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Khera and McKinley (*130*) studied the prenatal and postnatal effects of 2,4,5-T in Wistar rats, using four samples containing no TCDD (detection limit: 0.5 mg/kg) [Table 23]. Twenty-five to one hundred fifty mg/kg body weight per day were administered to the dams, orally in gelatin or corn oil, on days 6 to 15 of gestation. At 25 and 50 mg/kg, the differences between experimental and control values were minimal. However, at 100 and 150 mg/kg, there were significant ($p < 0.05$) effects on fetal weight, number of dead fetuses, and percentage of malformed fetuses per litter.[a] The larger proportion of malformed fetuses in the treated groups resulted from either an increased incidence of skeletal anomalies also seen in the controls or a low incidence of abnormalities not observed in the controls. The former category included wavy ribs, retarded ossification, extra ribs, and a variety of sternal defects; the latter included fused ribs, small-sized distorted scapula, malformed humerus shaft, and bent radius or ulna. Abnormal kidneys were observed in 7 to 45% of the examinined fetuses treated with sample T-1, compared with a control value of 20 to 35%.

In the postnasal portion of the study, after normal delivery, survival rate, sex ratio, and pup weight on days 1 and 21 were compared. Although treated pups surviving from day 2 to 21 were slightly smaller at some dose levels, there were no significant differences from controls for any variable. In some experiments, litters were standardized at 8 pups on day 2, and the remaining littermates examined for defects. The increased incidences of malformations among treated groups were comparable to those found in the prenatal study. Assuming the same incidence for pups not examined, the investigators concluded that there were no real differences in survival rates among control and treated groups. The butyl ester of 2,4,5-T produced similar toxic effects.

Sokolik (*131*) orally administered 100 and 400 mg/kg and 50 and 200 mg/kg of 2,4,5-T and its butyl ester to rats of the Rappolovo line on each of days 1 to 14 or 1 to 16 of pregnancy. At 100 mg/kg, 2,4,5-T produced embryos with a combination of deformities including absence of lower jaw, abnormal hind limbs, and exophthalmos. At 400 mg/kg, the embryos of treated rats evidenced cleft palate, hydrocephalus, hydronephrosis, and abnormalities of the upper limbs which included tridactyly, webbed toes, and abnormal shortness.

The butyl ester of 2,4,5-T was more toxic than the parent compound, causing more than 30 percent embryonic mortality at 200 mg/kg. The lower dose, 50 mg/kg, also caused high mortality among the embryos. Cleft palate, hydronephrosis, hydrocephalus, and extensive gastrointestinal hemorrhages were also observed within the treated groups. From these results, the author concluded that 2,4,5-T and its derivatives have a high potential for teratogenic activity.

Collins and Williams (*124*) tested seven samples of 2,4,5-T from different sources for embryotoxic effects in golden Syrian hamsters (*Mesocricetus auratus*) [Table 23]. The dioxin contents ranged from not detectable (detection limit <0.1 ppm) to 45 ppm. Daily oral doses of 20 to 100 mg/kg body weight were administered in acetone:corn oil:carboxymethyl cellulose (1:5.8:10) on days 6 to 10 of gestation. 2,4,5-T with no detectable dioxin significantly ($p < 0.05$) reduced fetal weight and fetal viability per litter at all levels tested.

Total fetal mortality was greatly increased at all levels when compared with controls and was dose-dependent, as was the effect on fetal viability. The increased incidence of gastrointestinal hemorrhage also appeared to be dose related. At 100 mg/kg, "pure" 2,4,5-T caused increased incidences of malformations and reductions in the number of live fetuses per litter. One "pure" sample, F, at 100 mg/kg significantly reduced fetal weight from 1.8 to 1.6 grams, reduced fetal viability from 90.7 to 71.4 percent, and increased abnormalities from 3.5 to 40 percent. The anomalies associated with 2,4,5-T containing no dioxin were exencephaly, eye abnormalities, delayed head ossification, and hind limb deformities.

Increasing the level of dioxin contamination increased fetal mortality and the incidence of abnormalities per litter; fetal viability was reduced. A clear correlation was found between the level of dioxin and abnormalities per litter. Although the incidence of hemorrhages also increased, no relationship between it and dioxin level could be found. Bulging eyes (absence of eyelid) and delayed ossification were the most common anomalies seen among fetuses exposed to dioxin-contaminated 2,4,5-T; exencephaly, edema, cleft palate, ectopic heart, and fused ribs were also observed.

Emerson et al. (*141*) found no adverse effects of commercial 2,4,5-T, containing 0.5 ppm TCDD, on fetal development in Sprague-Dawley derived rats and New Zealand white rabbits. Daily oral doses of 2,4,5-T in gelatin were administered to the rats at 1 to 24 mg/kg on days 6 to 15 of gestation; to the rabbits at 10 to 40 mg/kg on days 6 to 18 of gestation. The investigators found no maternal or embryonic toxic effects in either species, nor was 2,4,5-T considered teratogenic under the conditions of these experiments. The most frequently observed abnormalities were accessory ribs, hydronephrosis, and retardation in the development of the sternebrae. With the exception of partially ossified sternebrae in both species and bilateral accessory ribs in the rabbit, the incidence of these anomalies was greater in the control animals than in the examined treated groups.

