Item ID Number 05210 ☐ **Not Scanned**

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Report/Article Title Environmental Protection Agency (EPA) Before the Administrator, In re: 2,4,5 -Trichlorophenoxyacetic Acid (2,4,5 -T), I. F. & R. No. 295, Reply Brief of Environmental Defense Fund, Consumers Union, and Wellford

Journal/Book Title

Year 1974

Month/Day March 11

Color ☐

Number of Images 43

Descripton Notes

ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE HEARING EXAMINER

In re:	)	
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2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T)	)	I.F. & R. No. 295
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REPLY BRIEF OF ENVIRONMENTAL DEFENSE FUND, CONSUMERS UNION, AND HARRISON WELLFORD

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I. INTRODUCTION

The decision of whether to allow continued usage of 2,4,5-T will be greatly influenced by whether there is substantial danger that TCDD exposures resulting from such usage will cause adverse health effects in humans and animals. Therefore, we have attempted in this document to estimate from the available information provided by opening briefs (1 - 2) and proposed exhibits the probability of such adverse effects in humans, intending to hypothesize the worst reasonable (but not extreme) foreseeable conditions and effects. This estimation is presented in sections II and III, below (pp. 3-10). Many of the other issues raised in opening briefs, which at this moment appear to be less urgent than the danger to human health, are not discussed or are only briefly discussed here. This should not be taken to mean we believe them unimportant.

As developed in the following sections, the available evidence indicates that it is possible that:

(1) levels of TCDD teratogenesis in humans may be affecting as many as 0.3% of human fetuses;

(2) TCDD exposures low enough to be "safe" as a single dose can, if continued, accumulate to toxic levels in body tissues of animals and man;

(3) there may therefore be no chronic "threshold" dose level which is safe for long-term intakes of TCDD; and

(4) TCDD may be generated from 2,4,5-T in the environment in amounts which are unacceptable, in view of 1) and 2).

Experiments required before the health hazard of 2,4,5-T usage can be assessed

In view of the above observations, there are a few crucially significant studies which should be required. Until they are completed, no one should be permitted to continue to expose human populations to 2,4,5-T. Three of these studies are specified below.

(1) 1/ A survey of present levels of TCDD in human adipose tissue should be conducted, with TCDD being accurately determined at the ppt level of sensitivity.

(2) 2/ Animal experiments (using animals with relatively long lifetimes and including reproducing females) should be conducted to determine what level of continued TCDD ingestion, if any, is low enough to be tolerated by a long-lived animal without adverse effect. In the same experiment it should be determined what steady state tissue levels can be tolerated for life without adverse effects.

(3) 3/ Multigeneration animal experiments using a

1/ Although there is reason to suspect that these levels may now be on the order of 30 ppt or more and that ppt levels may have adverse effects on health (see pp. 7-8, below), such a survey has not been done.

2/ In those experiments reported which have involved administration of TCDD on a daily and continual basis, the dose level has never been low enough to avoid the eventual appearance of toxicity (see pp. 17-18 below). Neither has a plateauing of tissue concentrations been reported.

3/ Any agent which exhibits delayed effects and which also affects cell division, as does TCDD, should automatically be checked in this manner before humans are exposed to it. However, so far as we know, such studies have not been conducted.

sensitive species should be conducted to test for effects of TCDD on longevity, reproductive success, and mutation rates.

(4) [1/] Studies of the effects of inhalation of aerosols containing TCDD (and 2,4,5-T) should be conducted).

II. What is a reasonable estimate of the maximum levels of TCDD in human tissues under present conditions of use?

Conclusion: Using reasonable assumptions, one can calculate that TCDD concentrations in humans may be as high as 300-400 ppt (nanograms/kg body weight) and that concentrations of 30-40 ppt may well be common.

The above conclusion follows from calculations based on observations of TCDD levels in animals and on reasonable deductions concerning the potential for gradual build-up of tissue concentrations with prolonged exposure.

1/ Although effects of other toxic agents are often more severe after inhalation exposure than after ingestion, studies such as these have, so far as we know, not been done. Some of the complaints which we have received have alleged severe adverse health effects in humans after inhalation of aerial drift from nearby spraying operations. Generation of TCDD in fires and the transportation of TCDD and 2,4,5-T in smoke plumes would constitute another possible mechanism of atmospheric exposure.

Cattle, sheep, and goats, after feeding on rangeland which had been sprayed with 2,4,5-T (contaminated with 0.04 ppm TCDD), were found to contain 6-41 ppt of TCDD in body fat (2, p. 36). That these values are not unrealistically high compared to actual current levels of TCDD in animals is indicated by the fact that TCDD levels in shrews have been found to be as high as 397 ppt with a mean of 202 ppt (2, p. 36). If one assumes as the worst reasonable case that 40 ppt is representative of the TCDD in the animal fat of the human diet, it can be calculated that the dietary TCDD concentration from this source alone would be as much as 3 ppt. 1/

Given a dietary TCDD concentration of 3 ppt, what might the human tissue concentration become? Humans eat approximately their body weight of food in one month. If all of the dietary TCDD is retained, 2/ then in one month the total body concentration of TCDD would be 3 ppt, in two months it would be 6 ppt,

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1/ This estimate assumes 500 gm of meat/day (3, p. 17) with a fat content of 20%, and 1.5 kg/day of total diet (1, p. 10).

2/ This assumption that TCDD is cumulative at low dose levels is disputed by Dow (1, p. 161) but is supported by experimental evidence and is substantiated in the discussion in section IV below, pp. 15-21.

and in 10 years, it would be 360 ppt. [1/] We therefore estimate that human body burdens of TCDD may now be as much as 300-400 ppt. If these represent upper levels, one may assume that levels one-tenth as high (30-40 ppt or 0.03-0.04 µg/kg of total body weight) are common. [2/]

Although no actual analytical data (at the required level of sensitivity) are available concerning TCDD concentrations in

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1/ This amounts to a bioconcentration factor of only 120 which is quite low in comparison to the factors of up to 14,000 which have been actually observed for TCDD in model ecosystems (2, p. 33).

