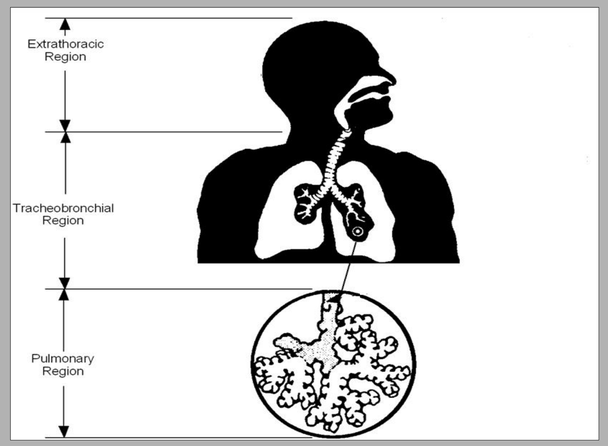
Oncogenic Potency and Risk to Workers and the General Public from Inhaled 1,3-Dichloropropene

A. Rubin, C. Aldous, I. Reeve, P. Lohstroh, S. Rinkus, C. Lewis, M. Wilbur, T. Barry, E. Kwok, S. Koshlukova, S. Beauvais and M. Verder-Carlos

Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA, USA



I. 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 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.
- 1,3-D induced adenoma formation in mouse liver (dietary), fibrosarcomas in mouse skin (injection site), transitional cell carcinomas in mouse urinary bladder (gavage), bronchioloalveolar adenomas in mouse lung (gavage), squamous cell papillomas and carcinomas in rat and mouse forestomach (gavage) and neoplastic nodules in rat liver (gavage).
- 1,3-D was implicated in two fatal cases of histiocytic lymphoma in responders to a tank truck spill. It was also correlated with pancreatic cancer in an epidemiological study in residents of Fresno, Kern and Tulare Counties.
- Respiratory exposure for 2 years induced bronchioloalveolar (BA) adenomas in male B63CF1 mice. We present a potency analysis of this phenomenon, followed by a lifetime exposure and risk evaluation in humans arising from long-term inhalation exposures projected to occur in California under occupational, bystander and ambient scenarios.

II. ONCOGENIC POTENCY (AIR UNIT RISK—AUR)

- Male mice exposed to 1,3-D for 2 years by the inhalation route 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 AUR, human equivalent doses and incidence rates were used to model the dose responsiveness with the linearized multistage cancer model (BMCS version 2.6).
- AURs were calculated for both portal of entry (PE) and systemic (SM) modes action.
- AUR-PE = 0.0059 ppm^{-1} and 0.018 ppm^{-1} (occupational and non-occupational exposure scenarios).
- AUR-SM = 0.02 ppm^{-1} and 0.062 ppm^{-1} (occupational and non-occupational exposure scenarios).

Reference: Stott, WT, KA Johnson, LL Calhoun, SK Weiss & LE Frauson (1987) Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in mice

Genotoxicity

1,3-D was 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 was 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 known or suspected 1,3-D metabolites are genotoxic: 3-chloroallyl alcohol (promutagen), 3-chloroacrolein, 3-chloropropenoic acid (promutagen), 1,3-D epoxide, 3-chlorolactaldehyde, acrolein

Induction of bronchioloalveolar adenomas

Table 1 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 of BA tumor incidence

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

Portal of entry (pulmonary + tracheobronchial)

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

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

MV_{mouse} = 0.044 L/min; MV_{human} = 13.8 L/min

SA_{mouse} = 503.5 cm^2; SA_{human} = 543,200 cm^2

RGDR = 3.44

Systemic

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

RGDR = 1 (default)

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HEC, human equivalent concentration

RGDR, regional gas dose ratio

D_a, duration of animal exposure (hr/day)

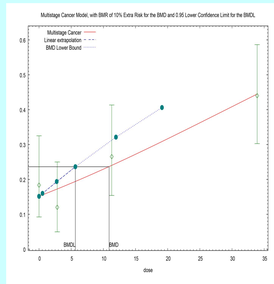
D_h, duration of human exposure (hr/day)

W_a, duration of animal exposure (days/wk)

W_h, duration of human exposure (days/wk)

MV, minute volume

SA, respiratory surface area



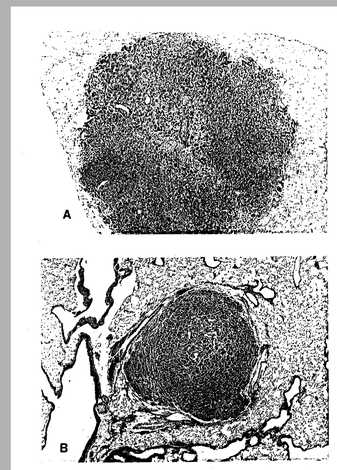


Figure 1. Bronchioloalveolar adenomas in B63CF1 mice exposed to 60 ppm 1,3-D for 2 years. H & E staining; 85x.

