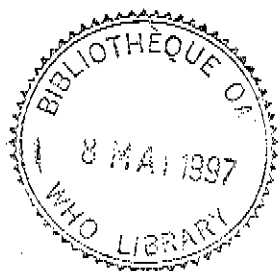




# WHO

REGIONAL OFFICE FOR EUROPE

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## *UPDATING AND REVISION OF THE AIR QUALITY GUIDELINES FOR EUROPE*

Report on a WHO Working Group on  
Volatile Organic Compounds

Brussels, Belgium  
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## TARGET 21

### AIR QUALITY

*By the year 2000, air quality in all countries should be improved to a point at which recognized air pollutants do not pose a threat to public health.*

### ABSTRACT

As part of the updating and revision of the WHO air quality guidelines for Europe, the WHO Working Group on Volatile Organic Compounds (VOCs) met in Brussels in October 1995. The Group discussed various qualitative and quantitative aspects of the health risks associated with exposure to selected organic air pollutants: benzene, butadiene, dichloromethane, formaldehyde, polycyclic aromatic hydrocarbons, styrene, toluene and tri- and tetrachloroethylene. The Group had received draft chapters on these pollutants, prepared by experts, before the meeting. The Group also discussed a brief summary of the work on total VOCs, performed within the framework of the European Collaborative Action "Indoor Air Quality and its Impact on Man", in which WHO is involved. The Group achieved its principal goal of finalizing the health risk evaluations of the pollutants discussed, which included reaching consensus on guideline values or risk estimates.

### Keywords

AIR POLLUTION – prevention and control  
AIR POLLUTANTS – toxicity  
AIR QUALITY  
GUIDELINES  
RISK ASSESSMENT  
EUROPE

## INTRODUCTION

New scientific data and new developments in health risk assessment methodologies for the volatile organic contaminants have appeared since publication of the 1987 Air Quality Guidelines for Europe. This new information required the updating and/or revision of the existing Air Quality Guidelines. The updating process, which is being conducted in collaboration with the European Commission and the International Programme on Chemical Safety (IPCS) began with a planning meeting held at the Bilthoven Division of the European Centre for Environment and Health of the World Health Organization (WHO) on 11-13 January 1993. That meeting was held to establish the framework for the updating and revision process. A recommendation was made to establish a number of specialized working groups to assess the effects of specific pollutants or groups of pollutants.

As part of this activity, a working group on volatile organic compounds (VOCs) was convened to assess the health effects of exposure to benzene, butadiene, dichloromethane, formaldehyde, PAHs, styrene, toluene and tri- and tetrachloro-ethylene. Draft chapters dealing with these issues had been prepared by scientific experts in these fields and were circulated among the members of the working group before the meeting. In addition, a short section on total VOCs (TVOCs) was prepared in the course of the meeting.

The meeting of the working group was held in Brussels, Belgium, on 2 to 6 October 1995 and was hosted by the European Commission (EC), Directorate-General (DG) XI (Environment, Nuclear Safety and Civil Protection), which also provided financial support.

The meeting was opened by Mr Prudencio Perera, Head of Unit DG XI-D3 (Urban Environment), on behalf of the Director of Directorate D (Quality of the Environment and Natural Resources), Mr Jorgen Henningsen. He welcomed the participants to the meeting and underlined the importance of the current level of cooperation between the EC and WHO in the field of air quality. DG XI is currently revising the Directives on air quality and recognises the potentially great value of the guidelines now being established by WHO to the process of setting air quality standards. Mr Perera expressed the expectation that this activity might lead to a long and fruitful cooperation and mutual assistance between EC and WHO.

The meeting was attended by 14 experts from 11 countries, a representative from EC DG XI, two observers, and staff members of the WHO European Centre for Environment and Health (Bilthoven, Netherlands), the Programme for the Promotion of Chemical Safety and the International Agency for Research and Cancer (IARC). Dr Bernd Seifert was elected Chairperson, Dr Robert L. Maynard Vice-chairperson, and Dr Paul Mushak Rapporteur. Dr F.X. Rolaf van Leeuwen was Scientific Secretary. The aim of the meeting was to finalize the draft chapters and to derive, by consensus, health-based air quality guideline values for the compounds reviewed.

## DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

The working group evaluated available data and the draft chapters for the indicated compounds, with special reference to the human health risk evaluation and the derivation of guidelines. Working group members also provided post-meeting comments to the Rapporteur and WHO Bilthoven.

The text of the summary report reflects the expert consensus of the entire group. Guidelines in this summary report that consist of a specific value or range of values are typically derived from epidemiological or animal data where exposures in the dose-response relationships are expressed as mean concentrations. In the case of tetrachloroethylene, however, derivation of the recommended guideline was based on worker exposures reported as a median value.

## **BENZENE**

### **Evaluation of Human Health Risks**

#### **Exposure Evaluation**

Sources of benzene in ambient air include cigarette smoke, combustion and evaporation of benzene-containing gasoline (up to 5% benzene), petrochemical industries and combustion processes.

Mean ambient air concentrations of benzene in rural and urban areas are about  $1 \mu\text{g}/\text{m}^3$  and  $5\text{--}20 \mu\text{g}/\text{m}^3$ , respectively. Indoor and outdoor air levels are higher near such sources of benzene emissions as filling stations.

Inhalation is the dominant pathway for benzene exposure in humans. Smoking is a large source of personal exposure, while high short-term exposures can occur during refuelling of automobiles. Extended travel in automobiles having elevated air benzene levels (from combustion and evaporative emissions) produces exposures reported from various countries that are second only to smoking as contributors to the intensity of overall exposure. The contribution of this source to cumulative ambient benzene exposure and associated cancer risk was noted to comprise about 30% when the travel time is one hour, an interval not untypical for urban and suburban commuting by the general population.

#### **Health Risk Evaluation**

The most significant adverse effects from prolonged exposure to benzene are haematotoxicity, genotoxicity and carcinogenicity.

Chronic benzene exposure can result in bone marrow depression expressed as leucopenia, anemia and/or thrombocytopenia, leading to pancytopenia and aplastic anemia. Decreases in haematological cell counts and in bone marrow cellularity have been demonstrated in mice after inhalation of concentrations as low as  $32 \text{ mg}/\text{m}^3$  for 25 weeks. Rats are less sensitive than mice. In humans, haematological effects of varying severity have occurred in workers occupationally exposed to high levels of benzene. Decreased red and white blood cell counts have been reported above median levels of approximately  $120 \text{ mg}/\text{m}^3$ , but not at  $0.03\text{--}4.5 \text{ mg}/\text{m}^3$ . Below  $32 \text{ mg}/\text{m}^3$ , there is only weak evidence for effects.

The genotoxicity of benzene has been extensively studied. Benzene does not induce gene mutations in *in vitro* systems, but several studies have demonstrated induction of both numerical and structural chromosomal aberrations, sister chromatid exchanges, and micronuclei in experimental animals and humans after *in vivo* benzene exposure. Some studies in humans have demonstrated chromosomal effects at mean workplace exposures as low as  $4\text{--}7 \text{ mg}/\text{m}^3$ . The *in vivo* data indicate that benzene is mutagenic.

