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1,1,2-TRICHLOROETHYLENE
(Trilene)

by

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(Consultant).

Biological Data

ASI 00004260

Biochemical aspects

Probably between 71-75% of inhaled trilene is rapidly absorbed through the lungs. In man most absorption occurs within the first few minutes of exposure and then decreases to an equilibrium between air/blood concentrations. Measurable absorption can occur through intact skin and from the gastro-intestinal mucosa after ingestion (von Oettingen, 1955).

In the rat, rabbit and dog absorbed trilene is distributed among all organs and tissues but concentrates mostly in fat and brain and less in skeletal muscle, lung and liver also retain low levels (Barrett et al., 1939; Clayton & Pantheuse, 1962; von Oettingen, 1955). Similar organ concentrations were found in guineapigs but high levels were also found in ovaries and adrenals (Fabre & Truhaut, 1952). In the rat trilene and trichloracetic acid may be selectively bound to erythrocytes hence giving high spleen levels (Fabre & Truhaut, 1952) but plasma proteins may also be involved (Soucek & Vlachová, 1960). In man trilene is detectable in the blood within 30 minutes of inhalation (Stewart et al., 1962).

Trilene is metabolised slowly to chloralhydrate (via an epoxide) and then rapidly to 2,2,2-trichloracetic acid (CCl_3COOH) and 2,2,2-trichloroethanol (CCl_3CH_2OH), which latter two metabolites are excreted as urinary glucuronides (e.g. trichloroethanol glucosiduronic acid) very little unchanged trilene appearing in the urine (Powell, 1941; Butler, 1949; Uhl & Haag, 1953; Williams, 1959; Smith, 1966). Dogs excrete 5-6% of absorbed trilene as trichloracetic acid and 15-20% as trichloroethanol up to 4 days after exposure (Barrett et al., 1939; Barrett & Johnson, 1939; von Oettingen, 1955). The lung and spleen, less so the liver are probably the main sites of metabolism

(Fabre & Truhaut, 1962; Defalque, 1961). Rats exposed for 4 hr to inhaled trilene as trichloro- [illegible] in urine [illegible] (Ahlmark, 1950). [illegible] oral [illegible] trichloroethanol [illegible] (Daniel, 1963; Defalque, 1961). [illegible] (Daniel, 1963). [illegible] in the blood (3.4%) [illegible] (10% [illegible]), 0.4% in the tissues and 7% [illegible] in the original dose. The metabolites were formed by intracellular [illegible] and were excreted for up to 14 days after single [illegible] (Fabre & Truhaut, 1962). In vitro studies on rat liver microsomes showed conversion of trilene [illegible] (Fabre & Truhaut, 1962). Rabbits excrete 0.5% of absorbed trilene as trichloroacetic acid (Fabre & Truhaut, 1962; Defalque, 1961) and after oral dosing by [illegible] as much as urochloralic acid, blood, glucose [illegible] or neutral [illegible] (Fabre et al., 1962). Cats display slow presence of trichloroacetic acid [illegible] urine after inhalation (Fabre & Truhaut, 1962). Calves exhibit metabolism [illegible] trilene to trichloroacetic acid (1%) and trichloroethanol (13-25%) appearing in their urine together with a trace of trilene. The balance is probably exhaled or excreted in the faeces (Soto & Schultze, 1955).

Man excretes 6%-16% of inhaled trilene as trichloroacetic acid (Ahlmark and Forssman, 1951); others found 7%-27% of retained trilene being excreted as trichloroacetic acid (Powell, 1945; Bouček et al., 1954) as well as trichloroethanol, monochloroacetic acid and chloroform (Bouček et al., 1972; Defalque, 1961). Small amounts of trichloroacetic acid may continue to be excreted in the urine for up to 12 days after single exposure (von Oettingen, 1955). 5 human subjects exposed for 5 hours to trilene excreted 4% of the retained dose as monochloroacetic acid, 19% as trichloroacetic acid and 9% as trichloroethanol over the next 14 days (Bouček & Vlachová, 1960; Defalque, 1961). In another experiment 6 subjects inhaled trilene for 5 hours. 51-64% of the inhaled trilene was retained the rest [illegible] exhaled unchanged. Of the retained trilene 38-50% was excreted as urinary trichloroethanol and 27-36% as urinary trichloroacetic acid. 8.4% of trichloroacetic acid and trichloroethanol was excreted in the faeces. Sweat and saliva contained also both metabolites (Bartoníček, 1962). In all species most of the trichloroacetic and trichloroethanol is excreted in the first 2 days after exposure but excretion may go on up to 52 days. Some 2-4 hours elapse after single exposure before trichloroacetic acid appears in the blood reaching a maximum in 20-50 hours (Ahlmark & Forssman, 1951; Defalque, 1961). Trichloroethanol appears to be the main metabolite and is much more toxic (Bartoníček & Teisinger, 1962). Disulfiram decreases the excretion of trichloroacetic acid and trichloroethanol by acting either on converting enzymes or on trilene released from fat depots (Bartoníček & Teisinger, 1962) while glucose and insulin increase production (Bouček & Vlachová, 1960).