A.Cell arrangement: "solid" pattern

B.Cell arrangement: papillary pattern

***from*: Stott *et al.* (1987)**

III. EXPOSURE ESTIMATION

Ambient lifetime dose modeling

- Due to a paucity of long term air concentration monitoring data, model-based simulations were conducted to develop long term concentration estimates.
- Lifetime exposure and risk to the general public was estimated using:
  - Soil Fumigant Exposure Assessment System (SOFEA) with Industrial Sources Complex Short Term Version 3 (ISCST3) air dispersion model as its computational engine
  - Stochastic human exposure assessment models: High End Exposure Version 5 Crystal Ball (HEE5CB) & Monte Carlo Annual Based estimate of Lifetime Exposure (MCABLE) models

Model Equations of the Population-Based Exposure Models:

1. HEE5CB – More Restrictive Mobility and Residency Assumptions (Worst Case)

$$LADD=\left(\sum_{i=1}^{10} RT_i\left[\frac{Conc_i \times BR_i}{BW_i}\right]\right) \times \frac{1}{70}$$

where the summation is over 10 age intervals,

- LADD = lifetime average daily dose (mg/kg/day)
- RT_i = number of years in age interval *i* that the person resides in the high 1,3-D use area
- $Conc_i$ = annual average of air concentrations (mg/m^3) in 5 locations weighted by the proportion of time spent in each location in interval *i* from SOFEA-ISCST3,
- BR_i = average breathing rate (m^3/day) at each of 4 activity levels weighted by proportion of time spent at each level in interval *i*,
- BW_i = body weight (kg) in interval *i*, and 70 years is the assumed lifetime

2. MCABLE – Less Restrictive Mobility and Residency Assumptions (Realistic)

$$ADD=\left((1-F_a)\left[\frac{Conc_i \times BR_i}{BW_i}\right]\right)$$

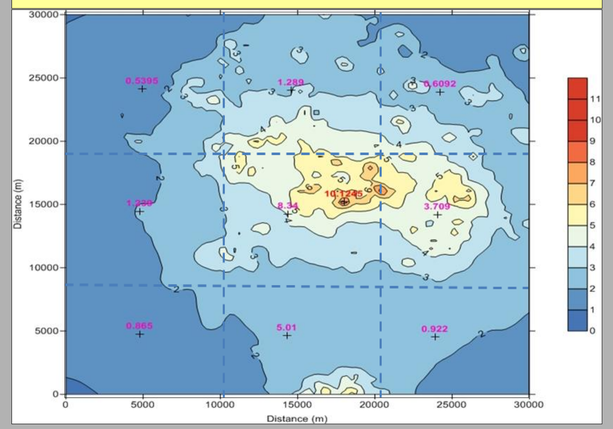
$$LADD=\left[\left(\sum_{i}^{n} ADD_i\right)+Background\right] \times \frac{1}{lifetime}$$

where the summation is over a stochastically determined interval from i to n. For example, $\sum_{10}^{30} ADD$ would be equivalent to the assumption that an individual entered the community at the age of 10 (i.e., i = 10) and left at the age of 30 (i.e., n =30) after staying for 20 years.

- ADD = average daily dose (mg/kg/day)
- F_a = fraction of time spent away from the high 1,3-D use area
- $Conc_i$ = annual average of air concentrations (mg/m^3) in 5 of the 9 townships weighted by the proportion of time spent in each location in interval *i* from SOFEA-ISCST3
- BR_i = age and gender specific average breathing rate (m^3/day)
- BW_i = age and gender specific body weight (kg) in interval *i*
- Lifetime = 70 years (assumption for both males and females)
- Background = total ADD due to background exposure, calculated by adding ADD values from 100—(n-i) simulation years

The main differences between these models include residential-mobility assumptions employed for estimating exposures. HEE5CB has a more restrictive assumption than MCABLE in the time that an individual lives (i.e., residency) and spends (i.e., mobility) within different townships in a high 1,3-D use area. Accordingly, for a given scenarios, HEE5CB generated a higher exposure estimate and, therefore, cancer risk than MCABLE.

Figure 2. Merced county—site of the highest 1,3-D applications. Contour plot of ISCST3 modeled annual average 1,3-D air concentrations (mg/m^3). Black crosses are the locations of the monitored air concentrations. Purple text are the measured 14.5-month 1,3-D air concentrations.



