EPA/635/R-00/001

TOXICOLOGICAL REVIEW

OF

1,3-DICHLOROPROPENE

(CAS No. 542-75-6)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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contain confounding chemicals as well, as it is unstable when exposed to heat and oxygen or heat and light (Watson et al., 1987). Degradation products will also form at room temperature if dichloropropene is stored for several weeks in the presence of oxygen (Watson et al., 1987).

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

1,3-Dichloropropene toxicokinetics in humans appear to be similar to those observed in rodents. Inhalation studies with both humans and animals have shown that 1,3-dichloropropene vapors are readily absorbed, conjugated with glutathione (GSH) via glutathione S-transferase (GST), and rapidly excreted in the urine as N-acetyl-(S-3-chloroprop-2-enyl)cysteine (3CNAC), a mercapturic acid metabolite (see Figure 1). Thus, the major metabolic pathway for 1,3-dichloropropene leads to its detoxification and excretion. Ingestion studies in animals have demonstrated that the toxicokinetics of oral exposures are similar to those of inhalation exposures. 1,3-Dichloropropene is unlikely to accumulate in the body.

3.1. ABSORPTION

Stott and Kastl (1986) studied the inhalation pharmacokinetics of technical-grade 1,3-dichloropropene by exposing male Fischer 344 (F344) rats to mean vapor concentrations of 30, 90, 300, and 900 ppm (136, 409, 1,363, and 4,086 mg/m^3, respectively) for 3 hours. These air concentrations produced vapor uptakes of 147, 307, 880, and 1,810 nanomoles per minute, and corresponding absorption fractions of 82%, 65%, 66%, and 62%, respectively. Based upon the uptake of dichloropropene vapors, average amounts of dichloropropene absorbed by rats over the 3-hour exposure period were approximately 14, 29, 85, and 171 mg/kg in the 136, 409, 1,363, and 4,086 mg/m^3 exposure groups, respectively. Even though the rate of uptake increased with increasing exposure, the increase was not linear at higher concentrations. The decrease in vapor uptake at higher concentrations was associated with an exposure-related depression in ventilatory frequency, which was statistically significant at 409 mg/m^3 and higher. Stott and Kastl (1986) indicate that Alarie (1973) observed exposure-related depression in ventilatory frequency with numerous respiratory irritants; they suggest that 1,3-dichloropropene is a respiratory irritant.

The major site of absorption of inhaled 1,3-dichloropropene in the rat is the lung rather than the nasal mucosa (Stott and Kastl, 1986). The localized uptake of vapors in rats exposed to 90 or 150 ppm (409 or 682 mg/m^3, respectively) was examined by surgically isolating the upper and lower respiratory tract. The lower respiratory tract absorbed approximately 50% of inhaled dichloropropene vapors whereas the upper respiratory tract absorbed only 11%–16% of vapors. Total absorption rates were approximately 73% and 79% at 409 and 682 mg/m^3, respectively.

In 1992, Waechter et al. showed that absorption of 1,3-dichloropropene from inhalation exposure in humans was similar to absorption in rats (Stott and Kastl, 1986). Six male volunteers were exposed to 1 ppm (4.54 mg/m^3)[1] commercial Telone II® (50.6% cis isomer,

[1]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25^o C.