Sparschu et al. (*140*) orally administered 2,4,5-T, containing 0.5 ppm TCDD, to rats in daily doses of 50 and 100 mg/kg on days 6 to 15 and 6 to 10 of gestation, respectively. Results are given in Table 24. At 50 mg/kg, there were no significant maternal or embryonic toxic effects attributable to 2,4,5-T except for an increased incidence of delayed skull ossification, and a single fetus with in-

[a] Statistical significance was determined using the average value per dose level. Data from T-4 were not used in this analysis.

Table 23. Embryotoxic Effects of 2,4,5-T in Hamsters[a]

Compound	Dioxin Content (ppm)	Dose (mg/kg)	Fetuses: % Total Mortality	Fetuses: Avg # Live per Litter	Fetuses: Avg Weight[b] (grams)	% Fetal Viability per Litter	% Abnormalities per Live Litter	% Hemorrhages per Total Live Fetuses
Control	---	---	3.4	11.0	1.8	96.7	3.5	0.32
A	45	20	32.3	7.3	1.7	68.1[d]	25.0[d]	28.4
		40	74.3	3.7	1.7	25.8[d]	33.3[d]	75.7
		80	94.4	0.8	1.6	5.3[d]	100.0[d]	42.9
		100	100.0	0	---	0[d]	---	---
B	2.9	40	7.2	9.1	1.7	93.1	0	0
		80	9.8	10.4	1.7	90.1[d]	12.5	2.4
		100	11.4	12.8	1.7	88.5[d]	50.0[d]	13.0
C	0.5	20	8.5	12.6	1.7[d]	90.8[d]	0	8.6
		40	4.0	13.4	1.6[d]	95.9	11.1	2.5
		80	43.6	6.6	1.6[d]	58.3[d]	40.0[d]	12.5
		100	51.2	5.1	1.5[d]	40.2[d]	40.0[d]	7.6
D	0.1	40	2.4	11.4	1.8	97.8	0	0
		80	33.3	7.8	1.7	68.3[d]	0	2.1
		100	37.1	6.0	1.6[d]	57.2[d]	0	5.6
E	ND[c]	40	10.7	11.2	1.5[d]	88.2[d]	0	1.5
		80	29.9	8.7	1.5[d]	69.1[d]	0	4.2
		100	56.3	6.3	1.5[d]	53.1[d]	36.4[d]	0
F	ND	100	31.3	7.3	1.6[d]	71.4[d]	40.0[d]	6.8
G	ND	100	30.0	8.4	1.6[d]	68.3[d]	0	16.7

[a] Data from Collins and Williams (124).
[b] Apparently normal weights for samples A and B attributed to edema.
[c] Not detected.
[d] $p < 0.05$.

Table 24. Effects of 2,4,5-T on Fetal Development of Rats[a/]

Parameter	Dose (mg/kg per day) 0	50	100
# Viable fetuses			
Total	252	203	13[b/]
Mean per litter	11	11	[illegible]
% Resorptions			
Litters	60	61	100
Total fetuses	6.7	12.1	75[c/]
Fetal weight (grams)			
Male	4.41	4.30	3.57[c/]
Female	4.17	4.15	3.52[c/]
Sex Ratio (M:F)	53:47	44:56	23:77
Abnormalities (% fetuses examined)			
Poorly ossified sternebrae			
Fifth	15.2	22.1	57.1[c/]
Second and fifth	3.0	4.2	14.3
Multiple	8.3	12.6	14.3
Malaligned sternebrae	0.8	2.1	28.6[c/]
Delayed ossification			
Interparietal	3.8	16.8[c/]	28.6[c/]
Parietals	3.0	16.8[c/]	57.1[c/]
Frontals	0.8	7.4[c/]	14.3

a/ Data from Sparschu et al. (140).
b/ All viable fetuses from one litter.
c/ $p < 0.05$

testinal hemorrhage. At 100 mg/kg, 2,4,5-T was toxic to both dams and fetuses.[b]

Resorptions were observed in all litters; 75 percent were totally resorbed. Fetal weight was significantly ($p < 0.001$) reduced in both sexes and the sex ratio was shifted in favor of females. Abnormalities observed which had significantly ($p < 0.05$) higher incidences than in the controls were poorly ossified and malaligned sternebrae and delayed skull ossification. The investigators concluded that the delayed ossification observed in this study was a reversible manifestation, rather than a true teratogenic effect.

(b) *Adverse Reproductive Effects in Other Mammalian Test Systems.* Adverse reproductive effects of 2,4,5-T exposure have been observed in other mammalian test systems. Lloyd et al. (*173*) reported on *in vivo* enzymatic studies showing reduced uptake and metabolism of testosterone by the prostate gland in male mice treated orally with doses of 2,4,5-T (6.25, 12.5, or 25 mg/kg, ten times daily).

