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World Health Organization
Regional Office for Europe
Copenhagen

Air Quality Guidelines

for Europe

Second Edition

WHO Regional Publications, European Series, No. 91

5.2 Benzene

Exposure evaluation

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

Mean ambient air concentrations of benzene in rural and urban areas are about 1 μg/m^3 and 5–20 μg/m^3, respectively. Indoor and outdoor air levels are higher near such sources of benzene emission 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 motor vehicles. Extended travel in motor vehicles with 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 comprises about 30% when the travel time is one hour, a duration 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 leukopenia, anaemia and/or thrombocytopenia, leading to pancytopenia and aplastic anaemia. Decreases in haematological cell counts and in bone marrow cellularity have been demonstrated in mice after inhalation of concentrations as low as 32 mg/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 mg/m^3, but not at 0.03–4.5 mg/m^3. Below 32 mg/m^3, there is only weak evidence of 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 4–7 mg/m^3. The *in vivo* data indicate that benzene is mutagenic.

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

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 in the human exposure studies is of major importance for the calculation of cancer risk estimates. 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 *(1)*, by Rinsky et al. *(2)*, and a newer and more extensive one by Paustenbach et al. *(3)*. 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 exposure levels 3–5 times higher than those calculated by Rinsky et al. Compared to the Crump & Allen estimates, Paustenbach et al. arrived at higher exposure estimates for some job classifications, and lower ones for some others.

Within the most recently updated Pliofilm cohort, Paxton et al. *(4, 5)* conducted an extended regression analysis with exposure description for the 15 leukaemia cases and 650 controls. They used all three exposure matrices, which gave estimates of 0.26–1.3 excess cancer cases among 1000 workers at a benzene exposure of 3.2 mg/m^3 (1 ppm) for 40 years (Table 8).

Crump *(7)* calculated unit risk estimates for benzene using the most recently updated data for the Pliofilm cohort and a variety of models

Table 8. Published leukaemia risk estimates for the Plioform cohort at two benzene exposure levels

Cases per 1000 workers exposed to:			
3.2 mg/m³ (1 ppm)	0.32 mg/m³ (0.1 ppm)	Exposure matrix	Reference
5.3	–	Rinsky et al. *(2)*	Brett et al. *(6)*
0.5–1.6	–	Rinsky et al. *(2)*	
		Crump & Allen *(1)*	Brett et al. *(6)*
1.3	0.12	Rinsky et al. *(2)*	Paxton et al. *(4, 5)*
0.26	0.026	Crump & Allen *(1)*	Paxton et al. *(4, 5)*
0.49	0.048	Paustenbach et al. *(3)*	Paxton et al. *(4, 5)*

(Table 9). 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.

As can be seen in Table 9, the concentration-dependent model gives a much lower risk estimate than the other models when the Paustenbach et al. 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, many of the essential data are preliminary and need to be further developed and peer reviewed.

Models giving equal weight to concentration and duration of exposure have been preferred here for the derivation of a risk estimate. Using multiplicative risk estimates and a cumulative exposure model, Crump *(7)* calculated a unit risk for lifetime exposure of $1.4–1.5 \times 10^{-5}$ per ppb with the Paustenbach et al. exposure matrix, and of 2.4×10^{-5} per ppb with the Crump & Allen exposure matrix. If expressed in μg/m³, the unit risk would thus range from 4.4×10^{-6} to 7.5×10^{-6}. 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

Table 9. Model-dependent worker risk and lifetime unit risk estimates for exposure to benzene for the Plioform cohort by Crump *(7)*[a]

Risk estimate	Linear	Nonlinear	Intensity dependent	Exposure reference
Cases per	5.1	5.0	5.1	Crump & Allen *(1)*
1000 workers exposed to 3.2 mg/m³ (1 ppm)	3.8	2.9	0.036	Paustenbach et al. *(3)*
Unit risk per ppb	2.4×10^{-5}	2.4×10^{-5}	2.4×10^{-5}	Crump & Allen *(1)*
	1.5×10^{-5}	1.4×10^{-5}	1.7×10^{-10}	Paustenbach et al. *(3)*
Unit risk per µg/m³ [b]	7.5×10^{-6}	7.5×10^{-6}	7.5×10^{-6}	Crump & Allen *(1)*
	4.7×10^{-6}	4.4×10^{-6}	5.3×10^{-11}	Paustenbach et al. *(3)*

[a] Multiplicative risk model, cumulative exposure.

[b] Calculated by converting ppb to µg/m³.

estimates by Paxton et al. (Table 8), unit risks lower by up to about one order of magnitude would result.

Guidelines

Benzene is carcinogenic to humans and no safe level of exposure can be recommended. For purposes of guideline derivation, it was decided to use the 1994 risk calculation of Crump rather than to derive new estimates. It was recognized that this use of existing analyses of the most recently updated cohort ruled out the inclusion of certain of the analyses noted earlier.

The geometric mean of the range of estimates of the excess lifetime risk of leukaemia at an air concentration of 1 µg/m³ is 6×10^{-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, 17, 1.7 and 0.17 µg/m³.

References

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