The carcinogenicity of benzene has been established in both humans and in laboratory animals. An increased mortality from leukemia has been demonstrated in workers occupationally exposed. Several types of tumours, primarily of epithelial origin, have been induced in mice and rats after oral exposure and inhalation exposure at 320–960 mg/m<sup>3</sup>; these include tumours in the Zymbal gland, liver, mammary gland and nasal cavity. Lymphomas /leukemias have also been observed, but with lesser frequency. The results indicate that benzene is a multi-site carcinogen.

Several quantitative cancer risk assessments have been presented in the past and these are described in detail in the background paper. The Pliofilm cohort is the most thoroughly studied. It was noted that significant exposures to other substances at the studied facilities were probably not a complicating factor, but that exposure estimates for this cohort vary considerably. Three different exposure matrices have been used to describe the Pliofilm cohort, i.e. those reported by Crump & Allen (1984), by Rinsky et al. (1987), and a newer and more extensive one by Paustenbach et al. (1992).

The main difference between the first two is that the exposure estimates by Crump & Allen are greater for the early years during the 1940s. Paustenbach et al. have, among other things, considered short-term, high level exposure, background concentrations and absorption through the skin, which leads to 3–5 times higher exposure levels than the ones by Rinsky et al. Compared to the Crump & Allen estimates, Paustenbach et al. arrive at higher exposure estimates for some job classifications and lower for some others.

Within the most recently updated Pliofilm cohort, Paxton et al. conducted an extended regression analysis with exposure description for the 15 leukemia cases and 650 controls. They used all three exposure matrices. The estimated numbers of cancer cases range from 0.26–1.3 excess cancer cases among 1000 workers at a benzene exposure of 1 ppm (3.2 mg/m<sup>3</sup>) for 40 years (Table 1).

Table 1. Published leukemia risk estimates for the plioform cohort at two benzene exposure levels

Cases /1000 workers		Exposure matrix	Reference
Exposed to 1 ppm (3.2 mg/m <sup>3</sup> )	Exposed to 0.1 ppm (0.32 mg/m <sup>3</sup> )		
5.3	–	a	Brett et al., 1989
0.5–1.6	–	a,b	Brett et al., 1989
1.3	0.12	a	Paxton et al., 1994 <sup>a, b</sup>
0.26	0.026	b	Paxton et al., 1994 <sup>a, b</sup>
0.49	0.048	c	Paxton et al., 1994 <sup>a, b</sup>

<sup>a</sup> Rinsky et al., 1987 case control study.

<sup>b</sup> Crump & Allen, 1984.

<sup>c</sup> Paustenbach et al., 1992.

Because benzene is characterized as a genotoxic carcinogen and recent data gathered in humans and mice suggest mutagenic potential *in vivo*, establishment of exposure duration and concentration for the calculation of cancer risk estimates is of major importance. Crump (1994) calculated unit risk estimates for benzene using the most recently updated data for the Pliofilm cohort and a variety of models (Table 2). Multiplicative risk models were found to describe the cohort data better than additive risk models and cumulative exposure better than weighted exposures. Dose-responses were essentially linear when the Crump & Allen exposure matrix was used, but according to the author, there was evidence of concentration-dependent nonlinearity in dose-responses derived using the Paustenbach et al. exposure matrix. In that case, the best-fitting model was quadratic.

Table 2. Model-dependent worker risk and lifetime unit risk estimates for exposure to benzene for the plioform cohort by Crump, 1994<sup>a</sup>

Risk estimate	Linear	Nonlinear	Intensity dependent	Exposure database
Cases/1000 workers at 1 ppm benzene	5.1	5.0	5.1	Crump & Allen, 1984
	3.8	2.9	0.036	Paustenbach et al., 1992
Unit risk ppb <sup>-1</sup>	$2.4 \times 10^{-6}$	$2.4 \times 10^{-6}$	$2.4 \times 10^{-6}$	Crump & Allen, 1984
	$1.5 \times 10^{-6}$	$1.4 \times 10^{-6}$	$1.7 \times 10^{-10}$	Paustenbach et al., 1992
Unit risk <sup>b</sup> (mg/m <sup>3</sup> ) <sup>-1</sup>	$7.5 \times 10^{-6}$	$7.5 \times 10^{-6}$	$7.5 \times 10^{-6}$	Crump & Allen, 1984
	$4.7 \times 10^{-6}$	$4.4 \times 10^{-6}$	$5.3 \times 10^{-11}$	Paustenbach et al., 1992

<sup>a</sup> Multiplicative risk model, cumulative exposure.

<sup>b</sup> Calculated by converting ppb to  $\mu\text{g}/\text{m}^3$ .

As can be seen in Table 2, the concentration-dependent model gives a much lower risk estimate than the other models when the Paustenbach exposure matrix is used. In such a model, the concentration of benzene is raised to the second power and thus given greater weight than the duration of exposure. Although there are biological arguments to support the use of a concentration-dependent model, much of the essential data are preliminary and need to be further developed and peer reviewed before being adopted. Models giving equal weight to concentration and duration of exposure have been preferred here.

Using multiplicative risk estimates and a cumulative exposure model, Crump (1994) calculated a unit risk for lifetime exposure of  $1.4\text{--}1.5 \times 10^{-5}$  with the Paustenbach exposure matrix and of  $2.4 \times 10^{-5}$  per ppb with the Crump & Allen exposure matrix. If expressed per  $\mu\text{g}/\text{m}^3$ , the unit risk would thus be  $4.4 \times 10^{-6}\text{--}7.5 \times 10^{-6}$  (Table 2). With an additive model instead of a multiplicative model, the risk estimate would have been somewhat smaller. If similar linear extrapolations were done on the occupational cancer risk estimates by Paxton et al. (Table 1), lower unit risks, by up to about an order of magnitude, would result.

## Recommended Guidelines

Benzene is carcinogenic to humans and no safe level of exposure can be recommended. For purposes of guideline derivation, the working group chose to use the 1994 risk calculation of Crump rather than to derive new estimates. The working group recognized that the decision to use existing analyses of the most recently updated cohort ruled out inclusion of certain of the analyses noted earlier, particularly the reports of Rinsky et al.

The range of estimates of the excess lifetime risk of leukemia at an air concentration of  $1 \mu\text{g}/\text{m}^3$  is  $4.4 \times 10^{-6}$ – $7.5 \times 10^{-6}$ . The concentrations of airborne benzene associated with an excess lifetime risk of 1/10 000, 1/100 000 and 1/1 000 000 are, respectively: 13–23, 1.3–2.3 and 0.13–0.23  $\mu\text{g}/\text{m}^3$ .