Yefimenko (*151*) reported on the effects of acute and chronic exposure to the butyl ester of 2,4,5-T on gonadal and somatic tissue in an *in vivo* cytogenetic study in male albino rats. Chronic effects on the gonads were observed after exposure to 0.1 ug/kg for two and one half months. Adverse effects (seen at seven months, when the experiment was terminated), which were considered persistent effects, included testicular atrophy, decreased sperm count, desquamated tubules, and aberrant cells in the germinal epithelium. Chromosomal aberrations were also observed during the chronic phase of the experiment. EPA evaluation of this study found inadequacies in the methodology which would prevent the drawing of firm conclusions from this data (*106*).

Recent studies in rats by Sjoden and Soderberg (cited in (*25*)) appear to show that prenatal exposure to 2,4,5-T leads to behavioral abnormalities and changes in thyroid activity and brain seritonin levels in the progeny. Single oral doses of 100 mg/kg were administered to the dams on days 7, 8, or 9 of pregnancy.

(c) *Adverse Effects in Avian Species.* Embryotoxic effects in avian species due to 2,4,5-T exposure have been reported. Verrett (*136*) studied the effects of 2,4,5-T, containing either 27 or 0.5 ppm TCDD, on chicken eggs. The 2,4,5-T was injected through the air cell of the eggs, either preincubation or on the fourth day of incubation. The sample containing 27 ppm TCDD was found to be more lethal (LD-50=25 ug/egg) than the less contaminated sample (LD-50=100 ug/egg). Both samples produced teratogenic effects, including chick edema, eye defects, beak defects (primarily cleft palate), and short, twisted feet resulting from tendon slippage. Teratogenic effects were observed at doses as low as 1 ppm (50 ug/egg) with the sample containing 0.5 ppm TCDD and as low as 0.125 ppm (6.25 ug/egg) with the sample containing 27 ppm TCDD.

Lutz and Lutz-Ostertag (*138*) studied the action of 2,4,5-T, in aqueous solution at a concentration of 2 to 10 g/liter, on the embryonic development of quail (*Coturnix coturnix japonica*), chicken (*Gallus gallus*), pheasant (*Phasianus colchicus*), and two partridge species (*Alectoris rufa* and *Perdrix perdrix*). The 2,4,5-T was administered by dipping, spraying, and organo-typic cultures. Abnormal genital tracts were observed in all species, indicating abnormal sexual differentiation. Further, morphological changes in the testes often gave the appearance of true testicular atrophy. In another study, 2,4,5-T affected fertility in birds of both sexes (*139*).

(d) *Studies in Avian Species in Which Adverse Effects Were Not Observed.* Using 2,4,5-T contaminated with less than 0.1 ppm dioxin, Stradge and Kerr (*142*) found no abnormal development in chicken embryos. Doses of 12.5, 25, 50, 75, 100, and 125 mg/kg were injected into eggs on days 0 and 5 of incubation; observations were made 48 hours later. At this developmental stage, kidneys were not sufficiently developed to detect the tubule lesions reported by Bjorklund and Erne (*143*).

(e) *Summary.* Studies have established that 2,4,5-T is fetotoxic and teratogenic at doses as low as 35mg/kg (0.05 ± 0.02 ppm TCDD) in mice (*125*); 4.6 mg/kg (approximately 30 ppm TCDD) in rats (*133*); and 20 mg/kg (0.5 ppm TCDD) in hamsters (*124*). Cleft palate and kidney anomalies have been observed in mice, rats, and hamsters. No fetotoxic or teratogenic effects (no-effect levels) have been observed at doses of 20 mg/kg (0.05 ± 0.02 ppm TCDD) in mice (*125*) and 25 to 150 mg/kg (0.05 ± 0.02 ppm TCDD) in rats (*125*).

30 ppm TCDD

No Exact Level

(3) *Exposure Analysis.* In order to determine whether a rebuttable presumption should be issued based on reproductive and fetotoxic effects, pursuant to § 162.11(a)(3)(ii)(B), the Working Group must determine whether or not an ample margin of safety exists between the levels of 2,4,5-T and/or TCDD which produce reproductive and fetotoxic effects, and the level(s) to which humans can reasonably be anticipated to be exposed.

The cancellation of uses of 2,4,5-T on food crops intended for human consumption and for use around the home, recreation sites, aquatic areas, and ditch banks in 1970 was thought to have eliminated the potential exposure to that portion of the population at risk (women of child bearing age).

Social changes over the last few years, however, have given women the opportunity for employment in areas that once were considered open only to men. Since women of child-bearing age are now employed in occupations such as pesticide applicators, operators of highway construction and maintenance equipment, foresters, and chemical formulators, they have become part of the

[b]The high rate of maternal mortality caused dosing to be stopped on day 10, instead of day 15. Significant reductions in weight gain were also observed.

population at risk with potential exposure to 2,4,5-T and/or TCDD.

