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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re:	)	
The Dow Chemical Company, et al.	)	FIFRA Docket Nos. 415, et al.

RESPONDENT'S PREHEARING BRIEF ON THE RISKS ASSOCIATED WITH THE REGISTERED USES OF 2,4,5-T AND SILVEX

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REGISTERED USES OF 2,4,5-T AND SILVEX

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re: THE DOW CHEMICAL COMPANY, et. al.	FIFRA Docket Nos. 415, et. al.

RESPONDENT'S PREHEARING BRIEF
ON THE RISKS ASSOCIATED WITH THE
REGISTERED USES OF 2,4,5-T AND SILVEX

INTRODUCTION

On February 28, 1979, the Administrator suspended certain uses of the herbicides 2,4,5-T and silvex, and issued notices of intent to cancel registrations of the suspended uses of these chemicals. Subsequently, on December 3, 1979, the Administrator issued notices of intent to hold a hearing on whether or not to cancel the non-suspended uses of these herbicides, thereby paving the way for this consolidated hearing to determine the fate of all registered uses of 2,4,5-T and silvex, two widely used phenoxy herbicides.*/

*/ The Administrator suspended the forestry, rights-of-way, and pasture uses of 2,4,5-T and silvex, and the home and garden, aquatic weed control/ditch bank, and commercial/ornamental turf uses of silvex. 44 FR 15874, 44 FR 15897, March 15, 1979. The non-suspended uses include the use of 2,4,5-T and silvex on rice and rangeland, and the use of silvex on orchard fruits such as apples, pears, and plums. 44 FR 72316, 44 FR 72328, December 13, 1979.

This hearing will explore the risks and benefits associated with the registered uses of 2,4,5-T and silvex. Risk issues will be considered during the first phase of this hearing. The risk associated with a chemical compound is a function of both the toxic properties of the chemical and the extent to which people or other sensitive organisms are exposed to the chemical. Accordingly, the risk phase of this hearing will ventilate toxicity and exposure issues relevant to determining the risks of 2,4,5-T, silvex and 2,3,7,8-tetrachloro-p-dibenzodioxin ("TCDD" or "dioxin"), a highly toxic chemical which is invariably present in commercial products containing 2,4,5-T and silvex.*/ The second phase of the hearing will focus on issues relating to the benefits of these herbicides and the relation between risks and benefits.

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*/ The phenoxy herbicides 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and silvex (2-[2,4,5-trichlorophenoxy]propionic acid) are very closely related, in terms of chemical properties, physical structure, and contamination by TCDD. Commercially, both compounds are made from the same starting material, 2,4,5-trichlorophenol, or one of its derivatives. During the manufacturing process, the very toxic contaminant, TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) is inevitably produced. The TCDD results from the combination of two molecules of the parent compound under heat and pressure, both of which exist during the normal manufacturing process.

By careful monitoring, manufacturers have been able to lower the level of TCDD contamination in commercial 2,4,5-T and silvex products. However, TCDD is always present in these products. In addition, control of the TCDD levels is not exact, and the amount present may vary from batch to batch. Recent analyses of some technical samples of 2,4,5-T and silvex indicate that TCDD levels in those samples were generally below 0.05 ppm. If careful monitoring of heat and pressure is not maintained, high levels of TCDD can be produced.

This brief reviews the scientific data which will be presented by Agency witnesses, and the scientific and policy premises which will be considered in assessing the significance of these data. The brief also discusses the burden of proof in FIFRA cancellation proceedings and the legal standards which govern the registration and cancellation of pesticides.

The Summary of Position introduces the four components of the Agency's risk case. Part I of the body of the brief reviews animal test data establishing that 2,4,5-T, silvex and/or TCDD produce tumors, cancer, birth defects, fetal death, and other adverse health effects in test animals. Part II presents epidemiological data relating increased incidences and risks of cancer in some human populations to exposure to 2,4,5-T (and other phenoxy herbicides) and TCDD, and associating an increased incidence in hospitalized spontaneous abortions with the use of 2,4,5-T for forest management. Part III presents data on the chemical properties and environmental fate of 2,4,5-T, silvex and TCDD, which indicate that these chemicals appear and remain in environmental media long after application. The use case histories reviewed in Part IV show that the use of these herbicides in accordance with label directions on forests, rights-of-way, and other use sites has resulted in movement of the herbicide from the application site to areas of human work and habitation.

APPLICABLE LEGAL PRINCIPLES

I. FIFRA Prohibits The Registration And Use Of Any Pesticide Which Causes Unreasonable Adverse Effects On Man Or The Environment.

FIFRA Sections 3(a) and 12(a)(1) provide that no person may distribute, sell, offer for sale, hold for sale, or ship any pesticide which is not registered by EPA. These provisions, for all practical purposes, prohibit the use of an unregistered pesticide, by making it virtually impossible for users to acquire unregistered pesticide products. Once a pesticide is registered, no person may use that pesticide except in accordance with the directions for use on its labeling*/ or in accordance with any other restriction put on its use by EPA regulations. FIFRA Sections 12(a)(2)(F) and (G). 7 U.S.C. §136j(a)(2)(F) and (G).

The Administrator may not approve the registration of a pesticide unless the applicant for registration demonstrates that the pesticide satisfies the statutory standard for registration. That standard requires (among other things) that the pesticide perform its intended function without causing "unreasonable adverse effects on the environment."

*/ The "labeling" consists of the label on a pesticide product as well as other written, printed, or graphic matter accompanying the pesticide product or referred to on the label.

FIFRA §3(c)(5), 7 U.S.C. §136a (c)(5). The term "unreasonable adverse effects on the environment" is defined as "any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide." FIFRA §2(bb), 7 U.S.C. §136(bb). In effect, this standard requires findings that (1) the benefits of each use of a pesticide exceed the risks of that use when the pesticide is used in accordance with the terms and conditions of registration, or in accordance with widespread and commonly recognized practice and (2) the risks are not higher than they need to be in light of available risk reduction technologies.*/

II. FIFRA Requires Cancellation of an Existing Registration of a Pesticide if it Appears that the Pesticide Causes Unreasonable Adverse Effects on Man or the Environment

Section 6 of FIFRA, 7 U.S.C. §136d, requires that the Administrator exercise continuous oversight over registered pesticides. This provision reflects the recognition that a pesticide which was once registered may later be found to pose unreasonable risks to man or the environment or not to satisfy the statutory registration standards in some other manner. If it appears to the Administrator that a registered pesticide, when used in accordance with widespread and commonly

*/ Among other things, an applicant for registration or a registrant must submit data which satisfy the Administrator's data requirements. FIFRA §3(c)(1)(D), 7 U.S.C. §136a(c)(1)(D). These requirements are intended to insure that the Administrator will have the data which he determines are necessary to assess the risks and benefits of pesticides.

recognized practice, poses unreasonable risks, the Administrator may issue a notice of intent either to cancel the pesticide's registration, FIFRA Section 6(b)(1), 7 U.S.C. §136d(b)(1), or to hold a hearing to determine whether or not its registration should be cancelled, FIFRA Section 6(b)(2), 7 U.S.C. §136d(b)(2).

The judgment of whether to issue a FIFRA §6(b)(1) or a §6(b)(2) notice is within the sole discretion of the Administrator (or his duly designated delegate). If the Administrator determines that the risks posed by a pesticide's continued use appear to outweigh its benefits, he may issue a notice of intent to cancel pursuant to FIFRA §6(b)(1). If, however, the Administrator's judgment concerning the risks and benefits associated with a particular pesticide use or concerning the appropriate regulatory response is only tentative, the Administrator may issue a notice under FIFRA §6(b)(2).*/

FIFRA requires that the Administrator weigh the risks and benefits associated with a particular use of a pesticide before he takes final action to fully cancel registrations for that use. If he determines for any particular use that the

*/ There is no distinction between a §6(b)(1) cancellation hearing and §6(b)(2) hearing as to the manner in which they are conducted, as to the allocation of the burden of proof, or as to the nature of the regulatory decision which the Administrative Law Judge may recommend at the conclusion of the hearings. Thus, the Administrator may recommend cancellation at the conclusion of either a §6(b)(1) cancellation hearing or a §6(b)(2) hearing if that action is supported by the record.

risks are unreasonable, he must then determine whether those risks can be sufficiently reduced by regulatory measures short of cancellation.*/ If he determines that adequate risk reduction cannot be achieved by such regulatory measures, the registration of the pesticide for that use must be cancelled.

III. FIFRA Allocates To The Proponents Of Registration The Burden Of Proving That A Pesticide Does Not Cause Unreasonable Adverse Effects On The Environment

One of the most fundamental principles of FIFRA is that the proponents of registration or continued registration of a pesticide (e.g., applicants for registration or registrants) bear at all times the burden of proving the registrability of that pesticide. Thus, the proponents of registration or continued registration are required to prove, among other things, that the benefits of a pesticide outweigh the risks that may result from its use. Environmental Defense Fund (EDF) v. Environmental Protection Agency (EPA) 548 F. 2d 998, 1004, 1012-1018 (D.C. Cir. 1976); EDF v. EPA, 510 F. 2d 1292, 1297, 1302 (D.C. Cir. 1975); Dow Chemical v. Ruckelshaus, 477 F.2d 1317, 1324 (8th Cir. 1973); Stearns Electric Paste Co. v. EPA, 461 F.2d 293, 304-305 (7th Cir. 1972); EDF v. Ruckelshaus, 439 F.2d 584, 593 (D.C. Cir. 1971). The statutory allocation of the burden of proof is incorporated into the EPA regulations which govern the procedures for Section 6(b)(1) and 6(b)(2)

*/ Such regulatory measures include the prescription of restrictions upon use through changes in the labeling and/or the classification of the pesticide for restricted use.

cancellation hearings. These regulations provide in part that:

> (a) At the hearing, the proponent of cancellation [e.g., EPA] . . . has the burden of going forward to present an affirmative case for the cancellation . . . In the case of a hearing called by the Administrator, the Respondent has the burden to present an affirmative case as to the statement of issues.
>
> (b) On all issues arising in connection with the hearing, the ultimate burden of persuasion shall rest with the proponent of the registration [e.g., the registrant]. 40 CFR 164.80(a) and (b).

Therefore, while the Agency has the burden of going forward with evidence supporting cancellation in a Section 6(b)(1) hearing and with a statement of issues in a Section 6(b)(2) hearing, the ultimate burden of proving that a pesticide does not cause unreasonable adverse effects rests with the proponents of registration. See EDF v. EPA, supra, 548 F.2d at 1004, 1012-1018.

Congress has allocated the burden of persuasion to proponents of registation in order to allow the Agency to resolve uncertainties concerning a pesticide's risks and benefits on the side of public safety. In finding that the burden of persuasion was borne by the registrant, the D.C. Circuit Court stated in EDF v. EPA, supra, that:

> Congress made clear that the public was not to bear the risk of uncertainty concerning the safety of a [pesticide]. 548 F. 2d at 1018.

In EDF v. EPA, 489 F.2d, 1247, 1252 (D.C. Cir. 1973), the Court found that it was bound to uphold the Agency's cancellation of DDT "even if the hazardous nature of DDT has not been proved beyond a reasonable doubt. Sufficient evidence has been adduced to show potentially urgent danger from DDT." In EDF v. EPA, supra, 510 F. 2d 1292 at 1298, the D.C. Circuit upheld as a valid resolution of uncertainty the Administrator's conclusion that the concept of a threshold exposure level has no practical significance when carcinogens are concerned. The court stated that "where the matter involved is as sensitive and fright-laden as cancer and the statute places [the burden of proof on the registrant], we shall not, assuming a substantial showing of danger, require the Administrator to make impossible proofs."

FIFRA's allocation of the burden of proof in effect permits the Agency to assess risks and benefits by making reasonable extrapolations from available data. These extrapolations may be based on reasonable assumptions or on unproven scientific theories which have received substantial support in the scientific community. Morever, in making these extrapolations, the Agency may resolve uncertainty as to the magnitude of risk in favor of higher estimates of risk so long as these higher estimates are consistent with the available data.

It should be noted that proponents of registration do not sustain their burden of proof in cancellation hearings merely

by demonstrating that the Agency's assessment of risks and benefits contain errors of fact, theory, or logic. Rather, they must affirmatively demonstrate that even when all uncertainties concerning risks and benefits are resolved on the side of public safety, the benefits outweigh the risks.

The soundness of FIFRA's burden of proof allocation from a public policy standpoint lies in the fact that chemical regulation is a process characterized by uncertainty. The available information on the risks and benefits of a pesticide is often imprecise or incomplete. In addition, estimating the magnitude of risks is a newly emerging field of science in which many concepts and assumptions are on the very frontier of scientific knowledge. If the Agency, rather than the proponents of registration, were to bear the burden of proof, the authority of the Agency to resolve uncertainties in risks and benefits on the side of public safety would be unreasonably limited. As a result, in some cases, the Agency would be unable to take action until severe irreversible harm to man and the environment had already occurred.

SUMMARY OF POSITION

The use of 2,4,5-T and silvex on forests, rights-of-way, pastures, rangeland and rice, the use of silvex on rice and fruit crops, and the other uses of these herbicides pose risks of a wide range of adverse health effects on humans. This conclusion is based on animal toxicity data, corroborated in part by newly developing epidemiological data, which show that human exposure to these chemicals may result in cancer, increased susceptibility to disease through suppression of the immune response, and increased risks of bearing defective children or of terminating a pregnancy by miscarriage or stillbirth. Because the use of 2,4,5-T and silvex results in distribution of these chemicals to the environment in which they are used, humans may be exposed to these chemicals and are therefore at risk of experiencing the adverse health effects reliably reported in exposed laboratory animals and exposed human populations.

Accordingly, the Agency's position on the risks which 2,4,5-T, silvex and TCDD present to human health has four principal components. The first component is animal toxicology data which unequivocably establish that 2,4,5-T, silvex, and TCDD produce several different effects in several different species of laboratory animals. Moreover, these adverse effects are observed at very low levels of exposure.

TCDD has been observed to induce cancer in laboratory animals at doses at least as low as one ten-millionth of a gram TCDD/kg body weight/day and tumors indicative of cancer risks at lower doses. TCDD injures or kills animal embryos at doses as low as one billionth of a gram TCDD/kg body weight/day. These data indicate that people who are exposed even to exceedingly small amounts of 2,4,5-T, silvex, and TCDD may develop cancer and/or experience abnormal pregnancies.

These predictions are borne out by the epidemiologic data which constitute the second component in the Agency's case. Those data indicate that humans are susceptible to the same kinds of effects which appear in test animals. Recent studies relating cancer to exposure to 2,4,5-T and/or TCDD in several different populations are particularly important. Workers who have been exposed to phenoxy herbicides contaminated with TCDD have increased incidences or risks of cancer of the stomach and other organs. In addition, the adverse reproductive effects observed in test animals appear with increased frequency in some human populations exposed to 2,4,5-T and silvex in comparison to unexposed populations.

The third component describes the potential for human exposure to 2,4,5-T, silvex, and TCDD in terms of information

on the distribution and fate of these chemicals in the environment and in living organisms. Technical limits on the analytical methodology for the detection of low-level environmental contaminants, and the absence of comprehensive monitoring activities limit the quality and quantity of data on the actual levels of these chemicals in the environment. However, the available data indicate that these chemicals are distributed to air, water, soil, and vegetation at the application site. As a result, applicators and bystanders at the application site may be exposed during and after the application. In addition, contamination of environmental media during or following application creates opportunities for exposure to humans who live and work away from the application site.

