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Occupational Chemicals Tested for Teratogenicity

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Summary. Literature was surveyed concerning the teratological testing of chemicals, to which large numbers of workers are occupationally exposed. They include metals, plastics monomers and additives, solvents, and other organic chemicals. The effective doses used in the studies were compared to the potential exposures in the occupational environment as regulated by hygienic standards. In light of the animal experiments, the TLVs for some organic chemicals, particularly for acrylonitrile, methacrylate esters, styrene, carbon disulfide, chloroform, methylene chloride, toluene and xylene, appeared too high to provide absolute safety for pregnant workers. The mechanisms of teratogenesis and the validity of the animal experiments were also considered.

Key words: Teratogenic testing – Occupational chemicals – Extrapolation to humans – TLVs – Pregnant workers

Epidemiological studies from several countries have indicated differences in the incidence of congenital malformations by parental social class (Leck 1977), and by parental occupation (Fedrick 1976; Bjerkedal and Lund 1978; Occupational Mortality 1978; Erickson et al. 1979, Hemminki et al. 1980). Such differences may be accounted for by a number of social and occupational factors. However, in a multivariate analysis on the association of the maternal occupation with malformations in the offspring, carried out in Finland, a number of social factors were controlled, and a significant association still remained between the maternal occupation in industry and malformations in the offspring (Hemminki et al. 1981). Specific occupational agents have also been implicated as teratogens in epidemiological studies (Hemminki et al. 1979). In view of such results and the variety of harmful chemicals used in the working environment, the possible relationship of the occupational exposures to teratogenicity in the offspring deserves further exploration.

Epidemiological methods have certain limitations which call for the use of experimental methods to provide additional evaluation on the teratogenic

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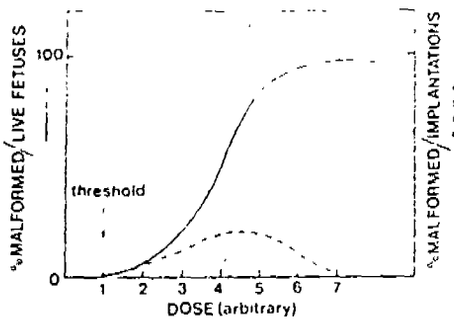

Fig. 1. Typical dose-effect relationships in teratogenicity testing, as modified from Beck and Hoe [1969] and Wilson [1973]

properties of chemicals. The limitations of the epidemiological methods in the investigation of occupational risks include difficulties in the identification of sufficiently exposed populations, reliability of the exposure data, incompleteness of registration, bias by the confounding factors, and the post hoc nature of the information obtained.

Several hundred chemicals have been tested for teratogenicity in experimental animals (Shephard 1976). In this paper, I will review the teratogenicity tests carried out with compounds to which large numbers of workers are exposed occupationally. Previously, occupational chemicals have been surveyed only shortly (Wilson 1977b, Zeuthen Heidam 1978). However, data on medicines and pesticides will not be assessed as comprehensive reviews on these topics are available (Wilson 1977a, b). The doses used in the animal tests are compared to the possible human exposures as regulated by hygienic standards. Additionally, mechanism of teratogenicity, dose-response relationships, and the general validity of the animal tests in relation to humans are shortly considered.

Dose-Response Relationships

The teratogenic responses are thought to follow a dose-response relationship as illustrated in Fig. 1 (Wilson 1973). The actual shape of the dose-response curve depends on whether the malformations are scored per live fetuses or per implantations, as the increasing concentrations of foreign compounds always confer embryotoxicity and fetal deaths. In most teratogenic systems it is thought that a threshold dose giving a zero-response can be determined. This is in contrast to mutagenic responses in general, where any dose may confer a probability of mutation (Auerbach 1976). It is conceivable that mutagenic properties of chemicals on the germ cells may cause malformations (Harbison 1978; Hemminki et al. 1979). In such cases, the dose-response relationships may resemble those of mutagenic responses in general.

