Abstract #2900

1,3-Dichloropropene: Hazard Identification and Risk Assessment for Occupational and Bystander Inhalation Exposures

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INTRODUCTION

cis (*Z*) isomer *trans* (*E*) isomer

- 1,3-dichloropropene (1,3-D; MW, 110.98) is a fumigant used to control nematodes, insects and disease organisms in soil. It promotes crop growth by minimizing competition with soil pests.
- 1,3-D is applied by pre-plant soil injection or post-plant drip irrigation. Volatilization creates opportunities for off-site movement and human exposure.
- Pesticidal action is attributed to enzyme inactivation via sulfhydryl or hydroxyl binding.
- In mammals, 1,3-D is a respiratory irritant and asphyxiant, and is also absorbed through the respiratory tract to generate systemic toxicity.
- The following health assessment concentrates exclusively on risks arising from inhalation exposures projected to occur in California under occupational, bystander and ambient scenarios.

HAZARD IDENTIFICATION & DOSE RESPONSE

Acute Toxicity

- Classified by USEPA as a Category IV inhalation toxicant - 4-hour inhalation LC50 for 1,3-dichloropropene (98% a.i) in rats is >585 ppm

Acute / short-term critical endpoint determination

- Endpoint: decrement in body weight gain after 3-7 days of exposure (6 h/day)
- $BMCL_{1sd}$ values ranged between 6 and 66 ppm for the six rat and mouse studies with statistically analyzable data (Table 2); the lowest value was excluded (uncharacterized test article purity)
- 49 ppm chosen as the critical point of departure (POD) based on weight decrement at 3 days (Stott et al., 1984)

Subchronic / seasonal critical endpoint determination

- Endpoint: histopathologic observations in rats after 13 weeks of exposure (6 h/day):
  - nasal turbinates (hyperplasia of nasal respiratory epithelium, degeneration, (olfactory epithelium), uterus (hypoplasia) and mesenteric tissue (adipose atrophy) (Stott et al., 1984)
  - decreased cytoplasm and disorganization of nuclei of nasal respiratory epithelium (Coate, 1979)
- $BMCL_{10}$ values ranged between 9 and 16 ppm for 2 rat studies with statistically analyzable data; the lower value was excluded (uncharacterized test article purity)
- 16 ppm chosen as the critical point of departure (POD) based on weight hyperplasia of nasal respiratory epithelium (Stott et al., 1984)

Chronic / annual critical (non-oncogenic) endpoint determination

- Endpoint: histopathologic observations in mice after 2 years daily exposure (6 h/day) (Stott et al., 1987)
  - urinary bladder (mucosal hyperplasia simple or nodular, chronic inflammation)
  - nasal respiratory epithelium (mucosal hypertrophy and hyperplasia)
  - olfactory epithelium (degeneration)
  - non-glandular stomach (hyperplasia with chronic inflammation, focal or multifocal)
- $BMCL_{10}$ of 6 ppm was chosen as the critical point of departure (POD) based on hyperplasia of nasal respiratory epithelium.

Oncogenic potency determination (air unit concentration—AUC)

- Male mice exposed to 1,3-D by the inhalation route for 2 years exhibited a statistically elevated incidence of bronchioloalveolar adenomas at a nominal air concentration of 60 ppm.(Stott et al., 1987)
- There was no evidence for a threshold model for the tumor formation, but dose-dependence and genotoxicity were evident.
- To calculate AUC, human equivalent doses and incidence rates were used to model the dose responsiveness with the linearized multistage cancer model (BMCS version 2.6)
- AUCs were calculated for both portal of entry and systemic modes action
- AUCs were calculated as 0.0059 ppm^{-1} and 0.018 ppm^{-1} (portal of entry mode) and 0.02 ppm^{-1} and 0.062 ppm^{-1} (systemic mode) for occupational and non-occupational exposure scenarios, respectively

Table 1. Benchmark concentration values based on body weight decreases after short term inhalation exposure of rats and rabbits to 1,3-dichloropropene