Additional evidence of human exposure is found in the case studies which constitute the fourth and final component of the Agency's case. These case studies document the presence of 2,4,5-T and silvex in water and soil, and on garden vegetables and fruits on property adjacent to areas in which these herbicides have been used in an ordinary manner. These studies demonstrate that persons living and working in areas adjacent to herbicide application sites may experience exposure through movement of the chemicals from the areas of herbicide application through air, water, and soil to non-target areas. Distribution of 2,4,5-T, silvex and TCDD to these non-target sites creates

opportunities for human exposure through inhalation of pesticide vapor or consumption of water and food which have become contaminated with the herbicide. In addition, the presence of pesticide residues on food intended for animal consumption, or on tobacco intended for commercial use also creates the opportunity for human exposure.

The information presented in this Statement of Position and the prospective testimonies of Agency witnesses in the hearing are based primarily on data from the bio-medical literature showing that animals and people who have been exposed to 2,4,5-T, silvex and/or TCDD are more likely to experience certain serious adverse health effects than unexposed populations. Additional data and information indicate that chemical properties and use practices permit human exposure to these chemicals. The combination of data from animal experiments, human populations, chemical studies, and case histories describes a risk to humans which is unacceptable under FIFRA.

I. Tumors and Reproductive Failure, Including Birth Defects and Stillbirths, Occur in Test Animals Exposed to 2,4,5-T, Silvex and/or TCDD

Laboratory animals have long been used to test chemicals for their possible toxic effects on living systems, and to predict the risk potential for humans who may be exposed to such chemicals in their work, home, or recreational environments. Data from test animals are also used to verify apparent relationships between human exposure to toxic chemicals and

health hazards which appear to result from such exposure.*/

The utility and validity of using animal test data to assess human health effects is well-established in law as well as in science. In upholding, in part, the EPA Administrator's decision to suspend the pesticides chlordane and heptachlor,**/ the U.S. Court of Appeals commented on the utility of animal test data as a basis for regulatory decisions.

> 'Reliance on general data, consideration of laboratory experiments on animals, etc.' has been held a sufficient basis for an order cancelling or suspending the registration of a pesticide. 548 F.2d 998 at 1005, quoting EDF v. EPA, 489 F. 2d 1247, 1254 (D.C. Cir. 1973).

As for heptachlor, chlordane, DBCP and other suspended or cancelled pesticides, animal test data constitutes a substantial portion of the available information on the adverse effects of 2,4,5-T, silvex and TCDD.

A. 2,4,5-T, Silvex and/or TCDD Produce Several Different Toxic Effects at Very Low Levels of Exposure

Studies investigating the possible adverse effects of 2,4,5-T, silvex, and TCDD, their common dioxin contaminant,

*/ Testing in laboratory animals accomplishes these objectives in several ways. First, testing establishes whether or not a suspected toxic agent is, in fact, toxic to living matter. Next, testing defines the range of toxic effects of a chemical. These data may also show whether a toxic chemical produces only a single, mild effect or a multiplicity of serious life-threatening effects. Finally, testing can establish whether a chemical exerts its toxic effects only at high dose levels or also at low levels of exposure.

**/ Environmental Defense Fund v. EPA, 548 F. 2d 998 (D.C. Cir. 1976).

in test animals, indisputably establish that these herbicides and/or their contaminant produce a wide range of different adverse health effects in several different animal species exposed to these chemicals. Exposure of these test animals to TCDD, 2,4,5-T or silvex induces cancer or tumors indicative of cancer risks, anatomical birth defects such as cleft palate and abnormal kidneys, other gestational effects such as stillborn animals and early death among newborn animals, and suppression of the immune system. Moreover, TCDD exerts fetotoxic or teratogenic effects not in one animal species only, but in each of the three species in which it has been tested.

Further, laboratory studies clearly demonstrate that TCDD is toxic at very low levels of exposure. For example, TCDD produces reproductive toxicity in rats at 0.001 ug/kg/day (one-billionth of a gram of TCDD), and immunological suppression at 1.0 ug/kg/week (one-millionth of a gram of TCDD). These results demonstrate that even at these very low doses effects occur often enough to be detected even in small populations of laboratory animals.

The adverse effects observed in the laboratory animal tests are comparable to adverse effects observed in humans following occidental exposure to TCDD-contaminated 2,4,5-T and silvex. For example, cancer, adverse effects on reproduction and immune function, chloracne, neuromuscular symptons, and liver dysfunction, including porphyria, has been observed in both laboratory animals and humans.

Because the testing of toxic chemicals in humans is ethically unacceptable, and the available human data come from retrospective studies in which the extent of human exposure is not well-defined, it cannot be determined whether humans would be more or less sensitive than the laboratory animals tested to the toxic effects of 2,4,5-T, silvex, and TCDD. However, it is impossible to ascertain a "safe" level of human exposure to TCDD. Because science has not established that there are "threshold doses" for chemical carcinogens below which there is no cancer risk, even very low levels of exposure to TCDD must be regarded as creating some risk of cancer to humans. This risk may be quite significant at even exceedingly low human exposure levels in view of data showing that TCDD is one of the most potent animal carcinogens known. As developed in Section II, epidemiologic data from human

populations confirms this conclusion. Moreover, "no-effect" levels have not been established for TCDD for adverse reproductive effects.*/

The discussion below reviews the available animal toxicity information as it relates to the oncogenic, adverse reproductive and immunologic effects in animals exposed to 2,4,5-T, silvex and/or TCDD.

*/ For adverse effects other than cancer and mutagenicity, it is often assumed that there is a threshold below which there is no risk. In regulating these effects, the classic approach is to find a "no effect" or "no observable effect level" in appropriate test animals, and to regulate exposures to chemicals which come too close to this level. A no observable effect level has not been established for the reproductive effects of TCDD.

B. Chronic Toxicity Studies On Laboratory Animals Indicate That Commercial 2,4,5-T And Commercial Silvex are Likely to Pose A Cancer Risk To Humans At Any Level Of Human Exposure.*/

Studies involving the exposure of laboratory animals to TCDD, an unavoidable contaminant of commercial 2,4,5-T and silvex, provide substantial evidence that TCDD is a very potent cancer causing agent (carcinogen) in rats and highly suggestive evidence that TCDD is a potent tumor causing agent (oncogen) in mice. These results lead to the conclusion

*/ In order to allow a fuller understanding of this discussion, the definitions and general meaning of several pathology terms are provided at this point:

The term "oncogenic" is defined as causing or inducing the formation and development of a neoplasm. Stedman's Medical Dictionary, 21st Ed.

The term "carcinogenic" is defined as causing cancer. Stedman's Medical Dictionary, 21st Ed.

"Neoplasm" has been defined as a "new growth comprising an abnormal collection of cells, the growth of which exceeds and is uncoordinated with that of the normal tissues." Robbins, S., Pathology 3rd Ed. 1967, p.89. Similarly, the term has been defined as an autonomous uncontrolled growth of abnormal tissue that is harmful to the host. Peery, T. and W. Miller, Pathology, A Dynamic Introduction to Medicine and Surgery, 2d Ed., 1971, pp 329-330.

The term "tumor", is generally used synonymously with the term "neoplasm." See Peery, supra, p. 330.

Neoplasms (or tumors) are classified as either benign or malignant. The term "cancer" refers to the presence of a malignant neoplasm. However, as explained in section I.B.1., the induction of either benign or malignant neoplasms is considered to be an indication of carcinogenic risk. Therefore, for regulatory purposes, any distinction between the two classes of neoplasms or between the terms carcinogenicity and oncogenicity is largely irrelevant.

that TCDD is likely to pose a risk of cancer to humans at any level of human exposure. Therefore, since any exposure to commercial 2,4,5-T and commercial silvex necessarily involves some exposure to TCDD, any human exposure to commercial 2,4,5-T or commercial silvex is likely to pose a risk of cancer to humans.

Moreover, a recently completed study in which rats were exposed to specially purified 2,4,5-T containing no detectable TCDD provides suggestive evidence that pure 2,4,5-T, independent of any TCDD contamination, is a cancer causing agent in rats. This result leads to the conclusion that commercial 2,4,5-T may pose a risk of cancer to exposed humans, which is in addition to the risk of cancer due to its TCDD contaminant.

The experimental animal studies relevant to assessing the oncogenicity of TCDD, 2,4,5-T and silvex are discussed in section I.B.3. below. First, however, the relevance of animal cancer studies to human risk assessment and the appropriate methodology for conducting animal cancer studies are discussed in sections I.B.1. and 2. below.

It should be noted that the substantial evidence of human carcinogenic risk which is provided by the animal cancer studies is strongly buttressed by the available epidemiological data. The relevant epidemiological studies are discussed in section II.B. below.

1. A Chemical Substance Which is Oncogenic In Laboratory Animals Must Be Considered To Pose A Risk of Cancer to Exposed Humans At Any Level Of Exposure

The Agency's assessment of the carcinogenic risk associated with the uses of 2,4,5-T and silvex is founded on principles developed and followed by EPA as well as other federal regulatory agencies and research institutions charged with measuring the risks associated with toxic chemicals in the environment. The Agency analyzes carcinogen risks in accordance with its "Interim Guideline for Carcinogen Risk Assessment" (Interim Guideline).*/ The policies described in the Interim Guideline are consistent with a recent report of the Interagency Regulatory Liaison Group (IRLG) entitled "Scientific Basis for Identification of Potential Carcinogens and Estimation of Risks" (IRLG Report).**/ The IRLG report reflects the consensus of scientists and policymakers of four major federal regulatory agencies, including EPA, which regulate carcinogenic

*/ U.S. Environmental Protection Agency. Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens. 41 F.R. 21402 (May 25, 1976).

**/ Work Group on Risk Assessment of the Interagency Regulatory Liaison Group (IRLG). 1979. Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks. 44 F.R. 39858-39879 (July 6, 1979).

substances as well as senior scientists from two major federal agencies involved in cancer research.*/

According to the Interim Guideline, the best evidence that a chemical substance is a human carcinogen comes from a combination of epidemiological studies on humans and experimental animal data. Substantial evidence is provided by animal tests which demonstrate that the substance induces in one or more animal species malignant tumors, or benign tumors which are generally recognized as precursors of malignant tumors. Suggestive evidence of a potential human cancer risk includes the induction in laboratory animals of non-life-shortening benign tumors which are generally considered not to progress to malignancy.**/

If epidemiological studies or animal tests indicate that a chemical substance is a potential human carcinogen, the

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*/ The four agencies comprising the IRLG at the time the IRLG Report was written were The Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA). The IRLG Report was written by scientists and policymakers from all these Agencies with the assistance of senior scientists from the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS). Scientists from the Food Safety and Quality Service of the Department of Agriculture, which subsequently joined the IRLG, reviewed and concurred in the report after it was completed.

**/ According to the IRLG Report, few if any benign tumor types are presently known to be incapable of progressing to malignancy.

Agency considers that substance to pose a carcinogenic risk to exposed humans at any level of exposure. As explained in the Preamble to the Interim Guideline, the Agency has adopted the no-threshold concept for cancer induction. According to this concept, any exposure to a carcinogen, however small, will confer some risk of cancer on the exposed population. The regulatory policy decision to adopt this concept is based on a consensus of scientific opinion and is supported by the IRLG Report.

2. Properly Designed Chronic Exposure Studies In Laboratory Animals Permit Assessment Of The Ability Of Chemicals To Produce Oncogenic Responses

The observation of a statistically significant*/ increase in the incidence of a particular type of tumor in laboratory animals exposed to a chemical substance as compared to the control animals**/ will generally be considered as evidence of

*/ An increase in the incidence of tumors in a treatment group is considered to be statistically significant if the probability that such an increase occurred only by chance is below a selected probability level, known as the "p" value. The probability level which is most commonly accepted as an indication of statistical significance is 0.05. Thus, if there is a 0.05 or less probability that an observed increase in tumors could have occurred by chance, that increase is generally recognized as being statistically significant. Scientists are ordinarily reluctant to draw more than tentative inferences from observed events which are not statistically significant. On the other hand, very strong inferences may be drawn from observed events, such as an increase in tumors, which are highly statistically significant (i.e., the "p" value is much smaller than 0.05).

**/Control animals are animals which are identical in every respect to the exposed animals, except for exposure to the test substance. Control animals are used as a point of reference against which the effects observed in the treated animals are compared.

the oncogencity of the substance in the species or strain of animal tested. This evidence is considered strong if there is a concomitant statistically significiant dose-response in the incidence of these tumors.*/ A statistically significant dose-response alone may be considered as suggestive evidence of an oncogenic effect. The importance of this latter type of response may be enhanced if the tumors involved are observed only rarely in the strain of animal used in the test.

Statistical and biological considerations require that tests of the oncogenicity of chemicals in laboratory animals meet certain standards to reasonably assure that possible oncogenic effects will not go undetected. In general, the substance being tested should be administered daily by an appropriate route of exposure (e.g., orally or on the skin), at several dose levels to separate groups of both male and female animals. Administration of the test substance to the animals should begin soon after the animals are born and should be continued during the entire lifetime or nearly the entire lifetime of the animal (i.e., the study should be a chronic toxicity study).

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*/ Demonstration of a "dose-response" involves the experimental finding that the incidence of tumors in each of the treated groups of animals shows an upward trend as dose is increased. A dose response is statistically significant if the probability that such an upward trend could have occurred by chance is less than the conventional probability level (usually 0.05).

The highest dose administered should be the maximum tolerated dose (MTD). The MTD is the highest dose, as determined by shorter term screening tests, which is not anticipated to cause significant life-shortening toxic effects. Control animals should also be maintained. In addition, samples of a sufficiently large number of different types of organs and tissues should be taken from all control and treated animals and examined both macroscopically (with the unaided eye) and microscopically (with a microscope). Other minimal standards include the use of a sufficiently large number of animals in the groups being dosed with the test substance and in the control groups, use of animals with low spontaneous tumor rates, and use of animals with good survival (i.e, animals which live to their life expectancy).

Any study which does not meet these minimum standards will be unnecessarily insensitive for purposes of detecting an oncogenic effect. The more severe the deficiencies in the design of the study, the more insensitive the study will be. Therefore, if a study which does not demonstrate an oncogenic effect suffers from severe deficiencies in design, that study cannot be considered to be valid evidence that the chemical substance tested is not oncogenic. On the other hand, the failure of a study to satisfy the minimum standards described above does not necessarily make a positive

oncogenic response unreliable. If the design only makes the study insensitive, then it is possible that the actual oncogenic potency of the tested substance may be considerably greater than indicated by the observed oncogenic response.

3. Chronic Animal Toxicity Studies Indicate That TCDD Is a Very Potent Oncogen Or Carcinogen In a Least Two Species Of Laboratory Animals.

a. Chronic Rat Studies Indicate that TCDD Is a Very Potent Carcinogen In Rats.

The results of two completed chronic studies and the preliminary results of one in-progress chronic study on TCDD indicate that TCDD is strongly carcinogenic at extremely low levels of exposure in rats. In a well conducted study by Kociba et al.,*/ orally administered TCDD induced significant increases of several types of carcinomas**/ and other tumors

*/ Kociba, R.J. et al. 1978. Results of two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. App. Pharmacol. 46: 279-303.

**/ The term "carcinoma" refers to a category of cancers which originate from epithelium (lining of internal and external surfaces of the body such as the skin and the lining of the gut and internal passages of the lung). There are several types of carcinomas, each of which is generally derived from different types of tissue. The nomenclature for these different types of carcinomas reflects the tissue of origin, e.g., squamous cell carcinomas of the tongue, hepatocellular (liver) carcinomas. "Sarcoma" is another category of cancer. Sarcomas are cancers which originate from connective tissue cells.

in both male and female rats at low dose levels.*/ The increases in some types of tumors, especially hepatocellular (liver) carcinomas and hepatocellular neoplastic nodules**/ in female rats, were very substantial and were consequently very highly statistically significant. Thus, the results of this study, standing alone, provide very strong evidence that TCDD is a very potent carcinogen in rats.***/

In a study by Van Miller et al.,****/ a significant increase in squamous cell carcinomas of the lung was observed in rats administered a very low oral dose of TCDD comparable to the

*/ In TCDD exposed female rats, statistically significant increases of hepatocellular carcinomas (liver cancers), hepatocellular neoplastic nodules, squamous cell carcinomas of the hard palate or nasal turbinates, and keratinizing squamous cell carcinomas of the lung were observed. In TCDD exposed male rats, statistically significant increases in stratified squamous cell carcinomas of the hard palate or nasal turbinates, squamous cell carcinomas of the tongue, and adrenal adenomas were observed.

