% of the total uptake of (+)alpha-pinene and 7.5% of the total uptake of (-)-alpha-pinene was eliminated. Urinary excretion of verbenol 4 hr after exposure to (+)alpha-pinene ranged from 1.7% at 450 mg/m^3 to 3.8% at a dose of 10 mg/m^3. Urinary excretion of (-)alpha-pinene was similar. A semilogarithmic plot of the excretion data suggested the existence of more than one rate constant for the elimination of (+)alpha-pinene and (-)alpha-pinene. Most of the verbenols were eliminated within 20 hr after a 2 hr exposure. The renal excretion of unchanged alpha-pinene was less than 0.001%. The determination of urinary verbenols may be useful as a biological exposure index for

exposure   to   terpenes.

Elimination of alpha-pinene from the blood was triphasic (Falk et al., 1990a). Half times for elimination of inhaled (+)-alpha-pinene from the blood during the three phases were 4.8, 39, and 695 minutes. Elimination half times for (-)-alpha-pinene were 5.6, 40, and 555 minutes.

5. Health effects

Effects of short-term exposure

Most of the studies identified relative to α-pinene were associated with human responses to one or several monoterpenes. Acute toxic effects of α-pinene are stated as similar to those resulting from turpentine exposures (Budavari, 1996; NIEHS, 2002).

Pulmonary function and subjective ratings of discomfort were described in two studies (Falk et al., 1990a; Falk Filipsson, 1996), whereby eight healthy male volunteers were exposed for 2 hr in an inhalation chamber (working load 50W with a cycle ergometer) to 0, 10, 225, or 450 mg/m^3 (+)-alpha-pinene or 450 mg/m^3 (-)-alpha-pinene and to 450 mg/m^3 turpentine vapour (composition in air: 54% alpha-pinene, 11% beta-pinene and 35% 3-carene) , respectively. Five among eight subjects complained of eye, nose and throat irritation, after being exposed to 450 mg/m^3 alpha-pinene. No exposure related changes in lung function were seen. At the concentration tested the capacity of the liver to metabolize alpha-pinene was not exceeded (Falk et al., 1990a). Subjects experienced discomfort in the throat and airways during exposure to turpentine vapour (450 mg/m^3) and airway resistance was increased after the end of exposure (Falk Filipsson, 1996).

In male and female volunteers (mean age: 35 years) exposed to 0 or 450 mg/m^3 of a 10:1:5 mixture of alpha- and beta-pinene and 3-carene (a synthetic turpentine) for 12 hr, 4 times during a 2 week period, an acute alveolar cellular inflamatory reaction was observed. Exposure did not significantly alter bronchial hyperreactivity to methacholine (Bingham et al., 2001).

Mølhave et al (2000) concluded that similarly to other 3 terpenes ((+)3-carene, (-)limonene, (rac)alpha-terpineol) α-pinene can probably be ruled out as cause of acute eye irritation indoors. After applying eye goggles, too few subjects reported eye-irritation for α-pinene to allow estimates of a threshold of this compound, having much less irritative potency than n-butanol, 3-carene, and limonene.

No acute effects on forced vital capacity or forced expiratory volume (1s) were detected after personal exposure to 10-214 mg/m^3 monoterpenes (alpha-pinene, beta-pinene and delta 3-carene) of 38 joinery workers (Eriksson et al., 1997) and to 11-158 mg/m^3 terpenes of 48 sawmill workers (Eriksson et al., 1996). A decrease in carbon monoxide lung diffusing capacity after a workshift was detected. Workers with ≥5 years of sawmill employment showed a higher reactivity to methacholine than those with < 5 years. Eye irritation increased during a workday (Eriksson et al., 1996). For single monoterpenes, mixtures of monoterpenes and for turpentine the Swedish occupational exposure limit (OEL) value is 150 mg/m^3. In U.S. no occupational exposure limits have been established for alpha-Pinene. For turpentine, workplace exposure limits for 8-h workshift are 557 mg/m^3 (OSHA), 557 mg/m^3 (NIOSH), and 111 mg/m^3 (ACGIH).

As in humans, turpentine acts as a CNS depressant, with symptoms progressing from lethargy, prostration, and convulsions to death in animals (Bystrom, 2000). Acute toxicity in animals included irritation of the skin, eyes, nose, and mucous membranes. Signs and symptoms of acute toxicity are CNS depression and increased respiration rate with a decrease in tidal volume. Major systemic effects include kidney and bladder injury, and are thought to be attributable to induction of an acute inflammatory response (Key et al., 1977; cited by Baxter, 2001).

In mice exposed by inhalation to turpentine, the RD_{50} (the concentration that causes a 50% decrease in respiratory frequency) of turpentine (6500 mg/m^3) was the same order of magnitude as those of α-pinene (5900 mg/m^3) and β-pinene (7100 mg/m^3) (Kasanen et al., 1999; Kasanen et al., 1998). The effect on breathing was most likely due to sedation or anesthesia since no histological observations were reported in the exposed animals.

Summary of short-term exposure effect levels

NOAEL mg/m^3	LOAEL mg/m^3	Target system; Critical effect studied	Remarks	Study	Source (Organization)
225	450	eyes, nose and throat irritation	Volunteers, 2h - work load 50W	Falk et al., 1990b	UBA, 2003 GV II: 2; GV I: 0.2

UBA, 2003

Effects of long-term exposure

No chronic exposure studies were identified for both α-pinene and turpentine.

Forty-eight subjects exposed to terpenes (mean air concentration 258 mg/m^3) and 47 unexposed subjects, all employed at sawmills, were studied with regard to symptoms and pulmonary function. Dyspnoea and chest oppression were significantly increased in the exposed subjects compared to the unexposed controls. A reduced FEV1, on spirometry and an increased CV% and slope of the alveolar plateau (phase III) on single breath nitrogen washout were seen on Monday morning before exposure to terpenes. There was no correlation between exposure time (duration of employment) and lung function impairment. A day of industrial exposure to terpenes caused no further change in any lung function variable. The unexposed controls showed normal spirometry and nitrogen washouts. The findings indicate a slight stable lung function impairment of an obstructive nature which does not necessarily undergo further deterioration with increased duration of exposure (Hedenstierna et al., 1983).

Prolonged exposure to terpenes may result in allergic contact dermatitis (Brun, 1975; Dooms-Goossens et al., 1977) or chronic impairment of lung function (Hedenstierna et al., 1983).

Chronic effects associated with occupational exposures to turpentine include cerebral atrophy, behavioral changes, anemia and bone marrow damage, glomerulonephritis, and dermatitis. Urinary disturbances, albuminuria, and urinary casts were observed in workers exposed to paints and varnishes. However, renal damage associated with occupational exposures to turpentine was transient and reversible (NIEHS, 2002).

Inhalation of turpentine (4000 mg/m^3), four hours per day, 45 or 58 days failed to result in any hematological changes in guinea pigs, though slight changes in the liver and moderate scattered tubular degeneration in the kidneys were observed. Subchronic inhalation of turpentine (1670 mg/m^3) in rats resulted in the accumulation of α-pinene in brain and perinephric fat. At higher concentrations (estimated at 5000 to 10,000 mg/m^3) for up to 293 hours over a period of time ranging to 14 months provided no histological evidence of nephritis or chronic Bright's disease. There were foci of pneumonitis and extensive lung abscesses in many of these animals (NIEHS, 2002).

Carcinogenic and genotoxic potential

The International Agency for Research on Cancer has not evaluated the carcinogenicity of this chemical. The US National Toxicology Program has not listed this chemical in its report on carcinogens. The American Conference of Governmental Industrial Hygienists has designated α-pinene as not classifiable as a human carcinogen (A4). No human information is available and the limited amount of animal information available is inconclusive.

Toxicity associated with turpentine oleoresin [CAS RN 9005-90-7] includes the development of benign tumors after chronic exposures (Budavari, 1996).

A case-control study of workers in particle-board, plywood, sawmill, and formaldehyde glue factories demonstrated a statistically significant association between chronic exposure (longer than 5 years) to terpenes (the principal component of turpentine) and the development of respiratory tract cancers (HSDB, 1989).

α-Pinene was not found to be mutagenic, assayed on TA98 or TA100 in the presence of S9 (Rockwell et.al., 1979), in a screening assay using the Ames test (Florin et. al., 1980) or using a battery of bacterial test strains (Connor et. al. 1985).

Interactions with other chemicals

It has recently been proposed that reactions between α-pinene (or other unsaturated volatile compounds) and ozone or reactive radicals produce chemically reactive products more likely to be responsible for eye and airway irritation than the chemically non-reactive VOCs usually measured indoors (Weschler and Shields, 1997; Wolkoff et al., 1997; 2000). Irritative effects in experimental animals exposed to these oxidation products, were also described in Clausen et al. (2001), Rohr et al. (2002) and Wilkins et al. (2003).

Reaction mixtures of excess alpha-pinene, limonene and isoprene with ozone considerably below their NOEL concentrations resulted in significant upper airway irritation (Wolkoff et al, 2000). The reduction of the respiratory rate was from 30% to about 50%. Chemical analysis of reaction mixtures by conventional methods showed that readily identified stable products and residual reactants at the concentrations found could not account for the observed reductions of the respiratory rate, assuming additivity of the reaction products. The results suggest that, in addition to known irritants (formaldehyde, acrolein, methacrolein, methyl vinylketone), one or more strong airway irritant(s) of unknown structure(s) were formed (Wolkoff et al, 2000). Effects of variation of reaction time, relative humidity and initial ozone concentration on irritant formation were described by Wilkins et al. (2003).

Odour perception

Source: Leffingwell & Associates

(1R,5R)-(+)-alpha-pinene : harsh, terpene-like, minty
Odour threshold: 12 mg/m^3 (2.1 ppm)
(1S,5S)-(-)-alpha-pinene : harsh, terpene-like, coniferous
Odour threshold: 18 mg/m^3 (3.3 ppm)

Summary of alpha-Pinene Dose Response Assessment

Exposure other than inhalation: Dermal: Potential hazard to the general population may derive from skin irritancy and sensitisation from use of consumer products.

Toxicokinetics: ~62% net uptake of the inhaled amount, high affinity for adipose tissue

Health effect levels of short- and long-term exposure

NOAEL mg/m³	LOAEL mg/m³	Target system; critical effects	Remarks	Study	Source; Ref. Value mg/m³
Short-term exposure					
225	450	eye, nose and throat irritation	Volunteers, 2h (50W)	Falk et al., 1990	UBA, 2003 GV II: 2; GV I: 0.2
Long-term exposure (no studies have been found in literature)					

Carcinogenicity: No information available for humans, the limited information for animals is inconclusive. Not classifiable as a human carcinogen (ACGIH).

Genotoxicity: Not found to be mutagenic

Odour threshold: 3.9 mg/m^3 (Devos); (+)-alpha-pinene (harsh, terpene-like, minty): 12 mg/m^3 ; (-)-alpha-pinene (harsh, terpene-like, coniferous): 18 mg/m^3 (Leffingwell & Associates)

Remarks: RD_{50}: 6 g/m^3; In addition to known irritant reaction products (formaldehyde, acrolein, methacrolein, methyl vinylketone), one or more strong airway irritant(s) of unknown structure(s) could be formed following the reaction between a-pinene and ozone or reactive radicals.

