Vinylcyclohexene

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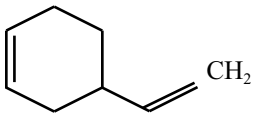
I. IDENTIFICATION[1–3]

Chemical Name: Vinylcyclohexene
Synonyms: 4-vinyl-1-cyclohexene; 4-vinylcyclohex-ene-1; butadiene dimer; 4-ethenyl-1-cyclohexene; 1-vinyl-3-cyclohexene; VCH
CAS Number: 100-40-3
Molecular Formula: C_8H_{12}
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–4]

Physical State: Clear to slightly yellow liquid
Odor: Sweet aromatic, very evident at 0.5 ppm. Odor threshold data are not available.
Molecular Weight: 108.18
Conversion Factor: 1 ppm v/v = 4.4 mg/m^3; 1 mg/m^3 = 0.2 ppm
Melting Point: -108.7°C (-163°F)
Boiling Point: 128.9°C (264°F)
Vapor Pressure: 15 mmHg at 25°C (77°F)
Saturated Vapor Concentration: 20,000 ppm at 25°C (77°F)
Flash Point: 21°C (69.8°F) Tag open-cup; 16°C (60.8°F) closed cup
Autoignition Temperature: 269°C (516°F)
Specific Gravity: 0.826 g/L at 25°C (77°F)
Solubility: Slightly soluble in water;
Vapor Density: 3.67 (air = 1)

III. USES[3,4]

4-Vinylcyclohexene (VCH), a dimer of 1,3-butadiene, is an intermediate in the production of vinylcyclohex-ene dioxide, which is used to manufacture epoxy resins. It is also used as a solvent and in the synthesis of synthetic rubber, flame retardants, flavors, fra-grances, and polyolefins. Commercial material con-tains up to 3% 1,5-cyclooctadiene and trace levels of antioxidants such as butylated hydroxytoluene (BHT) to prevent peroxide formation.

IV. ANMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

Rat: LD_{50} 2,550 mg/kg[5]

2. *Eye Irritation*

Rabbit: Moderate irritation, slight corneal injury.[5]

3. *Skin Absorption*

Rabbit: LD_{50} 16,520 mg/kg[5]

4. *Skin Irritation*

Rabbit: Moderate irritation[5]

5. *Skin Sensitization*

No data found for VCH.

6. *Inhalation*

Rats:	4-hr LC_{50}	6,095 ppm[6]
Rabbits:	4-hr LC_{50}	8,000 ppm[6]
Mice:	4-hr LC_{50}	10,610 ppm[6]

B. Subacute Toxicity

In a range-finding study, VCH was administered to male and female Fischer 344 rats and B6C3F1 mice by gavage in corn oil for 14 days at dosages of 0, 300, 600, 1250, 2500, or 5000 mg/kg/day. A significant incidence of mortality was observed in both rats and mice by the end of the study in ani-mals receiving dosages of 1250 mg/kg/day or higher. Body weights in surviving animals did not differ from controls. No treatment-related gross changes were observed at necropsy and no micro-scopic changes were noted in the stomach, the only tissue evaluated in this range-finding study.[4,7]

C. Subchronic Toxicity

A 13-week inhalation study was conducted with Sprague-Dawley rats and B6C3F1 mice. Rats were exposed for 6 hours/day, 5 days/week to concentrations of 0, 250, 1000, or 1500 ppm. Mice were exposed to 0, 50, 250, or 1000 ppm. Separate groups of rats and mice were also exposed to 1000 ppm butadiene to allow comparisons with VCH. In rats, lethargy, lower body weights, increased liver and kidney weights (males only) and hyaline droplet accumulation in the kidneys (males only) were observed at 1500 ppm. The latter is a well-recognized species and sex-specific effect. In mice, deaths, lethargy and ovarian atrophy were observed at 1000 ppm. Ovarian atrophy was also observed in butadiene-exposed mice, but the severity of ovarian damage was greater in the VCH-exposed mice. The NOAELs in rats and mice were 1000 and 250 ppm, respectively.[8]

Male and female Fischer 344 rats were dosed 5 days/week, for 13 weeks, by gavage with 50, 100, 200, 400, or 800 mg/kg/day VCH. Male and female B6C3F1 mice were dosed at the same schedule with 75, 150, 300, 600, or 1200 mg/kg/day. Final body weights were reduced in male rats receiving 400 or 800 mg/kg/day, in female rats receiving 800 mg/kg/day, and in female mice receiving 600 mg/kg/day. Extensive mortality was observed only in mice dosed at 1200 mg/kg/day. Compound-related histopathologic effects in the 13-week studies included observations of hyaline droplet degeneration in the proximal convoluted tubules of the kidney in male rats, the severity of which was dose-related. A reduction in the number of primary follicles and mature Graafian follicles in the ovaries was seen in female mice receiving 1200 mg/kg/day. No compound-related gross or histopathologic effects were evident in female rats or male mice in the 13-week studies. The overall NOAEL in the 13-week studies was 200 mg/kg/day.[4,7]