**/ Hepatocellular neoplastic nodules are a type of liver neoplasm. These have been demonstrated to have the capacity to progress over time into liver cancers (hepatocellular carcinomas).

***/ The concept of potency is discussed in more detail in Section I.B.3.c. below.

****/ Van Miller, J.P., F.J. Lalich, and J.R. Allen, 1977. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere 6(10): 625-632. The ultimate use of this study in this hearing depends in part on the manner in which the Allen subpoena notice is resolved.

highest dose administered to rats by Kociba. In addition, a type of liver tumor which is very rarely found in rats (cholangiocarcinoma) was observed in some animals in the two highest dose groups. This study has certain shortcomings which tend to lessen the reliance which can be placed on its results. However, it does confirm the findings of the Kociba study that TCDD is a very potent carcinogen.

The preliminary results of another study on TCDD (National Cancer Institute, in-progress), also confirm the findings of the Kociba study. While full details are not yet available, the preliminary data suggest that TCDD is carcinogenic in rats at oral dose levels comparable to those used in the Kociba study.

b. Chronic Mouse Studies Strongly Suggest That TCDD Is a Potent Oncogen in Mice.

The oncogenicity of TCDD in mice has been strongly suggested by the results of one completed study and by the preliminary results of one in-progress study on mice. In the completed study, conducted by Toth et al.,*/ a statistically significant increase in liver tumors was observed in male mice administered a very low oral dose of TCDD once a week for a year (the middle dose) when comparison is made to the control group most similar to the TCDD-treated groups

*/ Toth, et al. 1979. Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. Nature 278: 548-549.

(the matched control group) and when comparison is made to the combination of four control groups (the pooled controls). An increase in liver tumors was also observed in the high dose group when comparison is made to the matched controls. Although this increase is not statistically significant, it is probably of biological significance because the average survival of animals in the high dose group was much less than that of animals in the matched control group.*/ These results, are highly suggestive of a TCDD-induced oncogenic effect.**/

The preliminary results of an in-progress National Cancer Institute cancer study on mice suggest that TCDD is carcinogenic in mice at very low oral dose levels. Therefore, this study appears to confirm the results of the Toth study.

c. The Chronic Animal Toxicity Studies on TCDD Indicate that TCDD is One of the Most Potent Animal Carcinogens Known.

The studies on TCDD provide substantial evidence that TCDD is a very potent oncogen in two species of laboratory

*/ Because there is a latency or lag period between the time of exposure to carcinogens and the induction of tumors, the longer an animal exposed to a carcinogen survives, the greater is the likelihood of an observed oncogenic response. In addition, the incidence of spontaneous, or background, tumors generally increases in control animals as survival increases. Therefore, when treated animals survive less well than the controls, any increase in tumors observed in the treatment groups becomes especially noteworthy as evidence of a chemically-induced effect.

**/ The published account of this study did not describe the type of liver tumors observed.

animals. Based on the Kociba study, the carcinogenic potency of TCDD appears to be greater than that of aflatoxin B_1, which is generally considered to be one of the most potent carcinogens known. This conclusion follows from a comparison of the carcinogenic potency of TCDD in the Kociba study on TCDD to the carcinogenic potency of aflatoxin B_1 in a chronic study by Wogan et al.*/ in which rats administered aflatoxin B_1 orally at very low levels demonstrated a significant increase of hepatocellular carcinomas. The respective carcinogenic potencies of TCDD and aflatoxin in the two studies may be estimated by a calculation which takes into account the lowest dose level at which each of the substances caused an observed carcinogenic effect, the incidence of animals with the type of tumor whose incidence was the most statistically significant at that dose level, and the spontaneous incidence of the same type of tumor in the control animals. On the basis of this calculation, it is estimated that TCDD is approximately four times more potent a carcinogen than is aflatoxin B_1 .

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*/ Wogan, G. et al. 1974. Carcinogenic effects of low dietary levels of aflatoxin B_1 in rats. Food Cosmet. Toxicol. 12: 681-685.

4. A Chronic Oral Rat Study on Specially Purified 2,4,5-T Containing no Detectable TCDD Suggests that Pure 2,4,5-T is Carcinogenic in Rats.

The results of a chronic toxicity study by Kociba et al.*/ on specially purified 2,4,5-T containing no detectable TCDD (level of detection = 0.33 ppb), provides suggestive evidence that even pure 2,4,5-T is carcinogenic. In this study, a marginally statistically significant dose-related increase in stratified squamous cell carcinomas of the tongue was observed in male rats administered oral doses of 2,4,5-T for up to two years. This is suggestive of a carcinogenic effect. It is unlikely that this effect was caused by any TCDD present in the 2,4,5-T used in this study; even if TCDD were present at the level of detection, the study was probably too insensitive to detect a carcinogenic response caused by such a low level of TCDD. Therefore, to the extent this study suggests a carcinogenic effect, that effect should be attributed to 2,4,5-T.

Although this study was generally well-designed, certain factors reduced its sensitivity for purposes of detecting a possible carcinogenic effect. These factors were the reduced survival of animals in all treated groups and the unusually

*/ Kociba, R.J. et al. 1979. Results of a two-year chronic toxicity and oncogenic study of rats ingesting diets containing 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T). Fd. Cosmet. Toxicol. 17: 205-221

high incidence of spontaneous tumors among the control animals.*/

5. Chronic Animal Studies on Commercial 2,4,5-T and Silvex Fail to Prove That These Substances are not Oncogenic

Several chronic animals toxicity studies have been conducted on commercial 2,4,5-T and a limited number of such studies on commercial silvex. With one possible exception,**/ no significant compound related increases of any specific tumor type were reported in any of the studies. However, all these studies suffer from deficiencies which made them insensitive for purposes of detecting oncogenic effects. In some cases, the deficiencies were very severe and the insensitivity very great. In addition, the reporting of the

*/ As explained above, there is a latency period between exposure to carcinogens and the induction of tumors by those carcinogens. Therefore, treated animals which die substantially earlier than their life expectancy may not exhibit tumors which they may otherwise have exhibited.

A high incidence of spontaneous ("background") tumors among control animals may make the detection of small increases of tumors in the treatment group impossible.

**/ The one possible exception was a study conducted by Leuschner et al. ("Chronic oral toxicity of 2,4,5-T Batch No. 503, Control No. 1535746 -- called for short '2,4,5-T' in Sprague-Dawley (SIV50) rats. Laboratorium fur Pharmakologie und Toxikologie, Hamburg, Germany, April 9, 1979). In this study a significant increase in interstitial cell tumors of the testes was observed in rats treated with the high dose of commercial 2,4,5-T when comparison was made to matched controls. However, another less appropriate control had a greater incidence of these tumors than was found in the high dose animals. Therefore, these results are considered ambiguous.

results and protocol of some of the studies was so incomplete that evaluation of those studies was impossible. Therefore, none of the chronic animal studies on commercial 2,4,5-T and silvex provide significant evidence of either the oncogenicity or non-oncogenicity of those compounds.

6. The Chronic Animal Toxicity Studies, Considered as a Whole, Provide Strong Evidence that Commercial 2,4,5-T and Commercial Silvex are Likely to Pose a Carcinogenic Risk to Humans at Any Level of Human Exposure

In accordance with the policies set out in the Interim Guideline and the IRLG Report and widely accepted by the scientific community, it must be concluded that the chronic animal toxicity studies on TCDD provide substantial evidence that TCDD is likely to be a potent cancer causing agent in humans and therefore poses a risk of cancer to humans at any level of exposure, no matter how small. This conclusion is based on the fact that the chronic animal studies without question demonstrate that TCDD is a potent carcinogen in rats and strongly suggest that TCDD is a potent oncogen in mice.

Moreover, because commercial 2,4,5-T and commercial silvex are unavoidably contamininated with TCDD, it must be concluded that these pesticides pose a risk of cancer to exposed humans at any level of exposure, no matter how small. TCDD levels in commercial 2,4,5-T and silvex are quite low. However, this is counterbalanced by the fact that TCDD is one of the most potent carcinogens known. Therefore, the cancer risks

posed by TCDD contaminants in commercial 2,4,5-T and silvex to exposed humans may be quite significant.

On the basis of suggestive evidence that purified 2,4,5-T causes cancer in rats, it must also be concluded that there is suggestive evidence that 2,4,5-T uncontaminated with TCDD is a potential cancer causing agent in humans. Thus, commercial 2,4,5-T may pose a risk of cancer to humans over and above that which is due to its TCDD contamination alone.

It should be noted that the animal toxicity studies constitute only one portion of the evidence implicating commercial 2,4,5-T and silvex as human carcinogens. The substantial evidence provided by these studies is strengthened still further by the epidemiological cancer studies discussed below.

C. Exposure to TCDD, 2,4,5-T and/or Silvex Produces Developmental Toxicity and Impairs Reproductive Function in Test Animals.

Laboratory studies indisputably establish that TCDD-contaminated 2,4,5-T and silvex, and TCDD alone produce fetotoxic and/or teratogenic effects in the embryos and offspring of test animals exposed to these chemicals during pregnancy, and reproductive dysfunction in animals exposed both before and during pregnancy. The effects regularly observed in test animals include birth defects such as cleft palate and abnormal kidneys, and fetal loss in the form of resorbed embryos, abortions, and stillborn animals. The animal species affected include mice, rats, hamsters, and monkeys.

Moreover, these effects occur at very low levels of exposure. In rodents such as mice and rats, evidence of developmental toxicity occurs when pregnant animals are exposed to doses as low as 10 mg/kg body weight 2,4,5-T (containing less than 0.5 ppb TCDD); 50 mg/kg body weight silvex (containing less than 0.05 ppm TCDD); and 0.001 ug/kg body weight TCDD. In rhesus monkeys, maternal doses of TCDD as low as 50 ppt in the diet (approximately 0.002 ug/kg body weight) resulted in reduced fertility and increased fetal loss. Similar and more severe effects have been observed at higher doses in all species tested. Furthermore, TCDD is fetotoxic at the lowest dose used in every species tested.

In assessing a chemical's potential for reproductive toxicity in humans, the scientific and regulatory communities

have traditionally relied upon results obtained in experimental animals as indicators of potential human risk. Tests for adverse reproductive effects are designed to study the effects of exposure to a given chemical on an animal's reproductive function and/or offspring.*/ Based on the results of the study, predictions are made concerning the likelihood of similar effects occurring in humans, taking into consideration inter-species differences between the experimental animal and man, and intraspecies differences among humans. Generally, the closer the experimental animal's reproductive system is to man's, the more reliable the study is as an indicator of human toxicity.

*/ The reproductive effects most often studied fall into two broad categories, maternal toxicity and fetotoxicity/teratogenicity. Signs of maternal toxicity include decreased weight gain, systemic disorders, abnormal behavior, and death. Fetotoxicity has been defined as "all transient or permanent toxic effects induced in an embryo or fetus, regardless of the mechanism of action"; teratogenicity as "an abnormality originating from an impairment of an event typical for embryonic or fetal development." (Neubert, D. et al. 1973. A Survey of the Embryotoxic Effects of TCDD in Mammalian Species. Environ. Health Pers. 5:67.)

Using these definitions, fetotoxicity would include teratogenicity. Common examples of fetotoxicity are reduced fetal weight and neonatal survival, abnormal organ weight, delayed growth and maturation, and increased fetal wastage (abortions, resorptions, stillbirths). Teratogenicity would include grossly observable birth defects such as cleft palate, club foot, and exencephaly, as well as internal defects such as extra ribs or changes in kidney structure. However, use of the terms does not follow a consistent pattern. For example, "teratogenicity" is often used as the generic term (death being the ultimate birth defect), or "fetotoxicity"

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Two types of studies are generally used to assess reproductive toxicity. Each is designed to mimic a human exposure situation. Teratogenic studies are used to test the effects upon the offspring of short-term maternal exposure during a critical phase of pregnancy. In these studies dosing occurs for varying periods of time during fetal organ development, and maybe as short as a single maternal exposure. These experiments are designed to maximize the production of birth defects; however, fetal mortality, lowered birth weight, and other forms of fetotoxicity are also observed and evaluated.

Reproduction studies are designed to study the effects of long-term exposure on the reproductive process. In these studies, animals (often both males and females) are dosed over an extended period of time, beginning before mating. Dosing is often continued through several generations. The goal of reproduction studies is to evaluate the effects of long-term exposure on many different reproductive parameters. These studies are designed to measure and evaluate fertility, birth defects, survival, growth, and other forms of fetal and maternal toxicity.

(FOOTNOTE CONTINUED FROM PREVIOUS PAGE)

is used to define adverse effects exclusive of birth defects. "Developmental toxicity" is another generic term which is being used with more frequency, because it includes all types of adverse effects (physical, mental, behavioral) experienced from conception through the post-natal developmental stages.

If animal testing shows that adverse reproductive effects are produced at the lowest dose used, and that that dose is extraordinarily low, there is no basis on which to make a prediction about human reproductive risk. This is exactly the situation posed by TCDD. At one billionth of a gram,*/ the lowest dose tested in any species, maternal exposure to TCDD produces significant adverse effects on the offspring, such as reduced neonatal survival and an increased incidence of kidney anomalies. With an effect level this low, it must be assumed that even an infinitely small amount of TCDD could still be toxic. If it is impossible to assess human risk from TCDD alone, it is equally impossible to evaluate the potential human hazard from 2,4,5-T and silvex, which are contaminated with TCDD. Therefore, any exposure to 2,4,5-T and silvex should be considered hazardous.

1. TCDD, 2,4,5-T and Silvex Produce a Broad Spectrum of Reproductive Effects in Mammalian Test Species.

Studies in mammalian species clearly demonstrate that maternal exposure to TCDD, 2,4,5-T and/or silvex**/ results in toxicity to the offspring of treated animals. Fetotoxic and

*/ In more familiar terms, this is roughly the fractional equivalent of one ounce in 31,000 tons.

**/ Varying amounts of TCDD have contaminated the 2,4,5-T and silvex used in the studies, therefore reference to "2,4,5-T" or "silvex" actually means a combination of either of these compounds with TCDD. In the more recent studies, the TCDD contamination has been 0.05 ppm or less.

embryolethal effects occur in all species tested, including at least eight mouse strains, four rat strains, hamsters, and one subhuman primate. The most commonly observed effects are increased fetal mortality, intestinal bleeding, reduced neonatal survival and higher incidences of birth defects, such as cleft palate, kidney anomalies, and reduced hardening of the skeletal bones.*/ Increased fetal wastage, in the form of resorbed fetuses, abortion or stillbirth, is routinely observed in all species tested. Moreover, adverse effects on the fetus related to TCDD exposure have been observed at doses as low as 0.001 ug/kg body weight in mice and rats, and 0.002 ug/kg body weight in monkeys. Adverse effects related to 2,4,5-T or silvex exposure have been seen at 2,4,5-T doses as low as 10 mg/kg in rats, 15 mg/kg in mice, and 40 mg/kg in hamsters; and at silvex doses as low as 50 mg/kg in rats.

There is also some evidence that TCDD, or TCDD with other polychlorinated dibenzodioxins (dioxins),**/ affects the normal

*/ In addition to the commonly observed anomalies, silvex also produces cardiovascular abnormalities in rats.