## BUTADIENE

### Evaluation of Human Health Risks

#### Exposure Evaluation

Data for ambient air levels in Europe are quite limited, but reported concentrations of butadiene in urban air elsewhere generally ranged from less than  $2 \mu\text{g}/\text{m}^3$  to  $22 \mu\text{g}/\text{m}^3$ , with more recent U.S. EPA data showing an average for a number of U.S. cities of  $1.4 \mu\text{g}/\text{m}^3$ . Mean levels in indoor air in a small number of Canadian homes and offices were  $0.3 \mu\text{g}/\text{m}^3$ . Sidestream cigarette smoke contains 1,3-butadiene at approximately 0.4 mg/cigarette and levels of butadiene in smoky indoor environments are typically 10–20  $\mu\text{g}/\text{m}^3$ .

#### Health Risk Evaluation

Irritation or effects on the central nervous system may be associated with acute exposure to high concentrations of butadiene. However, carcinogenicity is considered the critical effect for derivation of air quality guidelines.

1,3-Butadiene has induced a wide variety of tumours in rats and mice, with mice being considerably more sensitive than rats. There are widely divergent points of view as to which animal species, the rat or the mouse, is more appropriate for use in human risk assessments for butadiene. Epidemiologic studies, while relatively few in number, suggest that there is equivocal evidence for an association between exposure to butadiene and lymphohaematopoietic cancer (LHC). In 1992 IARC classified butadiene in Group 2A (probably carcinogenic to humans). However, preliminary (unpublished) reports suggest that there may be an association between butadiene exposures and leukemias in workers in the synthetic rubber industry.

The genotoxicity of butadiene has been studied in a variety of *in vitro* and *in vivo* mutagenicity assays and the data overwhelmingly suggest that the induction of cancer requires metabolic activation of butadiene to DNA-reactive metabolites. Butadiene is mutagenic in both bacterial and mammalian systems. The butadiene metabolites, epoxybutene and diepoxybutane, are also carcinogenic and genotoxic *in vivo*. In studies in human tissues, butadiene is activated to epoxides to a significantly lesser extent than in mice and rats. The differences between mice and rats observed *in vitro* are supported by *in vivo* studies indicating mice form very high levels of epoxides compared to rats exposed to butadiene. In general, the data support the conclusion that humans are more similar to rats, a relatively insensitive species to butadiene carcinogenicity, than to mice, a highly sensitive species.

In the only published human study, 40 individuals occupationally exposed to butadiene at levels typical of an industrial setting (1–3 ppm) did not show significant increases in chromosome aberrations, micronuclei formation, or sister chromatid exchanges in peripheral blood lymphocytes compared to controls (N=30). This observation in humans exposed to butadiene is of particular interest since butadiene concentrations as low as 6.25 ppm increased the occurrence of the same measures of genetic damage in bone marrow and peripheral blood lymphocytes of mice.

Several risk assessments for occupational settings have been conducted for butadiene. The resulting risk estimates are based on different assumptions. Some estimates were adjusted for absorbed dose, since changes in butadiene absorption will occur in animals with changes in the inhaled concentration. For the most part, estimates were based on the multistage model. There was considerable variation in human cancer risk estimates depending on the animal species used for the calculations, with those based on mice being 100 to 1000 times higher than those based on tumour data in rats.

Estimated unit risks for cancer associated with continuous lifetime exposure to butadiene in ambient air have been reported by the California Air Resources Board (CARB, 1992), the Integrated Risk Information System (IRIS, U.S. EPA) and RIVM (1994). Values estimated by CARB based on adjustment of dose for absorption and tumour incidence in mice (NTP, 1990) and rats (NTP, 1987) were  $4.5 \times 10^{-6} (\mu\text{g}/\text{m}^3)^{-1}$  and  $3.6 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ , respectively. The value estimated by the U.S. EPA based on linearized multistage modelling of data from the earlier, limited NTP bioassay in mice was  $2.8 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ . Values estimated by RIVM (1994) based on linearised multistage modelling of the incidence of lymphocytic lymphoma and haemangiosarcomas of the heart in mice in the most recent NTP bioassay as reported by Melnick et al. in 1990 ranged from  $0.7 \times 10^{-5}$  to  $1.7 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$ .

Estimates of human cancer risk could be improved by inclusion of mechanistic information such as *in vivo* toxicokinetic data, genotoxicity data and data from the epidemiology reassessment. For example, new data on levels of butadiene epoxides in blood and tissues in laboratory animals can be used to replace the earlier absorption data. Additionally, PBPK models developed since earlier attempts to apply this approach to risk assessment, have been greatly improved, most notably by the incorporation of model parameters that have been experimentally measured rather than empirically estimated. Nonetheless, none of the PBPK models published to date incorporates the necessary information on the formation, removal and distribution of diepoxybutane.

### Recommended Guidelines

Quantitative cancer risk estimates for butadiene vary widely, particularly depending upon test species used. While evidence from laboratory animals suggests that the rat may be the more appropriate animal species for extrapolation, no definitive conclusions can yet be made as to whether the mouse or rat tumour data should be used for risk estimation. Furthermore, the preliminary ongoing reassessment of epidemiological data might impact on the risk estimates and hence, on the derivation of the guideline. Additionally, several PBPK models are available that could permit more accurate characterization of risk but the models still need further refinement.

In light of the above, no specific guideline value can be recommended at this time. Decisions regarding ambient air standards, however, should be made with prudence, given that there is some evidence, albeit equivocal, of the carcinogenicity of 1,3-butadiene in humans.

## DICHLOROMETHANE

### Evaluation of Human Health Risks

#### Exposure Evaluation

Mean outdoor concentrations of dichloromethane (DCM) are generally below  $5 \mu\text{g}/\text{m}^3$ . Significantly higher concentrations by at least one order of magnitude may occur at sites close to industrial emission sources. Indoor air concentrations are variable but tend to be about three times greater than outdoor values. Under certain circumstances, much higher values may be recorded indoors, particularly with use of paint stripping solutions. DCM exposures of the general population occur principally through use of DCM-containing consumer products. Exposure to DCM in outdoor air, water, and food is low.

#### Health Risk Evaluation

The critical effects of DCM include effects on the central nervous system (CNS), the production of carboxyhaemoglobin (CO-Hb) and carcinogenicity. The impairment of behavioural or sensory responses may occur in humans following acute inhalation exposure to DCM at levels exceeding  $1050 \text{ mg}/\text{m}^3$  (300 ppm) for short durations, and the effects are transient. The cytochrome P-450-related oxidative pathway resulting in carbon monoxide (CO) production is saturable, producing maximum blood CO-Hb levels of  $\leq 9\%$ . However, these CO-Hb levels are sufficiently high to induce acute effects on the CNS. It therefore appears that CNS effects are probably due to CO-Hb production. DCM does not appear to cause serious effects in humans at those relatively high levels reported in occupational settings.

Although there is no convincing evidence of cancer incidence associated with occupational DCM exposure, the available data have limitations and are considered inadequate to assess human carcinogenicity due to DCM. In test animal species (M/F mice, M/F rats), the National Toxicology Program's (NTP) bioassays led to the conclusion of clear evidence of DCM carcinogenicity in mice, clear evidence in female rats and equivocal evidence in male rats. IARC has classified DCM as Group 2B (possibly carcinogenic to humans) showing sufficient evidence of carcinogenicity in experimental animals.

