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Embryotoxicity and Fetotoxicity of Inhaled or Ingested Vinylidene Chloride in Rats and Rabbits[1,2]

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Embryotoxicity and Fetotoxicity of Inhaled or Ingested Vinylidene Chloride in Rats and Rabbits. MURRAY, F. J., NITSCHKE, K. D., RAMPY, L. W., AND SCHWETZ, B. A. (1979). *Toxicol. Appl. Pharmacol.* 49, 189–202. The teratogenic potential of inhaled or ingested vinylidene chloride was evaluated in Sprague–Dawley rats and New Zealand white rabbits. Both species were exposed to the test material by inhalation for 7 hr/day at concentrations of 20 (rats only), 80, or 160 ppm. For the ingestion study, rats were given drinking water containing 200 ppm vinylidene chloride. Rats were given vinylidene chloride from the 6th to the 15th days of gestation and rabbits on the 6th to the 18th days. A teratogenic effect was not seen in rats or rabbits inhaling concentrations of up to 160 ppm vinylidene chloride for 7 hr/day or in rats given drinking water containing 200 ppm vinylidene chloride. Toxicity to both the dams and their developing embryos was observed among the rats inhaling 80 or 160 ppm and among the rabbits inhaling 160 ppm. At exposure levels which caused little or no maternal toxicity (20 ppm in rats and 80 ppm in rabbits), there was no effect on embryonal or fetal development. Among the rats given drinking water containing 200 ppm VDC, there was no evidence of toxicity to the dams or their offspring.

Vinylidene chloride (1,1-dichloroethylene, VDC, $CH_2{=}CCl_2$) is used in the manufacture of various plastics, including films and coatings for food packaging. Reports on the acute toxicity of vinylidene chloride in laboratory animals have indicated moderate toxicity when given by inhalation or by gavage (Carpenter *et al.*, 1949; Rylova, 1953; Siegel *et al.*, 1971; Jenkins *et al.*, 1972; Jaeger *et al.*, 1973). Exposure by inhalation to 100 ppm vinylidene chloride for 6 weeks resulted in some weight loss in rabbits and monkeys, but not in rats, guinea pigs, or dogs (Prendergast, 1967). Rats exposed for up to 4 weeks to 500 ppm vinylidene chloride exhibited nasal irritation, decreased weight gain, and liver cell degeneration; at 200 ppm, the only sign of toxicity was slight nasal irritation (Gage, 1970).

Vinylidene chloride has been shown to be a weak mutagen in certain strains of bacteria (McCann *et al.*, 1975; Greim *et al.*, 1975; Bartsch *et al.*, 1975). This effect was seen in bacterial systems only under conditions of activation with microsomal enzymes, implicating a metabolite of vinylidene chloride rather than vinylidene chloride itself as the causative agent.

No information regarding the teratogenic potential of vinylidene chloride was found in

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Vinylidene chloride

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Saturable Metabolism and the Acute Toxicity of 1,1-Dichloroethylene[1,2]

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Saturable Metabolism and the Acute Toxicity of 1,1-Dichloroethylene. ANDERSEN, M. E., FRENCH, J. E., GARGAS, M. L., JONES, R. A., AND JENKINS, L. J., JR. (1979). *Toxicol. Appl. Pharmacol.* 47, 385–393. The toxic effects of single, oral doses of 1,1-dichloroethylene (1,1-DCE) are caused by its metabolites. When saturable, enzymatic production of a toxic intermediate regulates toxicity, the observed inhalation toxicity, at sufficiently high concentrations, will depend on the duration of exposure and be relatively independent of the ambient concentration. The inhalation toxicity of 1,1-DCE was examined in fasted male rats to ascertain its dependence on both 1,1-DCE concentration and the duration of exposure. Immature rats (100–150 g) were exposed to 200 ppm 1,1-DCE for durations up to 2 hr. Pentobarbital sleep times (PBST) were significantly increased after exposures as brief as 0.5 hr. Intubation of immature rats with 1,1-DCE produced extensive dilation and vacuolization of the endoplasmic reticulum (ER). While young rats were more susceptible to 1,1-DCE than older rats (> 200 g), extensive damage to the ER (the presumed site of 1,1-DCE metabolism) during exposure precluded their use in determining the inhalation dose–effect curves. With older rats, PBST were not increased during exposure. The concentration–mortality curve for 4-hr exposures increased sharply between 100 and 200 ppm, but was virtually flat (i.e., concentration independent) between 200 and 2000 ppm. The LT50 (the time of exposure required to kill half an exposed group at a given concentration) only varied between 4.1 and 2.4 hr as concentration increased from 200 to 2000 ppm. Failure of 1,1-DCE to adhere to a concentration × time relationship is further evidence of a role of saturable, enzymatic activation in the expression of its toxicity.

The overall toxicity of any particular chemical represents a composite of effects caused by the chemical and those attributable to metabolites produced from that chemical by the species under investigation. In many cases, the metabolites are more toxic than the parent chemical (Magee, [illegible]). This is true for carbon tetrachloride (Slater, [illegible]), bromobenzene ([illegible] et al., [illegible]), aflatoxin (Garner et al., [illegible]), dimethylnitrosamine (Barnes, [illegible]), and polycyclic hydrocarbons (Boyland, [illegible]). The importance of knowledge of metabolism to the overall understanding of toxicity has been widely recog-

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