2/ In the absence of actual analyses at the required level of sensitivity for TCDD in human tissues, it was necessary to use a number of assumptions in the above calculation, which probably involved both overestimations and underestimations. The assumption of 40 ppt in dietary animal fat may be an overestimation inasmuch as this level was found in animals which had grazed freshly sprayed rangeland, a condition that would pertain only intermittently. However, in view of the environmental stability of TCDD (2, p.33)the recency of the application is of less significance than it would be for a less persistent compound. The assumption of 100% retention of dietary TCDD also represents an obvious over-estimation. However, the arbitrarily chosen period of 10 years is short in terms of the human lifetime. A lower proportional retention over a longer period of time could produce the same concentration if a steady-state is not achieved.

Factors in the above calculation which would have produced probable underestimations include the assumptions that dietary animal fat is the only source of TCDD exposure in humans, ignoring possible TCDD intakes from other tissue fractions, other foods, water and air (see p.29 below), that 2,4,5-T released into the environment does not contain more than 0.04 ppm TCDD as an average value, and that there are not other environmental or pesticidal sources of TCDD (i.e. combustion of 2,4,5-T (see pp. 23-25 below) or Silvex) Although the calculation is an attempted estimate of the worst reasonable case, we assume for this purpose that the over- and underestimations are of approximately equal magnitude.

humans, or the frequency distributions of those concentrations, it is not unreasonable to suppose that the average value for the total population would be at least one-tenth of the estimated upper range of concentrations, since the TCDD was here assumed to come from dietary meat fat only. (Therefore, high individual body levels due to such circumstances as occupational exposure would not have contributed to the estimate of 300-400 ppt.)

III. In the worst reasonable case, what effects might be expected in humans with average whole-body TCDD levels of 30 ppt?

Conclusion: Assuming maternal body burdens of 30 ppt TCDD and a human sensitivity to TCDD equal to that of the less sensitive strains of mice, TCDD may be causing congenital abnormalities in as many as 0.3% of newborn infants in the U.S.

In Section II, above, it was estimated that in the worst reasonable case, TCDD concentration in humans may be as much as 400 ppt, and the average value may be on the order of 30 ppt.

In considering what the effect in the U.S. population of body burdens of 30 ppt TCDD might be, a number of additional assumptions will be made: it will be assumed that at the concentrations involved, the teratogenic effects of TCDD are the ones of most concern and therefore other possible effects will not be considered; it will be assumed that there is no

threshold dose for TCDD teratogenesis (see p. 11 below); it will be assumed that the sensitivity of humans to the teratogenic effect of TCDD is not less than that of mice; it will be assumed that a surface area factor of 10 for extrapolation from mouse to human exposure is applicable ; and it will be assumed that maternal human TCDD levels are uniformly 30 ppt.

In a paper given at the April 1973 conference on dioxins (4, p. 67) Neubert et al. presented data comparing sensitivities of different strains of mice to TCDD teratogenesis. Dose levels during pregnancy of 3 μg/kg/day produced cleft palate in 22% of the fetuses of the most sensitive strain (C57Bl) and in 3-4% of the fetuses of the other strains. Incidence in controls was 0.7%. For purposes of the present calculation, the value of 3% will be used here. Because the effect in different animal species of a toxic agent varies with surface area (or with body weight to the 2/3 power) rather than directly with body weight, 3 μg/kg body weight in the mouse will be considered to be equivalent to a dose level of 0.3 μg/kg body weight (300 ppt) in humans (5). Therefore this dose level of TCDD will be assumed to produce 3% incidence of teratogenesis in humans.

Assuming that the average body burden of TCDD in humans is 30 ppt and assuming the effect at 30 ppt to be one-tenth that at 300 ppt, one can conclude that present levels of TCDD in humans

may in the worst reasonable case be producing teratogenic effects in 0.3% of human fetuses, corresponding to about 13,000 infants per year for the U.S. population.

Because the incidences of congenital malformations are not systematically monitored at present in the U.S., because it is uncertain just what deformity or deformities, if any, are produced in humans by TCDD, because the deformity may occur with a relatively high "background" level or may not be obvious at birth, because the incidence of the deformity, if it occurs, would have increased gradually during recent years as TCDD body burdens accumulated, and because exposures to 2,4,5-T have been nationwide, leaving no well-defined unexposed control population for contrast, it is possible that such an increment of 0.3% of total births in the incidence of one or more birth defects could have occurred without being recognized as being due to 2,4,5-T usage. The incidence of congenital malformations in the U.S. is estimated to be 7.5% (6). Against such a background level, an additional 0.3% for which no specific search was made could be easily overlooked. 1/

1/ The independent reports from widely separated geographical areas circumstantially linking birth defects in humans to the use of 2,4,5-T (Ref. in 7) lend credence to the assumption that humans are no more immune than other animals to the teratogenic effects of TCDD. Although, in each individual case, causation by 2,4,5-T usage was uncertain , a multiplicity of such cases is cause for concern. These cases

(cont'd.)

Although we fully realize that the above calculation is based on several uncertain assumptions, these assumptions are not extreme. The sensitivity assumed was not that for the most sensitive strain of mice or for the most sensitive abnormality in those mice. No "safety factor" such as is usually employed in extrapolating from animals to humans was used. (The factor of 10 is not a safety factor but is a valid correction for the ratio of suface area to body weight, a correction supported by toxicological data). The human body burden assumed (30 ppt) was approximately equal to that observed in the fat of livestock feeding on rangeland treated with 2,4,5-T containing only 0.04 ppm TCDD, and was less than that observed in U.S. shrews (2) and in Vietnamese fish (4, p. 27).

We were forced to use assumptions, to calculate a worst reasonable case, because actual data are not available. Despite the experimental suggestions that TCDD dose levels in the parts per trillion range may have adverse effects on health, the observations that such levels do occur in environmental samples, and the calculation suggesting that they may well occur in

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(1/ cont'd. from p. 8).

also suggest that in humans, if exposure occurs during the first trimester of pregnancy, spina bifida is one of the malformations produced. In New Zealand, British Columbia, and possibly Vietnam this serious defect was present in infants of mothers who were pregnant at the time 2,4,5-T was used in nearby areas.

humans as well, human tissues have apparently not yet been analyzed for this contaminant at the required level of sensitivity. This fact alone should justify the termination of additional environmental releases of TCDD until the indicated evaluations can be made.