The health risks of exposure to DCM have been considered in detail by an IPCS Expert Group. Given the data on interspecies differences in metabolism and comparative cancer risks, that group concluded that carcinogenicity in humans was not the critical endpoint for risk assessment purposes. The working group accepted this, and, like IPCS, has adopted the conclusion that formation of carboxyhaemoglobin is a more direct indication of a toxic effect, can be monitored, and is more suitable as a basis for the derivation of a guideline. Furthermore, it was concluded that it is unlikely that ambient exposures represent a health concern with reference to any cancer endpoint, since concentrations of DCM in ambient air are orders of magnitude lower than levels associated with direct adverse effects on the CNS or on CO-Hb production in humans.

#### Recommended Guidelines

The selected biological endpoint of interest is the formation of CO-Hb, which is measured in the blood of normal subjects at levels of 0.5–1.5% of total haemoglobin. In heavy smokers, the level of CO-Hb may range up to 10%. Carbon monoxide from various sources may contribute to the formation of carboxyhaemoglobin levels. Since overall levels in many cases approach the

recommended maximum level of 3%, it is prudent to minimize any additional amounts of CO-Hb contributed from DCM. Therefore, it was concluded that no more than 0.1 % additional CO-Hb should be formed from DCM exposure. This maximum allowable increase in CO-Hb formation corresponds to a 24-hour exposure to DCM at a concentration of  $3 \text{ mg/m}^3$ . Consequently a guideline value of  $3 \text{ mg/m}^3$  is recommended to provide sufficient protection for the general population. In addition, the weekly average concentration should not exceed one seventh ( $0.45 \text{ mg/m}^3$ ) of this 24-hour guideline, given the half life of CO-Hb.

The application of PBPK models to the available animal data lead to low risk estimates. These risk estimates are much lower than the recommended guideline value using CO-Hb formation and were therefore not employed in guideline derivation.

## FORMALDEHYDE

### Evaluation of Human Health Risks

#### Exposure Evaluation

The major route of exposure to formaldehyde in humans is inhalation. Table 3 shows the contribution of various atmospheric environments to nonoccupational air levels. Indoor air concentrations are several orders of magnitude higher than levels in ambient air. Due to the extremely high concentrations of formaldehyde in tobacco smoke, smoking constitutes a major source of formaldehyde.

Table 3. Average exposure concentrations of formaldehyde and contribution of various atmospheric environments to the average exposure to formaldehyde

Source	Concentration ( $\text{mg/m}^3$ )	Intake ( $\text{mg/d}$ )
Ambient air	0.001–0.02	0.02–0.04
Indoor air		
–conventional	0.03–0.06	0.3–0.6
–mobile home	0.1	1.0
–environmental tobacco smoke	0.05–0.35	0.5–3.5
Smoking (20 cigarettes.day <sup>1</sup> )	60–130	0.9–2.0 <sup>a</sup>

<sup>a</sup> Total amount of formaldehyde in smoke from 20 cigarettes.

#### Health Risk Evaluation

Predominant symptoms of formaldehyde exposure in humans are irritation of the eyes, nose and throat, together with concentration-dependent discomfort, lachrymation, sneezing, coughing, nausea, dyspnoea and finally death.

Damage to the nasal mucosa such as squamous cell metaplasia and mild dysplasia of the respiratory epithelium have been reported in humans, but these findings may have been confounded by concomitant exposures to other substances.

There is convincing evidence that high concentrations of formaldehyde are capable of inducing nasal cancer in rats and possibly in mice. Formaldehyde has been shown to be genotoxic in a variety of *in vitro* and *in vivo* systems. There is also epidemiological evidence of associations between relatively high occupational exposure to formaldehyde and both nasopharyngeal and sinonasal cancers.

There is substantial interindividual variability in responses to formaldehyde in humans. Significant increases in signs of irritation occur at levels above  $0.1 \text{ mg/m}^3$  in healthy subjects. At concentrations above  $1.2 \text{ mg/m}^3$ , a progression of symptoms and effects occurs. Lung function of healthy nonsmokers and asthmatics exposed to formaldehyde at levels up to  $3.7 \text{ mg/m}^3$  was generally unaltered. The working group assumed that in these studies the observed effects were related more to peak concentrations than to mean values.

There is some evidence that formaldehyde induces pathological and cytogenetic changes in the nasal mucosa of humans. Reported mean exposures ranged from  $0.02$  to  $2.4 \text{ mg/m}^3$ , with peaks between  $5$  and  $18 \text{ mg/m}^3$ . Epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases. There are also epidemiological observations of an association between relatively high occupational exposures to formaldehyde and sinonasal cancer. Recently IARC interpreted the available data as limited evidence for the carcinogenicity of formaldehyde in humans, and classified formaldehyde as probably carcinogenic to humans (Group 2A).

Formaldehyde is a nasal carcinogen in rats. A highly significant incidence of nasal cancer was found in rats exposed to a level of  $16.7 \text{ mg/m}^3$ , but the dose-response curve was nonlinear, the risk being disproportionately low at low concentrations. It also appears that the dose-response curves were nearly identical for neoplastic changes, cell turnover, DNA-protein cross-links and hyperproliferation, when the relationship between nonneoplastic and neoplastic lesions in the nasal respiratory epithelium were analyzed. This close concordance indicates an association among the observed cytotoxic, genotoxic and carcinogenic effects. In conclusion, it is likely that hyperproliferation induced by cytotoxicity plays a significant role in the formation of nasal tumours by formaldehyde.

Despite differences in the anatomy and physiology of the respiratory tract between rats and humans, the respiratory tract defence mechanisms are similar. Therefore, it is reasonable to assume that the response of the human respiratory tract mucosa to formaldehyde will be similar to that of the rat. If, therefore, the respiratory tract tissue is not repeatedly damaged, exposure of humans to low, non-cytotoxic concentrations of formaldehyde can be assumed to be associated with a negligible cancer risk. This assumption is consistent with epidemiological findings of excess risks of nasopharyngeal and sinonasal cancers associated with concentrations above approximately  $1 \text{ mg/m}^3$ .

Simultaneous exposure of humans to formaldehyde and other upper respiratory tract toxicants, such as acrolein, acetaldehyde, crotonaldehyde, furfural, glutaraldehyde and ozone may

lead to additive or synergistic effects, with particular reference to sensory irritation and possibly cytotoxic effects on the nasal mucosa.

### **Recommended Guidelines**

The lowest concentration which has been recorded as associated with nose and throat irritation after short-term exposure is  $0.1 \text{ mg/m}^3$  (WHO/IPCS, 1989).

The working group, in its assessment of a guideline value for formaldehyde in ambient air, adopted the recommendation of IPCS and concluded that in order to prevent sensory irritation in the general population, an air quality guideline value of  $0.1 \text{ mg/m}^3$  is recommended. For the case of specially sensitive groups within the general population that show hypersensitivity reactions without immunological signs, the formaldehyde concentration should be kept to a minimum, and should not exceed  $0.01 \text{ mg/m}^3$  (as a 30 minute average).