Study	Air concentrations (ppm)	Exposure Duration (days)	BMC_{1s} (ppm)	$BMCL_{1s}$ (ppm)
Rat Dominant lethal (Gollapudi *et al.*, 1997)	0, 10, 60, 150	7	82[a]	66[a]
Rat 2-year chronic (Lomax *et al.*, 1987)	0, 5, 20, 60	6	59[b]	53[b]
Rat 13-week subchronic (Stott *et al.*, 1984)	0, 10, 30, 90, 150	3	(♂/♀) 64/68[c]	(♂/♀) 49/51[c]
Rat 13-week subchronic (Coate, 1979)	0, 10, 30, 90	7	(♀) 19[d]	(♀) 6[d]
Rat Developmental (John *et al.*, 1983)	0, 20, 60, 120	4	79[c]	61[c]
Mouse 2-year chronic (Stott *et al.*, 1987)	0, 5, 20, 60	7	(♂/♀) 58 /51[a]	(♂/♀) 44/40[a]

[a] BMDS 2.6.0 Exponential model [b] BMDS 2.6.0 Polynomial model [c] BMDS 2.6.0 Linear model [d] BMDS 1.10 Exponential model

BMC modeling & inhalation dosimetry—critical acute / short term study

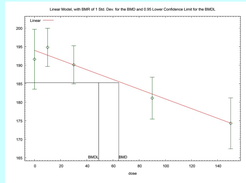
- Rat, 13-wk exposure, 6 h/day – 5 d/wk, BW gain decrement on exposure day 3 (Stott *et al*, 1984)
- BMR_{1sd}: default for continuous data (*e.g.*, BW decrements relative to control)
- BMC_{1sd} / $BMCL_{1sd}$ = 64 ppm / 49 ppm
- Dosimetry

HEC = BMCL x (D_a/D_h) x (W_a/W_h) x RGDR

RGDR = 1 (default for systemic effects)

HEC = 11 ppm (non-occupational)

= 33 ppm (occupational)



HEC, human equivalent concentration

RGDR, regional gas dose ratio

D_a, duration of animal exposure (hr/day)

D_h, duration of human exposure (hr/day)

W_a, duration of animal exposure (days/wk)

W_h, duration of human exposure (days/wk)

BMC modeling & inhalation dosimetry—critical subchronic study

- Rat, 13-wk exposure, 6 h/day – 5 days/wk (Stott *et al.*, 1984)
- Nasal epithelial hyperplasia
- BMC_{10} / $BMCL_{10}$ = 27 ppm / 16 ppm
- Dosimetry

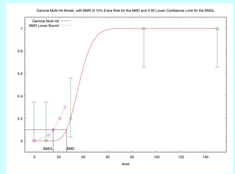
HEC = BMCL x (D_a/D_h) x (W_a/W_h) x RGDR

RGDR = (MV_{rat}/SA_{rat}) / (MV_{human}/SA_{human})

= 0.115

HEC = 0.30 ppm (non-occupational)

= 0.90 ppm (occupational)



MV, minute volume

SA, extrathoracic surface area

BMC modeling & inhalation dosimetry—critical chronic study

- Mouse, 2-yr exposure, 6 h/day - 5 days/wk (Stott *et al.*, 1987)
- Nasal epithelial hyperplasia
- BMC_{10} / $BMCL_{10}$ = 10 ppm / 6 ppm
- Dosimetry

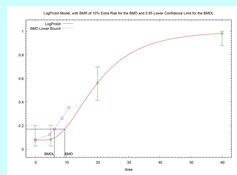
HEC = BMCL x (D_a/D_h) x (W_a/W_h) x RGDR

RGDR = (MV_{mouse}/SA_{mouse}) / (MV_{human}/SA_{human})

= 0.198

HEC = 0.20 ppm (non-occupational)

= 0.59 ppm (occupational)



Genotoxicity

1,3-D is positive in the following *in vitro* genotoxicity tests:

- mutagenicity---*Salmonella* (Haworth *et al.*, 1983; Neudecker & Henschler, 1986; Eder *et al.*, 2006)
- mutagenicity---mouse lymphoma cells: small colony-forming mutants (Myhr and Caspary, 1991)
- sister-chromatid exchange---Chinese hamster ovary cells (Loveday *et al.*, 1989)