IV. Comments on various points raised by the Dow Prehearing Memorandum #2 (the opening brief):

Our major intention in this submission was to calculate as the worst reasonable case the implications for human health of continued usage of 2,4,5-T. This calculation was presented in sections II and III. For the calculation, several assumptions were required and some of these will be disputed by the Dow Chemical Company as indicated by its prehearing memorandum #2 (1). Accordingly, in this section (A-D, below) we discuss some of the more crucial of these assumptions in more detail, indicating why we think they are reasonable and why we question the conclusions reached by Dow in considering the same questions. In addition, we will discuss (E, below) various other aspects in the Dow Prehearing Memorandum which seem to us to be objectionable. We do not, however, attempt to comment here on the entire spectrum of issues to be considered in the forthcoming hearing.

We will not, for example, discuss the issue of essentiality of 2,4,5-T except to point out that one, at least, of the major uses (use by highway departments) is so non-essential that even in the absence of prohibitions against such use, 25 state highway departments have chosen not to use it (8), and the U.S. Department of Transportation has dropped from the case.

As for the evidence from Vietnam, we expect that testimony will be presented by one or more EPA witnesses which will illustrate why the evidence of human birth defects resulting from herbicide use in Vietnam cannot be dismissed as insignificant. Therefore we do not address this point here. (See V at 33, below.)

A. Are there "Threshold" or "No-effect" dose levels for TCDD teratogenesis?

Conclusions: The existence of such levels has not as yet been convincingly demonstrated. In the absence of such a demonstration, it is only prudent to assume that any level of exposure of pregnant women to TCDD is unsafe.

There are several experiments, summarized in the Dow prehearing brief, in which administration of low doses of TCDD, with or without 2,4,5-T, to pregnant animals failed to produce detectable teratogenesis. However, there is a great difference between the valid demonstration of a no-effect or threshold

level and a mere failure to detect an effect. In the usual case, for the available TCDD experiments, the number of animals used has been so small that the experiment could not have detected the effect, with statistical reliability, at the frequency to be expected if no threshold exists. Thus in the experiment of Neubert & Dillman, the 0.3 μg/kg dose level, for which no cleft palates were seen, is described by Dow as a no-effect dose level (1, p. 51). If, however, one assumes that (1) the cleft palates observed at the next highest dose (9 per 271 fetuses at 3 μg/kg or 2.6 per 100 fetuses after correction for the control incidence of 0.7 per 100) were an accurate measure of teratogenesis at that dose; (2) that there is no threshold level; and (3) that cleft palates will decrease in proportion to the decrease in dose, then at 0.3 μg/kg for the 138 fetuses observed, one would have expected TCDD to cause less than 1 (0.3) cleft palates. The experiment with only 138 fetuses at the 0.3 dose was therefore incapable of indicating whether or not 0.3 is a no-effect dose. It did not demonstrate and should not be cited as having demonstrated a threshold level.

In the experiment of Sparschu et al. (see 1, p. 89), the number of skeletal deformities expected (on the basis of the lowest teratogenic dose) at the lowest dose used was 0.8 per

100 fetuses. It is therefore not significant that none were observed in a total of only 115 fetuses. Again, the number was too small to determine whether 0.03 was a non-teratogenic level for skeletal deformities.

The same type of statistical limitation characterizes the other studies which are alleged by Dow to demonstrate no-effect levels. It is true that experiments sufficient for the statistically valid demonstration of the existence of threshold values would be quite burdensome, requiring the examination of hundreds or thousands of fetuses rather than the dozens which have usually been used. Nevertheless, failures to observe an effect in inappropriate experiments should not be mistaken, as they are throughout the Dow brief, for demonstrations of no-effect levels in the meaningful sense of that term. Neubert et al. have used higher numbers of animals at the lower dose levels than have most if not all other investigators. Their work is frequently cited by Dow as having demonstrated no-effect or threshold levels (1, p. 7, 8, 29, 50, 60, 63). Even these authors state, however, that ". . . we are completely aware of the fact that there is no 'threshold dose', we use this term for convenience to indicate that dose . . . which gives just no significant increase of cleft palate frequency . . . when 300-500 fetuses . . . are evaluated" (4, p. 75).

It must be remembered that not 400 but 4 million human fetuses per year are at risk in the United States alone. Furthermore the duration of possible exposure in utero for each of them is 9 months, rather than the few days that are routinely utilized in studies of teratogenesis in animals. Thus, though it is possible to expose the common experimental animals to TCDD throughout the period of embryonic development, in order to mimic human exposure in terms of stages of development, it is not possible to prolong exposure of the animal fetus to 9 months. If the teratogen in question is one which is cumulative (see B, p. 15 below), so that the actual concentration of TCDD in fetal tissue at any given stage of embryonic development is dependent not only on the current dose but also on the previous duration of exposure to the teratogen, then it is to be expected that the lower doses will be a greater threat to animals with longer gestation periods. Therefore, in the absence of statistically valid demonstrations of no-effect levels even in experimental animals, it is surely not being overly conservative to assume that there may not be a "no-effect" level for pregnant women subjected, possibly, to intermittent lifetime exposures to TCDD.

B. Does ingested TCDD accumulate in animal tissues, producing the possibility that a low and initially harmless level of ingestion, if continued over a longer period of time, will eventually have adverse effects?

Conclusion: Experimental, environmental, and theoretical observations indicate that TCDD does indeed accumulate in animal tissues.

