Scientific Committee on Health and Environmental Risks

SCHER

Preliminary report on risk assessment on indoor air quality

Approved by the SCHER for public consultation during the 15th plenary of 30 January 2007

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHER

Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compound whose use may have harmful consequences for human health and the environment.

In particular, the Committee addresses questions related to new and existing chemicals, the restriction and marketing of dangerous substances, biocides, waste, environmental contaminants, plastic and other materials used for water pipe work (e.g. new organics substances), drinking water, indoor and ambient air quality. It addresses questions relating to human exposure to mixtures of chemicals, sensitisation and identification of endocrine disrupters.

Scientific Committee members

Herman Autrup, Peter Calow, Wolfgang Dekant, Helmut Greim, Colin Janssen, Bo Jansson, Hannu Komulainen, Ole Ladefoged, Jan Linders, Inge Mangelsdorf, Marco Nuti, Jerzy Sokal, Anne Steenhout, Jose Tarazona, Emanuela Testai, Marco Vighi, Matti Viluksela, Hanke Wojciech

Contact:

European Commission
Health & Consumer Protection DG
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

Sanco-Sc8-Secretariat@ec.europa.eu

ACKNOWLEDGMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion:

Prof. Wojciech Hanke, Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Poland

Prof. Bo Jansson, Stockholm University, Sweden

Dr. Hannu Komulainen, National Public Health Institute, Finland

Prof. Ole .Ladefoged, Institute of Food Safety and Nutrition, Denmark

Dr. Inge Mangelsdorf, Fraunhofer Institute for Toxicology and Experimental Medicine, Germany

Prof. Anne Steenhout, Université Libre de Bruxelles, Belgium

Dr. E. Testai, Senior Scientist, Environment and Primary Prevention Mechanisms of Toxicity Unit, Instituto Superiore di Sanità, Italy

External experts

Prof. Gunnar Damgård Nielsen, National Research Centre for Working Environment, Denmark

Prof. Philip Harteman, Département Environnement et Santé Publique, Faculté de Médecine, Université de Nancy, France

Dr. Aino Nevalainen, National Public Health Institute, Finland

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1. BACKGROUND

Air quality is one of the major environmental health concerns for Europe. The main goal of the Community policy on air pollution is to achieve levels of air quality that do not result in unacceptable risks to human health.

Until now, much progress has been made in Europe in tackling outdoor air pollutants with Community legislation on emission sources available since 1970 and on air quality standards since 1980. This legislation has been continuously updated. The most recent EU quality standards are defined within the Air quality framework directive from1996[1] and subsequent directives[2]. The air quality directives require Member States to set up and maintain a system for assessing outdoor air quality and to draw up action plans to reach the objectives of the EC directives. Limit values have been adopted for outdoor air concentration of the most common pollutants such as sulphur dioxide, lead and particulate matter[3]. In 2001, the Commission also launched an air quality programme Clean Air for Europe (CAFÉ)[4] to prepare a long term strategy on air pollution, which was adopted by the Commission on 21 September 2005.

In 2002, four priority areas to be tackled with urgent actions were identified in the EU's Sixth Community Environment Action Programme[5]. One of the priority areas is the Environment and health and quality of life. In 2003, the European Commission adopted a new Strategy on Environment and Health[6] with the overall aim to reduce diseases caused by environmental factors in Europe. Among others, air quality is one of the main identified problems of environmental pollution related to health problems such as respiratory diseases, asthma and allergies.

This strategy was followed by the EU Action Plan on Environmental and Health[7]. In this plan, the "action 12" intends to develop work on improving indoor air quality.

These initiatives recognize the importance of a complete integrated strategy on air pollution which considers not only the outdoor air but also includes possible solutions concerning indoor air pollutants. As reported in the communication on a European Environment and Health Strategy, a broad stakeholder involvement is also foreseen which includes a consultative group on "Environment and Health". The Commission will use this group to consult on analyses of environment and health data, and risk management measures. The analyses in question will rely in part on the work of the SCHER to identify missing links in existing monitoring systems.

Indoor exposures to air pollutants may occur in both private and public indoor environments such as homes, offices, schools, and transport systems.

Most indoor air pollutants consist of chemicals released, for example, from the use of cleaning products, air fresheners, pesticides and emissions from furniture and construction materials, heating and cooking. In addition, outdoor sources may contribute to indoor air pollution. Aspects such as thermal insulation and ventilation rates may also play a role. Microbiological contaminants which may induce allergies and asthma also require consideration as indoor air pollutants. Examples of potential serious effects include respiratory disorders, including asthma and cancer.

[1] OJ L296/55 21.11.1996

[2] OJ L163/41, 29.06.1999, OJ L313/12, 13.12.2000, OJ L67/14 9.03. 2002, L23/3 26.01.2005

[3] OJ L163/41 29.06.1999

[4] COM (2001) 245 final

[5] OJ L 242/1 10.09.2002

[6] COM (2003) 338 final

[7] COM (2004) 416 final

2. TERMS OF REFERENCE

To provide a basis for assessment of risks to human health from indoor air quality, and a sound scientific basis for the development and implementation of policies, the SCHER is asked:

1. To identify a Risk Assessment Strategy to support policy on indoor air quality. The Committee is particularly asked to take into account potentially vulnerable groups of population such as children, pregnant women and elderly. The committee is also asked to consider the practicality of a risk assessment which takes into account on combined exposure and cumulative effects of specific air pollutants.
2. To identify the adequacy of current information and data requirements for filling-in gaps on aspects such as exposure/effect and dose/response relationships, existing measurement standards and gaps in knowledge which will help to guide further research and monitoring efforts.
3. To consider risks associated with the use of air fresheners:

SCHER has given a separate opinion on this point (SCHER 2006).

4. To identify potential areas of concern in relation to:

- specific chemical compounds taking into account the recent outcome of the INDEX report prepared by DG JRC
- household – chemicals and other products (e.g. decorating materials, cleaners, furnishings, etc.)
- building dampness/moisture and microbial growth (moulds, bacteria)

3. OPINION

Indoor air constitutes a complex case for risk assessment and management due to a wide variety of pollutants, exposure levels, different possible health outcomes, differences in sensitivity of the population, cultural habits, way of living, building stock and climate across Europe.

