The INDEX project

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

Summary on recommendations and management options

December, 2004

JOINT RESEARCH CENTRE
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Foreword

In the past decades a large number of studies have indicated the presence of various chemical compounds 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 impact on human health and comfort is almost totally unknown and difficult to predict because of the lack of toxicological data and of 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 the investigation of acute and sub-acute 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 chemicals 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 on
- available toxicological information to allow the assessment the impact on 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.

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Contents

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 experiencing 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 human (population) exposure sufficiently into account. They have been up-to-now mainly oriented on outdoor air pollution. EU legislation addresses inter alia air quality standards, national emission ceilings and emissions from vehicles and industries. However, the Sixth 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 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 it possible to carry out reliable exposure and risk assessments. Due to the missing exposure and risk assessments, it has been difficult to regulate the presence of these chemicals in indoor environments up to now.

It is, therefore, highly 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. The INDEX project

The INDEX project (Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU) started in December 2002 with 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.

The key issues that have been addressed within the project are:

- the setting up of a list of compounds to be measured and regulated in indoor environments with priority, on the basis of health impact criteria
- to providing suggestions and recommendations on potential exposure limits for these compounds and
- to providing information on links with existing knowledge, ongoing studies, legislation etc. at world scale.

This has been achieved by:

- reviewing of exposure and dose/response information, plus regulatory actions for selected indoor pollutants across the world
- prioritizing of indoor pollutants for regulation purposes
- conducting a risk characterization of these pollutants
- proposing of exposure limit values or other exposure control regulations
- assessing of essential research needs for pollutants with high risk potential, but insufficient information for setting regulatory objectives or selecting regulatory options.

3. Methodology

3.1 Risk Assessment

The risk assessment in the frame of the INDEX project was carried out by collecting available indoor exposure data from Europe from scientific literature, databases and directly from researchers currently working in this area. Similarly, dose/response data were reviewed from scientific literature. Two working groups (WG) consisting of experts from several countries were established to collect and assess these data. Finally, risk characterisation, recommendations for risk management and conclusions were drawn within 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 1. The risk assessment approach applied to this project is presented in more detail in the following paragraphs.

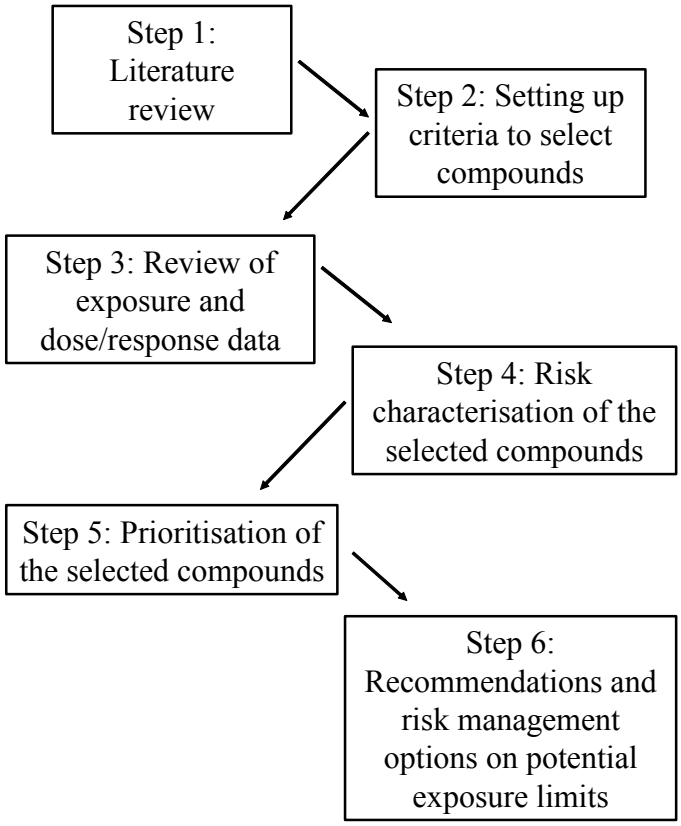

Fig. 1: The main steps of the INDEX project.

3.2 Selection of Indoor Air Chemicals (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 has shown 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 during this project, the steering committee defined the following criteria for the selection of the chemicals for risk analysis:

1. Only single compounds will be considered
2. The compound should have strong 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 the aforementioned 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 criteria. Simultaneously, 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 thorough evaluation 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.Molhave, 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 20-25 compounds for further analysis. In this phase the steering group excluded 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, 25 compounds were selected from the working groups for a more detailed exposure and risk analysis.

Phase 3: Compounds selected into the 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 pre-selected 25 chemical substances, the steering committee finally decided to conduct a detailed assessment for 14 compounds only.
The compounds that were considered hazardous in the hazard identification process are summarised in Figure 2. The compounds that remained in the list through the whole process (phase 3) were taken into a more detailed exposure and risk assessment.

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.

Fig. 2: Indoor originated compounds that were assessed and considered the most hazardous in the three phases of the hazard identification process.

3.3 Exposure Assessment

Exposure to selected indoor air pollutants was evaluated 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 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 1999), 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. Comparisons have been done with regard 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 Europeans.

Population exposures are typically reported in the 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 are log-normally distributed, which is a typical shape for the distributions of the naturally occurring pollutants.

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.

The 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 2002), toluene (EU 2003b) and a draft report for benzene (EU 2003c). 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.