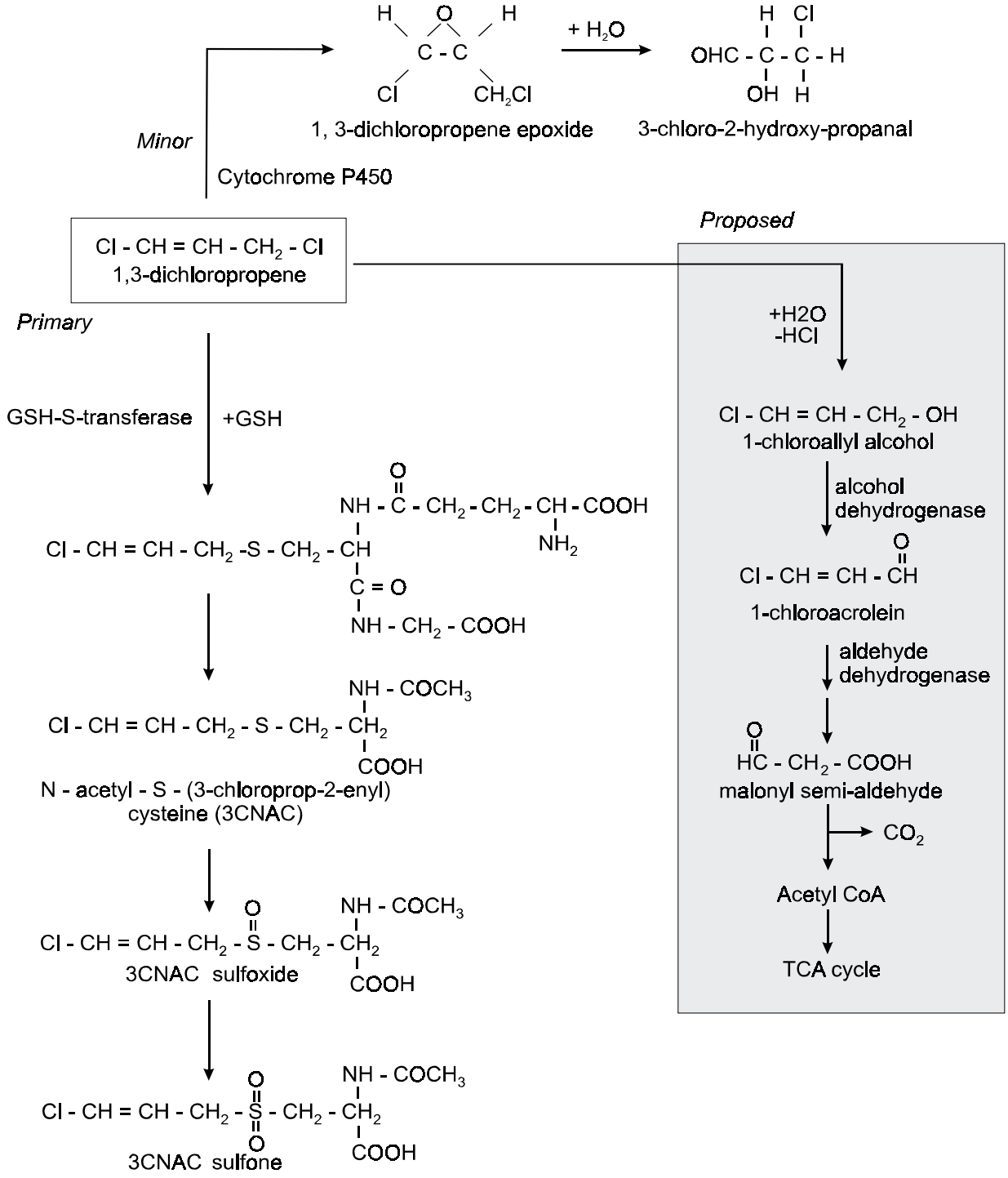

Figure 1. Metabolic pathways for 1,3-dichloropropene. Derived from Waechter and Kastl (1988) and Schneider et al. (1998a).

mg/m^3 and increased to more than 14 minutes for animals exposed to 4,086 mg/m^3. Rats exposed to trans-dichloropropene had a longer first-phase elimination half-life, averaging 6 minutes for the 136, 409, and 1,363 mg/m^3 groups and 27 minutes for the 4,086 mg/m^3 group. Following this first phase, both cis- and trans-dichloropropene exhibited a second, slower and longer phase of elimination in rats exposed to 1,363 or 4,086 mg/m^3, roughly 25 to 43 minutes, independent of isomer or exposure concentrations. The initial phase of elimination primarily represents the redistribution of dichloropropene from blood to tissues, whereas the second phase of elimination is determined by the rate of metabolism. Disproportionately large increases in blood levels at the end of exposure occurred in rats exposed to 4,086 mg/m^3 cis-dichloropropene and 1,363 and 4,086 mg/m^3 trans-dichloropropene, which indicated nonlinear elimination at high exposures. The longer half-lives and disproportionately higher blood levels at the higher doses suggest that metabolism was saturated. The data also indicate that elimination of dichloropropene at lower exposure levels is mediated primarily via metabolism and not via simple exhalation of the parent compound, a result consistent with Hutson et al. (1971).

