UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Diallate Quantitative Risk Assessment

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In response to your request of July 2, 1981, we have made a quantitative risk assessment of diallate. We have reviewed and evaluated the 18-month oral diallate study in hamsters submitted by Monsanto Company. In both male and female hamsters of the 600 and 2000 ppm dose groups, a statistically significant ($P < 0.01$) higher incidence of benign/malignant dermal melanomas are observed when compared to the control group. The data from combining male and female tumor incidence in Table 1 are used for the quantitative risk estimate. The cancer risk for diallate spray applicators is calculated using the exposure data provided to the CAG by EFB/HED (July 2 and July 9, 1981).

ESTIMATION OF THE CARCINOGENIC POTENCY

An estimation of the carcinogenic potency of diallate is based on the data obtained by combining male and female tumor incidence in Table 1. These incidence data are combined because the occurrence of dermal melanomas does not appear to be sex-specific and because some of the dose groups are small in sample size.

TABLE 1. INCIDENCE OF BENIGN/MALIGNANT DERMAL MELANOMAS IN HAMSTERS PER TISSUE EXAMINED HISTOLOGICALLY
(Monsanto Company)

Dose (ppm)	Male	Female
0	0/29	1/20
200	0/10	0/5
600	3/9	4/7
2000	16/30	10/16

Using the linearized multistage model (see Federal Register 45:231. Nov. 28, 1980), the carcinogenic potency of diallate is estimated as:

$$q_1^* = 6.10 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$$
$$= 6.10 \times 10^{-5} \text{ (ug/kg/day)}^{-1}$$

In the potency calculation, the dose in ppm is converted to mg/kg/day, assuming that the daily food consumption for a hamster is 7.5% of its body weight. Therefore, the human equivalent dose in mg/kg/day corresponding to 1 ppm in the hamster study is

$$1 \text{ ppm} \times 0.075 \times (0.15/70)^{1/3} = 9.67 \times 10^{-3} \text{ mg/kg/day}$$

where 0.15 kg is the average body weight of hamsters.

LIFETIME CANCER RISK FOR DIALLATE SPRAY APPLICATORS

To estimate the lifetime cancer risk, the exposure data in Table 2 provided by EFB/HED are converted to lifetime exposure d by the following formula:

$$d = X \frac{\text{ug/kg/yr}}{\text{365 days/yr}} \times \frac{\text{60 kg}}{\text{70 kg}} \times \frac{\text{40 yr}}{\text{70 yr}}$$

$$= 1.34 \times 10^{-3} \text{ X ug/kg/day}$$

where X is an entry from Table 2. In order to be consistent with the Carcinogen Assessment Group's (CAG) risk assessments of other agents, the factor (60 kg/70 kg) is used to express dose on the basis of a 70 kg human body weight instead of the basis 60 kg which is used in Table 2. The factor (40 yr/70 yr) represents the fraction of the lifetime an applicator would work.

The lifetime cancer risk associated with an exposure level d (ug/kg/day), calculated by $6.10 \times 10^{-5} \times d$, is presented in Tables 3 and 4.

TABLE 2. DIALLATE EXPOSURE ESTIMATES (ug/kg/yr) FOR SPRAY APPLICATORS (EFB/HED July 2, and July 9, 1981)

System	Inhalation		Dermal	
	Maximum	Average	Maximum	Average
Open*	13.7 (10.0)	6.1 (3.8)	650 (173.3)	156 (48.4)
Closed	13.7	6.0	37	36
Granular	1.9	1.6	63	35

*Values in parentheses are new estimates provided by EFB/HED, July 9, 1981.

TABLE 3. LIFETIME CANCER RISK FOR DIALLATE APPLICATORS ASSOCIATED WITH THE "AVERAGE" EXPOSURE d

Inhalation		
System	d (ug/kg/day)	Lifetime Probability of Cancer Due to Diallate
Open	8.17×10^{-3} 5.09×10^{-3}	4.99×10^{-7} 3.10×10^{-7}
Closed	8.04×10^{-3}	4.9×10^{-7}
Granular	2.14×10^{-3}	1.31×10^{-7}

Dermal		
System	d (ug/kg/day)	Lifetime Probability of Cancer Due to Diallate
Open	2.09×10^{-1} 6.48×10^{-2}	1.27×10^{-5} 3.95×10^{-6}
Closed	4.82×10^{-2}	2.94×10^{-6}
Granular	4.69×10^{-2}	2.86×10^{-6}

TABLE 4. LIFETIME CANCER RISK FOR DIALLATE APPLICATORS ASSOCIATED WITH THE "MAXIMUM" EXPOSURE d

Inhalation		
System	d (ug/kg/day)	Lifetime Probability of Cancer Due to Diallate
Open	1.84×10^{-2} 1.34×10^{-2}	1.12×10^{-6} 8.17×10^{-7}
Closed	1.84×10^{-2}	1.12×10^{-6}
Granular	2.55×10^{-3}	1.55×10^{-7}

Dermal		
System	d (ug/kg/day)	Lifetime Probability of Cancer Due to Diallate
Open	8.71×10^{-1} 2.32×10^{-1}	5.31×10^{-5} 1.41×10^{-5}
Closed	4.96×10^{-2}	3.02×10^{-6}
Granular	8.44×10^{-2}	5.15×10^{-6}

COMPARISON BETWEEN CAG'S AND MONSANTO'S RISK ASSESSMENTS

Based on the carcinogenic potency estimated from various animals studies, Monsanto has calculated the cancer risk associated with the maximum exposure to diallate-treated sugar and for diallate spray applicators. Since the CAG's quantitative risk assessment is based on the hamster study, only the risk calculations based on this study are compared in this report. Based on the benign/malignant melanomas incidence data (male and female combined) the company has estimated the carcinogenic potency of diallate as 1.0×10^{-4} $(ppm)^{-1}$, the point estimate of the linear component in a multistage model. Since cancer risk is linearly proportional to the exposures, one needs only to compare the relative magnitudes of the slopes estimated by the CAG and Monsanto. We found that the company's potency estimate (slope) is about 46 fold smaller than the CAG's estimate for the following reasons:

1. The CAG has used only the tissues examined histologically as the denominator of tumor incidence (taken from Appendix K of the Monsanto Hamster Study) while the company used as the demoninator all animals which survived beyond week 28 when the first melanoma was observed. As a result of the difference, the CAG's slope estimate is about six times greater than the company estimate. Since gross examination of these animals cannot guarantee that a lesion will or will not be reported, the CAG feels that the use of the number of tissues (i.e., skin) examined histologically per test group for the denominator is more appropriate for reporting tumor incidence rather than the figures the company used for their risk assessment.

2. The company assumed that the dietary consumption in ppm is equivalent for both hamsters and humans. This assumption is not made in the CAG's risk calculation because we feel that it is not justified. The calories/kg of food

is very different in the diet of man compared to laboratory animals, primarily due to the moisture content difference. The CAG has calculated the ppm dietary equivalance in terms of mg/kg/day in animals and then converted it to human equivalent dose by adjusting for the body surface difference. As a result of this discrepancy, the CAG's slope estimate is about 7.5-fold greater than the company's estimate.

3. A minor difference (less than twofold) is due to the fact that the CAG has used the 95% upper-limit of the linear component as the carcinogenic potency, while the company has used point estimate as the potency.