In order to determine whether an ample margin of safety exists, the Working Group must first determine how much 2,4,5-T a woman could be exposed to through oral, dermal, or inhalation exposure. For each of these analysis, the Working Group assumes a woman to weigh 60 kg. The following calculations are based on an exposure analyses for 2,4,5-T and TCDD performed by EPA's Criteria and Evaluation Division [CED] (*164*).

(a) *Oral Exposure.* For purposes of this analysis, the Working Group considered currently registered uses where the possibility of oral exposure to 2,4,5-T and/or TCDD existed. Treatment of range and pasture land could result in oral exposure through ingestion of meat and milk from animals grazing on the treated area. Since actual data on residues of 2,4,5-T in animals grazing on treated rangeland is unavailable, for purposes of the 2,4,5-T oral exposure analysis, the Working Group used residue information obtained in a feeding study (*37*) in which cattle were fed considerably higher amounts of 2,4,5-T than they would normally be exposed to in grazing on treated land. The following calculations are based on the average quantities of food eaten per day (1.5 kg), as reported by Lehman (*144, 165*).

Table 25.—2,4,5-T Oral Exposure Analysis

	Whole Milk	Meat (Beef)
No-adverse-effect level for teratogenicity in mice	20 mg/kg	20 mg/kg
Average level of 2,4,5-T identified	0.103 ppm[a/]	0.2 ppm[a/]
% of food item in total human diet	19.6%	4.6%
Average amount of food eaten per day	1.5 kg	1.5 kg
Exposure to 2,4,5-T per day	0.0005 mg/kg	0.0002 mg/kg

a/ Animals were fed at 300 ppm 2,4,5-T in the diet for 2 to 3 weeks. This is a worst case assumption for cows grazing on freshly-treated pasture without a withdrawal period; all milk and meat was obtained from such cows. Meat (beef) includes muscle, fat, and liver tissues which constitute the major portion of edible meat.

To find the average daily intake of a single food item, multiply the average daily food intake by the percent of that item in the total diet: For milk, 1.5 kg×19.6%=0.294 kg; and for meat (beef), 1.5 kg×4.6%=0.069 kg.

The quantity of 2,4,5-T in the average daily diet equals the average daily intake of each food item multiplied by the level of 2,4,5-T in the food item: For milk, 0.294 kg×0.103 ppm=0.03 mg; and for meat (beef), 0.069 kg×0.2 ppm=0.014 mg.

The theoretical exposure of an average woman equals the amount of 2,4,5-T in the daily diet divided by the weight of the average woman: For milk, 0.03 mg/60 kg=0.0005 mg/kg; and for meat (beef), 0.014 mg/60 kg=0.0002 mg/kg; total exposure from milk and beef products could be 0.0007 mg/kg per day.

Existing data on TCDD residues in animals grazing on treated rangeland are too meager to use for an analysis of TCDD exposure to humans through ingestion of meat or milk from animals so exposed.

The Working Group considers that the difference between the no-adverse-effect level of 2,4,5-T for teratogenic effects (20 mg/kg) and the calculated oral exposure level for 2,4,5-T (0.0007 mg/kg per day) does constitute an ample margin of safety. Since this risk criterion for other chronic adverse effects has not been met or exceeded, a rebuttable presumption does not arise.

(b) *Dermal Exposure.* In order to conduct these analyses, the Working Group must determine the amount of 2,4,5-T and/or TCDD which would come in contact with the skin and the amount that would be absorbed.

(1) *Spray Applicator: Back-pack Sprayer.* For purposes of this analysis, the Working Group assumes the applicator to be a 60-kg woman of child-bearing age, and the site of application either a right-of-way or spot treatment of pasture or rangeland. The equipment is a back-pack sprayer (*164*). The following calculations of exposure are based on dilution for spraying of three pints of formulated product per 32 pints of water. Typical 2,4,5-T formulations, based on inspection of a large number of registered labels (*164*), range from 4 to 6 pounds active ingredient (acid equivalent) per gallon. The product used in this exposure analysis has an assumed concentration of 4 pounds 2,4,5-T per gallon. Label recommendations vary from a recommended dilution of 0.004 to 4 pounds acid equivalent per 32 pints of water. A dilution rate of 1.6 pounds per 32 pints has been selected as representative of a typically-used spray mixture.

Wolfe et al. (*166*) studied dermal exposure to fenthion during hand back-pack spraying for mosquitoes for ten situations. Exposure ranged from 0.1 to 6.3 mg/hr, with a mean value of 3.6 mg/hr (6 ml/hr). Method of application was a hand pressure sprayer, using a 0.06 percent spray. Workers wore short-sleeved, open-necked shirts with no gloves or hat. Based on Wolfe's data, CED (*164*) calculated a dermal exposure of approximately 0.177 pints per day. CED (*164*) also determined that approximately 10 percent of the 2,4,6-T and TCDD coming in contact with the skin of the applicators would be absorbed even after washing, based on absorption studies with other pesticides (*145, 146, 163*).