**/ Available experimental data indicate that the polychlorinated dibenzodioxins produce qualitatively the same types of toxicity; however, the toxic potency varies with the number and position of the chlorines. To date, TCDD has been shown to be the most toxic dioxin.

functioning of the reproductive systems of both male and female test animals. In two studies, female monkeys exposed to TCDD prior to mating had reduced fertility rates, and failed to conceive even after repeated attempts at mating.*/ In another study, male monkeys fed "toxic fat," containing TCDD and other dioxins, exhibited reduced spermatogenesis.**/ Testicular anomalies and dysfunction have been observed in several rodent studies. Although these data are not conclusive, the results warrant concern regarding the possible effects of TCDD on reproductive function in adults, as well as its potential effect on their embryos and offspring through this route.

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*/ Barsotti, D.A., Abrahamson, L.J. and Allen, J.R. 1979. Hormonal Alterations in Female Rhesus Monkeys Fed a Diet Containing 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Bull. Environ. Contam. Toxicol. 21: 463-469.

Schantz, S.L., Barsotti, D.A. and Allen, J.R. 1979. Toxicological Effects Produced in Nonhuman Primates Chronically Exposed to Fifty Parts per Trillion 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Abstract of paper presented at the Eighteenth Annual Meeting of the Society of Toxicology on March 11-15, 1979. Personal Communications to EPA.

**/ Allen, J.R. and L.A. Carstens. 1967. Light and Electron Microscopic Observations in Macaca mulatta Monkeys Fed Toxic Fat. Am. J. Vet. Res. 28:1513-1526.

Finally, the results in two different test species suggest that exposure to TCDD in combination with 2,4,5-T results in an effect greater than the effect of either of the two compounds given separately. In rats, a significantly increased incidence of cleft palate was observed after combined exposure.*/ However, giving the same amount of either 2,4,5-T or TCDD separately did not result in any cleft palate.**/ A similar increase in cleft palate as a result of combined exposure has been seen in mice.***/ These results suggest that these chemicals are even more toxic in combination than separately, a fact which is of particular significance because commercial 2,4,5-T is always a combination of 2,4,5-T and TCDD.

2. Non-human Primate Studies are of Particular Significance.

Non-human primates are especially appropriate for evaluating the potential for human reproductive effects because of the fundamental similarities between the reproductive systems of man and

*/ Although either 2,4,5-T or TCDD alone produces cleft palate in mice, cleft palate occurs in rats only when the two compounds are given in combination.

**/ Sparchu, G.L. et al. 1971. The Effects of Various Doses of 2,3,7,8-Tetrachlorodibenzo-p-dioxin Administered with 2,4,5-Trichlorophenoxyacetic Acid on Rat Fetal Development. The Dow Chemical Co. Unpublished.

***/ Neubert, D. and Dillman, I. 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.

other primates.*/ Consequently, data from reproductive studies in non-human primates are particularly important. In the present instance, studies with the rhesus monkey are of primary importance because they are the only primate reproductive studies done with TCDD and 2,4,5-T.**/

Reproductive maturation in the rhesus monkey closely parallels that in humans, with both species experiencing the onset of menstruation, fertility, and menopause at comparable stages of the life cycle. Physically, the monkey uterus, placenta and fetal supportive structures are comparable to those in humans; implantation of the ovum and development of major organs follow similar time courses, occurring in the first third of the

*/ The value of primate studies, does not in any way negate or reduce the significance of results obtained in other species. Each study has its own purpose and requirements. Because certain physiological characteristics are common among mammalian species, other factors may weigh more heavily in the selection of the best species for a given study. For example, use of primates in large-scale or screening studies is both too expensive and too unwieldy. The same arguments would apply where confirmation of a very low incidence teratogenic effect is sought.

**/ Although there are other primates physiologically more similar to humans than the rhesus monkey, for practical reasons, the rhesus monkey is the primate which has been used most extensively in toxicological research. Research with more similar primates has been greatly hampered by several factors. For example, experimental use of chimpanzees is severely limited by exorbitant cost, limited availability, and restrictions on experimental design, such as prohibition on sacrificing animals solely to study effects on internal organs and tissues.

gestational period. In addition, the monkey's balance of the reproductive hormones, estrogen and progesterone, is almost identical to the human system, both in the menstrual cycle and in pregnancy. The ability of the placenta to take over from the ovaries and continue the production of the hormones necessary to maintain pregnancy is common to both. In both species, changes in the normal hormonal patterns have been associated with fetal distress, abortions, and menstrual irregularities.

Data showing that TCDD exposure impairs the reproductive capacity of rhesus monkeys constitute a significant indicator of possible human hazards. Long-term exposure to even minute quantities of TCDD results in an increased incidence of early abortions and reproductive dysfuntion, even where there is no evidence of maternal toxicity. In the reproductive phase of an ongoing study, monkeys exposed to 50 ppt TCDD in the diet (approximately 0.002 ug/kg before body weight and during pregnancy had a fertility rate of 75% (6/8), compared with 100% in the controls. Total fetal loss was 67% in the treated group (3 abortions and 1 stillbirth in 6 conceptions) compared to 0% in the controls. Attempts to re-breed one of the females which had aborted resulted in an additional abortion.*/

*/ Schantz, S.L. et al., 1979. The experiment is designed to study the total effect of chronic exposure to 50 ppt TCDD, and to compare the results with those obtained in the earlier study at 500 ppt. Reproductive function is one of the parameters being evaluated. The ultimate use in this hearing of information from this study will depend in part on the manner in which the Allen subpoena motion is resolved.

In an earlier study, of the eight female monkeys were exposed to 500 ppt TCDD in the diet (approximately 0.02 ug/kg body weight), only one animal was able to carry her infant to term. The fertility rate was 43% (3/7), with two of the subsequent pregnancies ending in abortions. In contrast, all of the eight control animals conceived and delivered healthy infants. Irregularities in menstrual cycles, including anovulation, and reduction in estrogen and progesterone were among the toxic effects seen in the treated group.*/ One of the animals was not bred because of general debilitation and anovulatory hormone levels; one animal died within a month of the beginning of the breeding program. The investigators concluded that the excessive infertility and other reproductive problems suffered by these animals were most likely the result of hormone imbalance, and were apparently the result of the TCDD treatment, rather than general toxicity. This is because the hormonal alterations and reproductive failure were observed before the animals became obviously ill.**/

Reproductive failure is also seen in rhesus monkeys where TCDD exposure occurs for only a short period of time during the

*/ After approximately two years of dietary treatment, the 50 ppt animals are showing signs of systemic toxicity and menstrual irregularities comparable to those observed in the 500 ppt animals at shorter exposure. The investigators are now treating animals with lower doses.

**/ Barsotti, D.A. et al., 1979.

pregnancy. An accumulated dose of 1 ug/kg TCDD (approximately 1000 ppt) over a three-week period resulted in a 75% (3/4) abortion rate, compared with 0% in the controls. All abortions were early in the gestational period, and the only evidence of maternal toxicity was slight chloracne in one animal, first observed after the abortion. The viable offspring produced at this dose had abnormal soft palate development, and three of the four at a lower dose had suggestive anomalies in the same facial region.*/

When viewed as a whole, the primate studies indicate that TCDD exposure presents a potential hazard for females of all ages (i.e., the hormonal/menstrual changes and low fertility demonstrated in the long-term studies), and a particular hazard for the unborn children of pregnant women (i.e., the increased abortions demonstrated in both the short- and long-term studies).

3. TCDD is Fetotoxic at the Lowest Dose Used in the Three Species Tested.

TCDD has been tested for fetotoxic effects in three species, mice, rats, and monkeys, and adverse effects have been reported for all three species at the lowest dose level to which each species has been exposed.

*/ McNulty, Wilbur P. Personal Communications to EPA dated July 27, 1978 and January 29, 1979.

In a study in which two sets of mice were treated with 0.001 ug/kg body weight on days 6-15 of gestation, one set experienced a higher incidence of resorptions among the treated mothers than in the controls.*/ Rats in a three-generation study exposed to the equivalent of 0.001 ug/kg body weight exhibited increased incidences of kidney anomalies and still--births, and decreased neonatal survival.**/ In the rhesus monkey study previously discussed, animals subchronically exposed to the equivalent of 0.002 ug/kg body weight had lower fertility and a higher rate of abortions than control animals.***/

In the rat and mouse studies, statistically significant effects were observed at the lowest dose of TCDD tested.

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*/ Smith, F.A., Schwetz, B.A. and Nitschke, K.D. 1976. Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin in CF-1 Mice. Toxicol. Appl. Pharmacol. 38: 517-523. A second set of animals was treated with 0.001 ug/kg because the original set exhibited an unusually high incidence of exencephaly (a birth defect characterized by an imperfect cranium, with the brain outside the skull). Although the investigators did not consider the incidence of exencephaly significant, calculations by an Agency contractor resulted in a "p" value of 0.051 as compared to the 0.05 value traditionally accepted as indicating statistical significance. When dealing with a birth defect of this magnitude, which usually results in stillbirth or very early death, results should not not be ignored because they fall short of the mathematical goal of significance by one-tenth of a percent.

**/ Murray, F.J. et al. 1979. Three Generation Reproduction Study of Rats Given 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in the Diet. Toxicol. Appl. Pharmacol. 50: 241-252.

***/ Schantz, S.L. et al., 1979.

However, in some instances dose-response relationships were not observed and/or the effect was not evident throughout the entire three-generation study. Several possible explanations for these observations could be offered, including (1) the number of animals used in the study was too small to reliably demonstrate the effect at all times; (2) the animals' detoxification mechanisms have adjusted to the dose over several generations; (3) abnormal control values have masked the detection of other effects; and (4) the dose is so close to the no-observed effect level (NOEL) that erratic effects are the result.*/ Regardless of the explanation, the Agency cannot ignore the warning sounded by the data. TCDD is one of the most toxic chemicals known. Its degree of toxicity, and its toxic manifestations, vary among the animal species, and its effects on the human reproductive system are largely unknown.

In addition, and most important, the effects observed at these low doses are comparable to those consistently observed

*/ The FIFRA Scientific Advisory Panel (Panel) used the fourth of these explanations in its assessment of the low-dose rodent studies. While agreeing that a NOEL has not been established for monkeys, and recognizing the existence of effects at 0.001 ug/kg, the Panel concluded that "for all practical purposes" a NOEL had been shown for TCDD in studies with rats and mice. Although the Panel interpreted the results in rodents at 0.001 ug/kg as suggestive of a NOEL, the Agency has assumed a more conservative position, and interprets the sporadic results as indicating a level of response which is relatively close to the minimum level which the study is able to detect. Whether it actually is close to the NOEL is dependent upon an as yet unknown dose-response relationship.

at higher doses and in other species. This is clearly demonstrated in the three-generation rat study cited above. At the highest dose level used, 0.1 ug/kg, the fertility and live birth rates were so severely reduced in the first generation that this dose level was discontinued. Significantly reduced survival was also seen at the lower dose levels. Among the first generations (first litters), 100% of the pups from mothers treated with 0.1 ug/kg, 13% from the 0.01 ug/kg mothers and 8% from the 0.001 ug/kg mothers had died within 24 hours of birth, compared with 1% in the controls. By 21 days after birth, the neonatal death rate was 32% at 0.01 ug/kg and and 16% at 0.001 ug/kg, compared with a control rate of 7%. In addition, statistically significant increases in dilated renal pelvis, an effect regularly reported in animals exposed to 2,4,5-T and TCDD, were seen in the weanlings of the 0.001 ug/kg group. Most significantly, this defect also appeared in all three of the offspring surviving maternal exposure to 0.1 ug/kg, when they were examined as adults. It would be irresponsible for the Agency to assume that these effects seen at 0.001 ug/kg are merely statistical artifacts and insignificant to risk assessment.

Generally, a NOEL is viewed as a toxicological endpoint, making a level of exposure in animals which is "safe" because there are no observed adverse effects. Toxicologists generally assume that the animal NOEL can serve as a base for

estimating exposure levels which would be "safe" for humans. The "safe" level for humans is set at some level lower than the animal NOEL to provide a "margin of safety" that takes into account differences in sensitivities between experimental animals and humans, and differences in sensitivities among humans. This "margin of safety" approach does not guarantee that the risk to humans is inconsequentially small. Error could be introduced because man is more sensitive than the test species by a greater factor than normally allowed, or by the incorrect choice of a NOEL. The thalidomide tragedy is probably the best known example of error in predicting human safety from animal data. There, although rodent testing indicated that a "safe" level could be predicted, when humans used the drug it became clear that the dose assumed to be safe when considered in terms of the animal test data was, in fact, dangerously toxic to the human fetus.*/

The lowest level at which TCDD has no-observed reproductive effects in test animals is crucial to the Agency's determination of the risk potential of 2,4,5-T and silvex. TCDD is present in these pesticides as a low-level contaminant and thus will be present in the environment at low levels whenever and wherever these pesticides are used. If there really is a no-effect level in animals for reproductive effects it is

*/ Subsequent studies in non-human primates indicated that the sensitivity of the rhesus monkey to thalidomide is comparable to that of the human.

possible to at least to begin to estimate a possible "safe" level for humans as to these effects, and to assess the potential reproductive risk to humans by relating this assumed "safe" level to the level of pesticide that may be in the environment, if that level is known.*/ Conversely, if there is no no-effect level, any use of 2,4,5-T and silvex would result in potentially significant exposure to TCDD, because there is no minimum level upon which to estimate a margin of safety.

In summary, it is unequivocal that exposure to TCDD, 2,4,5-T, and/or silvex results in reduced fertility, fetal death, birth defects and other forms of reproductive toxicity in mammalian test species. The effects of these substances upon human reproductive functions are unknown. However, an increased incidence of abortions has been reported among women exposed to the TCDD-containing herbicides, 2,4,5-T and silvex. This is precisely the same effect observed in non-human primates exposed to very low levels of TCDD.

Morever, in each of the three species in which TCDD has been tested, adverse effects have been observed at the lowest dose used. Accordingly, a no-observed-effect level has not been established. The lack of a known no-observed-effect level in test animals means that it is impossible to evaluate the full toxic potential of TCDD, and therefore, a "safe" level

*/ Such a "safe" level of exposure, if it were possible to establish, would, of course, apply only to reproductive effects. No level of exposure to a carcinogen can be regarded as "safe". See Section I, supra.

of human exposure cannot be estimated. This, taken with the human epidemiological evidence, makes it abundantly clear that every human exposure to TCDD, and therefore to 2,4,5-T and silvex, must be considered extremely hazardous.

D. Exposure to TCDD Produces Adverse Effects on the Immune Systems of Test Animals

Studies in rats, mice, guinea pigs, rabbits, and monkeys show that adverse effects on the immune system are one of the most consistent and sensitive parameters of TCDD exposure. In terms of possible human health consequences, adverse effects on the immune system can lead to or increase the risk of disease, incapacity, or death in the exposed person or the offspring of such persons. The repeated complaints of "flu-like" symptoms, such as aching muscles, respiratory problems, gastrointestinal symptoms, general weakness and debilitation, and reduced resistance to disease which persons alleging exposure to 2,4,5-T and silvex attribute to these herbicides mandate particular attention to the observations in laboratory animals.

Animals exposed to of TCDD exhibit adverse effects, primarily thymic atrophy, */ at doses well below those inducing toxic effects in other organs. Suppression of cell-mediated immunity, **/ particularly in young animals, appears to be the

*/ The thymus appears to be a master organ, important in the development of the immune system in the young, and in controlling immune responses throughout life. Other important organs in the immune system are the spleen and the lymph nodes.