6. Risk Characterization

Health hazard evaluation of long-term exposure

	Effect level - mg/m³		Assessment factor	EL mg/m³	Toxicological endpoint
Long-term Exposure Limit	Human LOAEL Volunteers	450	1000[abc]	0.45	Eyes, nose and throat irritation

[a] extrapolation from subacute to chronic exposure (10); [b] not considering a NOAEL (10) [c] intraspecies variability (10);

Relevance of EU-population exposure to α-Pinene

Population based studies		LOAEL 1000 [c]	Margin of safety (MOS)
Description (Study, Year)	N	0.45 mg/m³	50th (90th)
Athens (Expolis, 96-98)	42	<	59 (17)
Basel (Expolis, 96-98)	47	<	191 (43)
Helsinki (Expolis, 96-98)	188	<	46 (11)
Milan (Expolis, 96-98)	41	<	69 (10)
Oxford (Expolis, 98-00)	40	<	42 (11)
Prague (Expolis, 96-98)	46	<	73 (17)

Avg MOS: 80 (18)

< out of the evaluation range (i.e. <5% of the environments investigated)

Result

An attempt has been done in deriving an exposure limit (EL) for long-term effects associated with α-pinene exposure by refering to a study on volunteers exposed at sub-acute (2 hours) inhalation doses. When comparing this EL (450 μg/m³) with the results from six indoor surveys it is concluded that no irritative effects to the eyes, nose and throat would be expected at background α-pinene levels encountered in European homes, with median (90th percentile) levels at least 40 (10) times lower than the proposed EL. It is assumed that at 10-fold the level set as the EL, effects could be expected following acute exposure. Due to its widespread use as a flavouring agent in numerous consumer products, short-term exposures at levels in the order of some mg/m³ could not be excluded, although significative exposure data are lacking. An exacerbation of effects (not better defined) could be expected following the concomitant presence in residences of ozone emitting sources, due to the formation of irritant reaction products.

5. Risk management tools

The general boundary conditions of and options for indoor air risk management are discussed in the beginning of this report, in Chapter **3.2. Risk Management**. The present chapter focuses on the characteristics of alternative indoor air risk management tools, which are then applied for the indoor air pollutants in the first priority list (Chpt. 6.1). These tools are:

- IAQ Standards and guidelines
- Building codes and ventilation standards
- Equipment standards and permits
- Mandatory maintenance and inspections
- Limits, labelling and reporting of the contents of or releases from building products, furnishing materials, equipment and consumer products
- Public awareness raising and information

5.1 IAQ Standards and guidelines

Legally binding standards for indoor air pollution exist in most countries for a large selection of (industrial) workplace air contaminants. The maximum allowable contaminant levels (occupational exposure limits) specified in those standards apply for healthy adult individuals, controlled exposures and normal workweek exposure duration (40h/168h), with provisions for simultaneous exposures to more than one regulated contaminant. Consequently the maximum allowed concentration values (MAK-Werte, TLV, HTP etc.) are usually 1 - 3 orders of magnitude higher than those measured in residences, offices, schools, shops and public buildings. Clearly, neither the approach nor the levels are applicable for general indoor air risk management, although occupational exposure limit values divided by 10 (to allow for much longer exposure time and heterogeneous target population) have been sometimes used - in the absence of anything better - as indicative levels also in non-industrial indoor spaces.

Ambient air quality standards provide much more relevant reference values than occupational exposure limits for indoor air quality management. Crucial differences in indoor and ambient exposures, however, exist.   Occupancy is the first. While it is virtually impossible to avoid exposure to ambient air pollution, outdoors or indoors, some indoor spaces (residences) expose the most vulnerable occupants (infants & the old and sick) almost all the time, other indoor spaces (work, school) are occupied only a fraction of time, yet others by only select groups for a small fraction of time (gyms, warehouses etc). Weather is the second difference. The daily variation of weather, particularly wind, ensures that at any location the annual average ambient air pollution concentrations are far lower than the 24 h or 1 h peak levels, and the different ambient air pollution concentration standards for the different averaging times reflect this fact. Indoor ventilation rates and temperatures vary much less. The levels of pollutants indoors, if they come from frequently used indoor sources (e.g. gas appliance) or are off-gassed from building materials or furnishings (e.g. formaldehyde), can exert high peak values virtually every day, or high and constant levels through the year. On the other hand, elevated indoor air pollution level coming from, e.g. a fresh paint on the wall, may return to normal within days and not be repeated in the same room for a decade. Therefore, if ambient air quality standard values are applied to assess the quality of indoor air, it is important to know the sources of the measured pollutants, assess the long term exposures of the occupants, and apply short and/or long term ambient air quality standards accordingly.

Specific air quality guideline values for general indoor settings have been established for only a few air contaminants and only in some countries. The obvious reasons for these limited guideline values are on one hand the privacy of most indoor environments, and on the other the huge numbers of buildings/rooms in any country. Consequently, in contrast to ambient air, any indoor air monitoring data represent for short periods of time, and tiny, usually non-representative fractions of indoor spaces. We know of only two European national surveys to monitor indoor air pollution levels in a representative sample of residences, the three times repeated German Environmental Survey (since 1986), and the French Indoor Air Observatory (started in 2004). More limited, but locally representative, indoor air pollution surveys include the 7-city *EXPOLIS* study (1996-8) and the English Avon Study. Indoor air concentration guidelines exist in some countries for formaldehyde (to force building material development and selection), radon (to promote radon safe building practices and renovations in high radon regions), and CO_2 (used as ventilation sufficiency indicator). These three exhibit typically much higher indoor than outdoor concentrations. For pollutants with significant sources and concentrations both indoors and outdoors, indoor concentration limits cannot be managed without acknowledging the outdoor concentrations as an unavoidable and variable background.

5.2 Building codes and ventilation standards

Building codes and ventilation standards include both legally binding governmental regulations and industry standards or recommended professional practices (with much the same effect) and are in general more practical for indoor air risk management than air quality standards. On one hand they are often back calculated from guideline or other reference values to limit material and equipment/appliance emissions below certain levels (building codes) and to ensure that the unavoidable emissions or effluents (at minimum the bio-effluents and CO_2 from the occupants) are sufficiently diluted (ventilation standards). Compliance of all new and renovated buildings (and, as needs arise, non-residential old ones) with building codes and ventilation standards is routinely (if not always thoroughly) controlled, while actual indoor air quality monitoring to ensure compliance with guidelines will ever take place in only a small fraction of buildings.

5.3 Equipment/appliance standards and permits

Many indoor air risks can be managed by (i) setting standards for the design and performance of equipment (and their installations), which might contaminate indoor air (e.g. combustion devices for heating and cooking) or fail to exhaust the pollutants generated (e.g. kitchen extract vents/fans), (ii) implementing a mandatory test/inspection and permit procedure to ensure that the equipment and their installations meet the standards, and (iii) requiring special training and certification of the personnel authorised to install the equipment (e.g. gas and oil fired heaters). Such standards and permits can be quite effective, but it should be kept in mind that they may also hinder innovation, form *de facto* market barriers, unnecessarily complicate the equipment, reduce competition and thus increase the costs to end users.

5.4 Mandatory maintenance and inspections

All (combustion)heating, ventilation and air conditioning equipment need some maintenance to function properly over time, may malfunction without obvious signal to the occupants, and their malfunction may cause or amplify indoor hazards. Maintenance is mostly left to the judgement of the building owner or user, who may or may not know, understand or care until something goes notably wrong. An alternative is to set legal requirements for timed inspections and maintenance of such building equipment, which may pose health or safety risks if not functioning properly. This can be strengthened by setting special training and certification requirements for the personnel which inspects, maintains, repairs or in some cases even operates (e.g. public building HVAC systems) the equipment.

5.5 Limiting, labelling and reporting of the contents of or releases from building products, furnishing materials, equipment and consumer products

Legally mandated enforced bans on the use of defined toxic compounds, concentration or emission limit values for products which are used for constructing and furnishing buildings (e.g. asbestos, formaldehyde) and for consumer products used in buildings (e.g. benzene) can ensure that non-necessary exposures are avoided, and that maximum releases of these compounds to indoor air can be predicted e.g. for the calculation of ventilation needs. Legal processes, however, are heavy instruments, which often respond only slowly to changing knowledge and needs.

Voluntary industrial standards or recommended professional practices combined with consumer awareness and accessible information may bring the same benefits as legally mandated restrictions with better efficiency and more flexibility. Keeping the industrial, professional and consumer dimensions of product quality information relatively independent of each other would sacrifice some of the consistency, but improve the credibility and timeliness of the product information.

Clearly, a combination of both legal and voluntary actions are needed. Significant health hazards call for legal requirements, comfort and quality considerations are better managed by voluntary actions. Legal or voluntary, the labelling and product information schemes should be coordinated at European level. Otherwise they have the risk of (i) developing into de facto trade barriers reducing competition and increasing costs, or (ii) becoming too many and diverse to win common approval and have the wanted impact on product safety and public health.

5.6 Awareness-raising and public information

Most indoor air risk situations must - by the necessity of their sheer numbers - be detected and managed by the occupants themselves. Such management actions can only be based on 1) underlying general understanding of the potential and nature of a risk associated to certain action, equipment or indoor microenvironment, and 2) ability to find comprehensible and sufficiently detailed information for taking correct action. Therefore public awareness-raising and information should be essential components in all indoor air risk management programmes, in addition to being independent risk management tools.

Effective distribution of indoor air quality and risk information to the general public, which consists of individuals with highly variable levels of background knowledge, interest and needs, is a challenge. The first priority is to prepare and broadly distribute general information about indoor air quality and risks, aimed at awareness raising for everyone. Awareness raising should also point out specific topics such as tobacco smoke, combustion devices/appliances, consumer products, building materials, dampness & moisture damages, ventilation needs, etc.

This general information material should also provide links for finding more focused and detailed public information prepared for the needs of individuals living in specific environments (e.g. high radon areas), using specific equipment/appliances (e.g. fireplaces or gas stoves), having specific health needs (e.g. asthmatics), preferences (e.g. natural materials), or responsibilities (e.g. building managers). Reports, information packages and websites for finding more detailed, technical and focused information in domestic languages should be provided, so that all levels of information needs and sophistication could be met. Also professional personal guidance should be available to be found and consulted, when necessary.

While avoiding undue concern, public information should also be the prime method for helping people avoid or control those lesser indoor air quality nuisances and problems, which do not warrant strict regulatory action, such as minor odours and irritants (low TVOC levels and bioeffluents), or exposures of concern but no verified risks at common indoor air levels (e.g. glycol ethers). Such information empowers people to improve their own indoor air quality towards fresher and more pleasant even when other health benefits may be in doubt.

6. Recommendations and management options

The recommendations and management options proposed would - according to present knowledge - protect the general population and most individuals most of the time, but they will not prevent every cancer from indoor exposures nor protect the most susceptible individuals in all conditions, such as highly reactive asthmatics, individuals with other respiratory or cardiovascular disease, genetic predisposition to haemolytic anaemia, etc. Due to the principle of diluting the indoor air pollution by outdoor air, the outdoor air quality is a most significant factor for indoor air quality.

In addition to the specific recommendations reported below for each individual compound, the following general recommendations and management options apply to most or many indoor air contaminants in the high and low priority lists:

- Ban tobacco smoking in all indoor spaces under public jurisdiction, and working places. Raise public awareness on the hazards of tobacco smoke, and discourage smoking in the homes, particularly in the presence of children.
- Develop building codes to restrict the construction of attached garages, and to isolate the garages from living and working spaces (closing the doorways, sealing the structures and ensuring proper air pressure difference between garage and other indoor spaces).
- The design of ventilation systems should ensure the dilution of all known and predictable indoor emissions of the 1st priority list compounds below the recommended guideline levels, with margin of safety. Proper design should be complemented with maintenance and use instructions to ensure that the design objectives are met over time.
- Raise public awareness about the various acute and long term risks of exposure to indoor air pollution from indoor sources by campaigns focused on specific and concrete issues and on relevant target populations.