Validity of Animal Tests

The application of animal tests in the testing of teratogenic compounds implies that a qualitative correlation exists between the teratogenic properties of

Table 1. Animal te
to man

Compound	
Alcohol(ism)	
Aminopterin	
Androgens	
Cytostatic drugs	
— Busulfan	
— Chlorambucil	
— Cyclophosphan	
Diethylstilbestrol	
Diphenylhydantoin	
Halothane	
Mercury	
Polychlorinated bip	
Thalidomide	
Warfarin	

[a] Human evidence
established, + –
[b] Data as collecte
[c] Reduced litter s

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Table 1. Animal tests with compounds thought to be teratogenic to man

Compound	Man[a]	Animal tests[b]	
		Species	Outcome
Alcohol(ism)	+	Chick, mouse	+
Aminopterin	+ +	Chick, rat	+
Androgens	+ +	Several	+
Cytostatic drugs			
— Busulfan	+	Rat	+
— Chlorambucil	–	Rat	+
— Cyclophosphamide	+	Rat, mouse	+
Diethylstilbestrol	–	Rat	+
Diphenylhydantoin	+	Mouse, monkey	+
Halothane	+	Rat	+
Mercury	+ +	Rat, mouse	+
Polychlorinated biphenyls	+	Hog, rat	+[c]
Thalidomide	+ +	Several	+
Warfarin	+	Mouse, rabbit	–

[a] Human evidence as discussed by Wilson (1977a, b). + + = established. + = suspected
[b] Data as collected from the catalogue of Shephard (1976)
[c] Reduced litter size (Wilson 1977b)

chemicals in experimental animals and in man. This appears to be largely true as reviewed by several authors (Wilson 1973; Fraser 1977). One and perhaps the only way to validate the qualitative correlations between man and animals is to investigate the outcome of the animal testing results with compounds found to be teratogenic in man. Such a comparison is presented in Table 1. The human data were based on the evaluations of Wilson (1977a, b). The animal testing data were collected from Shephard (1976). Of 13 chemicals considered to be teratogenic to man, all but one (warfarin) have been found to be positive in one or more experimental animals. Two negative experiments have been carried out with warfarin, applying doses up to 100 times the effective human dose. The data suggest a reasonably good qualitative correlation between experimental results and data in humans.

The qualitative correlation between experimental and human data are not particularly helpful for practical risk evaluations, as very high doses of almost any compound are likely to be effective (Fig. 1). Thus, it would be desirable to establish quantitative correlations between the experimental and human data. Unfortunately, no dose-response data are available from human studies, making the quantitative analysis rather arbitrary. It is particularly difficult even to estimate the true human risk of malformations in a given exposure, because some data on the reported teratogenicity of medicines are derived from case reports, frequently failing to state the denominator (i.e., how many pregnancies were observed). Allowing for such errors, the literature on the teratogenic properties of

Table 2. Animal tests on chemicals with some evidence on teratogenicity in man after a quantitated exposure

Chemical	Human data			Experimental data		
	Dose, daily (mg/kg)	Risk	Reference	Species	Dose (mg/kg)	Reference
Aminopterin	0.02–0.04	(¹/₁–¹/₂)	Thiersch 1952; Goetsch 1962	Rat	0.075–0.2	Thiersch 1956; Ba... 196
Androgens (Testosterone derivatives)	~0.2	—	Grumbach and Ducharme 1960	Rabbit Rat	50 5–20	Courrier and Jost 1942; Calvet 1966
Anticonvulsants						
— Diphenylhydantoin	6	(6/100)*	Meadow 1970 Monson et al. 1973	Mouse Monkey	50 5–30	Hart... son and Bec... 196... Wilson 197...
Cytostatic drugs						
— Busulfan	0.1	—	Diamond et al. 1960	Rat	10–34	Murphy et al. 1958 Calvet 1966
— Chlorambucil	0.1	—	Shotten and Moore 1963	Rat Mouse	2–10 10–20	Murphy 1959 Calvet 1966
— Cyclophosphamide	2	—	Greenberg and Tanaka 1964	Chick Rabbit	0.1 2–50	Calvet 1966 Calvet 1966
Halothane	1–85 ppm/inhal.	(5.5/100)*	IARC 1976; Knill-Jones et al. 1975	Rat	... ppm/inhal.	Basford and ... 19...
Thalidomide	1–10	(1/2)	Lenz 1966	Chick Rabbit Rat Mouse Cat Dog Monkey	0.2–2.5 0.5–50 50–250 50–200 0.5 50–100 10	Calvet 1966 Calvet 1966 Calvet 1966 Calvet 1966 Calvet 1966 Calvet 1966 Calvet 1966