Table 26.—Back-pack Sprayer Dermal Exposure Data

	2,4,5-T	TCDD
Use Dilution rate	3 pints (1.6 pounds 2,4,5-T) per 32 pints water	3 pints (0.00000016 pounds TCDD) per 32 pints water
Amount of diluted material gotten on skin daily	0.16 pint	0.16 pint
% Diluted material absorbed	10%	10%
Exposure level	409 mg	0.0409 ug
Dose level	6.8 mg/kg	0.0007 ug/kg
No-Adverse-Effect level for teratogenic effects	20 mg/kg	0.03 ug/kg

The following calculations (see Table 27 for mathematics) will give the daily dermal exposure for both 2,4,5-T and TCDD: (1) Convert the dilution rate to grams; (2) multiply this figure by 1,000 (for 2,4,5-T) to convert to milligrams and by 1,000,000 (for TCDD) to convert to micrograms; (3) multiply this figure by the daily dermal dose of diluted material; (4) multiply this figure by the percent absorbed; and (5) divide this figure by the weight of the applicator for the daily exposure to 2,4,5-T or TCDD per 8-hour working day.

The Working Group considers that the difference between the no-adverse-effect level of 2,4,5-T for teratogenic effects (20 mg/kg) and this calculated dermal exposure level for 2,4,5-T (6.8 mg/kg), as well as the difference between the no-adverse-effect level of TCDD for teratogenic effects (0.03 µg/kg) and this calculated exposure level for TCDD (0.0007 µg/kg), do not constitute an ample margin of safety. The Working Group therefore recommends issuance of a rebuttable presumption against pesticide products containing 2,4,5-T and/or TCDD pursuant to 40 CFR Section 162.11(a)(3)(ii)(B).

(ii) *Spray Applicator: Tractor-mounted, Low-boom Spray Equipment.* For the purpose of this analysis, the Working Group assumes the applicator to be a 60-kg female of childbearing age clearing brush on either rangeland or rights-of-way. The same product cited above (2,4,5-T at 4 pounds/gal) is being used, and the dilution rate is 1.6 pounds of formulation to 32 pints of water (equal to 4 pounds of 2,4,5-T per 10 gallons of water). Based on exposure studies using similar equipment but a different herbicide (*147*), the Working Group determined that, during an eight-hour working day, the applicator would get 0.048 pints of diluted material on her skin. The Working Group determined that 10 percent of the pesticide on the skin would be absorbed (*145, 146, 153*).

The following calculations (see Table 29 for mathematics) will give the daily dermal exposure for both 2,4,5-T and TCDD: (1) Convert the dilution rate to grams; (2) multiply this figure by 1,000 (for 2,4,5-T) to convert to milligrams and by 1,000,000 (for TCDD) to convert to micrograms; (3) multiply this figure by the daily dermal dose of diluted material; (4) multiply this figure by the percent absorbed; and (5) divide this figure by the weight of the applicator for the daily exposure to 2,4,5-T or TCDD per 8-hour working day.

Table 27

2,4,5-T	TCDD
1) 1.6 pounds/32 pt X 454 g/pound = 22.70 g/pt;	1) 0.00000016 pounds/32 pt X 454 g/pound = 0.00000227 g/pt;
2) 22.70 g/pt X 1,000 mg/g = 22,700 mg/pt;	2) 0.00000227 g/pt X 1,000,000 ug/g = 2.27 ug/pt;
3) 22,700 mg/pt X 0.18 pt = 4,086 mg;	3) 2.27 ug/pt X 0.18 pt = 0.41 ug;
4) 4,086 mg X 10% = 408.6 mg	4) 0.41 ug X 10% = 0.041 ug;
5) 408.6 mg / 60 kg = 6.8 mg/kg per day	5) 0.041 ug / 60 kg = 0.0007 ug/kg per day

Table 28. Dermal Exposure Data (Tractor Mounted Equipment)

	2,4,5-T	TCDD
Use Dilution rate	3 pints (1.6 pounds 2,4,5-T) per 32 pints water	3 pints (0.00000016 pounds TCDD) per 32 pints water
Amount of diluted material gotten on skin daily	0.048 pint	0.048 pint
% Diluted material absorbed	10%	10%
Exposure level	109 mg	0.0109 ug
Dose level	1.8 mg/kg	0.00018 ug/kg
No-Adverse-Effect level for teratogenic effects	20 mg/kg	0.03 ug/kg

Table 29

2,4,5-T	TCDD
1) 1.6 pounds/32 pt X 454 g/pound = 22.70 g/pt;	1) 0.00000016 pounds/32 pt X 454 g/pound = 0.00000227 g/pt;
2) 22.70 g/pt X 1,000 mg/g = 22,700 mg/pt;	2) 0.00000227 g/pt X 1,000,000 ug/g = 2.27 ug/pt;
3) 22,700 mg/pt X 0.048 pt = 1,089.6 mg;	3) 2.27 ug/pt X 0.048 pt = 0.109 ug;
4) 1,089.6 mg X 10% = 108.96 mg;	4) 0.109 ug X 10% = 0.011 ug;
5) 108.96 mg / 60 kg = 1.8 mg/kg per day	5) 0.011 ug / 60 kg = 0.00018 ug/kg per day

The Working Group considers that the difference between the no-adverse-effect level of 2,4,5-T for teratogenic effects (20 mg/kg) and this calculated dermal exposure level for 2,4,5-T (1.8 mg/kg), as well as the difference between the no-adverse-effect level of TCDD for teratogenic effects (0.03μg/kg) and this calculated exposure level for TCDD (0.00018 μg/kg), do not constitute an ample margin of safety. The Working Group therefore recommends issuance of a rebuttable presumption against pesticide products containing 2,4,5-T and/or TCDD pursuant to 40 CFR 162.11(a)(3)(ii)(B).