Possible health risks of indoor air pollution and aspects of risk assessment have been addressed recently in European and international working groups and projects (WHO 1997, ECA 2000, INDEX 2005, California EPA 2005).

The opinion is aimed to cover indoor environments where the general public may be exposed to pollutants, such as private homes and public buildings e.g., schools, day care centres and offices. Industrial exposures, including professional cleaning in indoor environments are excluded because they do not represent the exposure of the general public and specific exposure limits for contaminants are established. In addition, the opinion does not cover active smoking but environmental tobacco smoke (ETS) is included.

3.1 Question 1

To provide a basis for assessment of risks to human health from indoor air quality, and a sound scientific basis for the development and implementation of policies, the SCHER is asked to identify a Risk Assessment Strategy to support policy on indoor air quality. The Committee is particularly asked to take into account potentially vulnerable groups of population such as children, pregnant women and elderly. The committee is also asked to consider the practicality of a risk assessment which takes into account combined exposure and cumulative effects of specific air pollutants.

Response to question 1

3.1.1 Risk Assessment for indoor air

The SCHER recommends to use the basic paradigm for toxicological risk assessment, (Commission Directive 93/67/EEC[8]; Council Regulation (EEC) 793/93[9]; TGD, 2003) in support of the indoor air quality policy. It takes into account all necessary elements in health risk assessment: the hazards, the dose-response, exposure and results in a science-based risk characterisation (Commission Regulation (EC) No. 1488/94[10]; TGD 2003). For risk characterisation, the margin of safety/exposure should be defined or the exposure should be compared with relevant health based guideline values.

3.1.1.1 Hazard identification

A number of factors in the indoor environment can affect well-being and health. The main factors are:

- Chemicals for intended use or unintentional emissions from different sources
- Radon
- Particles
- Microbes
- Humidity
- Pets and pests

Chemicals

Data requirement for hazard identification of chemicals is described in the TGD. Information on the acute and sub-acute health effects can be obtained from toxicological data-bases and sources. However, information on possible health effects (such as cancer) after long term exposures is not available for many of the chemicals reported to be present in indoor air. The relevance of such data gaps needs to be discussed on case-by-case.

Sensory irritation of the eyes and upper airways is a specific effect often related to exposure to indoor air pollutants (Alarie 1973; Alarie et al. 1998, Nielsen 1991; Doty et al. 2004) and needs particular attention. Sensory irritation may be induced by specific chemicals, but also by factors such as insufficient humidity.

Malodours are generally undesirable in indoor environments (Wolkoff et al. 2006a). Odours *per se* do not cause toxicological effects but may increase the reporting of symptoms (for example, headache, nausea, eye and throat irritation) (Wolkoff et al. 2006a). Other symptoms of odour exposures are hyperventilation or conditioned responses (Shusterman 2002).

Odors and sensory irritation and conditioned responses due to these challenges are the main causes of complaints regarding poor indoor air quality.

Radon

Radon in indoor air has been associated with lung cancer (WHO 1998, Darby et al., 2005). Radon gas diffuses through soil into residences in areas where bedrock contains uranium in excess. Radon evaporates also from household water into air upon warming. High radon concentrations have been measured indoors locally in several countries.

[8] OJ L227/9 8.09.1993

[9] OJ L84/1 5.04.1993

[10] OJ L161/3 29.06.1994

Particles

Particles (PM_{10}, $PM_{2.5}$, fine particles, ultrafine particles) in ambient air have been associated with adverse health effects, including respiratory and cardiovascular effects (WHO 2003, WHO 2005b).

Particles from outdoor air may contribute to particle load in indoor air, but there are also indoor sources such as combustion and cooking, and particles may be formed by reactions between ozone and some VOCs (Wainman et al. 2000, Sarwar et al. 2004, Afsari et al. 2005).

Man-made nanoparticles are increasingly used in consumer products but their impact as indoor air pollutants is not yet known.

Microbes

Microbial agents may play a role in the development of asthma and allergic airway diseases.

Many fungi contain allergens, and sensitization is possible by indoor exposure to fungi due to dampness and mould growth (see answer to Question 4c).

Additionally, virus infections may be transmitted by indoor air. In the first years of life, virus infections are common causes of wheezing. Some viruses are associated with an increase in asthma and allergy incidence (Schaub et al. 2006).

Humidity

Insufficient humidity results in increased reporting of skin symptoms (dryness, rash), eye irritation and nasal dryness (Reinikainen and Jaakkola 2003, Wolkoff et al. 2006b). High temperature may exacerbate these effects (Reinikainen and Jaakkola, 2001). In excessive humidity, water condenses onto (cold) surfaces, causing water damage and mould problems. High humidity also favours the growth of dust mites.

Pets and pests

Pests, house dust mites and cockroaches are important sources of indoor allergens (aeroallergens) (D'Amato et al. 1998; Platts-Mills et al. 2000; Nielsen et al. 2002). Exposures to aeroallergens may cause sensitization with production of IgE antibodies. The IgE antibodies promote development of the allergic airway diseases, rhinitis and asthma (Beasley et al. 2000).

The scientific literature on contact with pets and their effects on development of asthma is contradicting (for review e.g. Chan-Yeung and Becker 2006). Exposure may be different due to cultural habits, and cockroach and mouse allergens may be more important in inner cities (Eggleston 2001, Phipatanakul et al. 2000a; 2000b).

3.1.1.2 Dose-response assessment

Information about exposure-response relationship is crucial for risk assessment. Regarding local effects such as irritation, air concentrations of pollutants are directly relevant for the effects assessment. To evaluate possible systemic effects, air concentrations of pollutants may be transformed to internal doses using established values for breathing volumes and alveolar retention. When data from occupational exposures are used, they must be adjusted for differences in exposure duration (general population 20-21 hours indoors vs. a work shift of 8 hours) and the limitations of the occupational observations need to be considered for the exposed population. Both acute and chronic effects should be taken into account in the dose-response assessment (INDEX 2005).

Biomarkers, when available, may be used to establish the dose-response relationships.

3.1.1.3 Exposure assessment

More than 900 different organic compounds have been detected in indoor air (SCALE 2004) in addition to fine and ultrafine particles and biological material (microbes, allergens). Concentrations of pollutants in indoor air are determined by a number of factors including type and emission rates from sources, ventilation rate, adsorption/absorption of compounds on/in materials (sinks and possible secondary sources).