In the human study by Waechter et al. (1992), urinary excretion of 1,3-dichloropropene was an apparent first-order process at an inhalation exposure of 4.54 mg/m^3 for 6 hours. The elimination half-lives for the initial phase were 4.2 ± 0.8 hours for the cis isomer and 3.2 ± 0.8 hours for the trans isomer, whereas the half-lives for the terminal phase were 12.3 ± 2.4 hours (cis isomer) and 17.1 ± 6 hours (trans isomer).

Fisher and Kilgore (1988a) conducted a series of experiments to assess the relationship among dichloropropene inhalation, GSH reduction in tissues, and serum lactate dehydrogenase (LDH) activity. These studies demonstrate that very high inhalation exposures of dichloropropene are required to produce significant decreases in GSH in all target organs except nasal tissue. It should be noted that the technical-grade dichloropropene used in this study and others by Fisher and Kilgore (1988b, 1989) contained epoxidized soybean oil as the stabilizing agent instead of epichlorohydrin. Male Sprague-Dawley rats were exposed to 1,3-dichloropropene for 1 hour at average concentrations of approximately 0, 2, 5, 33, 306, 771, 954, or 1,716 ppm (0, 8, 20, 150, 1,390, 3,504, 4,334, or 7,791 mg/m^3, respectively)[2] for determination of GSH levels in the heart, kidney, liver, lung, and testes; 0, 5, 31, 70, or 222 ppm (0, 24, 143, 320, or 1,012 mg/m^3, respectively)[2] for measurement of GSH levels in nasal tissue; and 0, 25, 660, or 2,277 ppm (0, 113, 2,995, or 10,336 mg/m^3, respectively)[2] for assessment of lung dry weight/wet weight and serum LDH activity. The principal tissue affected by low exposure concentrations was nasal tissue. GSH in nasal tissue decreased in a concentration-dependent fashion to 27% at 24 mg/m^3, 23% at 143 mg/m^3, 18% at 320 mg/m^3, and 12% at 1,012 mg/m^3, compared to control values. Lung GSH also was decreased but remained relatively constant at approximately 70% of control values at all exposure concentrations up to 4,334 mg/m^3 and showed no evidence of further depletion. In the heart and testis, no significant reductions were observed at concentrations up to 4,334 mg/m^3. At the next highest dose of 7,791 mg/m^3, however, lung, heart, and testis GSH levels were decreased significantly, whereas kidney GSH levels were not. Liver GSH content showed an exposure-related decrease only between 3,504 and 7,791 mg/m^3. There were no changes in any lung weight parameters (wet weight,

[2]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25^o C.

percent wet weight/body weight, relative dry weight/wet weight, or dry weight/body weight) for animals sacrificed either 2 or 6 hours postexposure. Serum LDH activity measured 6 hours after dichloropropene exposure did not exhibit any significant changes except for a decrease at 10,336 mg/m^3.

The dose-dependency of GSH metabolism was evaluated in another study by Fisher and Kilgore (1988b). Male Sprague-Dawley rats were exposed to technical-grade dichloropropene vapors, nose only, for 1 hour at concentrations up to 789 ppm (3,582 mg/m^3)[3] dichloropropene. Urine was collected for 24 hours postexposure for measurement of the urinary mercapturic acid metabolite of cis-dichloropropene, cis-3CNAC. The amount of urinary cis-3CNAC exhibited a concentration-dependent increase in rats exposed from 0 to 284 ppm (1,289 mg/m^3)[3]. However, the amount of cis-3CNAC in the urine remained constant at exposures from 1,289 to 3,582 mg/m^3, a finding consistent with saturation of metabolism at higher doses of dichloropropene as suggested by the Stott and Kastl (1986) study.

