13 DISCUSSION AND EVALUATION OF HEALTH EFFECTS

Chlorobenzene (also known as monochlorobenzene or benzene chloride) is 1 of 12 possible chemical species in the group of chlorinated benzenes. At room temperature, chlorobenzene is a colorless, volatile liquid with an odor that has been described as almondlike, or like that of mothballs and benzene. Chlorobenzene is hardly soluble in water, but is freely soluble in lipids and various organic solvents.

Chlorobenzene has been used extensively in industry for many years, and its main use is as a solvent and intermediate in the production of other chemicals. In occupational settings, the main exposure is that following inhalation of chlorobenzene vapors.

Once absorbed, chlorobenzene is rapidly distributed to various organs in the body. Highest levels are found in fat, liver, lungs, and kidneys. Chlorobenzene is metabolically activated to two different intermediate electrophilic epoxides by cytochrome P450/P448-dependent microsomal enzymes. Chlorobenzene is not only bioactivated in the liver, but also in other organs and tissues such as the lungs and nasal mucosa. The reactive metabolites of chlorobenzene are converted either nonenzymatically to various chlorophenols, or enzymatically to the corresponding glutathione conjugates and dihydrodiol derivatives. The glutathione conjugates are then either eliminated as such, or transferred to even more water-soluble products and excreted in the urine as mercapturic acids. The dihydrodiol derivatives are converted to catechols and excreted as such in the urine. The absolute quantities and ratios between the various metabolites formed differs among various species.

The major human urinary metabolites of chlorobenzene are the free and conjugated forms of 4-chlorocatechol and p-chlorophenol. It has been recommended that measurements of these should be used as biological exposure indicators for monitoring occupational exposure. Recommended biological threshold limits at the end of a working shift are 116 mmol of total chlorocatechol and 22 mmol total p-chlorophenol per mol creatinine (**2**).

The toxic effects of chlorobenzene in experimental animals are relatively well documented, although many toxicity studies were unpublished reports or written in a language not familiar to the evaluator. No major data gaps could be identified, and the majority of the identified studies appeared to be of acceptable quality, permitting a meaningful risk identification. The amount of human data on the toxicity of chlorobenzene is, however, limited.

The acute toxicity of chlorobenzene in experimental animals is relatively low. The lowest acute inhalation LC_{50} value identified was 8,800 mg/m^3 (female mice exposed for 6 hr). The acute exposure to high concentrations of chlorobenzene is mainly associated with various CNS-effects. These are generally manifested as initial excitation followed by drowsiness,

adynamia, ataxia, paraparesis, paraplegia and dyspnea. Death is generally a result of respiratory paralysis. CNS-depressant effects (drowsiness, incoordination and unconsciousness) have also been observed in humans after acute poisoning or occupational exposure to high concentrations of chlorobenzene. The human probable oral acute lethal dose of chlorobenzene has been estimated at 0.5-5 g/kg b.wt.

An exposure chamber study of five male volunteers exposed to 60 ppm (275 mg/m^3) for 7 hr showed that this concentration of chlorobenzene induced acute subjective symptoms such as drowsiness, headache, irritation to the eyes, and sore throat. A significant decrease in flicker-fusion values, indicating lowered perception, was observed after 3 hr of exposure to the same concentration of chlorobenzene vapor. Inhalation of chlorobenzene vapor is irritating to the eyes and the mucous membranes of the upper respiratory tract. Prolonged skin contact may lead to mild chemical burns.

Repeated administration of chlorobenzene to experimental animals for several weeks or months, is mainly associated with various effects in the liver and kidneys. These organs are, with the CNS, the primary targets for chlorobenzene-induced toxicity. The hepatotoxicity of chlorobenzene is manifested as increased activities of serum liver enzymes, increased liver weight, hepatic porphyria and hepatocellular necrosis. Similar effects have also been observed in a man who ingested 140 ml of a 90% chlorobenzene solution in a suicide attempt. It may be useful to note that there is some evidence from in vitro studies, showing that humans, due to metabolic differences, may be more susceptible to the hepatotoxic effects of chlorobenzene than rodents. The nephrotoxic action is mainly manifested as increased kidney weight, focal coagulative degeneration, and necrosis of the proximal tubules.

Chlorobenzene differs from many polychlorinated aromatic hydrocarbons in not being a general inducer of the cytochrome P450/P448 enzyme system. Instead, chlorobenzene appears to lower the cytochrome P450 levels. Since administration of chlorobenzene induces an initial, but transient, depletion of the glutathione levels in the liver, exposure to this compound seems associated with a lowered capacity of both bioactivating and detoxifying enzyme systems.