Occupational lifetime exposure estimation

Sources of Data

1,3-D worker exposure studies

Chloropicrin worker exposure studies (surrogate approach)

Ambient 1,3-D air monitoring study conducted in a high-use county (Merced County) during the 1,3-D use season*

Basic Assumptions

Employee works for 40 years during lifetime

Employee's lifespan = 75 years

*Use season: months of the year where the number of pounds of 1,3-D applied is 5% or greater than the annual total

IV. ONCOGENIC RISK ESTIMATION

Table 2. Oncogenic risk—ambient 1,3-D exposure scenarios

	Portal of entry		Systemic	
	Male	Female	Male	Female
MCABLE				
With time away				
■ Variable	2.6×10^{-6}	2.5×10^{-6}	9.1×10^{-6}	8.6×10^{-6}
■ 30-yr fixed	2.5×10^{-6}	2.3×10^{-6}	8.4×10^{-6}	7.9×10^{-6}
■ 50-yr fixed	3.3×10^{-6}	3.0×10^{-6}	1.1×10^{-5}	1.1×10^{-5}
■ 70-yr fixed	4.3×10^{-6}	4.0×10^{-6}	1.5×10^{-5}	1.4×10^{-5}
Without time away				
■ Variable	2.9×10^{-6}	2.7×10^{-6}	9.9×10^{-6}	9.2×10^{-6}
■ 30-yr fixed	2.6×10^{-6}	2.5×10^{-6}	9.1×10^{-6}	8.6×10^{-6}
■ 50-yr fixed	3.6×10^{-6}	3.3×10^{-6}	1.2×10^{-5}	1.1×10^{-5}
■ 70-yr fixed	4.7×10^{-6}	4.3×10^{-6}	1.6×10^{-5}	1.5×10^{-5}
HEE5CB				
High mobility				
■ Birth to age 30	4.9×10^{-6}	4.8×10^{-6}	1.7×10^{-5}	1.6×10^{-5}
■ Birth to age 50	7.0×10^{-6}	6.8×10^{-6}	2.4×10^{-5}	2.3×10^{-5}
■ Birth to age 70	9.2×10^{-6}	8.8×10^{-6}	3.2×10^{-5}	3.0×10^{-5}
Intermediate mobility				
■ Birth to age 30	5.9×10^{-6}	7.0×10^{-6}	2.1×10^{-5}	2.4×10^{-5}
■ Birth to age 50	9.0×10^{-6}	8.2×10^{-6}	3.1×10^{-5}	2.8×10^{-5}
■ Birth to age 70	1.1×10^{-5}	1.1×10^{-5}	3.7×10^{-5}	3.6×10^{-5}
Low mobility				
■ Birth to age 30	6.3×10^{-6}	7.7×10^{-6}	2.2×10^{-5}	2.7×10^{-5}
■ Birth to age 50	1.0×10^{-5}	8.8×10^{-6}	3.6×10^{-5}	3.1×10^{-5}
■ Birth to age 70	1.2×10^{-5}	1.2×10^{-5}	4.1×10^{-5}	3.9×10^{-5}

Table 3. Oncogenic risk—occupational 1,3-D exposure

	Portal of entry	Systemic
Applicator		
■ shallow shank w/o tarp	3.2×10^{-5}	1.1×10^{-4}
■ shallow shank w/ tarp	1.0×10^{-4}	3.4×10^{-4}
■ deep shank w/o tarp	1.4×10^{-4}	4.6×10^{-4}
■ deep shank w/ tarp	4.3×10^{-4}	1.4×10^{-3}
■ drip w/o tarp	4.1×10^{-5}	1.4×10^{-4}
■ drip w/ tarp	1.9×10^{-5}	6.4×10^{-5}
■ injection auger	n/a	n/a
Loader		
■ shallow shank	5.9×10^{-4}	2.0×10^{-4}
■ deep shank	2.6×10^{-4}	8.8×10^{-4}
Tarp remover		
■ shallow shank	3.9×10^{-3}	1.3×10^{-2}
■ deep shank	1.7×10^{-2}	5.6×10^{-2}
■ drip	2.7×10^{-3}	9.2×10^{-3}
Reentry worker		
■ shallow shank	2.0×10^{-5}	6.8×10^{-5}
■ deep shank	7.1×10^{-5}	2.6×10^{-4}
■ drip	1.4×10^{-5}	4.8×10^{-5}
Occupational bystander		
■ shallow shank w/o tarp	1.9×10^{-6}	6.6×10^{-6}
■ deep shank w/o tarp	1.9×10^{-6}	6.6×10^{-6}
■ drip w/ tarp	1.9×10^{-6}	6.6×10^{-6}

V. CONCLUSIONS

- Calculated oncogenic risk varied with exposure scenario and assumed oncogenic mode of action.
- For the portal of entry mode, risk values ranged from 2×10^{-6} to 1×10^{-5} (ambient) and from 2×10^{-6} to 2×10^{-2} (occupational).
- For the systemic mode, risk values ranged from 8×10^{-6} to 4×10^{-5} (ambient) and from 7×10^{-6} to 6×10^{-2} (occupational).
- Potential regulation of 1,3-D will depend on the choice of negligible risk standard (10^{-4} - 10^{-6}).