Item ID Number	05234 ☐ **Not Scanned**
Author	
Corporate Author	Environmental Protection Agency
Report/Article Title	Pesticide Programs: Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing 2,4,5-T
Journal/Book Title	Federal Register
Year	1978
Month/Day	April 21
Color	☐
Number of Images	0
Descripton Notes	

federal register

FRIDAY, APRIL 21, 1978
PART II



ENVIRONMENTAL PROTECTION AGENCY

■

PESTICIDE PROGRAMS

Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing 2, 4, 5–T

[6560-01]

ENVIRONMENTAL PROTECTION AGENCY

[FRL 882-2; OPP-30000/26]

PESTICIDE PROGRAMS

Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing 2,4,5-T

AGENCY: Office of Pesticide Programs, Environmental Protection Agency (EPA).

ACTION: Notice of rebuttable presumption.

SUMMARY: 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) has been found to exceed certain risk criteria set forth in 40 CFR 162.11. This notice requests registrants and other interested persons to submit rebuttals and other information on the presumption and to submit any other data on the risks and benefits of this pesticide chemical. This notice is the first of several which will give public notification of the Agency's progress in reviewing this chemical.

DATE: Rebuttal evidence and other information must be received on or before June 5, 1978.

ADDRESS MATERIAL TO: Federal Register Section, Technical Services Division (WH-569), Office of Pesticide Programs, EPA, Room 401, East Tower, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

Harvey Warnick, Office of Special Pesticide Reviews, Office of Pesticide Programs (WH-566), Room 447, East Tower, EPA, 202-755-5754.

SUPPLEMENTARY INFORMATION: The Deputy Assistant Administrator, Office of Pesticide Programs, EPA, has determined that a rebuttable presumption exists against registration and continued registration of all pesticide products containing 2,4,5-T.[1]

I. Regulatory Provisions

A. *General.* Title 40, § 162.11, of the Code of Federal Regulations for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended (86 Stat. 973, 89 Stat. 751, 7 U.S.C. 136 et seq.), provides that a rebuttable presumption against registration shall arise if the Agency determines that a pesticide meets or exceeds any of the risk criteria relating to acute and chronic toxic effects set forth in § 162.11(a)(3). If it is determined that such a rebuttable presumption has arisen, the regulations require that the registrant be notified by certified mail and afforded an opportunity to submit evidence in rebuttal of the presumption. In addition, the Agency has determined that the public should also be given notice of the bases for the presumption to provide an opportunity for comment and to solicit additional information relevant to the presumption.

A notice of rebuttable presumption against registration is issued when the evidence related to risk meets the criteria set forth in § 162.11(a)(3). It is emphasized that a notice of rebuttable presumption against registration and continued registration of a pesticide is not a notice of intent to cancel the registration of a pesticide, and may or may not lead to cancellation. The notice of intent to cancel is issued only after the risks and benefits of a pesticide are carefully considered and it is determined that the pesticide may generally cause unreasonable adverse effects to the environment.

All registrants and applicants for registration are invited pursuant to 40 CFR 162.11(a)(4) to submit evidence in rebuttal of the presumptions listed in part II of this notice and, in the case of oncogenicity, to submit information which relates to the assessment of oncogenic risks as set forth in the Agency's Interim Procedures and Guidelines for Health Risk and Economic Impact Assessment of Suspected Carcinogens (May 25, 1976; 41 FR 21402). Registrants and other interested parties may submit for consideration data on benefits which they believe would justify registration or continued registration. In addition, any registrant may petition the Agency to voluntarily cancel a current registration pursuant to section 6(a)(1) of FIFRA.

B. *Rebuttal criteria.* Section 162.11(a)(4) provides that a registrant may rebut the presumption by sustaining the burden of proving:

(1) In the case of a pesticide presumed against pursuant to the acute toxicity or lack of emergency treatment criteria, "that when considered with the formulation, packaging, method of use, and proposed restrictions on the directions for use and widespread and commonly recognized practices of use, the anticipated exposure to an applicator or user and to local, regional, or national populations of nontarget organisms is not likely to result in any significant acute adverse effects" (40 CFR 162.11(a)(4)(i));

(2) In the case of a pesticide presumed against pursuant to the chronic toxicity criteria, "that when considered with proposed restrictions on use and widespread and commonly recognized practices of use, the pesticide will not concentrate, persist or accrue to levels in man or the environment likely to result in any significant chronic adverse effects" (40 CFR 162.11(a)(4)(ii)); or

(3) In either case, that "the determination by the Agency that the pesticide meets or exceeds any of the criteria for risk was in error" (40 CFR 162.11(a)(4)(iii)).

C. *Benefits information.* In addition to submitting evidence to rebut the presumption of risk, § 162.11(a)(5)(iii) provides that a registrant "may submit evidence as to whether the economic, social, and environmental benefits of the use of the pesticide subject to the presumption outweigh the risk of use." If the risk presumptions are not rebutted, the benefit evidence[2] submitted by the registrant, applicants, and other interested persons will be considered by the Administrator in determining the appropriate regulatory action. Specifically, § 162.11(a)(5)(iii) provides that if the benefits appear to outweigh the risks, the Administrator may issue a notice of intent to hold a hearing pursuant to section 6(b)(2) of FIFRA to determine whether the registration(s) should be cancelled or application(s) denied. Alternatively, if the "benefits do not appear to outweigh the risks, the Administrator shall issue a notice pursuant to section 3(c)(6) or section 6(b)(1) of the Act, as appropriate." Moreover, if at any time the Administrator determines that a pesticide poses an "imminent hazard" to humans or the environment, a notice of suspension may be issued pursuant to section 6(c) of the Act.

II. Presumptions

Registrations and applications for registration of pesticide products containing 2,4,5-T meet or exceed the 40 CFR 162.11(a)(3) risk criteria relating

[1] A position document, containing an appendix of references, background information, and other material pertinent to the issuance of this notice, has been prepared by the Agency Working Group on 2,4,5-T and is also published with this notice.

[2] Registrants or other interested persons who desire to submit benefit information should consider submitting information on the following subjects, along with any other relevant information they desire to submit:

1. Identification of the major uses of the pesticide, including estimated quantities used by crop or other application.
2. Identification of the minor uses of the pesticide, including estimated quantities used by category such as lawn and garden uses and household uses.
3. Identification of registered alternative products for the uses set forth in (1) and (2) above, including an estimate of their availability.
4. Determination of the change in costs to the user of providing equivalent pesticide treatment with any available substitute products.
5. Assessment of regulation impact upon user productivity (e.g., yield per acre and/or total output) from using available substitute pesticides or from using no other pesticides.
6. If the impacts upon either user costs or productivity are significant, a qualitative assessment of the regulation's impact on production of major agricultural commodities and retail food prices of such commodities.

to oncogenic effects and teratogenic and/or fetotoxic effects in mammalian test species. The Agency's basis for concluding that these risk criteria have been met or exceeded is set out in "2,4,5-T: Position Document 1," which follows. Copies of attachments to the Position Document which are not published with this notice are available for public inspection in the Office of Special Pesticide Reviews. Information protected from disclosure pursuant to FIFRA section 10 cannot be provided. Specific inquiries concerning the Position Document, as well as requests for access to these files, should be directed to Project Manager Harvey Warnick, Office of Special Pesticide Reviews (WH-566), EPA, Room 447, East Tower, 401 M Street SW., Washington, D.C. 20460, 202-755-5754.

A. *Oncogenicity.* 40 CFR 162.11(a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide "(i)nduces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure * * *." As a further clarification of the provision, the preamble to the Agency's Interim Procedures and Guidelines for Health Risk and Economic Impact Assessment of Suspected Carcinogens (May 25, 1976; 41 FR 21402) states that "a substance will be considered a presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals."

On the basis of scientific studies and information summarized in the Position Document, the Agency has concluded that all registrations and applications for registration of pesticide products containing 2,4,5-T and/or its dioxin contaminant (TCDD) exceed this risk criterion, and that a rebuttable presumption against new or continued registration of such products has arisen.

B. *Other chronic or delayed toxic effects.* 40 CFR 162.11(a)(3)(ii)(B) provides that rebuttable presumption shall arise if a pesticide "(p)roduces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety * * *."

On the basis of scientific studies and information summarized in the Position Document, the Agency has concluded that all registrations and applications for registration of pesticide products containing 2,4,5-T and/or TCDD exceed this risk criterion for teratogenic and/or fetotoxic effects and that a rebuttable presumption against new or continued registration of such products has arisen.

III. Additional Grounds for Review

As discussed in detail in the attached Position Document, some data has associated 2,4,5-T and/or TCDD with mutagenic effects in test animals and TCDD with toxic effects in humans. The data and analyses available at this time with respect to these effects are not sufficient to warrant the issuance of a Rebuttable Presumption. The Agency specifically solicits further evidence bearing on these possible adverse effects. All comments and information received with respect to the potential adverse effects, including analysis thereof, may serve as a basis for a final decision on registering pesticides containing 2,4,5-T and/or TCDD.

IV. Registrations and Products Subject to the Notice

All registrants and applicants for registration listed below are being notified by certified mail of the rebuttable presumption existing against registration and continued registration of their products.

The registrants and applicants for registration shall have 45 days from the date this notice is sent or until June 5, 1978, to submit evidence in rebuttal of the presumption. However, the Administrator may, for good cause shown, grant an additional 60 days during which such evidence may be submitted. Notice of such an extension, if granted, will appear in the Federal Register.

A registrant or applicant for registration may, if it desires, assert a business confidentiality claim covering part or all of the informaion submitted in rebuttal. The registrant or applicant may assert the claim by placing on or attaching to the information a cover sheet, stamped or typed legend, or other suitable form of notice employing language such as "trade secret," "proprietary," or "company confidential." Allegedly confidential portions of otherwise nonconfidential documents should be clearly marked.

If a confidentiality claim is asserted, the information covered by the claim will be disclosed by EPA only to the extent and by means of the procedures set forth in 40 CFR part 2, subpart B (41 FR 36906; September 1, 1976). If no confidentiality claim accompanies the information at the time it is received by EPA, EPA will place the information in the public comment file where it will be available for public inspection.

If a registrant or applicant does assert a confidentiality claim for some but not all, of the information submitted to EPA in rebuttal, the registrant or applicant should furnish two copies of the information to EPA. The first copy should contain all of the information submitted in rebuttal with information claimed as confidential clearly identified. The second copy should be identical to the first except that all information claimed as confidential should be deleted. The second copy will be placed in the public comment file. The first copy will be treated in accordance with the procedures set out above.

V. Duty to Submit Information on Adverse Effects

Registrants are required by law to submit to EPA any additional information regarding any adverse effects on man or the environment which comes to a registrant's attention at any time, pursuant to section 6(a)(2) of FIFRA and 40 CFR 162.8(d). If any registrant of 2,4,5-T products has any published or unpublished information, studies, reports, analyses, or reanalyses regarding any adverse effects in animal species or humans, residues, and claimed or verified accidents to humans, domestic animals, or wildlife, which have not been previously submitted to EPA, the material must be submitted immediately. When responding to this notice, each registrant shall submit a written certification to the Agency that all information regarding any adverse effects known to the registrant has been submitted. In addition, the registrants should notify EPA of any studies currently in progress, including the purpose of the study, the protocol, the approximate completion date, and a summary of all results observed to date.

VI. Public Comments and Inspection

During the time allowed for submission of rebuttal evidence, specific comments on the presumptions set forth in this notice and on the material contained in the Position Document are solicited from the public. In particular, any documented episodes of adverse effects to humans, domestic animals, or wildlife, and information as to any laboratory studies in progress or completed are requested to be submitted to EPA as soon as possible. Specifically, information on the fate and effects of 2,4,5-T, its impurities, metabolites, and degradation products on flora and fauna, particularly animals with metabolism similar to man, is solicited. Similarly, any studies or comments on the benefits from the use of 2,4,5-T are requested to be submitted. All comments and information received, as well as any other relevant information and analysis thereof, which come to the attention of the Agency may serve as a basis for final determination pursuant to § 162.11 (a)(5).

All comments and information should be sent to the Office of the Federal Register Section at the address given above, if possible in triplicate to facilitate the work of the

Agency and others interested in inspecting them. The comments and information should bear the identifying notation "OPP-30000/26." Comments received after the specified time period will be considered only to the extent feasible, consistent with the time limits imposed by 40 CFR 162.11(a)(5)(ii).

All written comments and information filed pursuant to this notice will be available for public inspection in the Office of the Federal Register Section from 8:30 a.m. to 4 p.m. during normal working days. Interested persons are encouraged to take advantage of the opportunity to inspect Agency files during normal working hours since: (1) All of the information received may serve as a basis for final determination pursuant to § 162.11(a)(5), and (2) the Agency will not generally publish a summary of information received in the FEDERAL REGISTER at the close of the rebuttal period.

Your cooperation is solicited in identifying any errors or omissions which may have been made in the following computer listings. Corrections to the listings may not necessarily be published in the FEDERAL REGISTER, but rather handled by mail with affected parties. Omissions will be corrected by notice in the FEDERAL REGISTER.

Dated: April 11, 1978.

EDWIN L. JOHNSON,
Deputy Assistant Administrator for Pesticide Programs.

2,4,5-T: POSITION DOCUMENT 1

2,4,5-T WORKING GROUP, U.S. ENVIRONMENTAL PROTECTION AGENCY

i. Background

A. *Chemical/physical characteristics.* The herbicide commonly known as 2,4,5-T (chemical name, 2,4,5-Trichlorophenoxyacetic acid) has an empirical formula of $C_8H_5Cl_3O_3$. The pure acid form occurs as white crystals and has a molecular weight of 255.49. The melting point is 156.6°C. Its solubility in water is 278 parts per million (ppm) at 25°C; it is also soluble in acetone, ethanol, ether, and alkaline solutions (*1*). The esters of 2,4,5-T are formulated to be emulsifiable in water and soluble in most oils, while its amine salts are soluble in water but insoluble in petroleum oils (*2, 3*).

B. *Manufacturing process and contaminants.* 2,4,5-T is produced commercially by a process using 1,2,4,5-tetrachlorobenzene as the starting material which is reacted with methanol and sodium hydroxide under high termperature and high pressure to give the sodium salt of 2,4,5-trichlorophenol (2,4,5-TCP).[1]

This product is reacted with chloroacetic acid under mildly alkaline conditions. Sulfuric acid (H_2SO_4) is then added to the product of this step to produce 2,4,5-T. The acid form of 2,4,5-T can be readily reacted with a variety of alcohols to produce a large selection of esters and with amines to produce amine salts (*3*).

During the first step in the manufacturing process of 2,4,5-T, if temperature and pressure are not carefully controlled, highly toxic contaminants, polychlorinated dibenzo-p-dioxins, may be formed in large quantities. The particular dioxin formed is dependent on the chlorophenols present (*4*). The term dioxin does not apply to any one compound but to a group of related substances, which are distinguished by the number and orientation of chlorine atoms they contain. Dioxin toxicity also varies with the position and numbers of chlorines attached to the phenol rings.

In the 2,4,5-T manufacturing process an especially toxic dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is formed when the reaction temperature is excessive (*8, 9, 10, 11, 12*), most commonly at temperatures above 160°C. Halogens at the 2, 3, and 7 positions are known to produce toxic dioxins (*13*). In the case of TCDD, the chlorine atoms are attached at the 2, 3, 7, and 8 positions which are considered the most toxic positions possible (*14*). The dioxin contaminant in 2,4,5-T is of particular concern because of its extremely high toxicity, and because of the apparent inability of manufacturers to produce 2,4,5-T without the contaminant, TCDD (*7*).[2]

TCDD occurs as a white crystalline solid. It is 99.5 percent decomposed at 800°C. TCDD has the following solubility in various solvents at 25°C (*7*).

Solvent	Solubility[3]
Acetone	0.011
Benzene	0.057
Dimethylsulfoxide	<00.01
Methanol	0.001
Water	[3]0.00000002

[3]Weight percent.
[3](0.2ppb)

It has been recognized for quite some time that chlorinated dibenzo-p-dioxins occur as possible by products (contaminants) in the manufacturing of chlorinated phenols (*15*). The formation of TCDD during production of 2,4,5-TCP was demonstrated by Kimmig and Schulz (*16*). TCDD was obtained from the pyrolyzing of 2,4,5-TCP by Higginbotham et al. (*11*). They noted that the specific dioxin formed depended on the chlorophenol pyrolyzed. Kearney et al. (*17*), however, reported that TCDD is historically associated with any pesticide derived from 2,4,5-TCP. A number of researchers (*12, 18, 19, 20, 21*) have reported on the formation of TCDD by thermal decomposition of the sodium salt of 2,4,5-TCP under alkaline conditions during the manufacturing process.

Since 1950, most of the chemical industry has known that large quantities of TCDD may be formed as a byproduct of the 2,4,5-TCP manufacturing process if the procedures are not carefully controlled. At one time, 2,4,5-T was produced which contained between 30 to 40 ppm of TCDD (*7, 22, 55*). Between 1968 and 1969, one manufacturer had a 90 percent decrease in the amount of TCDD present in the 2,4,5-T it produced. Different manufacturers produced 2,4,5-T with different TCDD contents (*17*).

After concern arose in 1969 about the extremely toxic effects of TCDD, manufacturing methods were changed and carefully controlled by manufacturers. By 1971 industry had reduced TCDD content in commercial samples of 2,4,5-T to less than 1 ppm (*9, 23, 24*). Current U.S. manufacturing specifications require 2,4,5-T presently being sold to contain less than 0.1 ppm TCDD (*7*). Several countries now produce commercial 2,4,5-T containing less than 0.05 ppm TCDD (*25*).

C. *Formulation and class.* 2,4,5-T is classed and used as a selective herbicide, especially for brush control (*2*). It is formulated in many forms of salts and esters which are available as emulsifiable concentrates containing 2, 4, or 6 pounds actual acid equivalent per gallon and as oil soluble concentrates with 4 or 6 pounds active ingredient (AI) per gallon. The most commonly used formulations are the low volatile esters (*26*). 2,4,5-T also occurs in registrations mixed with 2,4-D, Dicemba, Picloram, Silvex, and 2-(2-methyl-4-chlorophenoxy) propionic acid (*27*).

D. *Registered uses and production.* 2,4,5-T has been produced as a registered pesticide in the United States since 1948. According to EPA records, approximately 122 companies hold Federal registrations and formulate 424 registered products; eleven companies have former State registration[3] and fomulate 21 products.

Section 7(c) of FIFRA requires manufacturers and formulators to submit to EPA information on production, sales, and distribution. Under FIFRA sections 7(c) and 10, this information may not be made available to the public. A confidential memorandum containing this information has been sent to the Deputy Assistant Administrator for Pesticides (*28*). The Pesticide Review (*29*) reported that 11,626,000 pounds of 2,4,5-T acid, esters, and salts were produced in the United States in 1969 and 12,335,000 pounds in 1970. The Pesticide Review, (*29*) also reported that the United States imported 736,907 pounds of 2,4,5-T during 1971 through 1974.[4] Of this total 155,342 pounds were imported in 1974. This was down from nearly 392,000 pounds in 1973 but up from the 5-year average of 148,000 pounds. While The Pesticide Review (*29*) does not report export figures for 2,4,5-T alone, it does report exports of 2,4-D and 2,4,5-T together. Export of 2,4-D and 2,4,5-T was reported at 6.8 million pounds in 1972; 21 million pounds in 1973; and almost 22 million pounds in 1974.

A great deal of variability exists in reports on usage of 2,4,5-T. Agricultural end-use data obtained from the National Study of

[1]2,4,5-TCP is the subject of a separate Rebuttable Presumption Against Registration (RPAR) Position Document. It is discussed in this document because both it and its contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) may be present in some commercial 2,4,5-T and in 2,4,5-T samples used in animal experiments.

[2]Since manufacturers are unable to produce 2,4,5-T without TCDD, all references to 2,4,5-T in this document refer to 2,4,5-T contaminated with some level of TCDD.

[3]Pesticide products formerly registered under state pesticide registration laws and shipped or distributed for sale solely within intrastate commerce are subject to Federal pesticide regulations under 40 CFR 162.17(a). Application has been made to obtain Federal registration for intrastate use of these products. For a list of trade names under which 2,4,5-T is marketed, see the registrant/product list attached to this document. 000

[4]The level of TCDD in the imported 2,4,5-T was not reported.

Agricultural, Governmental, and Industrial Uses of Pesticides, conducted by this Agency (*30*), indicated the following uses of 2,4,5-T in the United States in 1974.

Crop	pounds AI applied	% total agriculture
Rangeland and Pastures	968,000	97.24
Rice[a/]	16,000	1.54
Nursery Crop	12,000	1.20
Turf and Ornamentals	200	0.02
Blueberries[b/]	8	--
Estimated total use in agriculture for 1974	996,000	100.00

a/ The Agency has looked at effects on aquatic organisms representative of species likely to be exposed from application of the triethylamine formulation of 2,4,5-T to rice. The calculated concentration of this formulation in a 6-inch layer of water at the highest recommended use rate is 0.9 ppm. The LC-50 bioassay values for bluegill and catfish are well above this level (ranging from a 24-hour LC-50 of 53 ppm for bluegill to a 96-hour LC-50 of >72 ppm for bluegill and channel catfish). Rainbow trout, which cannot be considered "representative of the organisms likely to be exposed" in the geographic areas where rice is grown, have a 96-hour LC-50 ranging from 0.7 to 0.07 ppm.
b/ This is no longer a registered use.

In addition, this survey reported that 324,491 pounds of active 2,4,5-T were used by Federal and State agencies and 659,463 pounds by industry.

Other sources have reported usages for 1974 as follow: Rights-of-way, 4 million pounds; rangeland, 1.5 to 2.3 million pounds; rice, 220,000 pounds; and forestry, 50,000 pounds.

E. *Metabolism in Experimental Systems.* Several studies have demonstrated that 2,4,5-TCP is the primary degradation product or metabolite formed in the breakdown of 2,4,5-T, by either physical or biological mechanisms. Crosby and Wong (*31*) found that 2,4,5-TCP was one of the major decomposition products in the photodecomposition of 2,4,5-T in water. Sharpee (*32*) found that microbial degradation of 2,4,5-T in culture, soil, and aquatic ecosystems resulted in the formation of small amounts of 2,4,5-TCP.

Shafik et al. (*33*) dosed Sprague-Dawley rats by gavage with 2,4,5-T at 50, 5, 0.05, and 0.005 mg/kg for three days. Two rats were dosed at each level. The authors found that, at 0.005 mg/kg, excretion of 2,4,5-T in urine was complete two days after the final dose. They also found 2,4,5-TCP excreted as a metabolite in the urine of rats given 50 mg/kg, but no detectable 2,4,5-TCP was found at the two lowest dose levels. A hydroxylated trichlorophenoxyacetic acid and a hydroxylated trichlorophenol were identified, by unconfirmed mass spectrometric analysis, as possibly being two additional metabolites of 2,4,5-T.

Grunow et al. (*34*) studied seven male Wistar rats fed a single 2,4,5-T dose at 50 mg/kg body weight. They found that the daily renal excretion of free 2,4,5-T was, in general, at its maximum on the second day after feeding. After seven days, free 2,4,5-T in the urine decreased to a value below 2 percent for all animals. In addition to 2,4,5-T excreted in the free form, the authors found it to be excreted as derivatives which could be converted into 2,4,5-T by acid hydrolysis. They were able to identify one of these as N(2,4,5-trichlorophenoxyacetyl) glycine.

Grunow and Bohme (*35*), in a study using Wistar rats and NMRI mice, fed doses of 2,4,5-T at 200 mg/kg body weight. These authors isolated N(2,4,5-trichlorophenoxyacetyl) taurine as a metabolite of 2,4,5-T, in addition to the metabolites named above.

Clark et al. (*36*) found residues of 2,4,5-TCP in the muscle, liver, and kidney of sheep which were fed rations containing 2,000 ppm of 2,4,5-T for 28 days. The 2,4,5-T used in this study had a purity of 99 percent and contained no detectable dioxin (detection limit: 0.5 ppm).

Leng (*37*) conducted a feeding study during 1969 and 1970, in which dairy and beef cattle and sheep were given 2,4,5-T at levels from 10 to 2,000 ppm in the total diet for intervals of two to four weeks at each level tested. The author reported that no residues (<0.05 ppm) occurred in milk or cream of cows ingesting 10 to 30 ppm 2,4,5-T. At 100 ppm 2,4,5-T in the diet, traces of 2,4,5-TCP (0.06 ppm) appeared in milk and cream. When given high levels of 2,4,5-T, equivalent to 300 and 1,000 ppm in the total diet, residues of 2,4,5-T and 2,4,5-TCP ranged from 0.05 to 0.5 ppm in the milk of individual cows.

Fitzgerald et al. (*38*), studying the degradation of 2,4,5-T in woody plants, reported that colorimetric analysis suggested, and chromatographic analyses confirmed, that the n-butyl ester of 2,4,5-T is degraded in sweet gum (*Liquidambar styraciflua*) and southern red oak (*Quercus falcata*) to yield 2,4,5-TCP.

F. *Environmental fate.*—(1) *Persistence: Soils.* Soil surface and foliage are the major recipients of phenoxy herbicides (*39*) whether applied by ground spray systems or from aircraft. Once 2,4,5-T reaches the soil it may be degraded chemically or biologically, volatilized and moved to other areas, absorbed on soil colloids or in organic matter, or leached to depths or location where it cannot be absorbed by plant roots (*47*).

Norris et al. (*176*) reported on the persistence of 2,4,5-T in a Pacific Northwest forest. The authors found that 6 months after application of 2,4,5-T at 2.24 kg/ha (2 pounds/acre), the level of herbicide in the forest floor declined 90 percent; after 1 year, less than 0.02 kg/ha remained in the forest floor. The authors found little leaching of 2,4,5-T from the forest floor into soil, and no residues were found deeper than 15 cm (maximum residue found was 0.08 ppm) despite rainfall of 24 cm the first month and 70 cm the first 3 months after application. Norris et al. (*176*) stated that the rapid disappearance of 2,4,5-T from the forest floor suggests abundant microbial activity. Norris (*40*) reported microbial activity to be important in the disappearance of 2,4,5-T from forest-floor material in the laboratory.

Wiese and Davis (*41*) found that, in an agricultural soil, 2,4,5-T remained in the upper 6 inches even after application of 4.5 inches of water over a short period of time.

Helling et al. (*39*) found that 2,4,5-T is relatively mobile in sandy soils but that movement decreases as organic content increases. Thus 2,4,5-T is moderately mobile in clay soils and only slightly mobile in muck (*42*).

Yoshido and Castro (*43*) studied the degradation of 2,4-D, 2,4,5-T, and Picloram in two Philippine soils under upland and submerged conditions. The authors found the degradation of 2,4,5-T to be rapid in Maahas clay. Slightly more 2,4,5-T residues were recovered in submerged than in upland Maahas soil. In Luisiana soil under submerged conditions, 2,4,5-T degraded rapidly in 8 weeks after a 4-week lag period, while it degraded gradually under upland conditions, with only about 40 percent of the 2,4,5-T recovered after 12 weeks.

Morton et al. (*44*), using technical grade 2,4,5-T labeled in the carboxyl position with carbon-14, found that its apparent half-life averaged 1.6 weeks in green tissues of native grasses at College Station and Spur, Tex., and 1.7 weeks in litter tissue. The authors stated that the amount and frequency of rainfall were conducive both to leaching and microbial decomposition of the herbicide,

and to growth of sideoats gramma plants, all of which were factors contributing to rapid reduction of herbicide concentrations.