Repeated administration of chlorobenzene to experimental animals is also associated with lesions of the thymus (lymphoid depletion and necrosis), spleen (lymphoid or myeloid depletion), bone marrow (leukopenia, myeloid depletion, general bone marrow depression), lungs (increased lung weights, necrotic lesions in the bronchial epithelium), and testes (bilateral or unilateral degeneration of the germinal epithelium). Of these effects, the hematopoietic toxicity is of special interest. When male and female mice were exposed to 100 mg/m^3 (22 ppm) of chlorobenzene, 7 hr/day for 3 months, they were reported to develop leukopenia and a general bone marrow depression.

It is generally assumed that the toxic effects of chlorobenzene are mediated by covalent binding of reactive metabolites to critical cell structures in the target organs. However, the exact molecular mechanisms of action behind the various toxic effects of chlorobenzene are still unknown. Several possible toxicological mechanisms may be involved. Whereas, for example, the hepatotoxic and nephrotoxic action of chlorobenzene may be a direct result of covalent

binding to critical structures and/or an indirect effect of oxidative stress, the CNS-depressant effect is most likely mediated by other toxicological mechanisms, probably induced by the unmetabolized substance itself.

It appears as if halogenated aromatic monocyclics form a complex group when it comes to the interpretation of their genotoxicity. In the case of chlorobenzene there is no problem with lack of information. At least 12 different published investigations representing various types of genetic endpoints and/or test systems were identified. Apart from the published information, there are also several unpublished studies mentioned in the present document. Even if some results only are presented as a figure or symbol in a summarizing table, the conceivable problem with condensed presentations of study designs, protocols and results do not seem of major importance in the case of chlorobenzene. There were no obvious differences in study qualities between those reporting absence of genotoxic effects and those showing effects.

The major problem in interpreting the existing genotoxicity data for monochlorobenzene relates to the fact that the compound was reported "negative" in some test systems, and "positive" in others. The interpretation becomes even more complex when one also has to consider that whereas some authors reported that chlorobenzene was genotoxic/mutagenic in a given test system, other investigators reported a "negative" result. In the case of chlorobenzene, this seems to be the situation in the L5178Y mouse cell lymphoma assay, the micronucleus test, and when measuring SCEs in vitro (at least when one includes unpublished information).

The combination of being positive in an L5178Y gene mutation assay and in a SCE assay and simultaneously being negative in the Ames test and in an assay for chromosomal aberrations in CHO cells, is not unique for chlorobenzene (**1, 89**). However, the mutagenic effect of chlorobenzene observed in the L5178Y cells, with and without exogenous metabolic activation, and its ability to induce sister chromatid exchanges in cultivated Chinese hamster cells in the absence of metabolic activation, are not isolated positive responses. Consequently, chlorobenzene has also been shown to increase the incidence of micronuclei in bone marrow cells of exposed mice in a dose-dependent manner. Although chlorobenzene apparently lacked DNA-damaging effects in a rat hepatocyte DNA-repair test, radioactivity from ^{14}C-chlorobenzene was reported to bind covalently directly to DNA in various organs, including the liver. This was shown in both mice and rats, in vivo as well as in vitro. The latter findings suggest that chlorobenzene, or more likely, some of its metabolites, can interfere directly with the DNA-molecule.

The data on DNA-binding should be interpreted with some care because it cannot be excluded that the relatively low levels of DNA-binding is an artifact resulting from protein contamination. The reported binding of [^{14}C]chlorobenzene-associated radioactivity to nucleic acids deserves particular attention and should be further examined. At present, it is suggested that chlorobenzene should be regarded as an agent capable of inducing a certain degree of DNA-binding after administration of large doses.

Beside the above-mentioned "positive" results from various short-term tests, chlorobenzene has also been reported to induce point mutations in *Actinomyces antibioticus* 400, abnormal mitotic cell-division in *Allium cepa*, and reciprocal recombination in *Saccharomyces cerevisiae*. However, the significance of these results remains unclear for various reasons.

Previously, when the number of available genotoxicity studies was limited, it was suggested that chlorinated benzenes, including chlorobenzene, appeared to lack significant genotoxic properties (**18**). However, paying attention to more recent findings it may be wise to reconsider such a conclusion, or at least to initiate more careful and exhaustive reevaluation of the potential genotoxicity of chlorobenzene. Although not always consistent and clear, the overall data are judged to show "limited evidence of genotoxicity" of chlorobenzene. This judgment is based on the fact that chlorobenzene has been reported "positive" in at least three different test systems measuring mutagenicity, chromosomal anomalies, and DNA damage/DNA-binding, at the same time as the majority of test results were reported as "negative." With regard to the question of how potent genotoxic agent chlorobenzene might be, the available "positive" studies showed that its genotoxic potential is low. The effects were generally observed only after administration of relatively high concentrations of chlorobenzene.