6.1 High priority chemicals

The high priority compound list consists of 5 gas/vapour phase chemicals, which may occur indoors in high concentrations due to indoor sources, which have uncontested individual and public health impacts, and for which effective risk management options are known.

Formaldehyde

The no-effect level (acute and chronic) is estimated to be at 30 $\mu g/m^3$ as 30-minute average. Pending the outcome of the current IARC revision of the carcinogenecity of formaldehyde, a guideline value should be as low as reasonably achievable.

Additional recommended formaldehyde risk management options are:

- Minimise the emissions of formaldehyde from building materials, products, furnishings and household/office chemicals.
- Require product labelling to inform about Formaldehyde content and potential formaldehyde release from household and building products
- Discourage the use of any formaldehyde containing products.
- Raise public awareness and provide information to the public about the sources, nature and levels of risks of formaldehyde in indoor air.

Nitrogen Dioxide

A long term guideline value of 40 $\mu g/m^3$ (1-week average) and a short term guideline value of 200 $\mu g/m^3$ are proposed. Additional recommended nitrogen dioxide risk management options are:

- Apply the indoor air concentration guideline in the building and ventilation design process.
- Develop building codes, ventilation standards and equipment/appliance standards (design, maintenance and use) so that all indoor combustion equipment will exhaust into chimneys/hoods/vents leading outdoors.
- Require standardised NO2 emission information - for normal use and extreme release - about all combustion devices which do not exhaust directly into a chimney.

- Provide public information about the sources, risks and means of controlling NO2 indoors.

Carbon Monoxide

The 1-hour average guideline value of 30 mg/m^3 and the 8-hour average guideline value of 10 mg/m^3 are recommended. Additional recommended indoor air carbon monoxide risk management options are:

- Apply the indoor air concentration guideline in the building and ventilation design process, considering the possibility of excessive releases from the sources to be installed.
- Develop building codes, ventilation standards and equipment/appliance standards so that they require all indoor combustion equipment to exhaust into chimneys/hoods/vents leading outdoors.
- Require standardised information CO emission under intended use for all combustion devices which do not exhaust directly into a chimney.
- Require regular mandatory inspections for indoor combustion equipment.
- Recommend alarm systems responding to abnormally high concentrations.
- Raise public awareness about the risks of indoor air CO, and provide public information about its sources, risks and reasons for suspecting high CO levels.

Benzene

As benzene is a human carcinogen, its concentration in indoor air should be kept as low as reasonably achievable. Indoor concentrations of benzene should not exceed outdoor concentrations.

Additional recommended indoor air benzene risk management options are:
- Sources emitting benzene should not be allowed in the indoor environment.
- Lower the permissible benzene content in any building material and consumer product, and report about known benzene levels also when below permissible levels.
- Raise public awareness and provide information to the public about the sources, nature and levels of risks of benzene in indoor air.

Naphtalene

A long term guideline value of 10 µg/m^3 is recommended based on irritation/inflammation/hyperplasia. This level is at the lower extreme of the olfactory perception range.
Additional recommended indoor air naphtalene exposure management options are:

- Restrict the use of naphthalene containing household products, particularly mothballs.
- Raise public awareness about the sources, risks, means of detecting and avoiding naphtalene in indoor air

6.2 Second priority chemicals

The steering committee did not feel that there exist sufficient evidence to propose indoor air concentration guidelines for the second priority chemicals in indoor air. These chemicals are commonly found in indoor air and they do exhibit toxic characteristics. Their indoor air concentrations, however, are almost always orders of magnitude below their lowest observed effect levels, and therefore are not presently judged to justify regulatory actions.

Because they do, however, contribute to annoyance and perception of poor indoor air quality, and may contribute to the sc. cocktail effects (presumably observable adverse effect of a complex chemical mixture in which each individual component exists clearly below its LOEL concentration), it is justified to make people aware of such potentials of these chemicals, and provide public information, which allows them to identify sources and means to reduce their own exposures, when it is possible, e.g. at their own home and via their personal choices.

Acetaldehyde

Not found to be a priority compound at present, because of the large interval between inhalation exposure levels and health effect levels. Should new information about sources, concentrations or health effects emerge, this could change the situation.

o-, p- and m-Xylene, and Toluene

Not found to be a priority compound at present, because of the large interval between inhalation exposure levels and health effect levels. Should new information about sources, concentrations or health effects emerge, this could change the situation.

Styrene

A long term guideline value of 200 $\mu g/m^3$ is recommended based on neurobehavioral effects. Styrene has also been discussed for a possible mutagenic and/or carcinogenic, but the evidence is so far inconclusive. Interaction with ozone causing biologically active products is suspected.

6.3 Chemicals requiring further research with regard to human exposue or dose response

The steering committee did not feel that the possible health impacts of these chemicals have been sufficiently studied to propose indoor air concentration guidelines for these chemicals in indoor air. These chemicals are commonly found in indoor air and they do exhibit toxic characteristics. Their indoor air concentrations, however, are usually orders of magnitude below their lowest observed adverse effect levels, and therefore are not presently judged to justify regulatory actions.
Because they do, however, contribute to annoyance, irritation, and ammonia also to perception of poor indoor air quality, and they may contribute to the sc. cocktail effects (presumably observable adverse effect of a complex chemical mixture in which each individual component exists clearly below its LOEL concentration), it is justified to make people aware of such potentials of these chemicals, and provide public information, which allows them to identify sources and means to reduce their own exposures, when it is possible, e.g. at their own home and via their personal choices.

Ammonia

A long term guideline value of 70 $\mu g/m^3$ and a short term guideline value of 100 $\mu g/m^3$ are recommended based on respiratory effects.

d-Limonene

There are insufficient toxicological data available to recommend a guideline value. Considering a widespread use such data should be made available. The odour threshold is 1-2 mg/m^3. It appears that at present there is a reasonable safety margin between the existing exposure levels and known odour and irritation thresholds. Interaction with ozone causing biologically active products is suspected.

a-Pinene

There are insufficient toxicological data available to recommend a guideline value. Considering a widespread use such data should be made available. The odour threshold is 10-20 mg/m^3. It appears that at present there is a considerable safety margin between the existing exposure levels and known odour and irritation thresholds. Interaction with ozone causing biologically active products is suspected.

Annex 1   Phase 1: Exposure and dose-response data for indoor air pollutants collected in the literature review.

Scientific literature was reviewed to provide information about candidate pollutants for the later stages of the project. A summary of the concentrations in residential indoor air, in workplaces, in residential outdoor air and in personal exposures was created for these compounds:

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
Alkanes									
Decane		I/W/O/P48h 13.8/14.0/4.1/17.4 µg/m3	adults, Athens, EXPOLIS	1					building materials, furnishings, consumer products
		I/W/O/P48h 8.6/62.9/0.6/48.8 µg/m3	adults, Basel	1					
		I/W/O/P48h 5.2/12.5/1.0/16.3 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 7.5/5.2/5.8/- µg/m3	adults, Milan	1					
		I/W/O/P48h 4.9/3.8/1.0/7.4 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/9.7 µg/m3	adults, Germany, GerESII	8					
Nonane		I/W/O/P48h 5.6/6.9/2.7/7.0 µg/m3	adults, Athens, EXPOLIS	1					building materials, furnishings, consumer products
		I/W/O/P48h 3.4/24.4/0.4/13.6 µg/m3	adults, Basel	1					
		I/W/O/P48h 2.1/7.0/1.0/7.9 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 6.9/3.1/3.2/- µg/m3	adults, Milan	1					
		I/W/O/P48h 5.4/4.1/1.6/6.4 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/6.0 µg/m3	adults, Germany, GerESII	8					
Undecane		I/W/O/P48h 6.8/8.5/2.5/8.7 µg/m3	adults, Athens, EXPOLIS	1					building materials, furnishings, consumer products
		I/W/O/P48h 8.8/38.8/0.5/15.0 µg/m3	adults, Basel	1					
		I/W/O/P48h 5.1/11.9/-/14.2 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 5.6/3.6/6.8/- µg/m3	adults, Milan	1					
		I/W/O/P48h 6.5/4.8/1.2/8.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/9.9 µg/m3	adults, Germany, GerESII	8					
Aromatics									
Benzene	C 1, H	I/W/O/P48h 11.1/13.7/10.5/17.8 µg/m3	adults, Athens, EXPOLIS	1	leukaemia, 4- 6#/Million when life	2; p65	WHO 5 µg/m3 1-yr avg	3	smoking

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
					long exposure to 1 µg/m3				
		I/W/O/P48h 3.0/7.8/1.5/5.6 µg/m3	adults, Basel	1			5 µg/m3 1-yr avg	4	
		I/W/O/P48h 2.2/3.8/1.6/3.4 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 13.2/14.0/10.4/- µg/m3	adults, Milan	1	NOAEL 0.53 ppm (1.7 mg/m3)	10	EPA/Cal, cREL 60 µg/m3 (20 ppb) (7.4 year exposure)	10	
		I/W/O/P48h 12.0/9.4/5.2/11.6 µg/m3	adults, Prague	1					
		I/W/O/P-1week 9.4/-/4.4/12.2 µg/m3	adults, Antwerp, MACBETH	7					
		I/W/O/P-1week 10.1/-/20.7/18.8 µg/m3	adults, Athens	7					
		I/W/O/P-1week 4.5/-/3.1/6.6 µg/m3	adults, Copenhagen	7					
		I/W/O/P-1week 12.3/-/11.7/23.1 µg/m3	adults, Murcia	7					
		I/W/O/P-1week 7.0/-/8.0/10.6 µg/m3	adults, Padua	7					
		I/W/O/P-1week 9.5/-/4.7/13.4 µg/m3	adults, Rouen	7					
		I/W/O/P-1week -/-/-/13.5 µg/m3	adults, Germany, GerESII	8					
		I/W/O/P24h 7.2/-/3.6/7.5 µg/m3	adults, 6 States in the US, NHEXAS	5					
Diisocyanate					irritant, "isocyanate asthma"	22			glues
Ethylbenzene	H	I/W/O/P48h 7.7/54.1/5.9/18.6 µg/m3	adults, Athens, EXPOLIS	1	NOEL 2150 mg/m3, increase of organ weight	11	WHO GV= 22 mg/m3 - 1-year	11	
		I/W/O/P48h 2.7/9.8/1.1/13.6 µg/m4	adults, Basel	1					
		I/W/O/P48h 2.8/15.0/-/7.7 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 9.1/9.6/3.3/10.2 µg/m3	adults, Milan	1	Irritation: eyes, skin, mucous membrane; headache; narcosis, coma	9	NIOSH REL: TWA 100 ppm (435 mg/m3) ST 125 ppm (545 mg/m3)		
		I/W/O/P48h 10.7/8.8/6.7/- µg/m3	adults, Prague	1			OSHA PEL†: TWA 100 ppm (435 mg/m3)		