Fisher and Kilgore (1989) postulated that dichloropropene entering the rat via inhalation exposure is rapidly transformed into its GSH conjugate, (S-3-chloroprop-2-enyl)GSH (GSCP), which is the precursor to the mercapturic acid metabolite 3CNAC (Figure 1), and that GSCP can be measured in blood over time. In an initial range-finding study using male Sprague-Dawley rats, the blood level of GSCP did not significantly change when measured at 15, 30, 45, and 60 minutes during a 1-hour exposure to 610 ppm (2,769 mg/m^3)[3] technical-grade dichloropropene. In the main study, the concentrations of GSCP in blood following inhalation exposures to 78, 155, and 404 ppm (354, 704, and 1,834 mg/m^3, respectively)[3] dichloropropene were examined using equations for both monophasic and biphasic decay. GSCP was detected in the blood of rats at all concentrations. No significant differences were found between the regression lines of the mathematical equations expressed as either monophasic or biphasic decay at any exposure concentration. Thus, these results could fit either a one- or two-compartment model of elimination. Moreover, no significant differences were found between the regression lines for any exposure concentrations, which indicates that the elimination of GSCP was independent of exposure concentration. The apparent half-life of GSCP was 17 hours. These findings suggest that the formation of GSCP may occur by dose-independent mechanisms, or that the mechanisms responsible for formation of GSCP may be saturated at the exposure levels selected for the experiment. Alternatively, on the basis of the results of Stott and Kastl (1986), an initial rapid phase of GSCP elimination may have been present but not detected in the Fisher and Kilgore (1989) study because the first blood samples following exposure were collected after the initial, rapid elimination phase had already occurred. The significance of these findings is unclear.

Two biological monitoring studies in humans have demonstrated that there is a dose-dependent relationship between respiratory occupational exposure to 1,3-dichloropropene and excretion of the urinary mercapturic acids, cis- and trans-3CNAC (van Welie et al., 1991). In this study of 12 male workers in the flower bulb industry, exposure to cis- and trans-1,3-dichloropropene measured by personal air samplers ranged from 0.3 to 18.9 mg/m^3 during 1- to 11-hour shifts. Urinary excretion of 3CNAC followed first-order elimination kinetics following

[3]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25° C.

Data from the environmental monitoring study indicated that the fumigators were exposed to TWA concentrations of 1.9–18.9 mg/m^3 1,3-dichloropropene. The Dutch standard of 5 mg/m^3 was exceeded about 30% of the exposure time. A decrease in serum total bilirubin concentration was the only parameter of liver function to be significantly affected by 1,3-dichloropropene. Urine albumin and retinol binding protein concentration were significantly increased and serum creatinine concentration was significantly decreased by the end of the spraying season. Blood GSH concentration and erythrocyte GST activity were also significantly decreased. The authors felt that a subclinical nephrotoxic effect due to exposure to 1,3-dichloropropene over a spraying season could not be ruled out. Alternately, changes in serum chemistry and urine analysis parameters may have been adaptive responses to detoxification and elimination of 1,3-dichloropropene. The serum chemistry and urine analysis parameters of the exposed workers were not evaluated subsequently to assess whether the observed alterations returned to normal values. The decreases in GSH and GST values indicate that GSH conjugation is involved in 1,3-dichloropropene elimination and likely detoxification.