The ability of chlorobenzene to induce neoplastic transformation has also been tested with conflicting results. Whereas the compound was found to induce a low, but definite, anchorage-independency in cultured rat liver cells, it was without activity in a rat liver foci bioassay. The significance of these results remains unclear.

Chlorobenzene induced benign liver tumors in male rats, but was without tumorigenic effects in female rats and male and female mice given the compound by gavage, 5 days/week for 103 weeks (60 or 120 mg/kg b.wt./day). The inadequate/equivocal evidence of carcinogenicity in experimental animals, in combination with the limited evidence of genotoxicity from short-term tests and the absence of epidemiological data, implies that chlorobenzene, at present, should be regarded as an agent not classifiable as to human carcinogenicity.

Animal experiments on the potential teratogenicity and reproductive toxicity of chlorobenzene did not show any significant teratogenic potential of the compound. However, there was some evidence of embryotoxic effects in both rabbits (skeletal anomalies and an increased incidence of early embryonic deaths) and rats (delayed skeletal development), but these effects were only seen at doses found toxic to the adult animal (LOEL with regard to embryotoxicity was established to 590 ppm (i.e., 2,714 mg/m^3). A two-generation reproductive toxicity study in rats did not show any chlorobenzene-induced adverse effects on the reproductive performance or fertility.

Apparently, chlorobenzene is without immunotoxic effects in mice after multiple exposures at 75 ppm (345 mg/m^3), and the compound was reported not to induce skin sensitization in a maximization test on male guinea pigs.

CNS effects (i.e., prenarcotic effects) are judged to be the most critical effects following acute exposure to chlorobenzene vapors. An exposure chamber study involving five male volunteers

exposed to 60 ppm (276 mg/m^3) for up to 7 hr, showed that this relatively low concentration of chlorobenzene vapor resulted in acute subjective symptoms such as drowsiness, headache, irritation of the eyes, and sore throat.

Based on what is presently known about the various toxic effects of chlorobenzene, the hepatotoxic and nephrotoxic (LOEL in the most sensitive species after 11 weeks of inhalation was 50 ppm), and possibly also the hematopoietic effects (leukopenia was observed in mice after 3 months of exposure to 22 ppm), are judged to be the most critical effects observed after exposure to chlorobenzene. Consequently, it is on these effects that various threshold limit values should be based.

So far, there is no reliable scientific data showing that oral doses and/or inhalation of air concentrations below the indicated LOEL values would induce other types of significant adverse effects in experimental animals.

14 SUMMARY

B. Hellman: NIOH and NIOSH Basis for an Occupational Health Standard: Chlorobenzene. Expert Group for Documentation of Occupational Exposure Limits. Arbete och Hälsa 1992:31, pp. 1-73.

In the present document, relevant data are summarized and evaluated for the purpose of establishing permissible levels of occupational exposure to chlorobenzene. Of the various effects described, the effects on the central nervous system (prenarcotic effects) of chlorobenzene, together with its hepatotoxic effects, should be considered in setting occupational exposure limits. At present, there is "limited evidence" indicating that chlorobenzene is genotoxic and that it may induce hematopoietic toxicity at relatively moderate doses. It is presently not classifiable as to human carcinogenicity. 105 references.

Key-words: Chlorobenzene; occupational exposure limits; CNS effects; hepatotoxicity; genotoxicity, hematopoietic toxicity.

15 SAMMANFATTNING PÅ SVENSKA

B. Hellman: NIOH and NIOSH Basis for an Occupational Health Standard: Chlorobenzene. Expertgruppen för Gränsvärdesdokumentation. Arbete och Hälsa 1992:31, sid 1-73.

I det aktuella dokumentet görs en genomgång och utvärdering av den litteratur som befunnits vara relevant som underlag för fastställande av ett hygieniskt gränsvärde för yrkesmässig klorbensenexponering. Av de effekter som beskrivs, bör hänsyn tas till klorbensens påverkan på det centrala nervsystemet (prenarkotiska effekter), samt dess levertoxiska effekter, när de hygieniska gränsvärdena fastställs. För närvarande föreligger även misstanke om att klorbensen är en lågpotent genotoxisk substans, och att man inte kan utesluta en påverkan på blodbilden vid relativt måttliga exponeringsnivåer. För närvarande kan man inte med säkerhet uttala sig om huruvida klorbensen är att betrakta som varande en kemisk carcinogen eller ej. 105 referenser.

Nyckelord: Klorbensen; hygieniska gränsvärden; centralnervösa effekter; levertoxicitet; genotoxicitet, benmärgstoxicitet.

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