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
					LOAEL 250 ppm (1250 mg/m3) NOAEL 75 ppm (375 mg/m3)	10 10	EPA CA, cREL 2 mg/m3 (0.4 ppm) (103-week exposure)	10	
		I/W/O/P-1week -/-/-/24.0 µg/m3	adults, Germany, GerESII	8					
m&p-Xylene	H	I/W/O/P48h 24.0/121/20.1/54.6 µg/m3	adults, Athens, EXPOLIS	1	NOAEL 304 mg/m3 CNS effects, LOAEL 870 mg/m3 neurotoxicity in rats, OT 4.35 mg/m3 odor annouyance	11	GV= 4.8 mg/m3 - 24h GV= 0.87 mg/m3 - 1-year	11	
		I/W/O/P48h 7.9/34.6/3.3/39.9 µg/m3	adults, Basel				EPA CA, cREL 0.7 mg/m3 (0.2 ppm) (7-year exposure)	11	
		I/W/O/P48h 7.8/35.2/3.0/24.9 µg/m3	adults, Helsinki		LOAEL 14.2 ppm (49.7 mg/m3)	10			
		I/W/O/P48h 36.5/28.8/23.4/- µg/m3	adults, Milan		Nervous system; respiratory system	10			
		I/W/O/P48h 21.5/25.5/8.0/25.1 µg/m3	adults, Prague						
		I/W/O/P-1week -/-/-/50.5 µg/m3	adults, Germany, GerESII	8					
Naphtalene	H	I/W/O/P48h 90.1/7.5/4.4/45.5 µg/m3	adults, Athens, EXPOLIS	1	LOAEL 10 ppm (52.6 mg/m3), Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia		EPA/Cal, cREL 9 µg/m3 (2 ppb) (104 week exposure)	10	moth repellents
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h -/-/-/- µg/m3	adults, Helsinki	1					
		I/W/O/P48h 4.1/2.2/1.5/- µg/m3	adults, Milan	1					
		I/W/O/P48h 2.8/2.2/1.0/3.0 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/2.3 µg/m3	adults, Germany, GerESII	8					
o-Xylene	H	I/W/O/P48h 8.3/28.7/7.2/15.0 µg/m3	adults, Athens, EXPOLIS	1	NOAEL 304 mg/m3 CNS effects, LOAEL 870 mg/m3 neurotoxicity in rats, OT 4.35 mg/m3 odor annouyance	11	GV= 4.8 mg/m3 - 24h GV= 0.87 mg/m3 - 1-year	11	
		I/W/O/P48h 2.7/11.3/1.2/11.5 µg/m3	adults, Basel	1					
		I/W/O/P48h 2.4/15.0/1.0/9.9 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 11.5/9.3/7.8/- µg/m3	adults, Milan	1					
		I/W/O/P48h 7.1/7.7/3.0/7.8 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/13.6 µg/m3	adults, Germany, GerESII	8					

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
Propylbenzene		I/W/O/P48h 3.1/4.1/2.2/4.1 µg/m3	adults, Athens, EXPOLIS	1					
		I/W/O/P-1week -/-/-/4.6 µg/m3	adults, Germany, GerESII	8					
Styrene	C 2B, H, Ir	I/W/O/P48h 2.4/7.1/1.8/5.4 µg/m3	adults, Athens	1	LOAEL 34 mg/m3 by German expert group	6	GV II = 0.34 mg/m3 1-week	6	material emissions
		I/W/O/P48h 1.1/-/-/1.0 µg/m3	adults, Helsinki	1			GV I = 0.03 mg/m3 1-week		
		I/W/O/P48h 5.5/2.9/1.9/- µg/m3	adults, Milan	1	carcinogenity in experimental animals, IARC 2B	2 p;106	WHO 0.26 mg/m3 1-week	2 p;107	
		I/W/O/P48h 3.9/3.7/1.6/3.3 µg/m3	adults, Prague	1			WHO 70 µg/m3 30-minutes	2 p;107	
		I/W/O/P-1week -/-/-/5.1 µg/m3	adults, Germany, GerESII	8					
Toluene	H	I/W/O/P48h 20.1/32.4/6.4/31.1 µg/m3	adults, Basel	1	LOAEL 280 mg/m3 by German expert group	6	GV II = 3 mg/m3 1-2 week	6	
		I/W/O/P48h 20.3/24.7/5.6/25.2 µg/m3	adults, Helsinki	1			GV I = 0.3 mg/m3 1-2 week	6	
		I/W/O/P48h 68.0/53.5/43.3/- µg/m3	adults, Milan	1	LOAEL 332 mg/m3, CNS effects by WHO	2 p;113	GV = 0.26 mg/m3 1-week	11, p;53	
		I/W/O/P48h 74.2/69.1/25.6/88.4 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/130.2 µg/m3	adults, Germany, GerESII	8					
Trimethylbenzenes		I/W/O/P48h 18.2/19.4/13.8/27.3 µg/m3	adults, Athens, EXPOLIS	1					
1,2,4-		I/W/O/P-1week -/-/-/11.8 µg/m3	adults, Germany, GerESII	8					
Alcohols									
2-Ethyl-1-hexanol		I/W/O/P48h 3.6/3.9/1.6/6.2 µg/m3	adults, Athens, EXPOLIS	1	mucous irritant	20;p505			
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 3.5/2.6/-/3.0 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 2.2/4.4/2.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 6.8/5.7/2.3/5.4 µg/m3	adults, Prague	1					

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P-1week -/-/-/4.4 µg/m3	adults, Germany, GerESII	8					
Phenol	H	I/W/O/P48h 25.5/0.0/1.0/- µg/m3	adults, Athens, EXPOLIS	1	Systemic effects including liver and nervous system effects	10	EPA/Cal, cREL 200 µg/m3 (50 ppb)		
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1				10	
		I/W/O/P48h -/-/-/- µg/m3	adults, Helsinki	1	LOAEL 26 ppm	10			
		I/W/O/P48h 0.8/3.7/-/- µg/m3	adults, Milan	1	NOAEL 5 ppm	10			
		I/W/O/P48h 6.4/-/-/8.4 µg/m3	adults, Prague	1					
Esters									
2-Buthoxyethanol		I/W/O/P48h 14.8/12.0/4.1/15.0 µg/m3	adults, Athens, EXPOLIS	1	skin contact allergen III, NKB	12	HTP (corresb. to ¨TLV" in the USA) 98 mg/m3 (20 ppm) 8-hr	19	
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 2.0/18.8/-/6.5 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 7.6/14.7/0.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 8.5/10.1/-/6.5 µg/m3	adults, Prague	1					
Terpenes									
alpha-pinene		I/W/O/P48h 11.4/17.4/2.7/9.0 µg/m3	adults, Athens, EXPOLIS	1	reactions with O_3 may form strong airway irritants, see ref. 23	23			scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 15.9/4.7/1.5/9.9 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 14.5/1.3/6.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 11.9/4.8/1.4/7.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/18.3 µg/m3	adults, Germany, GerESII	8					
d-Limonene		I/W/O/P48h 82.5/14.4/5.3/55.5 µg/m3	adults, Athens, EXPOLIS	1	skin contact allergen II B	12			scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 31.5/13.8/-/18.7 µg/m3	adults, Helsinki	1	reactions with O_3 may form strong airway irritants, see ref. 23	23			
		I/W/O/P48h 46.6/10.5/6.2/- µg/m3	adults, Milan	1					
		I/W/O/P48h 42.2/23.1/8.6/26.3 µg/m3	adults, Prague	1					

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P-1week -/-/-/53.5 µg/m3	adults, Germany, GerESII	8					
3-carene		I/W/O/P48h 2.8/3.1/3.9/2.1 µg/m3	adults, Athens, EXPOLIS	1	reactions with O$_3$ may form strong airway irritants, see ref. 23	23			scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 5.6/1.6/-/3.2 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 2.2/0.5/2.0/- µg/m3	adults, Milan	1					
		I/W/O/P48h 8.0/2.1/-/2.9 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/9.8 µg/m3	adults, Germany, GerESII	8					
Halogenated									
Dichloromethane	C 2B	I/W/O/P48h 15/-/5/- µg/m3	USA, Canada	2; p83	carcinogenity in experimental animals LOAEL 690 mg/m3 - 1.5 hr		WHO 3 mg/m3 24 -h	2; p83	paint stripping
							WHO 0.45 mg/m3 1-week	2; p83	
							GV II = 2 mg/m3 24h	6	
							GV I = 0.2 mg/m3 24h	6	
Pentachlorophenol	H						1 µg/m3 requires mitigation	6	
							after mitigation 0.1 µg/m3 should be attained		
Tetrachloroethylene	C 2A, H	I/W/O/P48h 7.7/4.7/15.3/6.4 µg/m3	adults, Athens, EXPOLIS	1	effects in kidney	2:p110			dry-cleaned clothes
		I/W/O/P48h 1.2/1.4/0.7/1.3 µg/m3	adults, Basel	1	LOAEL 102 mg/m3 for humans	2:p110	WHO 0.25 mg/m3	2:p111	
		I/W/O/P48h -/-/-/2.8 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 12.8/7.8/12.6/- µg/m3	adults, Milan	1	sensory effects, odour	2:p36	WHO 8 mg/m3	2:p36	
		I/W/O/P48h 12.3/6.2/5.7/8.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/3.8 µg/m3	adults, Germany, GerESII	8					
Trichloroethylene	C 2A, H	I/W/O/P48h 11.4/7.5/9.9/11.2 µg/m3	adults, Athens, EXPOLIS	1	unit risk for cancer 0.43 #/Million	2:p116			

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 1.0/2.2/0.6/1.4 µg/m3	adults, Basel	1					
		I/W/O/P48h -/-/-/- µg/m3	adults, Helsinki	1					
		I/W/O/P48h 89.4/10.2/3.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 13.6/5.1/5.4/9.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/2.7 µg/m3	adults, Germany, GerESII	8					
Tris-(2-chloroethyl) phosphate		indoor in homes, schools and offices 0.01-0.25 µg/m3		24;p301	neurotoxic		GV II = 0.05 mg/m3	6	
							GV I = 0.005 mg/m3 24h	6	
Aldehydes									
Acetone		I/W/O/P48h 31.4/7.3/1.7/23.6 µg/m3	adults, Helsinki, EXPOLIS	1	odour annouyance, OT 240 mg/m3	11;p51			
Acetaldehyde	C 2B, H	I/W/O/P48h 10.1/2.6/1.5/7.9 µg/m3	adults, Helsinki, EXPOLIS	1	unit risk for cancer 0.15 -0.9 #/Million	11;p56	EPA/Cal, cREL 9 µg/m3	10	
Formaldehyde	C 2A, H	I/W/O/P48h 33.3/12.0/2.6/21.4 µg/m3	adults, Helsinki, EXPOLIS	1	irritant above 0.1 mg/m3	2;p88	WHO 0.1 mg/m3 - 30 min	2;p90	insulation, furnishing, ETS
		indoor air 30 - 60 µg/m3		2;p87	LOAEL 0.26 mg/m3	10	EPA/Cal, cREL 3 µg/m3 (2 ppb) (10 years)	10	
					NOAEL 0.09 mg/m3	10			
		living rooms 79 µg/m3	adults, East-Germany						
Methyl-ethyl-ketone	H	I/W/O/P48h 0.71/0.58/0.32/0.89 µg/m3	adults, Helsinki, EXPOLIS	1					
Propionaldehyde	H	I/W/O/P48h 0.91/0.54/0.14/0.74 µg/m3	adults, Helsinki, EXPOLIS	1					
Classical pollutants									
CO		I/W/O/P48h -/-/-/1.7 mg/m3	adults non-ETS, Athens	13	40 ppm (47 mg/m3) for 8-hours results in 5% COHb for an adult	15;p33	WHO 10 mg/m3 (10 ppm) 8-hour, 30 mg/m3 (25 ppm) 1-hour, 60 mg/m3 (50 ppm) 30-minutes, 100 mg/m3 (90 ppm) 15-minutes	2;p77	badly flued gas cookers and heaters, environmental tobacco smoke, attached garage.
		I/W/O/P48h -/-/-/0.82 mg/m3	adults, Basel	13	COHb in blood: 2.5%	14; p88-104			