When considering the persistence of 2,4,5-T, the persistence of its manufacturing contaminant, TCDD, must also be considered. Helling et al. (*39*) found that TCDD was not photodecomposed on soil. TCDD was found to be immobile in Norfolk and Lakeland sandy loams, Hagerstown silty clay loam, Barnes Clay loam, and Celeryville muck, and was not leached further into soil by rainfall or irrigation. During surface erosion of soil, however, lateral transport of TCDD could occur. The persistence of TCDD in Lakeland loamy sand and Hagerstown silty clay loam at 1, 10, and 100 ppm was studied by Kearney et al. (*46*) for 360 days. After 1 year these researchers recovered 56 and 63 percent of the originally applied TCDD in Hagerstown and Lakeland soils, respectively. Helling et al. (*39*) observed that TCDD's persistence was predictable since it is insoluble in water.

(2) *Persistence: Water.* Current information indicates that, although some 2,4,5-T may enter streams flowing through or adjacent to areas being sprayed, residue levels in streams will be very low. Norris (*47*) reported the results of an intensive study of stream contamination from spray projects on range and forest lands in Oregon which showed that peak concentrations of phenoxy herbicides seldom exceeded 0.1 ppm and that herbicide residues persisted for only a few hours in nearly all streams. Norris (*47*) speculated, however, that application of herbicides to marshy areas may result in high-level, long persistence of chemical residues in nearby streams.

The Report of the Advisory Committee on 2,4,5-T to the Administrator of the Environmental Protection Agency (*48*) stated that all available data indicated that the amount of 2,4,5-T entering water is small and does not persist long. It is adsorbed on clay or absorbed by biota within a matter of days.

Phenoxy chemicals entering water may be lost by volatilization, degradation, adsorption on sediment, adsorption by biota, and dilution as additional stream water passes through the site. Almost all authorities agree that there is adsorption on bottom sediment (*48, 49, 50*).

Kenaga (*51*) stated that esters of 2,4,5-T in most kinds of water, except highly acidic waters, are usually hydrolyzed within a matter of days. When the 2-ethylhexyl ester of 2,4,5-T was applied to water in the laboratory at a concentration of 1 ppm for an hydrolysis study, 58 percent remained after 4 hours; 33 percent after 8 hours; and 12 percent after 16 hours.

Trichell et al. (*52*), studying the loss of herbicides in runoff water, found 2 μg/ml of 2,4,5-T in runoff water 24 hours after it was applied at 2.24 kg/ha, after which 1.3 cm of rainfall was simulated on sod-covered plots of 3 percent slope. Four months after application, concentrations of 2,4,5-T in runoff water had diminished to 0.04 μg/ml.

Edwards and Glass (*53*) monitored runoff and percolation of 2,4,5-T at Coshocton, Ohio, for 14 months following application of 11.2 kg/ha of 2,4,5-T and found that 5.5 g/ha, or over 0.05 percent of the herbicide, was lost from the treated area. Most of the 2,4,5-T was removed in runoff water during the first 4 months after application, and more than half of the loss occurred the first month after treatment.

Kearney et al. (*46*) concluded that contamination of underground water supplies with TCDD seemed very unlikely, since vertical movement of TCDD did not occur in a wide range of soil types. The fact that no leaching occurred, however, would not preclude runoff loss when soil erosion is significant (*39*).

(3) *Transport.* Isensee and Jones (*54*) measured uptake of TCDD from soil by two crop species. Oats (*Avena sativa*) and soybeans (*Glycine max*) were grown in Lakeland sandy loam soil treated with 0.06 ppm TCDD. The concentration of TCDD in soil was approximately 4,000 times greater than the amount that would be deposited in soil from an application of 2,4,5-T (with 1 ppm TCDD) at a rate of 2 pounds/acre in the top one-third inch of the soil surface. The tops of these plants were harvested at intervals to maturity. Mature oats and soybean tops contained less than 1 part per billion (ppb) TCDD. TCDD was detected (with a detection limit of 1 ppb) in mature oat grain, while no TCDD was found in the bean of soybeans. The authors concluded that soil uptake of TCDD by plants was highly unlikely, since little or no TCDD was taken up by oats or soybeans under the conditions of this experiment (*54*).

(4) *Bioaccumulation.* Woolson et al. (*55*) conducted a study to determine if TCDD residues could be detected in bald eagle (*Haliaectas leucocephalus*) tissue extracts, as a representative of the top of a food chain. Scientists at the Patuxent Wildlife Center (U.S. Department of the Interior, Laurel, Md.) collected, and furnished to these researchers, 19 bald eagle carcasses from Alaska, Maine, North Dakota, Wisconsin, Michigan, Minnesota, Arkansas, Illinois, Missouri, Maryland, Virginia, Iowa, New York, New Jersey, and Florida between 1966 and 1971. These States were selected as sampling sites in order to provide a widely dispersed sample population. The eagle tissues were prepared and extracted as described by Mulhearn et al. (*56*). Woolson et al. (*55*) detected no dioxin residues at a level of 0.05 ppm TCDD, the lower limit of detection for most pesticides in tissue samples run by the Patuxent Wildlife Research Center at that time. The authors stated that the nondetection of dioxin residues could imply that there was no dioxin buildup in the food chain; that the buildup was less than the [then] currrent detectable level of 0.05 ppm [50 ppb]; that the eagles examined were not contaminated although other samples might be; or that other species could feed on a different food chain to accumulate dioxins.

Isensee and Jones (*57*) exposed several organisms in a model aquatic ecosystem to ^{14}C-labeled TCDD for up to 31 days to determine the distribution and bioacumulation potential in the aquatic environment. Soil containing from 0.0001 to 7.45 ppm adsorbed ^{14}C-TCDD was placed in aquaria, containing eight snails (*Physa sp.*) a few strands of algae (*Oedogonium carduacum*), and 10 ml of old aquarium water containing various diatoms, protozoa, and rotifers. Fifteen duckweed (*Lemna minor*) plants were also added to one aquarium. Samples of daphnids were taken for analysis at 30 days, and two mosquito fish (*Gambusia affinis*) were added to each tank. Three days later all of the organisms were removed for analysis, and two fingerling channel catfish (*Ictalurus punctatus*) were added to each tank and exposed for 6 days.

The authors stated that all organisms in both treatment and control tanks prospered during this exposure period, indicating that TCDD was not toxic at the concentrations used. TCDD accumulated in all organisms. At the highest TCDD concentration (7.45 ppm) algea accumulated 6,690±960 ppb TCDD; snails, 1,820±170 ppb; daphnids, 10,400±480 ppb; and Gambusia, 1,380±220 ppb. Catfish were not analyzed for TCDD residues. At the second highest TCDD concentraion (3.17 ppm), however, catfish accumulated 720±130 ppb TCDD. The authors stated that accumulation in all of the test organisms from soil containing 0.1 ppb TCDD is important since this concentration approaches the concentration which would occur under normal field use of 2,4,5-T. The authors concluded that the data suggested that under certain circumstances (discharge of storm runoff from recently treated rangeland into a small pond), water-eroded surface soil or debris may contain enough TCDD for measurable residues (parts per thousant (ppt) quantities) to accumulate in fish or other aquatic organisms. However, the authors speculated that TCDD, originating from 2,4,5-T applications, discharged into large lakes, streams, or estuaries would probably become sufficiently diluted so that no measurable accumulation would occur.

As part of a broad study to determine whether 2,4,5-T use leads to TCDD accumulation in the environment, Shadoff et al. (*58*) collected samples of fish, mud, water, and human milk from areas in Texas and Arkansas. The Texas samples of water, mud, catfish, and walleyed pike were collected from the San Angelo Reservoir, an impoundment of the North Concho River. The authors stated that this watershed has large acreages that have been sprayed with 2,4,5-T at 0.5 pounds/acre (2,4,5-T acid equivalent) for brush control. These researchers also obtained six samples of human milk from mothers residing in general area of the San Angelo Reservoir. In addition, bass from a 125-acre pond in the heart of the Arkansas rice-growing area were collected. Water from this pond is used to flood rice fields treated with the equivalent of 1.25 pounds/acre of 2,4,5-T, acid, 4 to 8 weeks prior to flooding. The water is later drawn off the fields and pumped back into the pond for reuse. In addition, the pond is supplemented by water from wells and by water collected as runoff from surrounding rice fields during the rainy season. The authors stated that this cycle had been in use (including the proper use of 2,4,5-T) for 18 years up to the time of their study. The authors stated that no TCDD was detected in the tissues sampled, using a gas chromatography-mass spectrometry procedure with a detection limit which averaged less than 10 ppt. No evidence was found that TCDD is accumulating in the environment from the use of 2,4,5-T described in this study.

G. *Residues.*—(1) *Soil.* Woolson et al. (*55*) studied Lakeland sandy soil to determine if TCDD residues could be detected in soil receiving exceedingly large applications of 2,4-D and 2,4,5-T. The heaviest rate of 2,4,5-T application was 947 pounds-acre applied aerially during 1962 through 1964, while the lightest rate was 160 pounds-acre applied aerially during 1968 and 1969. During this period, it was not uncommon for commercial samples of 2,4,5-T to contain levels of 30 to 40 ppm TCDD.

The authors were able to detect small amounts of 2,4,5-T in the soil samples. They observed that the residue level decreased with time after application and stated that leaching and microbial decomposition could account for this decrease. Using a detection

limit of less than 1 ppb, the authors did not detect any TCDD at any depth in 36-inch core samples of the soil.

(2) *Water.* In October 1965, the U.S. Geological Survey initiated a limited program of pesticide monitoring on 11 waterways in the west United States (*59*). The streams, representing agricultural areas were the probability of observing pesticide residues would be greater, included the Missouri, Brazos, Yellowstone, Sacramento, Colorado, Arkansas, Yakima, Rio Grande, and Snake Rivers. Pesticides chosen for analysis included the insecticides aldrin, DDD, DDE, DDT, dieldrin, endrin, heptachlor, heptachlor epoxide, and lindane, and the herbicides 2,4-D, 2,4,5-T, and silvex. The authors reported that no herbicide was found at any time at any station during the first year of the sampling program. The lower limit of sensitivity (detection) was 5 ppt.

Manigold and Schulze (*60*), reporting on the results of the U.S. Geological Survey stream monitoring program for the 2-year period October 1966 to September 1968, observed that beginning in August 1967 2,4-D, silvex, and 2,4,5-T had been detected frequently. 2,4,5-T was found in 28 of the 320 samples and ranged from 0.01 to 0.07 ppb. The authors stated that the established criteria permitted 100 μg/liter (ppb) for herbicides. These authors reported that the analytical procedures were changed from the preceding report to use Law's sample cleanup procedure, which permits routine detection of pesticides at 0.005 μg/liter in most waters.

Norris (*47*) observed that peak concentrations of phenoxy herbicides seldom exceeded 0.1 ppm in streams contaminated from spray projects on range and forest lands in Oregon.

Lawson (*61*) studied 2,4,5-T residues in storm runoff from three small watersheds in Arkansas. Two watersheds, one cleared and the other partially cut, were sprayed with the isooctyl ester of 2,4,5-T. A third watershed, adjacent to the two treated ones, was used as a control. Spraying was done in September 1971, June 1972, and July 1973, either to control woody sprouts and broadleaf vegetation or just to provide herbicide application for monitoring. The cleared watershed was treated with 4 pounds acid equivalent per acre and the partially cut site with 2 pounds/acre.

In water samples taken after the first runoff-producing storm in October 1971, Lawson (*61*) detected an average of 2.1 ppm 2,4,5-T from the cleared watershed and 1.0 ppm from the partially cut site. Maximum amounts detected were 2.2 and 1.3 ppm for the two areas. No 2,4,5-T was detected from the control site.

Only trace amounts (less than 0.2 ppm) were detected from each of the two treated sites after the next runoff-producing storms in November 1971. None was detected from the control.

In approximately 90 samples taken after storms during the period December 1971 through September 1973, no 2,4,5-T was detected by Lawson (*61*) in the runoff from the treated or control water sheds.

Since TCDD is immobile in soil (*39*) and soluble in water at only 0.2 ppb (*7*), the possibility of ground water contamination is virtually nonexistent (*46*). TCDD could be present in runoff when soil erosion is significant (*39*), and thus TCDD contamination of water bodies could occur.

A recent National Academy of Sciences report on drinking water stated that 2,4,5,-T and TCDD have never been detected in drinking water; the limit of detection was in the parts per trillion. However, the report did project the toxicity of 2,4,5,-T and TCDD, their acceptable daily intake, and suggested no-adverse-effect levels (*62*).

(3) *Air.* Prior to 1970, phenoxy herbicides were widely used for early postemergence control of weeds in wheat. Johnson (*63*) reported that air samples collected during spring and summer in the state of Washington where these crops are grown contained as much as 0.06 $\mu g/m^3$ 2,4-D and 2,4,5-T. Assuming that a man inhales about 30 m^3 of air per day, the authors estimated that exposure to 0.06 $\mu g/m^3$ would amount to inhalation of 1.8 μg phenoxy herbicide/day or 0.025 μg/kg of body weight per day for a 70 kg man.

Ambient air monitoring for pesticides in predominantly agricultural areas of 28 states was conducted by the National Air Monitoring Program in calendear years (CY) 1970 through 1972 using ethylene glycol impinger type samples. Table 1 records the arithmetic mean of residues of 2,4,5-T detected in this program (*64*).

Table 1. Air Monitoring Data for 2,4,5-T in 28 State Monitoring Programs (1970 to 1972)

Name of State or City	2,4,5-T Ester Monitored For	ng/m^3 CY 1970	ng/m^3 CY 1971	ng/m^3 CY 1972
Louisana	Isopropyl ester	-	ND	1.9
Montana		ND	ND	0.8
New Mexico		-	ND	1.0
Idaho		ND	ND	1.7
Illinois	BOEE	ND	3.6	ND
Oregon		ND	0.5	ND
Tennessee		1.1	ND	ND
Tennessee	Isooctyl ester	ND	2.7	ND
Oklahoma		ND	14.6	ND

ND = Not Detected.

(4) *Animals.* Phenoxy acetic acids are relatively strong acids, and animals rapidly excrete them unchanged in their urine (*36*). In their study of the fate of atrazine, kuron, silvex, and 2,4,5-T in the dairy cow, St. John et al. (*65*) found that dairy cows given 2,4,5-T and silvex in their feed at 5 ppm for four days, completely eliminated both 2,4,5-T and silvex as soluble salts in the urine two days after dosing stopped.

Zielinski and Fishbein (*66*) treated female C57BL/6 mice with a single subcutaneous injection of 100 mg/kg body weight of 2,4,5-T in dimethylsulfoxide solution. They sacrificed the animals at various intervals after injection and analyzed in toto for 2,4,5-T. The amounts recovered as percentage of the amount injected indicated decreasing levels at the following time intervals after dosing: at 0 hours, 77.1±5.0%; at 16 hours, 56.9±4.2%; and at 24 hours 23.7±3.6%.

In a preliminary report of a two-year chronic toxicity feeding study, Dow Chemical USA (*110*) reported the following residue data for rats fed indicated TCDD doses: 24,000 ppt in liver and 8,100 ppt in fat of females ingesting 2,200 ppt/day; 5,100 ppt in liver and 1,700 ppt in fat of females ingesting 220 ppt/day; and 540 ppt in liver and fat of females ingesting 22 ppt/day. The preliminary report gives no residue data for treated males, or for controls of either sex.

Piper et al. (*67*) studied the fate of 2,4,5-T following oral administration to rats and dogs. Four groups of three male and three female Sprague-Dawley rats (Spartan strain) and two male and two female adult beagle dogs were given single doses of ^{14}C-labeled 2,4,5-T by intubation at 5, 50, 100, and 200 mg/kg body weight in rats and 5 mg/kg body weight in dogs. The authors combined data obtained for males and females since the pharmacokinetics of 2,4,5-T were essentially the same in each sex. In this study, the clearance half-life for 5 mg/kg 2,4,5-T from dog plasma was 77.0 hours; in rats the half-life was 4.7 hours at 5 mg/kg and 4.2 hours at 50 mg/kg. At doses of 100 and 200 mg/kg body weight, the clearance half-life for rats increased to 19.4 and 25.2 hours, showing that the pharmacokinetics of 2,4,5-T varies with dose as well as with species. The authors suggested that the half-life values at 100 and 200 mg/kg body weight indicated that these doses may have exceeded the excretory capacity of the rats.

Zitko (*68*) assayed chlorinated dibenzodioxin residues in aquatic animals, but was unable to detect these compounds (detection limit: 0.04 μg/g [ppm] for TCDD) in any of several aquatic animals from Canadian locations. The author had selected species from high trophic levels of the aquatic food web to measure cumulative pesticide contamination. More recently, using improved analytical methods for detection of dioxin at ppt levels, Baughman and Meselson (*69*) found mean TCDD levels ranging from 18 ppt to 810 ppt in fish and crustaceans taken from Vietnamese rivers in August and September 1970. TCDD levels tended to be higher in fish from interior rivers than in those from seacoast locations. In comparison, Baughman and Meselson found less than 3 ppt TCDD in fish obtained in a market in Cape Cod, Massachusetts. In another study, Matsumura and Benezet (*70*) placed TCDD-coated sand directly in an aquarium containing brine shrimp, mosquito larvae, and fish (silverside). TCDD pickup was low in fish (2 ppb) and brine shrimp (157 ppb) under the experimental conditions. But mosquito larvae, which are bottom feeders, showed a surprisingly high rate of pickup (4,150 ppb). The authors concluded that TCDD was not likely to accumulate in as many biological systems as DDT because of TCDD's low solubility in water and lipids, as well as its low partition coefficient in lipids.

(5) *Plants.* Clark et al. (*36*) reported that, when herbicides are applied to rangeland, the levels of phenoxy herbicides available for ingestion by grazing livestock depend upon the nature and degree of cover, the rate and mode of application, time after application, and climate conditions. Studies by Morton et al. (*44*) showed that residues on grass immediately after application of 2,4,5-

T are not likely to exceed 100 to 150 ppm for each pound of actual herbicide applied per acre.

Leng (*37*) stated that herbicide residues in or on plants declined rapidly, with a half-life of one to two weeks, due to photodecomposition by sunlight, wash-off by rain, metabolism by plants, and dilution from growth of plants. 2,4,5-T was applied to grass in four states at an application rate of 4 pounds/gallon, 3 gallons/acre; initial residues immediately after treatment in California averaged 684 ppm (or 57 ppm/pound applied per acre); 1,668 ppm (or 139 ppm/pound) in Michigan; 1,464 ppm (or 122 ppm/pound) in North Carolina; and 1,332 ppm or (111 ppm/pound) in Texas. After two weeks, residues in the four locations averaged 26 to 34 ppm/pound per acre. After 16 weeks, all residues had declined to an average 3 ppm/pound applied per acre.

Bauer et al. (*71*) treated grass species indigenous to Victoria County, Tex., with 2 pounds/acre 2,4,5-T ester. One month after application the concentration averaged 4,060 ng/g (ppb) for 2,4,5-T acid and 2,890 ng/g (ppb) for 2,4,5-T ester. Six months after application the concentration averaged 60 and 170 ng/g (ppb) for 2,4,5-T acid and ester, repectively.

Getzendaner and Hummel (*72*)[6] described a 1969 study in which a 2,4,5-T propylene glycol butyl ether ester formulation was sprayed on Texas grass at an application rate equivalent to 12 pounds of 2,4,5-T per acre; this rate was 6 to 24 times the usual rate applied to grazing lands for brush control. At this time, manufacturing specifications for no detectable TCDD in 2,4,5-T used a method sensitive to 1ppm. The authors found that residues of TCDD decreased rapidly from about 500 ppt TCDD within one day of application, to about 35 ppt TCDD after four weeks, and about 15 ppt TCDD after 16 weeks. The TCDD decrease roughly paralleled the loss of 2,4,5-T from the same grass.

(6) *Humans.* Matsumura (*73*) studied 2,4,5-T in the blood and urine of human male volunteers who had ingested the chemical. After ingesting 150 mg (2.2 mg/kg), the plasma concentration of 2,4,5-T in one subject reached a peak of 21.1 μg/ml after four hours. A linear, semi-logarithmic concentration-time curve (a gradient of −0.065) four hours post-treatment indicated first order elimination and absorption kinetics.

In a second part of this study, Matsumura gave two male volunteers single oral doses of 100 mg 2,4,5-T. Urine samples were collected over 72 hours. About 45 percent of the orignial dose was found in urine collected during the first 24 hours after treatment; 60 percent had been recovered 36 hours after treatment; and after 72 hours, more than 80 percent of the original dose of 2,4,5-T had been recovered.

Gehring et al. (*74*) also studied the fate of 2,4,5-T following oral administration to man. Five male volunteers, ages 31 to 58 years, each ingested a single 5 mg/kg oral dose of analytical grade 2,4,5-T, with a purity greater than 99 percent and less than the detectable level (0.05 ppm) TCDD, directly or as a slurry in milk. Blood, urine and feces were collected at intervals for up to 96 hours after ingestion. Essentially all (88.5±5.11 percent) of the 2,4,5-T ingested by these subjects was excreted unchanged in the urine after 96 hours. The plasma 2,4,5-T concentration increased rapidly following ingestion and after 7 hours reached a peak of approximately 57 μg/ml, after which the plasma contained 65 percent of the 2,4,5-T in the body, of which 99 percent was bound reversibly to protein.

Kohli et al. (*75*) also studied absorption and excretion of 2,4,5-T in man. Eight male volunteers, age 25 to 35 years, received a single oral dose (2, 3, or 5 mg/kg) analytical grade 2,4,5-T with a purity greater than 99 percent. Urine was collected up to 96 hours, and blood samples were collected up to 168 hours. 2,4,5-T was detected in some two-hour urine samples, indicating rapid excretion of the compound. More than half of the 2,4,5-T was excreted in the urine in the first 48 hours, although small quantities were still being excreted at 96 hours.

2,4,5-T appeared in all plasma samples 1 hour after 2,4,5-T ingestion, indicating rapid absorption. Maximum concentration (approximately 25 μg/ml for the 5 mg/kg dose) was reached between 7 and 24 hours after ingestion and began to decline at a first-order rate after 32 hours.

These investigators concluded that 2,4,5-T was readily absorbed from the gastrointestinal tract, that it was eliminated unchanged in the urine, and that the half-life for plasma clearance was 18.8±3.1 hours. These authors pointed out that, in general, higher recoveries were reported by Gehring et al. (*74*) who used an electron capture detector, instead of the flame-ionization detector used in their study.

The National Human Monitoring Program for Pesticides, through its cooperative arrangement with the Health and Nutritional Examination Survey II (Hanes II project), is currently analyzing human urine samples for silvex, 2,4,5-T, and 2,4,5-TCP (*64*). The survey is scheduled for completion in 1979, but some extremely tentative results are available. No quantifiable 2,4,5-T residues have been detected in the first 400 samples; however, trace amounts (<10 ppb) have been found in a few samples.

Dougherty and Piotrowska (*177*) reported on screening of human urine for environmental contamination with toxic residues by negative chemical ionization mass spectrometry. The procedure is based on solvent extraction with minimal clean-up followed by examination with negative chemical ionization mass spectrometry for organochlorine residues and related compounds with masses greater than 130 daltons. Urine for the screening procedure was obtained from students at Florida State University (25 dorm residents; 21 football team members; and 11 swimming team members). The authors reported that the limited survey of human urines indicates contamination of the subjects with 2,4,5-T, pentachlorophenol, other polychlorophenoxy acids, and numerous unknown compounds. The authors indicated that 2,4,5-T was found in 36 percent (9/25) of the dorm residents; 24 percent (5/21) of the football team; and 9 percent (1/11) of the swimming team. The authors attempted to define the source of the contamination by applying the same screening procedure to environmental substrates and suggested the food chain (beef fat in the case of 2,4,5-T) as one significant source of the contamination.

(7) *Animal products.* Kocher et al. (*76*) surveyed beef fat from cattle grazing on land where 2,4,5-T had been applied to determine if TCDD was present in this tissue. None of the 2,4,5-T samples used were available for analysis for TCDD content. The authors did not know whether the samples were produced before 1972 (when maximum allowable TCDD content was 1 ppm) or after 1972 (when maximum allowable TCDD content was 0.1 ppm). None of the 16 samples from Sugarland (Tex., Mo., and Okla.), showed TCDD residues when analyzed by a gas chromatography-mass spectrometry detection technique (detection limits: 3 to 6 ppt). Three of the eight samples from Mertzon, Tex., where animals had grazed for 30 days in a fenced pasture sprayed in its entirety with 2,4,5-T, gave positive responses at the detection limit of 3 to 4 ppt TCDD.

In another surveillance study, Mahle et al. (*77*) analyzed milk from cows grazing on grass treated with 2,4,5-T in accord with normal agricultural practices. Twenty-five samples were collected from different farms in Oklahoma, Arkansas, and Missouri; these areas were selected as representative of those where 2,4,5-T is used to control broadleaf weeds and brush in pasture and rangeland. Milk purchased in Midland, Mich., an area where 2,4,5-T is not used, provided control samples. Based on gas chromatography-mass spectrometry data (detection limit: 1 ppt), the authors stated that control samples were indistinguishable from the samples from treated areas and concluded that TCDD was not present.

The residue levels reported in animal products in the studies cited below were obtained in laboratory feeding studies and not from animals grazing on pastures and rangelands treated at dosage rates recommended on registered product labels. Nevertheless, residues obtained in these feeding studies could occur in the environment and at these same levels since animals grazing on forage plants immediately after treatment at recommended rates of application could ingest 2,4,5-T in amounts similar to those fed in the studies.

Leng (*37*) found no residues greater than 0.05 ppm in milk or cream of cows ingesting 10 to 30 ppm 2,4,5-T. At 100 ppm 2,4,5-T in the diet, traces of 2,4,5-TCP (0.06 ppm) were found in milk and cream. When the diet contained high levels of 2,4,5-T, equivalent to 300 and 1,000 ppm in the total diet, residues of 2,4,5-T and 2,4,5-TCP ranged from 0.15 to 0.5 ppm in milk of individual cows.

Leng (*37*), reporting on residues in meat and meat byproducts, stated that calves slaughtered after ingesting 300 ppm 2,4,5-T in total diet contained average residues of 0.12 to 0.28 ppm in muscle, fat, and liver, and 3.3 ppm in kidney. Animals fed 900 to 2,000 ppm 2,4,5-T in the total diet and slaughtered without withdrawal had proportionally higher average residues in tissue. No residues were detected (detection limit: 0.05 ppm) in most tissues when animals were given untreated feed for one week after they had been on the highest levels (1,800 and 2,000 ppm) of 2,4,5-T for 4 weeks. Residues of 2,4,5-T declined rapidly in tissues as soon as animals started to eat untreated feed.

Clark and Palmer (*78*) found 0.08 ppm 2,4,5-T in omental fat of each of two sheep given four oral doses of either 0.15 or 0.75 mg/kg of the propylene glycol butyl ester of 2,4,5-T. They also found 368 ppm 2,4,5-T in kidneys of animals killed by 4 daily 250 mg/kg doses of a 2,4,5-T ester.

Clark et al. (*36*) found 2,4,5-T no higher than 0.05 ppm in muscle or fat of sheep held one week on untreated feed. Residues

[6]Studies submitted by registrants as part of petitions for residue tolerances are classified confidential, pending outcome of litigation in U.S. District Court.

of the metabolite 2,4,5-TCP were not detected in the fat of any of the animals. They also found that the 2,4,5-T level in liver and kidneys was less than 0.05 ppm after the animals were on untreated feed for 7 days.