* Rate is about twice as high as the rate in the nonexposed population

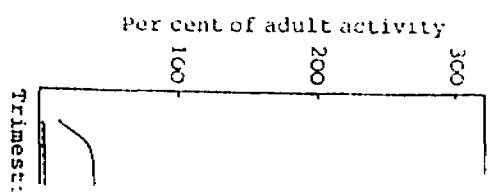

Fig. 2. Development... (Peltonen 1979). ... chrome P-448-linked ... cytochrome P-450-lin...

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Thalidomide	1–10	(1/2)	Lenz 1966	Kelly-Jones et al. 1975

Chick	0.2–2.5	Cohen 1966	Beckett and Hoyt 1968
Rabbit	0.5–50	Cohen 1966	
Rat	50–250	Cohen 1966	
Mouse	50–500	Cohen 1966	
Cat	0.5	Cohen 1966	
Dog	30–100	Cohen 1966	
Monkey	10	Cohen 1966	

* Rate is about twice as high as the rate in the nonexposed population

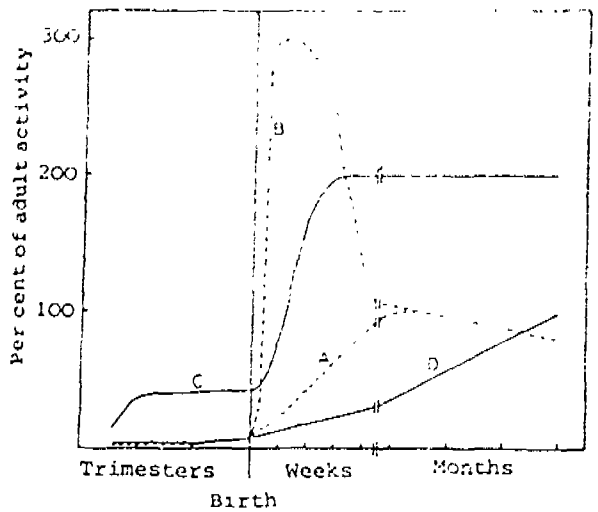

Fig. 2. Development of drug-metabolizing enzyme activities in laboratory animals and in humans (Pelkonen 1979). *A, C* = cytochrome P-450-linked enzymes in animals and man. *B, D* = cytochrome P-448-linked enzymes in animals and man, respectively. Note the early activity of cytochrome P-450-linked enzymes in man

chemicals in humans and in experimental animals was analysed in quantitative terms (Table 2). The reported daily dose (mg/kg body wt.) in humans was compared to the doses applied in animal studies. The observed risk in the treated humans was indicated, if available in the original reports. It may be assumed that the animal experiments reported relate to risks in the linear portion of the dose-response curve (Fig. 1). The most extensive data were available for thalidomide. The human embryo appeared to be as sensitive as the most sensitive animal species, chick, rabbit, cat, and monkey, but the human was about 50 times more sensitive than the common laboratory animals, rat and mouse. In each case certain inbread strains were used and it is possible that the strains as well as species differ in their sensitivity. Relatively complete data were also available for aminopterin, diphenylhydantoin, and halothane, if halothane is assumed to be the effective teratogen in operation rooms. Man appeared to be more sensitive to aminopterin and halothane than rat, while the sensitivity of man to diphenylhydantoin appeared to be roughly equal to mouse and monkey. The data on the other drugs and chemicals did not allow exact evaluation on the species differences. The only observation to be made suggested the humans described in the case reports were generally exposed to lower or much lower concentrations than those used in the animal experiments. As a conclusion, the limited data suggest that man appears to be at least as sensitive, if not more sensitive, to the teratogenic effects of chemicals as compared to the experimental animals.