4.1.7. Hayes, WJ. (1982) Pesticides studied in man. Baltimore: Williams and Wilkins, pp. 139-171

In a collision between two trucks, a tank carried by one truck ruptured and spilled approximately 4,542 L 1,3-dichloropropene. An estimated 80 people were exposed to vapors. The most common signs and symptoms were headaches in six people, irritation of mucous membranes in five people, dizziness in five people, and chest discomfort in four people. Three persons became unconscious at the scene of the accident. Of 41 persons tested, 11 had slightly elevated serum glutamic oxaloacetic transaminase and/or glutamic pyruvic transaminase values. Within 48–72 hours, values reverted to normal in eight people, but five still had slightly elevated serum glutamic oxaloacetic transaminase.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Inhalation Studies

4.2.1.1. *Parker, CM; Coaste, WB; Voelker, RW. (1982) Subchronic inhalation toxicity of 1,3-dichloropropene/1,2-dichloropropene (D-D) in mice and rats. J Toxicol Environ Health 9:899-910*

Groups of F344 rats and CD-1 mice (28/sex/group) were exposed to vapors of D-D at nominal concentrations of 0, 5, 15, or 50 ppm (0, 22.7, 68.1, or 227 mg/m^3)[4] 6 hours/day, 5 days/week for either 6 (10/sex/group) or 12 weeks (19/sex/group). The D-D formulation contained 25% cis-1,3-dichloropropene; 27% trans-1,3-dichloropropene; 29% 1,2-dichloropropane; and minor amounts of 3,3-dichloropropene, 2,3-dichloropropene, and other related chlorinated hydrocarbons. Clinical symptoms, body and organ weights, hematology,

[4]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25^o C.

mg/kg/day (50 mg/kg/day Telone II® × 0.1 epichlorohydrin × 3 days/7 days). The chronic feeding study by Stott et al. (1995), which did not include epichlorohydrin, reported forestomach hyperplasia in rats but no carcinomas or papillomas.

With regard to the mouse studies, NTP concluded that the male mouse study was inadequate for investigation of carcinogenicity because of the greatly reduced survival in the vehicle control group. In females, however, there was clear evidence of carcinogenicity, based on the increased incidence of transitional cell carcinoma of the urinary bladder, a very rare form of rodent cancer. Supporting evidence for carcinogenicity of Telone II® in female mice included the increased incidences of alveolar/bronchiolar adenomas of the lung and combined squamous cell papillomas and/or carcinomas of the forestomach (not statistically significant) at the highest dose, 100 mg/kg. Chronic toxicity of Telone II® was evidenced by hyperplasia of the forestomach in both sexes of rats and mice, and epithelial hyperplasia of the urinary bladder in male and female mice. Based on the serial-sacrifice (ancillary) study, development of both hyperplasia and carcinogenicity of the forestomach in rats was dependent on exposure duration.

On the basis of forestomach and liver neoplasms in rats, and urinary bladder and lung neoplasms in mice, the LOAEL for cancer in the NTP (1985) study is 21.4 mg/kg (50 mg/kg/day × 3 days/7 days). The NOAEL for rats is 10.7 mg/kg (25 mg/kg/day × 3 days/7 days). There is no NOAEL for mice.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Breslin, WJ; Kirk, HO; Streeter, CM; et al. (1989) 1,3-Dichloropropene: two-generation inhalation reproduction study in Fischer 344 rats. Fundam Appl Toxicol 12:129-143

The reproductive and developmental effects of inhaled technical-grade 1,3-dichloropropene were studied using F344 rats. The formulation was 92% 1,3-dichloropropene, 2% epoxidized soybean oil, and unknown amounts of chlorinated and unchlorinated alkanes and alkenes. The F_0 generation animals (30/sex/group) were exposed via whole-body inhalation to 0, 10, 30, or 90 ppm (0, 45.4, 136, or 409 mg/m^3, respectively)[5] 1,3-dichloropropene for 6 hours/day, 5 days/week for 10 weeks before mating and for 6 hours/day, 7 days/week during mating, gestation, and lactation. Weaned F_1 rats were subjected to the same dosing regimen. The animals were evaluated for fertility, pup survival, length of gestation, litter size, pup body weight, pup sex ratio, gross pathology, and histologic alterations.