Since this recommended guideline value of  $0.1 \text{ mg/m}^3$  is more than one order of magnitude lower than a presumed threshold for cytotoxic damage to the nasal mucosa, this guideline value is considered low enough to avoid any significant risk of upper respiratory tract cancer in humans.

## **POLYCYCLIC AROMATIC HYDROCARBONS**

### **Evaluation of Human Health Risks**

#### **Exposure Evaluation**

Polynuclear aromatic hydrocarbons (polycyclic aromatic compounds, PAHs) are formed during incomplete combustion or pyrolysis of organic material and in connection with the worldwide use of oil, gas, coal and wood in energy production. Additional contributions to ambient air levels arise from tobacco smoking, while the use of unvented heating sources can increase PAH concentrations in indoor air. Because of such widespread sources, PAHs are present almost everywhere. PAHs are complex mixtures of hundreds of chemicals, including derivatives of PAHs, such as nitro-PAHs and oxygenated products, and also heterocyclic PAHs. The biological properties of the majority of these compounds are as yet unknown. Benzo[a]pyrene (BaP) is the PAH most widely studied and the abundance of information on toxicity and occurrence of PAHs is related to this compound.

Current annual mean concentrations of BaP in major European urban areas are in the range of  $1\text{--}10 \text{ ng/m}^3$ . In rural areas, the concentrations are  $< 1 \text{ ng/m}^3$ .

Food is considered the major source of human PAH exposure due to PAH formation during cooking or from atmospheric deposition of PAHs on grains, fruits and vegetables. The relative contribution of airborne PAH pollutants to food levels (via fallout) has not been well characterized.

#### **Health Risk Evaluation**

Data from animal studies indicate that several PAHs may induce a number of adverse effects, such as immunotoxicity, genotoxicity, carcinogenicity, reproductive toxicity (affecting both male and female offspring), and possibly also influence development of atherosclerosis. However, the critical endpoint for the health risk evaluation is the well documented carcinogenicity of several PAHs.

BaP is by far the most intensively studied PAH in experimental animals. It produces tumours of many different tissues, depending on species tested and the route of application. BaP is the only PAH that has been tested for carcinogenicity following inhalation, and it produced lung tumours in hamsters, the only species tested. Induction of lung tumours in rats and hamsters has also been documented for BaP and several other PAHs following direct application, e.g. intratracheal instillation into the pulmonary tissue. The lung carcinogenicity of BaP can be enhanced by coexposure to other substances such as cigarette smoke, asbestos and probably also airborne particles. Several studies have shown that the benzene soluble fraction, containing 4-7 ring PAHs of condensates from car exhaust (gasoline, diesel), domestic coal stove emissions, and tobacco smoke contains nearly all the carcinogenic potential of PAHs from these sources.

Because several PAHs have been shown to be carcinogenic, and many more have been shown to be genotoxic in *in vitro* assays, a suitable indicator for the carcinogenic fraction of the large number of PAHs in ambient air is desirable. The most appropriate indicator for the carcinogenic PAHs in air seems to be BaP concentrations, given our present knowledge and the existing database. Assessment of risks to health of a given mixture of PAHs, using this indicator approach, would entail, first, measurement of the concentration of BaP in a given mixture present in a medium such as air. One then assumes the given mixture resembles that from coke ovens and applies the unit risk estimate in tandem with the measured BaP air concentration to obtain the lifetime cancer risk at this exposure level.

The proportions of different PAHs detected in different emissions and workplaces sometimes differ widely from each other and from PAH profiles in ambient air. However, the profiles of PAHs in ambient air do not seem to differ very much from one area to another, although large variations may be seen under special conditions. Furthermore, the carcinogenicity of PAH mixtures may be influenced by synergistic and antagonistic effects of other compounds emitted together with PAHs during incomplete combustion. It should also be recognized that the carcinogenic 4-7 ring PAHs (representing the majority of PAHs monitored in ambient air) in ambient air are preferentially attached to particles, and only a minor fraction, depending on the temperature, exists as volatiles. A few studies indicate that the toxicokinetic properties of inhaled BaP attached to particles are different from those of pure BaP alone. Virtually nothing is known about other PAHs in this respect.

Risk assessments and potency assessments of various individual PAHs and complex mixtures of PAHs have been attempted. BaP is the only PAH for which a database is available, allowing a quantitative risk assessment. Risk assessment of BaP is, however, hampered by the poor quality of the data sets available.

Attempts to derive relative potencies of individual PAHs (relative to BaP) have also been published, and the idea of summarizing the contributions from each of the selected PAHs into a total BaP equivalent dose (assuming additivity in their carcinogenic effects) has emerged. There are doubts, however, about the scientific justification for these procedures.

Risk estimates considered in the United States for coke-oven emissions were used in the 1987 Air Quality Guidelines for Europe. Using a linearized multistage model, the most plausible upper-bound individual lifetime unit risk estimate associated with a continuous exposure to  $1 \mu\text{g}/\text{m}^3$  of benzene-soluble compounds of coke-oven emissions in ambient air was approximately  $6.2 \times 10^{-4}$ . Using BaP as an indicator of general PAH mixtures from emissions of coke ovens and similar combustion processes in urban air, and a reported value of 0.71% BaP in the benzene-soluble fraction of coke oven emissions, a lifetime risk of respiratory cancer of  $8.7 \times 10^{-5} (\text{ng}/\text{m}^3)^{-1}$  BaP was calculated.

From the lung tumour rates obtained in a recent rat inhalation study with coal tar/pitch condensation aerosols containing two different levels of BaP, a lifetime tumour risk of  $2 \times 10^{-5}$   $(\text{ng}/\text{m}^3)^{-1}$  BaP as a constituent of a complex mixture was calculated using a linearized multistage model.

### **Recommended Guidelines**

No specific guideline value can be recommended for PAHs as such in ambient air. These compounds typically are constituents of complex mixtures. Some of the PAHs are also potent carcinogens, which may interact synergistically with a number of other compounds. In addition, PAHs in air are attached to particles, which may also play a role in their carcinogenicity. Although food is thought to be the major source of human exposure to PAHs, part of this contamination may arise from air pollution with PAHs. The levels of PAHs in air should therefore be kept as low as possible.

In view of the difficulties in dealing with guidelines for PAH mixtures the working group considered the advantages and disadvantages of using a single indicator carcinogen to represent the carcinogenic potential of a fraction of PAH in ambient air. The well studied common constituent of PAH mixtures, BaP, was chosen as indicator, although the limitations and uncertainties in such an approach were recognized. For example, evaluation of BaP alone will likely underestimate the carcinogenic potential of airborne PAH mixtures, since other co-occurring substances are carcinogenic as well. Furthermore, the content of BaP in such mixtures is variable and it may also be the case that those PAH mixtures associated with the occupational exposures that form the basis of the cancer risk derivations (coke oven workers) differ significantly from those mixtures typically occurring in ambient air.