The biological basis for the differential species sensitivity may depend, among other parameters, on the feto-placental transfer of the chemicals (Mirkin 1973;

Pelkonen 1977), and on the metabolism of the chemicals to reactive intermediates (Hemminki 1979, Fuster et al. 1979, Metzler and Mauch 1977), usually requiring enzymes containing cytochrome P-450 or P-448 as cofactors. The development of the enzyme activities in the embryo and in the placenta are likely to relate to the teratogenic hazards of the compounds. Figure 2 shows the developmental appearance of the two enzyme activities in humans and in commonly used laboratory nonprimate species (e.g., rat, mice) (Pelkonen 1979). The activity of cytochrome P-450 enzymes appear very early, during the first trimester, in the developing human embryo as compared to the laboratory animals. This may suggest that the human embryo is more susceptible than the laboratory animals to the teratogenic action of the compounds oxidized by cytochrome P-450.

Teratogenicity Tests on Industrial Chemicals

The literature on chemicals tested for teratogenicity was surveyed for the compounds that are in extensive industrial use. Only those compounds for which some positive results are available, were reported. For some compounds, several test results have been reported, and in those cases only one or a few illustrative reports have been considered. The reports were listed in Tables 3–6 giving the species, doses, effects noted, references, and the calculated human daily intake for women working at TLV concentrations. The doses were calculated as mg/kg body wt. as given in a single injection or by gavage. The inhalation concentrations are indicated specifically. The human doses are calculated assuming a TLV (OSHA 1974) concentration of the chemical, person (50 kg by weight) inhaling 10 m^3 of air during the working day and absorbing 50% of the dose. All the parameters are rough estimations of the true exposure. The outcome of the testing is indicated as M (= malformations) for the major malformations described given as per cent of the live fetuses. In some cases, particularly when low concentrations of chemicals were used, "minor skeletal" malformations or delayed ossification were reported. In the tables such findings are stated specifically. In a few cases no malformations were noted but instead embryotoxicity (embryonic deaths) was found. Such findings are also indicated in the tables.

Metals

Several metals have been tested for teratogenicity in experimental animals (Table 3). Aluminium chloride has been shown to cause malformations at relatively high doses 40–200 mg/kg. Several tests have been carried out with arsenates. Four different tests are listed in Table 3, each conducted with different species. The doses range from less than 6 to 45 mg/kg. In the chick, growth inhibition was reported, while in the mammals the indicated concentration caused a high frequency of malformations. The daily human dose for persons working at TLV would amount to about 0.05 mg/kg, far below the effective experimental dose. Cadmium salts have been tested in several species. In the injections, the teratogenic doses have been 2–6 mg/kg. The TLV concentration would lead to a total daily dose of 0.01 mg/kg in the humans. Chromium salts have been tested in the chick (< 1.2 mg/kg) and in the hamster (15 mg/kg), both

Table 3. Teratogenicity in some of industrially important metals

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)
Aluminium-chloride	Rat	40–200	M	Bennets et al. 1974	—
Arsenic-sodium arsenate	Chick	<6	Growth inhibition	Ridgway and Karnofsky 1952	0.05 (as As)
sodium arsenate	Hamster	20	M	Ferm and Carpenter 1968a	
sodium arsenate	Mouse	45	M + R[c]	Hood and Pike 1979	

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Table 3. Teratological testing of industrially important metals

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)
Aluminium-chloride	Rat	40–200	M	Bennett et al. 1974	—
Arsenic-sodium arsenate	Chick	~6	Growth inhibition	Ridgway and Karnofsky 1952	0.05 (as As)
-sodium arsenate	Hamster	20	M	Ferm and Carpenter 1968a	
-sodium arsenate	Mouse	45	M (63%)	Hood and Pike 1972	
-sodium arsenate	Rat	30	M	Beaudoin 1974	
Cadmium-sulfate	Hamster	2	M (65%)	Ferm and Carpenter 1968b	0.02 (as Cd)
	Mouse	10 (ppm, oral)	M (14%)	Schroeder and Mitchener 1971	
-chloride	Rat	6	M (35%)	Chernoff 1973	
Chromium-sodium dichromate	Chick	≥ 1.2	M	Ridgway and Karnofsky 1952	0.01 (as Cr(VI))
-trioxide	Hamster	15	M (64%)	Gale 1978	
Cobalt-chloride	Chick	< 10	M	Ridgway and Karnofsky 1952	0.01 (as Co)
-chloride	Chick	~10	M (22%)	Kurz and Crosby 1966	
Copper-sulphate	Hamster	7	Embryotoxic	Ferm and Hanson 1974	0.1 (as Cu)
Lead-nitrate	Chick	~2	M (96%)	Ridgway and Karnofsky 1952	0.02 (as Pb)
-nitrate, -chloride, -acetate	Hamster	50	M (90–100%)	Ferm and Carpenter 1967	
-tetraethyl	Mouse	25 (ppm, oral)	M (95%)	Schroeder and Mitchener 1971	
-tetraethyl	Rat	7.5–30 (oral)	Embryotoxic	McClain and Becker 1972	
Mercury methylmercury dicyanidamide	Mouse	8	M (50%)	Spyker and Smithberg 1972	0.001 (alkyl Hg)
methylmercury chloride	Hamster	8	M	Harris et al. 1972	
methylmercury chloride	Cat	0.25 (oral)	M (30%)	Khera 1973a	
Nickel-acetate	Hamster	10–30	Embryotoxicity	Ferm 1972	0.1 (as Ni)[c]
-carbonyl	Rat	0.3 mg/l air 15 min	M (28%)	Sunderman et al. 1979	
-chloride	Mouse	4.6	M (51%)	Lu et al. 1979	