Leng (*79*) found low levels of 2,4,5-T in muscle and fat of calves receiving 300 to 900 ppm 2,4,5-T in the diet and much higher residues in tissues of animals fed 1,800 ppm 2,4,5-T for 28 days. Calves fed 300 ppm 2,4,5-T showed 0.12 and 0.28 ppm 2,4,5-T in muscle and fat, respectively. Calves fed 900 ppm showed 0.24 and 0.38 ppm in muscle and fat, respectively. And at 1,800 ppm in the diet, calves showed 1.2 and 2.0 ppm in muscle and fat, respectively. In this same study, Leng found relatively low residues of 2,4,5-T in liver at feeding levels of 300 and 900 ppm (0.2 and 1.0 ppm, respectively) and sharply increased residues (7.9 ppm) at 1,800 ppm, indicating that the threshold level may have been exceeded at this higher dosage level. Residues of 2,4,5-T in kidney appeared to be proportional to the level in the diet.

Eighty-five samples of beef fat were analyzed for TCDD content under the auspices of the EPA Dioxin Implementation Plan (see section II). These beef fat samples included 18 samples from control areas and 67 samples from areas previously treated with 2,4,5-T. None of the 18 control samples had detectable amounts of TCDD at a detection limit of 10 ppt. Of the 67 samples from areas previously exposed to 2,4,5-T, one showed a positive TCDD level of 60 ppt; two appeared to have TCDD at 20 ppt; and five may have had TCDD levels which ranged from 5 to 10 ppt. The values for these five samples were at or below the limits of detection of 10 ppt. Forty-three beef liver samples were analyzed and showed no TCDD residues at a detection limit of 10 ppt.

(8) *Food.* Evidence that very little 2,4,5-T gets into food is seen in results of Market Basket Surveys conducted by the Food and Drug Administration (FDA). Of the 134 total diet samples involving 1,600 food composites (Market Basket Survey) analyzed from 1964 through April 1969, only three contained 2,4,5-T. Two were dairy products containing 8 to 13 percent fat with 0.008 and 0.19 ppm in the fat. A single meat, fish, and poultry composite from Boston consisting of 17 to 23 percent fat was found to contain 0.003 ppm 2,4,5-T on a fat basis (*81, 82, 83, 84*).

FDA Market Basket Survey samples from 1969 through July 1974 showed no 2,4,5-T residues (detection limit: 0.02 ppm) in 155 total diet samples involving 1,869 food composites (*85, 86, 87, 88, 89*).

(9) *Human exposure via industrial accidents.* There have been a number of industrial accidents during manufacture of chlorinated phenols that have resulted in human exposure to TCDD.

Whiteside (*90*) reported on a 1949 explosion at a chemical plant producing 2,4,5-T in Nitro, W. Va. The release of intermediate chemicals led to 228 cases of chloracne among exposed workers. Whiteside stated that symptoms of affected workers included skin eruptions, shortness of breath, intolerance to cold, palpable and tender liver, loss of sensation in extremities, damage to peripheral nerves, fatigue, nervousness, irritability, insomnia, loss of libido, and vertigo.

Goldmann (*91*) reported on a 1953 accident at a 2,4,5-TCP production plant in Germany. Temperature and pressure rose explosively in the autoclave, forming previously unknown, very toxic chlorinated hydrocarbons; 42 persons contracted serious cases of dermatitis, in which 14 persons suffered consequent damage to internal organs, and seven persons experienced disturbances of the nervous system. A similar accident occurred in Amsterdam in 1963 when an explosion in a 2,4,5-T factory resulted in 50 workers contracting chloracne (*90*).

In 1954, 31 workers in a Hamburg, Germany, chemical plant producing 2,4,5-T from technical 2,4,5-TCP contracted chloracne (*10, 16, 92*) and suffered the physical and psychological symptoms associated with it (*93*). Kimmig and Schulz (*10*) extensively investigated the workers' conditions and conducted experiments treating the skin of a rabbit's ear with chemicals to which workers had been exposed. These researchers tentatively identified the causative agent of the chloracne as TCDD. Bauer et al. (*15*) conclusively identified TCDD as the cause of chloracne.

In 1964 workers in a 2,4-D and 2,4,5-T plant in the United States developed chloracne (*93, 94*). Bleiberg et al. (*94*) found evidence of porphyria cutanea tarda (PCT) of varying degrees of severity in 11 out of 29 workers. PCT had never before been described as related to chloracne, nor had it been ascribed to industrial exposure in the United States. The authors stated that either the finished chemicals or some intermediate were responsible for both diseases.

The Fine Chemicals Unit of Coalite and Chemical Products Ltd. located at Bolsover, Derbyshire, in England had been producing 2,4,5-TCP for nearly 3 years without incident when an explosion occurred at midnight on April 23, 1968. As a result of this exothermal reaction, TCDD had accidentally been produced. Workers at this plant where accidentally exposed to TCDD, and 79 cases of chloracne were recorded, many of them severe (*9, 95*).

Beginning in May 1971 an accidental poisoning episode occurred in the United States that affected humans, horses, and other animals. The exposure was related to the spraying of waste oil, contaminated with TCDD, on riding arenas to control dust. Three days after spraying, sparrows and other birds were found dead on the arena floor. Of 85 horses exercised within the arena, 62 became ill, and 48 died. The first horse died on June 20, 1971. Horses continued to die as late as January 1974. Human illnesses were less severe, but did include one case of hemorrhagic cystitis in a 6-year-old girl who frequently played in the arena. Analysis showed the arena contained 31.8 to 33.0 μg/g TCDD (*96, 97, 162*).

Beale et al. (*98*) presented follow-up information on the 6-year-old girl involved in this accidental poisoning. These authors stated that the girl's symptoms resolved in three to four days and did not recur. Results of a repeat voiding cystogram three months later appeared normal. Cystoscopy at this time did, however, demonstrate numerous punctate haemorrhagic areas in the bladder, especially in the region of the trigone. Five years later, an investigation showed that this girl had grown normally; results of a physical examination, including a detailed neurological examination, were normal. Cystogram and liver-function tests were also normal, as was the urinary excretion of uroporphyrins, coproporphyrins, and thyroid function.

On July 10, 1976, an accident at the ICMESA chemical plant in the Seveso Region of Italy released 2 to 10 pounds of TCDD over a wide area (*90, 99, 100*). Hundreds of animals died, many area residents reported skin disorders, and an area of 110 hectares was evacuated (*101*). Reports of the immediate symptoms and indications of many long-term effects are just becoming available.

Seveso inhabitants initially experienced numerous, burnlike skin lesions which gradually receded; Whiteside (*90*) believed this type of lesion was probably due to direct contact with the sodium hydroxide and phenolic components of the fallout. Two and a half months after the explosion, however, children and young people in the zone most affected by the fallout developed symptoms of true chloracne, a sign of dioxin poisoning, on their faces, arms, and bodies. By November 1976, 28 people had developed confirmed cases of chloracne, and the number rose to 38 by December 1976; one year later, the number of confirmed cases of chloracne was 130.

A number of Seveso women were pregnant at the time of the accident. Whiteside (*90*) reported that the number of legal and illegal abortions performed after the accident probably totalled 90. Results of a survey by an epidemological commission showed that 183 babies were delivered in the two months following the accident and that there were 51 spontaneous abortions as distinct from induced abortions (approximately double the rate of spontaneous abortions previously reported for the area). Whiteside (*90*) reported that eight cases of birth abnormalities have been noted to date among babies born to women in the Seveso area who were pregnant at the time of the explosion. Physicians in the Seveso area have had difficulty relating this directly to the explosion, however, since this incidence of birth abnormalities was not disproportionate to the usual incidence of abnormal births.

H. *Tolerances.* There are no tolerances established for 2,4,5-T in or on food crops. Likewise, no tolerances have been set specifically for TCDD in or on food crops. However, 40 CFR 180.302 does establish a tolerance of 0.05 ppm for hexachlorophene on cotton seed (a nonhuman dietary food item), with a stated limitation that the technical grade hexachlorophene used in the formulation shall not contain more than 0.1 ppm TCDD. The limitation does not constitute a tolerance (*102*).

I. *Pesticide episode reports system (PERS).* EPA's Pesticide Episode Response Branch of the Office of Pesticide Programs maintains a Pesticide Episode Reports System (PERS) which collects reports of pesticide exposure affecting humans, domestic animals, livestock, and wildlife (*103*). According to their records, there were 96 episodes from 1966 to April 1977 involving 2,4,5-T.

Many of these 96 episodes recorded effects in more than one area of the environment. Plant damage was reported 60 times, effects on humans 16 times, water contamination 14 times, effects on domestic animals and soil contamination 7 times each, general environmental contaminations 3 times, and fish kills and complaints against use of 2,4,5-T twice each.

There was substantial evidence in 13 of the 96 episodes linking 2,4,5-T to the episode's effects; there was circumstantial evidence in 20 of the episodes for involvement of 2,4,5-T; there was insufficient evidence in 62 of the episodes to prove or disprove involvement of 2,4,5-T; and one episode had no verification status listed.

Of the 13 episodes for which there was substantial evidence linking 2,4,5-T to the

episode's effects, two involved humans (including one suicide); 2,4-D was also involved in both episodes. Three episodes involved plant damage from drift of herbicides; 2,4,5-T residues were found in plant samples in two episodes; 2,4-D was also involved in one of these episodes. Two episodes involved fish kills resulting from accidental spills into streams, with 2,4-D involved in both incidents; in one of these episodes, 6,000 fish (90 percent juvenile salmon) were killed; residues of both 2,4-D and 2,4,5-T were found in these fish. Two incidents involved soil contamination when two warehouses were destroyed by a tornado and fire; many other pesticides were involved in both instances. Two episodes involved domestic animals; in one, 24 cows died after herbicide application. Arsenic residues were found in two cows, and arsenic contamination of the herbicide mix was suspected. In the other instance, 8 cows drank water contaminated with 2,4,5-T; residue levels of 0.03 and 0.02 ppm were found in the milk five and eight days, respectively, after the incident. Two hundred and forty gallons of milk were dumped. One incident involved water contamination as a result of a warehouse fire; many other pesticides were also involved.

II. Regulatory History

2,4,5-T was developed during World War II and was first registered as a pesticide on March 2, 1948 (*3*). Since then, it has been the subject of several Federal regulatory actions.

On April 13, 1966, the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) published an announcement in the FEDERAL REGISTER abolishing the "No Residue and Zero Tolerance" concepts as scientifically untenable. Future registrations would be granted on the basis of either "Negligible Residue" or "Permissible Residue." Industry was given until December 31, 1967, to comply by obtaining tolerances for residues of 2,4,5-T in all treated food, feed products, and byproducts (in addition no registrations would be continued beyond December 31, 1970).

Following this action, a series of Pesticide Registration (PR) Notices were issued over several years, extending certain "no residue" and "zero tolerance" registrations beyond the December 31, 1967, deadline for obtaining residue tolerance. (These and all following PR Notices are cited in Reference 104.) Among uses of 2,4,5-T extented beyond the deadline were uses on pasture grasses and rangeland; on apples (McIntosh), blueberries (low bush), cereal grains (undesignated), rice, and sugarcane; and in lakes and ponds.

PR Notice 70-8 issued by the USDA on March 10, 1970, identified data needs for certain compounds. 2,4,5-T was identified as one of the compounds requiring further teratogenic studies.

PR Notice 70-11 published on April 20, 1970, suspended 2,4,5-T products bearing certain directions for use. The suspended uses were all uses in lakes, ponds, or on ditch banks; and liquid formulations for use around the home, recreation areas, and similar sites.

PR Notice 70-13 issued by the USDA on May 1, 1970, cancelled 2,4,5-T products bearing certain directions for use. The cancelled uses were all granular 2,4,5-T formulations for use around the home, recreational areas, and similar sites; and all 2,4,5-T uses on food crops intended for human consumption.

All registrants were advised of these actions, and two of the 2,4,5-T registrants, Dow Chemical and Hercules Incorporated, exercised their right under Section 4(e) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 135 et seq.) to petition for referral of the cancellation (rice use only) to an Advisory Committee.

As provided by Section 4(c) of FIFRA (1964 amendment), a nine-member Advisory Committee of scientists was appointed to consider all relevant facts, submit a report and recommendations regarding registration for certain uses of 2,4,5-T, and state the reasons or bases for these recommendations. Their report was submitted to the Administrator of the Environmental Protection Agency on May 7, 1971 (48). The Committee recommended that use of 2,4,5-T be permitted in forestry, range land, and rights-of-way providing that the limit of 0.1 ppm of contamination with TCDD be set for all future production of 2,4,5-T; that 2,4,5-T be applied no more than once a year at any one site; and that 2,4,5-T be applied with proper caution so that it will not contaminate other areas where it may come into contact with humans.

The Committee also recommended that this action be reviewed again when existing deficiencies in information about possible magnification of TCDD in the food chain have been rectified by specific research.

In the meantime, PR Notice 70-22, published by the USDA on September 28, 1970, addressed the presence of chlorodioxin contaminants in economic poisons. This notice stated that the USDA had determined that certain toxic chlorodioxins (such as TCDD) may be present as contaminants in the basic materials used in formulating 2,4,5-T and silvex. The notice also stated that the presence of such chlorodioxins constituted a possible hazard to man since they had been found to be extremely toxic to laboratory animals, and that appropriate regulatory action would be taken under provisions of FIFRA since products containing chlorodioxins are considered to be in violation of FIFRA.

Dow Chemical obtained an injunction against EPA in July 1972, enjoining further administrative action against 2,4,5-T. The United States Court of Appeals for the Eighth Circuit overturned the injunction in 1973, and administrative proceedings were allowed to go forward.

On July 20, 1973, a notice of intent to hold public hearings on *all* uses of 2,4,5-T was filed with the EPA Hearing Clerk under section 6(b)(2) of FIFRA, as amended 1972. All federally approved uses of 2,4,5-T were to be explored in a public hearing scheduled for April 1974, following completion of an intensive monitoring program for detecting dioxin in the ppt range (38 FR 19869, July 29, 1973).

On May 10, 1974, the information hearing was expanded to include all insecticides and herbicides having 2,4,5-TCP in their manufacturing process. These included silvex, erbon, and ronnel, as well as 2,4,5-T and 2,4,5-TCP, all of which may contain TCDD.

On June 24, 1974, EPA withdrew cancellation and information-gathering proceedings initiated against 2,4,5-T and related compounds because of its inability to monitor food for TCDD residues with the necessary analytical precision. Although the 2,4,5-T notice of hearing was withdrawn, the Agency stated that it "will continue its TCDD residue monitoring program and will take such further action as it deems appropriate once the results of the monitoring project are available" (39 FR 24050 June 28, 1974).

On July 25-26, 1974, the Agency held a Dioxin Planning Conference in Washington, D.C., primarily for those parties having an interest in the withdrawn 2,4,5-T/dioxin hearings, to address data analysis and retrieval (in the areas of analytical methodology, toxicology, and monitoring) with emphasis on analytical methodology for TCDD at the ppt level. As a result, the Agency established a Dioxin Implementation Plan (DIP) intended to identify a preferable analytical methodology to monitor human and environmental samples for TCDD.

On-going TCDD studies under the DIP include: An analytical method validation study to produce statistically defensible data; monitoring for residues in human milk in the Pacific northwest; additional beef fat residue studies; additional technical pesticide residue studies; and an environmental monitoring program for TCDD residues in soil, water, and biota.

III. Summary of Scientific Evidence Relating to Rebuttable Presumption

The following adverse effects of 2,4,5,-T and/or TCDD have been found to exceed the criteria for issuance of a rebuttable presumption as stated in § 162.11 of the Code of Federal Regulations (CFR 40). Because of industry's apparent inability to produce 2,4,5-T without TCDD contamination, none of the studies cited are for pure 2,4,5-T. The effects of TCDD must also be considered when assessing 2,4,5-T by the Agency's risk criteria.

A. *Oncogenic effects.* 40 CFR 162.11(a)(3)(ii)(A) provides that a rebuttable presumption shall arise "if a pesticide's ingredient(s) * * * (i)nduces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure * * *." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals."

The studies summarized below indicate that 2,4,5-T containing less than .05 ppm TCDD and/or TCDD alone have oncogenic effects in two mouse strains and one rat strain. Since 2,4.5-T, as currently formulated, contains TCDD (at a maximum amount of 0.099 ppm), a rebuttable presumption against the registration of 2,4,5-T products has arisen because of the oncogenic effect of 2,4,5-T and its contaminant, TCDD.

(1) *2,4,5-T*—(a) *Effects of dietary 2,4,5-T (<0.05 ppm TCDD) on rodents.* In their bioassy of 2,4,5-T for carcinogenicity in mice, Muranyi-Kovacs et al. (*105*) administered 2,4,5-T (containing <0.05 ppm TCDD)[6] to inbred C3Hf and XVII/G mice. The mice were given 100 mg/liter of 2,4,5-T in the drinking water for two months beginning at six weeks of age. During the succeeding 15 to 20 months, the mice were given 2,4,5-T mixed in the diet at a concentration of 80 ppm *ad libitum.*

In C3Hf mice, 48 percent of the treated females (15/31) and 55 percent of the treated males (17/29) developed tumors, compared with control values of 21 percent (9/44) and 49 percent (21/43), respectively (Table 2). The differences between the number of tumors observed and the number expected were sig-

[6]This TCDD level is less than the 0.1 ppm TCDD currently found in most commercial formulations (see Section I.B).

nificant for female mice at all sites ($p<0.03$) and for the combined sexes ($p<0.01$).[7] For non-incidental tumors, the differences were significant for each sex and the combination; no significant differences were found in incidental tumors.[8] No other strain-sex combination yielded statistically significant values (*106*). Rare types of tumors, not seen in the control animals, were observed in the treated C3Hf females.

A decrease in survival time for mice with tumors was noted in both male and female treated C3Hf mice when compared with controls. C3Hf treated male mice survived an average of 511 days compared with 630 days for control male mice. According to the evaluation by EPA's Carcinogen Assessment Group (CAG), (*106*), this difference was significant ($p<0.001$). Treated female C3Hf mice survived 620 days compared with 680 days for control females. Chemically induced oncogenic effects typically show long latency periods. The finding of reduced longevity among treated animals as compared with controls complicates the assessment of the potential oncogenic effects of 2,4,5-T.

In XVII/G mice, 84 percent of the treated females (16/19) and 75 percent of the treated males (15/20) developed tumors, compared with control values of 53 percent (21/40) and 78 percent (25/32), respectively.

An increase in survival time for mice with tumors over controls was noted among the XVII/G treated animals. There was an average survival time of 583 days for treated male mice compared with 521 days for control male mice. Treated females survived 641 days compared with 569 days for control females. According to CAG (*106*), the difference was significant ($p<0.01$) in females.

(b) *Effects of subcutaneous injection and oral administration of 2,4,5-T (30 ppm TCDD) on rodents.* Innes et al. (*107*) studied the tumorigenicity of 2,4,5-T, containing about 30 ppm TCDD, in two hybrid strains of mice, designated as "X" and "Y", after oral or subcutaneous administration of the maximum tolerated dose (table 3). The testing was performed at Bionetics Research Laboratores, under contract from the National Institutes of Health. Results of the studies were calculated comparing treated groups with matched and pooled controls.[9]

In the subcutaneous study, mice were given a single injection of 21.5 mg/kg of 2,4,5-T in a dimethyl sulfoxide (DMSO) solution at approximately 18 months of age. Seventeen percent ($\frac{3}{18}$) of the treated "Y" males developed pulmonary adenomas, compared with 1 percent ($\frac{1}{71}$) of the matched controls and 3 percent ($\frac{4}{122}$) of the pooled controls. This increased incidence of pulmonary adenomas was significant relative to both control groups ($p=0.024$ matched and $p=0.04$ pooled) (*106*).

In the oral study, 21.5 mg/kg of 2,4,5-T in gelatin was administered daily by stomach tube, beginning at 7 days of age. After weaning, 60 ppm of 2,4,5-T was mixed in the diet and provided ad libitum until the end of the study at approximately 18 months. Gross and histological examinations were made of all major organs and visible lesions; thyroid glands were not examined. According to CAG's evaluation (*106*), there were no significant differences between 2,4,5-T treated and control groups of mice with respect to tumors at specific sites or total number of tumor-bearing animals.

Table 2. Oncogenic Effects of 2,4,5-T on Mice[a/]

Strain	Sex	Dietary Level (ppm)[b/]	Mean Survival Time (days)	Mice with Leukemia and Lung and Liver Tumors No/Total No[c/]	%	Incidence of Tumors: Total	Lung	Liver	Leukemia	Other
C3HF	M	0	630	21/43	49	22	2	19	--	1[d/]
		80	511[k/]	12/22	55	13	--	10	2	1[e/]
	F	0	680	9/44	21	9	5	3	1	--
		80	620	12/25	48	13	--	4	3	6[f/]
XVII/G	M	0	521	25/32	78	27	22	4	--	1[g/]
		80	583	15/20	75	16	14	--	1	1[h/]
	F	0	569	21/40	53	24	20	--	2	2[i/]
		80	641[j/]	16/19	84	16	15	--	1	--

a/ Data from Muranyi-Kovacs (105).
b/ Estimated daily oral dose = 12 mg/kg body weight.
c/ Effective number of mice are mice surviving longer than 300 days or developing a tumor before 300 days of age.
d/ Pleomorphic salivary gland tumor.
e/ Fibrosarcoma; one hyperplastic urinary bladder and one hyperplastic forestomach not included.
f/ One osteogenic sarcoma; two sarcomas; two cutaneous tumors; one cervical tumor.
g/ Forestomach tumor.
h/ Urinary bladder papilloma; two hyperplastic lesions of urinary bladder not included.
i/ Two hemangiomas.
j/ $p < 0.01$ compared with controls.
k/ $p < 0.001$ compared with controls.

Table 3. Tumors in Mice Ingesting 2,4,5-T

Strain	Sex	Dose (ppm)	Mice with Tumors No/Total No	%	Mice with Specific Tumors: Reticulum Cell Sarcoma	Tumor Type Pumonary Adenoma & Carcinoma	Hepatoma
X	M	0 (matched)	5/15	33	0	2	3
		0 (pooled)	22/79	28	5	5	8
		60	6/18	33	1	1	4
	F	0 (matched)	2/18	11	1	1	--
		0 (pooled)	8/87	9	4	3	--
		60	1/81	6	--	1	--
Y	M	0 (matched)	3/18	17	--	3	--
		0 (pooled)	16/90	18	1	10	5
		60	3/18	17	2	--	1
	F	0 (matched)	1/15	7	1	--	--
		0 (pooled)	7/82	9	3	3	1
		60	2/18	11	1	--	--

[7] The investigators found no significant sex-related differences.

[8] Incidental tumors are tumors discovered at necropsy of an animal which died from some other cancer; nonincidental tumors are tumors diagnosed during life or which caused the death of the animal.

[9] Because this was a large scale screening study, several control groups were used. No significant differences were found among these groups.

(2) *TCDD.*—(a) *Oncogenic effects of low levels of TCDD on rodents.* Van Miller et al. (*109*) recently reported the results of a 2-year feeding study with male Sprague-Dawley rats. Ten groups of ten animals per group were fed ground chow containing 0, 1, 5, 50, or 500 ppt ($=10^{-12}$ gram TCDD/gram food), and 1, 5, 50, 500, or 1,000 ppb ($=10^{-9}$ gram TCDD/gram food) TCDD.

Food intake (10=±4g/day) was significantly lower in rats ingesting the three highest dose levels (50,500, or 1,000 ppb TCDD) than in controls (21±2 g/day), and none of the rats in these three groups gained weight after the start of the experimental diet. All rats receiving these three dose levels died between the second and fourth week of treatment.

On the other hand, food intake for rats on other dose levels was similar to controls (20±2 g/day). Weight gain was significantly less for rats given 5 ppb TCDD (391±54 g) as compared to controls (531±44 g). In these seven groups only one animal died before the 30th week, and that death occurred in the 500-ppt group at the 17th week. In the 5- and 1-ppb groups, all animals died by the 90th week of the experiment. Table 4 shows the mortality figures for all groups.

TABLE 4.—*Mortality in rats ingesting various levels of TCDD*

Dose	Week of 1st death	Number of rats dead at 95th week[a]
0[b]	68	6/10 (60%)
1 ppt[c]	86	2/10 (20%)
5 ppt[d]	33	4/10 (40%)
50 ppt[e]	69	4/10 (40%)
500 ppt[f]	17	5/10 (50%)
1 ppb[g]	31	10/10 (100%)
5 ppb[h]	31	10/10 (100%)
50 ppb[i]	3	10/10 (100%)
500 ppb[j]	2	10/10 (100%)
1,000 ppb[k]	2	10/10 (100%)

[a] Surviving animals sacrificed at 95 weeks.
[b] Control group. Diet contained no TCDD.
[c] Approximate weekly dose was 0.0003 μg/kg body weight.
[d] Approximate weekly dose was 0.001 μg/kg body weight.
[e] Approximate weekly dose was 0.01 μg/kg body weight.
[f] Approximate weekly dose was 0.1 μg/kg body weight.
[g] Approximate weekly dose was 0.4 μg/kg body weight.
[h] Approximate weekly dose was 2.0 μg/kg body weight.
[i] Approximate weekly dose was 24 μg/kg body weight.
[j] Approximate weekly dose was 240 μg/kg body weight.
[k] Approximate weekly dose was 500 μg/kg body weight.

Laparotomies were performed on all rats surviving through the 65th week, and all tumors observed were biopsied. Rats were maintained on these diets until the 78th week and were then placed on the control diet. Surviving animals were killed at 95 weeks. Complete necropsies were done at death or sacrifice, and tissue samples were microscopically examined. Special staining methods were used to "aid in the diagnosis of neoplasms."

Tumorigenic and toxic effects were observed in rats in the six lowest dose groups. The overall incidence of neoplasms in the six experimental groups was 38 percent (23/60), compared with 0 percent (0/10) in the control group. The difference is statistically significant (*106*). Neoplastic nodules and cholangiocarcinomas of the liver were observed in 40 percent (4/10) of the rats ingesting 5 ppb TCDD; two animals had both neoplastic nodules of the liver and cholangiocarcinomas. One rat (10 percent) in the 1 ppb group had hepatic carcinoma compared to none of the controls. Hepatic tumors were not found in other dose groups (table 5).

Table 5. Liver Tumors in Rats Ingesting TCDD[a]

Dose (ppb)	Rats With Neoplastic Nodules		Rats With Cholangio-carcinomas		Rats With Nodules plus Carcinomas	
	No.	%	No.	%	No.	%
0	0/10	0	0/10	0	0/10	0
1	0/10	0	1/10	10	1/10	10
5	4/10	40[b]	2/10	20[b]	4/10	40[b]

a/ Data from Van Miller (109).
b/ Two animals had both neoplastic nodules of the liver and cholangiocarcinomas.

Tumors developed in 46 percent (23/50) of the rats ingesting 5, 50, or 500 ppt and 1 or 5 ppb TCDD, compared to none (0/10) in the control rats. Van Miller et al. noted that "nineteen (57 percent) (sic—Agency calculation is 54 percent (19/35)) of the animals that died in the six groups fed subacute levels of TCDD had neoplastic alternations." Carcinomas were observed in the ear duct, kidney, and liver. Three retriperitoneal histiocytomas were described as metastasizing to the "lungs, kidney, liver, and skeletal musculature." According to CAG's evaluation (*106*), statistically significant increases in tumors at all sites were found in rats fed 5, 500, 1,000, and 5,000 ppt as compared with control animals (p=0.05) (table 6). Three of the ten deaths which occurred in the 5-ppb dose group were attributed to aplastic anemia. One animal in the 500-ppt group had a severe liver infarction.

Dow Chemical U.S.A. (*110*) has provided EPA with a preliminary report of a study of TCDD's chronic toxic effects in Sprague-Dawley rats. Groups of 50 rats of each sex were fed 0.1, 0.01, or 0.001 μg TCDD/kg body weight daily for 2 years. To provide these dose levels, the concentrations or TCDD in the diet were approximately 2,200, 210, and 22 ppt. Eight-six animals of each sex were used as controls.