1,3-D is positive in the following *in vivo* genotoxicity tests:

- feeding exposure: sex-linked recessive lethals---*Drosophila* (Valencia *et al.*, 1985)
- ip injection; bone marrow: chromosome damage and micronuclei---B6C3F1 mice (unpublished data from NTP archives; Shelby *et al.*, 1993)
- gavage; bone marrow: micronuclei—NMRI female mice (Kevekordes *et al.*, 1996)
- ip injection & gavage; liver, gastric mucosa, kidney: DNA damage---rats (Ghia *et al.*, 1993)
- gavage; liver: DNA damage—rats (Kitchin *et al.*, 1993; Kitchin & Brown, 1994)

Some 1,3-D metabolites (known or suspected) are genotoxic

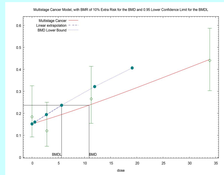
Oncogenesis

Table 2 Human equivalent doses and incidence rates used to model the dose responsiveness of 1,3-D-induced bronchioloalveolar adenomas in male mice

Nominal dose	RGDR	HEC dose (resident -bystander-ambient)	HEC dose (occupational)	Incidence rate
Portal of entry scenario				
0 ppm	3.44	0 ppm	0 ppm	9/49 (18%)
5	3.44	2.83	8.48	6/50 (12%)
20	3.44	11.30	33.91	13/49 (27%)
60	3.44	33.91	101.73	22/50 (44%)
Air unit risk Upper confidence limit (ppm^{-1})		0.018	0.0059	n/a
Systemic scenario				
0 ppm	1	0 ppm	0 ppm	9/49 (18%)
5	1	0.82	2.46	6/50 (12%)
20	1	3.29	9.86	13/49 (27%)
60	1	9.86	29.57	22/50 (44%)
Air unit risk Upper confidence limit (ppm^{-1})		0.062	0.020	n/a

Quantitative dose modeling & inhalation dosimetry, tumor incidence

- Mouse (male), 2-yr exposure, 6 h/day - 5 days/wk (Stott *et al.*, 1987)
- Bronchioloalveolar adenomas
- Dosimetry (see Table 2 above)



EXPOSURE

Table 3. Data sources for exposure scenarios

Exposure Scenario	Worker Exposure Data	Simulated Data	Surrogate Data	Air Monitoring Data
applicator (shallow shank, w/o tarp) [a]	X			
applicator (shallow shank, w/ tarp) [b]			X	
applicator (deep shank w/ and w/o tarp) [b]			X	
applicator (drip w/ and w/o tarp) [b]			X	
applicator (injection auger) [b]			X	
loader [a]	X			
tarp remover [b]			X	
reentry worker [a]	X			
occupational bystander (shallow shank w/o tarp) [c]		X		X
occupational bystander (deep shank w/o tarp) [c]		X		X
occupational bystander (drip w/ tarp) [c]		X		X
residential bystander (exposure to 1,3-D at 100 ft from edge of treated field) [d]		X		
residential bystander (exposure to ambient levels of 1,3-D) [e]		X		X

Note: Specific exposure estimation techniques indicated by footnotes available on request.

RISK ESTIMATION

Table 4. Target MOEs and calculated MOEs for non-occupational and occupational 1,3-D exposure scenarios