[a], [b] see Table 4

species exhibiting malformations. The daily human occupational dose would be far less, about 0.01 mg/kg. Cobalt and copper have only exhibited weak teratogenic properties at concentrations far higher than the calculated human exposures at TLV. Several tests have been conducted with lead salts and organic lead compounds. The concentrations used have caused a high incidence of malformations, and the safety evaluation is difficult as the results may apply to the extreme right-hand portion of the dose-response curve (Fig. 1). Several test results are available on the teratogenicity of organic mercury derivatives, which are relatively potent teratogens as compared to many other metals. An acute occupational exposure would amount to a far lower daily dose. However, mercury is known to accumulate in the fetal tissues, particularly in the brain (Yang et al. 1972), and a chronic occupational exposure may result in tissue concentrations much higher than those predictable after an acute exposure. Three nickel salts have been tested for teratogenicity. Nickel carbonyl appeared to be a particularly potent teratogen as a transient 15 min exposure to 0.3 ml/l in the air caused malformation, particularly eye malformation in 28% of the rat fetuses.

Plastics Monomers and Additives

The production of plastics monomers has increased markedly during the past decades and today the most widely used monomers, ethene and vinly chloride, are among the major organic compounds produced. The plastics monomers are reactive because of their chemical application in forming large polymers. Plastics production has created new occupational safety problems which have been objects of intense toxicological research in recent years.

Several plastics monomers have been tested for malformations in experimental animals (Table 4). Acrylonitrile was tested in the rat using an oral dose of 25 mg/kg and an inhalation dose of 80 ppm for 6 h. Both types of exposures caused malformations. The TLV for acrylonitrile is so high (40 ppm) that the daily exposure of the workers may be as high as the one used in the animal experiment. Only one published report on the teratogenic properties of epoxy resins has been found. In this report an undefined dose caused fetotoxicity. NIOSH (1978) has referred to an unpublished study on the teratogenicity of phenyl glycidyl ether, which is a component in some epoxy resins. The result of this study was reported to be negative. Methylacrylate esters are used in industry, as well as in dentistry and medicine for prosthetic devices and artificial eyes. Methacrylates were tested in the rat with a large concentration range and found to be teratogenic. The test concentration covered the potential extent of exposure in the workplaces. Phthalate esters are common additives in plastics products, and they may account for a large proportion of the weight of the products. Phthalate esters have been found to be teratogenic to chick and rat embryos.