Chronic exposure may cause disturbance of protein metabolism by an increase in the β-globulin to 16%-21% (normal 10%-14%) and in fat metabolism by an increase in unsaturated fatty acids (Guyot-Jeannin & Van Steenhiste, 1958). Repeated inhalation or oral ingestion by rats causes transitory elevation of SGOT levels for 24 hours after the last exposure, the SGPT levels remaining normal. SGOT levels return to normal within 9 days after exposure. No such transitory effects are seen in rabbits (Tolot et al., 1966; Viallier & Casanova, 1965). Previous ingestion of ethanol potentiates trilene toxicity in rats as shown by a rise in SGOT, SGPT and SICD (isocitric dehydrogenase) and wide-spread degenerative lipid infiltration as well as early centrilobular necrosis of the liver (Cornish & Adefuin, 1966).

Single exposure of mice to the inhalation LD_{50} of trilene showed some hepatotoxicity as evidenced by a rise in SGPT (Gehring, 1963).

[illegible] fatal [illegible] in higher [illegible] (Plaa & Larson, 1965). [illegible] has no effect on the liver [illegible] levels (Jenner, [illegible].

[illegible] a variety of the [illegible] (0.1 [illegible], 1961). [illegible] R.S. [illegible] (Defalque [illegible] [illegible] (von Oettingen, [illegible]). [illegible] air (Bloomfield & [illegible], 1963).

Acute Toxicity

Animal	Route	LD_{50} ml/kg bodyweight	$LD_{[illegible]}$	Reference
Mouse	inhalation	-	7000 ppm (2 hrs)	von Oettingen, 1955
	s.c.	11.0	-	Plaa et al., 1958
	i.p.	2.2	-	Klaassen & Plaa, 1966
Rat	oral	4.92	[illegible]	Smyth et al., 1969
	inhalation	-	20000 p[illegible]	Adams et al., 1951
Guineapig	inhalation	-	37000 p[illegible] (40min)	von Oettingen, 1955
Rabbit	s.c.	-	1800 [illegible]	Darsow & Saad, 1934
	inhalation	-	11000 [illegible]	Bernardi et al., 1956
	percutaneous	> 20	-	Smyth et al., 1969
Dog	i.v.	-	150 mg/[illegible]	Berrow & Saad, 1957
	i.p.	1.9	-	Klaassen & Plaa, 1966

Mice, rats, guineapigs and rabbits dying acutely from inhalation, show no toxic effects on the tissues, liver or kidney nor after s.c. or i.v. administration (Browning, 1965). I.p. injection of 2.5 ml/kg trilene in mice had no effect on PSP excretion and produced no proteinuria or glycosuria nor histological renal changes (Plaa & Larson, 1965). Oral doses of 3-4 ml/kg bodyweight were fatal to rats, mice and guineapigs with signs of gastro-intestinal irritation (von Oettingen, 1955). Chronic oral poisoning has caused some liver and renal damage in dogs and rabbits (von Oettingen, 1955).

Acute human poisoning cases have recovered without hepatic or renal sequelae. After ingestion there is some burning of the oral mucosa, later nausea and vomiting with vertigo, ataxia, somnolence, confusion, delirium and coma (Browning, 1965). Excessive inhalation has been blamed for hepato-nephritis but the incidence is very low and it is possible that liver and renal involvement are the result of underlying previous disease (Roche et al., 1958). Untoward effects on the circulation, cardiac irregularities and excessive capillary oozing with tachycardia but no adverse hepatic effects have been reported after anaesthetic use (von Oettingen, 1955). Ingestion of 60 ml appears to be fatal in man (Pebay-Peyroula et al., 1966). At elevated temperatures trilene reacts with soda lime to form dichloroethylene and this reacts further to generate phosgene carbonylchloride and various acids which are all toxic (Defalque, 1961). The present FLV is 100 ppm, in Sweden 30 ppm, in USSR 6 ppm (Browning, 1965). Spice oleoresins may contain a maximum of 30 ppm, decaffeinated ground coffee 25 ppm and decaffeinated soluble coffee extract 10 ppm (FDA, 1963).