In contrast to this conclusion, Dow asserts that "neither 2,4,5-T or TCDD accumulates in body tissue." Whichever conclusion is correct, the question is very relevant to the problem of whether the use of 2,4,5-T should be terminated. If one is concerned with a toxic contaminant of 2,4,5-T which, on ingestion by animals, is retained in the tissues, and if 2,4,5-T is used so widely and repeatedly that intermittent lifetime human exposures are possible, then decreasing the concentration of the toxic contaminant in 2,4,5-T will not remove the hazard. Such decreases may merely prolong the exposure time required for tissue concentrations to reach dangerous levels. This question therefore goes to the issue of whether TCDD in 2,4,5-T is a hazard even at a level of 0.1 ppm or less. Even if it were possible to guarantee 2,4,5-T with zero levels of TCDD, which Dow significantly fails to do for good reason, the potential for formation of new TCDD during incineration of 2,4,5-T-treated plants (see p. 23 below),

coupled with a potential for bioaccumulation, would ensure that the threat of TCDD intoxication would remain as long as 2,4,5-T was used.

In considering bioaccumulation, Dow cites the study of Piper et al. (4, p. 241) which assessed the fate of labelled TCDD following ingestion. In this study, the total body half-life for a single large dose of TCDD was found to be 17 $\pm$ 6 days. The experiment was continued for only 21 days, presumably because of the poor condition of the animals. Dow concludes on the basis of this study that upon repeated exposure to small levels of TCDD a "steady-state level will be attained within... approximately 90 days." In fact, however, most of the animals in the experiment on which this conclusion was based would not have lived for 90 days. The dose of TCDD in this experiment was approximately twice the LD_{50}. As the authors point out, "with doses which do not induce untoward effects the compound may be excreted at a different rate." It is not to be expected that an organism will be able to cope with a massive, lethal or near lethal dose of a toxicant in the same manner that a non-stressful dose would be handled, a principal that is also stressed repeatedly in the Dow statement (1, p. 11, 20, 28, 34) which points out that "...large doses cannot be used as a reliable prediction of results from the administration of small doses" (1, p. 34). Therefore this study has little

relevance to the question of whether prolonged exposure to low dose levels produces bioaccumulation of TCDD in animals.

In an experiment using lower dose rates of TCDD, Fries placed rats on diets containing 7 and 20 ppb of TCDD (see 2, p. 24). After 42 days, a steady-state level of tissue concentration had still not been attained, although decreased weight gain was observed. Therefore, in this experiment with repeated small doses, the dose level was also too high to permit assessment of long-term accumulation at non-stressful dose levels. In other words, with continued low doses, tissue accumulation continued in this experiment until toxic effects became apparent. Apparently no experiment as yet has demonstrated that with continuous low dose levels, a steady-state non-toxic level of TCDD in animal tissues is achievable.

There is other experimental evidence which indicates that the toxicity of TCDD is a function of the total dose administered, whether it is given as a single dose or is generated cumulatively from repeated smaller doses. Thus, in the experiment of Allen and Carstens (9) monkeys were fed "toxic fat" containing chlorodioxins. Diets containing the toxic fat at 6 different concentrations, ranging from 0.125% to 10%, were all lethal. The survival time however varied inversely with the concentration of toxic fat in the diet. The lowest level allowed a mean survival time of 445 days while the two highest (5% and 10%) produced mean survival times of 91 days. The major clinical and pathological changes

were similar and occurred during the terminal 30 days whether the diet was fed for more than a year (at 0.125%) or for only 3 months (at 5% and 10%). This experiment suggests therefore that dioxin is cumulative in monkeys and that the biological half-life must be at least two years. In another study, Harris et al. (4, p. 108) observed that the dosage schedule used did not change the threshold level of TCDD toxicity in rats: once the total administered dose exceeded approximately 20 μg/kg (whether as a single dose, as repeated weekly doses, or as repeated daily doses) toxicity was observed as evidenced by decreased weight gain.

In addition to the experimental evidence of cumulation cited above, there is also environmental evidence proving that TCDD does indeed undergo bioconcentration in various species of animals including cattle, sheep, goats, shrews, fish, and crustaceans, notwithstanding the statement by Dow that TCDD "has not been found in the environment of the United States; thus it does not accumulate" (1, p. 161). This evidence was cited in prehearing briefs (2, 6) and will not be reiterated here.

The three studies cited by Dow (Bowes et al., Woolson et al. and Zitko; 1, p. 124) which failed to detect TCDD in animals represent a peculiar selection. The analytical procedures of the first of these (Bowes et al.) provided qualitative identification of various chlorinated dibenzofurans in wildlife samples (as well as quantitative results for PCB

and DDE) but specific analysis for TCDD was not carried out. The sensitivities for TCDD of the other two studies (Woolson et al. and Zitko) were 50 and 40 ppb respectively, whereas the initial concentrations of TCDD on forage after spraying with 2,4,5-T (contaminated with 0.1 ppm TCDD) would be about 30 ppt (10, p. 58). Thus a 1000- to 2000-fold concentration would have been possible without detection by the studies cited by Dow.

Other studies (see 2, pp. 35-36) have shown that under various conditions of 2,4,5-T application, TCDD does occur in food-chain organisms.

Studies with model ecosystems cited in the prehearing briefs (1, 2, 7) have also demonstrated directly that bioaccumulation of TCDD can occur.

Finally, the probability of bioaccumulation can be considered from a theoretical viewpoint. As pointed out by Dow (1, p. 119) "to persist and bioaccumulate in the environment, a compound must be stable under most environmental conditions" ("most" should be deleted from this phrase) "and must partition selectively from the treated environment to certain surfaces or tissues of organisms." Indicator properties for bioaccumulation are "(a) very low water solubility, (b) high organic solvent solubility, (c) high partitioning coefficient of fat solvents over water, (d) partitioning selectively into fat

tissues in animal organisms, (g) stability in soil, and (h) low volatility." (Properties e and f were not given in the Dow document.)

We agree that properties d, g, and h above are good indicators of probability of bioaccumulation (as is (c) insofar as (c) is an indicator of (d)). We believe that Dow would agree that a and b would be more accurately stated as "low water solubility relative to organic solvent solubility (equivalent to property (c)) since it is this relative solubility rather than absolute solubilities which will determine whether the compound will partition selectively into fatty as compared to aqueous tissue fractions." Properties a - h therefore reduce to d, g, and h: fat/water partition coefficient, stability, and volatility (although we suggest that volatility is of a lower order of significance for bioaccumulation than partition coefficients and stability).