Styrene is one of the major monomers produced in the plastics industry. In industrial hygiene styrene is of special importance as it is used in the reinforced plastics industry, where exposures are frequently high. Styrene is teratogenic to the chick embryo. It has produced minor skeletal malformations (called variants by the authors) in rats and rabbits when exposed to 300–600 ppm by inhalation. In mice and hamsters fetotoxicity was observed at concentrations of 250 and

Table 4. Teratological testing of plastics monomers and additives

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)
Acrylonitrile	Rat	25	M	Murray et al. 1978a	5 (20 ppm)
		80 ppm/6 h, inhal	M	Murray et al. 1978a	
Epoxy resin (Epidian 5)	Guinea pig	Skin painting	Fetotoxicity	Weyton et al. 1975	—
Methacrylate esters	Rat	5, 700	M	Singh et al. 1975a	3.5 (100 ppm)

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Table 4. Teratological testing of plastics monomers and additives

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)[c]
Acrylonitrile	Rat	25	M	Murray et al. 1978a	5 (20 ppm)
		80 ppm/6 h, inhal.	M	Murray et al. 1978a	
Epoxy resin (Epidian 5)	Guinea pig	Skin painting	Fetotoxicity	Woyton et al. 1975	—
Methacrylate esters	Rat	5–700	M	Singh et al. 1972a	3.5 (10 ppm)
Phthalate esters	Chick	Unspecified	M	Lee et al. 1974	—
	Rat	300–1000	M	Singh et al. 1972b	
Styrene	Chick	2.5	M (7%)	Vainio et al. 1977	42 (100 ppm)
	Rat	300–600 ppm/7 h inhal.	M (minor skeletal)	Murray et al. 1978b	
	Rabbit	300–600 ppm/7 h inhal.	M (minor skeletal)	Murray et al. 1978b	
	Mouse	250 ppm/6 h inhal.	Fetotoxicity	Kankaanpaa et al. 1980	
	Hamster	1000 ppm/6 h inhal.	Fetotoxicity	Kankaanpaa et al. 1980	
Urethane Monomer	Mouse	15	M	Sinclair 1950	
Vinyl chloride	Mouse	50 ppm/7 h inhal.	M	John et al. 1977	0.3 (1 ppm)
	Rat	500 ppm/7 h inhal.	M (minor skeletal)	John et al. 1977	
	Rabbit	500 ppm/7 h inhal.	M (minor skeletal)	John et al. 1977	

[a] Dose referring to the injected amount unless stated otherwise
[b] Figures in parentheses indicate the percentage of malformed animals if stated in the reference
[c] Human dose as calculated by taking the TLV concentration (defined by OSHA 1974) and assuming a daily inhalation of 10 m³ and absorption of 50% of dose by the lungs of a person weighing 50 kg

Table 5. Teratological testing of industrially important solvents

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)
Benzene	Mouse	2500	M (8%)	Watanabe et al. 1970	3 (10 ppm)
	Mouse, Rabbit	500 ppm/7 h inhal.	M (minor skeletal)	Murray et al. 1979	
Carbon disulfide	Rat	100 mg/m³/8 h inhal.	M (27%)	Tabacova et al. 1978	6 (60 mg/m³)
Chloroform	Rat	100 ppm/7 h inhal.	M	Schwetz et al. 1974a	(50 ppm)
Dimethyl formamide	Mouse	600	M (18%)	Scheufler and Freye 1975	3 (10 ppm)
Dimethyl sulfoxide	Hamster, Mouse	3300–10000	M	Staples and Pechan 1973	—
	Hamster	2500–8250	M (33%)	Ferm 1966	
Methylene chloride	Chick	40	M (14%)	Elovaara et al. 1979	174 (500 ppm)
	Rat	1500 ppm/7 h inhal.	M (minor skeletal)	Schwetz et al. 1975	
	Mouse	1500 ppm/7 h inhal.	M (minor skeletal)	Schwetz et al. 1975	
Propylene glycol	Chick	850	M (65%)	Gehlhardt 1968	—
Trichloroethane, 1,1,1-	Chick	13	M (25%)	Elovaara et al. 1979	—
Trichloroethane, 1,1,2-	Chick	13	M (14%)	Elovaara et al. 1979	5 (10 ppm)
Trichloroethylene	Rat	1800 ppm/6 h inhal.	M (minor)	Dorfmueller et al. 1979	54 (100 ppm)
	Chick	13	M (33%)	Elovaara et al. 1979	
Tetrachloroethane	Mouse	700	M (9%)	Schmidt 1976	3.5 (5 ppm)
Tetrachloroethylene	Chick	17	M (29%)	Elovaara et al. 1979	67 (100 ppm)
Toluene	Rat	1500 mg/m³/24 h inhal.	M (minor skeletal)	Hudák and Ungváry 1978	75 (750 mg/m³)
Xylene	Rat	1000 mg/m³/24 h inhal.	M (minor skeletal)	Hudák and Ungváry 1978	43 (435 mg/m³)