**/ Cell mediated immunity includes the following immune processes: (1) classical protective immunity which is predominately effective against fungi, viruses, and some bacteria; (2) delayed hypersensitivity which is involved in graft rejection, tuberculin hypersensitivty, antimicrobial immunity, and contact dermatitis; and (3) the rejection of tumors and foreign tissues such as transplants.

most significant symptom of the TCDD effect on the immune/lymphoid system. Levels of TCDD which do not produce overt clinical or pathological changes still reduce host defenses. Mice exposed to 1 ug/kg once a week for four weeks demonstrated a markedly decreased resistence to Salmonella infection, in the form of increased mortality and decreased time from infection to death, prior to any observed thymic atrophy.*/ In other experiments, lymphopenia (reduction in number of lymphocytes), increased suspectibility to a bacterial toxin, decreased sensitivity to tuberculin, and prolonged allograft rejection times have been among the observed effects.**/

Maternal treatment with TCDD during the latter half of gestation results in adverse effects on the offspring, such as depletion of lymphocytes and impaired cellular immunity. Moreover, the reduction of thymus-dependent immune functions as a result of exposure of the developing immune system to TCDD appears to be a lasting effect. A significant reduction

*/ Thigpen, J.E., Faith, R.E., McConnell, E.E., and Moore, J.A. 1975. Increased Suspectibility to Bacterial Infection as a Sequela of Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Infect. Immu. 12: 1319-1324.

**/ A recent confidential report from Dow Chemical Company indicates that immunotoxicologic effects have been observed at doses even lower than the 1 ug/kg/week cited above.

in delayed hypersensitivity was detected 145 days after birth in rats perinatally exposed to TCDD.*/

In monkeys, animals fed 500 ppt TCDD for nine months became anemic within six months, and pancytopenic**/ after nine months of exposure. Death occurred in 65% (5/8) of the animals after 7-12 months of exposure. At autopsy, in addition to extensive hemorrhage, there were distinct decreases in the normal number of cells present in the bone marrow and lymph nodes.***/

In summary, TCDD acts on the immune systems of test animals, causing thymic atrophy and suppression of immune responses. At present, it is unclear whether the "flu-like" symptoms and lowered resistance complained of by people alleging exposure to 2,4,5-T or silvex are manifestations of TCDD-induced immune function impairment. However, these effects could be signs of immunosuppression, and the possibility of a relationship between the symptoms and TCDD exposure is real enough to warrant concern.

*/ Faith, R.E. and Moore, J.A. 1977. Impairment of Thymus-Dependent Immune Function by Exposure of the Developing Immune System to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). J. Toxicol. Environ. Health 3: 451-464.

**/ "Pancytopenic" means exhibiting reduction of all three elements of blood: erthrocytes (red blood cells), leukocytes (white blood cells), and blood platelets.

***/ Allen, J.R. et al. 1977. Morphological Changes in Monkeys Consuming a Diet Containing Low Levels of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin. Fd. Cosmet. Toxicol. 15: 401-410.

Summary

Toxicity studies on laboratory animals clearly demonstrate that 2,4,5-T, silvex, and TCDD induce a wide range of adverse effects in several animal species. These adverse effects include cancer, impairment of reproductive function, suppression of immunological defenses against disease, liver dysfunction, and other harmful effects. The induction of several of these effects has been observed in laboratory animals administered exceedingly low doses of TCDD, indicating that TCDD has extremely great toxic potency. For example, the animal studies indicate that this substance is one of the most potent cancer-causing agents known. Moreover, there has not been demonstrated a level of exposure to TCDD below which adverse reproductive effects do not occur. Thus, it must be concluded that there is no "safe" level of human exposure to 2,4,5-T, silvex, and TCDD, and that these substances may pose significant health risks to exposed humans at exceedingly low levels of exposure.

II. Epidemiological Studies Indicate that Human Populations Exposed to 2,4,5-T and TCDD Experience an Increased Risk of Cancer and Reproductive Disorders.

At least six recent separate epidemiological studies have found a significant relationship between exposure to 2,4,5-T, silvex and/or TCDD and cancer or reproductive disorders in human populations.*/ These epidemiologic findings are especially meaningful because they appear in several separate human populations and because the same types of adverse health effects have also been observed in experimental animals. Moreover, because negative epidemiologic findings may be consistent with an actual health effect of considerable magnitude, detection of a statistically significant increase in risk of cancer in several different populations is impressive evidence of a human health hazard.

A. Epidemiological Evidence is a Reliable Indicator of Human Risk.

Epidemiology is the study of the distribution and determinants of disease in human populations. Rather than relying on direct experimental evidence,**/ epidemiologists seek to identify and study "natural experiments," or situations

*/ Other disorders have been observed in human and animal populations. For example, more than 60 horses died and humans and other animals experienced a wide range of adverse health effects upon exposure to TCDD-contaminated oil. Kimbrough, R.D., C. Carter, J.A. Liddle, R.E. Cline, P.E. Phillips. 1977. Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Arch. Environ. Health 32(2): 77.

**/ Deliberate clinical exposure of humans to suspected toxic agents is generally regarded to be ethically unacceptable. See, e.g., EPA Order 1000.7.

in which groups of people have been exposed to suspected causative agents as part of their occupational or residential environment. The best epidemiological evidence of the effects of exposure to a toxic chemical is often found in an occupational context, where exposures tend to be substantial and protracted, and work place monitoring data are often available for comparison with employee health records.

Epidemiological data are recognized as valuable indicators of the risks associated with human exposure to toxic chemicals. In recent years, regulatory agencies have increasingly relied on epidemiological information as a means of identifying human exposure hazards. Moreover, the courts have consistently and explicitly endorsed administrative reliance on epidemiological data.*/

To be sure, epidemiological studies have certain fundamental limitations. Unlike studies with experimental animals or human test subjects, epidemiological studies cannot be designed and controlled in advance of exposure. As a consequence, methods of study design and statistical analysis must be utilized to minimize the influence of factors which might otherwise lead to spurious or misleading results. However, once the most likely sources of bias and confounding have been identified and, to the extent possible, controlled,

*/ See, e.g., American Iron and Steel Institute v. OSHA, 577 F. 2d 825, 831-2 (D.C. Cir., 1978); Ethyl Corp. v. EPA, 541 F. 2d 1, 26, 42-3 (D.C. Cir., 1976); Reserve Mining Co. v. EPA, 514 F. 2d 492, 507-9, 514 (8th Cir., 1975); Society of Plastics v. OSHA, 509 F. 2d 1301, 1308 (2d Cir., 1975).

a statistically significant excess risk or excess incidence of adverse effects in an exposed human population must be regarded as compelling evidence of human toxicity. Thus, in Ethyl Corp. v. EPA, the D.C. Court of Appeals affirmed the EPA Administrator's reliance on an epidemiological study indicating a relationship between exposure to automobile exhaust and blood lead levels in children, even though the children's prior exposure to lead paint could not be controlled or measured. The Court noted,

> Of course, the results were "only" a statistical correlation; such are the results of all epidemiological research. But the Newark study presented a strong correlation, consistent with an existing theory that makes biological sense and with existing evidence. Such data are worthy of great respect, and may even be taken as casual proof. [Emphasis added] 541 F. 2d at 65.

Scientists usually evaluate the significance of epidemiological findings by estimating the probability that the observed result could have come about by chance. Standard statistical tests are available for this purpose. The role of chance is usually expressed as "p," the probability that the observed result could have arisen simply by random variation, rather than as a result of exposure to the suspected causative agent. Values of "p" less than .05 are usually considered to indicate an acceptably low probability of chance association. The results in each of the six recent epidemiological studies satisfy this criterion of statistical significance.

Epidemiological findings based on human experience and toxicological data derived from controlled laboratory experiments complement one another. The Agency's Interim Guidelines on cancer risk assessment*/ state that, "The best evidence that an agent is a human carcinogen comes from epidemiological studies in conjunction with confirmatory animal studies." This observation need not be restricted solely to cancer. Whatever the health effect, the best available evidence of the toxicity of a chemical is provided by corroborative results from epidemiologic studies and laboratory experiments.

Receipt of positive data from both toxicological and epidemiological sources is especially meaningful because each type of data contributes different kinds of information for use in assessing risk. While the laboratory scientist can control many aspects of the environment in which test animals are studied, the epidemiologist must employ study design and statistical analysis techniques to minimize the impact of uncontrolled confounding variables. On the other hand, while the epidemiologist can measure human responses to suspected toxic chemicals, the toxicologist utilizes assumptions and models to assess the significance for human health of data developed in animal populations.

The complementary relationship between epidemiologic and laboratory data can be illustrated by comparing the health effects data reported for human and animal populations which have been

*/ Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens, 41 FR 21402 et seq., May 25, 1976.

exposed to the same toxic chemical. Indeed, the International Agency for Research on Cancer utilizes epidemiological evidence demonstrating that a substance is a human carcinogen as a basis for assessing the reliability of corresponding animal data. The extent of agreement is striking. Of more than 20 chemicals identified as human carcinogens in epidemiologic studies, only arsenic has not yet been shown to produce cancer in experimental animals.*/

B. Cancer Risk is Increased in Populations Exposed to 2,4,5-T and TCDD.

A growing body of epidemiological evidence establishes a clear association between exposure to 2,4,5-T and/or dioxin and carcinogenic effects in humans. Four separate studies linking exposure to 2,4,5-T and TCDD to two types of human cancer are now available.**/ This evidence confirms the toxicological studies in which TCDD was

*/ Tomatis, L. 1977. The value of long-term testing for the implementation of primary prevention. In: Hiatt H. H., et al. eds. Origins of Human Cancer, Coldspring Harbor Laboratory.

**/ A fifth study demonstrating a significant excess relative risk of malignant lymphomas among individuals exposed to phenoxy herbicides (including 2,4,5-T) has just been completed and will be published by Hardell et al. in a Swedish journal. Pending receipt and translation of the text of this new study, Agency counsel will defer further discussion of its content. The clinical observations which resulted in initiation of the study are described in Hardell, L., 1979. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols, Lancet 1 (8106): 55-56.

shown to be carcinogenic in animals and reinforces Agency concern about the oncogenic properties of pesticide products containing 2,4,5-T and silvex.

1. Case-Control Studies Demonstrate a Significant Excess Risk of Soft-Tissue Sarcomas for Individuals Exposed to Phenoxy Herbicides (Including 2,4,5-T) and to Other Dioxin-Contaminated Chemicals

Two recent case-control studies*/ of the relation between cancer and occupational exposure to phenoxyacetic acids and chlorophenols present persuasive evidence that human exposure to pesticide products containing 2,4,5-T and/or dioxin constitutes a carcinogenic hazard. Each of these new studies found statistically significant increases in the risk of malignant mesenchymal tumors of the soft-tissue (soft-tissue sarcomas) related to occupational exposure to phenoxy herbicides and to occupational exposure to chlorophenols. Each study utilized an entirely separate population of cases and controls, and the studies thus clearly corroborate and replicate one another.

*/ In a matched case-control study, the investigator initially identifies a group of individuals who have a disease (cases) and selects for each case a set of individuals who do not have the disease (controls) and who have otherwise similar characteristics (sex, age, place of residence, etc.). The relationship between a particular type of exposure and the risk of the disease in question can then be analyzed by establishing the prior exposure history of each subject and calculating the relative risk, which is the rate at which the disease develops in exposed persons divided by the rate at which the disease develops in persons who have not been exposed.

In a case-control study of the risk of soft-tissue sarcomas in a population in Northern Sweden which includes forestry, sawmill, and paper pulp workers,*/ Hardell and Sandstrom found that individuals previously exposed to phenoxyacetic acid herbicides, primarily 2,4,5-T and 2,4-D, had a relative risk for soft-tissue sarcomas 5.3 times greater than unexposed individuals.**/ They also found that individuals previously exposed to chlorophenols, which like 2,4,5-T and silvex contain chlorinated dibenzodioxins as impurities, had a relative risk for soft-tissue sarcomas 6.6 times greater than unexposed individuals. Each of these findings was highly significant in statistical terms. In both instances, p was less than .001, indicating that the observed relative risk would occur by chance alone less than one time in a thousand.

Soft-tissue sarcomas are a rare variety of cancer. A case-control study like the one conducted by Hardell and Sandstrom is generally recognized as the most effective epidemiologic method for documenting the relationship between a particular causative factor and a rare type of tumor. The protocol used by Hardell and Sandstrom in selecting controls

*/ Hardell, L. and Sandstrom, A., 1979. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols, Brit. J. Cancer 39: 711-717.

**/ Although Hardell and Sandstrom did not calculate a separate relative risk for individuals previously exposed to 2,4,5-T, this figure may be readily derived from their data. Individuals exposed to 2,4,5-T had a relative risk for soft-tissue sarcomas 5.2 times greater than unexposed individuals (p less than .001).

excluded confounding factors such as sex, age, place of residence, and year of death. In addition, the authors evaluated the possible confounding effect of factors such as occupation, smoking habits, DDT exposure, and exposure to exhaust from motorized sawing and found no evidence that any of these factors accounted for the observed increase in relative risk. Thus, it is extremely unlikely that the results obtained by Hardell and Sandstrom were materially affected by uncontrolled confounding factors or other defects in the design or execution of the study.

In a subsequent case-control study in an entirely separate population in southern Sweden*/, Eriksson et. al. found that individuals previously exposed to phenoxy herbicides had a relative risk for soft-tissue sarcomas 6.8 times greater than unexposed individuals (p less than .001).**/ They also found that individuals previously exposed to chlorophenols had a relative risk for soft-tissue sarcomas 3.3 times greater than unexposed individuals (p less than .01). Thus, the

*/ Eriksson, M., Hardell, L., Bern, N., Moller, T., and Axelson, O., 1979. (In Swedish) Case-control-studie over maligna mesenkymala mjukdelstumorer och exposition for kemiska substanser, Lakartidningen 76:3872-5 (EPA translation available).

**/ Although Eriksson et al. did not calculate a separate relative risk for individuals previously exposed to 2,4,5-T, this figure may be readily derived from their data. Individuals exposed to 2,4,5-T had a relative risk for soft-tissue sarcomas 17.0 times greater than unexposed individuals (p less than .001).

results in the case-control study by Eriksson et.al. confirm and essentially replicate the results obtained by Hardell and Sandstrom.

2. Cohort Studies Demonstrate a Significant Excess Incidence of Stomach Cancer Among Workers Exposed to Phenoxy Herbicides (Including 2,4,5-T) and to TCDD.

Studies of the incidence of disease in cohorts*/ of exposed workers provide additional evidence that human exposure to pesticide products containing 2,4,5-T and/or TCDD constitutes a carcinogenic hazard. Two separate epidemiological studies of cohorts of workers exposed to 2,4,5-T and to TCDD have each documented a statistically significant increase in the incidence of stomach cancers among such workers.

In a recent updating**/ of an initially inconclusive study of mortality and tumor incidence in a cohort of Swedish

*/ In a cohort study, the investigator compares the incidence of disease over time among a discrete group of individuals (cohort) who have previously been exposed to a particular chemical agent to the incidence of disease in a reference group of individuals who have not been exposed to the agent or have been exposed to a lesser degree.

**/ Axelson, O., Edling, C., Kling, H., Andersson, K., Högstedt, C., and Sundell, L., 1979. (In Swedish) Uppdatering av mortaliteten hos bekampningsmedelsexponerade banarbetare, Lakartidningen 76:3505-6 (EPA translation available).

railroad workers,*/ Axelson et al. reported a significant excess incidence of stomach cancer among those workers first exposed to phenoxy herbicides more than ten years earlier. Individuals in the Axelson cohort had previously been exposed to a number of herbicides, particularly phenoxyacetic acids (including 2,4,5-T) and amitrole. In the subcohort exposed to phenoxy herbicides but not to amitrole, the observed incidence of stomach tumors was 6.1 times greater than the expected incidence, after allowing for a ten year induction period. In the subcohort of all workers exposed to phenoxy herbicides (including those also exposed to amitrole), the observed incidence of stomach tumors was 5.9 times greater than the expected incidence, after allowing for a ten year induction period.**/ Despite the relatively small size of each of these subcohorts, each of these findings was statistically significant. In both instances, p was less than .01, indicating that the observed excess incidence would occur by chance alone less than one time in a hundred.