These criteria indicate that TCDD will bioaccumulate. It is stable in the environment and in biological tissues (11; 2, pp. 33-36) and its solubility in organic solvents exceeds that in water by several orders of magnitude (1, p. 130). Dow places considerable stress on the low bioaccumulation of TCDD, as compared to DDT (which we consider to be true but largely irrelevant) and on the low absolute solubility of TCDD in water and other solvents. Because of

its extraordinary toxicity, this insolubility of TCDD is insufficient to provide protection against its effects. The toxicologically pertinent observation is that TCDD is soluble enough to be lethal.

In summary, 5 types of evidence indicate that TCDD does accumulate in animals: (1) in feeding experiments, tissue concentrations of TCDD have failed to plateau at sub-toxic concentrations; (2) other experiments have indicated that the cumulative lethal dose is approximately constant and relatively independent of the dosage schedule by which it is administered; (3) TCDD has been found in animals at concentrations exceeding the demonstrated or calculated concentrations in soil or treated foliage; (4) studies with model ecosystems have directly demonstrated bioaccumulations of TCDD; and (5) consideration of the physical and chemical characteristics of TCDD leads to the prediction that it will undergo bioaccumulation.

C. Can chronic low level exposure to TCDD cause delayed lethality?

Conclusion: Delayed lethality is apparently typical for TCDD toxicity, whether the exposure level is high or low.

Dow dismisses the question of delayed lethality as having no bearing on low exposure rates, citing only the study by

Schwetz et al. which demonstrated mortality delayed by as much as 40 days after administration of a lethal dose of TCDD to guinea pigs and rats (1, p. 114). However, the experiments of Harris et al. with rats (4, p. 101), of Allen and Carstens with monkeys (9) and of Miller et al. with fish (4, pp. 177-186) each suggest or demonstrate that once the lethal dose is absorbed, death will ensue some weeks or months later and that withdrawal or continued administration of dioxin during this post-lethal-dose period does not modify the remaining survival time. This phenomenon was observed at high or low chronic exposures with a total survival time of over one year being observed at the lowest level of chronic exposure in the Allen and Carstens study.[1/] The period ensuing between the time the animal is given or accumulates a lethal dose and the time of death can be estimated to be 90 days in monkeys (Allen and Carstens) about 30 days in rats (Harris et al. and Schwetz et al.), 10-90 days in fish (Miller et al.) and 5-34 days in guinea pigs (Schwetz et al.). Because of this characteristic of delayed lethality, experiments in which observation of treated animals is not continued for at least three months after TCDD administration may fail to detect a lethal effect, leading to erroneous conclusions regarding the toxicity of TCDD or the relative sensitivities of different species to this compound.

1/ The toxic fat used in this study contained a mixture of dioxins with the tetrachlorinated compound comprising 64% of the total dioxins (4, p. 233).

D. Are there possible significant sources of TCDD in the environment other than the amounts present in 2,4,5-T formulations?

Conclusion: Yes. These possibly significant sources include other pesticides (especially Silvex and other phenoxy herbicides) and 2,4,5-T itself, degraded by incineration or cooking.

Although no assumption of additional sources of TCDD was made for the estimation of possible current TCDD levels in humans (pp. 3 - 6 , above) the value calculated there is more likely to be an underestimation if such sources exist than if they do not.

Dow concludes that such products as 2,4,5-T trichlorophenol, Ronnel, and Silvex, each containing dioxin at <0.1 ppm, contribute such small amounts of TCDD to the environment that they do not constitute a health risk (1, p. 187). (Dow makes these same claims, of course, for 2,4,5-T. It is not clear whether or not Dow regards 2,4,5-T to be more of a hazard in this respect than the other compounds.)

Dow also concludes that no significant amounts of TCDD can be generated in the environment by thermal stress to 2,4,5-T or its metabolites (1, p. 115). They then describe experiments which demonstrated conversion of 2,4,5-T to TCDD to the extent of 0.1% after heating for 60 hours at 100°, 200°, and 400°. The conditions were described as an effort to

exaggerate the pyrolysis conditons which might occur in a fire and the 0.1% was described as a low yield.

Although the 60 hours of heating employed is indeed a long period, exaggerated as compared to duration at one site of rangeland fires, the temperatures employed (up to 400° C) are relatively low. Furthermore, it should be realized that the "low-yield" conversion of 0.1% of 2,4,5-T to TCDD would correspond to a contamination level of 1,000 ppm in the original 2,4,5-T. Heating under the same conditions for a more realistic 6 hours instead of the exaggerated 60 hours might be expected to produce TCDD equivalent to a contamination level of 100 ppm: far in excess of acceptable levels by anyone's standards. Even a 30 minute pyrolysis under these conditions could presumably produce TCDD equivalent to a contamination of about 10 ppm.

To put it another way, if 2,4,5-T containing no TCDD was used and if only 1% of that 2,4,5-T was burned under the conditions described, the effect would be the same as if the original 2,4,5-T had contained 10 ppm of TCDD. To hypothesize even more realistic conditions, if the duration of pyrolysis was only one-tenth as long as in the Dow experiment, and if only 1% of applied 2,4,5-T was subjected to these conditions, the TCDD produced could still be equivalent to an original contamination of 1 ppm in the applied 2,4,5-T: still an

unacceptable level. Thus, although in the Dow experiment the yield of TCDD from pyrolysis of 2,4,5-T is low, if one chooses to express yield in terms of % rather than ppm, it is not at all clear that the yield is low in terms of significance.

Another study cited by Dow involved actual combustion of 2,4,5-T (1, p. 118) and demonstrated TCDD production equivalent to a contamination level of 0.2 ppm (0.00002%). In other experiments, as reported in the EPA brief (2, p. 28) Baughman and Meselson have repeatedly observed TCDD formation at levels of 1000-2000 ppm when the sodium salt of 2,4,5-T is heated and these results have been confirmed by others. Therefore although the extent of post-application formation of TCDD in the environment is admittedly unknown, it cannot be assumed that such formation is of negligible significance.