Table 6. Teratological testing of industrially important organic compounds

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)
Aminoazobenzene	Mouse	200–700	M	Sugiyama et al. 1960	—
Azo dyes, trypanblue etc.	Rat	~50	M (~20%)	Beck and Lloyd 1966	—

Trichloroethylene	Rat	1000 ppm/6 h/day	M (mouse)	Hardin-Bell et al. 1979	54 (100 ppm)
	Chick	13	M (SP)	Hayama et al. 1979	
Tetrachloroethane	Mouse	700	M (SP)	Schmidt 1976	3.5 (5 ppm)
Tetrachloroethylene	Chick	17	M (SP)	Hayama et al. 1979	67 (100 ppm)
Toluene	Rat	1500 mg/m³/24 h/day	M (mouse skeletal)	Hudák and Ungváry 1978	75 (750 mg/m³)
Xylene	Rat	1000 mg/m³/24 h/day	M (mouse skeletal)	Hudák and Ungváry 1978	44 (435 mg/m³)

Table 6. Teratological testing of industrially important organic compounds

Compound	Species	Dose[a] (mg/kg)	Effects[b] (M = malformations)	Reference	Calculated human dose at TLV (mg/kg/day)
Aminoazobenzene	Mouse	200–700	M	Sugiyama et al. 1964	—
Azo dyes, trypanblue etc.	Rat	50	M (SP)	Beck and Lloyd 1966	—
Detergents					
— alkylbenzene sulphonate	Mouse	300	M (mouse TF)	Palmer et al. 1978a	—
— alcohol sulphate	Mouse	600	M (mouse TF)	Palmer et al. 1978a	—
— olefin sulphonate	Mouse, Rabbit	300–600	M (50–100%)	Palmer et al. 1978b	—
— Triton X	Mouse	200	M	Roussel and Eschbaum Duplessis 1968	—
7,12-Dimethylbenz(a)anthracene	Rat	0.25	M (100%)	Currie et al. 1970	—
Ethylenethiourea	Rat	80	M (50%)	Khera 1973b	—
Halothane	Rat	0.8%/12 h/day	M (skeletal SP)	Bruce and Fabro 1966	—
Hydrazine	Chick	2	M (SP)	Stoll et al. 1967	0.1 (3 ppm)
Pentachlorobenzene	Rat	200	M (81%)	Khera and Vallejo-Freire 1978	—
Tetrachlorodibenzo-p-dioxin (2,3,7,8-)	Mouse	0.1–0.6	M (cranial skeletal SP)	Neubert et al. 1973	—
Tetrachlorophenol	Rat	30	Teratogenicity declared possible	Schwetz et al. 1978b	—
Thiurams					
— thiram	Hamster, Rat	250	M (50%)	Rudnai 1969	0.5 (2 mg/m³)
— thiram	Mouse	300–500	M (60%)	Ball 1973	
— disulfiram	Hamster	125	M (40%)	Rudnai 1969	

[a] [b] see Table 4

1,000 ppm, respectively. Urethane at a dose of 15 mg/kg has been found to be positive in the rat. Vinyl chloride has been tested in mice by inhalation exposure to 50 ppm and found to produce malformations, higher concentrations were found to cause skeletal anomalies in rats and rabbits.

Solvents

Solvents are a group of organic compounds, to which large numbers of employees are heavily exposed in many types of industries. Literature on the teratogenicity of the industrial solvents in laboratory animals was compiled in Table 5. Benzene was found to be positive in the mouse after a large injected dose. Minor skeletal malformations were observed in an inhalation exposure to 500 ppm. These doses are higher than the expected human exposures at TLV. Carbon disulfide, a solvent extensively used in the viscose rayon industry, was found to produce malformations at a relatively low dose of 100 mg/m^3 in the rat. Chloroform, previously used even in anaesthetics, was found to be teratogenic in rats at a 100 ppm concentration, a concentration only twice as high as the TLV of OSHA (1974). Dimethyl formamide, dimethyl sulfoxide, and propylene glycol have been tested at very high concentrations.