Table 6. Total Tumors in Rats Ingesting TCDD[a]

Dose[b]	Tumors			Rats With Tumors	
	Benign	Malignant	Total	No.	%
0	0	0	0	0/10	0%[c]
1 ppt	0	0	0	0/10	0%
5 ppt	1	5	6[d]	5/10	50%[a]
50 ppt	2	1	3[f]	3/10	30%
500 ppt	2	2	4[g]	4/10	40%[h]
1 ppb	0	5	5[i]	4/10	40%
5 ppb	8	2	10[j]	7/10	70%

a/ Data from Van Miller (109).
b/ Rats administered 50, 500, and 1,000 ppb were all dead within four weeks.
c/ Forty male rats used as controls for another study that were received at the same time and kept under identical conditions did not have neoplasms when killed at 18 months.
d/ One rat had ear duct carcinoma and lymphocytic leukemia. The following tumor types were each observed in one rat: adenocarcinomas (kidney), malignant histiocytoma (retroperitoneal), angiosarcoma (skin), and Leydig cell adenoma (testis).
e/ Three rats died with aplastic anemia.
f/ The following tumor types were each observed in one rat: fibrosarcoma (muscle), squamous cell tumor (skin), and astrocytoma (brain).
g/ The following tumor types were each observed in one rat: fibroma (striated muscle), carcinoma (skin), sclerosing seminoma (testis), and adenocarcinoma (kidney).
h/ One rat had a severe liver infarction.
i/ One rat had cholangiocarcinoma and malignant histiocytomas (retriperitoneal). The following tumor types were each observed in one rat: angiosarcoma (skin), glioblastoma (brain), and malignant histiocytoma (retroperitioneal).
j/ One rat had squamous cell tumor (lung) and neoplastic nodule (liver). Two rats had cholangiocarcinoma and neoplastic nodule (liver). Three rats had squamous cell tumors (lung). One rat had neoplastic nodule.

Dow (*110*) reported "discernible increases" in the incidence of hepatocellular carcinomas of the liver and of squamous cell carcinomas of the lung, hard palate/nasal turbinates, and tongue in rats at 0.1 μg/kg. They also reported decreased incidences of pituitary, uterine, mammary gland, pancreatic, and adrenal gland tumors at this dose level. Dow also reported that this dose level produced increased mortality, decreased body weight gain, and changes in blood chemistry values which suggested severe toxicity. Hepatocellular nodules and alveolar hyperplasia were observed in the 0.01 μg/kg group. A squamous cell carcinoma of the hard palate was observed in one female receiving this dose; Dow considered this unrelated to TCDD treatment because a similar tumor occurred in "other concurrent studies." At 0.001 μ/kg there were no "discernible effects in male rats and an increased incidence of [reversible] swollen hepatocytes in female rats."

Dow's preliminary report does not include control data, quantitative data on tumor incidence, or statistical analyses. CAG has not evaluated this study. Table 7 describes the available tumor information. Dow has submitted the final report for this study, which CAG is currently reviewing.

Table 7. Tumors in Sprague-Dawley Rats Ingesting TCDD[a/]

Dose		Tumors
ug/kg/day	ppt	
0	0	----
0.001	22	----
0.01	210	Hepatocellular Nodules
		Squamous Cell Carcinoma[b/]
		Alveolar Hyperplasia
0.1	2,220	Hepatocellular Carcinoma[c/]
		Squamous Cell Carcinoma[d/]

a/ Data from Dow Chemical USA (110), a preliminary report.
b/ Hardpalate squamous cell carcinoma observed in only one female rat.
c/ Observed only in females.
d/ Squamous cell carcinoma observed in lungs, hardpalate/-nasal turbinate, or tongue.

(b) *Effects closely related to oncogenicity in test animals.* Many chemically nonreactive carcinogens are enzymatically converted to biologically active carcinogens. The enzyme aryl hydrocarbon hydroxylase (AHH) is strongly implicated in this process (*112*). For example, the incidence of bronchiogenic carcinomas in humans (*113*) and mouse sarcomas induced by 3-methyl-cholanthrene (*114*) have been related to the level of inducibility of AHH (*99*).

Kouri et al. (*114*) studied AHH induction in human lymphocyte cultures by TCDD. The authors stated, "TCDD itself is not a potent carcinogen in mice; however, the synergistic action of TCDD with 3-methylcholanthrene (MC) produces cancer in different strains of mice in direct proportion to the degree of elevation of the induced hydroxylase activity and associated cytochrome P_1–450 content." Their study showed a positive correlation between basal enzyme activity and enzyme levels maximally inducible by either TCDD or MC. They also found that TCDD is about 40 to 60 times more potent than MC as an inducer of hydroxylase activity in cultured human lymphocytes. These authors further suggested that, because of the relatively high levels of TCDD in certain parts of the world, TCDD may also present considerable long-term risk because of possible synergism in chemically initiated oncogenesis, in addition to short-term risks posed by its toxic and teratogenic properties.

The implication of TCDD in AHH inducibility has also been reported by Poland and Glover (*115, 116*) and Poland et al. (*117*). In their studies on chick embryo livers, Poland and Glover (*115*) found that all dioxins which are potent inducers have halogens at three of the four lateral ring positions and at least one nonhalogenated carbon atom. Poland and Glover (*116*) compared the potency of TCDD as an inducer of hepatic AHH with that of MC, the most commonly employed inducing agent. They stated that analysis of the data by a computer program for bioassay showed that TCDD was 28,640 times as potent as MC on a molar basis. (The 95 percent confidence interval of the potency ratio is 2.07 to 3.95√10 *) The index of precision, *, was 0.18. Poland et al. (*117*) suggested that a hepatic cytosol species which binds TCDD is the receptor for the induction of hepatic aryl hydrocarbon hydroxylase.

Allen et al. (*118*) conducted a study in which female rhesus monkeys were fed diets containing 500 ppt TCDD for nine months. Anemia, thrombocytopenia, and leukopenia were the most debilitating changes. The altered lymphopoiesis could be associated with immune suppresion. The authors reported widespread hypertrophy, hyperplasia, and metaplasia in the epithelium of monkeys exposed to TCDD, and related this to data showing increased tumor frequency in TCDD fed rats.

(3) *Preliminary epidemiological studies.* Two epidemiological studies lend support to a finding of increased tumorigenicity due to 2,4,5-T exposure. The English summary of a Swedish paper by Hardell (*108*) stated that "there were seven cases of malignant mesenchymal tumors in 87 persons [who had been] exposed to 2,4,5-T over a period of 10-20 years." In five of the cases, exposure had been direct and comparatively massive. The latent period of 10 to 20 years is in agreement with that assumed for chemical car-

cinogenesis. The statistical distribution of 7 of the 87 patients deviated from the national average with a dominance of tumors in males.

Tung (*120*) reported an elevated incidence of primary liver cancers among Vietnamese following the wide application of "Agent Orange" as a defoliant during the years 1961 to 1962. "Agent Orange" is composed of equal parts 2,4,5-T and 2,4-D (2,4-dichlorophenoxyacetic acid) and is contaminated with TCDD. During 1962 to 1968, 10 percent (791/7911) of all cancers were liver cancers, compared with 3 percent (159/5442) during 1955 to 1961. The latent period involved is shorter than that normally assumed for chemical carcinogenesis; the possibility of a shorter latent period for some chemicals, however, cannot be eliminated. Neither of these studies is sufficient to be the basis of any firm conclusions concerning a causal connection between 2,4,5-T and cancer. But in view of the results obtained in experimental animals, they warrant noting.

The Working Group concludes that there is sufficient evidence to indicate that 2,4,5-T, containing TCDD at levels as low as 0.05 ppm, and TCDD alone can produce oncogenic effects in mamalian species. Since 2,4,5-T, as currently formulated, contains TCDD (at a maximum amount of 0.099 ppm), a rebuttable presumption against registration of 2,4,5-T products has arisen because of the oncogenic effects of 2,4,5-T and TCDD.

B. *Other chronic or delayed toxic effects.* 40 CFR 162.11(a)(3)(ii)(B) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s) * * * (p)roduces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety." This section reflects concern that chronic exposure to chemicals may result in injury to the reproductive system and/or the fetus and provides that a rebuttable presumption shall arise if chronic chemical exposure in test animals produces such results.

The studies summarized below show that 2,4,5-T containing 0.5 ppm or less TCDD produces teratogenic and/or fetotoxic effects in mice at 30 mg/kg, in rats at 100 mg/kg, in hamsters at 40 mg/kg, and in birds at 1 mg/kg. Other studies show that pesticide-free TCDD is fetotoxic and/or teratogenic at doses as low as 0.125 μg TCDD/kg in rats and 0.1 μg TCDD/kg in mice. Specifically, these studies show that exposure to TCDD and/or 2,4,5-T containing TCDD during pregnancy is associated with statistically significant increases in the incidence of cleft palate, kidney anomalies, skeletal and intestinal tract anomalies, and embryonic resorption. (Maternal toxicity has also been observed in many of these studies, primarily in the form of reduced weight gain and increased liver-to-body weight ratio. Whenever it has appeared particularly relevant, details have been cited in the individual studies.)

The Working Group has concluded from these studies that 2,4,5-T containing TCDD, 2,4,5-T without detectable dioxin, and TCDD alone produce fetotoxic and teratogenic effects in mammals. The Working Group has also concluded that an ample margin of safety does not exist for the population at risk (women of child-bearing age) for dermal and inhalation exposure and for cumulative oral, dermal, and inhalation exposure to both 2,4,5-T and/or TCDD. For these reasons, the Working Group recommends issuance of a rebuttable presumption based on the fetotoxic and teratogenic effects of 2,4,5-T and/or TCDD.

(1) *Pesticide-free TCDD.* A Bionetics Research Institute study on 2,4,5-T provided the first indication that TCDD adversely affected mammalian development (*123*). In this study, detailed with later confirming studies in Section III.B.(*2*) below, 2,4,5-T significantly increased the frequency of cleft palate, kidney anomalies, and fetal mortality in the litters of treated dams. The 2,4,5-T used in this study contained approximately 30 ppm TCDD. Subsequent studies, detailed in this section, using pesticide-free TCDD have established that TCDD alone produces these effects, and that the TCDD contaminant may be the principal chemical determinant of the fetotoxic and teratogenic effects in mammals exposed to the pesticide 2,4,5-T.

(a) *Studies in which TCDD produced teratogenic and/or fetotoxic effects in mice.* Courtney and Moore (*128*) studied TCDD's embroytoxic and teratogenic effects in three mouse strains (Table 8). Test animals were administered 1 or 3 μg TCDD/kg body weight subcutaneously in solutions of 100 percent dimethylsulfoxide (DMSO) on days 6 to 15 of gestation. DMSO was administered as the control. TCDD produced cleft palates in all three strains. At 3 μg/kg, 30 percent (9/30) of the CD-1 litters had fetuses with cleft palates compared to 0 percent (%) of the controls; 71 percent (5/7) of the C57BL/6 litters had cleft palates at 3 μg/kg as compared to 0 percent (0/23) of the controls; and 22 percent (2/29) of the DBA/2 litters had cleft palates, as compared to 0 percent (0/23) of the controls. The authors also found a marked increase in the incidence of kidney anomalies in all strains. One especially sensitive strain, C57BL/6, developed kidney anomalies in 100 percent (7/7) of the litters as compared to 9 percent (2/23) in the controls. Maternal liver-to-body weight ratio was significantly increased in the inbred strains, C57BL/6 and DBA/2, but not in the randomly bred CD-1 mice. TCDD had no effect on fetal mortality, fetal weights, or maternal weights at the doses administered.

Table 8. Teratogenic Effects of TCDD in Mice and Rats[a/]

Strain	Dose (ug/kg)	Litters Affected/Live Litters: Cleft Palate #	Cleft Palate %	Kidney Anomalies #	Kidney Anomalies %	Average Fetuses Affected/Live Litters: Cleft Palate #	Cleft Palate %	Kidney Anomalies #	Kidney Anomalies %
Mouse									
CD-1	0(DMSO)	0/9	0	3/9	33	0/9	0	1/9	11
	1	1/9	11	5/9	56	2/9	22	4.6/9	51
	3	3/10	30	10/10	100	1/10	10	6.5/10	65
DBA/2	0(DMSO)	0/23	0	3/23	13	0/23	0	1/23	4
	3	2/29	22	8/9	89	1/9	11	1.8/9	20
C57BL/6	0(DMSO)	0/23	0	2/23	9	0/23	0	1/23	4
	3	5/7	71	7/7	100	2.6/7	37	3/7	43
Rat									
CD	0(DMSO)	0/9	0	0/9	0	0/9	0	0/9	0
	0.5	0/6	0	4/6	67	0/6	0	1.8/6	30

a/ Data from Courtney and Moore (128).

In another study in which six dioxins were administered subcutaneously and orally to CD-1 mice, Courtney (*133*) found TCDD to be the most fetotoxic and teratogenic of the dioxin compounds, by either route of exposure at all dose levels tested (Table 9). On days 7 to 16 of gestation, TCDD was administered orally at 25 to 400 μg/kg body weight and subcutaneously at 25 to 200 μg/kg.

Mortality per litter increased with the dose and reached 97 percent (oral) and 76 percent (subcutaneous) in the litters administered TCDD, as compared with a mortality of 6 and 14 percent in the oral and subcutaneous control groups, respectively. The most common anomalies observed were cleft palates and malformed kidneys. All of the fetuses in the 200 and 400 μg/kg (oral) and 200 μg/kg (subcutaneous) groups exhibited cleft palates as compared to 0 percent of the controls. Of the fetuses in the 200 μg/kg (oral) group, 100 percent had kidney malformations as compared to 1 percent of the controls. Other anomalies observed were hydrocephalus, open eye, and club foot. Edema and petechiae were also observed in fetuses administered the high doses.

Table 9. Fetotoxic and Teratogenic Effects of TCDD in CD-1 Mice[a/]

Dose (ug/kg per day)	Route of Administration	% Average Fetal Mortality/Litter	Average # Abnormal Fetuses per Litter	Abnormal Anomalies/Total Fetuses: Cleft Palate %	Kidney Anomalies %	Club Foot %
25	Oral	6	4.6	3	34	3
50	Oral	13	8.1	19	72	7
100	Oral	14	8.3	66	71	13
200	Oral	87	1.5	100	100	14
400	Oral	97	0.4	100	50	50
25	Subcutaneous	36	6.7	82	53	11
50	Subcutaneous	56	5.0	79	58	17
100	Subcutaneous	72	3.5	85	95	0
200	Subcutaneous	76	3.1	100	38	18
5% anisole corn oil (0.1 ml)	Oral	6	0.8	0	1	4
DMSO[b/]	Subcutaneous	14	0.2	0	0	1

a/ Data from Courtney (133).
b/ DMSO = dimethylsulfoxide.

Moore et al. (*174*) also found that TCDD caused fetotoxic and teratogenic responses in C57BL/6 mice at 1 μg/kg administered on days 10 through 13 of gestation. Compared with 0 percent incidence (0/27) in the control litters, 94 percent (15/16) of the treated litters exhibited kidney anomalies, and 19 percent (3/16) had cleft palates. At 3 μg/kg, the incidence of these anomalies was 100 percent (14/14) and 86 percent (12/14), respectively.

Neubert and Dillman (*127*) tested the embryotoxic and teratogenic effects of TCDD in NMRI mice (Table 10). In one test, pregnant mice were given varying doses of TCDD (0.3 to 9 μg/kg) by intubation on days 6 to 15 of gestation. At 9 μg/kg, 100 percent (%) of the viable litters had resorptions; 67 percent (%) of all litters had total resorptions. Oil control values were 32 and 0 percent for litters with resorptions and litters with total resorptions, respectively. Cleft palate was observed in all of the litters and 82 percent of the fetuses at 9 μg/kg; comparable oil control values were 6 and 0.7 percent, respectively, statistically significant ($p<0.01$) proportions of the fetuses evidenced cleft palate at 3, 4.5, and 9 μg/kg (3, 13, and 82 percent, respectively) when compared with the oil control.

Table 10. Embryotoxic and Teratogenic Effects of TCDD on NMRI Mice[a/]

Dose[b/] (ug/kg)	Litters Affected/Viable Litters: Resorptions #	Resorptions %	Cleft Palate #	Cleft Palate %
0	23/95	24	6/95	6
oil	21/65	32	4/65	6
0.3	7/13	54	0/13	0
3.0	16/24	67	7/24	29
4.5	5/12	42	6/12	50
9.0	3/3	100	3/3	100
9.0	3/6	50	5/6	83

a/ Data from Neubert and Dillman (127).
b/ All doses administered on days 6 to 15, except second 9.0 ug/kg dose which was administered on days 9 to 13.

In this study, a single oral dose of 45 μg/kg TCDD on day 6 produced resorption in 100 percent of the viable litters; 23 μg/kg on day 10 led to 50 percent resorptions. Seventy-one percent of the viable litters had embryos with cleft palate when 45 μg/kg was given as a single dose on day 11. Control values were 24 percent for litters with resorption and 6 percent for litters with cleft palates.

Smith et al. (*135*) administered 0.001, 0.01, 0.1, 1.0, and 3.0 μg TCDD/kg body weight per day to CF-1 mice by gavage from days 6 through 15 of gestation (Table 11). The percentage of resorptions per implantation was significantly higher in treated mice than in the controls only in the 1.0 μg/kg group. Cleft palate occurred in 71 percent of the litters treated at 3.0 μg/kg and in 21 percent of the litters treated at 1.0 μg/kg; bilateral dilated renal pelvises occurred in 28 percent of the litters treated at 3.0 μg/kg, and in 5 percent of the litters treated at 1.0 μg/kg. No significant increase in either cleft palate or dilated renal pelvis was observed at 0.1, 0.01, or 0.001 μg/kg. None (0/34) of the control litters had cleft palate or abnormal kidneys.

Table 11. Fetotoxic and Teratogenic Effects of TCDD in CF-1 Mice[a/]

Dose (ug/kg)	Incidence of Cleft Palate in Litters per Live Litters #	%	Litters With Resorbed Fetuses per Live Litters #	%	Litters With Dilated Renal Pelvis per Live Litters #	%
0	0/34	0	25/34	74	0/34	0
0.001	2/41	5	30/41	73	0/41	0
0.01	0/19	0	17/19	89	0/19	0
0.1	1/17	6	16/17	94	0/17	0
1.0	4/19	21[b/]	18/19	95	1/19	5
3.0	10/14	71[b/]	11/14	78	4/14	28[b/]

a/ Data from Smith et al. (135).
b/ Statistically different from controls by the Fishers exact probability test ($p < 0.05$).

Neubert et al. (*175*) estimated the ED-50 for cleft palate in fetuses to be 40 μgTCDD/kg per day (Table 12). The no-effect-level during days 6 to 15 of gestation was estimated to be 2 μg/kg per day for NMRI mice. No pronounced fetal mortality was observed when 3 μgTCDD/kg body weight was administered on days 6 to 15 of pregnancy.

Table 12. Occurrence of Cleft Palate in Offspring of Mice Fed TCDD[a/]

Strain	Dose (µg/kg)	% Cleft Palates per Total Fetuses Examined	Affected Litters/Total Litters #	%
CD-1	0	<0.3	0/29	0
	3	3	3/10	30
DBA	0	<1	0/23	0
	3	4	2/9	22
NMRI	0	0.7	10/160	6
	3	3	7/24	29
C57B1	0	<1	0/23	0
	3	22	5/7	71

a/ Data from Neubert et al. (175).

(b) *Studies in which TCDD produced teratogenic and or fetotoxic effects in rats.* Sparschu et al. (*129*) administered TCDD to Sprague-Dawley rats by gavage at 0.03, 0.125, 0.5, 2.0 and 8.0 µg/kg per day on days 6 through 15 of gestation (Table 13). Intestinal hemorrhages were observed in 14 percent (18/127) of the fetuses at 0.125 µg/kg; 36 percent (36/99) at 0.5 µg/kg; and 57 percent (4/7) at 2.0 µg/kg; none (0/246) of the control fetuses had intestinal hemorrhages. At 8.0 µg/kg per day, all fetuses (100 percent) were resorbed as compared to 20 percent (63/309) in the controls. Fetal weights were depressed at 0.125, 0.5, and 2 µg/kg. This effect was statistically significant ($p<0.05$) in all groups except females at 0.5 µg/kg. No adverse effects were noted in the fetuses whose mothers were fed 0.03 µg/kg. The authors concluded that TCDD induced a high level of maternal and fetal toxicity and that 0.03 µg/kg per day was the no-effect-level for fetal and embryotoxic effects in rats.

Table 13. Intestinal Hemorrhages in Offspring of Sprague-Dawley Rats Fed TCDD[a/]

Dose (ug/kg per day)	Fetuses Affected/-Fetuses Examined #	%	Litters Affected/-Litters Examined #	%
0 (control)	0/246	0	0/24	0
0.03	0/115	0	0/10	0
0.125	18/127	14	7/10	70
0.5	36/99	36	10/12	83
2.0	4/7	57	2/4	50
8.0	---	---	---	---

a/ Data from Sparschu et al. (129).

Khera and Ruddick (*6*) studied the perinatal effects of TCDD in Wistar rats. In one test, rats were orally administered 0.125, 0.25, 0.5, and 1.0 µg TCDD/kg per day on days 6 through 15 of gestation (Table 14). Visceral lesions were observed at 0.25 µg/kg and above; slight decreases in fetal weight were also seen. Postnatal effects of prenatal exposure to TCDD were studied by allowing offspring of treated dams to be reared by untreated dams until weaning. Reduced survival, body weight gain, and reproductive ability in the progeny were observed after maternal treatment with 0.5 and 1.0 µg/kg. No fetotoxic effects were observed at 0.125 µg/kg.

In a second experiment, rats were treated orally with 1, 2, 4, 8, and 16 µg TCDD/kg body weight per day on days 6 through 15 of gestation. TCDD treatment reduced fetal weight, and the number of live fetuses per litter, and produced visceral lesions in 50

percent (%) of the 1.0 μg/kg fetuses and 43 percent (%) of the 2.0 mg/kg fetuses, as compared to none (%) in the controls. The incidence of skeletal anomalies was comparable to that in the controls at all dose levels. Doses of 1 μg/kg or more produced maternal toxicity; 4 μg/kg or more produced 100 percent embryomortality. The authors concluded that oral treatment of pregnant Wistar rats with 0.25 μg (or more)/kg per day on days 6 to 15 of gestation adversely effected rat development.

Table 14. Teratogenic Effects of TCDD in Wistar Rats[a/]

Dose (ug/kg)	Avg. # Live Fetuses/Litter	Avg. Fetal Weight (grams)	Fetuses with Skeletal Anomalies/-Total # Examined #	%	Fetuses with Microscopic Visceral Lesions/Total # Examined #	%
Test 1						
Untreated control	10.7	4.82	5/107	5	0/13	0
Treated control	11.0	4.51	21/116	18	0/11	0
0.125	10.6	4.64	3/121	2	0/38	0
0.25	10.9	4.79	6/109	6	1/33	3
0.5	10.5	4.46	10/105	10	3/31	10
1.0	9.3	4.10	6/81	7	3/10	30
Test 2						
Untreated control	11.5	4.68	8/116	7	0/10	0
Treated control	9.8	4.77	9/89	10	0/10	0
1.0	6.5	4.17	7/80	9	3/6	50
2.0	6.0	3.31	7/57	12	3/7	43
4.0	3					
8.0	-					
16.0	0					

a/ Data from Khera and Ruddick (6); treated controls given anisole-corn oil.

Courtney and Moore (*128*) administered TCDD to CD rats subcutaneously in solutions of 100 percent DMSO on days 6 through 15 of gestation (Table 8). DMSO was administered as the control. Kidney anomalies were found in four of the six litters (67 percent) whose dams were administered 0.5 μg/kg as compared to 0 percent (0/9) in the controls. TCDD did not affect fetal mortality, fetal weight, or cleft palates in the fetuses.

Dow Chemical USA (*110*) conducted a three-generation reproductive study on Sprague-Dawley rats continuously fed the equivalent of 0.001, 0.01, or 0.1 μg TCDD/kg per day. A preliminary report cites reduced fertility and litter survival in f_0 rats as the reasons for discontinuing the 0.1 μg/kg dose level; significantly reduced fertility was also observed at 0.01 μg/kg. "Clearly evident" indications of toxicity at 0.01 μg/kg among f_1 and f_2 litters included smaller litter size at birth, plus decreased survival and growth of neonates. Dilated renal pelvis was observed in each of the three f_1 rats at 0.1 μg/kg which survived to adulthood. Increased fequency of this anomaly was also seen among weanlings at lower doses; however a dose-related or generational correlation could not be made. In summary, Dow concluded that "the reproductive capacity of rats ingesting TCDD was clearly affected at dose levels of 0.01 and 0.1 μg/kg per day, but not at 0.001 μg/kg per day, through three successive generations." The preliminary report did not include the numerical data necessary for Agency evaluation. Analysis will continue as these become available.

Adverse reproductive effects due to TCDD

have also been observed in hamsters and chickens. Gastrointestinal hemorrhage was noted in hamster fetuses after administration of TCDD at 0.5 μg/kg per day on days 6 to 10 of gestation (*48; 62*). Buu Hoi et al. (*111*) established that 0.02 μg/kg TCDD caused teratogenic effects in chick embryos. Bowes et al. (*137*) and Verrett (*136*) confirmed these results. They found abnormalities in the beaks, eyes, and feet of chick embryos after TCDD exposure.

(c) *Summary.* Studies have established that TCDD is fetotoxic and teratogenic at doses as low as 0.125 μg/kg in rats (*129*) and at 0.3 μg/kg in mice (*127*); preliminary data from Dow (*110*) indicates that TCDD may have effects at 0.01 μg/kg in rats. Cleft palate and kidney anomalies have been observed in rats, mice, and hamsters. No fetotoxic or teratogenic effects have been observed at doses of 0.03 μg/kg in rats (*129*) and 0.1 μg/kg in mice (*135*). Table 15 lists the no-effect-levels in rats and mice for teratogenicity from TCDD.

Table 15. No-Effect-Levels for Teratogenesis from TCDD

Species	Route of Administration	No-Effect-Level ug/kg per day	Reference
Rat	Subcutaneous	<0.5	Courtney and Moore (128)
	Oral	0.125	Khera and Ruddick (6)
	Oral	0.03	Sparschu et al. (129)
Mouse	Subcutaneous	<1.0	Courtney and Moore (128)
	Oral	<0.3	Neubert and Dillman (127)
	Oral	0.1	Smith et al. (135)

(2) *2,4,5-T (TCDD contamination ranging from undetectable to 30 ppm)*—(a) *Teratogenic and fetotoxic effects in rodents.* Courtney et al. (*123*) developed the first evidence that a 2,4,5-T pesticide product was teratogenic and fetotoxic (Table 16).[10] The 2,4,5-T used in this study contained approximately 30 ppm TCDD. The pesticide was administered daily either orally or subcutaneously on days 6 to 14 of gestation in C57BL/6 mice, days 6 to 15 in AKR mice, and days 10 to 15 in Sprague-Dawley rats. Subcutaneous administration of 113 mg/kg body weight resulted in significant increases in the incidence of cleft palate and cystic kidneys[11] in the embryos of both strains of mice, and fetal mortality in the C57BL/6 mice. Oral administration of the same dose caused increased incidence of cleft palate and fetal mortality in both strains and cystic kidneys in C57BL/6 mice. Courtney et al. also reported increases in liver-to-body weight ratios in fetal mice.