E. Other mistakes or misrepresentations in the Dow prehearing memorandum #2.

1. Dietary intake of 2,4,5-T:

The discussion on pp. 102 and 103 of the Dow opening brief (1) concerning possible human exposures from food is a good example of the specious underestimation of possible human exposures which is characteristically employed for calculations of allowable pesticide residues in food. Such underestimations are due not merely to arithmetic errors

(item a, below) but are consistently achieved by several other procedures, two of which (b and c) are illustrated here:

a) An arithmetic error occurs in the calculation for meat. An intake of 0.4 kg of meat containing 0.1 ppm 2,4,5-T would contribute 40 rather than 4 ugm of 2,4,5-T per day -- a tenfold difference.

b) The fallacious assumption is made that a representative amount of food (i.e., 400 gm/day as the 9th decile intake of meat) divided by a representative body weight (60 kg) is descriptive of the representative intake/kg/day (giving 6.7 gm/kg body weight/day to represent the 9th decile for meat intake). In fact, when meat intake for each individual is expressed as gm/kg body weight/day, the 9th decile from the USDA data is approximately 10 rather than 6.7 as represented (after arithmetic correction) in the table on page 102. The 9th decile for dairy products is 41 gm/kg body weight/day rather than 18 as represented in the table (12). Therefore, with contaminations of 0.1 and 0.05 ppm respectively, the 9th decile intakes of 2,4,5-T on a body weight basis would be not 0.7 (corrected) and 0.8, as represented in the table, but 1 and 2 μg/kg/day: increases of 43% and 150% for meat and milk respectively.

c) The population at risk if often irrationally defined. This fallacy is illustrated by the calculation for rice in the

table, where the ninth decile intake for rice is represented as being 6 gm of rice per day.

Among those people for whom rice is a dietary staple, 6 gm of raw rice per day (approximately 1.5 tablespoons of cooked rice per day) would be an extremely low intake. Virtually all people for whom rice is a dietary staple would exceed this arithmetic "9th decile intake" for rice. In calculating possible pesticide exposures from any food one should use consumption data derived from those members of the population who routinely use that food. By using instead as a data base for rice consumption, for example, the entire population of the U. S., with its preponderance of non-rice-eaters, EPA, FDA, USDA and the concerned commercial interests consistently underestimate possible pesticide intakes of the people who actually eat the food in significant quantities in their daily diets, just as they underestimate pesticide intakes from other foods which are not eaten in significant amounts by the entire population. In estimating possible pesticide exposures from consumption of a food, one should obviously be concerned with intakes by that fraction of the population for whom the food in question is a significant dietary item. This becomes especially important if this fraction of the total population is a small one. To assume, for purposes of calculation of rice intake, that a single undifferentiated population is involved

leads one to the arithmetically correct but realistically ridiculous position that 1.5 tablespoons per day of cooked rice is a high rice consumption.

If one assumes that within the population for whom rice is a dietary staple, the 9th decile intake is 200 gm/day of raw rice,[1/] contamination by 2,4,5-T at the tolerance level of 0.1 ppm would produce 2,4,5-T intake from rice of 20 µg (or 0.3 µg/kg on a 60 kg basis: 30 times the value assumed by Dow).

On the basis of the arguments presented above, corrections for the table given on p. 102 of the Dow opening brief (1) can be suggested as in the table below:

1/ Two hundred gm of raw rice corresponds to approximately 3 cups of cooked rice. This is merely an estimate, since we do not at this time have access to actual rice consumption data. 500 gm/day of raw rice has been estimated to be the required average daily intake (men, women and children) in China. Therefore 200 gm/day is probably an underestimation of the 9th decile intake of Americans of Oriental dietary habits, as well as of the residents of those Asian countries which import much of the U.S. rice crop.

Foods with tolerances for 2,4,5-T residues	9th decile of food eaten daily gm/kg/day		Assumed residue level 2,4,5-T ppm	Resultant 2,4,5-T intake µg/kg/day	
	Dow 1/	Corrected		Dow 2/	Corrected
Meat	6.7	10	0.1	0.07 3/	1.0
Dairy Products	18.3	41	0.05	0.8	2.1
Rice	0.1	3.3 4/	0.1	0.01	0.3
Total				0.9	3.4

1/ Second column of Dow table converted to body weight (60 kg) basis

2/ Last column of Dow table converted to body weight (60 kg) basis

3/ Based on arithmetic error; intended value was 0.7

4/ Estimate, not based on actual data. See footnote p. 28.

It can be seen that the corrected estimate of possible 2,4,5-T intake from these three sources is approximately 4 times the amount estimated by Dow. This value does not, of course, include 2,4,5-T from other sources (as from water, air, and other food crops contaminated by spray drift or other means) nor does it include other sources of dioxins.

2. Mutagenicity tests:

The statement that dominant-lethal studies, in particular, are the most reliable for evaluating mutagenicity (1, p. 96) is true but misleading. Dominant-lethal tests are the most reliable because they are easiest. However, they cannot detect many types of mutations (e.g. point mutations).

3. Synergism of TCDD and 2,4,5-T:

The last sentence on p. 8 of the Dow opening brief (1) is incorrect. It would be less inaccurate if it were modified to read "such results, extrapolated to humans, indicate that 1 ppm or less of TCDD in 2,4,5-T does not pose a greater danger to the public health and safety than does the TCDD or the 2,4,5-T alone." (underlined words added). Perhaps this was the implication intended by Dow. Even with this modification, however, the sentence and the two immediately preceding it misrepresent the results of the experiments referred to (Neubert, et al., 4, pp. 67-79). In these experiments it was found that at teratogenic doses of 2,4,5-T, potentiation was observed by TCDD in amounts corresponding to contamination level of about 1 ppm but not by combinations containing less than 0.5 ppm (note Dow's statement: "for such potentiation to occur, more than 1.5 ppm TCDD was required"). (If just non-teratogenic doses of 2,4,5-T were used, potentiation by TCDD was demonstrable, but not below TCDD levels corresponding to 10-20 ppm.)