No effects in any animals were noted at 45.4 or 136 mg/m^3. At 409 mg/m^3, males in the F_0 and F_1 generations exhibited a statistically significant decrease in body weight compared to controls, but the decrease was less than 10% and is not considered to be toxicologically significant. Gross and histologic examinations were conducted on all F_0 and F_1 adults and on randomly selected F_{1b} and F_{2b} weanlings. 1,3-Dichloropropene exposure had no significant effect

[5]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25^o C.

on either behavior or clinical appearance of the animals. In both adults and litters, no toxicologically significant changes in mating and fertility indices, including cohabitation time required for mating, gestation length, litter size, pup survival, and pup body weights, were observed. There were no increases in either physical or behavioral abnormalities of the pups. Parental toxicity was observed only at 409 mg/m^3 and consisted of histopathological changes of the nasal mucosa of the adult male and female rats. The alterations consisted of slight focal hyperplasia of the respiratory epithelium and/or focal degenerative changes of the olfactory epithelium. The nasal mucosa histopathology resulting from inhalation exposure to 1,3-dichloropropene has been observed in other high-dose inhalation exposure studies and is most likely due to a localized irritant effect (Linnett et al., 1988; Stott et al., 1988).

These results demonstrate that 1,3-dichloropropene is not a reproductive or developmental toxicant via inhalation in a two-generation reproduction study with F344 rats at exposures as high as 409 mg/m^3. The NOAEL for reproductive/developmental toxicity is 376 mg/m^3 because the formulation was 92% 1,3-dichloropropene. There is no LOAEL for reproductive/developmental toxicity. The NOAEL and LOAEL for parental toxicity are 125 and 376 mg/m^3, respectively, based on nasal histopathology.

4.3.2. Linnett, SL; Clark, DG; Blair, D; et al. (1988) Effects of subchronic inhalation of D-D (1,3-dichloropropene/1,2-dichloropropene) on reproduction in male and female rats. Fundam Appl Toxicol 10:214-223

The reproductive toxicity of D-D was determined in a single-generation study with Wistar rats. Groups of 30 male rats of proven fertility and 24 virgin females were exposed by inhalation to nominal concentrations of 0, 10, 30, or 90 ppm (0, 45.4, 136, or 409 mg/m^3, respectively)[6] D-D for 6 hours/day, 5 days/week for 10 weeks. The major components of D-D are cis-1,3-dichloropropene (28.1% weight/weight), trans-1,3-dichloropropene (25.6% weight/weight), and 1,2-dichloropropene (25.6% weight/weight). Minor components include 2,3-dichloropropene, 3,3-dichloropropene, 1,2,3-trichloropropane, trichloropropene, and allyl chloride. The fertility of 20 males per exposure level (male fertility subgroup) was evaluated at intervals during and after treatment by mating them with unexposed females. On the 12th day following confirmed mating, each female was killed and examined according to standard indices of mating and fertility, including numbers of corpora lutea, uterine implantation and uterine resorption sites, and percent preimplantation and postimplantation losses. Males were sacrificed 5 weeks postexposure and given standard toxicological evaluations, including semen analysis.

The fertility of 15 females per exposure level (female fertility subgroup) was assessed by mating them with unexposed proven males at the end of the 10-week treatment period and allowing them to deliver a litter. Exposure was not continued during gestation because this study was designed to evaluate the effects of D-D on female libido, estrus cycling, and indices of mating, conception, gestation, and fertility, rather than effects on fetal development. All females

[6]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25^o C.

External, visceral, and skeletal examination of the pups revealed no major abnormalities or malformations. A slight but statistically significant increase in delayed ossification of the vertebra central was observed among fetuses in the 545 mg/m^3 exposure group compared with controls. This increase was considered to have little toxicological significance because it was judged to be secondary to the significant maternal toxicity observed among females in the 545 mg/m^3 group.

Because no significant developmental effects were detected, the NOAEL for developmental toxicity in rats was 490 mg/m^3 (90% of 545 mg/m^3 formulation) and there was no LOAEL. Based on decreased body weight, the NOAEL for maternal toxicity in rats was 245 mg/m^3 and the LOAEL was 490 mg/m^3 1,3-dichloropropene (both corrected for 90% 1,3-dichloropropene).