These investigators also found that 4.6, 10, or 46.4 mg/kg 2,4,5-T given orally to Sprague-Dawley rats produced kidney renal alkaline phosphatase in fetal mice. Highman et al. (*45*) attributed the increased incidence of "cystic kidneys" in the offspring of 2,4,5-T treated animals to retarded development, rather than true teratogenesis. Reduction in fetal weight and increased incidence of cleft palate were also observed among the fetuses of treated dams.

[10]Results of this study were published by the Department of Health, Education, and Welfare (*121*) and by Clegg (*122*).

[11]In a recent report on studies measuring

Table 16. Teratogenic Evaluation of 2,4,5-T[a/] in Mice[b/]

Mouse Strain	Route of Administration	Dose (mg/kg)	Per Litter: # Litters	Avg. # Live Fetuses	Abnormal Fetuses %	% Fetuses with Cleft Palate	% Fetuses with Cystic Kidney	Fetal Mortality %	Abnormal Litters %
C57BL/6[a/]									
Nontreated	----	---	72	5.8	11	<1	1	26	38
Control	Subcutaneous	f/	106	5.5	12	<1	2	29	42
Control	Stomach tube	g/	32	7.1	14	0	1	15	41
Treated	Subcutaneous	21.5[h/]	6	7.7	12	0	0	3	50
Treated	Subcutaneous	113.0[h/]	18	4.4	57[j/]	22[j/]	41[j/]	42	86[j/]
Treated	Stomach tube	46.4[i/]	6	8.5	37[k/]	2	33[j/]	8	100[k/]
Treated	Stomach tube	113.0[i/]	12	4.8	70[j/]	23[j/]	48[j/]	47[j/]	100[j/]
C57BL/6[d/]									
Nontreated	----	---	8	5.1	31	0	7	36	71
Control	Subcutaneous	f/	10	6.1	8	0	0	23	30
Treated	Subcutaneous	113.0[h/]	10	7.7	77[j/]	29[j/]	60[j/]	11	100[j/]
AKR[e/]									
Nontreated	----	---	58	7.1	5	<1	<1	16	19
Control	Subcutaneous	f/	72	6.9	4	<1	<1	15	24
Control	Stomach tube	g/	12	8.8	0	0	0	9	0
Treated	Subcutaneous	113.0[h/]	14	6.9	29[j/]	28[j/]	1	23	71[j/]
Treated	Stomach tube	113.0[i/]	7	5.3	55[j/]	55[j/]	0	42[k/]	100[j/]

a/ Contained approximately 30 ppm TCDD.
b/ Data from Courtney et al. (123).
c/ Treated from day 6 through 14 of pregnancy. Killed on day 18 of gestation.
d/ Treated from day 9 through 17 of pregnancy. Killed on day 18 of gestation.
e/ Treated from day 6 through 15 of pregnancy. Killed on day 19 of gestation.
f/ Dose, 100 ul DMSO per mouse.
g/ Dose, 100 ul honey solution (honey to water, 1:1) per mouse.
h/ Administered as a solution of 2,4,5-T in 100% DMSO in a volume of 100 ul per mouse.
i/ 2,4,5-T was suspended in a honey solution (honey to water, 1:1) in a volume of 100 ul per mouse.
j/ p = 0.01.
k/ p = 0.05.

anomalies and other embryotoxic effects at all levels (Table 17). The occurrence of hemorrhagic gastrointestinal tracts in rat fetuses was also reported.

Roll (*125*) found embryotoxic and teratogenic effects in NMRI mice after prenatal exposure to 2,4,5-T containing 0.05±0.02 ppm dioxin (Table 18). 2,4,5-T at 20 to 130 mg/kg body weight was administered orally to the dams on each of days 6 to 15 of gestation. At 90 or 130 mg/kg, the percentage of resorptions and/or dead fetuses was markedly increased relative to the controls; however, maternal toxic effects were also observed at these dose levels.[11] Statistically significant, dose-related reductions in fetal weight were observed at 20 mg/kg and above.

Cleft palate increased among fetuses exposed to 35 mg/kg or more and was significant when compared with control values. Skeletal retardation effects, manifested as insufficient ossification, were also observed. The teratogenic no-effect level in mice for this 2,4,5-T was considered to be 20 mg/kg. Later studies with a specially prepared sample of 2,4,5-T with no detectable amounts of dioxin (detection limit: <0.02 ppm) confirmed these results in mice (*125, 126*). By contrast, daily oral administration of 25 to 150 mg/kg of either the dioxin-free or commercial grade 2,4,5-T (<0.1 ppm dioxin) did not produce teratogenic effects in FW 49 rats (*236*).

Neubert and Dillman (*127*) also studied the effects of 2,4,5-T in NMRI mice, using three samples containing either (A) less than 0.02 ppm dioxin, (B) 0.05±0.02 ppm dioxin (provided by Dr. Roll), or (C) an unknown amount of dioxin (Table 19). Their results confirmed those obtained by Roll (*125*). 2,4,5-T was administered to the dams orally in rape-seed oil on each of days 6 through 15 of gestation at 8 to 120 mg/kg body weight.

The average number of resorptions was significantly higher than the oil control at 60, 90, and 120 mg/kg of sample (A), and 90 mg/kg of samples (B) and (C). Total resorption of one litter was observed in four of the groups (30, 45, 60, and 90 mg/kg) treated with sample (A) and in three of the litters treated with 90 mg/kg of sample (B); none was seen in the controls. Fetal weight was significantly depressed in all treated groups compared with the oil control.

The percentage of fetuses with cleft palate was significantly higher than the control group in all 2,4,5-T groups treated with 45 mg/kg or more. In the group treated with 120 mg/kg 2,4,5-T containing <0.02 ppm dioxin, 54% (7/13) of the litters and 11% (18/166) of the fetuses exhibited cleft palate compared with oil control values of 6% (1/16) and 0.7% (1/144), respectively.

These investigators also tested the butyl ester of 2,4,5-T and found similar effects. In experiments combining 2,4,5-T and TCDD, potentiation of teratogenic effects was observed. Sixty mg/kg of 2,4,5-T (sample A) combined with 0.3 ug/kg TCDD increased cleft palate frequency among fetuses from 5 to 14%. In this study no cleft palates were observed among fetuses treated only with 0.3 ug/kg TCDD.

Table 17. Teratogenic Evaluation of 2,4,5-T[a/] in Rats[b/]

Test Animal	Route of Administration	Dose (mg/kg)	# Litters	Per Litter: Avg. # Live Fetuses	Abnormal Fetuses %	% Fetuses with: Enlarged Renal Pelvis	% Fetuses with: Cystic Kidney	Fetal Mortality %	Abnormal Litters %
Rats[c/]									
Nontreated	----	---	7	9.9	9	9	0	11	43
Control	Stomach tube	d/	14	8.7	12	12	<1	1	57
Treated	Stomach tube	4.6[e/]	8	8.2	36[g/]	18	21	12	88
Treated	Stomach tube	10.0[e/]	7	7.1	46[g/]	17	30[g/]	28[g/]	86
Treated	Stomach tube	46.4[e/]	6	2.7	60[h/]	27	33[h/]	59[g/]	67

a/ Contained approximately 30 ppm TCDD.
b/ Data from Courtney et al. (123).
c/ Treated from day 10 through 15 of pregnancy. Killed on day 20 of gestation.
d/ Dose, 200 ul honey solution (honey to water, 1:1) per rat.
e/ 2,4,5-T was suspended in a honey solution (honey to water, 1:1) in a volume of 200 ul per rat.
f/ p = 0.01.
g/ p = 0.05.
h/ The sample size was possibly too small to show a significant difference.

Table 18. Embryotoxic Effects of 2,4,5-T in NMRI Mice[a/]

Dose mg/kg	Implantations per Pregnancy	Resorptions and/or Dead Fetuses No./Total No.	%	Fetal weight (grams)	Cleft Palate No./Viable No.	%
0	10.1	19/332	5.7	1.23	6/313	1.9
20	9.8	30/348	8.7	1.09	6/314	1.9
35	9.5	22/248	8.9	1.06	14/226	6.2
60	9.9	15/208	7.2	1.05	19/193	9.8
90	9.8	35/293	11.9	0.86	39/258	15.1
130	9.6	191/316	60.4	0.73	61/125	48.8

a/ Data from Roll (125).

[11] Although the LD-50 for female NMRI mice had been previously determined to be 778 mg/kg, an increased maternal mortality rate was seen at 130 mg/kg and weight gain was depressed at doses above 60 mg/kg (*125*).

Table 19. Embryotoxic Effects of 2,4,5-T[a/]

Treatment	Dioxin Content (ppm)	Dose (mg/kg)	Resorption (RES): % Litters with RES	Resorption (RES): % RES/Implantation Sites	RES/Single Litter w/RES (M)	Fetal Weight (grams)	Cleft Palate (CP): % Litters with CP	Cleft Palate (CP): % Fetuses with CP
None	---	---	24	4	0.6	1.26[b/]	6	0.6
Oil control	---	0.4 ml	32	4	0.5	1.30	6	0.7
2,4,5-T (A)	<0.02	8.0	35	3	0.4	1.27[b/]	<7	<1
		15.0	38	5	0.5	1.15[b/]	8	1
		30.0	56	7	0.8	1.09[b/]	11	1
		45.0	55	6	0.6	0.98[b/]	16	3[b/]
		60.0	63	11	1.2[b/]	1.01[b/]	20	5[b/]
		90.0	53	8	1.1[b/]	1.02[b/]	35	8[b/]
		120.0	54	10	1.3[b/]	0.95[b/]	54	11[b/]
2,4,5-T (B)	0.05	30.0	44	6	0.6	1.11[b/]	22	2
		60.0	57	7	0.4	1.11[b/]	71	9[b/]
		90.0	71	8	1.0[b/]	0.99[b/]	86	23[b/]
2,4,5-T (C)	unknown	90.0	71	13	1.4[b/]	1.00[b/]	72	26[b/]

a/ Data from Neubert and Dillman (127); 2,4,5-T sample (b) received from Roll (125).
b/ $p \leq 0.01$.

Bage et al. (*132*) injected NMRI mice subcutaneously with 50 and 110 mg/kg 2,4,5-T (<1.0 ppm dioxin) on each of days 6 through 14 of gestation. At 110 mg/kg, 2,4,5-T was teratogenic, causing fetal death, cleft palate, and other anomalies.

Courtney and Moore (*128*) studied the effects of 2,4,5-T in CD-1 random-bred mice, two strains of inbred mice, DBA/2J and C57BL/6J, and CD rats (Table 20). 2,4,5-T containing 0.5 ppm (technical) or 0.05 ppm (analytical) TCDD was administered subcutaneously to mice at 50 to 150 mg/kg in DMSO and orally to rats at 10 to 80 mg/kg in sucrose on each of days 6 to 15 of gestation. At 100 mg/kg or more, both 2,4,5-T samples produced significant reductions, which appeared to be dose related, in fetal weight in all strains of mice; rats were not affected. 2,4,5-T was fetocidal at two doses, but the investigators considered this effect to be due to maternal toxicity.

Both 2,4,5-T samples produced cleft palate in mice. For CD-1 dams treated with 100 mg/kg of either 2,4,5-T sample, 40% of the litters and two fetuses per affected litter evidenced cleft palate compared with 0% in the control (Expt. 3). No cleft palates were

Table 20. Embryotoxic Effects of Analytical and Technical 2,4,5-T[a/]

Species	Compound	Dose (mg/kg)	% Fetal Mortality per Litter	Fetal Weight (grams)	Cleft Palate (CP): % Litters Affected	Cleft Palate (CP): # CP per Affected Litter	Kidney Anomalies: % Litters Affected	Kidney Anomalies: # Affected Fetuses per Affected Litter
CD-1 Mouse								
Expt. 1	DMSO	---	6.6	1.35	0	0	0	0
	2,4,5-T (Tech.)	50	6.6	1.26	0	0	0	0
	2,4,5-T (Tech.)	100	7.5	1.00	33	3.0	0	0
	2,4,5-T (Tech.)	150[b/]	51.7	0.91	100	5.3	0	0
Expt. 2	DMSO	---	8.8	1.02	0	0	33	1.0
	2,4,5-T (Analy.)	100	9.6	0.73[d/]	89	4.4	78	1.7
Expt. 3	DMSO	---	8.4	1.09	0	0	63	2.0
	2,4,5-T (Tech.)	100	10.7	0.85[d/]	40	2.0	80	2.4
	2,4,5-T (Analy.)	100	11.6	0.86[d/]	40	2.0	100	4.2
	2,4,5-T (Analy.)	125	12.9	0.71[d/]	78	5.4	67	4.3
DBA/2 Mouse	DMSO	---	26.1	0.85	0	0	13	1.0
	2,4,5-T (Tech.)	100	27.0	0.67[d/]	27	1.0	9	1.0
C57B1/6 Mouse	DMSO	---	10.8	0.99	0	0	9	1.0
	2,4,5-T (Tech.)	100	15.9	0.75[d/]	40	1.2	0	0
CD Rat	Sucrose	---	3.4	2.48	0	0	0	0
	2,4,5-T (Tech.)	10	1.8	2.40	0	0	20	1.0
	2,4,5-T (Tech.)	21.5	1.4	2.54	0	0	38	1.3
	2,4,5-T (Tech.)	46.4	3.8	2.20	0	0	14	2.0
	2,4,5-T (Tech.)	80.0[c/]	52.1	2.30	0	0	50	4.0

a/ Data from Courtney and Moore (128).
b/ Investigators thought this data to be close to a maternal toxic dose.
c/ Maternal LD-40.
d/ $p < 0.05$.

observed among the rat fetuses. To verify this observation, a second group of rats was given two 150 mg/kg doses of technical 2,4,5-T subcutaneously at the time of palate closure (days 13 to 14). Again, no cleft palates were observed; however, there was a significant increase in fetal mortality among treated animals (14%) when compared with the controls (0%).

Fetuses of CD-1 mice treated with analytical 2,4,5-T also showed increased incidences of kidney anomalies; the response to technical 2,4,5-T was not as great. At 100 mg/kg, 100% of the litters and 4.2 fetuses per affected litter of dams treated with analytical 2,4,5-T displayed kidney anomalies, compared with 80% and 2.4 for technical 2,4,5-T and 63% and 2.0 for controls (Expt. 3). The effect in inbred strains of mice was comparable with control values. In rats, technical 2,4,5-T at all dose levels produced higher incidences of litters affected and numbers of fetuses per litter affected than seen in the control animals. The maximum effects on kidney anomalies in rats were 50% of the litters and 4.0 fetuses per litter at 80 mg/kg, compared with 0% in the control litters.

In another study using CD-1 mice, Courtney (*134*) administered 0.45 to 1.0 mM/kg body weight per day of 2,4,5-T (0.05 ppm dioxin) either orally or subcutaneously during various segments of the gestation period (Table 21).[13] Cleft palate was seen in all groups treated with 2,4,5-T; there were no instances of this anomaly within the control groups. At 0.8 mM/kg, 48% of total fetuses and 37% of the litters evidenced this malformation. Statistically significant ($p \leq 0.05$) increases in the percentage of fetuses dead and/or resorbed were observed at the highest doses. All dose levels had adverse effects on fetal weight. The author noted that by slightly altering experimental conditions, the cleft palate effect and the effects on fetal mortality and fetal weight could be produced independently.

[13]Maternal toxicity was also observed, evidenced by reductions in maternal weight gain and increased liver-to-body weight ratios (*134*).

Table 21. Embryotoxic Effects of 2,4,5-T in CD-1 Mice[a/]

Vehicle	Dose (mM/kg)	Days Dosed	Viable Normal Fetuses #/total #	Viable Normal Fetuses %	% Fetal Mortality	Fetal Weight (grams)	Cleft Palate (avg. %) Fetuses	Cleft Palate (avg. %) Litters
oil:Ac[b/]	---	10-15	75/80	94	6	0.95	---	---
	---	11-13	99/112	88	11	0.94	---	---
	---	12-15	108/126	86	13	1.01	---	---
	0.45	10-15	86/107	80	17	0.89	7	6
	0.80	11-13	88/122	72	14	0.87	16	14
	0.80	11-14	21/59	36	29[e/]	0.87	48	37
	1.00[d/]	12-15	75/82	91	8	0.96	1	1
DMSO[c/]	---	12-15	152/171	89	12	1.03	---	---
	1.00	12-15	11/68	16	72[f/]	0.70	48	67

a/ Data from Courtney (134).
b/ Corn oil:Acetone (9:1)--oral.
c/ Dimethylsulfoxide -- subcutaneous.
d/ This concentration exceeded the solubility characteristics of the vehicle. Doubling the volume of vehicle resulted in effects more consistent with those found at lower doses.
e/ $p \leq 0.05$.
f/ $p \leq 0.001$.

Table 22. Effects of 2,4,5-T on Wistar Rat Fetuses[a/]

Compund	Dose (mg/kg)	# of Litters	Avg. # per Litter Viable Fetuses	Avg. # per Litter Dead Fetuses	Fetal Weight (grams)	Avg. % Malformed Fetuses per Litter[b/]
T-1	Treated	14	11.1	0.6	4.65	15
	Control					
	50	7	12.9	1.3	4.84	24
	100	9	11.3	1.9	4.60	29
T-2	Treated	10	9.2	0.6	5.34	10
	Control					
	25	13	10.5	0.8	5.06	15
	50	12	11.7	0.5	5.15	9
	100	9	8.6	2.4	4.57	32
	Treated	10	12.6	0.7	4.67	26
	Control					
	25	11	12.7	0.5	5.15	10
	50	14	11.5	1.4	4.91	28
	100	10	11.0	0.6	4.35	36
	150	5	11.6	2.2	3.98	56
T-3	Treated	10	11.8	0.7	5.31	17
	Control					
	25	14	12.2	0.9	5.00	11
	50	2	11.0	0.5	4.75	56
	100	12	12.6	0.9	5.00	37
	150	1	11.0	1.0	3.00	91
T-4[c/]	50	8	11.3	1.1	4.94	14

a/ Data from Khera and McKinley (130).
b/ One or more skeletal malformation (viable fetuses).
c/ No treated control given.

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 22]. 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.[14] 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 46% 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.

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

Table 21. 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	66.1[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	57.2	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	47.1	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/ $p < 0.05$.

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 96.7 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-

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	---
% Resorptions			
Litters	68	61	100
Total fetuses	6.7	12.1	75[c/]
Fetal weight (grams)			
Male	4.41	4.38	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.[16]

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, Strange 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 (*123*); 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*).

(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

[16]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.

(i) *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 (*166*). 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 0.094 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 2,4,5-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	0.18 pint	0.18 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, 163*).

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	
	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
% 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 mg 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 (*164*). 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 [16]) was 109 microns. Based on work by Akesson and Yates (*168*), 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 (*168*), 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.

[16]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.

The following calculations (see Table 33 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.

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 X 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 X 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 (2 × 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 (0.026 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).

[17]Johnson (63) (see Section I.G.(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 Washingon during spring and summer and analyzed for phenoxy herbicides. The author did not specify how soon after application the samples were taken.

Table 34. 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 Golia (*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_1 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 2,000.

(b) *Negative Studies.* The mutagenicity of 2, 4, 5-T was evaluated by Ercegovich 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 10^{-7} to 10^{-4} M of 2, 4, 5-T, which contained 0.09 ppm TCDD. Breaks, deletions, and rings were observed. Chromatid breaks increased with increasing concentrations of 2, 4, 5-T. It was not possible to distinguish whether this was a toxic effect or a potential genetic effect (*150*).

Majumdar and Hall (*169*) reported on the cytogenetic effects of 2,4,5-T[18] on in vivo bone-marrow cells of Mongolian gerbils. The animals were injected with total amounts of 2,4,5-T at the rate of 50, 150, 250, 350, or 500 mg/kg body weight over the 5-day period of the study. Increasing numbers of chromatic gaps, breaks, and fragments were observed at 250, 350, and 500 mg/kg doses. No exchange figures or isochromosome gaps or breaks were observed. This is not a definitive experiment for indicating the potential of 2,4,5-T for causing heritable chromosome damage (*170*). Toxicity effects of the chemical could give similar results (*170*).

Davring and Hultgren (*171*) reported on an *in vivo* study on the cytogenetic effects on bone-marrow cells of *Mus musculus* (male mice) induced by a Swedish commercial 2,4,5-T ester formulation[19] and its components. The study showed that 2,4,5-T commercial products can affect chromosomal and reproductive mechanisms. Two different strains of mice were used with similar results for both. These results correlated with effects seen in Drosophila. The authors stated that chromatid inter- or intraexchanges were never observed. This study was not carried out sufficiently for the demonstration of chromosomal effects such as rearrangements in future generations of somatic cells (*170*).

Davring and Sunner (*172*) demonstrated cytogenetic effects of a Swedish commercial 2,4,5-T formulation[20] on oogenesis and early embryogenesis in *Drosophila melanogaster*. A 50 percent decrease in fertility for the flies was determined to be 250 ppm. This level is 40 to 60 times less than field use concentration levels. Reproductive and chromosomal effects were observed.

[18]The 2,4,5-T used in this study was purchased from Eastman Kodak Co., Rochester, N.Y., and contained no measurable amount of TCDD. The authors do not indicate the limit of sensitivity.

[19]The concentration of TCDD was guaranteed to be less than 0.1 ppm in the product.

[20]TCDD concentration was less than 0.1 ppm in this formulation which was tested at practical field use concentrations or lower.

(2) *TCDD*—(a) *Positive Studies.* Hussain et al. (*24*) evaluated the mutagenic activity of TCDD (99 percent pure) on three different microbial test systems. In the first study, TCDD significantly increased the incidence of reverse mutations in *Escherchia coli* Sd-4 administered 2 μg/ml TCDD from streptomycin dependence to streptomycin independence. This was the only dose at which mutations were clearly observed. No details of the experimental protocol were given, and statistical methods were apparently not employed in assessing the data.

The second test by Hussain et al. (*24*) studied reverse mutation from histidine dependence to histidine independence in *Salmonella typhimurium* (Strains TA 1532 and TA 1530). TCDD was positive in TA 1532 but negative in TA 1530. This indicated that TCDD acts as a frameshift mutagen. ICR-170 was used as a positive control in the test with TA 1532. No positive or negative controls were tested in TA 1530.

In the third test Hussain et al. (*24*) observed slight prophage induction in *E. coli* K-39. However, data from this test were difficult to evaluate because the solvent used, dimethyl sulfoxide, causes cellular effects.

A preliminary report on the chromosomal analysis of hospital patients exposed to TCDD in the accident at the Seveso, Italy, factory was presented at the Department of Health, Education, and Welfare meeting on October 12, 1976 (*152*). An increased number of chromosomal lesions (gaps, chromatidic and chromosomal breaks, and rearrangements) were observed in somatic cells of the 2- to 28-year-old males and females tested. Cytogenetic studies of tissues from therapeutic abortions performed on women who were exposed to TCDD during the accident indicated that there was chromosomal damage to cells in maternal peripheral blood, and placental and fetal tissues. These preliminary results were based on a small number of samples, and no specific data are available at this time (*150*).

(b) *Negative Studies.* Khera and Ruddick (*6*) conducted dominant lethal tests in which male Wistar rats received TCDD at dosages of 4 and 8 μg/kg per day. The studies indicated that no dominant lethal mutations arose during the 35 days after treatment. The period examined corresponded to postmeiotic stages of spermatogenesis.

A cytogenetic screening study of the effects of TCDD on bone marrow cells of male Osborne-Mendel rats was performed by the Food and Drug Administration (*119*). Two separate experiments were performed. The first was a multiple dose test in which 10 μg TCDD/kg per day was administered by intubation for 5 consecutive days. In the second test, single doses of 5, 10, and 15 μg TCDD/kg were administered intraperitoneally and 20 μg/kg (the highest dose) was administered orally. There was no evidence from these studies to indicate that TCDD produced cytogenetic damage in the bone marrow of these male rats. Toxicity, which was indicated by a slight weight loss, was noted in rats that received a single dose of 15 or 20 μg/kg (the highest dose levels).

Green (*119*) conducted a short-term investigation of several dioxins, using male Osborne-Mendel rats, to determine what potential these substances had to produce cytogenetic damage in rat bone-marrow. In one study all of the dioxins were tested by being intubated in the rats for five consecutive days at 10 μg/kg per day. A second study involved TCDD alone administered orally at 20 μg/kg and intraperitoneally at 5, 10, and 15 μg/kg. The author found no evidence that any of the substances tested produced cytogenetic damage in the bone marrow of male rats.

In conclusion, although Hussain et al. (*24*) have demonstrated that TCDD does appear to act as a point (gene) mutagen, the evidence is weak for heritable genetic effects since the level of mutagenic testing is meager and there were some major deficiences in some tests. However, the study by Hussain et al. does not fulfill the criterion of multitest evidence as prescribed in 40 CFR 162.11. Although TCDD does appear to have the potential to act as a chromosomal mutagen from the *in vivo* cytogenetic studies (*152*), specific data are not yet available from the Seveso accident.

(3) *Chromosomal Damage.* The Working Group also wishes to call attention to three studies (previously discussed in Sections III.B.(2)(b), IV.(1), and IV.(2)(b)), which indicate that 2,4,5-T and/or TCDD may cause chromosomal damage. Fujita et al. (*149*) reported chromosomal abnormalities in *in vitro tests on human lymphocytes exposed* to 2,4,5-T; abnormalities included breaks, deletions, and rings. Yefimenko (*167*) reported damage to bone-marrow cell chromosomes (including breaks, true aberrations, or rearrangements) in *in vivo* tests on rat gonadal and somatic tissue exposed to butyl ester 2,4,5-T. The preliminary HEW report (*152*) on the Seveso incident indicated an increased number of chromosomal lesions (gaps, chromatic breaks, and rearrangements) in somatic cells of 2- to 28-year-old humans exposed to TCDD.

The Working Group concludes that there is a data gap on mutagenic effects and that further evidence and testing is needed on the mutagenicity of 2,4,5-T and TCDD. The Working Group would like to evaluate more detailed and specific information as it becomes available from the Seveso accident. Relevant information or studies on the mutagenetic effects of 2,4,5-T and/or TCDD should be submitted to the Agency, and the option for re-evaluating their mutagenic properties must be left open should more conclusive evidence become available.

B. *Toxicity to Humans: TCDD*—(1) *Chloracne.* A number of researchers have reported illness ascribed to TCDD (*90, 93, 95, 153*). Most of these toxic effects have occurred in chemical plant workers after accidental exposure to the dioxin. While a number of ill effects have been reported, the most widely known is chloracne.

Chloracne is a severe skin disease resulting from exposure to highly chlorinated dibenzo dioxins. It is a disease of the follicular and sebaceous glands. Its symptoms and signs include skins lesions, follicular hyperkeratosis, and the formation of large sebaceous cysts, inflammed tubercles, and pustules. In addition to these symptoms, chloracne is often accompanied by a brownish keratinization of the skin, cystitis, pyelonephritis, depression, hirsutism, fatigue, neurological disturbances, raised cholesterol levels, liver damage, and psychological manifestations (*10, 15, 16, 154, 155, 156, 157*). Several researchers have observed that chloracne is not only irritating and persistent but also very difficult to cure. It is one of the most frequently contracted forms of occupational dermatitis, occurring primarily in chemical plant employees engaged in the production of 2,4,5-T and 2,4,5-TCP (*16, 95, 155, 156, 158*).

The first report on a toxic material being the causative agent for an occupational skin disease appears to have been by Dr. Karl Herxheimer in 1899. Dr. Herxheimer diagnosed the cause of dermatological problems in a German factory worker as exposure to chlorine ions in the production of caustic potash (*159*). It is from this early diagnosis that we get the name chloracne. During the early 1950's there were a series of industrial accidents in Germany resulting in an outbreak of chloracne in the employees of chemical plants manufacturing 2,4,5-T and 2,4,5-TCP. The symptoms of the employees of one of these factories in Hamburg, Germany, were extensively investigated by Kimming and Schulz (*16*). These researchers, using the rabbit ear test, proved that the cause of the chloracne was a contaminant found in crude 2,4,5-TCP and not the formulated 2,4,5-TCP. Later on, Bauer et al. (*15*) conclusively identified TCDD as the causative agent of chloracne.