BaP, however, is often used as indicator for the carcinogenic PAH in air. To set priorities with respect to control, an excess lifetime cancer risk, expressed in terms of the BaP concentration and based on observations in coke oven workers exposed to mixtures of PAHs, is presented here. It must be emphasized that the composition of PAHs to which coke oven workers are exposed may not be similar to that in ambient air. The working group also considered some recent animal data, but concluded that the occupational epidemiology data should serve as the basis for the risk estimate.

Keeping in mind that no safe level of any carcinogenic substance can be recommended, the unit risk for BaP is estimated to be  $8.7 \times 10^{-5}$   $(\text{ng}/\text{m}^3)^{-1}$ . The corresponding concentrations of BaP producing excess lifetime cancer risks of 1/10 000, 1/100 000 and 1/1 000 000 are 1.2, 0.12 and 0.01  $\text{ng}/\text{m}^3$  respectively.

## **STYRENE**

### **Human Health Risk Evaluation**

#### **Exposure Evaluation**

Concentrations of styrene in rural ambient air are generally less than  $1 \mu\text{g}/\text{m}^3$ , while indoor air in such locales may be several  $\mu\text{g}/\text{m}^3$ . Levels in polluted urban areas are generally less than  $20 \mu\text{g}/\text{m}^3$  but can be much higher in newly built houses containing styrene-based materials.

## Health Risk Evaluation

Potentially critical effects for the derivation of a guideline for styrene are considered to be carcinogenicity/genotoxicity and neurological effects, including effects on development.

Styrene in its pure form has an odour detection threshold of  $70 \mu\text{g}/\text{m}^3$ . Its pungent odour is recognized at concentrations 3 to 4 times greater than this threshold value.

In epidemiological studies conducted to date, there have been small but significant increases in risk from lymphatic and haematopoietic cancers in some studies of workers from several industries with mixed exposures to styrene and other chemicals (i.e. those manufacturing styrene-butadiene rubber, styrene/polystyrene, and fibrous glass products). The available evidence for any association of styrene exposure with mortality from lymphatic and haematopoietic cancers, however, is limited, owing to such factors as concurrent exposure to other substances, uncertainties concerning the lack of specificity and absence of a dose-response relationship. The limited numbers of carcinogenicity bioassays in animal species provide little evidence that styrene is carcinogenic. On the basis of the available data, IARC has recently classified styrene in Group 2B (possibly carcinogenic to humans).

Styrene was genotoxic *in vivo* and *in vitro* after metabolic activation. In cytogenetic studies on peripheral lymphocytes of reinforced plastics workers, there were increased rates of chromosomal aberrations at mean levels of styrene above 20 ppm. Elevated levels of single strand breaks and styrene-7,8-oxide adducts in DNA and haemoglobin have also been observed. Though these genotoxic effects have been observed at relatively low concentrations, they were not considered as critical endpoints for development of a guideline, in view of the equivocal evidence of carcinogenicity for styrene.

The available data, although limited, indicate that neurotoxicity in the form of neurological developmental impairments, is among the most sensitive of endpoints. In the offspring of rats exposed to  $260 \text{ mg}/\text{m}^3$  (60 ppm) styrene, there were effects on biochemical parameters in the brain and behaviour.

## Recommended Guidelines

In occupationally exposed populations, subtle effects such as reductions in visuomotor accuracy and verbal learning skills, and subclinical effects on colour vision have been observed at concentrations as low as 25–50 ppm ( $108\text{--}217 \text{ mg}/\text{m}^3$ ). Adjustment of this value to allow for conversion from an occupational to continuous pattern of exposure (a factor of 4.2) and incorporating a factor of 10 for interindividual variation and 10 for use of a Lowest Observed Adverse Effect Level (LOAEL) rather than a No Observed Adverse Effect Level (NOAEL) results in a guideline of  $0.26 \text{ mg}/\text{m}^3$ . This value should also be protective for developmental neurological effects as observed in animal species.

The air quality guideline could be based on the odour threshold. The peak concentration of styrene in ambient air should also be kept below the odour detection threshold level of  $70 \mu\text{g}/\text{m}^3$  as a 30 minute average.

## TETRACHLOROETHYLENE

### Human Health Risk Evaluation

#### Exposure Evaluation

Ambient air concentrations of tetrachloroethylene (perchloroethylene, PCE) are generally below  $5 \mu\text{g}/\text{m}^3$  in urban areas and typically below  $1 \mu\text{g}/\text{m}^3$  in rural areas. Indoor concentrations are generally less than  $5 \mu\text{g}/\text{m}^3$ . Indoor PCE air levels may rise to  $\text{mg}/\text{m}^3$  concentrations in close proximity to dry cleaning operations where PCE is used as a cleaning solvent or in homes where dry-cleaned clothing is often worn. Inhalation of PCE is the major route of exposure in the general population.

#### Health Risk Evaluation

The main health effects of concern with PCE are cancer and effects on the CNS, liver and kidney. PCE is classified by IARC as a 2A carcinogen (probably carcinogenic to humans).

In carcinogenicity studies, an increased incidence of adenomas and carcinomas in liver of exposed mice was observed. There is evidence from mechanistic studies that humans are likely to be less sensitive to the development of these tumours after PCE exposure. A low incidence of kidney tumours among male rats has been reported. It is concluded from this small, not statistically significant increase, in combination with the data on the mechanism of induction, that the result in male rats is equivocal evidence only for a risk of renal cancer in humans. The significance of the increased incidences of mononuclear cell leukemias, as observed in the study in F344 rats, is unclear due to the high background incidence in this study. This finding is considered only weak evidence for the carcinogenic action of PCE.

Epidemiological studies in humans show positive associations between exposure to PCE and risks for oesophageal and cervical cancer and non-Hodgkin's lymphoma. Confounding factors cannot be ruled out and the statistical power of the studies is limited. Therefore, these studies provide only limited evidence for carcinogenicity of PCE in humans.

From the weight of the evidence from mutagenicity studies, it was concluded that PCE is not genotoxic. Several *in vitro* studies indicate that conjugation of PCE with reduced glutathione, a minor biotransformation route demonstrated to occur in rodents, produces renal metabolites that are mutagenic in *S. typhimurium* TA 100. In the absence of further data on this point, the significance of the latter results for humans cannot be established.

Short-term studies in volunteers (duration 1 or 5 days) have shown effects on the CNS at  $\geq 678 \text{ mg}/\text{m}^3$ . A recent study of dry-cleaning workers with long-term exposure showed that renal effects may develop at lower exposure concentrations, with the reported onset of renal damage occurring after exposure to a median concentration of  $102 \text{ mg}/\text{m}^3$  (range: trace to  $576 \text{ mg}/\text{m}^3$ ).

Although carcinogenicity studies in experimental animals are available, adequate long-term toxicity studies are not. A chronic LOAEL of  $678 \text{ mg}/\text{m}^3$  (100 ppm) for the systemic toxicity (in kidney and liver) of PCE in mice may be derived from the NTP carcinogenicity study in this species.