Differences in cultural habits of people throughout Europe may result in large qualitative and quantitative differences in indoor air quality. The results of the EXPOLIS-INDEX study concerning exposure to European indoor environments in Athens, Basel, Grenoble, Milan, Helsinki, Oxford and Prague (e.g. VOCs and $PM_{2.5}$) showed variation in exposure larger within city than average variations between cities (EXPOLIS-INDEX 2004). The health consequence of these variations is insufficiently understood.

Emissions of chemicals may occur from building materials (e.g. Bornehag et al. 2005a), cooking activities (e.g. Afshari et al. 2005), cleaning activities (Nazaroff and Weschler 2004, Singer et al. 2006), and combustion of biomass fuels in general (e.g. SCHER 2006) but the exposure patterns are not sufficiently known.

Models have been developed to predict emissions and distribution patterns of pollutants. Such models are essential for the development of indoor exposure and risk assessment (ECA 2006, Kephalopoulos et al. 2007). However, no comprehensive general model has yet emerged and been validated.

Exposures to indoor air pollutants may occur directly by inhalation, or indirectly by ingestion of e.g., dust, while volatile compounds such as formaldehyde and benzene are mainly present in the gas phase.

Less volatile substances are also to some extent bound to particles and dust, and exposure via those media may contribute to the total exposure. Many semivolatiles such as phthalates, flame retardants, PAHs, chlorophenols, pesticides, organotins and metals may adsorb to house dust (Butte and Heinzow, 2002).

Particles may abrade from materials containing the chemicals of interest, e.g. PVC particles containing phthalates. House dust forms a long-term sink and may be regularly resuspended representing a secondary source for pollutants. The particle size of house dust is, however, typically large and only a fraction of the dust is respirable (Butte and Heinzow 2002, Maertens et al. 2004). Ingestion is likely the main exposure route for house dust (Butte and Heinzow 2002) in small children due to licking and biting on articles and "hand to mouth" pattern. However, there is insufficient information whether this route of exposure actually leads to notably increased uptake of pollutants.

In the absence of measured data, the exposure should be estimated using validated models and information on local conditions. Modelling of chemical substances has the longest tradition (WHO 2005a). At present, there are no reliable models for exposure to indoor air microbial exposure.

SCHER states that it is important to evaluate effects of inhalation exposure. It also underlines the importance to assess the contribution of indoor air exposures to the total exposure to a chemical through all routes (ingestion, inhalation and dermal) to assess systemic effects to obtain an overall risk assessment and to estimate the contribution of indoor air pollution.

The frequent focus on VOCs and other selected compounds in measurement campaigns may neglect a possible impact of compounds with high toxicity present in low concentrations or of compounds which are difficult to detect. Moreover, the SCHER recommends to use realistic exposure scenarios and to avoid conclusions on exposures based on the content of potentially toxic chemicals in materials such as wallpaper or furnishings. Biomonitoring will make a very valuable contribution to the exposure assessment.

3.1.1.4 Risk characterisation

For some pollutants occurring in indoor air, international (WHO 2000) and national (EPA, OEHHA, ATSDR, UBA, Health Canada, cited e.g. in the INDEX-report, INDEX 2005) health-based exposure limit/guidelines exist. They may not be aimed specifically for indoor air but may be used considering the specific exposure situation.

In risk characterisation, the whole exposure range should be included and not only average or median exposures since variations in exposures may expand over several magnitudes. Analysis of EXPOLIS study data on VOCs has shown that the group at the upper 95% end of the distribution may get exposed significantly more than the median group (Edwards et al. 2005). On the other hand, the most sensitive subgroups may react at notably lower exposures. Accordingly, the range of plausible risk estimates (not only the central estimate) is useful. The precision and the uncertainty related to risk estimates should also be given in assessments.

Indication of the association between exposure and health effects may be difficult when the primary causing factor/agent is not known though the association is evident. This is typical for indoor air problems caused by microbes. For those cases, exclusion of other contributing factors may strengthen the association.

3.1.1.5 Vulnerable groups

In the opinion, vulnerable groups are represented by children, pregnant women, elderly persons over 65 years of age, and persons suffering from asthma or other respiratory diseases, and cardiovascular diseases. For some pollutants (e.g. microbes) other health compromises (immunodeficiency) may render people more vulnerable.

The assumption of different susceptibility of vulnerable groups (children, pregnant, elderly) to pollutants is based on age-dependent differences in physiology and toxicokinetics, and varying responses due to existing diseases and genetic factors (e.g. IPCS 1993, Tamburlini et al. 2002, Pediatrics 2004).

Vulnerability to chemical toxicity after birth may be highest during the first 6 months (Scheuplein et al. 2002, Ginsberg et al. 2004) and continue for years before maturation. However, children may also be less sensitive and tolerate higher doses of chemical substances than adults, depending on the age and the compound (Schneider et al. 2002, Dourson et al. 2002). Higher exposure due to specific exposure patterns (e.g. hand-to-mouth activity in children) may increase the risk for children. Air pollutants may affect adversely foetal and infant lung development, cause post-neonatal infant mortality due to respiratory diseases, cause cough and bronchitis and aggravate asthma (WHO 2005b). The effect on lung function during development has been observed below the NOEL of effects of single air pollutants in adults, suggesting a higher susceptibility of children. The causative pollutants have not been identified but the association to adverse effects has been detected most consistently with outdoor particulate matter (PM), nitrogen dioxide and ozone (WHO 2005b). Studies addressing specifically the indoor environment, where the concentrations are different, are so far limited. Children's higher susceptibility is known for lead and environmental tobacco smoke (Tamburlini et al. 2002, DiFranza et al. 2004); some concern has been expressed also for organophosphate pesticides (see bullet 4a in the opinion).

Altered physiology and toxicokinetics (e.g. reduced renal clearance) make elderly people potentially more sensitive (IPCS 1993) due to reduced capacity for elimination. However, elderly people may also be less sensitive to some effects (Kjaergaard et al. 1992, Shusterman et al. 2003) including nasal (Schusterman et al. 2003) and eye irritation (Kjaergaard et al. 1992) indicating that aging may also decrease the susceptibility.