Chlorinated hydrocarbons make a large group of industrial solvents, which have been of concern because of the carcinogenic properties of some derivatives in this series. Methylene chloride, 1,1,1-trichloroethane, 1,1,2-trichloroethane, trichloroethylene, and tetrachloroethylene were found to cause malformations in chick embryos. Methylene chloride, thrichloroethylene, and tetrachloroethylene were tested in mammals, and a weak teratogenic activity was noted at relatively high doses. Toluene and xylene are among the most widely used industrial solvents, and the exposures in painting and printing are quite high. Minor skeletal defects were noted in rats exposed to toluene and xylene at 1,500 and 1,000 mg/m^3, respectively.

Other Organic Compounds

This section includes a number of compounds with large but versatile use. For most of these compounds no industrial standards have been set. Aminoazobenzene and other azo dyes, used on a large scale, have produced malformation in mice and rats. Detergents have a large application as washing powder and as industrial emulsifiers. Some detergents, such as alkylbenzene sulphonate, alcohol sulphate, olefin sulphonate, and Triton, were found to cause malformations or minor defects at high doses. 7,12-Dimethylbenz(a)anthracene, one representative of a large group of polycyclic aromatic hydrocarbons, was found to be a potent teratogen in the rat. Ethylenethiourea is used in the rubber industry and it is also a degradation product of the ethylenebisthiocarbamate group of fungicides. It was found to be teratogenic in rats at a dose of 40 mg/kg. Halothane caused skeletal malformations in rats inhaling it at 0.8% concentration. Hydrazine is commonly used as an oxygen trapping agent in water containers. It was found to be teratogenic in the chick. Pentachlorobenzene is used as fire retardant and fungicide. A dose of 200 mg/kg of pentachlorobenzene caused skeletal mal-

formations in the rat
contaminant in comm
such as 2,4,5-T. TCDi
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Conclusions

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formations in the rat. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a common contaminant in commercial polychlorinated phenols and chlorinated pesticides, such as 2,4,5-T. TCDD is an extremely potent teratogen producing malformations at a dose of 0.006 mg/kg. Tetrachlorophenol was tested for teratogenicity in the rat, and fetotoxicity and delayed ossification were observed with a dose of 30 mg/kg. The preparations were assayed for TCDD contamination (<0.05 ppm), and the authors concluded that the observed effects were mainly due to tetrachlorophenol. The two thiuram compounds, thiram and disulfiram, are used in the rubber industry, thiram also as a pesticide and disulfiram as a medicine. They were shown to be teratogenic to several species at high doses.

Conclusions

The most hygienic standards and norms have been established to protect most of the workers from acute toxicity of industrial exposures. Teratogenic properties of industrial compounds have not been an important factor influencing the setting of the hygienic standards. This is understandable as very few epidemiological studies are available to show an association between a parental occupational exposure and malformations in the offspring. Moreover, the power of the animal tests has not been firmly established.

The present analysis suggested, based on the limited data available in the literature, that the human embryo is at least as sensitive as the embryos of the common laboratory animals. However, the thalidomide studies appear to justify even more conservative safety factors as the human embryo was about 50 times more sensitive to this drug than the rat and mouse embryo. Other factors that should be taken into account in the setting of hygienic standards are the metabolic heterogeneity of the human populations and the chronic exposure of the humans. The metabolic heterogeneity implies that the sensitivity of the individuals may vary extensively. Thus, hygienic standards attempting to provide absolute safety have to take such variation into account. Chronic exposure of the humans may lead to the accumulation of the compound and the short-term animal experiment cannot predict the levels attained.

The review of the teratogenicity tests indicated that the effective concentration of the metals in animal tests generally exceeded the calculated human exposures by about 100 times or more. By contrast, many organic compounds had generally such high TLV values that they probably do not guarantee the safety of the developing human embryo exposed in utero. Particularly, the present standards of acrylonitrile, methacrylate esters, styrene, carbon disulfide, chloroform, methylene chloride, and possibly of toluene and xylene may not provide an absolute safety of the human embryo, as extrapolated from the results of the animal experiments. Even though the extrapolation from animal tests is compounded by uncertainties, the revision of the hygienic standards concerning the pregnant worker appears justifiable in such cases.

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