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 1.2/1.3/1.5/1.3 mg/m3	adults, Helsinki	21	symtoms in patients with cardiovascular diseases, headache with 20-30%, dizziness with 30-50% and death with >50% concentration of COHb				
		I/W/O/P48h -/-/-/2.17 mg/m3	adults, Milan	13					
		I/W/O/P48h -/-/-/1.5 mg/m3	adults, Prague	13					
		peak conc. 60 mg/m3	In the UK homes	14;p19					
NO_2	Ir	I/W/O/P48h 27/36/36/30 μg/m3	adults, Basel	16	complex and not fully understood, irritant	2;p		2;p179	badly flued gas cookers and heaters, environmental tobacco smoke
		I/W/O/P48h 18/27/24/25 μg/m3	adults, Helsinki	16	respiratory symptoms in asthmatics and COPD patients				
		I/W/O/P48h 43/30/61/43 μg/m3	adults, Prague	16	LOAEL 375-565 μg/m3	2;p178			
		home indoors 13-40 μg/m3	UK	17;p43-44	respiratory infection, 20% increase/15 ppb (28.3 μg/m3) 2-week average			6;p46	
Inorganic comp.									
Cd	C 1	I/W/O/P48h -/-/-/4.8 ng/m3	adults, Athens, EXPOLIS	21	renal effects	2;p138	WHO 5 ng/m3 -1 year	2;p138	tobacco smoke, contaminated dust
		I/W/O/P48h -/-//7.8 ng/m3	adults, Basel	21					
		I/W/O/P48h -/-/-/22.9 ng/m3	adults, Helsinki	21					
		I/W/O/P48h -/-/-/4.3 ng/m3	adults, Prague	21					
Pb	C 2B	I/W/O/P48h 97.8/154/149/93 ng/m3	adults, Athens, EXPOLIS	21	hematological and nervous system effects	2;p150	WHO 0.5 μg/m3 -1 year	2;p152	contaminated dust, paint
		I/W/O/P48h 15.3/16.6/20.5/24.5 ng/m3	adults, Basel	21	LOAEL for children 100μg/l in blood	2;p151			
		I/W/O/P48h 3.4/5.6/5.0/12.3 ng/m3	adults, Helsinki	21					
		I/W/O/P48h 111/132/101/- ng/m3	adults, Milan	21					

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 46.2/-/45.4/58.7 ng/m3	adults, Prague	21					
Mercury		I/W/O/P48h >89% below LOD (50 ng/m3)	adults, Athens, EXPOLIS	21	renal effects, LOAEL 15 - 30 µg/m3	2;p160	WHO 1.0 µg/m3 -1 year	2;p160	paints, spills of mercury-containing products
		I/W/O/P48h >91% below LOD	adults, Basel	21			GV II = 0.35 µg/m3	6	
		I/W/O/P48h >89% below LOD	adults, Helsinki	21			GV I = 0.035 mg/m3 24h	6	
		I/W/O/P48h >97% below LOD	adults, Milan	21					
		I/W/O/P48h >90% below LOD	adults, Prague	21					
NH3	Ir	home indoors (new building) 15-51 µg/m3	Finland	18;p137	effects on pulmonary function LOAEL 25 ppm (17.8 mg/m3) NOAEL 9.2 ppm (6.5 mg/m3)	10 10 10	EPA/Cal, cREL 200 µg/m3 (300 ppb) (12.2 years)	10	cleaning solutions, meatbolic activity

A = allergen

C = carcinogen classified by IARC; 1 = carcinogenic to humans, 2A = propably carcinogenic, 2B= possibly carcinogenic

H = hazardous air pollutant classified in Californian Clean Air Act Amendments of 1990

Ir = irritant

I/W/O/P(time)

HTP = Finnish occupational treshold limit value corresbonding to ¨TLV" in the USA

Annex 2.   Phase 2: The selection of compounds to the further analysis

In this phase the steering group excluded compounds from the previous list based on the following criteria:
- no expressed concerns for health at present levels (for example acetone, decane, ethylbenzene, phenol , propylbenzene, trimethylbenzene)
- compound already regulated by use restrictions for indoor materials (pentachlorophenol)
- incomplete or no dose-response data available at present levels (methyl-ethyl-ketone, propionaldehyde)
- the main route/media for the exposure to the compound is other than indoor air (lead, mercury).

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
Aromatics									
Benzene	C 1, H	I/W/O/P48h 11.1/13.7/10.5/17.8 µg/m3	adults, Athens, EXPOLIS	1	leukaemia, 4-6#/Million when life long exposure to 1 µg/m3	2; p65	WHO 5 µg/m3 1-yr avg	3	Smoking
		I/W/O/P48h 3.0/7.8/1.5/5.6 µg/m3	adults, Basel	1			5 µg/m3 1-yr avg	4	
		I/W/O/P48h 2.2/3.8/1.6/3.4 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 13.2/14.0/10.4/- µg/m3	adults, Milan	1	NOAEL 0.53 ppm (1.7 mg/m3)	10	EPA/Cal, cREL 60 µg/m3 (20 ppb) (7.4 year exposure)	10	
		I/W/O/P48h 12.0/9.4/5.2/11.6 µg/m3	adults, Prague	1					
		I/W/O/P-1week 9.4/-/4.4/12.2 µg/m3	adults, Antwerp, MACBETH	7					
		I/W/O/P-1week 10.1/-/20.7/18.8 µg/m3	adults, Athens	7					
		I/W/O/P-1week 4.5/-/3.1/6.6 µg/m3	adults, Copenhagen	7					
		I/W/O/P-1week 12.3/-/11.7/23.1 µg/m3	adults, Murcia	7					
		I/W/O/P-1week 7.0/-/8.0/10.6 µg/m3	adults, Padua	7					
		I/W/O/P-1week 9.5/-/4.7/13.4 µg/m3	adults, Rouen	7					
		I/W/O/P-1week -/-/-/13.5 µg/m3	adults, Germany, GerESII	8					
		I/W/O/P24h 7.2/-/3.6/7.5 µg/m3	adults, 6 States in the US, NHEXAS	5					
m&p-Xylene	H	I/W/O/P48h 24.0/121/20.1/54.6 µg/m3	adults, Athens, EXPOLIS	1	NOAEL 304 mg/m3 CNS effects, LOAEL 870 mg/m3 neurotoxicity in rats, OT 4.35 mg/m3 odor annouyance	11	GV= 4.8 mg/m3 - 24h GV= 0.87 mg/m3 - 1-year	11	solvents, antiknock agents in gasoline
		I/W/O/P48h 7.9/34.6/3.3/39.9 µg/m3	adults, Basel				EPA CA, cREL 0.7 mg/m3 (0.2 ppm) (7-year exposure)	11	

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 7.8/35.2/3.0/24.9 µg/m3	adults, Helsinki		LOAEL 14.2 ppm (49.7 mg/m3)	10	HTP 50 ppm or 220 mg/m3 - 8hr, 100 ppm or 440 mg/m3 - 15 min	19	
		I/W/O/P48h 36.5/28.8/23.4/- µg/m3	adults, Milan		Nervous system; respiratory system	10			
		I/W/O/P48h 21.5/25.5/8.0/25.1 µg/m3	adults, Prague						
		I/W/O/P-1week -/-/-/50.5 µg/m3	adults, Germany, GerESII	8					
Naphtalene	H	I/W/O/P48h 90.1/7.5/4.4/45.5 µg/m3	adults, Athens, EXPOLIS	1	LOAEL 10 ppm (52.6 mg/m3), Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia		HTP 10 ppm or 53 mg/m3 - 8hr, 20 ppm or 110 mg/m3 - 15 min	19	Moth repellents
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h -/-/-/- µg/m3	adults, Helsinki	1					
		I/W/O/P48h 4.1/2.2/1.5/- µg/m3	adults, Milan	1			EPA/Cal, cREL 9 µg/m3 (2 ppb) (104 week exposure)	10	
		I/W/O/P48h 2.8/2.2/1.0/3.0 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/2.3 µg/m3	adults, Germany, GerESII	8					
o-Xylene	H	I/W/O/P48h 8.3/28.7/7.2/15.0 µg/m3	adults, Athens, EXPOLIS	1	NOAEL 304 mg/m3 CNS effects, LOAEL 870 mg/m3 neurotoxicity in rats, OT 4.35 mg/m3 odor annouyance	11	GV= 4.8 mg/m3 - 24h	11	solvent
		I/W/O/P48h 2.7/11.3/1.2/11.5 µg/m3	adults, Basel	1			GV= 0.87 mg/m3 - 1-year		
		I/W/O/P48h 2.4/15.0/1.0/9.9 µg/m3	adults, Helsinki	1			HTP 10 ppm or 53 mg/m3 - 8hr, 20 ppm or 110 mg/m3 - 15 min	19	
		I/W/O/P48h 11.5/9.3/7.8/- µg/m3	adults, Milan	1					
		I/W/O/P48h 7.1/7.7/3.0/7.8 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/13.6 µg/m3	adults, Germany, GerESII	8					
Styrene	C 2B, H, Ir	I/W/O/P48h 2.4/7.1/1.8/5.4 µg/m3	adults, Athens	1	LOAEL 34 mg/m3 by German expert group	26	GV II = 0.34 mg/m3 1-week	26	Material emissions
		I/W/O/P48h 1.1/-/-/1.0 µg/m3	adults, Helsinki	1			GV I = 0.03 mg/m3 1-week		
		I/W/O/P48h 5.5/2.9/1.9/- µg/m3	adults, Milan	1	carcinogenity in experimental animals, IARC 2B	2 p;106	WHO 0.26 mg/m3 1-week	2 p;107	
		I/W/O/P48h 3.9/3.7/1.6/3.3 µg/m3	adults, Prague	1			WHO 70 µg/m3 30-minutes	2 p;107	

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P-1week -/-/-/5.1 µg/m3	adults, Germany, GerESII	8					
Toluene	H	I/W/O/P48h 20.1/32.4/6.4/31.1 µg/m3	adults, Basel	1	LOAEL 280 mg/m3 by German expert group	26	GV II = 3 mg/m3 1-2 week	26	solvent
		I/W/O/P48h 20.3/24.7/5.6/25.2 µg/m3	adults, Helsinki	1			GV I = 0.3 mg/m3 1-2 week	26	
		I/W/O/P48h 68.0/53.5/43.3/- µg/m3	adults, Milan	1	LOAEL 332 mg/m3, CNS effects by WHO	2 p;113	GV = 0.26 mg/m3 1-week		11, p;53
		I/W/O/P48h 74.2/69.1/25.6/88.4 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/130.2 µg/m3	adults, Germany, GerESII	8					
Alcohols									
n-butanol	Ir	I/W/O/P48h 12.3/5.7/-/7.7 µg/m3	adults, Helsinki	27	eye irritant (human) 50 ppm	29	HTP 50 ppm or 150 mg/m3 - 8hr, 75 ppm or 230 mg/m3 - 15 min	19	
		I/W/O/P-1week -/-/-/6.9 µg/m3	adults, Germany, GerESII	25	oral NOAEL: 125 mg/kg/day	28			
					oral LOAEL: 500 mg/kg/day	28			
2-Buthoxyethanol	A, Ir	I/W/O/P48h 14.8/12.0/4.1/15.0 µg/m3	adults, Athens, EXPOLIS	1	skin contact allergen III, NKB	12	HTP 98 mg/m3 (20 ppm) 8-hr	19	
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 2.0/18.8/-/6.5 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 7.6/14.7/0.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 8.5/10.1/-/6.5 µg/m3	adults, Prague	1					
Terpenes									
Alpha-pinene		I/W/O/P48h 11.4/17.4/2.7/9.0 µg/m3	adults, Athens, EXPOLIS	1	reactions with O_3 may form strong airway irritants	23			Scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 15.9/4.7/1.5/9.9 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 14.5/1.3/6.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 11.9/4.8/1.4/7.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/18.3 µg/m3	adults, Germany, GerESII	8					
d-Limonene	A	I/W/O/P48h 82.5/14.4/5.3/55.5 µg/m3	adults, Athens, EXPOLIS	1	skin contact allergen II B	12	HTP 25 ppm or 140	19	Scented deodorisers, polishes, cigarettes