Even with correction of the incorrect numbers in the Dow opening brief (1) in the last sentence begun on p. 7 (change "1.5" to 0.5), in the next sentence (change "1" to 0.5), and in the last sentence p. 8 (change "1" to 0.5), the conclusion of the last sentence, that 1 (or 0.5) ppm TCDD does not pose a danger to human health, would be unjustified. The experiment on which this statement is based determined the levels of TCDD low enough not to produce statistically significant potentiation of effects of 2,4,5-T in 300-500 fetuses when the mixture was administered only during days 6-15 of pregnancy. Further, it did not use the most sensitive strain of mice or the most sensitive effect. In other experimental conditions, effects of TCDD at much lower contamination levels have been noted (2, p. 12). Furthermore, as noted above, human exposures, although predictably lower than the experimental ones when expressed as $\mu g/kg/day$ or as $\mu g/m^2/day$, will involve millions of fetuses rather than hundreds and may occur daily for many years in the mother and throughout gestation in the fetus, rather than for 10 days. Therefore the conclusion that 0.5 ppm TCDD poses no danger to public health and safety must be regarded as little more than wishful thinking.

4. <u>Teratogenicity of TCDD</u>:

The bias of the Dow Prehearing Brief is perhaps most clearly illustrated by the reluctance of the authors to admit

that TCDD is a potent teratogen. They concede that "TCDD probably is a teratogen" (1, p. 5, emphasis added) but that it is not really a "potent teratogen" according to Dow's definitions of the term (1, p. 31) and that its effects are not really very serious as compared to those of aspirin and vitamin A (p. 5), fasting, stress and table salt (p. 48), and thalidomide and other really potent teratogens (p. 52). In point of fact, TCDD causes congenital malformations at extremely low doses, as compared to the doses required for the action of other teratogens. Whether or not Dow chooses to regard this characteristic as definitive of a "potent teratogen", EDF does so regard it.

The terata caused by TCDD in humans, if any, are as yet unidentified. If spina bifida is one of them, as some incidents suggest (see p. 9 , above), the nature of the teratogenic effect in humans is very serious indeed. However, even if the effects in humans are confined to the fetal deaths, skeletal abnormalities and cleft palates which are produced in experimental animals, these defects will rightly seem to the victims to be very serious and should not be regarded otherwise by Dow. No matter what the economic benefits of 2,4,5-T usage, and given alternatives, we contend they are slight anyway, it should not be allowed if there are indications that it may be producing birth defects in animals, including humans, in the neighborhood of its use.

V. Legal Issues

Several legal issues have surfaced as a result of the exchange of briefs so far.[1/] These include the following:

1) Burden of Going Forward and Ultimate Burden of Proof

We agree with EPA's statement on this matter in its opening brief: Respondent and supporting intervenors have the burden of going forward, and the registrants have the continuing and ultimate burden of proving that their product complies with the law. The extent of Respondent's burden, and when and whether it has met it, is a matter for determination by the trier of fact, cannot be stated with precision in the abstract, and must await a factual context. The case law cited by Dow (13,18-20) either supports this observation, or is inapposite since it deals with a different statute, agency and factual context: i.e., the summary withdrawal from the market by the FDA without hearing of a product allegedly in violation of the Food Drug and Cosmetic Act.

2) Prehearing Exclusion of Issues as a Matter of Law

Dow seems to suggest that on the basis of the exchange of pretrial briefs, the issues of mutagenicity, carcinogenicity,

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1/ We have here replied to legal arguments made by Dow in its reply as well as its opening brief. We do not think in responding to Dow's reply brief that in ours we have been given an unfair advantage since (1) no new legal arguments were raised for the first time in Dow's reply brief, (2) our intent is to identify the legal issues early, which is to everyone's benefit, and (3) Dow will have ample opportunity to respond to our position on these issues at the subsequent prehearing conferences and during the hearing itself.

delayed lethality, sublethal chronic toxicity, other sources of dioxins in the environment, creation of dioxins in the environment by thermal stress, and unintended destruction of environmental habitat by 2,4,5-T should be excluded from the case as a matter of law (13, 3-9). With all deference, we think such a ruling would be distinctly premature, especially since all parties agree there is some evidence on all these points, the evidence on some is contested, and more relevant material may come to light during the hearing.[1/] The trier of fact under §§6B1 and 2 of FEPCA deserves as full a presentation of all the facts as possible. Dow apparently fears regarding these issues it will be required to do the logically impossible, i.e. to prove the nonexistence of some unspecified harm, but this fear is groundless. Unless some positive evidence is presented during the

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1/ For example, public availability of the National Academy of Science's study on defoliants with attendant underlying data is expected shortly.

We hasten to point out in addition that in many of these areas of relevant concern, the scientific consensus is that insufficient testing has been performed on 2,4,5-T and TCDD to form a reasonably certain scientific opinion. Since the ultimate burden of proof to show that a product is safe for human health and the environment rests throughout upon the registrant, it is incumbent upon Dow, not EPA or EDF, to show what efforts it has made to investigate these potential problem areas, and what have been the results. Dow has no right to use the public at large as guinea pigs, nor the environment as a Dow laboratory. Our position is that absent substantial negative evidence on the questions here discussed, 2,4,5-T should be removed from

(cont'd.)

EPA/EDF case on an issue, proponents of 2,4,5-T's continued registration will have nothing to rebut. Regarding the allegedly "new" issue of unintended destruction of environmental habitat, the recent passage of the Endangered Species Act in December of 1973 adds even greater importance to what is in reality an old issue in the benefit/risk equation.

3) Alternatives

Dow is incorrect in stating, at least for EDF et al., that all the registered alternatives to 2,4,5-T are environmentally acceptable (13,32). We would expect this hearing to produce helpful evidence on that very point, and further expect by the time of the submission of our final brief to the Administrative Law Judge to be able to refine our views and to rank alternatives in order of preference for the various uses at issue. We would further feel free at that time to state that some potential alternatives are unacceptable to us. On the basis of the evidence as we now see it, for example, Silvex may be one such case.