## Recommended Guidelines

PCE is classified by IARC as a 2A carcinogen. However, in deriving a guideline value non-neoplastic effects were employed as significant endpoints rather than a carcinogenicity endpoint, given the limitations of the weight of the epidemiological evidence and our understanding of the mechanisms of induction of tumours in animals exposed to PCE.

Based on a long-term LOAEL for kidney effects of  $102 \text{ mg/m}^3$  in dry-cleaning workers (exposure for 40 hours/week) a guideline value of  $0.25 \text{ mg/m}^3$  is calculated. In deriving this guideline value, the LOAEL is converted to continuous exposure (dividing by a factor of 4.2,  $168/40$ ) and divided by an uncertainty factor of 100 (10 for use of an LOAEL and 10 for intraspecies variation). It was recognized that some uncertainty in the LOAEL exists because the effects observed at this level are not clear-cut and because of fluctuations in exposure levels. Therefore an alternative calculation was made, based on the LOAEL in mice of  $680 \text{ mg/m}^3$ , and using an appropriate uncertainty factor of 1000. This calculation would yield a guideline value of  $0.68 \text{ mg/m}^3$ .

Based on the overall health risk evaluation a guideline of  $0.25 \text{ mg/m}^3$  is recommended, and it is judged that this guideline value will be protective against less well established effects, including deficits in colour vision.

## TOLUENE

### Human Health Risk Evaluation

#### Exposure Evaluation

Mean ambient air concentrations of toluene in rural areas are generally less than  $5 \text{ } \mu\text{g/m}^3$ , while urban air concentrations are in the range of  $5\text{--}150 \text{ } \mu\text{g/m}^3$ . Close to industrial emission sources concentrations may be higher.

#### Health Risk Evaluation

The acute and chronic effects of toluene on the CNS are the effects of most concern. Toluene may also cause developmental decrements and congenital anomalies in humans, and these effects are supported by findings of studies on animals, e.g. fetal development retardation, skeletal anomalies and low birth weights. Toluene's potential effects on reproduction and hormonal imbalances in women, coupled with findings of hormonal imbalances in exposed males, are also of concern. Limited information suggests an association between occupational toluene exposure and spontaneous abortions. Both the human and animal data indicate that toluene is ototoxic at elevated exposures. Sensory effects have also been found. There has been no indication that toluene is carcinogenic in bioassays conducted to date and the weight of available evidence indicates that it is not genotoxic. Toluene has minimal effects on the liver and kidney, except in cases of toluene abuse.

The lowest level of chronic toluene exposure unequivocally associated with neurobehavioural functional decrements is  $322 \text{ mg/m}^3$  (88 ppm). CNS effects in humans are supported by findings in exposed animals. For example, rat pups exposed to either 100 or 500 ppm toluene (1–28 days postnatal), demonstrated histopathological changes in the hippocampus.

Women occupationally exposed to toluene at an average concentration of 322 mg/m<sup>3</sup> (88 ppm) incurred higher spontaneous abortion rates and menstrual function disturbances. The interpretation of these observations was hampered, however, by confounding factors. Men occupationally exposed to toluene at 5–25 ppm have also been shown to have hormonal changes.

With regard to short-term exposure, subjective effects have been reported at 100 ppm (6 hours exposure) while symptoms at lower levels cannot be ruled out. Numerous confounding factors, however, need to be considered.

Exposure data related to CNS endpoints were best characterized in certain occupational studies and these data have been employed in the derivation of the guideline. A NOAEL for chronic effects of toluene has not been identified.

### **Recommended Guidelines**

The LOAEL for effects on the CNS from occupational studies, is approximately 332 mg/m<sup>3</sup> (88 ppm). A guideline value of 0.26 mg/m<sup>3</sup> can be calculated from these data adjusting for continuous exposure (dividing by a factor of 4.2) and dividing by an uncertainty factor of 300 (10 for interindividual variation, 10 for use of a LOAEL rather than a NOAEL, and an additional factor of 3, given the potential effects on the developing CNS).

Also for reproductive effects (spontaneous abortions) a LOAEL of 332 mg/m<sup>3</sup> has been observed in women occupationally exposed. Applying again the factors of 4.2, 10 and 10, a figure of 0.79 mg/m<sup>3</sup> can be derived. It was, however, concluded that the reproductive studies are less conclusive than those on the CNS and therefore the figure of 0.26 mg/m<sup>3</sup> is recommended as the guideline value. This guideline value should be applied as a weekly average. It is also recommended that the odour threshold of 1 mg/m<sup>3</sup> should not be exceeded during this period.

## **TRICHLOROETHYLENE**

### **Human Health Risk Evaluation**

#### **Exposure Evaluation**

The average ambient air concentrations of trichloroethylene (TCE) in rural areas are below 1 µg/m<sup>3</sup>. Average concentrations of TCE in urban air range up to 10 µg/m<sup>3</sup>. Concentrations in indoor air are typically in this same range. Higher concentrations may be expected in certain areas, e.g. in proximity-to-industrial operations. Inhalation of airborne TCE is the major route of exposure for the general population.

#### **Health Risk Evaluation**

The main health effects of concern with TCE are cancer, and effects on the liver and the CNS.

Studies in animals and humans show that the critical organs or systems for non-carcinogenic effects are the liver and the CNS. The dose-response relationship for these effects is insufficiently known, making health risk assessment for the occurrence of these effects in case of long-term exposure to low levels of TCE difficult.

In the classification system of the IARC, TCE has been categorized as a Group 2A carcinogen (probably carcinogenic to humans). This classification was based on sufficient evidence in animals and limited evidence in humans.

The available data suggest that TCE may have a weak genotoxic action *in vivo*. Several of the animal carcinogenicity studies that have been carried out with TCE show limitations in design. In mice, increased incidences of adenomas and carcinomas in lungs and liver were observed. In two rat studies, incidences of testicular tumours were increased. Evidence from mechanistic studies suggests that humans are likely to be less susceptible to the production of tumours as a result of exposure to TCE. However, the relevance of the observed increased lung tumours in mice and testicular tumours in rats for human cancer risks cannot be excluded. The results of the mechanistic studies do not provide full elucidation or guidance on this point.

Positive associations between exposure to TCE and risks for cancer of the liver and biliary tract and non-Hodgkin's lymphomas were observed in epidemiological studies on cancer in humans. Confounding cannot be ruled out. From these human data a quantitative risk estimate cannot be made. In light of the actual data base available, the increased tumours in lungs and testes as observed in the animal bioassays are considered the best available basis for the risk evaluation. From the available evidence, it cannot be conclusively established whether a threshold with regard to carcinogenicity in the action of TCE may be assumed. Therefore, linear extrapolation from the animal tumour data is used, providing a conservative approach for estimating human cancer risk.

Using the data on the incidence of pulmonary adenomas in B3C6F1 mice and on pulmonary adenomas/carcinomas in Swiss mice unit risks of  $9.3 \times 10^{-8}$  and  $1.6 \times 10^{-7}$ , respectively, can be calculated by applying the linearized multistage model. Applying the same model on the incidence of Leydig cell tumours in the testes of rats, a unit risk of  $4.3 \times 10^{-7}$  can be derived.