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1			mg/m3 - 8hr, 50 ppm or 280 mg/m3 - 15 min		
		I/W/O/P48h 31.5/13.8/-/18.7 µg/m3	adults, Helsinki	1	reactions with O$_3$ may form strong airway irritants, see ref. 23	23			
		I/W/O/P48h 46.6/10.5/6.2/- µg/m3	adults, Milan	1					
		I/W/O/P48h 42.2/23.1/8.6/26.3 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/53.5 µg/m3	adults, Germany, GerESII	8					
3-carene		I/W/O/P48h 2.8/3.1/3.9/2.1 µg/m3	adults, Athens, EXPOLIS	1	reactions with O$_3$ may form strong airway irritants, see ref. 23	23			Scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 5.6/1.6/-/3.2 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 2.2/0.5/2.0/- µg/m3	adults, Milan	1					
		I/W/O/P48h 8.0/2.1/-/2.9 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/9.8 µg/m3	adults, Germany, GerESII	8					
Halogenated									
Dichloromethane	C 2B	I/W/O/P48h 15/-/5/- µg/m3	USA, Canada	2; p83	carcinogenity in experimental animals		WHO 3 mg/m3 24 -h	2; p83	Paint stripping
					LOAEL 690 mg/m3 - 1.5 hr		WHO 0.45 mg/m3 1-week	2; p83	
							GV II = 2 mg/m3 24h	26	
							GV I = 0.2 mg/m3 24h	26	
Tetrachloroethylene	C 2A, H	I/W/O/P48h 7.7/4.7/15.3/6.4 µg/m3	adults, Athens, EXPOLIS	1	effects in kidney	2:p110	WHO 0.25 mg/m3	2:p111	Dry-cleaned clothes
		I/W/O/P48h 1.2/1.4/0.7/1.3 µg/m3	adults, Basel	1	LOAEL 102 mg/m3 for humans	2:p110			
		I/W/O/P48h -/-/-/2.8 µg/m3	adults, Helsinki	1			HTP 10 ppm or 70 mg/m3 - 8h	19	
		I/W/O/P48h 12.8/7.8/12.6/- µg/m3	adults, Milan	1	sensory effects, odour	2:p36	WHO 8 mg/m3	2:p36	
		I/W/O/P48h 12.3/6.2/5.7/8.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/3.8 µg/m3	adults, Germany, GerESII	8					

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
Trichloroethylene	C 2A, H	I/W/O/P48h 11.4/7.5/9.9/11.2 µg/m3	adults, Athens, EXPOLIS	1	unit risk for cancer 0.43 #/Million	2:p116	HTP 30 ppm or 160 mg/m3 - 8hr, 45 ppm or 250 mg/m3 - 15 min	19	
		I/W/O/P48h 1.0/2.2/0.6/1.4 µg/m3	adults, Basel	1					
		I/W/O/P48h -/-/-/- µg/m3	adults, Helsinki	1					
		I/W/O/P48h 89.4/10.2/3.7/- µg/m3	adults, Milan	1					
		I/W/O/P48h 13.6/5.1/5.4/9.1 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/2.7 µg/m3	adults, Germany, GerESII	8					
Tris-(2-chloroethyl) phosphate	Ir	indoor in homes, schools and offices 0.01-0.25 µg/m3		24;p301	neurotoxic, irritant, may act as an carsinogen	29	GV II = 0.05 mg/m3	26	plasticizer
					oral-rat LD50 1230 mg kg-1		GV I = 0.005 mg/m3 24h	26	
Aldehydes									
Acetaldehyde	C 2B, H	I/W/O/P48h 10.1/2.6/1.5/7.9 µg/m3	adults, Helsinki, EXPOLIS	1	unit risk for cancer 0.15 -0.9 #/Million	11;p56	HTP 25 ppm or 46 mg/m3 - 15min	19	
							EPA/Cal, cREL 9 µg/m3	10	
Formaldehyde	C 2A, H	I/W/O/P48h 33.3/12.0/2.6/21.4 µg/m3	adults, Helsinki, EXPOLIS	1	irritant above 0.1 mg/m3	2;p88	WHO 0.1 mg/m3 - 30 min	2;p90	insulation, furnishing, ETS
		indoor air 30 - 60 µg/m3	WHO	2;p87	LOAEL 0.26 mg/m3	10	HTP 0.3 ppm or 0.37 mg/m3 - 8h	19	
		workplaces 30 - 60 µg/m3	WHO	2;p87	NOAEL 0.09 mg/m3	10	EPA/Cal, cREL 3 µg/m3 (2 ppb) (10 years)	10	
		living rooms 79 µg/m3	adults, East-Germany		skin contact allergen				
Hexanal	Ir	I/W/O/P48h 11.8/8.7/4.8/10.1 µg/m3	adults, Athens, EXPOLIS	1					
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h 11.5/3.9/-/8.1 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 4.7/2.2/1.0/- µg/m3	adults, Milan	1					
		I/W/O/P48h 10.3/10.0/2.7/10.2 µg/m3	adults, Prague	1					
Benzaldehyde	Ir	I/W/O/P48h 7.4/11.0/5.5/8.9 µg/m3	adults, Athens, EXPOLIS	1	oral rat LOEL: 400 mg/kg/day	28			
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1	oral rat NOEL: 200 mg/kg/day	28			

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 5.0/4.9/2.6/4.7 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 10.6/12.3/8.9/- µg/m3	adults, Milan	1					
		I/W/O/P48h 9.5/9.1/4.5/11.2 µg/m3	adults, Prague	1					
PAHs									
BaP	C 2A	indoor air 0.77 / 0.52 ng/m3	nighttime / daytime	30	unit risk for lung cancer 87 000 #/Million		HTP 0.01 mg/m3 - 8h	19	smoking
		outdoor air 1-10 ng/m3		2;p92					
Classical pollutants									
CO		I/W/O/P48h -/-/-/1.7 mg/m3	adults non-ETS, Athens	13	40 ppm (47 mg/m3) for 8-hours results in 5% COHb for an adult	15;p33	WHO 10 mg/m3 (10 ppm) 8-hour, 30 mg/m3 (25 ppm) 1-hour, 60 mg/m3 (50 ppm) 30-minutes, 100 mg/m3 (90 ppm) 15-minutes	2;p77	badly flued gas cookers and heaters, environmental tobacco smoke, attached garage.
		I/W/O/P48h -/-/-/0.82 mg/m3	adults, Basel	13	COHb in blood: 2.5% symtoms in patients with cardiovascular diseases, headache with 20-30%, dizziness with 30-50% and death with >50% concentration of COHb	14; p88-104			
		I/W/O/P48h 1.2/1.3/1.5/1.3 mg/m3	adults, Helsinki	21					
		I/W/O/P48h -/-/-/2.17 mg/m3	adults, Milan	13					
		I/W/O/P48h -/-/-/1.5 mg/m3	adults, Prague	13					
		peak conc. 60 mg/m3	In the UK homes	14;p19					
NO2	Ir	I/W/O/P48h 27/36/36/30 µg/m3	adults, Basel	16	complex and not fully understood, irritant	2;p	WHO 40 µg/m3 - annual, 200 µg/m3 - 1hour	2;p179	badly flued gas cookers and heaters, environmental tobacco smoke
		I/W/O/P48h 18/27/24/25 µg/m3	adults, Helsinki	16	respiratory symptoms in asthmatics and COPD patients				
		I/W/O/P48h 43/30/61/43 µg/m3	adults, Prague	16	LOAEL 375-565 µg/m3	2;p178			
		home indoors 13-40 µg/m3	UK	17;p43-44	respiratory infection, 20% increase/15 ppb (28.3 µg/m3) 2-week average			6;p46	
Isocyanates									
Diisocyanate	A, Ir				irritant, "isocyanate asthma"	22	HTP 0.035 mg/m3 - 8h	19	plastics and rubber chemicals, glues, polyuretan foam
Inorganic comp.									
Pb	C 2B	I/W/O/P48h 97.8/154/149/93 ng/m3	adults, Athens, EXPOLIS	21	hematological and nervous system effects	2;p150	WHO 0.5 µg/m3 -1 year	2;p152	contaminated dust, paint

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 15.3/16.6/20.5/24.5 ng/m3	adults, Basel	21	LOAEL for children 100µg/l in blood	2;p151			
		I/W/O/P48h 3.4/5.6/5.0/12.3 ng/m3	adults, Helsinki	21					
		I/W/O/P48h 111/132/101/- ng/m3	adults, Milan	21					
		I/W/O/P48h 46.2/-/45.4/58.7 ng/m3	adults, Prague	21					
NH3	Ir	home indoors (new building) 15-51 µg/m3	Finland	18;p137	effects on pulmonary function	10	HTP 20 ppm or 14 mg/m3 - 8h, 50 ppm or 36 mg/m3 - 15min	19	cleaning solutions, meatbolic activity
					LOAEL 25 ppm (17.8 mg/m3)	10			
					NOAEL 9.2 ppm (6.5 mg/m3)		EPA/Cal, cREL 200 µg/m3 (300 ppb) (12.2 years)	10	

A = allergen

C = carcinogen classified by IARC; 1 = carcinogenic to humans, 2A = propably carcinogenic, 2B= possibly carcinogenic

H = hazardous air pollutant classified in Californian Clean Air Act Amendments of 1990

Ir = irritant

I/W/O/P(time)   residential indoor/workplace/residential outdoor/ambient/personal exposure concentration (mean concentration in a given time period)

HTP = Finnish occupational treshold limit value corresbonding to ¨TLV" in the USA

Annex 3.   Phase 3: Compounds selected into the detailed risk assessment.