(2) *Porphyria cutanea tarda and δ-Aminolevulinic Acid Synthetase.* Porphyria cutanea tarda (PCT), a form of hepatic porphyria, is another disease caused by exposure to TCDD and often accompanies chloracne. PCT occurs primarily in industrial workers associated with the manufacture of 2,4,5-T (*93, 94, 160*).

The symptoms of porphyria cutanea tarda, a defect in hepatic metabolism of porphyrins, are fragility of the skin, photosensitivity of the skin, hyperpigmentation, over-production of porphyrins, hirsutism, and neurological and intestinal disorders (*94, 160*). It is also characterized biochemically by an increase in the activity of the mitochondrial enzyme δ-aminolevulinic acid (ALA) synthetase, which is the first and rate-limiting enzyme in heme biosynthesis (*160*). TCDD was thought to be a potent inducer of ALA activity in chick embryo liver (*115*). Goldstein et al. (*161*) reported that TCDD was found to induce ALA synthetase and hepatic prophyria in mice. These researchers stated that at that time [1973] TCDD was the most potent porphyrogenic chemical known. Poland and Kende 1976 (*4*) found that the duration of ALA induction from TCDD exposure is prolonged, most likely due to the long biological half-life of TCDD. These researchers also found that ALA synthetase inducers have halogen atoms occupying at least three of the four lateral ring positions (positions 2, 3, 7, and 8), and that there is at least one free, nonhalogenated ring position. TCDD fulfills all of these requirements.

2,4,5-T: Position Document 1

REFERENCES

* 1. Raw, G.R., ed. 1970. CIPAC handbook, Vol. I, analysis of technical and formulated pesticides. Collab., Intntl. Pest. Anal. Council Ltd., Hertfordshire, England.

* 2. Meister. R.T., ed. 1977. Farm chemicals handbook. Meister Publishing Co., Willoughby, Ohio.

* 3. Report on 2,4,5-T: a report of the Panel on Herbicides of the President's Science Advisory Committee. 1971. Executive Office of the President, Office of Science and Technology, Washington, D.C.

* 4. Poland, A., and A. Kende, 1976. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: environmental contaminant and molecular probe. Fed. Proc. 35:2404-2411.

* 5. Crossland, J., and K.P. Shea. 1973. The hazards of impurities. Environment 15(5):35-38.

* 6. Khera, K.S., and J.A. Ruddick. 1973. Polychlorodibenzo-*p*-dioxins: perinatal effects and the dominant lethal test in Wistar rats. Pages 70-84 *in* E.A. Blair, ed., Chlorodioxins—origin and fate. Advances in Chemistry Series, No. 120. Am. Chem. Soc., Washington, D.C.

* 7. Harvey, R.G. 1973. Dioxin, a contaminant in 2,4,5-T. Presented at Wisconsin Pest Control Conference with Industry: January 17, 1973 (unpublished).
* 8. Fishbein, L. 1973. Mutagens and potential mutagens in the biosphere: I. DDT and its metabolites, polychlorinated biphenyls, chlorodioxins, polycyclic aromatic hydrocarbons, haloethers. Sci, Tot. Environ., 4:305-340.
* 9. Milnes, M.H. 1971. Formation of 2,4,7,8-tetrachlorodibenzodioxin by thermal decomposition of sodium 2,4,5-trichlorophenate. Nature 232:395-396.
* 10. Schulz, K.H. 1968. On the clinical aspects and etiology of chloracne. (Transl. from German.) Arbeitsmedizin Sozialmedizin Arbeitshygiene 3(2):25-29.
* 11. Higginbotham, G.R., A. Huang, D. Firestone, J. Verrett, J. Ress, and A.D. Campbell. 1968. Chemical and toxicological evaluations of isolated and synthetic chloro derivatives of dibenzo-*p*-dioxin. Nature 220:702-703.
* 12. Muelder. W.W., and L.A. Shadoff. 1973. The preparation of uniformly labeled ^{14}C-2,7-dichlorodibenzo-*p*-dioxin, and ^{14}C-2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Pages 1-6 *in* E.A. Blair, ed., Chlorodioxins—origin and fate. Advances in Chemistry Series, No. 120. Am. Chem. Soc., Washington, D.C.
* 13. Burger, E.J., Jr. 1973. Summary: conference on dibenzodioxins and dibenzofurans, National Institute of Environmental Health Services, April 2-3, 1973. Environ. Health Perspec. 5:279-282.
* 14. Schwetz, B.A., J.M. Norris, G.L. Sparschu, V.K. Rowe, P.J. Gehring, J.L. Emerson, and C.G. Gerbig. 1973. Toxicology of chlorinated dibenzo-*p*-dioxins. Environ. Health Perspec. 5:87-99.
* 15. Bauer, H., K.H. Schulz, and U. Spiegelberg. 1961. Occupational intoxication in the production of chlorinated phenol compounds. (Transl. from German.) Arch. Indust. Path. Indust. Hyg. 18:538-555.
* 16. Kimmig, J., and K.H. Schulz. 1957. Occupational acne (chloracne) caused by chlorinated aromatic cyclic ether. (Transl. from German.) Dermatologica, 115:540-546.
* 17. Kearney, P.C., E.A., Woolson, A.R. Isensee, and C.S. Helling. 1973. Tetra- chlorodibenzodioxin in the environment: sources, fate, and decontamination. Environ. Health Perspec. 5:273-277.
* 18. Buser, H. 1975. Polychlorinated dibenzo-*p*-dioxins: separation and identification of isomers by gas chromatography-mass spectrometry. J. Chromatog. 114:95-108.
*19. Kimbrough, G. D. 1972. Toxicity of chlorinated hydrocarbons and related compounds: a review including chlorinated dibenzodioxins and chlorinated dibenzofurans. Arch. Environ. Health 25(1):125-131.
*20. Firestone, D., J. Ress, N. L. Brown, R. P. Barron, and J. N. Damico. 1972. Industrial chemicals: determination of polychlorodibenzo-*p*-dioxins and related compounds in commercial chlorophenols. J. Ass. Offic. Anal. Chem. 55(1):85-92.
*21. Jones, E. L., and H. Krizek. 1962. A technic for testing acnegenic potency in rabbits, applied to the potent acnegen, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. J. Invest. Dermatol, 39:511-517.
*22. Anonymous. 1970. Another herbicide on the blacklist. Nature 226:309-311.
*23. Grieg. J. B., G. Jones, W. H. Butler, and J. M. Barnes. 1973. Toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fd. Cosmet. Toxicol. 11:585-595.
*24. Hussain, S., L. Ehrenberg, G. Lofroth, and T. Gejvall. 1972. Mutagenic effects of TCDD on bacterial systems. Ambio 1(1):32-33.
*25. World Health Organization, International Agency for Research on Cancer. 1977. IARC mongraphs on the evaluation of the carcinogenic risk of chemicals to man: some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals, Vol. 15. International Agency for Research on Cancer, Lyon, [France].
*26. Thomson, W. T. 1975. Agricultural chemicals: book II herbicides. Thomson Publications, Indianapolis, Indiana.
27. Memo: Representative 2,4,5-T labels, dated June 30, 1977. From Harvey L. Warnick, Project Manager, Office of Special Pesticide Reviews, to Files.
28. Memo: 2,4,5-T production, dated September 30, 1977. From Harvey L. Warwick, Project Manager, Office of Special Pesticide Reviews, to Edwin L. Johnson, Deputy Assistant Administrator, Office of Pesticide Programs. (CONFIDENTIAL.)
29. U.S. Department of Agriculture, Agricultural Stabilization and Conservation Service. 1976. The pesticide review 1975. U.S. Department of Agriculture, Washington, D.C.
30. Memo: Request for usage data—2,4,5-T, 2,4,5-TP, erbon and ronnel, dated September 16, 1977. From A. Hale Vandermer, Program Planning and Analysis Officer, Human Effects Monitoring Branch, to Harvey L. Warnick, Project Manager, Office of Special Pesticide Reviews.
*31. Crosby, D. G., and A. S. Wong. 1973. Photodecomposition of 2,4,5-tri- chlorophenoxyacetic acid (2,4,5-T) in water. J. Agr. Food Chem. 21(6):1052-1054.
*32. Sharpee, K. 1973. Microbial degradation of phenoxy herbicides in culture, soil, and aquatic ecosystems. Ph.D. Thesis. 94 pp. University Microfilms, Ann Arbor, Mich.
*33. Shafik, M. T., H. C. Sullivan, and H. F. Enos. 1971. A method for determination of low levels of exposure to 2,4-D and 2,4,5-T. Intntl. J. Environ. Anal. Chem. 1:23-33.
*34. Grunow, W., Chr. Bohme, and B. Budczies. 1971. Renal excretion of 2,4,5-T by rats. (Transl. from German.) Fd. Cosmet. Toxicol. 9:667-670.
*35. Grunow, W., and Chr. Bohme. 1974. Metabolism of 2,4,5-T and 2,4-D in rats and mice. (Transl. from German.) Arch. Toxicol. 32:217-225.
*36. Clark, D. E., J. S. Palmer, R. D. Radeleff, H. R. Crookshank, and F. M. Farr. 1975. Residues of chlorophenoxy acid herbicides and their phenolic metabolites in tissues of sheep and cattle. J. Agr. Food Chem. 23(3):571-578.
*37. Leng, M. L. 1972. Residues in milk and meat and safety to livestock from the use of phenoxy herbicides in pasture and rangeland. Down to Earth 28(1):12-20.
*38. Fitzgerald, C. H., C. L. Brown, and E. G. Beck. 1967. Degradation of 2,4,5-trichlorophenoxyacetic acid in woody plants. Plant Physiol. 42:459-460. D
*39. Helling, C. S., A. R. Isensee, E. A. Woolson, P. D. J. Ensor, G. E. Jones, J. R. Plimmer, and P. C. Kearney. 1973. Chlorodioxins in pesticides, soils, and plants. J. Environ. Quality 2(2):171-178.
*40. Norris, L. A. 1966. Degradation of 2,4-D and 2,4,5-T in forest litter. J. Forest. 64(7):475-476.
*41. Wiese, A. F., and R. G. Davis. 1964. Herbicide movement in soil with various amounts of water. Weeds 12(2):101-103.
*42. Anonymous. 1971. A close look at TCDD. Agr. Res. 20(4):8-10.
*43. Yoshida, T., and T. F. Castro. 1975. Degradation of 2,4-D, 2,4,5-T, and picloram in two Philippine soils. Soil Sci. Plant Nutr. 21(4):397-404.
*44. Morton, H. L., E. D. Robison, and R. E. Meyer. 1967. Persistence of 2,4-D, 2,4,5-T, and dicamba in range forage grasses. Weeds 15(3):268-271.
*45. Highman, B., T. B. Gaines, and H. J. Schumacher. 1977. Retarded development of fetal renal alkaline phosphatase in mice given 2,4,5-trichlorophenoxyacetic acid. J. Toxicol. Environ. Health 2:1007-1018.
*46. Kearney, P. C., E. A. Woolson, and C. P. Ellington, Jr. 1972. Persistence and metabolism of chlorodioxins in soils. Environ. Sci. Technol. 6(12):1017-1019.
*47. Norris, L. A. 1971. Chemical brush control: assessing the hazard. J. Forest. 69(10):715-720.
48. Report of the Advisory Committee on 2,4,5-T to The Administrator of the Environmental Protection Agency. May 7, 1971. (unpublished.)
*49. Bailey, G. W., A. D. Thruston, Jr., J. D. Pope, Jr., and D. R. Cochrane. 1970. The degradation kinetics of an ester of silvex and the persistence of silvex in water and sediment. Weed Sci. 18(3):413-418.
*50. Frank, P. A., and R. D. Comes. 1967. Herbicidal residues in pond water and hydrosoil. Weeds 15(3):210-213.
*51. Kenaga, E. E. 1974. 2,4,5-T and derivatives: toxicity and stability in the aquatic environment. Down to Earth 30(3):19-25.
*52. Trichell, D. W., H. L. Morton, and M. G. Merkle. 1968. Loss of herbicides in runoff water. Weed Sci. 16(4):447-449.
*53. Edwards, W. M., and B. L. Glass. 1971. Methoxychlor and 2,4,5-T in lysimeter percolation and runoff water. Bull. Environ. Contam. Toxicol. 6(1):31-34.
*54. Isensee, A. R., and G. E. Jones. 1971. Absorption and translocation of root and foliage applied 2,4 - dichlorophenol, 2,7 - dichlorodibenzo - *p* - dioxin and 2,3,7,8 - tetrachlorodibenzo - *p* - dioxin. J. Agr. Food Chem. 19(6):1210-1214.
*55. Woolson, E. A., P. D. J. Ensor, W. L. Reichel, and A. L. Young. 1973. Dioxin residues in lakeland sand and bald eagle samples. Pages 112-118 *in* E. A. Blair, ed., Chlorodioxins—origin and fate. Advances in Chemistry Series, No. 120. Am. Chem. Soc., Washington, D.C.
*56. Mulhern, B. M., W. L. Reichel, L. N. Locke, T. G. Lamont, A. Belisle, E. Cromartie, G. E. Bagley, and R. M. Prouty. 1970. Organochlorine residues and autopsy data from bald eagles, 1966-68. Pest. Mon. J. 4(3):141-144.
*57. Isensee, A. R., and G. E. Jones. 1975. Distribution of 2,3,7,8 - tetrachlorodibenzo - *p* - dioxin (TCDD) in aquatic model ecosystem. Environ. Sci. Technol. 9(7):668-672.
*58. Shadoff, L. A., R. A. Hummel, L. Lamparski, and J. H. Davidson. Undated. A search for 2,3,7,8 - tetrachlorodibenzo - *p* - dioxin (TCDD) in an environment exposed annually to 2,4,5 - trichlorophenoxyacetic acid ester (2,4,5-T) herbicides. (In Press, Bull. Environ. Contam. Toxicol.)
*59. Brown, E., and Y. A. Nishioka. 1967. Pesticides in selected western streams—a contribution to the National Program. Pest. Mon. J. 1(2):38-46.
*60. Manigold, D. B., and J. A. Schulze. 1969. Pesticides in selected western streams—a progress report. Pest. Mon. J. 3(2):124-135.
*61. Lawson, E. R. 1976. 2,4,5-T residues in storm runoff from small watersheds. J. Soil Water Conserv. 31(5):217-219.
*62. National Research Council, Safe Drinking Water Committee. 1977. Drinking

water and health: Part II. National Academy of Sciences, Washington, D.C.

*63. Johnson, J. E. 1971. The public health implications of widespread use of the phenoxy herbicides and picloram. BioSci. 21(1):899-905.

64. Memo: Environmental monitoring data on 2,4,5-T, 2,4,5-TP (silvex), erbon, and ronnel, dated July 6, 1977. From Frederick W. Kutz, Acting Chief, Ecological Monitoring Branch, to Harvey L. Warnick, Project Manager, Office of Special Pesticide Reviews.

*65. St. John, L. E., Jr., D. G. Wagner, and D. G. Lisk. 1976. Fate of atrazine, kuron, silvex, and 2,4,5-T in the dairy cow. J. Dairy Sci. 47(11):1267-1270.

*66. Zielinski, W. L., Jr., and L. Fishbein. 1967. Gas chromatographic measurement of disappearance rates of 2,4-D and 2,4,5-T acids and 2,4-D esters in mice. J. Agr. Food Chem. 15(5):841-844.

*67. Piper, W. N., J. Q. Rose, M. L. Leng, and P. J. Gehring. 1973. The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to rats and dogs. Toxicol. Appl. Pharmacol. 26:339-351.

*68. Zitko, V. 1972. Absence of chlorinated dibenzodioxins and dibenzofurans from aquatic animals. Bull. Environ. Contam. Toxicol. 7:105-110.

*69. Baughman, R., and M. Meselson. 1973. An analytical method for detecting TCDD (dioxin): levels of TCDD in samples from Vietnam. Environ. Health Perspec. 5:27-34.

*70. Matsumura, F., and H. J. Benezet. 1973. Studies on the bioaccumulation and microbial degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ. Health Perspec. 5:253-258.

*71. Baur, J. R., R. W. Bovey, and J. D. Smith. 1969. Herbicide concentrations in live oak treated with mixtures of picloram and 2,4,5-T. Weed Sci. 17(4):567-570.

*72. Getzendaner, M. E., and R. A. Hummel. 1975. Disappearance of TCDD from grass following field treatment with esteron 245 herbicide. Dow Chemical Co., Midland, Michigan. (Confidential.)

*73. Matsumura, A. 1970. The fate of 2,4,5-trichlorophenoxyacetic acid in man. Sangyo Igaku 12:446-451.

*74. Gehring, P. J., C. G. Kramer, B. A. Schwetz, J. Q. Rose, and V. K. Rowe. 1973. The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to man. Toxicol. Appl. Pharmacol. 26:352-361.

*75. Kohli, J. D., R. N. Khanna, B. N. Gupta, M. M. Dhar, J. G. Tandon, and K. P. Sircar. 1974. Absorption and excretion of 2,4,5-trichlorophenoxyacetic acid in man. Arch. Intntl. Pharmacodyn. Ther. 210 (2):250-255.

*76. Kocher, C. W., N. H. Mahle, R. A. Hummel, L. A. Shadoff, and M. E. Getzendaner. Undated. A search for the presence of 2,4,7-8-tetrachlorodibenzo-p-dioxin in beef fat. (In Press, Bull. Environ. Contam. Toxicol.)

*77. Mahle, N. H., H. S. Higgins, and M. E. Getzendaner. Undated. Search for the presence of 2,3,7,8-tetrachlorodibenzo-p-dioxin in bovine milk. (In Press, Bull. Environ. Contam. Toxicol.)

*78. Clark, D. E., and J. S. Palmer. 1971. Residual aspects of 2,4,5-T and ester in sheep and cattle with observations on concomitant toxicological effects. J. Agr. Food. Chem. 19(4):761-764.

*79. Leng, M. L. 1977. Comparative metabolism of phenoxy herbicides in animals. Pages 53-76 *in* G. W. Ivie and H. W. Dorough, eds., Fate of pesticides in large animals. Academic Press, New York. [Scheduled for publication September, 1977.]

80. U.S. Environmental Protection Agency, Dioxin Working Group. 1977. Dioxin: position document. (Draft—unpublished.)

*81. Duggan, R. E., H. C. Barry, and L. Y. Johnson. 1967. Pesticide residues in total diet samples (II). Pest. Mon. J. 1(2):2-12.

*82. Martin, R. J., and R. E. Duggan. 1968. Pesticide residues in total diet samples (III). Pest. Mon. J. 1(4):11-20.

*83. Corneliussen, P. E., 1969. Pesticide residues in total diet samples (IV). Pest Mon. J. 2(4):140-152.

*84. Corneliussen, P. E. 1970. Pesticide residues in total diet samples (V). Pest. Mon. J. 4(3):89-105.

*85. Corneliussen, P. E. 1972. Pesticide residues in total diet samples (VI). Pest Mon. J. 5(4):313-341.

*86. Manske, D. D., and P. E. Corneliussen, 1974. Pesticide residue in total diet samples (VII). Pest. Mon. J. 8(2):110-124.

*87. Manske, D. D., and R. D. Johnson, 1975. Pesticide residues in total diet samples (VIII). Pest. Mon. J. 9(2):94-105.

*88. Johnson, R. D., and D. D. Manske. 1976. Pesticide residues in total diet samples (IX). Pest Mon. J. 9(4):157-169.

*89. Manske, D. D., and R. D. Johnson. 1977. Pesticide and other chemical residues in total diet samples (X). Pest. Mon. J. 10(4):134-148.

*90. Whiteside, T. 1977. A reporter at large: the pendulum and toxic cloud. The New Yorker, July 25, 1977.

*91. Goldmann, P. J. 1972. Extremely severe acute chloracne due to trichlorophenol decomposition products. (Transl. from German.) Indust. Med. Soc. Med. Indust. Hyg. 7(1)12-18.

*92. Shulz-Hamburg, K. H. 1957. Clinical and experimental investigations in the etiology of chloracne. (Transl. from German.) Arch Klin. Exp. Dermatol. f206:589-596.

*93. Poland, A. P., D. Smith, G. Metter, and P. Possick. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant with special attention to chloracne, porphyria cutanea tarda, and psychologic parameters. Arch. Environ. Health 22:316-327.

*94. Bleiberg, J. M. Wallen, R. Brodkin, and I. L. Applebaum. 1964. Industrially acquired porphyria. Arch Dermatol. 89:793-797.

*95. May, G. 1973. Chloracne from the accidental production of tetrachlorodibenzodioxin. Br. J. Indust. Med. 30:276-283.

*96. Carter, C. D., R. D. Kimbrough, J. A. Liddle, R. E. Cline, M. M. Zack, Jr., and W. F. Barthel, R. E. Koehler, and P. E. Phillips. 1975. Tetrachlorodibenzodioxin: an accidental poisoning episode in horse arenas. Science 188:738-740.

*97. U.S. Environmental Protection Agency, Office of Solid Waste Management Programs. 1975. Hazardous waste disposal damage reports, document no. 2: a current report on solid waste management [EPA/530/SW-151.2]. Washington, D.C.

*98. Beale, M. G., W. T. Shearer, M. M. Karl, and A. M. Robson. 1977. Long-term effects of dioxin exposure. Lancet 1(8014):743.

*99. Dewse, C. D. 1976. Dangers of T.C.D.D. Lancet 11 (7981):363.

*100. HAY, A. 1976. Seveso: the aftermath. Nature 263: 538-540.

*101. Young, A. L., C. E. Thalken, E. L. Arnold, J. M. Cupello, and L. G. Cockerham. 1976. Fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the environment: summary and decontamination recommendations. Department of Chemistry and Biological Sciences, USAF Academy, Colorado.

*102. Memo: Rationale for 0.1 ppm limit for tetrachlorodibenzo-p-dioxin in hexachlorophene, dated April 19, 1977. From Orville E. Paynter, Chief, Toxicology Branch, to Mary Reece, OSPR.

*103. U.S. Environmental Protection Agency, Human Effects Monitoring Branch. 1977. Episode summary for reports involving 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Washington, D.C. (unpublished)

*104. U.S. Department of Agriculture. 1968. PR Notice 68-1. Looseleaf pub. 5 pp.

U.S. Department of Agriculture. 1968. PR Notice 68-2. Looseleaf pub. 5 pp.

U.S. Department of Agriculture. 1968. PR Notice 68-9. Looseleaf pub. 5 pp.

U.S. Department of Agriculture. 1969. PR Notice 69-1. Looseleaf pub. 6 pp.

U.S. Department of Agriculture. 1969. PR Notice 69-2. Looseleaf pub. 4 pp.

U.S. Department of Agriculture. 1969. PR Notice 69-3. Looseleaf pub. 3 pp.

U.S. Department of Agriculture. 1970. PR Notice 70-8. Looseleaf pub. 1 p.

U.S. Department of Agriculture. 1970. PR Notice 70-10. Looseleaf pub. 2 pp.

U.S. Department of Agriculture. 1970. PR Notice 70-11. Looseleaf pub. 2 pp.

U.S. Department of Agriculture. 1970. PR Notice 70-13. Looseleaf pub. 2 pp.

U.S. Department of Agriculture. 1970. PR Notice 70-22. Looseleaf pub. 1 p.

*105. Murahyi-Kovacs, I., G. Rudali, and J. Imbert. 1976. Bioassay of 2,4,5-trichlorophenoxyacetic acid for carcinogenicity in mice. Br. J. Cancer 33:626-633.

*106. U.S. Environmental Protection Agency, Carcinogen Assessment Group. 1977. Preliminary report on 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T), 2,4,5-trichlorophenol (2,4,5-TCP), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). (unpublished.)

*107. Innes, J. R. M., B. M. Ulland, M. G. Valerio, L. Petrucelli, L. Fishbein, E. R. Hart, A. J. Pallotta, R. R. Bates, H. L. Falk, J. J. Gart, M. Klein, I. Mitchell, and J. Peters, 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Natl. Cancer Inst. 42:1101-1114.

*108. Hardell, L. 1977. Malignant mesenchymal tumours and exposure to phenoxy acids—a clinical observation. (Transl. from Swedish—abstract.) Lakartidningen 74:2753-2754.

*109. Van Miller, J. P., J. J. Lalich, and J. R. Allen. Undated. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. (In Press, Chemosphere.)

*110. Dow Chemical USA. 1977. Preliminary assessment of chronic toxicity study and three-generation reproduction study of 2,3,7,8-tetrachlorodibenzo-p-dioxin. The Dow Chemical Company, Midland, Michigan (unpublished—CONFIDENTIAL.)

*111. Buu-Hoi, N.P., D. Hien, G. St-Ruf, and J. Servoin-Sidoine. 1971. Biochemistry: carcinomimetic properties of tetrachloro-2, 3, 7, 8 dibenzo-p-dioxine. (Trans. from French.) C. R. Acad. Sci. Paris 272: 1447-1450.

*112. Marquardt, H., J. E. Sodergren, P. Sims, and P. L. Grover. 1974. Malignant transformation *in vitro* of mouse fiboblasts by 7, 12-dimethylbenz(a)anthracene and 7-hydroxymethylbenz(a)anthracene and by their k-region derivatives. Int. J. Cancer 13:304-310.

*113. Kellerman, G., M. Luyten-Kellermann, and C. R. Shaw. 1973. Genetic variation of aryl hydrocarbon hydroxylase in human lymphocytes. Amer. J. Hum. Genet. 25:327-331.

*114. Kouri, R. E., R. A. Salerno, and C. E. Whitmire. 1973. Relationships between aryl hydrocarbon hydroxylase inducibility and sensitivity to chemically induced subcutaneous sarcomas in various strains of mice. J. Natl. Cancer Inst. 50(2):363-368.

*115. Poland, A., and E. Glover. 1973. Studies on the mechanism of toxicity of the chlorinated dibenzo-*p*-dioxins. Environ. Health Perspec. 5:245-251.

*116. Poland, A., and E. Glover. 1974. Comparison of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin, a potent inducer of aryl hydrocarbon hydroxylase, with 3-methylcholanthrene. Molec. Pharmacol. 10:349-359.

*117. Poland, A., E. Glover, and A. S. Kende. 1976. Stereospecific, high affinity binding of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin by hepatic cytosol. J. Bio. Chem. 251(16):4936-4946.

*118. Allen, J. R., D. A. Barsotti, J. P. Van Miller, L. J. Abrahamson, and J. J. Lalich. Undated. Morphological changes in monkeys consuming a diet containing low-levels of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin. (In Press, Fd. Cosmet. Toxicol.)

*119. Green, S. 1975. Cytogentic evaluation of several dioxins in the rat. (DRAFT-unpublished.)

*120. Tung, T. T. 1973. Primary cancer of the liver in Vietnam. (Transl. from French.) Chirurgie 99: 427-436.

121. U.S. Department of Health, Education, and Welfare, 1969. Report of the Secretary's Commission on pesticides and their relationship to environmental health. Washington, D.C.

*122. Clegg, D. J. 1971. Embryotoxicity of chemicals contaminants of foods. Fd. Cosmet. Toxicol. 9:195-205.

*123. Courtney, K. D., D. W. Gaylor, M. D. Hogan, H. L. Falk, R. R. Bates, and I. Mitchell. 1970. Teratogenic evaluation of 2, 4, 5-T. Science 168:864-866.