*/ Axelson, O. and Sundell, L., 1974. Herbicide exposure, mortality and tumor incidence: An epidemiological investigation on Swedish railroad workers. Work Environ Health II: 21-28.

**/ In the subcohort exposed to amitrole but not to phenoxy herbicides, no stomach tumors were observed, thereby reinforcing the inference that the excess incidence of stomach cancer among workers exposed to both phenoxy herbicides and amitrole is attributable to phenoxy exposure.

In another study of a cohort of workers exposed to TCDD during and after a runaway reaction in 1953 at a trichlorophenol plant in Ludwigshafen, Germany,*/ Thiess and Frentzel-Beyme also reported an excess incidence of stomach cancer among exposed workers. Immediately following the Ludwigshafen incident, many of the exposed workers developed chloracne, indicating dioxin exposure.**/

The observed incidence of stomach cancer in the cohort of Lundwigshafen workers who may have been exposed to TCDD during the incident or subsequent cleanup operations, was approximately five times greater then the expected incidence. (p less than .025). Moreover, further analysis indicates that the observed incidence of stomach cancer in the Ludwigshafen cohort is more than seven times greater than the expected incidence, after allowing for a ten year induction or latency

*/ Thiess, A.M. and Frentzel-Beyme, R., 1977. Mortality of persons exposed to dioxin after an accident which occurred in the BASF on 13th November, 1953. Paper presented at MEDICHEM Congress V. San Francisco, September 5-9, 1977. A revised and updated study containing additional data and analysis is in preparation.

**/ Although a number of steps were taken to clean up the plant following the incident, these measures were later found to be inadequate to eliminate all residual dioxin. Thus, dioxin exposure may have continued until 1969, when the entire building was demolished according to a detailed plan.

period. Thus, the results obtained by Thiess and Frentzel-Beyme corroborate the findings of Axelson, indicating that exposure to TCDD or preparations containing TCDD has been clearly associated with an excess risk of stomach cancer in humans.

C. Human Reproductive Failure Correlates with the Use of 2,4,5-T and in the Alsea, Oregon Area

The Alsea study provides correlative evidence that reproductive failure in some women living in the Alsea, Oregon, area is related to the use of 2,4,5-T and silvex contaminated with dioxin on forests in the area.*/ Data from this study are important because they tend to confirm the initial reports of eight women that they experienced miscarriages shortly after 2,4,5-T and silvex were sprayed in the area.**/ The Alsea data also comport with the animal toxicology data showing that reproductive failure occurs in pregnant animals such as rodents and monkeys

*/ EPA 1979. Report of Assessment of a Field Investigation of six-year spontaneous abortion rates in three Oregon areas in relation to forest 2,4,5-T spray practices (Alsea Report). In response to the comments and suggestions of reviewers of the Alsea Report, the Agency is currently collecting additional data and information on herbicide use practices and miscarriages in the Alsea area.

**/ Letter from Bonnie Hill of Alsea, Oregon. 1978. 2,4,5-T RPAR Rebuttal Submission 30000/26: #363. In one of almost 3000 letters responding to the Agency's Rebuttable Presumption Against Registration of 2,4,5-T, 43 FR 17116, April 19, 1978, Mrs. Bonnie Hill reported that she and seven other Alsea area residents had experienced miscarriages within a few weeks of 2,4,5-T or silvex application in the area. The similiarity between these reports and the observations of reproductive effects in test animals led the Agency to begin the investigation which resulted in the Alsea Report. The Agency has received many other such letters from forest areas in Oregon and from other use areas in other parts of the country.

when these animals are exposed to these chemicals. Accordingly, information from the Alsea, Oregon area agrees with other epidemiologic information showing a relation between exposure to 2,4,5-T and adverse human health effects.

1. The Hospitalized Spontaneous Abortion Rate Increased Shortly After Spring Spraying in the Alsea Area

The Alsea Report showed an increase in hospitalized spontaneous abortions (less than five months of gestation) among Alsea area women in June and July for the six-year period from 1972 through 1977, this increase did not occur in a control area where 2,4,5-T and silvex were not known to be used. The June peak followed by about two months the spring peak of 2,4,5-T spraying in the Alsea basin. Statistical analyses showed that the correlation between herbicide use in March and April and the corresponding increase in spontaneous abortions approximately two to three months later was significant by several different methods of analyses.

The data in the Alsea report thus suggest that the use of 2,4,5-T and silvex in Alsea may lead to human exposure to these chemicals and that such exposure may be responsible for the increase in spontaneous abortions. The likelihood that the Report mesures herbicide-related changes in the reproductive health of the Alsea women is reinforced by data comparing reproductive function in test animals and humans as well as by information on use practices in the Alsea area.

2. The Reproductive Effects Observed in the Alsea Women are Consistent with the Reproductive Effects Observed in Test Animals and Other Women

The relationship between miscarriage and potential exposure to 2,4,5-T reported for the Alsea women corresponds to the reproductive effects observed in test animals which have been exposed to these chemicals. The comparability of reproductive effects in monkeys exposed to TCDD is readily recognizable. Monkeys exposed to TCDD prior to and during pregnancy show increased numbers of abortions compared to animals which have not been exposed to this chemical. The Alsea study also shows an increase in hospitalized spontaneous abortions a short time following the use of 2,4,5-T contaminated with TCDD for forest management in the area.

The data on reproductive effects in rodents is also applicable to humans but the comparison is not as immediately recognizable because of differences in the structure of the rodent uterus and the uterus of primates such as humans and monkeys. When the effects of exposure to a chemical are evaluated by sacrificing pregnant rodents prior to normal delivery times, lost conceptions are identifiable by inspecting the uterus for resorptions or, at later gestational ages, dead fetuses. Damage of the type that leads to resorptions or retained dead fetuses in rodents leads to explusion of the non-living conceptus as a spontaneous abortion or miscarriage in humans. In rodents which are allowed to continue their

pregnancies to term, the birth of smaller numbers of pups in a litter is an indicator that some animals either did not conceive a normal size litter or that some of the conceptuses were lost before birth. Smaller litter size is frequently observed in rodents exposed to TCDD, 2,4,5,-T and silvex.

These considerations together with the long-established scientific data showing that 2,4,5-T, silvex and TCDD produce abortions, stillbirths, and other fetotoxic effects in laboratory mammals justifies concern that women who are exposed to these chemicals may also experience abnormal pregnancies, including spontaneous abortions. Initially, a group of eight women, neighbors in the Alsea area, noticed what seemed to them to be an unusual number of spontaneous abortions in their group. They noticed also that their abortions followed the spring-time use of 2,4,5-T in the area. The Alsea Report on the relation between spontaneous abortions in a larger group of women and spring use of the herbicide is consistent with the animal data as well as with observations of individual women.

3. The Use of 2,4,5-T and Silvex for Forest Management Creates Opportunities for Human Exposure

Intensive herbicide use practices coupled with the topo- topography and climate of the Alsea area facilitate distribution of 2,4,5-T and silvex away from the mountain reforestation sites to the watercourses and residential valleys in the area. Moreover, the forest use of 2,4,5-T*/ and silvex is concentrated in the spring of each year when these herbicides are used for forest management purposes. Generally, the herbicides are applied twice**/ during the first five years of the eighty year life of most tree stands in the Oregon coastal range in which the Alsea study area is located. Within a given area, there may be many different tree stands in different growth stages, several of which may require herbicide application during the same spring season. Consequently, pesticide applications may occur in a particular area several times during the spring spray season and there may be multiple applications in a particular area in any given five year period.

*/ The Bureau of Land Management manages forests in the Alsea area but uses silvex only. The BLM stopped using 2,4,5-T before 1972.

**/ The chemicals are first applied when a recently harvested "clear-cut" area is prepared for re-forestation. Later, when the tree seedlings are planted and growth has begun, the same site is sprayed again to control young hardwood trees which might outgrow the conifers which are more valuable commercially.

Exposure to humans results from the combination of frequent, concentrated use and climatic and topographic conditions which permit distribution of the herbicides from the application site to non-target areas where humans reside and work. The Alsea area is made up of steep, densely forested mountains laced with numerous streams and creeks flowing through and from the application sites. Homes and farms in the area directly abut on forest application sites, or lie downwind of application sites. Many homes in the area draw their water supplies from the creeks and streams which flow from and near the application sites. 2,4,5-T and silvex are sprayed by helicopters flying across the application sites.

These use practices and topographic conditions permit the distribution of these herbicides to non-target areas where humans reside and work. The pesticide may be distributed by aerial drift to a residential site immediately following application. Herbicide also may be transported to non-target areas in the streams which become contaminated during application, or later by run-off from the application site into the streams and rivers which collect from the watersheds in which the treated tree stands are located. While there is little chemical residue information available here as elsewhere, the available information supports the Agency's presumption that heavy use of herbicide during the spring spraying seasons, coupled with topographical conditions

which facilitate distribution of the herbicide to nearby residences, means that women residents of the area may be exposed to these herbicides.

Summary

A substantial and growing body of epidemiological evidence clearly links exposure to 2,4,5-T, silvex, or TCDD to adverse health effects in humans. Statistically significant increases in the risk of cancer and reproductive disorders have been documented in six separate human populations. These same types of adverse health effects have also been observed in experimental animals exposed to 2,4,5-T, silvex and/or TCDD. This combination of positive epidemiological findings and corroborative animal data provides a sound basis for the conclusion that exposure to pesticide products containing 2,4,5-T or silvex constitutes a human health hazard.

III. 2,4,5-T, Silvex and TCDD are Present in the Tissues of Humans, Animals, and Plants and in Environmental Media to which Humans are Exposed

Environmental monitoring data and data on the environmental and metabolic fate of 2,4,5-T, silvex and TCDD provide information on the potential for human exposure to these chemicals. Such data can indicate whether or not a particular kind of toxic chemical is present in the air, water, soil, or in biological materials. These data can also provide information on the amount of toxic material in various media, and the duration of the toxic material in the environment or in living tissues of plants, animals, and humans. Scientists and regulatory agencies often utilize information on the distribution and duration of a toxic chemical to estimate the likelihood that human exposure will occur, and that such exposure may result in injury to the people who are exposed.

Although large amounts of 2,4,5-T and silvex are used each year,*/ there is very little reliable monitoring information on 2,4,5-T, silvex, and TCDD residues in the environment. In the case of TCDD, the scarcity of data is the direct result of

*/ Prior to the emergency suspension of these herbicides, more than nine million pounds of 2,4,5-T and 3 million pounds of silvex were used annually. These amounts include 3.8 million pounds 2,4,5-T on rights-of-way, 2.6 million pounds 2,4,5-T on forests, 300,000 pounds 2,4,5-T on rice, 2 million pounds silvex on ornamental turf, and 300,000 pounds silvex on aquatic sites.

the extraordinary difficulty in measuring TCDD at very low levels.*/ It has taken many years to develop and validate the analytical techniques which can reliably detect TCDD at levels which are in animal and environmental samples. New extraction procedures had to be developed for the different types of samples; mass spectrometry techniques had to be refined. Even now that the methodology has been developed, the number of samples analyzed is limited by time and expense. Each sample tested for TCDD requires many hours of extraction and analysis, and costs approximately $1,000. Because of the low sensitivity required, an extra number of control and blank samples must be run. At present, there are only a handful of laboratories which are able to analyze human, animal, and environmental samples for TCDD at the very low levels at which it is known to be toxic.

The scarcity of monitoring information on 2,4,5-T and silvex residues appears to result primarily from a lack of monitoring programs, or a lack of monitoring at the right time relative to the stability of the chemical. 2,4,5-T and silvex are not generally considered to persist in the environment for long periods, therefore the monitoring must be done within a

*/ The analytical method must be able to detect TCDD at least as low as the parts per trillion level. This is because TCDD is toxic at very low levels of exposure, and the levels of contaminant distributed in the environment are also likely to be low.

reasonable time after application or exposure. Ideally, the monitoring should be designed for continuous sampling. The value of such a design is illustrated by a simple metaphor. Suppose the county wants to monitor the traffic density on a country road, in order to determine whether to limit the use of the road. If the monitoring office goes out once and takes a single photograph, it might very easily conclude that the road is not traveled and that there is no problem, because the photograph shows nothing. If, however, the monitoring office were to take a continuous motion picture, it would find that the road is traveled once a week by a convoy of heavy trucks. An analogous situation to the country road exists regarding 2,4,5-T and silvex monitoring. Much of the available data on 2,4,5-T and silvex, which is itself very limited, is based on random-sample monitoring. Therefore, only sheer luck favors the detection of a positive sample, before the 2,4,5-T and silvex have degraded from the environment.

In the absence of sufficient monitoring data, whether from lack of monitoring or inappropriate sampling, scientists cannot draw firm conclusions regarding the presence or absence of 2,4,5-T, silvex and TCDD in the environment. Moreover, any analysis is limited by the methodologic constraints of the technique, and permit no conclusion other than that the chemical was not detected at the detection limit of the method. This is particularly relevant to TCDD, where very low levels are

extremely toxic. Nevertheless, based on the limited available monitoring information which demonstrates the presence of these chemicals in the environment, and the environmental and metabolic fates which predict their presence in the environment, it is reasonable to conclude that there is a significant potential for human exposure to 2,4,5-T, silvex, and TCDD.

A. Monitoring Data on 2,4,5-T Silvex and TCDD are Sparse but Indicative of Human Exposure Potential

2,4,5-T and silvex are distributed beyond the application site during and after use of these herbicides for forest management. For example, the Chief of the U.S. Forest Service for Region IX, which includes Oregon and Washington, reports that water contamination occurs during herbicide application in these Northwest forest areas.

> "Most applications of 2,4,5-T in forest and range situations necessarily involve water to some extent, and although we have very stringent criteria for preventing unnecessary water contamination, it is not possible to completely avoid it. We are becoming increasingly aware of this with improvements in analytical detection capabilities."*/

*/ Letter from Region Chief John R. McQuire to Douglas M. Costle, November 13, 1978.

Though sparse, the available monitoring data are consistent with the presumption that application of these chemicals under conditions which allow distribution to water and other environmental media result in the presence of chemical residues in these media. A monitoring project designed to determine the distribution of silvex to water during forest spraying in Oregon reported residues of silvex in 9 of the 11 monitored streams flowing near but not through the application site.*/ Similar information is available for other use sites and practices. Because rice is grown in water, 2,4,5-T and silvex are applied to rice in water which later is drained from the rice paddy for distribution to other waterways, or to collecting bins for catfish culture in southern rice-growing areas. Silvex residues have been reported on fruit crops grown in Canada, and both silvex and 2,4,5-T are reported to be present at various other sites.

The information that use practices distribute the herbicides to non-target sites, the data showing some residues in areas where reliable monitoring occurs, and the absence of any monitoring information from many other use sites create uncertainties as to the actual location and amounts of 2,4,5-T, silvex, and TCDD in the environment. Once applied, and until degraded or otherwise removed from avenues of human exposure, these

*/ Cameron, J. and John W. Anderson. Results of the Stream Monitoring Program Conducted during FY 1977 Herbicide Spray Project.

chemicals present potential risks to humans. The fact that these chemicals are present at some sites and suspected in others is important in view of the data showing toxic effects in test animals, and epidemiologic data showing that humans exposed to these chemicals experience adverse health effects. In these circumstances, FIFRA's allocation of the burden of proof to the proponents of registration requires the registrants to show that humans are not exposed to these chemicals.