(iii) *Aerial Application: Exposed Population Directly Beneath Spray Plane.* Caplan et al. (*167*), working with aerially applied malathion in oil sprays applied at 0.46 pounds per 0.76 gallons water/acre, determined a dermal exposure to persons directly beneath the spray plane for bare skin (head, neck, shoulders, forearms, hands, and thighs) of 3.556 mg/day. With these data, an equivalent dermal exposure for 2,4,5-T and TCDD, aerially applied at 4 pounds acid equivalent 2,4,5-T per 10 gallons water/acre, can be determined.

Table 30.—Dermal Exposure Data (Aerial Application)

Dermal exposure to aerially applied malathion	3.556 mg/0.46 pounds malathion per acre	
Use Dilution rate	2,4,5-T 4 pounds 2,4,5-T per 10 gallons of water/acre	TCDD 0.0000004 pounds TCDD per 10 gallons of water per acre
% Diluted material absorbed	10%	10%
Exposure level	3.1 mg	0.0003 ug
Dose level	0.051 mg/kg	5×10^{-6} ug/kg
No-Adverse-Effect level for teratogenic effects	20 mg/kg	0.03 ug/kg

The following calculations (see Table 31 for mathematics) will give the daily dermal exposure for both 2,4,5-T and TCDD: (1) Divide the dermal exposure to malathion by the malathion application rate and multiply by the application rate of 2,4,5-T and TCDD to obtain the dermal exposure; for TCDD, multiply this figure by 1,000 to convert to micrograms; (2) multiply this figure by the percent absorbed; and (3) divide this figure by the weight of the applicator for the daily exposure to 2,4,5-T or TCDD per 8-hour working day.

Table 31

2,4,5-T	TCDD
1) 3.556 mg/0.46 pounds X 4 pounds = 31 mg;	1) 3.556 mg/0.46 pounds X 0.0000004 pounds = 0.000003 mg X 1,000 = 0.003 ug;
2) 31 ug X 10% = 3.1 mg;	2) 0.003 ug X 10% = 0.0003 ug;
3) 3.1 mg/ 60 kg = 0.051 mg/kg per day	3) 0.0003 ug / 60 kg = 5×10^{-6} ug/kg per day

The Working Group considers that the difference between the no-adverse-effect level of TCDD for teratogenic effects (0.03 μg/kg) and this calculated dermal exposure level for TCDD (5×10^{-6} μg/kg) does constitute an ample margin of safety. The Working Group also considers, however, that the difference between the no-adverse-effect level of 2,4,5-T for teratogenic effects (20 mg/kg) and this calculated dermal exposure level for 2,4,5-T (0.051 mg/kg) does not constitute an ample margin of safety. The Working Group therefore recommends issuance of a rebuttable presumption against pesticide products containing 2,4,5-T pursuant to 40 CFR 162.11(a)(3)(ii)(B).

(c) *Inhalation Exposure: Aerial Application.* There are no studies available on inhalation exposure of 2,4,5-T. There are, however, several studies on inhalation exposure to malathion (167, 168) which CED used as a model for this 2,4,5-T exposure analysis (*166*). Caplan et al. (*167*) determined an air concentration, for unprotected persons directly beneath the spray plane during application and for two hours afterward, of 0.067 mg malathion/m^3 from aerial application of 0.46 pounds AI/gallon per acre. The collection period spanned the course of the actual application time plus two hours thereafter. The authors considered the sampling technique to be equivalent to average inspira-

tion through the nostrils. This inhalation exposure (amount available for inhalation) was 12 percent of the applied malathion. Caplan et al. further reported that the average median diameter (=volume median diameter, or vmd [18]) was 109 microns. Based on work by Akesson and Yates (*165*), CED (*164*) estimated that the size of the malathion droplets which could be inhaled was under 60 microns. Since 2,4,5-T is typically applied as a medium or coarse spray, while malathion is applied as a fine spray, the percent of 2,4,5-T droplets small enough to be inhaled (under 60 microns) would be less than the percent of malathion droplets small enough to be inhaled. According to Akesson and Yates (*165*), 2 percent of 2,4,5-T spray droplets would be available for inhalation (or ⅙ the amount of malathion droplets available for inhalation), on a "worst case" basis.