Exposure scenario	Target MOE	Calculated MOE: Acute / sh.term	Calculated MOE: Seasonal	Calculated MOE: Annual
Occupational scenarios				
Applicator	30 (adult)			
shallow shank w/o tarp		122	28	61
shallow shank w/ tarp		39	9	18
deep shank w/o tarp		122	13	14
deep shank w/ tarp		39	4	4
drip w/o tarp		118	23	45
drip w/ tarp		143	50	98
injection auger		28	n/a	n/a
Loader				
shallow shank		47	15	31
deep shank		47	7	7
Tarp remover				
shallow shank		1	0.23	0.49
deep shank		1	0.11	0.11
drip		1	0.35	0.69
Reentry worker				
shallow shank		892	60	92
deep shank		892	28	25
drip		892	90	134
Occupational bystander				
shallow shank w/o tarp		17	750	952
deep shank w/o tarp		55	750	952
drip w/ tarp		30	750	952
Non-occupational scenarios				
Near application site, edge of buffer zone	30 (adult) 100 (child)			
shallow shank		20	17	n/a
deep shank		96	22	n/a
drip		61	60	n/a
tree & vine		120	n/a	n/a
Ambient		135	67	1000

Table 5. Oncogenic risk—occupational 1,3-D exposure [a]

	Portal of entry	Systemic
Applicator		
shallow shank w/o tarp	$3.2x10^{-5}$	$1.1x10^{-4}$
shallow shank w/ tarp	$1.0x10^{-4}$	$3.4x10^{-4}$
deep shank w/o tarp	$1.4x10^{-4}$	$4.6x10^{-4}$
deep shank w/ tarp	$4.3x10^{-4}$	$1.4x10^{-3}$
drip w/o tarp	$4.1x10^{-5}$	$1.4x10^{-4}$
drip w/ tarp	$1.9x10^{-5}$	$6.4x10^{-5}$
injection auger	n/a	n/a
Loader		
shallow shank	$5.9x10^{-4}$	$2.0x10^{-4}$
deep shank	$2.6x10^{-4}$	$8.8x10^{-4}$
Tarp remover		
shallow shank	$3.9x10^{-3}$	$1.3x10^{-2}$
deep shank	$1.7x10^{-2}$	$5.6x10^{-2}$
drip	$2.7x10^{-3}$	$9.2x10^{-3}$
Reentry worker		
shallow shank	$2.0x10^{-5}$	$6.8x10^{-5}$
deep shank	$7.1x10^{-5}$	$2.6x10^{-4}$
drip	$1.4x10^{-5}$	$4.8x10^{-5}$
Occupational bystander		
shallow shank w/o tarp	$1.9x10^{-6}$	$6.6x10^{-6}$
deep shank w/o tarp	$1.9x10^{-6}$	$6.6x10^{-6}$
drip w/ tarp	$1.9x10^{-6}$	$6.6x10^{-6}$

[a] Negligible oncogenic risk = $1x10^{-6}$

RISK APPRAISAL

Table 7. Prominent uncertainties in the 1,3-D inhalation risk analysis

Toxicology	Exposure
BW gain decrements drove the acute / short term evaluation BW gain decrements were deemed systemic, not portal-of-entry, effects 3x pharmacokinetic UF was reduced to 1x due to use of RGDR approach Chronic risk was evaluated using portal-of-entry, not systemic, effects Rodent-to-human extrathoracic RGDRs were <<1 Oncogenic risk from exposure to very young people was not evaluated	Surrogate data from chloropicrin studies used to estimate certain 1,3-D handler scenarios Tarp remover estimates assumed no respiratory protection Reentry worker exposures calculated from data gathered at 3.8 days, not the REI of 7 days Field acreage used in bystander exposure simulations may differ from actual acreages used HEE5CB used more stringent criteria for secting 1,3-D concentration from SOFEA-2 than MCABLE