On the basis of the available information and after an extensive discussion on the chemical substances, the steering group decided to conduct detailed assessment for the compounds listed in the following table:

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
Aromatics									
Benzene	C 1, H	I/W/O/P48h 11.1/13.7/10.5/17.8 µg/m3	adults, Athens, EXPOLIS	1	leukaemia, 4-6#/Million when life long exposure to 1 µg/m3	2; p65	WHO 5 µg/m3 1-yr avg	3	Smoking, attached garages, impurities in common solvents (consumer products)
		I/W/O/P48h 3.0/7.8/1.5/5.6 µg/m3	adults, Basel	1			5 µg/m3 1-yr avg	4	
		I/W/O/P48h 2.2/3.8/1.6/3.4 µg/m3	adults, Helsinki	1					
		I/W/O/P48h 13.2/14.0/10.4/- µg/m3	adults, Milan	1	NOAEL 0.53 ppm (1.7 mg/m3)	10	EPA/Cal, cREL 60 µg/m3 (20 ppb) (7.4 year exposure)	10	
		I/W/O/P48h 12.0/9.4/5.2/11.6 µg/m3	adults, Prague	1					
		I/W/O/P-1week 9.4/-/4.4/12.2 µg/m3	adults, Antwerp, MACBETH	7					
		I/W/O/P-1week 10.1/- /20.7/18.8 µg/m3	adults, Athens	7					
		I/W/O/P-1week 4.5/-/3.1/6.6 µg/m3	adults, Copenhagen	7					
		I/W/O/P-1week 12.3/- /11.7/23.1 µg/m3	adults, Murcia	7					
		I/W/O/P-1week 7.0/-/8.0/10.6 µg/m3	adults, Padua	7					
		I/W/O/P-1week 9.5/-/4.7/13.4 µg/m3	adults, Rouen	7					
		I/W/O/P-1week -/-/-/13.5 µg/m3	adults, Germany, GerESII	8					
		I/W/O/P24h 7.2/-/3.6/7.5 µg/m3	adults, 6 States in the US, NHEXAS	5					
m&p-Xylene	H	I/W/O/P48h 24.0/121/20.1/54.6 µg/m3	adults, Athens, EXPOLIS	1	NOAEL 304 mg/m3 CNS effects, LOAEL 870 mg/m3 neurotoxicity in rats, OT 4.35 mg/m3 odor annouyance	11	GV= 4.8 mg/m3 - 24h GV= 0.87 mg/m3 - 1-year	11	solvents, antiknock agents in gasoline

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P48h 7.9/34.6/3.3/39.9 µg/m3	adults, Basel				EPA CA, cREL 0.7 mg/m3 (0.2 ppm) (7-year exposure)	11	
		I/W/O/P48h 7.8/35.2/3.0/24.9 µg/m3	adults, Helsinki		LOAEL 14.2 ppm (49.7 mg/m3)	10	HTP 50 ppm or 220 mg/m3 - 8hr, 100 ppm or 440 mg/m3 - 15 min	19	
		I/W/O/P48h 36.5/28.8/23.4/- µg/m3	adults, Milan		Nervous system; respiratory system	10			
		I/W/O/P48h 21.5/25.5/8.0/25.1 µg/m3	adults, Prague						
		I/W/O/P-1week -/-/-/50.5 µg/m3	adults, Germany, GerESII	8					
o-Xylene	H	I/W/O/P48h 8.3/28.7/7.2/15.0 µg/m3	adults, Athens, EXPOLIS	1	NOAEL 304 mg/m3 CNS effects, LOAEL 870 mg/m3 neurotoxicity in rats, OT 4.35 mg/m3 odor annouyance	11	GV= 4.8 mg/m3 - 24h GV= 0.87 mg/m3 - 1-year	11	solvent
		I/W/O/P48h 2.7/11.3/1.2/11.5 µg/m3	adults, Basel	1					
		I/W/O/P48h 2.4/15.0/1.0/9.9 µg/m3	adults, Helsinki	1			HTP 10 ppm or 53 mg/m3 - 8hr, 20 ppm or 110 mg/m3 - 15 min	19	
		I/W/O/P48h 11.5/9.3/7.8/- µg/m3	adults, Milan	1					
		I/W/O/P48h 7.1/7.7/3.0/7.8 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/13.6 µg/m3	adults, Germany, GerESII	8					
Naphtalene	H	I/W/O/P48h 90.1/7.5/4.4/45.5 µg/m3	adults, Athens, EXPOLIS	1	LOAEL 10 ppm (52.6 mg/m3), Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia		HTP 10 ppm or 53 mg/m3 - 8hr, 20 ppm or 110 mg/m3 - 15 min	19	Moth repellents
		I/W/O/P48h -/-/-/- µg/m3	adults, Basel	1					
		I/W/O/P48h -/-/-/- µg/m3	adults, Helsinki	1					
		I/W/O/P48h 4.1/2.2/1.5/- µg/m3	adults, Milan	1			EPA/Cal, cREL 9 µg/m3 (2 ppb) (104 week exposure)	10	
		I/W/O/P48h 2.8/2.2/1.0/3.0 µg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/2.3 µg/m3	adults, Germany, GerESII	8					
Styrene	C 2B, H, Ir	I/W/O/P48h 2.4/7.1/1.8/5.4 µg/m3	adults, Athens	1	LOAEL 34 mg/m3 by German expert group	26	GV II = 0.34 mg/m3 1-week	26	Material emissions
		I/W/O/P48h 1.1/-/-/1.0 µg/m3	adults, Helsinki	1			GV I = 0.03 mg/m3 1-week		
		I/W/O/P48h 5.5/2.9/1.9/- µg/m3	adults, Milan	1	carcinogenity in experimental animals, IARC 2B	2 p;106	WHO 0.26 mg/m3 1-week	2 p;107	

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		μg/m3							
		I/W/O/P48h 3.9/3.7/1.6/3.3 μg/m3	adults, Prague	1			WHO 70 μg/m3 30-minutes	2 p;107	
		I/W/O/P-1week -/-/-/5.1 μg/m3	adults, Germany, GerESII	8					
Toluene	H	I/W/O/P48h 20.1/32.4/6.4/31.1 μg/m3	adults, Basel	1	LOAEL 280 mg/m3 by German expert group	26	GV II = 3 mg/m3 1-2 week	26	Solvent
		I/W/O/P48h 20.3/24.7/5.6/25.2 μg/m3	adults, Helsinki	1			GV I = 0.3 mg/m3 1-2 week	26	
		I/W/O/P48h 68.0/53.5/43.3/- μg/m3	adults, Milan	1	LOAEL 332 mg/m3, CNS effects by WHO	2 p;113	GV = 0.26 mg/m3 1-week		11, p;53
		I/W/O/P48h 74.2/69.1/25.6/88.4 μg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/130.2 μg/m3	adults, Germany, GerESII	8					
Terpenes									
alpha-pinene		I/W/O/P48h 11.4/17.4/2.7/9.0 μg/m3	adults, Athens, EXPOLIS	1	reactions with O_3 may form strong airway irritants	23			Scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- μg/m3	adults, Basel	1					
		I/W/O/P48h 15.9/4.7/1.5/9.9 μg/m3	adults, Helsinki	1					
		I/W/O/P48h 14.5/1.3/6.7/- μg/m3	adults, Milan	1					
		I/W/O/P48h 11.9/4.8/1.4/7.1 μg/m3	adults, Prague	1					
		I/W/O/P-1week -/-/-/18.3 μg/m3	adults, Germany, GerESII	8					
d-Limonene	A	I/W/O/P48h 82.5/14.4/5.3/55.5 μg/m3	adults, Athens, EXPOLIS	1	skin contact allergen II B	12	HTP 25 ppm or 140 mg/m3 - 8hr, 50 ppm or 280 mg/m3 - 15 min	19	Scented deodorisers, polishes, cigarettes
		I/W/O/P48h -/-/-/- μg/m3	adults, Basel	1					
		I/W/O/P48h 31.5/13.8/-/18.7 μg/m3	adults, Helsinki	1	reactions with O_3 may form strong airway irritants, see ref. 23	23			
		I/W/O/P48h 46.6/10.5/6.2/- μg/m3	adults, Milan	1					
		I/W/O/P48h 42.2/23.1/8.6/26.3 μg/m3	adults, Prague	1					

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		I/W/O/P-1week -/-/-/53.5 µg/m3	adults, Germany, GerESII	8					
Aldehydes									
Acetaldehyde	C 2B, H	I/W/O/P48h 10.1/2.6/1.5/7.9 µg/m3	adults, Helsinki, EXPOLIS	1	unit risk for cancer 0.15 -0.9 #/Million	11;p56	HTP 25 ppm or 46 mg/m3 - 15min	19	Cigarettes, fireplaces, building materials, consumer products
							EPA/Cal, cREL 9 µg/m3	10	
Formaldehyde	C 2A, H	I/W/O/P48h 33.3/12.0/2.6/21.4 µg/m3 indoor air 30 - 60 µg/m3	adults, Helsinki, EXPOLIS	1	irritant above 0.1 mg/m3	2;p88	WHO 0.1 mg/m3 - 30 min	2;p90	Insulation, furnishing, ETS
				2;p87	LOAEL 0.26 mg/m3	10	HTP 0.3 ppm or 0.37 mg/m3 - 8h	19	
					NOAEL 0.09 mg/m3	10	EPA/Cal, cREL 3 µg/m3 (2 ppb) (10 years)	10	
		living rooms 79 µg/m3	adults, East-Germany						
Classical pollutants									
CO		I/W/O/P48h -/-/-/1.7 mg/m3	adults non-ETS, Athens	13	40 ppm (47 mg/m3) for 8-hours results in 5% COHb for an adult	15;p33	WHO 10 mg/m3 (10 ppm) 8-hour, 30 mg/m3 (25 ppm) 1-hour, 60 mg/m3 (50 ppm) 30-minutes, 100 mg/m3 (90 ppm) 15-minutes	2;p77	Badly flued gas cookers and heaters, environmental tobacco smoke, attached garage.
		I/W/O/P48h -/-/-/0.82 mg/m3	adults, Basel	13	COHb in blood: 2.5% symtoms in patients with cardiovascular diseases, headache with 20-30%, dizziness with 30-50% and death with >50% concentration of COHb	14; p88-104			
		I/W/O/P48h 1.2/1.3/1.5/1.3 mg/m3	adults, Helsinki	21					
		I/W/O/P48h -/-/-/2.17 mg/m3	adults, Milan	13					
		I/W/O/P48h -/-/-/1.5 mg/m3	adults, Prague	13			GV II = 15 mg/m3 8-hour	26	
							GV II = 60 mg/m3 30-min	26	
		peak conc. 60 mg/m3	In the UK homes	14;p19			GV I = 1.5 mg/m3 8-hour	26	
							GV I = 6 mg/m3 30-min	26	
NO$_2$	Ir	I/W/O/P48h 27/36/36/30 µg/m3	adults, Basel	16	complex and not fully understood, irritant	2;p	WHO 40 µg/m3 - annual, 200 µg/m3 - 1hour	2;p179	Badly flued gas cookers and heaters, environmental tobacco smoke
		I/W/O/P48h 18/27/24/25 µg/m3	adults, Helsinki	16	respiratory symptoms in asthmatics and COPD patients				
		I/W/O/P48h 43/30/61/43 µg/m3	adults, Prague	16	LOAEL 375-565 µg/m3	2;p178	GV II = 60 µg/m3 1-week	26	
							GV II = 350 µg/m3 30-min	26	

Compound	Health relevance	Exposure Assessment	Population	Ref. No.	Exposure/ Dose/Response Ass. or risk assessment for stochastic effects	Ref. No.	Risk Management Regulatory standards	Ref. No.	Sources inside the buildings
		home indoors 13-40 µg/m3	UK	17;p 43-44	respiratory infection, 20% increase/15 ppb (28.3 µg/m3) 2-week average			6;p46	
Inorganic comp.									
NH₃	Ir	home indoors (new building) 15-51 µg/m3	Finland	18;p 137	effects on pulmonary function LOAEL 25 ppm (17.8 mg/m3) NOAEL 9.2 ppm (6.5 mg/m3)	10 10	HTP 20 ppm or 14 mg/m3 - 8h, 50 ppm or 36 mg/m3 - 15min EPA/Cal, cREL 200 µg/m3 (300 ppb) (12.2 years)	19 10	Cleaning solutions, meatbolic activity

A = allergen

C = carcinogen classified by IARC; 1 = carcinogenic to humans, 2A = propably carcinogenic, 2B= possibly carcinogenic

H = hazardous air pollutant classified in Californian Clean Air Act Amendments of 1990

Ir = irritant

I/W/O/P(time)   residential indoor/workplace/residential outdoor/ambient/personal exposure concentration (mean concentration in a given time period)

HTP = Finnish occupational treshold limit value corresbonding to ¨TLV" in the USA

Annex 4. The EXPOLIS study: parameters describing the indoor air concentration distributions plotted to the graphs of this report.