People suffering from cardiovascular diseases are more vulnerable to particles (WHO 2003, Dominici et al., 2006) and persons suffering from asthma and other respiratory diseases are more susceptible to several air pollutants (WHO 2004a, 2005b). For

example, sensory irritation may occur at lower exposure level in persons with allergic rhinitis (Shusterman et al. 2003, WHO 2005b).

Therefore, the SCHER recommends a science-based health risk assessment addressing vulnerable groups by applying a case-by-case approach. The SCHER also reminds that the Margin-of-Safety approach already includes specific safety factors to account for especially vulnerable groups.

3.1.1.6 Mixtures/combined effects

The SCHER was asked to consider the practicality of a risk assessment which takes into account combined exposures and cumulative effects of specific air pollutants. In this opinion, the SCHER interprets the combined effects as the total effects caused by exposure to all chemical and biological (allergens and microbes) stressors present in indoor air.

At present the (quantitative) risk characterization must mostly be done on a single chemical basis because there are seldom relevant data and established methods to evaluate mixture effects. In indoor environment, exposures are always to complex mixtures of substances from different sources which may jointly contribute to toxic effects. Due to the complexity of indoor air pollution and its variability with time, estimation of risk associated with exposure to the complex mixture as such and the generalization of the obtained results is rarely feasible. This approach has been used only in a few cases, when sensory irritation was the end-point (Hempel-Jørgensen et al. 1999, Nielsen et al. 2007b).

The majority of toxicology data refer to exposures to single chemicals. Such data can be used directly if chemicals in a mixture act independently with different endpoints, i.e. the effect of each component of the mixture is not influenced by the presence of the other components ('dissimilar joint action'). The single chemical approach is supported by the results of some studies, which indicate that interactions were unlikely to occur at environmentally relevant concentrations (which often are well below the NOAEL values). Interactive effects giving rise to possible health concern have been reported, starting from concentrations around the LOAEL (Cassee et al. 1998).

However, the single chemical approach is not applicable when the components affect each others response. Such combined effects may be additive (a 'similar joint action'; similar endpoints, similar mechanism of action and /or toxicokinetics properties) or there may be interactions (antagonistic or synergistic effects). Combined effects have been demonstrated e.g. by mixtures of pesticides when potentially harmful effects were observed at concentrations of each single component below or approaching the individual NOAEL value (Cavieres 2002).

Models to evaluate toxicity of chemical mixtures have focused primarily on quantifying dose addition, as in the EPA assessment of health risk at hazardous waste sites (US EPA 1986). The methods for dose addition which have been most frequently used are the Relative Potency Factor (RPF), the Toxic Equivalent Factor (TEF) and the Hazard Index (HI). When extensive mechanistic information is not available, the HI is the preferred approach. HI is a dimensionless figure, corresponding to the sum of the ratios between the exposure level and the reference dose (RfD) of each component, representing the relative potency. When HI for the whole mixture is equal to 1, it is supposed that the exposure correspond to the RfD of the mixture; when values are higher than 1, potential health concerns should be considered. HI derivation can be revised in order to be able to incorporate interaction data, when available, introducing a weight of evidence evaluation and an adjustment factor for the relative potency of each component (US EPA 2001).

With respect to indoor air pollution, a number of studies have dealt with the combined effects of indoor air pollutants, including effects of fine particles and gases in ambient air. The results have suggested that e.g. particles may behave as carriers for the toxicant

into the lungs and that exposure to particulate matter may facilitate airway sensitisation in susceptible individuals (e.g. Hamada et al. 2000).

An additive approach has been considered useful for evaluation of mixtures of airborne sensory irritants above the threshold level (e.g. Cometto-Muñiz and Hernãndez 1990; Hempel-Jørgensen et al. 1999) and may be assumed as a first approximation of sensory irritation effects of mixtures based on animal and human studies (Nielsen et al. 2007b).

Some efforts have also been made to evaluate combined effects of a larger group of indoor air pollutants. The Committee of the Health Council in the Netherlands tentatively evaluated the health impact of volatile organic compounds (VOCs) from building materials (HCN 2000). The Dutch committee considered the air quality guidelines developed by the WHO for outdoor air (WHO 2000) and estimated the maximum tolerable pollution of indoor air by VOCs to be between 0.2 and 3.0 mg/m^3, giving as recommended cumulative limit value of 0.2 mg/m^3 for VOCs not showing carcinogenic, reprotoxic or sensitizing properties. However, because the composition of total VOCs varies from place to place, this may only be used as a very general indicator of indoor air quality. Moreover, the compounds of highest concentrations are not necessarily those with offending effects in indoor air (Wolkoff and Nielsen 2001).

The main problems encountered in applying the combined effect approach is that few data are available on interactions among more than two chemicals and they usually do not address issues of chronic toxicity at concentrations representative of actual human exposure. The use of PBPK and PBPD modelling may help (ATSDR 2002, De Rosa et al. 2004). The use of mechanistic data derived from testing with binary mixtures may be extrapolated to more complex mixtures by means of PBPK models, as demonstrated with a mixture of benzene, toluene, ethylbenzene and xylene (BTEX) (Haddad et al. 2000) and may be very useful for the evaluation of metabolic interactions. In general, the issue of toxicity due to chemical mixture or multiple exposures suffers of the lack of both experimental data on the mode/mechanisms of actions and a generally accepted strategy for the related risk evaluation (McCarty and Borgert 2006).

At present at the EU level there is not a general recommended approach to conduct the risk assessment for chemical mixtures or for combined effects due to concomitant exposure to different chemicals through different routes.

Altogether, the SCHER considers that the risk assessment which takes into account the combined exposure and cumulative effects of the pollutants in indoor environment is seldom possible. Mostly, there are not enough relevant data and the available methods may not fit the case. However, the SCHER recommends that the possibility of combined effects is considered in the risk assessment and is evaluated on a case-by-case approach. Interactions between chemicals and other factors such as microbes are insufficiently known to provide guidance.

3.2 Question 2

To provide a basis for assessment of risks to human health from indoor air quality, and a sound scientific basis for the development and implementation of policies, the SCHER is asked to identify the adequacy of current information and data requirements for filling-in gaps on aspects such as exposure/effect and dose/response relationships, existing measurement standards and gaps in knowledge which will help to guide further research and monitoring efforts.

