Item ID Number	05224 ☐ **Not Scanned**
Author	Fullerton, Raymond W.
Corporate Author	United States Department of Agriculture (USDA), Office
Report/Article Title	Memorandum with attachment: From USDA, Office of the General Counsel with enclosed final report on the 2,4,5 -T scientific workshop, March 8-9, 1974, Washington, D.C.
Journal/Book Title	
Year	1974
Month/Day	
Color	☐
Number of Images	47
Descripton Notes	

1974

DEPARTMENT OF AGRICULTURE
OFFICE OF THE GENERAL COUNSEL
WASHINGTON, D.C. 20250

TO: Administrative Law Judge Frederick Denniston
Workshop Participants
Parties to 2, 4, 5-Trichlorophenoxyacetic Acid Hearing

FROM: USDA, Office of the General Counsel

Enclosed you will find the final report on the 2, 4, 5-T scientific workshop held in Washington, D. C. on March 8 and 9, 1974. The report is broken down into the following headings.

I. Toxicology

1. Teratology

2. Human Toxicology

3. Other Toxicology

4. Carcinogenicity/Mutagenicity

II. Chemistry

1. Environmental Impact

2. Analytical Methods

3. Residues

4. Sources of Dioxin

5. Statistics

III. Rule of Reason

Raymond W. Fullerton
Margaret Bresnahan Carlson
Alfred R. Nolting

I. Toxicology

I. Teratology

The workshop was opened by Dr. Gehring stating the objectives of the conference. These objectives were to answer a series of questions which had been posed to the participants prior to the meeting, to test the validity of the data, and to discuss and hopefully elucidate the meaningfulness of the data for assessing the risk of using 2,4,5-T for currently registered purposes. A list of individuals attending the conference is attached.

In order to initiate the conference discussion, Dr. Gehring presented the essence of his testimony on the pharmacokinetics of 2,4,5-T and TCDD. Immediately following, Dr. Schwetz presented the essence of his testimony on the teratology of 2,4,5-T and TCDD.

Pertinent points alluded to in a short dicussion following these presentations were more thoroughly discussed when the participants addressed themselves to the questions posed prior to the workshop.

The questions and the subsequent significant discussion were as follows:

1. Has an adequate no-effect level for teratogenicity been determined in experiments for 2,4,5-T and TCDD?

The consensus of the group was that a no-effect level cannot be established statistically. No-effect is an absolute term and it cannot be rigorously demonstrated experimentally. Dr. Gaylor pointed out that an experimental no-effect level may be established but that the large confidence limits for even an experimental no-effect preclude utilization of the terminology in the absolute sense it implies. Thus it is necessary to use the judgment of the experimentalists and other qualified people to assess the hazard of any material.

There was some discussion about the pertinence of the pharmacokinetic studies in the projection of a dose-response curve. As indicated in his proposed testimony, Gehring asserted that it is scientifically unsound to estimate the incidence of an untoward effect of a trace dose of an agent from studies in which does superseding excretory and/or degradation thresholds have been administered. Drs. Gaylor and Holson from the NCTR took some issue with the assertion, indicating that the mechanism for such effects, whatever they may be, may be the same at smaller doses. Dr. Gehring agreed that the mechanism, that is the molecular interaction

between 2,4,5-T and various receptors, may not change qualitatively with the dose. However, the a priori assumption of dose-response methodology assumes that the kinetics for the clearance of a chemical from tissues of the body do not change. Otherwise, one is in essence comparing two different populations. It would be invalid to compare the dose-response for animals excreting or clearing the material from the body with a half-life of 48 hours with the dose-response curve for animals excreting the material from the body in 24 hours.

Drs. Young and Holson indicated that they are initiating pharmacokinetic studies in mice and relating the results to teratogenicity.

2. What are the quantative and qualitative teratogenic characteristics of 2,4,5-T and TCDD?

This subject was covered very adequately by Dr. Schwetz and thus there was little additional information presented during the discussion. Dr. Moore stated that 2,4,5-T and TCDD have very little teratogenic potential in rats. In mice, 2,4,5-T and TCDD produce terata--cleft palates and abnormal kidneys.