The potential for VCH to produce ovarian toxicity is well established (see below). Special studies have been conducted to better understand the temporal aspects and mechanism-of-action of VCH-induced ovotoxicity. One study investigated the relationship between VCH-induced follicular destruction, plasma follicle stimulating hormone (FSH) levels and ovarian preneoplastic changes. Female B6C3F1 mice were given 800 mg/kg/day VCH, intraperitoneally, in sesame seed oil for 30 days and measurements were made at 30, 60, 120, 240, and 360 days following the beginning of treatment. At all time points, ovarian weights and oocytes contained in preantral follicles were significantly lower than controls. FSH was only increased at 240 and 360 days. Oocyte loss was observed at all times but small to medium irregularly shaped foci of hypertrophic cells were only present at 240 and 360 days. Blood-filled cystic structures were also seen at 360 days. The study showed that oocyte destruction and follicle loss were associated with increases in plasma FSH at the same time ovarian failure was observed.[9]

In a limited study conducted in the USSR, exposure of rats and mice to 226 ppm by inhalation for 6 hours/day over 4 months was reported to inhibit weight gain and cause leukocytosis, leucopenia, and impairment of hemodynamics.[6]

Overall, the inhalation LOAEL in subchronic studies was 226 ppm for hematological changes in rats and mice. The NOAEL of 250 ppm for ovarian atrophy was slightly higher than this value.

D. Chronic Toxicity and Carcinogenicity

VCH (with peroxide formation inhibitors) was administered by gavage in corn oil to $B6C3F_1$ mice of each sex at doses of 200 or 400 mg/kg/day, 5 days/week, for 103 weeks. Female mice showed clear evidence of a carcinogenic effect, as shown by increased incidences ($P < 0.01$) of uncommon benign and malignant ovarian neoplasms at both doses. The incidence of granulosa-cell tumors was 1/49, 10/48, and 13/47 in controls, at 200 mg/kg/day, and 400 mg/kg/day, respectively. The incidence of mixed tumors composed of germinal epithelial cells and granulosa cells was 0/49, 25/48, and 11/47. The incidence of granulosa cell carcinomas was 0/49, 1/48, and 2/47. A slight, but dose-related (0/50, 3/49, 4/48) increase in adrenal gland adenomas was also seen in female mice. Effects in male mice included marginal increases in malignant lymphomas and alveolar/bronchiolar adenomas/carcinomas, but the interpretation of these findings was confounded by the low survival in treated and control animals in this study. Because of the extensive mortality observed, the National Toxicology Program (NTP) concluded that the male mouse experiment was an inadequate study of carcinogenicity. Tumors have also been observed in the ovaries, skin, and lungs in studies conducted with the VCH-diepoxide and VCH-monomer (1,3-butadiene). Non-malignant changes observed in this study included inflammation, epithelial hyperplasia and ulceration of the forestomach (LOAEL=200 mg/kg/day). The WEEL Committee used the US EPA Benchmark Dose software to derive a benchmark dose (BMD_{10}) of 123 mg/kg/day, with a lower bound ($BMDL_{10}$) of 86 mg/kg/day, from the granulosa cell tumor data for female mice.[4,10]

Two-year oral gavage studies in male and female rats were considered inadequate studies of carcinogenicity because of early and extensive mortality in both control and experimental groups. However, the observation of clitoral gland tumors in females and skin tumors in males cannot be completely discounted.[4,10]

Application of VCH (45 mg) in benzene (0.1 mL per dose) to the skin of 30 Swiss mice 3 days/week, for 54 weeks, resulted in one squamous cell carcinoma. This effect may be attributed to contamination with small amounts of vinylcyclohexene hydroperoxide, a known carcinogen, that can be generated by auto-oxidation when VCH contacts oxygen.[11] In a subsequent study, "oxygen-free material" (0.1 mL of a 10% solution in benzene) was applied three times per week for life to 30 male Swiss mice. No carcinogenic effect was observed.[12]

In summary, in chronic/carcinogenicity studies, dosages as low as 200 mg/kg/day produced significant increases in benign and malignant ovarian tumors and other non-neoplastic changes in mice. A 10% increased incidence in granulosa cell tumors corresponds to an oral dose of 123 mg/kg/day, with an 86 mg/kg/day lower bound.