Response to question 2

3.2.1 Adequacy of current information

The SCHER notes that, taking into account all the variability and complexity in the indoor environment, the data for risk assessment are scarce and often insufficient. Recently, the THADE-project (THADE 2004) has summarised several aspects on indoor air pollution in

dwellings in Europe, including policies and actions taken in different countries. The evaluation indicates large differences between countries, in all aspects, and also lack of relevant data, both in general and specific Member States.

In relation to exposure, information on concentrations of indoor air pollutants in Europe and information on determinants of personal exposure (e.g. EXPOLIS 1999, GerES I, GerES II, GerES III), German study on Indoor Factors and Genetics (INGA), the National survey of air pollutants in English homes) is available. These data give indications on the levels for some indoor pollutants and help to identify the compounds with highest concentrations and of highest concern.

Most of this information is on "classical" pollutants, such as carbon monoxide, nitrogen oxide, radon, asbestos, and organic compounds such as VOCs (INDEX 2005). Effects and risks for most of them are known to the extent that strategies to mitigate the problems can be created. But also new sources have emerged for "old" pollutants (e.g. VOCs in air fresheners, lead from candle wicks) and some of them (e.g. terpenes) may react to produce secondary products whose effects are poorly defined (Weschler et al. 2006, Wolkoff et al. 2006a).

Due to privacy of the indoor spaces (e.g. homes), enforceable indoor air standards are not preferred since their systematic surveillance monitoring would be difficult. Instead, the SCHER supports the development of health-based guideline values and other guidance for key pollutants (as identified in this opinion) to help risk assessment and management. In this context, indicators other than concentrations of the pollutants (ventilation rate, general cleanliness, signs of dampness) may also be applicable for monitoring.

At present, outdoor air quality is monitored for some pollutants (e.g., PM_{10}, nitrogen oxide, ozone) but the data cannot predict the concentration in buildings and replace measurement, because several local factors contribute to the access of pollutants indoors (e.g. tightness of the building). The variability in indoor levels has been shown for both organic compounds (e.g. Ilgen et al. 2001, Hodgson et al. 2003, Saarela et al. 2003, Gilbert et al. 2005) and particles (e.g. Lazaridis et al. 2006).

3.2.2 Data requirements and gaps of knowledge

The SCHER has identified the following requirements for a more comprehensive and reliable health risk assessment of indoor air pollution. The needs range from broad and general to specific ones.

The data needs and gaps of knowledge are compiled into two groups, exposure assessment and health effects assessment. The SCHER considers that items indicated by "++" should have the highest priority.

3.2.2.1 Data requirements and gaps in knowledge related primarily to identification and exposure to pollutants:

Need for compilation of existing data:

- Comprehensive review of the existing data on the indoor air pollutants; definition of the major pollutants and their concentrations range in each Member State of EU, and set up of a pan European database (++). The process would compile the existing information on indoor pollutants, including allergens as background for future work, and would facilitate the use of the data at an EU level to identify differences among Member States and data gaps. This information could drive both possible regular monitoring program and future research.

Need for more research

- Exposure patterns (short and long term in different environments) to indoor air pollutants, in quantitative terms, and identification of the most relevant exposure indicators (++). Description of typical exposure patterns would help to assess the typical levels and variability of exposure.
- Source apportionment of the pollutants in indoor environment, including ambient air, preferably in quantitative terms (++). Identification of the main sources would help their mitigation.
- Emissions of chemicals from consumer products (++). More data on levels of the emissions in realistic use situations is needed in view of the large part of population handling such products.
- Existing indoor source and transport/fate models should be identified, evaluated, validated and harmonized (+). Taxonomy of sources consistent data sharing should also be developed.
- Information on harmful emissions in water damaged buildings, including compounds from decomposing building material, contributing to toxicity (++). See also a detailed answer to question 4c.
- Evaluation of potentially harmful emissions from indoor combustion processes (e.g. halogenated dioxins). Low burning temperature may favour production of halogenated dioxins.

3.2.2.2 Data requirements and gaps in knowledge related primarily to health effects of indoor air pollutants:

Need for more research:

- Effects due to combined exposure to indoor air pollutants and objective methods for their evaluation, including development of validated modelling tools (++).
- Adverse health effects of microbes and bioaerosols present in indoor air, especially other than respiratory tract effects; responsible microbes and their components and toxins (++).
- Contribution of indoor air pollutants to childhood respiratory diseases (++).
- Exposure-effect-relationships especially in vulnerable groups (++).
- Effects and risks of products which emit indoor air pollutants that can react in indoor air (+). This is, for example, the case with terpenes that can react with ozone. The true role of such reaction products as indoor air pollutants is not clear.
- Possible effects and risks of man-made nanoparticles in indoor air (+).
- Contribution of fine and ultrafine particles from indoor sources to adverse health effects.
- Controlled clinical studies (including biochemical markers of effect) among persons suffering symptoms in water damaged buildings to clarify the associations and possibly to identify the most harmful microbes.

3.2.3 Existing measurement standards

There are some international measurement standards developed for indoor air quality both from CEN and ISO (often identical standards). Some of the standards developed for ambient air measurements can also be applied for the indoor environment, while methods for workplaces often are developed for higher concentrations of the substance. The SCHER does not see development of new measurement standards as a high priority,

but recommends the validation and harmonization of the existing ones, in particular those concerning with indoor material emissions (ECA 2005). Development of passive samplers is in a very active phase and has to be followed, but the technique is not ready for standardisation.

3.3 Question 4

To provide a basis for assessment of risks to human health from indoor air quality, and a sound scientific basis for the development and implementation of policies, the SCHER is asked to identify potential areas of concern in relation to a) specific chemical compounds taking into account the recent outcome of the INDEX report prepared by DG JRC, b) household – chemicals and other products (e.g. decorating materials, cleaners, furnishings, etc.) and c) building dampness/moisture and microbial growth (moulds, bacteria).

Response to question 4

3.3.1 Concerns in relation to specific chemical compounds

Indoor environment contains a large number of different chemical compounds. Availability of data on exposures to specific chemicals, their toxicity and associated health risks are highly variable. Therefore, a priority ranking of chemicals and exposures which cause concern is difficult and uncertain. However, the SCHER considers that **formaldehyde**, **carbon monoxide**, **nitrogen dioxide**, **benzene**, **naphthalene**, **environmental tobacco smoke (ETS)**, **radon**, **lead** and **organophosphate pesticides** are compounds of concern in indoor environment.