	Sampling period	n	Athens	n	Basel	n	City Helsinki	n	Milan	n	Oxford	n	Prague
Aromatics													
Benzene	30-hour[a]	42	10.1 ± 7.8	47	2.7 ± 1.7	188	2.2 ± 1.9	41	17.0 ± 23.4	40	3.6 ± 3.4	46	8.0 ± 4.6
Naphtalene	30-hour[a]	42	83.5 ± 197	47	0.7 ± 0.3	188	0.6 ± 0.5	41	21.0 ± 81.6	40	1.3 ± 1.5	46	2.0 ± 1.9
Styrene	30-hour[a]	42	1.8 ± 1.5	47	0.7 ± 0.6	188	1.1 ± 1.5	41	30.3 ± 157.4	40	1.8 ± 2.3	46	2.0 ± 1.7
Toluene	30-hour[a]	42	82.7 ± 141	47	19.5 ± 13.2	188	20.1 ± 24.4	41	77.6 ± 70.1	40	23.7 ± 41.5	46	86.2 ± 95.7
m,p,o-Xylenes	30-hour[a]	42	30.4 ± 14.6	47	10.2 ± 8.2	188	10.1 ± 7.5	41	88.2 ± 184.1	40	12.5 ± 21.7	46	22.2 ± 12.2
Terpenes													
alfa-Pinene	30-hour[a]	42	10.7 ± 13.2	47	4.1 ± 6.9	188	15.7 ± 23.7	41	17.9 ± 52.3	40	16.5 ± 23.5	46	10.2 ± 15.9
d-Limonene	30-hour[a]	42	78.3 ± 121	47	15.0 ± 19.4	188	30.7 ± 61.5	41	71.5 ± 150.5	40	19.0 ± 28.6	46	27.1 ± 26.4
Classical pollutants													
Carbon monoxide	1-minute		-		-	258785	1.2 ± 0.6	4822	1.9 ± 1.3[b]		-		-
Nitrogen dioxide	48-hour		-	50	23.8 (1.7)	175	14.7 (2.1)		-	43	26.9 ± 21.9	33	37.7 (1.9)
Aldehydes													
Formaldehyde	30-hour[a]	-	-	-	-	15	41.4 ± 22.3	-	-	-	-	-	-
Acetaldehyde	30-hour[a]	-	-	-	-	15	18.2 ± 9.7	-	-	-	-	-	-

x±y = arithmetic mean ± standard deviation, x (y) = geometric mean (geometric standard deviation)

[a] Nominal sampling time

[b] 15 min sampling time

Annex 5.   The National Survey of air pollutants in English homes: parameters describing the indoor air concentration distributions plotted to the graphs of this report.

	Unit	Sampling period	n	Min	Max	GM	10%	50%	75%	95%	Reference
Aromatics											
Benzene	µg/m^3	28-day	796	< 0.1	93.5	3	1	3.3	5.8	14.6	Brown VM et al 2002
Toluene	µg/m^3	28-day	796	0.3	1783.5	15.1	4.4	14.9	27.9	74.9	Brown VM et al 2002
m,p -xylene	µg/m^3	28-day	796	0.1	152.8	3.8	0.9	3.7	7.5	30.3	Brown VM et al 2002
											Brown VM et al 2002
Terpenes											
d-Limonene	µg/m^3	28-day	796	< 0.1	308.4	6.2	1.3	7.1	15.5	51	Brown VM et al 2002
Classical pollutants											
Carbon monoxide	mg/m^3	14-day	830	< 0.01	4.45	0.47	0.14	0.5	0.9	2.07	Raw et al 2002
Nitrogen dioxide	µg/m^3	14-day	845	0.8	620	21.8	7.2	21.8	40.1	90	Coward et al 2002
Aldehydes											
Formaldehyde	µg/m^3	3-day	833	1	171	22.2	9.8	24	35.2	61.2	Brown VM et al 2002

n = number of samples, min = minumum, max = maximum, GM = geometric mean, 10%, 50%, 75% and 95% = ith percentile of the cumulative distribution

Annex 6. **The French National Survey on Indoor Air Quality (preliminary results from the ongoing project): parameters describing the indoor air concentration distributions plotted to the graphs of this report (Golliot et al 2003, Kirchner 2004).**

	Unit	Sampling period	n	Mean	STD	Min	Max
Aromatics							
Benzene	µg/m^3	7-day	109	2.8	2.3	0.0	13.8
Styrene	µg/m^3	7-day	109	1.4	1.7	0.2	17.0
Toluene	µg/m^3	7-day	110	25.7	35.5	2.2	196
m+p+o-Xylenes	µg/m^3	7-day	102	17.2	24.7	1.4	143
Classical pollutants							
Carbon monoxide	mg/m^3	5-min	550666	0.47	1.63	0.0	62.9
Aldehydes							
Acetaldehyde	µg/m^3	7-day	201	18.4	14.0	2.6	95.0
Formaldehyde	µg/m^3	7-day	201	23.1	11.8	2.9	63.7

n = number of samples, Mean = arithmetic mean, STD = standard deviation, Min = minumum, Max = maximum

Annex 7. Relevant National and International Guidelines and Recommendations

		Formaldehyde	CO	NO$_2$	Naphthalene	Toluene	Styrene	NH$_3$	Monoterpene (α-Pinene)
		µg/m^3	mg/m^3	µg/m^3	µg/m^3	µg/m^3	µg/m^3	µg/m^3	µg/m^3
Finland[1]	**S1**	30	2					30	
	S2	50	3					30	
	S3	100	8					40	
Germany[2,3,4]	GV II		15 (8-h)	60 (1-w)	20	3000 (1-w)	300 (1-w)		2000 (1-w)
	GV II		60 (30-min)						
	GV I		1.5 (8-h)		2	300 (1-w)	30 (1-w)		200 (1-w)
	GV I		6 (30-min)						
Norway[5]		100 (30-min)	10 (8-h)						
			25 (1-h)	100 (1-h)					
UK[6]		100 (30-min)	100 (15-min)	300 (1-h)					
			60 (30-min	40 (1-y)					
			30 (1-h)						
			10 (8-h)						
WHO[7]		100 (30-min)	100 (15-min)	200 (1-h)		260 (1-w)	260 (1-w)		
			60 (30-min	40 (1-y)					
			30 (1-h)						
			10 (8-h)						

Abbreviations for averaging times: (-min) = minute, (-h) = hour, (-w = week), and (-y) = year

[1] Target values for indoor air quality and climate; S1 = very good indoor air climate (Individual Indoor Climate), S2 = good indoor air climate, S3 = satisfactory indoor climate. Values given in the table are maximum values for S1, S2 and S3. Source: Finnish classification of indoor climate. Finnish Society of Indoor Air Quality and Climate (FiSIAQ), 2000 (in English).

[2] Guidelines values (GV) for indoor air pollutants; GV II is a health-related value based on current toxicological and epidemiological knowledge. If the concentration corresponding to GV II is reached or exceeded immediate action must be taken because permanent stay in a room at this concentration level is likely to represent a threat to health especially for sensitive people. GV I is the concentration level at which a substance, taken individually, does not give rise to adverse health effects even at life-long exposure. An exceedance of GV I is linked with an exposure beyond normal which is undesirable from a hygienic viewpoint. GV I and GV II are given as 1-week average, except carbon monoxide, which was given as 8-hour (8-h) and 30-minute (30-min) average. Source: Seifert B. et al. (1999). Guidelines values for indoor air pollutant, Proceedings of Indoor Air '99, Edimburgh, Vol. 1: 499-504. [3] Sagunski H, Heger W (2004). Richtwerte fur die Innenraumluft: Naphthalin. Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz. 47:705-712 (in German). [4] Sagunski H, Heinzow B (2003). Richtwerte fur die Innenraumluft: Bicyclische Terpene (Leitsubstanz α-Pinen). Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz. 46:346-352 (in German).

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Formaldehyde

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Organization	Shortcut	Document link
World Health Organization - Air Quality Guidelines for Europe – 2000	[WHO]	Not available on web
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA1]	http://www.oehha.ca.gov/air/chronic_rels/pdf/50000.pdf
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA2]	http://www.oehha.ca.gov/air/acute_rels/allAcRELs.html
Agency for Toxic Substances and Disease Registry	[ATSDR]	http://www.atsdr.cdc.gov/phshome.html
National Institute for Working Life - The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards	[NIWL]	www.arbetslivsinstitutet.se/
National Environment Protection Council - Australia	[NEPC]	www.ephc.gov.au/nepms/air/air_toxics.html

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Naphthalene

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Authority	Shortcut	Link to original document
Environmental Protection Agency	[EPA]	http://www.epa.gov/safewater/ccl/pdf/naphthalene.pdf
Environmental Protection Agency - Integrated Risk Information System	[IRIS]	http://www.epa.gov/iris/subst/0436.htm
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA]	http://www.oehha.ca.gov/air/chronic_rels/pdf/91203.pdf
European Chemical Bureau Risk Assessment Report: Naphthalene EUR 20763 EN	[ECB]	http://ecb.jrc.it/
Agency for Toxic Substances and Disease Registry	[ATSDR]	http://www.atsdr.cdc.gov/toxprofiles/tp67.html

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Acetaldehyde

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U.S.EPA - Integrated Risk Information System	[IRIS]	http://www.epa.gov/iris/subst/0290.htm
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA]	http://www.oehha.ca.gov/air/chronic_rels/index.html
National Institute of Public Heatlh and Environmental – The Netherlands	[RIVM]	http://www.rivm.nl/bibliotheek/rapporten/650270003.pdf
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Organization	Shortcut	Document link
World Health Organization - Air Quality Guidelines for Europe – 2000	[WHO]	Not available on web
U.S.EPA - Integrated Risk Information System	[IRIS]	http://www.epa.gov/iris/subst/0118.htm
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA1]	http://www.oehha.ca.gov/air/chronic_rels/index.html
"	[OEHHA2]	http://www.oehha.ca.gov/air/acute_rels/allAcRELs.html
European Chemical Bureau - Institute for Health and Consumer Protection IHCP	[ECB]	http://ecb.jrc.it
Agency for Toxic Substances and Disease Registry	[ATSDR]	http://www.atsdr.cdc.gov/phshome.html

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Xylenes

Main sources:

Organization	Shortcut	Document link
EPA – Toxicological Review of Xylenes EPA 635/R-03/001 - In Support of Summary Information on the Integrated Risk Information System IRIS	[EPA]	http://www.epa.gov/iris/toxreviews/0270.htm
Environmental Protection Agency - Integrated Risk Information System	[IRIS]	http://www.epa.gov/iris/subst/0270.htm
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA1]	http://www.oehha.ca.gov/air/chronic_rels/index.html
"	[OEHHA2]	http://www.oehha.ca.gov/air/acute_rels/allAcRELs.html
Agency for Toxic Substances and Disease Registry	[ATSDR]	http://www.atsdr.cdc.gov/phshome.html

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Styrene

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Organization	Shortcut	Document link
World Health Organization - Air Quality Guidelines for Europe 2000	[WHO]	Not available on web
Environmental Protection Agency - Integrated Risk Information System	[IRIS]	http://www.epa.gov/iris/subst/0104.htm
EPA - Technology Transfer Network – Air Toxics Website	[EPA]	http://www.epa.gov/ttn/atw/hlthef/styrene.html
Office of Environmental Health Hazard Assessment of the Californian Environmental Protection Agency	[OEHHA1]	http://www.oehha.ca.gov/air/chronic_rels/index.html
"	[OEHHA2]	http://www.oehha.ca.gov/air/acute_rels/allAcRELs.html
Agency for Toxic Substances and Disease Registry	[ATSDR]	http://www.atsdr.cdc.gov/phshome.html

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