E. Developmental/Reproductive Toxicity

A continuous breeding protocol was used to evaluate the reproductive toxicity of VCH. Swiss (CD-1) mice were gavaged with 0, 100, 250, or 500 mg/kg/day for one week and then cohabited in breeding pairs for 14 weeks. Various parameters of reproductive capacity and performance were measured in the F0 and F1 animals. Despite measurable decreases in testicular spermatid count and reduced numbers of primordial, growing and antral oocytes at 500 mg/kg/day, there were no adverse effects observed on reproductive competence, including fertility, litters per pair, live litter size, or the proportion of pups born alive. There was an insignificant decrease (4%) in pup weight at 500 mg/kg compared to controls. The NOAEL for reproductive toxicity was 250 mg/kg/day.[13]

F. Genotoxicity

VCH was not mutagenic in *Salmonella typhiruriium* strains TA 100, TA 1535, TA 1537, or TA 98 in the presence or absence of rat or hamster liver S9. However a key metabolite, 4-vinylcyclohexene diepoxide, is mutagenic in *Salmonella* and has induced chromosomal damage and sister chromatid exchanges *in vitro*, but did not produce an increase incidence of micronuclei in mammalian cells *in vivo*.[4,14] In inhalation micronucleus tests, rats and mice exposed for 2 days at concentrations up to 1000 and 2000 ppm, respectively or for 13 weeks at concentrations up to 1000 and 1500 ppm, showed no statistically significant increases in micronucleated polychromatic erythrocytes.[15]

G. Metabolism and Pharmacokinetics.

Following a single oral dose of 400 mg/kg ^{14}C-labeled VCH in corn oil in B6C3F1 mice, and Fischer 344 rats, the T_{max} was between 1 and 2 hours. Ninety-five percent of the administered dose was eliminated within 24 hours in mice and within 48 hours in rats. VCH was shown to concentrate in adipose tissue (10-fold higher concentration compared to liver, skin and ovary) and was eliminated primarily in the urine (50–60%) and expired air (30–40%).[16] Microsomal enzymes metabolize VCH to 4-vinyl-1,2-epoxycyclohexane and 4-epoxyethyl-1,2-dihydroxycyclohexane with trace amounts (less than 0.001%) of vinylcyclohexene diepoxide being produced. In mouse microsomes, 4-vinyl-1,2-epoxycyclohexane is formed 13 times faster than in human microsomes and six times faster than in rat microsomes.[17] Administration of VCH can cause enzyme induction, resulting in increased production of VCH-diepoxide.[18–20] VCH was shown to induce the cytochrome P-450 isoforms in the ovaries of female mice that convert VCH to the mono- and diepoxides associated with ovarian toxicity.[21] Structure activity studies have demonstrated that the diepoxide is the most potent epoxide of VCH in producing ovarian toxicity.[22]

V. HUMAN USE AND EXPERIENCE

Average time-weighted average (TWA) exposures to VCH during synthetic rubber production were below 0.12 ppm.[23] A 1968 Russian publication on exposures at a manufacturing site indicates average exposures of 271–542 ppm. The study associated these exposures with reports of keratitis, rhinitis, headache, hypotonia, leucopenia, neutrophilia, lymphocytosis, and impairment of pigment and carbohydrate metabolism.[6]

VI. RATIONALE

VCH has a relatively low order of acute toxicity with an oral LD_{50} of 2550 mg/kg, a dermal LD_{50} of 16,520 mg/kg, and 4-hour LC_{50}s of 6095 to 10,610 ppm, but repeated exposure causes ovarian toxicity in rodents, including benign and malignant tumors in this organ. The chemical is moderately irritating to the eyes and skin. VCH is not mutagenic in the microbial mutagenicity assay but it can be metabolized to VCH-diepoxide, the predominant ovotoxic metabolite, which is genotoxic, and also presumed to be responsible for the tumors observed. Mice are more susceptible than rats and humans to the ovotoxic effects of VCH

because they metabolize VCH to the VCH-diepoxide much more rapidly and are less able to detoxify the reactive metabolite via an epoxide hydrolase. A physiologically-based pharmacokinetic model has not been developed to compare ovarian tissue doses in mice and humans at equivalent doses. The NOAEL was 250 mg/kg/day for effects on reproduction in mice. Hematological effects were noted in a subchronic study in rats at 226 ppm. NOAELs of 250 ppm and 200 mg/kg/day for ovarian toxicity were derived from 13-week studies in mice. Ovarian tumors were observed in the chronic gavage study in female mice at 200 and 400 mg/kg/day.[4,10] Using the NOAELs/LOAELs from the subchronic studies and the BMD_{10} of 123 mg/kg ($BMDL_{10}$ = 86 mg/kg/day lower bound) from the chronic/carcinogenicitiy study, an OEL guide of 1 ppm is recommended. This OEL incorporates uncertainty factors addressing interindividual variability, interspecies extrapolation and residual uncertainties regarding the production of the genotoxic VCH-diepoxide metabolite and the dose-response relationship for VCH-induced ovarian changes and tumorigenesis. Exposures may need to be controlled below the OEL because some individuals may find the odor objectionable at this level.

VII. RECOMMENDED OEL

8-hour time-weighted average (TWA): 1 ppm (4.4 mg/m^3)

VIII. REFERENCES

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