The question was raised as to whether the mouse may be a false lead in assessing the teratogenic hazard of either 2,4,5-T or TCDD by Dr. Gehring. The mouse is very susceptible to stress of various types including airplane rides and it has been demonstrated that such stress may cause terata (cleft palates). Dr. Holson from the NCTR pointed out that although this was the case perhaps humans are also susceptible to such stress and we must, therefore, use the mouse to assess the hazard of 2,4,5-T and TCDD. Dr. Gehring asked Dr. Holson if they had measured water consumption and urinary output in the teratogenic studies of 2,4,5-T in mice. He indicated that this was not done, however, it was being considered. Urinary output appears important because 2,4,5-T does cause diuresis.

3. To What extent are results of extreme dosage tests relative to the evaluation of teratological potential at anticipated exposures?

This question was alluded to in Question 1 above. The consensus was that when regimens supersede thresholds for excretion and/or degradation, the data have very limited value for assessing what effects may be incurred with regimens which do not supersede the thresholds.

Dr. Moore indicated that it was important to ascertain whether retarded kidney development may continue with continued postnatal exposure of mice to 2,4,5-T or TCDD. This is important because kidney development is not complete at birth.

Dr. Gaylor raised the point of whether all defects in teratology studies should be combined and evaluated in toto or should specific defects be evaluated. Dr. Schwetz stated both should be done. Dr. Holson agreed saying rodents are polytocious species and embryos in the same uterus may be in different stages of development. Therefore, the same agent may produce multiple effects in the same litter; the specific effect seen in each individual will depend on its stage of development when exposure to the agent occurs.

Dr. Golberg stated that metabolic data are essential for assessing the teratogenic potential of different species. In man, imipramine is rapidly demethylated to desmethylimipramine. Rabbits are unable to demethylate imipramine as readily and in rabbits the compound is a teratogen. Teratogenicity in man given recommended regimens would not be expected.

Dr. Poland indicated that thus far experiments have demonstrated that TCDD is not degraded to a polar compound and is not very reactive. Therefore, one is hard pressed to conclude that TCDD reacts irreversibly with genetic material to induce teratogenesis.

4. What is the statistical reliability of teratology tests?

Since projections of dose-response curves to guesstimate what may occur at lower doses is stochastic, such procedures are useful only to guesstimate the extreme of the potential risk. Dr. Holson asked if effects discerned at doses below those superseding thresholds be used to predict responses to lower doses. Dr. Gehring agreed that this is valid. However, it must be pointed out such projections are stochastic. The tailing of a normal distribution curve for dose-response to either lower or higher doses is ficticious but useful representation of data.

5. What is the teratogenic impact of other dioxins?

This question was, for the most part, skipped over because very little information is available. That which is available was presented in Dr. Schwetz's summary.

6. What are the factors to be considered in extrapolating from the teratogenicity animal testing to humans?

The consensus was that the factors are many and many are unknown. Basically, it boils down to a matter of judgment. Dr. Golberg indicated that dilantin may be a human teratogen. He suggested epidemiological studies should be conducted to ascertain whether 2,4,5-T is a teratogen in man. Dr. Holson asked if an epidemiological study had been conducted. Gehring said no and suggested that such a study may be impossible because he doubts whether many women have been exposed in a manner which would allow characterization of the degree of exposure even if it had occurred. Dr. Schwetz added that for the most part such studies are only feasible for prescribed drugs.

7. What is the significance of the thalidomide instance to the current teratological prognosis?

This was only briefly discussed. Dr. Gehring indicated in a reference by B. B. Brody it was stated "that there was a very good correlation between the blood levels of thalidomide and its teratogenic effect in various species". Dr. Holson from the NCTR, pointed out, however, that the determination of thalidomide is a very difficult one and thus any such correlation may be meaningless. Thalidomide is too labile to allow gathering of data that could meaningfully be interpreted scientifically.

8. What is the significance of the chick embryo tests?

This question was discussed for a very short time, because the group quickly reached the concensus that chick embryo is a very poor test system for teratogens as well as toxic effects of chemicals. Dr. Colberg indicated that in work supported by the FDA the chick embryo test system was clearly shown to be inadequate. The chick embryo is in a captive environment with no possibility of eliminating the chemical from its environment. In addition, the chick's metabolic capabilities to degrade and detoxify chemicals are minimal at best.