In rabbits, statistically significant exposure-related decreases in maternal weight gain were observed at 272 and 545 mg/m^3. There were no treatment-related adverse effects on pregnancy rate, implantation and resorption rates, preimplantation losses, litter size, or fetal measurements among any of the exposed groups. External, visceral, and skeletal examination of the pups did not show evidence of treatment-related abnormalities or malformations. Statistically significant decreases in the incidence of two minor skeletal variants among the exposed groups (delayed ossification of the hyoid in the high-dose group, and the presence of cervical spurs in the low- and high-dose groups) were considered to be indicative of the normal variability among rabbit pups and thus not toxicologically significant.

The NOAEL for developmental toxicity in rabbits was 490 mg/m^3 (90% of 545 mg/m^3) as no effects were detected. There was no LOAEL. Based on decreased body weight, the NOAEL for maternal toxicity in rabbits was 82 mg/m^3 (90% of 91 mg/m^3), with a LOAEL of 245 mg/m^3 (90% of 272 mg/m^3).

The weight and strength of evidence from three well-conducted reproductive/ developmental toxicity studies in two species indicates that 1,3-dichloropropene is not a reproductive or developmental toxicant.

4.4. OTHER STUDIES

4.4.1. Acute Toxicity

Oral LD_{50}s range from 140 to 710 mg/kg 1,3-dichloropropene for rats and 300–640 mg/kg for mice (U.S. EPA, 1998c). The LC_{50} for Telone II® for a 4-hour exposure in rats was 904 ppm (4,104 mg/m^3)[7] for females and between 846 and 990 ppm (3,841 and 4,495 mg/m^3)[7] for males (Streeter et al., 1987).

[7]Calculated using conversion of 1 ppm = 4.54 mg/m^3 at 25^o C.

BMC results: nasal hypertrophy/hyperplasia in female B6C3F1 mice

Model	Chi-square goodness-of-fit *p*-value	*p*-value > 0.05	Visual rank	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma	0.4654	X	1	5.91	3.66
Logistic	0.0614	X	4	5.43	4.38
Multistage	0.1066	X	5	5.01	2.63
Probit	0.0219			5.23	4.36
Quantal-linear	0.0085			1.92	1.54
Quantal-quadratic	0.1312	X	2	6.34	5.43
Weibull	0.2202	X	3	4.97	3.14

3. Applied adjustment for HEC for a Category 1 gas to BMC_{10} and $BMCL_{10}$. The HEC for a Category 1 gas is derived by multiplying the animal BMC_{10} and $BMCL_{10}$ by an interspecies dosimetric adjustment for extrathoracic effects according to the following calculation (U.S. EPA, 1994b):

$$RGDR(ET) = (MV_a/S_a)/(MV_h/S_h)$$

where

RGDR(ET) = regional gas dose ratio for the extrathoracic area of the respiratory tract
MV_a = animal minute volume (mouse = 0.041 L/min)
MV_h = human minute volume (13.8 L/min)
S_a = surface area of the extrathoracic region in the animal (mouse = 3 cm^2)
S_h = surface area of the extrathoracic region in the human (200 cm^2).

Using default values, the RGDR(ET) = (0.041/3)/(13.8/200) = 0.014/0.069 = 0.198.

The animal BMC_{10} and $BMCL_{10}$ are then multiplied by 0.198 to yield the HECs of these values:

$BMC_{10\,HEC} = BMC_{10} \times 0.198 = 5.91 \times 0.198 = 1.17\ mg/m^3$
$BMCL_{10\,HEC} = BMCL_{10} \times 0.198 = 3.66 \times 0.198 = 0.725\ mg/m^3$

4. Derived RfC by applying necessary UFs to BMC_{10HEC} and $BMCL_{10HEC}$.

UF = 3 for interspecies extrapolation × 10 for intraspecies extrapolation = 30

$BMC_{10\,HEC} = 1.17\ mg/m^3 \div 30 = 0.039\ mg/m^3$
$BMCL_{10\,HEC} = 0.725\ mg/m^3 \div 30 = 0.024\ mg/m^3$

The RfC is 0.02 mg/m^3.