B. Data on the Distribution and the Persistence of 2,4,5-T, Silvex, and TCDD Present in Biological Materials and Environmental Media Indicate that Humans Have Been or May Be Exposed to These Chemicals.

Human exposure to any pesticidal chemical is largely dependent upon the environmental and metabolic fate of that chemical. Generally, a chemical which is persistent in the environment and which accumulates in the body is likely to provide prolonged human exposure, even if there is only a single application or exposure incident. Conversely, a chemical which is rapidly degraded in the environment and readily metabolized and excreted from the body is unlikely to result in prolonged human exposure, unless there are repeated exposure incidents. In either case, the conditions of a single exposure incident could produce sufficient exposure to cause adverse effects which arise as a result of the direct, acute exposure. In the present instance, studies have shown that TCDD persists in the environment, appears to accumulate

in food sources and is slowly excreted from the body. On the other hand, 2,4,5-T and silvex appear to be rapidly degraded in the environent and readily excreted from the body.

1. There is a Significant Potential for Prolonged Human Exposure to TCDD.

Studies using TCDD or TCDD combined with herbicide, and studies of TCDD accidents indicate that TCDD is persistent in the environment. Because of this persistence, the potential for human exposure extends well beyond the time of application. In addition, there is evidence that TCDD accumulates in some food sources. Also, studies in mammalian species show that once TCDD enters the body, it is slowly absorbed and excreted, and tends to distribute in lipid-rich tissues. Again, potential human exposure is prolonged because of the extended period that TCDD stays in the body. Thus, the potential human hazard resulting from a single application of TCDD, or TCDD-containing herbicide, persists long after the application has taken place. Repeated exposures to TCDD compound the problem.

a. TCDD is Relatively Persistent in the Environment, and Appears to Accumulate in Food Sources.

The chemical characteristics of TCDD make its persistence in the ecosystem predictable. Because TCDD is chemically stable, lipid (fat) soluble, and almost water insoluble, it has the

potential for accumulation in the food chain, as well as long term persistence in the environment. TCDD has limited movement through soil once it has been applied, and it is not broken down by most microorganisms. Of 100 microbial strains with the capability to degrade persistent pesticides, only five showed some ability to degrade TCDD.*/ In a study using two types of soil, the half-life**/ of TCDD in soil was estimated to be approximately one year.***/ However, TCDD half-life appears to be influenced by several factors, such as soil-type, atmospheric conditions, and degree of sunlight.

Work done at Eglin Air Force Base is of particular interest on the question of soil half-life. Between 1962 and 1964, an area was sprayed with Agent Orange containing TCDD at levels comparable to those used in Vietnam. Ten years later, when soil samples were taken from the area, they showed TCDD concentations averaging over 300 ppt.****/ One author,

*/ Matsumura, F. and H.H. Benezet. 1973. Studies on the Bioaccumulation and Microbial Degradation of 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Environ. Health Perspect. 5:235-258.

**/ "Half-life" is the amount of time required for 50% of the substance applied (taken in) to be broken down (processed or eliminated). The longer the half-life, the greater the potential for exposure.

***/ Kearney, P.C., E.A. Woolson, and C.P. Ellington, Jr., 1972. Persistence and Metabolism of Chlorodioxins in Soils. Envir. Sci. Technol. 6:1017-1019.

****/ Young, A.L., C.E. Talken, W.E. Ward. 1975. Studies of the Ecological Impact of Repetitive Aerial Applications of Herbicides on the Ecosystem of Test Area C-52A, Eglin AFB, Florida. US Air Force Report No. AFATL-TR-75-142.

assuming that the Agent Orange contained approximately 4.5 ppm TCDD, has calculated a TCDD half-life of 2.9 years.*/

The possibility of water contamination as a route of TCDD exposure cannot be eliminated, even though TCDD is almost insoluble in water. TCDD can be carried into a water source by way of soil runoff, drift during application of TCDD-containing herbicides, or airborne particles contaminated with TCDD. Once the TCDD has gotten into the water, there are several possible sources of human exposure. First, TCDD is soluble in water at concentrations of approximately 200 ppt, and with its extreme toxicity, small amounts of dissolved TCDD as a possible source of exposure cannot be ignored. Second, TCDD readily adsorbs onto organic particulate matter in the water, and if the matter is fine enough to remain suspended or has not yet settled to the bottom, the TCDD would travel with the particles through the water.**/

*/ Westing, A.H. 1978. Ecological Considerations Regarding Massive Environmental Contamination With 2,3,7,8-Tetrachloro-dibenzo-para-dioxin. Ecol. Bull. 27: 285-294.

**/ The detection of approximately 3 ppt TCDD in filtered scrubber water at the Dow Chemical Company plant supports the contention that exposure to TCDD can be gotten from water, either because measurable amounts of TCDD are water soluble or because TCDD-bound particulate matter fine enough to escape filtration may exist in water. (Dow Chemical Company. 1978. The Trace Chemistries of Fire - A Source of and Routes for the Entry of Chlorinated Dioxins Into the Environment. Unpublished.)

Finally, even if the particulate-bound TCDD has settled to the bottom of the water source, climatic and seasonal changes could stir up the sediment and redistribute the TCDD in water, or bottom-feeding organisms, such as snails and catfish, could introduce the TCDD into the food chain. In fact, in areas where these bottom feeders are dietary staples (e.g., in the South where catfish is extensively eaten), this mechanism is a direct source of TCDD exposure. In lake sediments, TCDD has been shown to be very stable with a half-life of approximately 600 days.*/

As previously noted, the extent of TCDD's persistence is dependent upon the prevailing environmental circumstances. Much has been written about the breakdown of TCDD in sunlight to lower chlorinated, less toxic dioxins as the primary route of TCDD degradation. Prerequisites for this type of degradation are the presence of a hydrogen donor (usually the herbicide solvent), adequate sunlight intensity, and exposure of the TCDD to the sunlight. Very little actual-use data are available on TCDD photochemical degradation. However, the theoretical model does not always apply to actual situations, because the required conditions are clearly not always available. Breakdown can be expected to be even slower in the shade, even if efficient hydrogen donors were available. This is particularly relevant to certain uses of TCDD-containing

*/ Matsumura and Benezet, 1973.

herbicides, such as in forestry, where shade is a prevailing condition. Moreover, an efficient hydrogen donor is not always available, as when a TCDD-containing herbicide is applied in water.

Information from two well-documented field situations indicate that natural photodecomposition may not proceed as rapidly as might be predicted from the half-life studies. In the Eglin Air Force Base studies, an apparently longer half-life than the expected one year was observed (see page 79 above). Similar results have been obtained in Seveso, based upon later analysis of soil exposed to TCDD during the 1976 incident.*/

That TCDD persists in the environment long enough to contaminate food sources is evident by the detection of TCDD residues in several of the limited number of materials tested. It should be noted that very few food sources have ever been tested for TCDD residues.**/ However, notwithstanding the paucity of data, TCDD residues have been detected in fish,

*/ Westing, A.H., 1978. It was found that a 2-3 year lapse was necessary to obtain a 50% reduction in the 1976 values.

**/ Because of the extremely expensive and sophisticated techniques involved, only a handful of laboratories in the country are able to conduct analysis at the required parts-per trillion level. The Agency is currently analyzing a limited number of food sources, tissues and environmental samples from areas of extensive TCDD-contaminated herbicide usage. However, at present there are no routine TCDD monitoring programs being conducted by either government or private concerns.

beef fat, deer, and elk in studies using animals exposed to TCDD under natural conditions.*/ Carrots and onions grown in the contaminated soil at Seveso, as part of an ongoing study of plant life in the area, contained measurable amounts of TCDD. In discussing the Seveso results, authors of a report to the Italian Parliament reported that "[I]t was verified that TCDD is always absorbed by plants and presumably circulates in their systems, transported by water."**/

These data demonstrate that TCDD is very persistent in the environment. The results from Seveso and Eglin suggest that it is even more persistent than previously believed. Thus, TCDD has a greater potential for long-term human exposure than previously thought.

b. In Mammals, Ingested TCDD is Slowly Absorbed and Excreted, and Tends to Distribute in Lipid-Rich Tissues.

Studies in mammalian test species indicate that TCDD is slowly absorbed and excreted, and that once absorbed, the TCDD tends to distribute in lipid-rich tissues. This metabolic pattern means that a brief external exposure to TCDD can result in a much longer internal exposure than expected, because of TCDD's slow movement through the body. In addition, repeated exposures to TCDD can lead to much higher internal effective

*/ EPA. Results from Dioxin Implementation Plan; Dow. Trace Chemistries of Fire.

**/ Lombardy Regional Commission. 1978. Report to Italian Parliament on Conditions in Seveso. (EPA Translation).

doses than the actual exposure suggests, because TCDD is concentrated in the body, primarily in fat tissues.

TCDD is slowly eliminated from the body, almost entirely in the feces, and for the most part unmetabolized.*/ In studied species, the half-life for clearance of TCDD varies from 2-3 weeks in the rat**/ to several times that in cattle,***/ with a month being a commonly reported value.

The recently reported detection of TCDD residues in the adipose (fat) tissue of Vietnam veterans raises serious questions about the half-life of TCDD in humans. If the TCDD residues detected are the result of exposure to Agent Orange****/ during the 1960's, it is very unlikely that the human half-life is as short as that measured in other species. Consequently, the threat of prolonged exposure to TCDD would be especially great for people. The significance of these results cannot be overestimated.

Data derived from studies in rats, sheep, cattle, and monkeys indicate that although TCDD tends to accumulate in lipid-rich tissues in all species, the sites and apportionment

*/ Recent studies indicate that there is a limited amount of biological degradation of TCDD, producing an as yet unidentified metabolite(s).

**/ Rose, J.Q. et al. 1976. The Fate of TCDD Following Single or Repeated Oral Doses to Rats. Toxicol. Appl. Pharmacol. 36: 209-226.

***/ Dow confidential study.

****/ Agent Orange is a mixture of equal parts of 2,4,5-T and 2,4-D.

of the accumulation varies among species. In rats*/ and sheep,**/ TCDD accumulates primarily in liver and fat, with approximately equal distribution. Cattle also accumulate TCDD primarily in liver and fat; however, the concentration of TCDD in the fat is several times higher than in the liver.**/ Monkeys, however, do not show the same tendency for liver accumulation, but instead accumulate TCDD primarily in the skin and fat.***/ This pattern of accumulation in monkeys, with high levels of TCDD in the skin may explain the acne and alopecia (loss of hair) seen in monkeys, but not in most other species.

A very important category of TCDD tissue distribution involves transplacental exchange between the mother and the fetus. In pregnant rats treated with a single dose of radioactive TCDD and sacrificed 6 hours later, radioactivity was found in maternal liver and blood, placenta and fetus.****/ Assuming that the radioactivity was present as TCDD, these results indicate that maternal exposure to TCDD can result in direct fetal exposure to TCDD because of its ability to cross the placenta.

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*/ Rose, J.Q. et al., 1976.

**/ Dow Confidential Studies.

***/ Van Miller, J.P., Marlar, R.J. and Allen, J.R., 1976. Tissue Distribution and Excretion of Tritiate Tetrachlorodibenzo-p-dioxin in Non-Human Primates and Rats. Fd. Cosmet. Toxicol. 14: 31-34.

****/ Khera, K.S. and Ruddick, J.A. 1973. Polychlorodibenzo-p-dioxins: Perinatal Effect and the Dominant Lethal Test in Wistar Rats. Chlorodioxins - Origin and Fate. Advances in Chemistry Series 120, Am. Chem. Soc., pp. 70-84.

2. There is a Significant Potential for Human Exposure to 2,4,5-T or Silvex.

Humans can be exposed to potentially toxic levels of 2,4,5-T and silvex through several mechanisms. Sufficient acute exposure may occur in a single incident, to result in adverse effects. In addition, residues of 2,4,5-T and silvex have been detected in dietary sources, notwithstanding the theoretically rapid decomposition of these herbicides in the environment. Therefore, ingestion of contaminated food can be a continuous source of exposure. Morever, the rapid absorption and excretion of 2,4,5-T and silvex in mammalian species do not negate the possibility of toxic effects. The adverse effects resulting from exposure to 2,4,5-T and/or silvex, or the initial steps in the mechanisms of those effects, may take place within the span of the metabolic half-life.

a. The Relatively Short Half-Life of 2,4,5-T and Silvex in the Environment Do Not Negate the Potential for Significant Human Exposure

Although 2,4,5-T and silvex are generally considered short-lived in the environment, and non-accumulative in environmental media, they often persist long enough to result in significant human exposure. Morever, there are some indications of 2,4,5-T and silvex residues in food sources. The half-life of 2,4,5-T residues in the environment is 1-4 weeks. However, work by Norris indicates that under certain circumstances, the half-life of 2,4,5-T might be much longer. In a study on "throughfall precipitation" (the amount of 2,4,5-T being added to the forest

floor from the canopy), after 9 months he found 10 times the expected amount based on a half-life of 4 weeks. In the same study the soil concentration had dropped to only 10% of the original, where a half-life of 4 weeks would have produced only 0.02%.*/

In soil, the primary route of 2,4,5-T decomposition is microbial degradation; photodecomposition and volatilization have also been reported. Movement of 2,4,5-T into the soil is dependent upon the nature of the soil and the amount of organic matter in it, with extensive movement in sandy soils and slight movement in muck. Runoff appears to be a major source of 2,4,5-T contamination of water, with concentrations after a runoff event reported as high as 2-3 ppm.**/

There is very little available data on the environmental fate of silvex. However, studies on the degradation of phenylalkanoic acids, a chemical group including silvex, indicate that these chemicals can be degraded biologically and photochemically.

Studies on the levels of 2,4,5-T or silvex in or on dietary sources are limited. However, the available information indi-

*/ Norris, L.A. et al. 1978. 2,4,5-T Persistence in a West Virginia Watershed. Presented at 1978 Annual Meeting of Weed Society of America, Dallas, Texas, February 9, 1978. In addition, the Agency is currently analyzing data which indicate that the half-life of 2,4,5-T may be even longer.

**/ Bovey, et al. 1974. Occurrence of 2,4,5-T and Picloram in Surface Runoff Water in the Backlands of Texas. J. Environ. Quality. 3: 61-64.

cates that the diet could be a source of exposure to 2,4,5-T or silvex. As previously discussed, 2,4,5-T and silvex monitoring information indicate that both compounds are routinely detected in surface water, which may be used for human consumption. In addition, silvex residues have been found in apples which had been sprayed with silvex to prevent fruit drop.

b. The Rapid Mammalian Excretion of 2,4,5-T and Silvex is not Inconsistent with Toxic Effects.

The toxic potential of 2,4,5-T and silvex is not solely dependent upon the fact that they are readily absorbed and excreted in mammalian species. The actual toxic event may take place during the short time that the chemical is present in the body. This is particularly relevant to teratogenic effects, where very short exposures may result in devasting consequences. In addition, repeated exposures, as in the case of applicators, mean that the body can build up to the maximum concentration it can contain (steady-state concentration), and, more important, the body can accumulate increasing amounts of the TCDD contaminating the 2,4,5-T and silvex.

For 2,4,5-T, the metabolic half-life ranged from 14-87 hours, with humans at approximately 23 hours.*/ Human subjects

*/ Gehring, P.J. et al. 1973. The Fate of 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) Following Oral Administration to Man. Tox. Appl. Pharm. 26: 352-361.

exposed to silvex excreted in the urine 65% of the ingested dose with 24 hours.*/ Using human pharmacokinetic data, it has been calculated that daily ingestion of a given dose of 2,4,5-T would result in a steady-state concentration in the blood of approximately 17 times the daily dose after 3 days.**/

Studies done in pregnant mice with radioactive 2,4,5-T show that 2,4,5-T crosses the placenta and reaches the fetus. After exposure on gestational day 13, fetal concentration of 2,4,5-T were initially highest in the liver, skin, eyes, and ventricles of the brain; later, distribution extended to skeletal muscles.***/ As with TCDD, these results indicate that maternal exposure to 2,4,5-T during pregnancy can result in direct exposure to the unborn child.