The following calculations (see Table 32 for mathematics) will give the daily inhalation exposure for both 2,4,5-T and TCDD: (1) Multiply the air concentration of malathion by the amount of 2,4,5-T and TCDD applied, then multiply this figure by ⅙ for the inhalation exposure to 2,4,5-T and TCDD; for TCDD, multiply this figure by 1,000 to convert to micrograms; (2) multiply this figure by the breathing rate; (3) multiply this figure by eight (8) to get the 8-hour exposure total; and (4) divide this figure by the weight of the applicator for the inhalation exposure to 2,4,5-T or TCDD per 8-hours exposure.

The Working Group considers that the difference between the no-adverse-effect level of TCDD for teratogenic effects (0.03 μg/kg) and this calculated dermal exposure level for TCDD (2×10^{-4} μg/kg) does constitute an ample margin of safety. The Working Group also considers, however, that the difference between the no-adverse-effect level of 2,4,5-T for teratogenic effects (20 mg/kg) and this calculated dermal exposure level for 2,4,5-T (0.026 mg/kg[17]) does not constitute an ample margin of safety. The Working Group therefore recommends issuance of a rebuttable presumption against pesticide products containing 2,4,5-T pursuant to 40 CFR 162.11(a)(3)(ii)(B).

(d) *Cumulative Exposure.* The Working Group has also considered the possibility of a single individual being exposed through two or more of the above routes. The results (derived from Tables 27, 29, and 31) are shown in Table 34. The Working Group also notes that possible cumulative exposure to several dioxin-containing pesticides could increase the total body burden and increase total risk from dioxin exposure.

The Working Group considers that the differences between the no-adverse-effect level of TCDD for teratogenic effects (0.03 μg/kg) and the calculated cumulative exposure levels for TCDD in Situations 2 and 3 (see Table 34) do constitute an ample margin of safety. The Working Group also considers, however, that the differences between the no-adverse-effect levels of 2,4,5-T and TCDD for teratogenic effects (20 mg/kg and 0.03 μg/kg, respectively) and the calculated cumulative exposure levels for 2,4,5-T in Situations 1, 2, and 3 and TCDD in Situation 1 (see Table 34) do not constitute an ample margin of safety. The Working Group therefore recommends issuance of a rebuttable presumption against pesticide products containing 2,4,5-T pursuant to 40 CFR 162.11(a)(3)(ii)(B).

[18] The vmd is that droplet size which divides the total volume of drops in half, i.e., 50 percent of the volume is in drops above the vmd size and 50 percent below it.

[17] Johnson (*63*) (see Section I.C.(3)), in a review article, calculated a daily inhalation exposure to phenoxy herbicides of 0.025 μg/kg for a 70-kg adult. The calculations were based on actual air monitoring data of air samples collected in two wheat-growing areas in the state of Washington during spring and summer and analyzed for phenoxy herbicides. The author did not specify how soon after application the samples were taken.

Table 32. Inhalation Exposure Data (Aerial Application)

Air concentration of aerially applied malathion	0.067 mg/m^3 with application rate of 0.46 pounds malathion per gallon per acre	
	2,4,5-T	TCDD
Use Dilution rate	4 pounds 2,4,5-T per 10 gallons of water/acre	0.0000004 pounds TCDD per 10 gallons of water per acre
Lung Absorption Rate	100%	100%
Breathing Rate	1.8 m^3/hr	1.8 m^3/hr
Exposure level	0.34 mg per 2 hr	0.000032 ug per 2 hr
Dose level	0.023 mg/kg per 8 hr	2×10^{-6} ug/kg per 8 hr
No-Adverse-Effect level for teratogenic effects	20 mg/kg	0.03 ug/kg

Table 33.

2,4,5-T	TCDD
1) 0.067 mg/cu m per 0.46 pounds X 4 pounds = 0.58 mg/cu m X 1/6 = 0.097 mg/cu m;	1) 0.067 mg/cu m per 0.46 pounds X 0.0000004 pounds = 0.000000058 mg/cu m X 1/6 = 0.000000009 mg/cu m X 1,000 = 0.000009 ug/cu m;
2) 0.097 mg/cu m X 1.8 cu m/hr = 0.17 mg/hr;	2) 0.000009 ug/cu m X 1.8 cu m/hr = 0.000016 ug/hr;
3) 0.17 mg/hr X 8 = 1.36 mg;	3) 0.000016 ug/hr X 8 = 0.000128 ug;
4) 1.36 mg / 60 kg = 0.026 mg/kg exposure per day	4) 0.000128 / 60 kg = 2×10^{-6} ug/kg per day