3.4 Dose/Response Assessment

In preparing the dose-response assessment fact sheets for the 14 chemicals selected, information was retrieved from scientific literature (mainly by electronic search), comprehensive toxicological reviews of leading health organizations, risk evaluation documents and available databases, as outlined in Table 1. In addition, Toxline and Medline were searched for relevant scientific communications published until 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 2. Where relevant, studies conducted on susceptible sub-populations (e.g. asthmatics, infants, children, pregnant etc.) were quoted and taken into consideration in the risk characterization.

Key-studies were summarised within 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.

Table 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 2: Exposure limits/guidelines established by health organisations and their summary definitions

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 lifethreatening effects. Each of these three acute exposure levels is determined for a 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 meaning ful, 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.

Table 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	

3.5 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 evaluated. It is pointed out that the assessment of risk is based on scientific considerations, and 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, since 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 for the management of risk. Nevertheless, Limits of Exposure (ELs) have to be established for individual chemicals, following inhalation exposure in indoor environments, for both short-term (indoor-activity related) and long-term exposures (background indoors). An EL was derived for each chemical on the basis 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 are the product of the individual factors outlined in Table 4.

Table 4: 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 appropriate 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 the evaluation of risk for cancer for the entire population than on 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, was 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.

3.5.1 The Risk assessment approach

Following the revision of world literature and the setting up of criteria applied on the selection for the candidate chemicals, the steering committee decided the inclusion into a final assessment of 14 compounds. Each of these compounds was submitted to a general risk assessment with the associated tasks divided onto two working groups responsible for the collection and reporting of the existing exposure data and the required dose response data.

Exposure to selected indoor air pollutants was assessed 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 worldwide. Results from population-based studies have been preferred in order to be able to generalise the results from studies of individuals to larger populations, targeting to assess exposures of all the Europeans.

In preparing the dose-response assessment fact sheets for the selected 14 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.

3.5.2 Prioritisation of Indoor Air Chemicals on the basis of the health risk characterisation

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. 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.
Information from the exposure assessment and toxicity assessment were integrated and a risk characterization is performed for 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 : 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 $\mu g/m^3$; 90^{th} (percentile) ±sd: 59±7 $\mu g/m^3$; 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 starting from about 30 $\mu g/m^3$.
Reported formaldehyde concentrations were lower (99^{th} percentile < 150 µg/m3) 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 : 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 experiences 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 (mean) 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, 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} percentile levels±sd: 11.5±11.1 $\mu g/m^3$) 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: Low 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 to 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 to irritating 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 (90^{th} 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 (no better defined) could be expected following the concomitant presence of ozone indoors. The reaction of limonene with ozone leads to the formation of volatile compounds and possibly of radicals with irritating properties.

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 irritating effects to the eyes, nose and throat would be expected at background α-pinene levels encountered in European homes, with median (90^{th} 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 of ozone indoors. a-Pinene reacts with ozone forming chemicals and possibly radicals with irritating properties.

4. 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 all cancer from indoor exposures nor protect the most susceptible individuals in all conditions, such as individuals with serious respiratory or cardiovascular disease, highly reactive asthmatics, genetically predisposed individuals developing haemolytic anaemia from naphthalene, etc.
In addition to specific recommendations reported below, the following general recommendations and management options apply to most or many indoor air contaminants in the high and low priority lists:

- Use of appropriate ventilation practices based on the well defined standards for indoor environments according to the recommendations of the relevant professional organisations.
- Ban tobacco smoking in all indoor spaces under public jurisdiction. Raise public awareness on the hazards of tobacco smoke, and discourage smoking in private residences, 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 quarters (closing the doorways, sealing the structures and ensuring proper air pressure difference between garage and other indoor spaces).

High priority chemicals

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 carcinogenicity of formaldehyde, a guideline value should be as low as reasonably achievable.

Management options:

- Restrict emissions of formaldehyde from building products, furnishings and household/office chemicals.
- Discourage the use of formaldehyde containing products.

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.

Management options:

- Apply the indoor air concentration guideline in the building design process
- Develop building codes, ventilation standards and equipment/appliance standards (design, maintenance and use) so that all indoor combustion equipment will exhaust to chimneys/hoods/vents leading outdoors.

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.

Management options:

- Apply the indoor air concentration guideline in the building design process
- Develop building codes, ventilation standards and equipment/appliance standards (design, maintenance and use) so that all indoor combustion equipment will exhaust to chimneys/hoods/vents leading outdoors
- Require regular mandatory inspections for indoor combustion equipment
- Recommend alarm systems responding to abnormally high concentrations (e.g. 50 mg/m^3).

Benzene

As benzene is a human carcinogen, its concentration in the air should be as low as reasonably achievable. Indoor concentrations of benzene should not exceed outdoor concentrations.

Management options:

- Sources emitting benzene (tobacco smoking, etc.) should not be allowed in the indoor environment
- Lower the permissible benzene content in any building material and consumer product.

Naphthalene

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.

Management options:

- Restrict the use of naphthalene containing household products, particularly mothballs.

<u>Low priority chemicals</u>

Specific management options should be defined when more information on sources, human exposure and health effects will become available.

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.

Xylenes, 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.

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

Specific management options should be defined when more information on sources, human exposure and health effects will become available.

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. Interaction with ozone causing biologically active products is suspected. Considering its widespread use such data should be made available. The odour threshold is 1-2 mg/m^3.

a-Pinene

There are insufficient toxicological data available to recommend a guideline value. Interaction with ozone causing biologically active products is suspected. Considering its widespread use such data should be made available.

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