Summary

In summary, the chemical, environmental and metabolic fate characteristics of 2,4,5-T, silvex, and TCDD demonstrate

*/ Sauerhoff, M.W. et al. 1977. Fate of Silvex Following Oral Administration to Humans. J. Tox. Environ. Health. 3: 941-952. Both 2,4,5-T and silvex have been detected in urine of the general population: (1) in urine collected as part of the Second Health and Nutrition Evaluation Survey, and (2) in urine from Florida Students. Dougherty, R.C. and Piotrowska, K. 1976. Screening by Negative Chemical Ionization mass Spectrometry for Environmental Contamination with Toxic Residues: Application to Human Urines. Proc. Natl. Acad. Sci. 6: 1777-1781.

**/ Gehring, P.J. et al., 1973.

***/ Courtney, K.D., Ebron, M.T. and Tucker, A.W. 1977. Distribution of 2,4,5-Trichlorophenozyacetic Acid in the Mouse Fetus. Toxicol. Letters 1: 103-108.

that there is a significant potential for human exposure to these substances. Although 2,4,5-T and silvex are not very persistent in the environment, and are excreted rapidly in mammals, the possibility of toxic levels of exposure cannot be ignored. Very short exposures may be sufficient to cause adverse effects. In addition, repeated exposures may lead to accumulation of the TCDD contaminating the 2,4,5-T and silvex. On the other hand, TCDD is very persistent in the environment, and accumulates in the fat tissues of animals. Recent results indicate that TCDD may remain in the fat tissues of man for many years after the exposure incident. This persistence of TCDD means that the potential for human exposure, and consequently human adverse effects, extends long after the direct exposure incident.

IV. Use Case Histories Demonstrate that Humans and Other Non-target Organisms Are Exposed to 2,4,5-T and Silvex

Case histories of human exposure incidents following the application of herbicide under ordinary use conditions demonstrate that 2,4,5-T and silvex are not confined to the site of initial application. Rather, these chemicals may subsequently move into adjacent non-target areas where humans live and work, thereby contaminating water, garden vegetables and other non-target vegetation away from the application sites with 2,4,5-T, silvex and TCDD. Information in these cases which shows that use practices distribute 2,4,5-T, silvex and TCDD into avenues of human exposure complements monitoring data showing the presence of 2,4,5-T and silvex residues in water supplies and in human urine.*/

Four elements are common to these reports of human exposure. First, 2,4,5-T, silvex, or another phenoxy herbicide was

*/ The case histories relating the use of 2,4,5-T and silvex to human exposure to these herbicides come from reports contained in the Agency's Pesticide Incident Monitoring System (PIMS) and from letters and information submitted to the Agency in response to the Rebuttable Presumption Against registration and Continued Registration of Pesticide Products Containing 2,4,5-T (RPAR), 43 FR 17116, April 19, 1978.

The documents in these Agency files range from hand-written letters describing an exposure incident to well-documented reports by state and federal investigators. There are reports of exposure incidents involving all of the major uses of 2,4,5-T and silvex at application sites in use areas throughout the nation. Case histories involving phenoxy herbicides other than 2,4,5-T provide useful information because use practices and transport dynamics are similar.

used in the application which led to the report of the incident. Second, each herbicide application resulted in 2,4,5-T or silvex contamination of water and/or vegetation, as evidenced by reports and photographs of plant damage characeristic of phenoxy herbicides, or by the presence of chemical residues of 2,4,5-T or silvex in the water or vegetation. Third, use of these herbicides led to contamination of water and vegetation located away from the application site and, in most cases, on the property of families living near the application site.*/ Finally, in all cases, contemporaneous documentation of the event is available through the reports of official investigators for state or federal agencies, and/or the affidavits and other sworn statements of persons involved in the event.

A. 2,4,5-T and Silvex May Be Transported from the Application Site into Adjacent Non-target Areas

1. Herbicide Drift May Be Significant Even When Meteorological Conditions are Consistent with Label Directions

Because meteorological factors such as wind speed and temperature can profoundly affect the magnitude of off-target movement, the labels of 2,4,5-T and silvex products usually

*/ Although many of the witnesses to these case histories reported that they experienced adverse health effects, as of this time the Agency has generally investigated only the claims relating to water contamination, vegetation damage or other contamination on the property of the witnesses.

advise applicators to avoid application of herbicide when wind speed or temperature are excessive. Accordingly, drift and other off-target movement should not occur if the applicator avoids unfavorable meteorological conditions identified on the label and otherwise follows label directions. However, case histories of actual applications demonstrate that the precautions specified on product labels are often insufficient to prevent drift. Even when wind speed, temperature, and other meteorological conditions are within the range considered acceptable, substantial drift may nevertheless occur.

For example, an application of 2,4,5-T and 2,4-D to a clear-cut in a forest area in Blyn, Washington, resulted in drift of the herbicide 1/3 mile down a steep slope and onto the residential property and gardens of three families, although wind speed was only 3 mph, the temperature was only 38° F, and meteorological conditions were otherwise favorable.

2. Unexpected Meteorological Conditions May Enhance Off-Target Movement

Drift may be a problem even when meteorological conditions at the start of application are generally favorable. Common but unexpected meteorological conditions during or after application can intensify off-target movement, thereby augmenting potential exposure. High temperatures following an application can cause the herbicide to revolatilize, resulting in migration of herbicide vapor from the application site to areas of human

work and habitation. The extent of revolatization is dependant on the chemical composition of the formulation used. In addition, local temperature inversions can result in suspension of herbicide in warm moist air and subsequent deposit of the suspended herbicide in non-target areas.

In Houston County, Tennessee, an application of 2,4,5-T and 2,4-D to land undergoing conversion from forest to pasture exposed more than 20 families living adjacent to the application site to these chemicals. A combination of warm temperatures and a local temperature inversion substantially aggravated off-target movement by providing conditions for retention of a substantial quantity of herbicide in humid air over the application site. Subsequently, the suspended herbicide moved as much as two miles off the application site and, as temperatures declined, 2,4,5-T and 2,4-D were gradually deposited on the nearby fields and farms, resulting in damage to timber, tobacco, food crops, and gardens.

Temperature may have been a factor in the off-target movement reported in human exposure incidents in Rose Lodge, Oregon and in Alsea, Oregon. In Rose Lodge, damage characteristic of phenoxy herbicides appeared in local garden vegetables several weeks after application of the phenoxy herbicides 2,4-D and 2,4-DP to a nearby forest site. Oregon agricultural experts attributed the damage to herbicide revolatization.

3. Streams and Watercourses May Transport Herbicides from the Application Area to Areas of Human Activity

Herbicide may also be carried a considerable distance from an application site by running water. Streams and watercourses may serve as both a means of transport and a medium of human exposure. Although product labels for herbicides containing 2,4,5-T and silvex generally warn applicators to avoid contamination of water, particularly water used for domestic and agricultural purposes, application practices designed to prevent contamination of surface water are often ineffective. In addition to monitoring data showing contamination of rivers and streams following spray operations, individual case histories provide further evidence that contamination of surface water is an intrinsic hazard in certain locations and types of terrain.

Water flowing through an application site is especially likely to serve as a vehicle for the off-target movement of 2,4,5-T and silvex and thus as a source of human exposure. Despite the use of "buffer zones," which are often specified by the label or required by state regulation, streams located on an application site are usually contaminated to some degree. For example, although the buffer zone concept was utilized in planning the Blyn, Washington application, a stream running through the clear-cut application area was contaminated with 2,4,5-T and 2,4-D and transported the

herbicide away from the application site. In North Bend, Oregon, following application of 2,4,5-T to a forest site, 2,4,5-T residues were present in the stream which ran from the application site to the water intake from which one nearby household draws water.

Water which does not actually flow through an application site may also be contaminated. For example, a case study of an application of 2,4,5-T and 2,4,-D to a clear-cut tract in a forest area in Dabob Bay, Washington shows that streams a considerable distance from an application site may be contaminated by drift and then transport the herbicide even further from the original target area.

Use of herbicides for vegetation management on rights-of-way may also result in contamination of streams. The hazard of such contamination is especially pronounced in uneven or mountainous terrain because of the frequent contiguity or intersection of power distribution lines, highways, and other local rights-of-way with surface watercourses. For example, a case study of an application of 2,4,5-T, 2,4-D, and picloram to a power distribution line right-of-way in Calhoun County, West Virginia, shows that streams and creeks running adjacent to or under the power line were contaminated at at least seven separate locations.

B. Off-Target Movement Creates Opportunities for Human Exposure

1. Strong Odors in Areas Adjacent to Application Sites Provide Evidence of Human Exposure

The existence of an inhalation hazard can be inferred from evidence that herbicides may be transported from the application site to off-target locations in an aerosol or vapor form. Complaints concerning strong or unpleasant odors by citizens residing in areas affected by drift provide direct evidence of an inhalation hazard. Strong chemical odors were reported by citizens following herbicide applications in Blyn, Washington; Houston County, Tennessee; Perry County, Arkansas, and Alsea, Oregon.

While a particular unpleasant odor may in some cases be partially attributable to the odor of the carrier rather than the odor of the herbicide itself, the herbicide does not separate from the carrier as it drifts. Moreover, Arkansas residents reported chemical odors even when water was used as a carrier. Such odors should be considered presumptive evidence of inhalation as a source of exposure. When 2,4,5-T and/or silvex are present in residential areas, humans may also be exposed by deposition of the chemical on exposed skin, food and water.

2. Humans and Domestic Animals May Be Exposed by Consuming Contaminated Surface Water

Contaminated water is likely to be a major source of potential human exposure to herbicides, especially in rural communities where surface water is widely used for domestic consumption. 2,4,5-T residues were detected in domestic water supplies following herbicide applications in Blyn, Washington; Dabob Bay, Washington; Perry County, Arkansas; Alsea, Oregon; and North Bend, Oregon. Such contamination is most likely to occur either when a stream flows through an application site, as in Blyn and North Bend, or when a stream or pond adjacent to an application area is contaminated by drift, as in Dabob Bay. In Perry County, Arkansas, 2,4,5-T was detected in the pond water on a farm near the forest site where 2,4,5-T had been applied for conifer release.

Some surface water bodies, such as intermittent streams and small ponds, exist only on a seasonal basis. Since surface water of this variety does not generally appear on maps and often is not readily visible from the air, aerial spray operations are likely to result in inadvertant contamination by direct overspray. For example, an aerial application of 2,4,5-T, 2,4,-D, and picloram to a power distribution line right-of-way in Calhoun County, West Virginia resulted in contamination of an intermittent stream used to water livestock.

3. Humans and Domestic Animals May Be Exposed to 2,4,5-T and Silvex by Consuming Contaminated Garden Vegetables, Food Crops, or Fodder.

Direct application of herbicide to food crops destined for human consumption or for livestock forage clearly constitutes a potential source of human exposure. For example, humans or animals may be exposed to residues of these chemicals or TCDD from the use of 2,4,5-T on rice or grazing land and the use of silvex on rice, sugarcane or fruit orchards.

Use case histories demonstrate that off-target movement of herbicides may also result in contamination of food and forage in areas adjacent to the application site. In the rural forest, range, rice and pasture areas where 2,4,5-T and silvex are most often used, the residents grow much of their own produce. These garden vegetables may be a significant part of the diet for many of these families.

Widespread damage of food crops and garden vegetables resulting from contamination with 2,4,5-T and 2,4-D was observed on property near the application site in Houston County, Tennessee. Although some sensitive crops like watermelons were completely destroyed, other damaged crops and garden vegetables later recovered and could have been harvested and used for human consumption. Drift following the herbicide applications in Alsea, Oregon; Rose Lodge, Oregon; Perry County, Arkansas; and Blyn, Washington also resulted in contamination of garden vegetables such as

lettuce and peppers, fruits such as peaches, and animal forage crops such as clover and alfalfa.

Finally, 2,4,5-T contamination of tobacco raises the possibility that humans may inhale smoke containing TCDD. Off-target movement following the herbicide application in Houston County, Tennessee caused damage to tobacco crops on a number of nearby farms, and analysis of samples of damaged tobacco confirmed the presence of 2,4,5-T and 2,4-D. Nevertheless, although the affected crops never recovered completely and failed to cure properly, the contaminated tobacco was later sold for human consumption. The 2,4,5-T contamination in tobacco is clearly a matter of toxicological concern.

Summary

Case histories of actual herbicide applications demonstrate that, even under favorable meteorology and topographic conditions, 2,4,5-T and silvex are not necessarily confined to the site of initial application, but may subsequently be transported into adjacent non-target areas. Moreover, variations in meteorological conditions or terrain can substantially augment the degree of off-target movement. Case histories also provide actual examples of human exposure to 2,4,5-T or silvex which can result from inadvertant movement from the application site to areas where humans live and work.

V. SUMMARY

FIFRA requires the Administrator, in his exercise of continuous oversight over registered pesticide, to initiate proceedings to cancel a pesticide if it appears that the risks of continued use of the pesticide outweigh the benefits of that use. These cancellation proceedings were instituted on the bases of animal toxicology data, human epidemiology data and data on the use, distribution, and environmental fate of 2,4,5-T, silvex, and TCDD which indicate that the registered uses of 2,4,5-T and silvex pose risks to human health.

The quality, quantity and variety of data demonstrating that the continued use of 2,4,5-T and silvex contaminated with TCDD presents risks to human health is unprecedented and overwhelming. In previous proceedings leading to the cancellation of pesticide registrations, the evidence has been limited to animal toxicity data showing a single type of effect. Thus, both the aldrin/dieldrin and heptachlor/chlordane cancellations were predicated on evidence of carcinogenicity in rodent test systems; evidence of other toxic effects in test animals was not available.

By contrast, there is a multiplicity of data reflective of the multiple effects and intense scientific interest in the toxic characteristics of 2,4,5-T, silvex, and their TCDD contaminant. Each of the several toxic effects which these chemicals produce in test animals has been confirmed in several

different studies. These studies establish without question that low level exposure to TCDD produces cancer and reproductive failure in test animals, and that commercial 2,4,5-T and/or silvex have comparable reproductive effects at higher exposure levels. Moreover, the cumulative evidence of multiple effects in several animal species confirms the general toxicity of these chemicals in living tissue.

The evidence against 2,4,5-T, silvex, and TCDD also includes epidemiology studies which show that these chemicals have toxic effects in humans as the animal studies predicted. Not only do these studies show the general toxicity of these chemicals in humans, but they provide specific confirmation of human susceptibility to the same effects that are observed in laboratory animals. Thus, humans, as well as animals, develop cancer and reproductive effects.

Information on the chemical properties of these compounds and use practices demonstrates that humans may be exposed to these chemicals, and enlarges the bases for concern about the continued use of these chemicals. Residues of these chemicals are detected in various environmental media to which humans may be exposed. Further indications of human exposure came from the case studies which are simple examples showing that use practices distribute 2,4,5-T and silvex into populated areas or into human food and water sources.

In sum, the data on toxic effects in animals and humans together with the data on exposure potential establish that the continued use of 2,4,5-T and silvex contaminated with TCDD pose risks of adverse effects on human health.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that copies of "Respondent's Prehearing Brief on the Risks Associated with the Registered Uses of 2,4,5-T and Silvex", were hand-delivered or mailed first class postage prepaid on January 25, 1980 to the persons on the attached list.

Dorothy E. Patton

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January 25, 1980