*124. Collins, T. F. X., and C. H. Williams. 1971. Teratogenic studies with 2, 4, 5-T and 2, 4, 5-D in the hamster. Bull. Environ. Contam. Toxicol. 6(6):559-567.

*125. Roll, R. 1971. Studies of the teratogenic effect of 2, 4, 5-T in mice. (Trans. form German.) Fd. Cosmet. Toxicol. 9:671-676.

*126. Roll, R. 1973. Toxicological evaluation of special organochlorinated compounds. Environ. Qual. Safety 2:117-124.

*127. Neubert, D., and I. Dillmann. 1972. Embryotoxic effects in mice treated with 2, 4, 5-trichlorophenoxyacetic acid and 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin. Naunyn-Schmiedeberg's Arch. Pharmacol. 272:243-264.

*128. Courtney, K. D., and J. A. Moore. 1971. Teratology studies with 2, 4, 5-trichlorophenoxyacetic acid and 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin. Toxicol. Appl. Pharmacol. 20:396-403.

*129. Sparschu, G. L., F. L. Dunn, and V. K. Rowe. 1971. Study of the teratogenicity of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin in the rat. Fd. Cosmet. Toxicol. 9:405:412.

*130. Khera, K. S., and W. P. McKinley. 1972. Pre-and postnatal studies on 2, 4, 5-trichlorophenoxyacetic acid, 2, 4-dichlorophenoxyacetic acid and their derivatives in rats. Toxicol. Appl. Pharmocol. 22:14-28.

*131. Sokolik, I. Yu. 1973. Effect of 2, 4, 5-trichlorophenoxyacetic acid and its butyl ester on embryogenesis of rats. Bull. Exp. Biol. Med. 76(7):831-833.

*132. Bage, G., E. Cekonova, and K. S. Larsson. 1973. Teratogenic and embryotoxic effects of the herbicides di- and trichlorophenoxyacetic acids (2, 4-D and 2, 4, 5-T). Acta Pharmacol. Toxicol. 32(6):408-416.

*133. Courtney, K. D. 1976. Mouse teratology studies with chlorodibenzo-p-dioxins. Bull. Environ. Contam. Toxicol. 16:(6)674-681.

*134. Courtney, K. D. Undated. Prenatal effects of herbicides: evaluation by the prenatal development index. (In Press, Arch. Environ. Contam. Toxicol.)

*135. Smith, F. A., B. Z. Schwets, and K. D. Nitschke. 1976. Teratogenicity of 2,3,7,8-tetrachlorodibenzy-*p*-dioxin in CF-1 mice. Toxicol. Appl. Pharmacol. 38:517-523.

136. Verrett, J. 1970. Statement of Dr. Jacqueline Verrett, Food and Drug Administration, Department of HEW. Pages 190-203 *in* Effects of 2,4,5-T on man and the environment; hearings before the Subcommittee on Energy, Natural Resources, and the Environment of the Committee on Commerce, Unites States Senate, Ninety First Congress, Second Session on Effects of 2,4,5-T on Man and the Environment: April 7 and 15, 1970. U.S. Government Printing Office, Washington, D.C.

*137. Bowes, G. W., B. R. Simoneit, A. L. Burlingame, B. W. de Lappe, and R. W. Risebrough. 1973. The search for chlorinated dibenzofurans and chlorinated dibenzodioxins in wildlife population showing elevated levels of embryonic death. Environ. Health Perspec. 5:191-198.

*138. Lutz, H., and Y. Lutz-Ostertag. 1972. The action of different pesticides on the development of bird embryos. Adv. Exp. Med. Biol. 27:127-150.

139. Bal, H. S. 1977. Validation report. U.S. Environmental Protection Agency, Washington, D.C. (unpublished.)

*140. Sparschu, G. L., F. L. Dunn, R. W. Lisowe, and V. K. Rowe. 1971. Study of the effects of high levels of 2,4,5-trichlorophenoxyacetic acid on foetal development in the rat. Fd. Cosmet. Toxicol. 9:527-530.

*141. Emerson, J. L., D. J. Thompson, R. J. Streging, C. G. Gerbig, and V. B. Robinson. 1971. Teratogenic studies on 2,4,5-trichlorophenoxyacetic acid in the rat and rabbit. Fd. Cosmet. Toxicol. 9:395-404.

*142. Strange, J. R., and W. E. Kerr. 1976. Teratogenic and toxicological examination of 2,4,5-trichlorophenoxyacetic acid in developing chick embryos. Toxicol. 6:35-40.

*143. Bjorklund, N., and K. Erne. 1972. Phenoxy-acid-induced renal changes in the chicken. I. ultrastructure. Acta Vet. Scand. 12:243-256.

*144. Lehman, A. J. 1962. The annual per capita consumption of selected items of food in the United States. Qtly. Bull. Assoc. Food & Drug Offic. 26(3):149-151.

*145. Wolfe, H. R., K. C. Walker, J. W. Elliott, and W. F. Durham. 1959. Evaluation of the health hazards involved in house-spraying with DDT. Bull. World Health Org. 20:1-14.

146. Federal Working Group on Pest Management. 1974. Occupational exposure to persticides: report to the Federal Working Group on Pest Management from the Task Group on Occupational Exposure to Pesticides. Washington, D.C.

*147. Staiff, D. C., S. W. Comer, J. R. Armstrong, and H. R. Wolfe. 1975. Exposure to the herbicide, paraquat. Bull. Environ. Contam. Toxicol. 14(3):334-340.

*148. Ercegovich, C. D., and K. A. Rashid. 1977. Mutagensis in mutant strains of *Salmonella typhimurium* by pesticides. Presented at 174th Amer. Chem. Soc. Ntl. Meeting, August 30, 1977. (Unpublished.)

*149. Fujita, K., H. Fujita, and Z. Funazaki. 1975. Chromospheric abnormalities brought about by the use of 2,4,5-T. (Transl. from Japanese.) J. Jap. Assoc. Rural Med. 24(2):77-79.

150. Memo: TCDD-dioxin: mutagenicity, dated August 26, 1977. From Ruth Pertel, OSPR, to Mary Reece and Harvey Warnick [Project Managers, OSPR].

*151. Yefimenko, L. P. 1974. Data for assessing the gonadotropic and mutagenic effect of the herbicide butyl ether 2,4,5-T. (Transl. from Russian.) Gig. Tv. Prof. Zabol. 18(4):24-27.

152. Communication presented at the HEW seminar on Environmental Mutagenicity, October 12, 1976.

*153. Jensen, N. E., I. B. Sneddon, and A. E. Walker. 1972. Tetrachlorobenzodioxin and chloracne. Trans. St. John's Hosp. Derm. Soc. 58(2):172-177.

*154. Kleu, G., and R. Goltz. 1971. Late and long-term injuries following the chronic occupational action of chlorophenol compounds: catasmnetic neurologic-psychiatric and psychological studies. (Transl. from German.) Med. Klin. (Munich) 66(2):53-58.

*155. ter Beek, F., R. Bokhorst, M. v.d. Plas, K. Olsthoorn, P. Vergragt, and G. v.d. Zwan. 1973 Dioxine, a dangerous pollutant in a widely used herbicide. (Transl. from Dutch.) Chemisch Weekblad 69(23):5-6.

*156. Zelikov, A. Kh., and L. N. Danilov. 1974. Occupational dermatitis (acne) in workers engaged in the production of 2,4,5-trichlorophenol. (Transl. from Russian.) Sovetskaya Meditsina 7:145-146.

*157. Oliver, R. M. 1975. Toxic effects of 2,3,7,8 tetrachlorodibenzo 1,4 dioxin in laboratory workers. Br. J. Indust. Med. 32:49-53.

*158. Dugois, P., and L. Colomb. 1957. Remarks on halogen acne (as regards an outbreak of cases resulting from the preparation of 2,4,5-trichlorophenol). [Transl. from French.] J. Med. Lyon 38:899-903.

*159. Herxheimer, K. 1899. Concerning chlorine acne. (Transl. from German). Munch. Med. Wochr. 9:278-279.

*160. Woods, J. S. 1973. Studies of the effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on mamalian hepatic δ-aminolevilinic acid synthetase. Environ. Health Perspec. 5:221-225.

*161. Goldstein, J. A., P. Hickman, H. Bergman, and J. G. Vos. 1973. Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Res. Comm. Chem. Path. Pharmacol. 6(3):919-928.

*162. Commoner, B., and R. E. Scott. 1976. Accidental contamination of soil with dioxin in Missouri: effects and countermeasures. CBNS, Washington Univ., St. Louis, Missouri.

*163. Durham, W. F., and H. R. Wolfe. 1962. Measurement of the exposure of workers to pesticides. Bull. World Health Org. 26:75-91.

164. Memo: Exposure analysis, 2,4,5-T, dated February 1978. From Chief, Chemistry Branch, Criteria and Evaluation Division, to Project Manager, Office of Special Pesticide Reviews.

165. Association of Food & Drug Officials of the United States. 1965. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Topeka, Kans.

*166. Wolfe, H. R., J. F. Armstrong, and W. F. Durham. 1974. Exposure of mosquito control workers to fenthion. Mosquito News 34(3):263-267.

*167. Caplan, P. E., D. Culver, and W. C. Thielen. 1956. Human exposures in populated areas during airplane application of malathion. AMA Arch. Indust. Health 14:326–332.

168. Akeson, N. B., and W. E. Yates. Undated. Pesticides in the air environment. (Unpublished.)

*169. Majumdar, S. K., and R. C. Hall. 1973. Cytogenetic effects of 2,4,5-T on *in vivo* bone marrow cells of Mongolian gerbils. J. Hered. 64:213–216.

170. Memo: 2,4,5-T studies: further review, Undated. From Ruth Pertel, Office of Special Pesticide Reviews, to Harvey Warnick, Project Manager, Mary Reece, Project Manager, Office of Special Pesticide Reviews.

*171. Davring, L., and K. Hultgren. 1977. Cytogenetic effects on in vivo bone-marrow cells of *Mus musculus* induced by a commercial 2,4,5-T ester product. Hereditas 85:123–134.

*172. Davring, L., and M. Sunner. 1971. Cytogenetic effects of 2,4,5-trichlorophenoxy-acetic acid on oogenesis and early embryogenesis in *Drosophila melanogaster*. Hereditas 68(1):115–122.

*173. Lloyd, J. W., J. A. Thomas, and M. G. Mawhinney. 1973. 2,4,5-T and the metabolism of testosterone-1,2-^3H, by mouse prostate glands. Arch. Environ. Health 26:217–220.

*174. Moore, J. A., B. N. Gupta, J. G. Zinkle, and J. G. Vos. 1973. Postnatal effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Environ. Health Perspec. 5:81–85.

*175. Neubert, D., P. Zens, A. Rothenwallner, H. J. Merker. 1973. A survey of the embryotoxic effects of TCDD in mammalian species. Environ. Health Perspec. 5:67–79.

*176. Norris, L. A., M. L. Montgomery, and E. R. Johnson. 1977. The persistence of 2,4,5-T in a Pacific Northwest forest. Weed Sci. 25:417–422.

*177. Dougherty, R. C., and K. Piotrowska. 1976. Screening by negative chemical ionization mass spectrometry for environmental contamination with toxic residues: application to human urines. Proc. Natl. Acad. Sci. USA 73(6):1777–1781.

*178. Majumdar, S. K., and J. K. Golia. 1974. Mutation test of 2,4,5-trichlorophenoxyacetic acid on *Drosophila melanogaster*. Can. J. Genet. Cyutol. 16:465–466.

*179. Wolfe, H. R. 1972. Protection of individuals who mix or apply pesticides in the field. Pages 35–39 *in* Federal Working Group on Pest Management, Proc. Natl. Conf. on protective clothing and safety equipment for pesticide workers. Washington, D.C.

**** PRODUCT SEARCH LISTING **** PAGE 1

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000004	BONIDE CHEMICAL CO. INC. 2 HUNT AVE. RINGVILLE NY 14094

**********PRODUCT NAME**********

0010 BONIDE KILBRUSH

REGISTRANT	*NAME AND ADDRESS*
* 000100	BRULIN & COMPANY INC PO BOX 270-H INDIANAPOLIS IN 46206

**********PRODUCT NAME**********

0004 CINNEBATE CONCENTRATE

REGISTRANT	*NAME AND ADDRESS*
* 000198	THOMPSON-HAYWARD CHEMICAL COMPANY BOX 2383 KANSAS CITY KS 66110

**********PRODUCT NAME**********

0021 DE-PESTER DED-WEED LV-35

0021 DED-WEED LV-6 BRUSH KIL LOW VOLATILE ESTER

0027 DEMPESTER DED-WEED AMINE-I AMINE SALT

0045 DED-WEED LV-6 BRUSH KIL

0049 2,4,5-T ISOOCTYL ESTER TECHNICAL

**** PRODUCT SEARCH LISTING **** PAGE 2

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

*CONTINUED REGISTRANT BOUND

0119 DED-WEED AMINE-T AMINE SALT

0120 DED-WEED 638 BRUSH KIL

0120 DED-WEED LV 2-1 BRUSH KIL

REGISTRANT	*NAME AND ADDRESS*
* 000168	WASATCH CHEMICAL DIVISION ENTRADA IND INC P O BOX 6219 SALT LAKE CITY UT 84106

**********PRODUCT NAME**********

0022 WASLO 2,4,5-T LOW VOLATILE ESTER 4LB. E.C.

0023 WASLO 2,4,5-T BUTYL ESTER 4# E.C.(2,4,5-T EMUL.(CONC.)

0026 WASCO BRUSH KILLER LOW VOLATILE 2,4-D 2,4,5-T EMUL. C.

REGISTRANT	*NAME AND ADDRESS*
* 000179	NOBLE H M COMPANY BOX 588 ALEXANDRIA VA 22300

**********PRODUCT NAME**********

0006 BU-HID K. D. BRUSH KILLER BKE-4

0006 BU-HID K. D. BRUSH KILLER BKE-6

0006 BU-HID K.D. BRUSH KILLER BKE- 2+2

**** PRODUCT SEARCH LISTING **** PAGE 3

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000228	TOBACCO STATES CHEMICAL COMPANY BOX 479 LEXINGTON KY 40501

**********PRODUCT NAME**********

0012 TOBACCO STATES BRAND ESTER BRUSH KILLER 2-2

0015 TOBACCO STATES BRAND LOW-VOL BRUSH KILLER 2-20

REGISTRANT	*NAME AND ADDRESS*
* 000228	RIVERDALE CHEMICAL COMPANY 420 E 17TH ST CHICAGO HGTS IL 60411

**********PRODUCT NAME**********

0015 RIVERDALE BRUSH KILLER 1 CONTAINS LOW VOLATILE 2,4,5-T+ 2,4,0

0016 RIVERDALE WEEDESTROY 2,4,5-T

0027 2,4,5-T LOW VOLATILE ESTER

0028 RIVERDALE BRUSH KILLER 2 ESTER

0045 RIVERDALE BRUSH KILLER 2

0075 RIVERDALE FORMULA 4 BRUSH KILLER

0077 RIVERDALE 2,4,5-T AMINE BRUSH KILLER

0078 WEEDESTROY 2,4,5-T ESTER 4

0091 2,4,5-T LVG

0119 RIVERDALE HOTJOY 2,4,5-T LOW VOLATILE ESTER

0120 RIVERDALE HOTJOY BRUSH KILLER 2 LOW VOLATILE ESTER

**** PRODUCT SEARCH LISTING **** PAGE 4

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000239	CHEVRON CHEMICAL COMPANY ORTHO DIVISION 940 HENSLEY WAY RICHMOND CA 94804

**********PRODUCT NAME**********

1256 ORTHO LV BRUSH KILLER 1U-2

REGISTRANT	*NAME AND ADDRESS*
* 000264	ANCHEM PRODUCT INC BROOKSIDE AVE AMBLER PA 19002

**********PRODUCT NAME**********

0009 WEEDONE 2,4,5-T

0010 WEEDONE BK 32

0019 WEEDONE BK 64

0021 WEEDONE T.B.K.

0053 WEEDAR AMINE BK

0062 WEEDAR 2,4,5-I

0071 2,4,5-T LOW VOLATILE ESTER BRUSH KILLER

0075 2,4-D-2,4,5-T LOW VOLATILE ESTER BRUSH KILLER

0086 ANCHEM TWINJUG

0086 AMINE 2,4,5-T FOR RICE

0089 WEEDONE 2,4,5-T SPECIAL AIR SPRAY FORMULA

0103 ANCHEM DINJUG

**** PRODUCT SEARCH LISTING **** PAGE 5

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000464

**000121* ANCHEM ENVERT-D1
**000123* ANCHEM ENVERT-T
**000128* ANCHEM TRINOXOL SUPER - 6
**000132* D/NUXOL SUPER 6
**000361* ANCHEM EMULSAMINE 2,4,5-T
**000163* EMULSAMINE BR WOODY PLANT HERBICIDE
**002006* ASPLUNDH 1050-E BRUSHKILLER
**002068* EMULSAVERL 100
**002069* EMULSAVERL 200
**002384* TECHNICAL 2, 4, 5-T ESTER (FOR USE IN THE MANUFACTURE OF HERBICIDES)
**002688* WEEDONE FOR UNION INHIBITED
**002689* ENVERT-DT
**002827* ANCHEM BR WOODY PLANT HERBICIDE
**002833* ANCHEM BR WOODY PLANT HERBICIDE
**002834* ANCHEM 2,4,5-T WOODY PLANT HERBICIDE
**002864* ANCHEM 2,4,5-T WOODY PLANT HERBICIDE
**002871* WEEDONE 2,4,5-T WOODY PLANT HERBICIDE UNION INHIBITED
**002888* WEEDONE 2,4,5-T SPECIAL AIR SPRAY FORMULA

****

REGISTRANT *NAME AND ADDRESS*

* 000314 MYSAN CORPORATION
#19 N 35TH ST
CHICAGO IL 60609

********** PRODUCT NAME **********

**** PRODUCT SEARCH LISTING **** PAGE 6

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000314

**000253* GCC 429
**000308* GCC-429

****

REGISTRANT *NAME AND ADDRESS*

* 000356 NOTT MANUFACTURING COMPANY INC
PLEASANT VALLEY NY 12569

********** PRODUCT NAME **********

**080994* NOTT'S POISON IVY KILLER

****

REGISTRANT *NAME AND ADDRESS*

* 000359 RHODIA INC, AGRICULTURAL DIVISION
P.O. BOX 125
MONMOUTH JUNCTION, NJ 08852

********** PRODUCT NAME **********

**081174* RHODIA 2,4,5-T LOW VOLATILE ESTER 4L
**081179* RHODIA LOW VOLATILE BRUSH KILLER NO. 2
**000412* RHODIA LOW VOLATILE BRUSH KILLER NO.3
**000434* RHODIA 2,4,5-T LOW VOLATILE ESTER 4L
**000580* UTILITY BRUSH KILLER NO. 4
**000594* CHIPMAN AMINE BRUSH KILLER
**000764* CHIPMAN AEROSOL SPECIAL MIXTURE NO. 1
**080580* RHODIA 2,4,5-T ISOOCTYL ESTER (TECHNICAL)

**** PRODUCT SEARCH LISTING **** PAGE 7

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000359

**000582* CHIPMAN 2,4-D AND 2,4,5-T ESTER MIX TECHNICAL
**000605* CHIPMAN D AND T MIX NO. 8
**000612* T & C LAWN WEED KILLER CONCENTRATE
**000615* SHIFT MIX NO. 1
**000616* SHIFT MIX NO. 2
**000665* VISKO-RHAP LOW VOLATILE ESTER (D-)T FOR AIR APPLICATION
**000666* VISKO-RHAP LOW VOLATILE ESTER (D-)T FOR GROUND APPLICATION
**000649* VISKO-RHAP WATER-SOLUBLE AMINE A-3T
**000651* VISKO-RHAP LOW VOLATILE ESTER 2T FOR GROUND APPLICATION
**000652* VISKO-RHAP LOW VOLATILE ESTER 2T FOR AIR APPLICATION
**000653* VISKO-RHAP H LOW VOLATILE 2 T
**000655* VISKO-RHAP LOW VOLATILE ESTER 3T

****

REGISTRANT *NAME AND ADDRESS*

* 000007 IMPERIAL INC
BOX 423
SHENANDOAH IA 51601

********** PRODUCT NAME **********

**000345* IMPERIAL LO-VOL BRUSH KILLER
**000346* IMPERIAL LO-VOL 2,4,5-T
**000365* IMPERIAL NO.4 LOW VOLATILE 2,4,5-T BRUSH AND WEED KILLER
**000366* IMPERIAL NO. 2 + 2 LOW VOLATILE BRUSH AND WEED KILLER

**** PRODUCT SEARCH LISTING **** PAGE 8

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

****

REGISTRANT *NAME AND ADDRESS*

* 000413 DANIELS & SHUKES CHEMICAL COMPANY
1000-02 ST LOUIS AVE
KANSAS CITY, MO 64101

********** PRODUCT NAME **********

**000223* PIONEER BRAND BRUSH KILLER NO. 23 BUTYL ESTER

****

REGISTRANT *NAME AND ADDRESS*

* 000449 TELONE CORPORATION
C/O REGULATORY AFFAIRS DEPT. FARMLAND IND., INC.
P. O. BOX 7305
KANSAS CITY, MO 64116

********** PRODUCT NAME **********

**000014* WOODKILL ESTER
**000026* WOOD-KILL CONCENTRATE (ESTER)
**000065* WOOD-KILL 4LB. BUTYL ESTER CONCENTRATE
**000126* LOW VOL 4 LB WOOD KILL
**000127* NO. 4 LOW VOLATILE 2,4,5-T
**000317* 2,4,5-T 4LB BUTYL ESTER

****

REGISTRANT *NAME AND ADDRESS*

* 000468 DOW CHEMICAL U S A
PO BOX 1706
MIDLAND MI 48640

********** PRODUCT NAME **********

**** PRODUCT SEARCH LISTING **** PAGE 9

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000454

000199 VEON 245
000272 TIPTON 10 BRUSH AND WEED KILLER
000273 TIPTON 2-2
000280 VERTON CE WEED AND BRUSH KILLER
000388 VERTOX 7 HERBICIDE
000388 BRUSH KILLER 4T
000524 BRUSH KILLER 2-2
000644 DOW TORDON 155 MIXTURE BRUSH KILLER
000674 TORDON 225 MIXTURE HERBICIDE
000822 VERTOX 2T
000491 2,4,5-T BUTOXY ETHANOL ESTERS
000492 2,4,5-T ISOBUTOXY PROPYL ESTERS
000499 2,4,5-T BUTYL ESTERS
000595 2,4,5-T ISOOCTYL ESTERS
000527 DOW BRUSH KILLER H HERBICIDE
000528 DOW BRUSH KILLER IN HERBICIDE

REGISTRANT	*NAME AND ADDRESS*
* 000476	STAUFFER CHEMICAL COMPANY LABELING & REGISTRATION DEPT 1200 SOUTH 47TH ST RICHMOND, CA 94804

*********** PRODUCT NAME **********

000000 2,4,5-T TRIETHYLAMINE 4#S
000823 2,4-D+2,4,5-T AMINE 2-2 #S

**** PRODUCT SEARCH LISTING **** PAGE 10

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000476

000901 2,4-D+2,4,5-T ISOOCTYL ESTER 2-2E LOW VOLATILE BRUSH KILLER
000902 2,4,5-T ISOOCTYL ESTER 4-E LOW VOLATILE BRUSH KILLER
000938 2,4,5-T BUTYL ESTER 4-E
000938 2,4-D 2,4,5-T BUTYL ESTERS 1.33+.66-E
000950 STAUFFER 2,4-D 2,4,5-T BUTYL ESTERS 2-2-E EMULSIFIABLE LIQUID

REGISTRANT	*NAME AND ADDRESS*
* 000524	MONSANTO COMPANY AGRICULTURAL PRODUCTS 800 N. LINDBERGH BLVD. ST. LOUIS, MO 63166

*********** PRODUCT NAME **********

000047 2,4,5-T ISOPROPYL ESTER TECHNICAL GRADE
000067 TECHNICAL GRADE 2,4,5-T BUTYL ESTER
000075 MONSANTO 2,4-D + 2,4,5-T BUTYL ESTER BRUSH KILLER
000081 2,4,5-T LOW VOLATILE ESTER BRUSH KILLER
000095 D-61 MONSANTO 2,4,5-T ISOOCTYL ESTER
000097 MONSANTO 2,4,5-T ESTER BRUSH KILLER
000099 2,4-D + 2,4,5-T AMINE BRUSH KILLER
000148 MONSANTO 2,4,5-T AMINE BRUSH KILLER
000118 BRUSH-O-CIDE BRUSH KILLER
000111 BRUSH BLITZ
000149 2,4-D/2,4,5-T MIXED ESTERS N-BUTYL AND ISOBUTYL
000150 2,4-D/2,4,5-T BUTYL ESTERS
000250 2,4-D/2,4,5-T LOW VOLATILE ESTER BRUSH KILLER (CODE 34)

**** PRODUCT SEARCH LISTING **** PAGE 11

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000524

000258 2,4,5-T ISOBUTYL ESTER TECHNICAL GRADE

REGISTRANT	*NAME AND ADDRESS*
* 000551	BAIRD & MCGUIRE INC SOUTH ST HOLBROOK MA 02343

*********** PRODUCT NAME **********

001114 4DT AMINE BRUSH KILLER
001164 4T AMINE BRUSH KILLER
001574 4T-ESTER BRUSH KILLER
001584 4DT-ESTER BRUSH KILLER
001834 BRUSH KILLER (LOW VOLATILE EMULSIFIABLE CONCENTRATE) LV 30/6T
001844 BRUSH KILLER (LOW VOLATILE EMULSIFIABLE CONCENTRATE) LV-6T

REGISTRANT	*NAME AND ADDRESS*
* 000554	AGSCO INC 6014 4S0 WPANO FORKS ND 58201

*********** PRODUCT NAME **********

000564 AGSCO BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 12

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000572	HIGHLAND CHEMICAL CO. INC. P.O. BOX 849 CALDWELL, NJ 07006

*********** PRODUCT NAME **********

000354 HIGHLAND BRUSH KILLER (ESTER FORM) LOW VOLATILE

REGISTRANT	*NAME AND ADDRESS*
* 000577	SHERWIN-WILLIAMS COMPANY 101 PROSPECT AVE NW CLEVELAND OH 44101

*********** PRODUCT NAME **********

000512 ALMS POISON IVY KILLER

REGISTRANT	*NAME AND ADDRESS*
* 000632	MUTUAL DEALERS WHOLESALE INC 2361 HAMPDEN AVE ST PAUL MN 55114

*********** PRODUCT NAME **********

000022 NORTHRONE L V BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 13

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000882	THOMPSON CHEMICALS CORP 2529 S FIGUEROA ST WILMINGTON CA 90744

**********PRODUCT NAME**********

**000208* TECHNICAL 2-ETHYLHEXYL ESTER OF 2,4,5-T

**000203* TECHNICAL N-BUTYL ESTER OF 2,4,5-T

REGISTRANT	*NAME AND ADDRESS*
* 000677	DIAMOND SHAMROCK CORP. AGRICULTURAL CHEM. DIVISION A UNIT OF DIAMOND SHAMROCK CORP 1100 SUPERIOR AVE CLEVELAND OH 44114