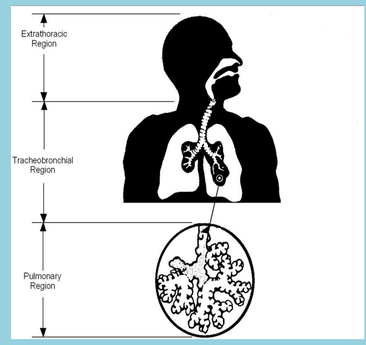


Table 6. Oncogenic risk—-ambient 1,3-D exposure scenarios

	Portal of entry: Male	Portal of entry: Female	Systemic: Male	Systemic: Female
MCABLE				
With time away				
Variable	2.64×10^{-6}	2.49×10^{-6}	9.09×10^{-6}	8.56×10^{-6}
30-yr fixed	2.45×10^{-6}	2.30×10^{-6}	8.44×10^{-6}	7.91×10^{-6}
50-yr fixed	3.27×10^{-6}	3.04×10^{-6}	11.26×10^{-6}	10.44×10^{-6}
70-yr fixed	4.28×10^{-6}	3.97×10^{-6}	14.72×10^{-6}	13.64×10^{-6}
Without time away				
Variable	2.87×10^{-6}	2.69×10^{-6}	9.88×10^{-6}	9.23×10^{-6}
30-yr fixed	2.63×10^{-6}	2.49×10^{-6}	9.06×10^{-6}	8.57×10^{-6}
50-yr fixed	3.60×10^{-6}	3.31×10^{-6}	12.40×10^{-6}	11.39×10^{-6}
70-yr fixed	4.66×10^{-6}	4.27×10^{-6}	16.02×10^{-6}	14.68×10^{-6}
HEE5CB				
High mobility				
Birth to age 30	4.85×10^{-6}	4.75×10^{-6}	16.70×10^{-6}	16.34×10^{-6}
Birth to age 50	6.99×10^{-6}	6.76×10^{-6}	24.08×10^{-6}	23.25×10^{-6}
Birth to age 70	9.18×10^{-6}	8.77×10^{-6}	31.56×10^{-6}	30.17×10^{-6}
Intermediate mobility				
Birth to age 30	5.88×10^{-6}	6.97×10^{-6}	20.22×10^{-6}	23.99×10^{-6}
Birth to age 50	9.01×10^{-6}	8.16×10^{-6}	30.98×10^{-6}	28.08×10^{-6}
Birth to age 70	10.77×10^{-6}	10.6×10^{-6}	37.06×10^{-6}	35.45×10^{-6}
Low mobility				
Birth to age 30	6.25×10^{-6}	7.73×10^{-6}	21.51×10^{-6}	26.57×10^{-6}
Birth to age 50	10.43×10^{-6}	8.83×10^{-6}	35.89×10^{-6}	30.38×10^{-6}
Birth to age 70	11.75×10^{-6}	11.46×10^{-6}	40.44×10^{-6}	39.41×10^{-6}

[a] Negligible oncogenic risk = $1x10^{-6}$

CONCLUSIONS

Acute / short term occupational MOEs (analyzed for adults only): Five of the 18 scenarios examined showed calculated MOEs lower than the target MOE of 30.

Subchronic / seasonal occupational MOEs: Eleven of 18 scenarios showed calculated MOEs lower than the target MOE of 30.

Chronic / annual occupational MOEs: Eight of 18 scenarios showed calculated MOEs lower than the target MOE of 30.

Acute / short term resident / bystander (non-occupational) MOEs: In adults, 1 of 4 scenarios showed a calculated MOE lower than the target MOE of 30. In children 3 of the same 4 scenarios showed calculated MOEs lower than the target MOE of 100.

Seasonal resident / bystander (non-occupational) MOEs: In adults, 2 of the 3 scenarios showed a calculated MOE lower than target MOE of 30. In children all three scenarios were lower than the target MOE of 100.

Annual resident / bystander (non-occupational) MOEs: Annual exposure to residential bystanders was not expected.

Ambient air MOEs, acute / short term, subchronic / seasonal and chronic / annual: The acute / short term ambient MOE of 135 exceeded both the target MOEs of 30 for adults and 100 for children. The subchronic / seasonal ambient MOE of 67 exceeded the target MOE of 30 for adults, but did not exceed the target MOE of 100 for children. The chronic / annual ambient MOE of 1000 exceeded the target MOE of 30 for adults both the target MOEs of 30 for adults and 100 for children.

Oncogenic risk, occupational and ambient: Calculated oncogenic risk values were higher than the negligible oncogenic risk standard of $1x10^{-6}$ for every occupational and non-occupational scenario analyzed including all ambient scenarios, which were analyzed using computer simulations. This was the case regardless of the assumed oncogenic mode of action---portal of entry or systemic---of 1,3-D.