We also wish to correct an impression left by Dow (13,2) that existence of an alternative is necessary for cancellation under FEPCA. On the contrary, while the existence vel non of

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(1/ cont'd. from p. 34)

the market until the appropriate experimentation has been conducted. In short, when dealing with a substance of the toxicity of TCDD, it is better to be safe than sorry, especially when alternatives exist for most if not all uses.

an acceptable alternative is obviously relevant to the Administrator's decision, nothing in the Act nor its legislative history makes existence of an alternative, chemical or not, a sine qua non for cancellation.

4) Relevance of the Vietnamese Evidence

We are relieved to see general agreement on the relevance of the Vietnamese evidence (1, 42-44; 13, 10-12), although of course the weight to be given this evidence depends upon the comparability of a number of relevant variables in the two countries, such as use patterns and dosage strength. It would now seem all parties are in agreement that the presumption is that chemical properties and human response to specific chemicals are not specific to particular nationalities.

5) Tolerances

We are also pleased to see Dow's agreement to re-examination of existing tolerances in this proceeding (13, 21-22) although we would hasten to caution against Dow's inference that because food levels tested to date do not exceed the current tolerances, therefore there is no hazard to human health from 2,4,5-T (1,102-03). The human health hazard, of course, if the very one under re-examination here, and a presumption of safety from current tolerance levels would beg the major question at issue. We would suggest for logical reasons as well as practical ones that tolerance questions be handled sequentially and commence

after decision on cancellation issues, since findings regarding the latter obviously will affect the former. This is the procedure being followed in the Aldrin/Dieldrin cancellation hearing currently being heard before the Agency.

6) Use-by-Use Risk/Benefit Analysis

Dow suggests (13,12, fn.1) that if the human health risk from use of 2,4,5-T on rice were to be found minimal, the safety of other uses would follow *a fortiori*. We do not accept this argument, and suggest that it is essential to conduct a use-by-use risk/benefit analysis. Various uses of 2,4,5-T around the home, for example, may be even more hazardous to human health than rice uses.

7) Undefended But Currently Registered Uses

To date only the use of 2,4,5-T on rice has been cancelled, with all other uses being merely under investigation. It appears that various currently registered but as yet uncancelled uses are not being defended by any party. Providing a *prima facie* case is made by EPA/EDF regarding 2,4,5-T's hazard to human health, thereby meeting our production burden, we believe these undefended uses should be cancelled, and further believe that cancellation notices need not await ultimate determination of the rice issue, but should be issued at the conclusion of the EPA/EDF opening testimony if the facts so warrant.

8) Field Hearings

We agree with EPA that the key issues, especially regarding risks, are scientific and technical, lending themselves primarily but not exclusively to expert testimony. We also recognize, however, the right of a reasonable number of lay witnesses to be heard regarding 2,4,5-T's alleged benefits (or risks) at mutually convenient hearing sites other than Washington (1, 204, 13, 23-13). We reach the latter conclusion despite the recognition that our own financial status will not permit us to attend such field hearings or put on witnesses there, thereby requiring at the least our de facto waiver of cross-examination with attendant prejudice. To lessen this prejudice, we propose adoption of past ground rules applied by the Agency regarding field hearings in comparable cases. Among these are as follows: field hearings should be strictly limited in number; lay testimony should not be cumulative of either expert or other lay testimony; field hearings should be held in major population centers where we and other parties of modest financial means at least have a chance of obtaining pro bono representation; expert testimony should where possible precede field hearings to reduce the amount of lay testimony subsequently necessary at field hearings; and finally, expert testimony should wherever possible occur in Washington where all parties can participate in cross examination. By adoption

of these procedures, field hearings and numbers of lay witnesses can be reduced to a minimum, with consequent savings of time and money to all concerned, and prejudice to parties like ourselves who cannot afford to travel about the country is at least partially mitigated without depriving lay witnesses of any party of their day in a conveniently located court.

9) Pending Studies

Dow's briefs reveal at least two relevant studies currently underway: One dealing with TCDD in the human body (1, 37), the other with residues in fish (1, 11). We trust other parties will be kept apprised of progress in these studies, and that their results will be made available to all as soon as possible. This scientific inquiry is no place for trial by surprise.

Respectfully submitted,

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VI. References

1. Opening Brief, Dow Chemical Co, FIFRA Docket 295.

2. Opening Brief, EPA, FIFRA Docket 295.

3. Pesticide Residues in Food: Joint Report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, 1966, FAO Agricultural Studies Report #73.

4. Environmental Health Perspectives, Sept. 1973.

5. Freireich, et al. Cancer Chemother. Rep. 50 (1966) 219; see also Rall, D.P.: Environmental Research 2 (1969) 360.

6. McIntosh, R., et al. Pediatrics 14 (1954) 505. (This was a prospective study of 5739 deliveries of fetuses weighing more than 500 gm. Malformations recorded were major ones. Among those infants who survived for at least one month, less than 1/2 (43.2%) of the malformations present were noted or suspected at birth. In another study (P.M. Marden, et al., J. Pediatrics 64 (1964) 357) 15.3% of infants were found to have one or more major or minor anomalies which were apparent by surface examination at birth.)

7. Opening Brief, EDF, FIFRA Docket 295: References No. 26, 27, and 28.

8. Memorandum from the Maintenance Branch to Gregory Wolfe of the Department of Transportation (enclosed with letter of Feb. 27, 1974 to Judge Perlman from J. Thomas Tidd, with copies distributed to all parties to FIFRA Docket #295).

9. Allen, J.R. & Carstens, L.A., Am.J.Vet.Res. 28 (1967) 1513.

10. Report on 2,4,5-T: A Report of the Panel on Herbicides of the Presidents Science Advisory Committee, March 1971.

11. Helleng, C.S., et al., J.Environ. Qual. 2 (1973) 171.

12. Bomkamp, D., & R. Hale, entered in the record as EPA Ex. 38B of the Aldrin/Dieldrin cancellation hearings (Tables 2 & 3)

13. Reply Brief, Dow Chemical Company, FIFRA Docket 295.

CERTIFICATE OF SERVICE

I hereby certify that copies of the foregoing Reply Brief of Environmental Defense Fund, Consumers Union, and Harrison Wellford was mailed, first-class postage prepaid, or hand-delivered to the following, this 11th day of March, 1974:

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