[illegible] is a local irritant on the skin, causing [illegible] and necrosis in man and dermatitis with ulceration in rabbits (von Oettingen, 1955).

Chronic Toxicity

None available

Long-Term Studies

None available.

Special Studies

Observations in animals exposed for varying periods up to ten months show disturbed coordination and hyperexcitability but no effects on liver or kidney or blood chemistry. Only the CNS showed some oedema and ganglion cell degeneration (Browning, 1965). Mice, guinea-pigs, rats, rabbits and dogs were exposed to 3,415 mg/m^3 for 6 weeks without significant adverse effects. Exposure to 189 mg/m^3 for 90 days also revealed no significant pathological changes (Svensgaard et al., 1967). Groups of 20 mice were exposed for 1-8 weeks to 200 or 1600 ppm daily for 4 hours. Only slight transient fatty hepatic degeneration and no renal effects were seen (Nylin et al., 1965).

Guinea-pigs were exposed to vapour of trilene for 2½ - 4 months without adverse effects on bodyweight, haematological findings or urinalysis results but there was slight evidence of hepatic parenchymal degeneration and renal glomerular and tubular degeneration (Lande et al., 1937). Rabbits given for 1 - 5 months 0.074 g/kg trilene showed little adverse effect on bodyweight, haematological finding, urinary analysis but some hepatic and renal lesions were seen (Lande et al., 1939). Dogs were exposed to 100-750 ppm daily for 2-8 weeks. Hepatic injury as evidenced by BSP excretion, glycogen depletion and parenchymal degeneration as well as weight loss, lethargy and diarrhoea occurred but cleared on stopping exposure (Seifter, 1944).

Soyabean meal extracted with trilene but not with hexane or carbon tetrachloride has caused fatal refractory haemorrhagic aplastic anaemia in cattle (Picken et al., 1955). The toxic factor was shown to be associated with the protein fraction (Soto et al., 1953). Similar effects were produced by trilene-extracted meat scrap (Rehfeld et al., 1958). However, chicks fed trilene-extracted meat scraps showed improved growth (Balloun, et al., 1955). The toxic factor has been identified as S-trans-(dichlorovinyl)-L-cysteine, a reaction product of trilene and protein which becomes freed on protein hydrolysis (McKinney et al., 1957).

Groups of 20 male and female rats were fed instant decaffeinated coffee solid extracted with trilene for 2 years at 0% or 5% of their diet (equivalent to a residue of 0.5 ppm trilene in the diet) without deleterious effects on survival, behaviour, growth, food consumption, urinalysis, haematology, organ weights and histopathological findings (Zeitlin, 1963).

8 males and 16 female rats were fed on a diet containing 0% or 5% of instant decaffeinated coffee solids extracted with trilene (equivalent to a residue of 0.5 ppm trilene in the diet). 2 generations were studied as regards paternal and filial mortality, conception rate, resorption, litter size, growth and survival of litter. Organ weights, blood chemistry, urinalysis and histopathology of the F_2 generation were normal (Zeitlin, 1967).

A teratogenicity study in rats fed 5% of trilene [illegible] decaffeinated coffee solids [illegible] of 0.5 ppm trilene) [illegible] 2 weeks before mating until the 20th day of [illegible]. Foetuses were examined and [illegible]. No abnormalities or deformities were noted in the [illegible]. [illegible] (Schultz, 1976).

[illegible]

There is much [illegible] of trilene as an anaesthetic for man and from [illegible] other [illegible] e.g. [illegible] (see [illegible], 1955). Some authorities recognise a [illegible] (Goodman, 19[illegible]) others admit only to a [illegible] 1957). [illegible] or the liquid [illegible]. No evidence exists of serious haematological effects. Neurological disturbances are similar to neurasthenic conditions with rarely apparent cardiac disturbances. Trigeminal palsies and optic nerve involvement may have been due to impurities but have not been seen with pure material. Irritation of the lungs and gastro-intestinal symptoms have been reported after industrial overexposure. Addiction has been reported (Cardaci j & Vyskocil, 1956; Browning, 1965; [illegible], 1953; Defalgue, 1961; Milby, 1968; Mitchell & Parsons-Smith, 1969). Psychomotor performance is not affected by exposure to 100 ppm but there is a decline in performance at higher inhalation levels (Stopps & McLaughlin, 1967).

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