Table 3a. Cumulative Exposure to 2,4,5-T and TCDD

Situation #1: 2,4,5-T		Situation #1: TCDD	
Oral-	0.0007 mg/kg	Oral-	-----
Dermal-	6.8 mg/kg	Dermal-	0.0007 ug/kg
Inhal.-	0.2 mg/kg[a/]	Inhal.-	negligible[a/]
Cum. =	7.0 mg/kg	Cum. =	0.0007 ug/kg
Situation #2: 2,4,5-T		**Situation #2: TCDD**	
Oral-	0.0007 mg/kg	Oral-	-----
Dermal-	1.8 mg/kg	Dermal-	0.00018 ug/kg
Inhal.-	0.05[a/]	Inhal.-	negligible[a/]
Cum. =	1.85 mg/kg	Cum. =	0.00018 ug/kg
Situation #3: 2,4,5-T		**Situation #3: TCDD**	
Oral-	0.0007 mg/kg	Oral-	-----
Dermal-	0.051 mg/kg	Dermal-	5×10^{-6} ug/kg
Inhal.-	0.026 mg/kg	Inhal.-	2×10^{-6} ug/kg
Cum. =	0.0777 mg/kg	Cum. =	7×10^{-6} ug/kg

[a/] Calculations were made on a worst-case basis as 3% of dermal exposure based on Wolfe (179) who states, "over 97% of the pesticide to which the body is subjected during most exposure situations, and especially to applicators of liquid sprays, is deposited on the skin." TCDD inhalation exposure values were negligible: Situation #1, 21×10^{-6} ug/kg; Situation #2, 54×10^{-7} ug/kg.

IV. STUDIES RELATING TO POSSIBLE ADVERSE EFFECTS

This section addresses other types of adverse effects of 2, 4, 5-T for which the Working Group has determined that insufficient evidence exists to initiate a rebuttable presumption. The Agency solicits comments from registrants and other interested parties on the evidence listed below, and requests submission of any additional studies or relevant information on 2, 4, 5-T and/or TCDD relative to these potential adverse effects.

A. *Mutagenicity.* Section 162.11(A)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) induce mutagenic effects, as determined by multitest evidence.

(1) *2, 4, 5-T*—(a) *Positive Study.* Majumdar and Golla (*178*) fed male *Drosophila melanogaster* either 250 or 1,000 ppm dioxin free 2, 4, 5-T (obtained from Eastman Kodak) for 15 days. They were then mated to sets of virgin females to generate three 4-day broods of offspring. F_1 flies were allowed to mate, and F_2 flies were scored for X-linked recessive lethals. No differences among broods were noted, and data from all broods were pooled. The percent lethals in controls, 250 and 1,000 ppm groups were dose-related and were 0.05, 0.026, and 0.66 percent, respectively. The control vs. 1,000 ppm lethal rates were significantly different from one another ($p < 0.01$). Ethyl methane sulfonate (250 ppm) was included as a positive control; it yielded 13.70 percent lethals. The total number of flies in each experimental group was no larger than 3,000.

(b) *Negative Studies.* The mutagenicity of 2, 4, 5-T was evaluated by Brusgovich et al. (*148*), employing the procedure of Ames, using five strains of *Salmonella typhimurium* without activation. They concluded that 2, 4, 5-T is not mutagenic.

Fujita et al. (*149*) reported chromosomal abnormalities in *in vitro* cytogenetic studies of human lymphocytes exposed to 1 10^{-4} M of 2, 4, 5-T, which contained ppm TCDD. Breaks, deletions, and were observed. Chromatid breaks inc with increasing concentrations of 2, It was not possible to distinguish wi this was a toxic effect or a potential g effect (*150*).

Majumdar and Hall (*169*) reported cytogenetic effects of 2,4,5-T[10] on b bone-marrow cells of Mongolian gerbil animals were injected with total amou 2,4,5-T at the rate of 50, 150, 250, 350, mg/kg body weight over the 5-day per the study. Increasing numbers of chro gaps, breaks, and fragments were ob at 250, 350, and 500 mg/kg doses. N change figures or isochromosome ga breaks were observed. This is not a c tive experiment for indicating the pot of 2,4,5-T for causing heritable chrom damage (*170*). Toxicity effects of the c cal could give similar results (*170*).

Davring and Hultgren (*171*) report an *in vivo* study on the cytogenetic e on bone-marrow cells of *Mus mu* (male mice) induced by a Swedish com cial 2,4,5-T ester formulation[11] and its ponents. The study showed that t commercial products can affect chro mal and reproductive mechanisms. Tw ferent strains of mice were used with s results for both. These results corre with effects seen in Drosophila. Th thors stated that chromatid inter- traexchanges were never observed. study was not carried out sufficient the demonstration of chromosomal e such as rearrangements in future ge tions of somatic cells (*170*).

Davring and Sumner (*172*) demonst cytogenetic effects of a Swedish comm 2,4,5-T formulation[12] on oogenesis and embryogenesis in *Drosophila melanog* A 50 percent decrease in fertility fo flies was determined to be 250 ppm. level is 40 to 60 times less than field us centration levels. Reproductive and chr somal effects were observed.

[10] The 2,4,5-T used in this study was chased from Eastman Kodak Co., Ro ter, N.Y., and contained no measu amount of TCDD. The authors do not cate the limit of sensitivity.

[11] The concentration of TCDD was gu teed to be less than 0.1 ppm in the pro

[12] TCDD concentration was less tha ppm in this formulation which was test practical field use concentrations or low

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