**********PRODUCT NAME**********

**000095* LINE KLEEN 22 BRUSH KILLER

**000097* LINE KLEEN 47 BRUSH KILLER

**000102* LINE KLEEN LV 30/31 BRUSH KILLER

**000103* BRUSH KILLER DORMANT CANE LV 30/31-38

**000104* DORMANT CANE CONCENTRATE LV-81-US

**000134* LINE KLEEN AMINE 41 BRUSH KILLER

**000135* PENCIL KLEEN 61 BRUSH KILLER

**000137* LINE KLEEN LV-21 BRUSH KILLER

**000172* LINE KLEEN INVERT T CONCENTRATE

**000174* LINE KLEEN INVERT 0/T CONCENTRATE

**001145* DACAMINE 4T BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 14

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUED REGISTRANT 000677

**000196* DACAMINE 2D/2I

**000218* TRAILMAY 2D/2I DIAMINE SALT OF 2,4-D & 2,4,5-T

**000247* TECHNICAL 2-ETHYLHEXYL-T (2,4,5-T)

**000248* TECHNICAL ISOPROPYL-T (2,4,5-T)

**000250* TECHNICAL BUTYL-T (2,4,5-T)

**000251* TECHNICAL ISOOCTYL-T (2,4,5-T)

**000273* TRAILMAY 4I CONTAINS 4.0 POUNDS 2,4,5-T ACID EQUIVALENT PER GALLON

**000297* AMINE 2D/2I

**000301* LO-VOL 2D/2I

**000303* LO-VOL-T

**000306* LO-VOL 4T

**000324* DIAMOND SHAMROCK BRUSH KILLER LO-VOL 2D/2I

**000325* DIAMOND SHAMROCK BRUSH KILLER 8D LO-VOL 4T

REGISTRANT	*NAME AND ADDRESS*
* 000704	NFA OIL CO P.O. BOX 519 COLUMBIA MO 65201

**********PRODUCT NAME**********

**000050* N.F.A. LO-V 2,4,5-T

**000051* N.F.A. 2,4,5-T BUTYL ESTER

**000052* N.F.A. LO-V SUPER BRUSH KILL

**000053* N.F.A. SUPER BRUSH KILL (BUTYL ESTER)

**000108* N.F.A. AERIAL ESTER NO. 42

**** PRODUCT SEARCH LISTING **** PAGE 15

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000802	LILLY CHAS M COMPANY MILLER RD DIV 7737 N.E. KILLINGSWORTH PORTLAND, OR 97218

**********PRODUCT NAME**********

**000128* MILLER'S 2,4,5-T AMINE 4

**000181* MILLER'S LV BRUSH KILLER

**000184* MILLER LV 2,4,5-T ESTER

**000229* MILLER'S BLACKBERRY & BRUSH KILLER

**000329* MILLER'S LV 2,4,5-T ESTER 6E

**000520* MILLER'S LV BRUSHKILLER D

**000523* MILLER'S LV 2,4,5-T ESTER FOUR 8P

**000529* MILLERS BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 000870	VELSICOL CHEMICAL CORP 341 EAST OHIO STREET CHICAGO IL 60611

**********PRODUCT NAME**********

**000169* BANVEL SIV JIL SOLUBLE INDUSTRIAL HERBICIDE

**000176* BANVEL - 710

**000179* BANVEL - 120 WATER SOL IND HERBICIDE FOR BRUSH & BROADLEAF WE

**000180* BANVEL SIV JIL SOL INDUS.HERB. FOR BRUSH AND BROADLEAF WEED CONTRO

**000214* VELSICOL VEGABROL A 2D-2T HERBICIDE FOR BRUSH CONTROL

**** PRODUCT SEARCH LISTING **** PAGE 16

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUED REGISTRANT 000870

**000216* VELSICOL VEGABROL LV-2D-2I HERBICIDE FOR BRUSH CONTROL

**000219* VELSICOL VEGABROL 8E-2D-2I HERBICIDE FOR BRUSH CONTROL

**000220* VELSICOL VEGABROL 8E-4T HERBICIDE FOR BRUSH CONTROL

**000226* VELSICOL VEGABROL 8-8I HERBICIDE FOR BRUSH CONTROL

**000228* VELSICOL VEGABROL LV-4T HERBICIDE FOR BRUSH CONTROL

**000229* VELSICOL VEGABROL LV-8T HERBICIDE FOR BRUSH CONTROL

**000230* VELSICOL VEGABROL 8-4I HERBICIDE FOR BRUSH CONTROL

**000231* VELSICOL VEGABROL 4-4I HERBICIDEFOR BRUSH CONTROL

REGISTRANT	*NAME AND ADDRESS*
* 000912	FARMERS UNION CENTRAL EXCHANGE INC POST OFFICE BOX "64" ST PAUL MN 55165

**********PRODUCT NAME**********

**000050* CO-OP BRUSH KILLER LV 262 BRUSH AND WEED KILLER

REGISTRANT	*NAME AND ADDRESS*
* 001145	AMOCO OIL CO. 200 E. RANDOLPH DR. CHICAGO IL 60601

**********PRODUCT NAME**********

**000016* AMOCO BRUSH KILLER

**000029* AMOCO 2, 4, 5-T LV ESTER FOR BRUSH CONTROL

**** PRODUCT SEARCH LISTING **** PAGE 17

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 001145

000879 AMOCO 2,4,5-T AMINE

REGISTRANT	*NAME AND ADDRESS*
* 001580	MIDLAND COUP INC 2021 EAST HENNEPIN AVE MINNEAPOLIS MN 55413

********** PRODUCT NAME **********

000017 MIDLAND 50-50 *** LOW VOLATILE BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 001200	U.S. EAGLE, INC. P.O. BOX 59031 DALLAS, TX 75229

********** PRODUCT NAME **********

000026 EAGLE BRUSH KILL 2,4,5-T SOLUTION

REGISTRANT	*NAME AND ADDRESS*
* 001222	INDIANA FARM BUREAU COOP ASSN INC 47 SO PENNSYLVANIA ST INDIANAPOLIS IN 46204

********** PRODUCT NAME **********

000034 COMP CONCENTRATED 2,4,5-T

000044 LO-UP LONG CHAIN LOW VOLATILE FOUR POUND BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 18

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 001258	JLIN CHEMICALS JLIN COMMUNATION 120 LONG RIDGE ROAD STAMFORD, CT 06904

********** PRODUCT NAME **********

001065 LV ESTER 22 BRUSH KILLER

001067 LV ESTER 40 BRUSH KILLER

002364 MATHESON BUTYL ESTER 22 BRUSH KILLER

002661 MATHESON BUTYL ESTER 70 BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 001269	DEMITT CHEMICAL COMPANY BOX 345 ATLANTA GA 30301

********** PRODUCT NAME **********

000033 DE MITT B-77 WEED KILLER

000104 DEMITT NO. 170 BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 001270	ZEP MANUF COMP BOX 2015 ATLANTA GA 30301

********** PRODUCT NAME **********

000055 ZEP M-61 WEED KILLER

**** PRODUCT SEARCH LISTING **** PAGE 19

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 001270

000125 ZEP B-70 BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 001381	LAND O'LAKES C/O IMPERIAL INC PO BOX 923 SHENANDOAH IA 51601

********** PRODUCT NAME **********

000020 FELCO SUPER BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 001386	UNIVERSAL COOPERATIVES INC PO BOX 456 ALLIANCE OH 44601

********** PRODUCT NAME **********

000028 BRUSH KILLER

000506 UNICO LO-V BRUSH KILLER CONTAINS 2,4-D AND 2,4,5-T LOW VOLATILE ES

000857 UNICO 2,4,5-T LO-V ESTER BRUSH KILLER

000556 UNICO LO V BRUSH KILLER 1-2

**** PRODUCT SEARCH LISTING **** PAGE 20

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 001685	STATE CHEMICAL MFG CO INC 3100 HAMILTON AVE 44114

********** PRODUCT NAME **********

000041 FORMULA 888 BRUSH-KIL SELECTIVE WEED AND BRUSH KILLER

000048 FORMULA 220 BRUSH KIL SELECTIVE WEED & BRUSH KILLER

000078 FORMULA 220-4 BRUSH-KIL

REGISTRANT	*NAME AND ADDRESS*
* 001769	NATIONAL CHEMSEARCH DIV USACHEM INC 2727 CHEMSEARCH BLVD IRVING TX 75060

********** PRODUCT NAME **********

000100 CHEMSEARCH CHENESTER 145

REGISTRANT	*NAME AND ADDRESS*
* 001772	MILDER CORP INC 1421 FIFTH AVE HUNTINGTON WV 25702

********** PRODUCT NAME **********

000772 CHEMFORM BRAND BUTOXY BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 21

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 001026	NAVY BRAND MFG COMPANY 5111 RW AVE ST LOUIS MO 63110

********** PRODUCT NAME **********

**000104* BKB-15

REGISTRANT	*NAME AND ADDRESS*
* 001969	RANSOMS CHEMICAL BOX 186 GRAND LEDGE MI 48837

********** PRODUCT NAME **********

**000715* POISON IVY & BRUSH KILLER #2

REGISTRANT	*NAME AND ADDRESS*
* 001990	FARMLAND IND., INC, C/O REGULATORY AFFAIRS DEPT, P. O. BOX 7305 KANSAS CITY, MO 64116

********** PRODUCT NAME **********

**000100* CLEAN WEED-OUT (2,4,5-T LOW VOLATILE ESTER 4 POUNDS)

**000101* CLEAN WEED-OUT BRUSH KILLER LOW VOLATILE

**000106* WEED-END 2,4,5-T BUTYL ESTER

**000227* CLEAN WEED OUT (BRUSH KILLER BUTYL ESTER)

**** PRODUCT SEARCH LISTING **** PAGE 22

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 002124	GRACE W R & COMPANY AGR CHEM C H TIDWELL PO BOX 277 100 N MAIN ST MEMPHIS TN 38101

********** PRODUCT NAME **********

**000137* NACL LOW VOLATILE 2# - 2?

**000705* NACL 2,4,5-T LOW VOLA BRUSH KILLER-4T CONT 4 LBS 2,4,5-T GAL

REGISTRANT	*NAME AND ADDRESS*
* 002155	SCHNEIDT,INC, 1420 FAIRMONT AVE N W ATLANTA GA 30314

********** PRODUCT NAME **********

**000045* FORMULA 406 BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 002169	PATTENSON CHEMICAL COMPANY INC 1800 UNION AVE KANSAS CITY, MO 64101

********** PRODUCT NAME **********

**000069* PATTENSON'S BRUSH KILLER NO. 200

**** PRODUCT SEARCH LISTING **** PAGE 23

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 002217	PBI-GORDON CORPORATION 300 SW 3RD ST KANSAS CITY KS 66118

********** PRODUCT NAME **********

**000074* LV BRUSH KILLER

**000078* LOW VOLATILE NO. 400 2,4,5-T ESTER WEED KILLER

**000098* SUPER BRUSH KILLER NO. 400 BUTYL

**000100* BUTYL ESTER 400 2,4,5-T BRUSH KILLER

**000556* 2,4,5-T AMINE

REGISTRANT	*NAME AND ADDRESS*
* 002382	KERR-MCGEE CHEMICAL CORP AGR PKG & LABELING KERR-MCGEE CENTER OKLAHOMA CITY OK 73102

********** PRODUCT NAME **********

**000638* POISON IVY KILLER

REGISTRANT	*NAME AND ADDRESS*
* 002393	MORNING GLRY CHEMICAL CO, P.O. BOX 7532 MADISON, WI 53707

********** PRODUCT NAME **********

**000309* LOW VOLATILE 2-4 BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 24

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 002518	DANIELL P A TREE EXPERT COMPANY 2770 SUMMER ST STAMFORD CT 06904

********** PRODUCT NAME **********

**000078* BANVEL-VENT COMPONENT A

REGISTRANT	*NAME AND ADDRESS*
* 002737	PUEBLO CHEMICAL & SUPPLY COMPANY BOX 1279 - 2200 W. ST. JOHN GARDEN CITY, KS 67846

********** PRODUCT NAME **********

**000012* PUEBLO 4 LB. BRUSH KILLER

**000033* PUEBLO BRUSH KILLER LOW. 20/2T

REGISTRANT	*NAME AND ADDRESS*
* 002738	STULL CHEM COMPANY 1000 PAULSON DRIVE SAN ANTONIO, TX 78219

********** PRODUCT NAME **********

**000045* INSTEMUL OTA 66

**** PRODUCT SEARCH LISTING **** PAGE 25

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 003635	OXFORD CHEMICALS PO BOX 80202 ATLANTA GA 30341

PRODUCT NAME

**000039* OXFORD WK-82 LOW-VOLATILE HERBICIDE FOR CONTROLLING WOODY PLANTS

REGISTRANT	*NAME AND ADDRESS*
* 003770	ECONOMY SPUD COMPANY BOX 237 HOSPERS, IA 51238

PRODUCT NAME

**000013* NO. 2 & 2 BRUSH KILLER

**000098* ECONOMY 2,4,5-T BUTYL ESTER 4E

REGISTRANT	*NAME AND ADDRESS*
* 004185	SMITH-DOUGLASS DIV. BARDEN CHEMICAL, NORDEN INC. 5100 VIRGINIA BEACH BLVD. NORFOLK, VA 23501

PRODUCT NAME

**001208* SMITH-DOUGLASS MANGLE BRUSH KILLER

**001268* SMITH-DOUGLASS 2,4,5-T LOW VOLATILE ESTER BRUSH KILLER

**** PRODUCT SEARCH LISTING **** PAGE 26

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000715	COLORADO INTERNATIONAL CORP 7800 MARBLE N.E. ALBUQUERQUE, N.M. 87110

PRODUCT NAME

**001738* BEST 4 SERVIS BRAND LO-VOL BRUSH KILLER

**001748* BEST 4 SERVIS BRAND LO-VOL 2,4,5-T BRUSH KILLER

**001828* BEST 4 SERVIS BRAND BUTYL ESTER 400 2,4,5-T BRUSH KILLER

**002488* BUTYL BRUSH KILLER 3-3

REGISTRANT	*NAME AND ADDRESS*
* 004828	ABCO INC 230 INDUSTRY BLVD NORTH HUNTINGTON, PA 15642

PRODUCT NAME

**000837* W. K. + BT 155

**000a3* ABCO WK-65 BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 004917	REVEL LITTLE TREE INJECTION COMPANY BOX 288 MADILL OK 73446

PRODUCT NAME

**000002* REVEL LITTLE TREE INJECTION FLUID FORMULA NO. 2

**** PRODUCT SEARCH LISTING **** PAGE 27

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 004931	GOOD-LIFE CHEMICALS INC BOX 687 EFFINGHAM IL 62401

PRODUCT NAME

**000086* GOOD-LIFE 2-2 LOW VOLATILE BRUSH KILLER ISOCTYLESTER 2,4-D+2,4,5-T

**000087* GOOD-LIFE 4 LB. 2,4,5-T LOW VOLATILE BRUSH KILLER

**000089* GOOD-LIFE 4 LB. 2,4,5-T BRUSH KILLER BUTYL

REGISTRANT	*NAME AND ADDRESS*
* 005905	HELENA CHEMICAL CO ULANA TOWER, 5100 POPLAR AVE, SUITE 2900 MEMPHIS TN 38137

PRODUCT NAME

**000748* HELENA 20-21 BRUSH KILLER

REGISTRANT	*NAME AND ADDRESS*
* 006294	COMET MANUFACTURING COMPANY 1381 DALTON DRIVE N E ATLANTA GA 30306

PRODUCT NAME

**000188* COM-O-BRUSH LV 20-10 LOW VOLATILE ISOOCTYL ESTER OF 2,4,5-T AND 2,4-D

**000198* COM-O-BRUSH ISOCTYL HRH KLN SLV LOW VOL ISOIL ESTR 2,4,5-TE,2,4-D

**** PRODUCT SEARCH LISTING **** PAGE 28

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 000720	SOUTHERN MILL CREEK PRODUCTS COMPANY INC BOX 1090 TAMPA FL 33601

PRODUCT NAME

**001124 SMCP SPECIAL ESTER LV D & T

REGISTRANT	*NAME AND ADDRESS*
* 006762	UTENN CHEM CORP BOX 5070 MONROE LA 71201

PRODUCT NAME

**000188* BEEVEX 150 LOW VOLATILE ESTER WEED GRASS AND BRUSH KILLER

**000218* BEEVEX-65 LOW VOLATILE ESTER WEED GRASS & BRUSH KILLER

**000832* 2,4,5-T TREE KILLER

REGISTRANT	*NAME AND ADDRESS*
* 006900	HILL J J COMPANY BOX 780 KALAMAZOO MI 49005

PRODUCT NAME

**000738* HILL 2,4,5-T LOW VOLATILE ESTER OIL BRUSH AND WEED KILLER

**** PRODUCT SEARCH LISTING **** PAGE 29

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT *NAME AND ADDRESS*

* 007273 CHUNN CHEMICAL INCORPORATED
4995 NINTH MAIN STREET
ROLLEDOWN IL 61101

********** PRODUCT NAME **********

**000824* BRUSH OFF 4-T AMINE BRUSH KILLER
**000866* BRUSH-OFF D & T BRUSH KILLER
**000879* BRUSH-OFF 2-2-LV BRUSH KILLER
**000938* WEED AND BRUSH-OFF AMINE FORMULA 400
**000988* BRUSH-OFF LOW VOLATILE BRUSH & WEED KILLER
**000991* BRUSH-OFF 2-2 AMINE BRUSH KILLER

REGISTRANT *NAME AND ADDRESS*

* 006123 MILLER PRANA & BOND INC
13851 SO EMERALD AVE
CHICAGO IL 60827

********** PRODUCT NAME **********

**000032* BRUSH & WEED KILLER TO CONTROL BROADLEAF WEEDS & WOOD PLANTS

REGISTRANT *NAME AND ADDRESS*

* 006823 NAGCO INC
10501 HAYZATA BLVD, SUITE 101
MINNING, MN 55343

********** PRODUCT NAME **********

**** PRODUCT SEARCH LISTING **** PAGE 30

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 006823

**000858* NAGCO LV-VOL 20/21
**000951* NAGLO LV-VOL 4T

REGISTRANT *NAME AND ADDRESS*

* 009389 PRECISION LABORATORIES INC
PO BOX 127
WAUKEGAN IL 60084

********** PRODUCT NAME **********

**000865* LIQUI-DATE BRUSH KILLER (ESTER FORM)

REGISTRANT *NAME AND ADDRESS*

* 009650 RANGE ENG DEV CORP
FORT MCHAVETT TX 76041

********** PRODUCT NAME **********

**000881* FOAMICIDE NO. 100 BRUSH & WEED KILLER

REGISTRANT *NAME AND ADDRESS*

* 000779 RIVERBLUE CHEM COMPANY
P.O. BOX 171199 855 RIDGE LAKE BLVD
MEMPHIS TN 38117

********** PRODUCT NAME **********

**000122* RIVERSIDE HERBICIDE LOW VOLATILE 4T

**** PRODUCT SEARCH LISTING **** PAGE 31

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 000779

**000123* RIVERSIDE HERBICIDE LOW VOLATILE 2-D-2T
**000126* RIVERSIDE HERBICIDE 4-4I 2,4,5-T

REGISTRANT *NAME AND ADDRESS*

* 010086 ATHEA LABORATORIES INC
4180 N FIRST ST
MILWAUKEE WI 53212

********** PRODUCT NAME **********

**000800* LYNX KILLS BROADLEAF WEEDS AND WOODY PLANTS LOW VOLATILE SELECTIVE
**000801* WEED & BRUSH KILLER NO. 2
**000910* 2,4,5-T LOW VOLATILE ESTER BRUSH AND WEED KILLER

REGISTRANT *NAME AND ADDRESS*

* 010273 HUNTER DIV. OF UBA CHEMICAL INC.
P.O. BOX 22265
IRVING TX 75062

********** PRODUCT NAME **********

**000006* HUNTER HAN WEED K-40

**** PRODUCT SEARCH LISTING **** PAGE 32

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT *NAME AND ADDRESS*

* 010345 CHEMLINE INTERNATIONAL CORPORATION
7525 SEBSEMEN AVE
CLEVELAND OH 44127

********** PRODUCT NAME **********

**000002* OLD GARDENER WEED'N FEED

REGISTRANT *NAME AND ADDRESS*

* 011515 ANE CHEMICAL CORPORATION
17000 W. EIGHT MILE ROAD
SOUTHFIELD, MI 48075

********** PRODUCT NAME **********

**000506* 1MIN ESTERS KILLS WOODY PLANTS LOW VOLATILITY

REGISTRANT *NAME AND ADDRESS*

* 033330 FORAGE UNLIMITED
PO BOX 7340 MARRENLY AVE STATION
LONGVIEW TX 75601

********** PRODUCT NAME **********

**000001* SIFON RANGELAND BRUSH SPRAY OLV 40-2T
**000005* FORAGE UNLIMITED INDUSTRIAL BRUSH SPRAY OLV 30-3T

**** PRODUCT SEARCH LISTING **** PAGE 33

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

REGISTRANT	*NAME AND ADDRESS*
* 039128	ENVIRONMENTAL PROCESS RESEARCH RIVER OAKS BANK TOWER 2BU KIRBY SUITE 614 HOUSTON, TX 77019

**********PRODUCT NAME**********

**000001* BEST 4 SERVIS BRAND BUTYL BRUSH KILLER 2-4
**000002* BEST 4 SERVIS BRAND BRUSH & RANGE CLEAR 3-3
**000003* BEST 4 SERVIS BRAND BRUSH & RANGE CLEAR 4-4

REGISTRANT	*NAME AND ADDRESS*
* 039511	VENTAC, INC. STE. 3200 CLARK TOWER 5100 POPLAR AVE. MEMPHIS, TN 38137

**********PRODUCT NAME**********

**000016* BRUSH-RHAP AMINE A-2D-2T HERBICIDE
**000017* BRUSH-RHAP A-4T HERBICIDE 2,4,5-T AMINE.
**000018* BRUSH-RHAP D A-4T HERBICIDE 2,4,5-T
**000019* BRUSH-RHAP BUTYL ESTER B-4T HERBICIDE,2,4,5-T
**000021* BRUSH-RHAP BUTYL-2D-2T HERBICIDE
**000022* BRUSH-RHAP LV-4T HERBICIDE 2,4,5-T
**000023* BRUSH-RHAP LV-5T HERBICIDE 2,4,5-T
**000024* BRUSH-RHAP LV-4T HERBICIDE
**000025* BRUSH-RHAP LV OXY-5T HERBICIDE
**000026* BRUSH-RHAP LV OXY-4T HERBICIDE

**** PRODUCT SEARCH LISTING **** PAGE 34

10/03/77 FEDERALLY REGISTERED PRODUCTS CONTAINING 2,4,5-T ESTERS/SALTS

**CONTINUE REGISTRANT 039511

**000027* BRUSH-RHAP LV OXY-6T HERBICIDE
**000028* BRUSH-RHAP LV OXY 3D-3T HERBICIDE
**000029* BRUSH-RHAP LV OXY-2D-2T HERBICIDE
**000030* BRUSH-RHAP LV 3D-5T HERBICIDE
**000032* BRUSH-RHAP LV-2D-2T HERBICIDE
**000033* BRUSH-RHAP JLV 2D-2T HERBICIDE
**000034* BRUSH-RHAP JLV-4T HERBICIDE
**000035* BRUSH-RHAP DLV-4T HERBICIDE
**000036* BRUSH-RHAP JLV 3D-3T HERBICIDE
**000050* AMINE DA-1.5D-1.5T HERBICIDE
**000051* TRANSAMINE DA-3T HERBICIDE 2,4,5-T OIL SOLUBLE AMINE
**000053* 2,4,5-T BUTYL ESTER
**000054* 2,4,5-T LOW VOLATILE ESTER
**000055* 2,4,5-T LOW VOLATILE OXY-ESTER

**** PRODUCT SEARCH LISTING **** PAGE 1

10/03/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING 2,4,5-T ESTERS/SALT

REGISTRANT	*NAME AND ADDRESS*
* 000108	THOMPSON-HAYWARD CHEMICAL COMPANY BOX 2383 KANSAS CITY KS 66110

**********PRODUCT NAME**********

**010180* DED-WEED LV-4
**010181* DED-WEED LV-33
**010182* DED-WEED LV-6

REGISTRANT	*NAME AND ADDRESS*
* 000269	AMCHEM PRODUCT INC WASHINGTON AVE AMBLER PA 19002

**********PRODUCT NAME**********

**010178* ENVERT DT
**015179* ENVERT DT

REGISTRANT	*NAME AND ADDRESS*
* 000464	DOW CHEMICAL U S A PO BOX 1706 MIDLAND MI 48640

**********PRODUCT NAME**********

**008119* MESQUITE T HERBICIDE
**008120* TURDON SPECIAL LV 225 HERBICIDE

**** PRODUCT SEARCH LISTING **** PAGE 2

10/03/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING 2,4,5-T ESTERS/SALT

**CONTINUE REGISTRANT 000464

**008121* TURDON 225E HERBICIDE
**008122* TURDON 225 MIXTURE HERBICIDE

REGISTRANT	*NAME AND ADDRESS*
* 000557	SWIFT AGRICULTURAL CHEMICAL CORP. 111 WEST JACKSON BOULEVARD CHICAGO IL 60604

**********PRODUCT NAME**********

**009852* SWIFTS GOLD BEAN BRUSH KILL 22
**009853* SWIFTS GOLD BEAN BRUSH KILL 55

REGISTRANT	*NAME AND ADDRESS*
* 000676	VELSICOL CHEMICAL CORP 341 EAST OHIO STREET CHICAGO IL 60611

**********PRODUCT NAME**********

**078194* BANVEL 2+2 HERBICIDE FOR PASTURE,RANGELAND GRASSES AND NONCROPLAN
**079344* BANVEL 2+2 HERBICIDE
**079443* BANVL 2+2 HERBICIDE

**** PRODUCT SEARCH LISTING **** PAGE 3

10/03/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING 2,4,5-T ESTERS/SALT

REGISTRANT	NAME AND ADDRESS
003200	STAUFFER CO. P.O. BOX 2380 SAN ANTONIO TX 78298

PRODUCT NAME

000000	STAUFFER'S 2,4,5,-T
010172	STAUFFER'S BRUSH KILLER NO.32

REGISTRANT	NAME AND ADDRESS
003579	DHEMEN CHEMICAL CORPORATION P O BOX 48 HONOLULU, HI 96810

PRODUCT NAME

032290	ULTHAMAN LV-WK

REGISTRANT	NAME AND ADDRESS
010827	INDUSTRIAL SOLVENTS PO BOX 312 SAN MARCOS TX 78666

PRODUCT NAME

038424	END-SOL 100

**** PRODUCT SEARCH LISTING **** PAGE 4

10/03/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING 2,4,5-T ESTERS/SALT

REGISTRANT	NAME AND ADDRESS
011465	NUMCO INC 11837 HARLOUCHES ROAD SAN ATONIO TX 78217

PRODUCT NAME

101714	NUMCHEM BRUSH CONTROL MIXTURE 1

REGISTRANT	NAME AND ADDRESS
005203	AMERICAN NATION CORP P.O. BOX 896 LONGMONT, CO 80501

PRODUCT NAME

104595	QUICK KILL 400 WEED KILLER LIQUID

REGISTRANT	NAME AND ADDRESS
037347	UNI-CHEM CORP. OF FLORIDA MIR 0334 - 2801 N.W. 55TH CT. FT. LAUDERDALE, FL 33310

PRODUCT NAME

031284	UNI CHEM BRUSH AND WEED KILLER

**** PRODUCT SEARCH LISTING **** PAGE 5

10/03/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING 2,4,5-T ESTERS/SALT

REGISTRANT	NAME AND ADDRESS
037391	COLORADO CHEMICAL & FERT. CO, INC. ROUTE 1, BOX 2548 LONGMONT, CO 80501

PRODUCT NAME

099923	COLORADO'S OMN SPOT GRASS KILLER

[FR Doc. 78-10340 Filed 4-20-78; 8:45 am]