The INDEX project (INDEX 2005) has evaluated health risks of volatile chemicals in indoor air in the European population, as a stepwise procedure, and set up a list of compounds with highest concern on the basis of health impact criteria. After consideration of the quantity and quality of all the data available, 25 compounds were selected for a more detailed analysis and a detailed risk assessment was performed for 14 of them. The highest priority chemicals were **formaldehyde**, **carbon monoxide**, **nitrogen dioxide**, **benzene** and **naphthalene.** SCHER agrees that these are compounds of concern because they have caused adverse health effects as indoor pollutants or have a high potential to cause health effects. However, the concern is not similar all over in Europe due to different exposure levels. For example, limited data on air fresheners indicate that burning of incense may produce abnormally high benzene and formaldehyde emissions in indoor air (SCHER 2006).

Though active smoking is excluded from this opinion, the SCHER reminds that tobacco smoking is the primary source of several emissions (benzene, fine and ultrafine particles) indoors and associated health effects. In adults, **ETS** has been associated e.g. with coronary heart disease, sensory irritation and exacerbation of respiratory symptoms, including asthma (IARC 2004). In children, the association with infant sudden death syndrome and middle ear infections and ETS has been observed (Tamburlini et al. 2002, DiFranza et al. 2004). The evidence clearly indicates that ETS requires risk management.

Radon in indoor air has been associated with lung cancer (WHO 1998). According to a recent analysis of European epidemiological studies (Darby et al. 2005) radon may be a common problem in Europe. Radon gas diffuses through soil into residences in areas where bedrock contains in excess uranium. Indoor radon concentrations can be decreased by technical means, even in existing buildings. Data on residential radon concentrations should be obtained by measurements in countries where such data do not yet exist and the associated health risk should be assessed.

Paint-related **lead** still exist in indoor environment in old houses in some EU countries though its use has been restricted or banned in indoor paints. Children are especially exposed through non-dietary ingestion of the dust. The evidence is increasing that

already low level of children exposure to lead is harmful (e.g. Lanphear et al. 2005). Therefore, it is essential to evaluate, if the lead level in indoor environment is still a problem in EU countries. The existing data on lead should be compiled, and thereafter, a need for further research considered.

The indoor use of **organophosphate pesticides** for treatment of cracks and crevices (Byrne et al. 1998) or the use of insect strips (Weis et al. 1998) may lead to high exposures to these compounds by inhalation or ingestion due to accumulation on surfaces including children's toys (Hore et al. 2005) and house dust (Butte and Heinzow 2002). This uptake may contribute considerably to the overall uptake of organophosphates by children (Gurunathan et al. 1998). The acute toxicity of organophosphate pesticides is well known (WHO 2004b): however, it is very unlikely that indoor levels can result in acute effects. Recently neuro-developmental effects, have been reported both in experimental animals (Aldridge et al., 2005) and humans (Berkowitz et al. 2004) raising concern for possible effects in children from the use of organophosphates in the indoor environment.

Health effects (mainly sensory irritation) of **VOCs** commonly found in indoor air have been investigated in numerous studies. An extensive evaluation of all available controlled human exposure studies by a group of experts (Andersson et al. 1997) found that effect levels for irritation were usually higher than concentrations in indoor air. These studies would not explain possible health effects at much lower concentrations reported in epidemiological studies; however, the exposure was not adequately measured and cause effect relationship could not be proved due to several confounders, such as temperature, ventilation, exposure from other chemicals, or moulds and mites, as well as psychosocial factors. Anderson et al. (1997) stated that the scientific literature is inconclusive with respect to TVOC as a risk index. This conclusion is still valid, when the publications since this review are taken into account. Recent comprehensive controlled human studies at VOC concentrations considerably above those in normal homes show no effects (e.g. Fiedler et al. 2005; Laumbach et al. 2005), and epidemiological studies give some indication of health effects (e.g. Hutter et al. 2006; Saiijo et al. 2004; Takigawa et al. 2004) but other factors than VOC may play a major role.

Several studies have reported associations between VOCs and asthma symptoms. However, a recent comprehensive review found no consistent association between the commonly measured indoor VOC exposures and onset of new asthma cases (Nielsen et al. 2007a).

Altogether, the available evidence on VOCs in causing health effects in indoor environment is not conclusive; VOCs may also be indicators for the presence of other stressors contributing to health effects.

More recently reaction products formed in indoor air have been investigated. **Terpenes** may react with ozone to produce secondary reaction products (Wolkoff et al. 2006a). Limonene reacts with ozone and has been reported to produce both gaseous reaction products and fine and ultrafine particles (Wainman et al. 2000, Sarwar et al. 2004). The highest terpene concentrations also produced high particle levels (Sarwar et al. 2004). Several other pollutants react in indoor air and on surfaces producing known and as yet unknown reaction products (Weschler et al. 2006). In some studies, the reaction products have shown irritating properties (Clausen et al. 2001, Nøjgaard et al. 2005) and poor perceived air quality (Tamás et al. 2006) at terpene and ozone concentrations that can be present in indoor air. Adverse health effects have not been observed in all studies (Laumbach et al. 2005, Fiedler et al. 2005). Altogether, the concentrations of VOCs and ozone causing mixture effects are as yet poorly known.

In addition to the compounds emitted from the intact materials in the indoor environment there may also be new compounds formed due to **decomposition of the materials**. The glue used to fasten PVC flooring can be hydrolysed by water (dampness) from the underlying material, especially if it is concrete with a high pH. The compounds

released from decomposing materials should be identified and their potential health effects evaluated.

Phthalates are common contaminants in the indoor environment occurring both in house dust and in indoor air and di(2-ethylhexyl) phthalate (DEHP) is the dominant component (Øie et al. 1997, Rudel et al. 2003, Fromme et al. 2004). The PVC flooring material is an important source for phthalates, but several other sources contribute in indoor environment (Bornehag et al. 2005a). PVC products indoors (different surface materials) have been associated with airway effects in epidemiological studies (Jaakkola et al. 2006) but only in one study the concentrations of di(2-ethylhexyl) phthalate (DEHP) and butyl benzyl phthalate (BBP) have been measured (Bornehag et al. 2004a). In that study DEHP was associated with asthma and BBP with rhinitis in children at the highest exposure quartile (Bornehag et al. 2004a). Phthalates are not skin sensitizers for humans and there is no evidence of respiratory sensitization (Medeiros et al. 1999, David et al. 2003, ECB 2001). Based on the lack of mechanistic support and taking into account the low exposure level of phthalates by inhalation (Nielsen et al. 2007a), the SCHER does not find consistent scientific evidence which indicate that phthalates should be high concern chemicals in indoor air. The draft RA report on DEHP (ECB 2001) suggests that MOSs from exposure in indoor air to reproductive effects, which are the basis for risk characterisation, remain large (over 200 for children, over 1000 for adults).