PBPK models have been developed for TCE. Use of these models for cancer risk estimate is not considered feasible because it is not known what an appropriate internal dose measure would be.

### **Recommended Guidelines**

Because the available evidence indicates that TCE is genotoxic and carcinogenic no safe level can be recommended. Based on the tumour data in mice and rats, unit risk estimates varying from  $4.3 \times 10^{-7}$  to  $9.3 \times 10^{-8}$  ( $\mu\text{g}/\text{m}^3$ )<sup>-1</sup> can be calculated. The corresponding ranges of ambient air concentrations of TCE corresponding to an excess lifetime risks of 1/10 000, 1/100 000 and 1/1 000 000 are 230–1100, 23–110, and 2.3–11  $\mu\text{g}/\text{m}^3$ , respectively.

### **VOC MIXTURES / TVOC**

The Air Quality Guidelines for specific substances, while they do not refer to specific environmental settings, may be difficult to apply to the indoor environment. For example, the relevant compounds often occur in mixtures at higher concentrations indoors than they do in outdoor air, thus providing multiple exposures. Indoor air samples may typically contain 100 or more VOCs at concentrations in the range of 1 to 100  $\mu\text{g}/\text{m}^3$  each.

Relatively few of these numerous VOCs are addressed quantitatively by these air quality guidelines. Furthermore, the guidelines mostly refer to health effects associated with the individual compounds. No provisions are made for assessing combined health and wellbeing effects from multi-substance, simultaneous exposures.

There is, nevertheless, a pressing need for adequate methods to assess the health and wellbeing consequences of exposures to multiple air pollutants, particularly given the general public's increasing concern about indoor air quality. Such concerns are prompted by increasing awareness of the high numbers of buildings in which occupants report adverse impacts on their health and wellbeing.

Three types of quantitative approaches can be envisioned for assessment of the public health impacts of VOC mixtures, particularly as they occur in indoor environments. One approach is the use of sensory effects, such as odour and sensory irritation, as substitutes for possible health and comfort effects. A second approach could be to add together the individual compound risks. These two approaches have not yet been developed to a level which can be recommended for general use in indoor environments. A third approach is the use of an entity called the Total Volatile Organic Compounds (TVOC) concentration, to characterize the pollutant load in terms of volatile organic compounds (VOC) in the study of health and comfort complaints.

The TVOC concentration has previously been used as an indicator, e.g. to localize the sources of VOCs in buildings or to identify leaks in, or contamination of, ventilation systems. Different procedures are currently applied to generate the TVOC value from the results obtained from the analysis of an air sample. They differ in the spectrum of compounds which are quantified and in the way that the TVOC index is calculated. The reported TVOC exposure values are, therefore, not often comparable.

It has been shown that the TVOC procedure corresponds to the assignment of a common average guideline to all the compounds included in the TVOC summation. The TVOC procedure is thus a simplification of the additivity procedure noted above. Presently, however, little toxicological knowledge supports the notion that such a simplified indicator of pollution load reflects the possibility of adverse effects on health and wellbeing.

Recognition of the urgent need for an acceptable approach to generating the TVOC value and for how to use it for health-related statements has prompted a European Collaborative Action (ECA), "Indoor Air and its Impact on Man" to establish a working group to develop guidance on this topic. This ECA working group has specified the procedures to be used in the calculation of TVOC analysis of VOC in air, including the spectrum of compounds, and in the determination of both individual VOC and the TVOC concentrations. The group also gives guidance on how to use the TVOC value as a measure for the likelihood of sensory irritation. The final outcome of this working group is expected in 1996. The current working group recommends that WHO gives serious consideration to adoption of the final recommendation of the TVOCs Group.

## **SUMMARY OF GUIDELINES**

A tabular summary of guidelines for each of the substances in this summary report is provided in Table 4, including statements on substances for which a specific guideline cannot be provided. Table 4 does not include any reference to TVOCs, since guidance in any form cannot

presently be provided by this working group. Guidelines for the carcinogens benzene and trichloroethylene are presented as unit lifetime cancer risk estimates, while a unit risk estimate for PAHs is presented for their surrogate indicator, BaP, rather than for the mixtures.

Guideline values for five substances are based on noncarcinogenic endpoints, including such diverse effects as those on the CNS and the kidney and in the form of sensory irritation responses. One of these substances, styrene, is represented by two guideline values, one based on CNS effects and an older one involving an air concentration corresponding to the odour threshold.

One substance, 1,3-butadiene, was not provided a guideline value but the group cautioned that some epidemiological evidence of cancer in humans and newly emerging reassessments and PBPK modelling required prudence in application to standard setting.

Table 4. Guidelines for volatile organic compounds

Substance(s)	Basis	Guideline
Benzene	Carcinogenicity in humans	Unit risk: $4.4 \times 10^{-6}$ – $7.5 \times 10^{-6}$ (mg/m <sup>3</sup> ) <sup>-1</sup>
1,3-butadiene	–	No guideline value at this time
Dichloromethane	Carboxyhaemoglobin formation	3 mg/m <sup>3</sup> , 24 hour average
Formaldehyde	1) Sensory irritation 2) Hypersensitive persons	0.1 mg/m <sup>3</sup> 0.01 mg/m <sup>3</sup> , 30 minute average
PAHs	Carcinogenicity of BaP	Unit risk: $8.7 \times 10^{-5}$ (ng/m <sup>3</sup> ) <sup>-1</sup>
Styrene	1) Neurobehavioural effects in workers 2) Odour threshold	1) 0.26 mg /m <sup>3</sup> 2) 70 mg/m <sup>3</sup> , 30 minute average
Tetrachloro-ethylene	Adverse effects on the kidney	0.25 mg/m <sup>3</sup>
Toluene	CNS effects in workers	0.26 mg/m <sup>3</sup> , weekly average
Trichloroethylene	Carcinogenicity in rats and mice	Unit risk: $4.3 \times 10^{-7}$ – $9.3 \times 10^{-8}$ (mg/m <sup>3</sup> ) <sup>-1</sup>

*Annex 1*

WORKING PAPERS

ICP/CEH 230/6	<i>Benzene</i> , by K. Victorin
ICP/CEH 230/7	<i>Butadiene</i> , by J.A. Bond
ICP/CEH 230/8	<i>Dichloromethane</i> , by G. Dura
ICP/CEH 230/9	<i>Formaldehyde</i> , by V.J. Feron
ICP/CEH 230/10	<i>PAHs</i> , by J.C.Larsen
ICP/CEH 230/11	<i>Styrene</i> , by M.Sorsa
ICP/CEH 230/12	<i>Toluene</i> , by M.M. Greenberg
ICP/CEH 230/13	<i>Trichloroethylene</i> , by P.J.C.M. Janssen, H.J. van Kranen & G.J.A. Speijers
ICP/CEH 230/14	<i>Tetrachloroethylene</i> , by P.J.C.M. Janssen & G.J.A. Speijers

*Annex 2*

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