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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

SPECIFICATIONS FOR IDENTITY AND PURITY OF FOOD ADDITIVES AND OTHER TOXICOLOGICAL EVALUATIONS: SOME EXTRACTION SOLVENTS AND CERTAIN OTHER SUBSTANCES

AND

GENERAL CONSIDERATIONS ON ADDITIVES IN BABY FOOD

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DICHLOROMETHANE
(Methylene chloride)

by

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Biological Data

Biochemical aspects

Dichloromethane (CH_2Cl_2) is rapidly absorbed by the lungs (70-75% of the inhaled vapour), uniformly distributed in organs and rapidly excreted via the lungs and in the urine. It is largely excreted unchanged (von Oettingen et al., 1949; Riley et al., 1966). Because chlorinated hydrocarbon extraction solvents can react with -SH groups of protein aminoacids, the reaction of dichloromethane with L-cysteine was studied. The theoretical reaction product is dicysteic acid (1,1-di-(1,1-aminocarboxy -2 thiaethyl)-methane) with an acute oral LD_{50} of >10 g/kg body weight in mice. Under normal technological conditions practically none is found in the extracted material (Klimmer, 1970). Absorbed dichloromethane is probably hydrolyzed in the liver to formaldehyde and HCl. Some of it also reacts with -SH groups of liver enzymes e.g. coenzyme A (Heppel and Porterfield, 1948).

Acute toxicity

Animal	Route	LD_{50}	LD_{100}	Reference
Mouse	inhalation	56 mg/l air	-	Svirbely et al.,1947
	inhalation	-	14 500 ppm	Flury & Zernik, 1931
	i.p.	1.5 ml/kg	-	Klaassen & Plaa,1966
	s.c.	76 m moles/kg	-	Kutob & Plaa, 1962
Rat	oral	2 g/kg	-	Klimmer, 1970
	oral	1.6-2 g/kg	-	Dow Chemical Co.,196
Guinea pig	inhalation	-	50 000 ppm	Nuckolls, 1933

Animal	Route	LD_{50}	LD_{100}	Reference
Rabbit	oral	-	1.9 g/kg	Spector, 1956
Dog	oral	-	3 g/kg	Barnes & Sand, 1954
	i.v.	-	200 mg/kg	Barnes & Sand, 1954
	i.p.	-	0.45 ml/kg	Klaassen & Plaa, 1967
	s.c.	-	2.7 g/kg	Barnes & Sand, 1954

This substance is a fairly strong but very volatile narcotic with an excitement stage, seen especially in rabbits and dogs, and incoordination in rats (Browning, 1965; Elkins, 1950). Mice were exposed to the [illegible] vapour concentration for 24 hours and their SGPT elevation was determined to estimate hepatotoxic potential. This was found to be low (Gehring, 1968). Administration i.p. to mice of 1.5 ml/kg produced albuminuria in 50% of animals with a decreased BSP excretion (Plaa & Larson, 1965). Administration i.p. of the LD_{50} to mice had no effect on BSP retention or SGPT activity. The livers appeared histologically normal, but the kidneys showed occasionally minimal necrosis of convoluted tubules (Klaassen & Plaa, 1966). Administration s.c. to mice of the LD_{50} caused some prolongation of pentobarbital sleeping time, little change in BSP retention with normal liver histology (Rutob & Plaa, 1962).

Oral administration to rats of 11.8 m moles/kg by gavage had no effect on liver glutathione levels (Johnson, 1965). Inhalation of 5000 ppm in air by rats for 7 hours depressed the activity of rats as measured on activity drums although normal inspection showed no abnormality (Heppel & Neal, 1944). Higher levels reduce blood pressure and may injure the myocardium (von Oettingen, 1955). Administration i.p. to dogs of the LD_{50} produced elevation of SGPT in 50% of animals. No histological liver necrosis was seen but moderate neutrophil infiltration of the sinusoids. Renal histology was normal (Klaassen & Plaa, 1967).

Use as anaesthetic in man caused prenarcotic excitement but no other ill effects (Grasset and Gauthier, 1950). Excessive inhalation (2300 ppm) produces nausea, vomiting, also acute bronchitis and irritation of the conjunctiva and nose with some anaemia (Moskowitz and Shapiro, 1952). Most commonly drunkenness is produced (Patty, 1958). If confined on the skin it is only absorbed to a small degree but causes considerable irritation (Torkelson et al., 1966). The TLV is 500 ppm (Patty, 1958). Spice oleoresins may have 30 ppm and decaffeinated coffee 10 ppm as residue (FDA, 1967).

Short-term studies

Rat

Four groups of 30 male and 30 female rats received either plain water, 4% alcohol, beer made with natural hops and beer made with a hop extract containing 2.2% dichloromethane for 13 weeks. However, no residues of dichloromethane were detectable in the beer. No difference was noted between test and control groups as regards haematology, urine analysis, major organ weights, blood chemistry and histology except for the expected fatty changes in the liver of the three test groups. The thyroids of the two test groups on beer had significantly smaller weights than the other two groups. No evidence of toxicity appeared in beer made with hop extract using dichloromethane (Bornmann et al., 1968).

2 groups of 60 rats each received for 3 months as drinking fluid either water, or the infusion containing 0.6% or 0.01% of aqueous dichloromethane. No significant differences were seen between test and control animals as regards growth or other biological findings (Lester, 1966).

Long-term studies

F 1

Groups of rats received daily by gavage 0, 0.5 ml or 1 ml of an aqueous solution equivalent to 0, 0.05 or 0.1 g dichloromethane for 2 years. No abnormal increase of tumours or any adverse effect on fertility and rates of F_1 and F_2 generations were seen. No adverse findings were registered in respect of general behaviour, weight gain, macroscopic and microscopic appearance of major organs, haematology, serum proteins and urinalysis (Hoesinger, 1966).

Hamster

Groups of hamsters received by daily gavage 0, 0.5 ml or 1 ml of aqueous solution corresponding to 0, 0.05 or 0.1 g dichloromethane for 2 years. No adverse findings were noted with regard to tumour incidence, fertility, appearance of F_1 and F_2 generation, general behaviour, weight gain, macroscopic and microscopic appearance of major organs, haematology, serum proteins and urinalysis (Hoesinger, 1966).

Special studies

Rats, rabbits, dogs and guinea pigs were exposed to dichloromethane up to 5000 ppm for varying periods up to 6 months. No serious adverse effects were seen except for occasional pulmonary oedema with focal necrosis and fatty degeneration of the liver. Reproduction was unaffected (Heppel et al., 1944).

Rabbit skin was treated with 0.5 g/kg for 5 days per week for 90 days without any adverse effects (Dow Chemical Co., 1966).

Human observations

4 human subjects had the skin of their thumb immersed in methylenechloride for 30 minutes. The mean peak alveolar concentration during exposure was 3 ppm. This fell to 0.7 ppm 2 hours after the exposure (Stewart & Dodd, 1964).

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