3.3.2 Concerns in relation to household-chemicals and other products (e.g. decorating materials, cleaners, furnishing, etc.)

Household-chemicals are a large, heterogeneous group containing e.g. cleaners, furnishings, air fresheners, products for laundering, glues, paints, paint strippers, personal care products etc. The products are used mostly as liquids but some are aerosols. Candles and some air fresheners (incense) may emit volatile and semivolatile compounds or release inhalable aerosols and particles when burned. The use of consumer products and the ensuing emission concentrations in indoor areas may differ a lot in households across EU.

Compounds emitting from consumer products have been identified mainly in chamber studies but there are little data on their contribution to indoor air pollution. Very little is known about true exposure (in relevant use context) to components of consumer products in indoor air, in quantitative terms. Without such knowledge their health risk(s) can not be properly assessed. At least the range of resulting concentrations in indoor air in typical use situations is needed, as well as validated exposure models. The data is gradually emerging (Singer et al. 2006).

The Danish EPA has investigated the emissions of chemicals from a large number of different consumer product categories and effects on the indoor climate of these emissions have been estimated (Jensen and Knudsen 2006). Concentrations were predicted using models and assumptions of different products being present in three different model rooms (children's room, kitchen/family room and utility room/hall). The assessment was focussed on eight VOCS (formaldehyde, acetaldehyde, phenol, benzene, toluene, xylenes, styrene and limonene) and three groups of SVOCs (phthalates, brominated flame retardants and perfluoroalkylated compounds). Of the 45 different product categories examined in the project, 33 were found to emit the selected VOCs; the exposure for the SVOCs was mainly estimated from levels in house dust. The highest concentrations were predicted in the children's room, and "typical" levels were in most cases acceptable, while worst case exposures for some of the compounds exceeded accepted limits. The worst emitters of the investigated consumer products were incense (benzene and styrene); spray paint, printed matter and electronic equipment (toluene and xylenes). It is mentioned in the report that also other sources, e.g. building materials, contribute to the total exposure but could not be taken into account, and that no assessment was done for combined exposures from several stressors.

VOCs from consumer products may contribute on average to 10-20 % of total VOCs in different indoor environments, roughly to a similar fraction as transport from outdoors (Edwards et al. 2001, Serrano-Trespalacios et al. 2004), depending on the quality of the outdoor air. Air fresheners, general purpose cleaners and floor care products have been estimated to be the major sources of VOC emissions among house-hold products e.g. in California, USA (Nazaroff and Weschler 2004). The hazards of selected categories of cleaning agents used in Denmark have been investigated (Wolkoff et al. 1998). There are a limited number of epidemiological studies where associations of adverse health effects with consumer products have been evaluated (Farrow et al. 2003, Caress and Steinemann 2003, Scheriff et al. 2005). In most studies the use of consumer products is one qualitative exposure category. Although some associations have been observed, the exact causal relationship remains unclear because the observed effects are associated concomitantly with a number of other factors being able to contribute as well. The heavy use of air fresheners may indicate indoor environment and/or type of living which contain several other risk factors. Therefore, due caution is needed at present in the interpretation of the results. This strengthens the need for a more integrated approach that includes determinants of exposure of different types.

Certain use conditions of consumer products (e.g. facilities in hobbies) also need more attention. Handling of products containing highly volatile components (e.g. organic solvents) in poorly ventilated spaces may result in high VOCs concentrations in air. Improved use instructions are required to avoid excess of exposure.

The research needs related to household-chemicals have been included to Answer to Question 2.

3.3.3 Concerns in relation to building dampness/moisture and microbial growth

Adverse health effects associated with building dampness and moisture problems have been reported since the 1980s but are a poorly understood phenomenon. The available data about details of this subject have recently been reviewed and summarised as a panel work (IOM 2004).

An association has been shown in numerous epidemiological studies in different environments, and in a number of countries (Bornehag et al. 2001, 2004b). Intervention studies have indicated that renovation of the building either decrease or abolish the symptoms (Sudakin 1998, Meklin et al. 2005). Furthermore, a dose-response relationship between the extent of damage and health effects has been shown (Haverinen 2002). Dampness and moisture problems in buildings are common in countries where comprehensive studies have been done, and are likely to be an underestimated indoor air problem in EU and should be evaluated more thoroughly.

The associated adverse health effects range from irritation of mucous membranes, respiratory symptoms and infections to permanent diseases, such as asthma and allergy (IOM 2004). However, only a fraction of the symptoms appears to be caused by IgE-mediated allergy, allergic alveolitis (hypersensitivity pneumonitis) or organic dust toxic syndrome and other, still poorly known patho-physiological mechanisms are involved. General symptoms, such as fever, fatigue, headache and difficulties to concentrate have also been reported. Clusters of cases of sarcoidosis, rheumatoid diseases as well as pulmonary haemorrhage among infants have also been associated with indoor dampness (Nevalainen and Seuri 2005).

The majority of the health effects associated with dampness and moisture of buildings are those of the respiratory system. Therefore, it is likely that the major route of the exposure to the causative agents is via the airways. There are many types of emission from a microbial growth e.g., particles of microbial origin including spores, vegetative cells and submicron-size fragments (Gorny 2004) that carry structural components, such as endotoxin and 1,3-beta-glucan, and non-volatile secondary metabolites, e.g. toxins (Croft et al. 1986). Volatile organic compounds emitted from microbial growth include

those that are known as odour of mould. Dampness and moisture may initiate chemical degradation of material which may contribute to emissions of degradation products into the indoor air and inadequate ventilation may increase the level (Bornehag et al. 2005b).

Although the association between moisture problems and adverse health effects has been demonstrated, the causative agents/exposures are not defined. This is likely to be due to the great complexity and variability of the contributing factors but also to the lack of basic knowledge. Respiratory inflammation, the most typical symptom, has been verified in laboratory animals by a few microbes typical for moisture problems (Jussila et al. 2001, Huttunen et al. 2003). Still, even in those cases, the principal components causing the effects are not known.

Dampness or moisture may accumulate into the building structures or finishing materials via leaks in roofs, windows or piping due to condensation as a result of insufficient ventilation or faulty construction, or moisture from the ground penetrating into the building structure by capillary movement. Excess of water stimulates microbial growth, usually fungi and bacteria, and in a more advanced damage, also protozoa, nematodes and higher organisms such as mites and insects. The substrate (material) in question and its moisture content regulate the microbial development and toxicity (Hyvärinen et al. 2002, Roponen et al. 2001, Murtoniemi et al. 2001). Many of the bacteria and fungal species detected in damp environments are the same as detected in "normal" indoor air but their concentrations may be higher. There are also species which typically exist in water damaged environments (indicator species of the dampness problem). Microbial diversity in various dampness situations varies and one water damaged site (environment) only poorly predicts another (Nevalainen and Seuri 2005). This may suggest that dampness is not equally harmful. There is also likely large individual variability in sensitivity to react to those exposures, depending on e.g. the immunological status.

SCHER considers that the adverse health effects associated with building dampness and moisture are a concern. The association between building dampness and the common health effects has been documented, however several other questions, indicated as data gaps in answer to Question 2, are open and need further research before the wideness and seriousness of the problem at EU level can be assessed.

4. CONCLUSIONS

Indoor environment is a complex issue in terms of toxicology and health risk assessment. There are many different types of pollutants which may give rise to combined effects. The exposed population is the general public including vulnerable groups. Many different factors influence air quality, e.g. ventilation, cleaning conditions, properties of buildings, products used in house-holds, cultural habits, climate, outdoor air etc. Thus, large variations in indoor environments can be expected across the EU.

The SCHER considers that the health risk assessment of the pollutants in indoor environments should be done according to the principles used in the EU for risk assessment of chemicals as this is an evidence based approach. The specific features related to indoor environment should be taken into account to the extent presently possible. The risk assessment paradigm should be used flexibly, taking into account that complaints and diseases related to indoor exposures may have a complex cause-effect relationship.

The SCHER considers that the data base for indoor air risk assessment is in general limited. Frequently, there are more data available for risk assessment of "classical" indoor air pollutants such as organic pollutants as compared to particles and microbes. In particular, more data on exposure, in quantitative terms, are required. Available dose-response data seldom cover vulnerable groups. The SCHER has identified several gaps in knowledge, presented in answer to Question 2, which should be addressed by European-wide multidisciplinary research.

As to single known compounds, SCHER considers carbon monoxide, formaldehyde, benzene, nitrogen oxides and naphthalene to be compounds of concern because they have caused adverse health effects as indoor pollutants or have a high potential to cause them. Environmental tobacco smoke, radon, lead and organophosphates are also of concern. For most other pollutants the data available are yet limited for risk assessment as indoor air pollutants.

Consumer products, one source of chemicals in indoor environment, emit mostly volatile organic compounds. Lack of data on true exposure for emissions from consumer products has hampered evaluation of the associations with possible health effects most of which are also caused by other factors. The recent data suggest that some of the emitted products may react further in air and on surfaces producing secondary products, including fine and ultrafine particles. The health effects of those reaction products are poorly known.

Association of adverse health effects with dampness and water damage in buildings is repeatedly shown in epidemiological studies but the causative factors and all health effects and consequences are not known. This is potentially a serious indoor air problem in EU. More research is needed to understand the associations with health effects and seriousness of the problem in EU countries.

Combined and mixture effects of indoor air pollutants can so far only rarely be assessed. There are not enough data on combined effects and the methodology is limited. The SCHER recommends the production of data in order to make the evaluation of combined effects of indoor air pollutants feasible. In addition, the SCHER recommends taking into account routes of exposure other than inhalation (dermal, oral) in risk assessment and contribution of indoor environment exposure to total exposure from other sources. The risk assessment should be transparent to allow the evaluation of its strengths and weaknesses.

The SCHER recommends the development of health based guideline values for key pollutants and other practical guidance in general to help risk management.

4.1 General conclusions and recommendations

Indoor air may contain over 900 chemicals, particles, biological materials with irritating and sensitizing potential. Since their concentrations are usually higher than outdoors and most humans spent more time indoors than outdoors, the SCHER recommends that any studies to correlate outdoor air concentration with health effects need to consider the impact of indoor exposure.

The composition and concentrations of the different components in indoor air vary widely and are influenced by human activities. Since it is not feasible to regulate all possible scenarios, prevention from possible health effects and protection of sensitive populations is best achieved by reducing exposure. As a consequence the SCHER recommends that all relevant sources that are known to contribute should be evaluated. Such sources include tobacco smoke, any open fires including candles, building materials, furniture, pets and pests, use of household products, as well as conditions that lead to the growth of moulds. Constructers, maintenance personnel and inhabitants should also be aware that appropriate humidity avoids annoyances and sufficient air exchange reduces accumulation of pollutants.

5. LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
DEHP	Di (2-ethylhexyl) phthalate
ETS	Environmental tobacco smoke
HI	Hazard Index
IPCS	International Programme on Chemical Safety

LOEAL	Lowest-Observed-Adverse-Effect-Level
MEHP	Mono (2-ethylhexyl) phthalate
MOS	Margin of Safety
NIOSH	National Institute of Occupational Safety, Health
NOAEL	No-Observed-Adverse-Effect-Level
NOEL	No-Observed-Effect-Level
ODTS	Organic dust toxic syndrome
OEHHA	Office of Environmental Hazard Assessment of Californian Environmental Protection Agency
PAH	Polyaromatic hydrocarbon
PBPD	Physiology-based pharmacodynamic model
PBPK	Physiology-based pharmacokinetic model
PCB	Polychlorinated Biphenyl
PVC	Polyvinyl Chloride
RfD	Reference Dose
RPF	Relative Potency Factor
SVOC	Semivolatile Organic Compound
TGD	Technical Guidance Document
TEF	Toxic Equivalent Factor
TVOC	Total Volatile Organic Compounds
UBA	Federal Environmental Agency of Germany (Umweltbundesamt)
VOC	Volatile Organic Compound

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