9. By definition, what is a teratogen?

Although this question wasn't in the set of questions supplied to the participants, it was alluded to in Dr. Schwetz's presentation. In general, there was a consensus agreement with the definitions proposed by Dr. Schwetz. However, again judgment must be used to differentiate between the fine lines in these definitions. For example, delay in ossification may not constitute a teratogenic response if ossification following birth is sufficient to quickly catch up. If ossification was so lacking that it would result in physical deformities or abnormal mobilization, this would, of course, have to be termed teratogenic. Dr. Holson pointed out that it is important to consider not only physical deformities, terata, but also functional deformities. For example, the effects of a chemical on the central nervous system function. It was concurred that such assessment is indeed in order. Also pointed out by Dr. Schwetz was that teratologists are now beginning to involve themselves in such evaluations.

An additional point which was not alluded to above is that an experimental no-effect level for TCDD has not been established in the mouse. Evidence of embryo and fetotoxicity has been shown at 1 ug/kg when given from the day 6 through 15 of pregnancy. Dr. Moore indicated that essentially equivalent results were obtained in a study in which 0.1 g/kg/day was given to mice. Another point which was not presented above was a short discussion of the approach of Jusko for evaluation of teratogenic effects. The consensus was that Jusko's approach is appropriate only for irreversible teratogens. That is to say for materials which react irreversibly with biological material such as protein and DNA.

Finally, Dr. Dougherty discussed briefly his data collected from teratology studies of 2,4,5-T in monkeys. His studies confirm the previously observed negative results reported by Wilson. Dr. Holson pointed out that in Wilson's studies a higher incidence of abortions occurred in monkeys given the higher dose levels. Dr. Golberg responded that in Wilson's studies the high incidence of spontaneous abortion in monkeys precludes interpreting this as being related to treatment. The normal incidence of spontaneous abortion in monkeys is 15-20%. Dr. Dougherty added that in his studies the incidence of spontaneous abortion in monkeys was 20%. In monkeys receiving the highest dose of 2,4,5-T (10 mg/kg) the incidence was lower.

Dr. Kramer reported on the medical surveillance of the Dow 2,4,5-T worker population with exposures dating back to 1940. There was no statistically significant increase in morbidity of disease processes monitored or mortality when compared to standard male population in the United States.

The Chairman, V. K. Rowe called for information regarding medical surveillance of any Vietnamese population and none was presented.

Dr. Morgan discussed some of the symptoms relayed by applicators such as headache, dizziness or not feeling well; and Dr. Kramer related that this was not a pattern heard from 2,4,5-T workmen.

The report of finding prophyria in 2,4,5-T exposed workmen by Dr. Jacob Bleiberg was discussed at some length. This finding has not been duplicated by other investigators in the field. It was the consensus of the group that investigation of this parameter would not be productive of success in developing a monitoring technique for 2,4,5-T exposure.

Dr. Kramer reported on the study of 61 workers exposed to dioxins in a chlorinated phenol process. Forty-nine workers developed some degree of chloracne and medical surveillance of this group is continuing. The present epidemiological survey revealed no increase in mortality or change in the morbidity rate except for the skin disease itself. Dr. Kramer will have a detailed report of this study at a later date. He emphasized that no case of chloracne has been seen in any of the 2,4,5-T workmen.

The question of immunological significance of 2,4,5-T exposure was raised and no one had any data to answer this question. It was suggested that following the human exposed population for infectious disease incidence or absenteeism rate could provide meaningful data in this area.

Dr. Kilian reported on the cytogenetic studies done on 2,4,5-T workers. A group of 49 workmen were evaluated approximately two years ago and recently a follow-up reevaluation of 40 employees was done. Neither group revealed cytogenetic evidence of an effect from 2,4,5-T exposure. He pointed out that groups of humans had been identified who had had exposures to uranium dust, radium and benzene and studies had shown a correlation between and an increased incidence of cancer. The negative cytogenetic data and the normal epidemiological findings are mutually supportive of the conclusion that 2,4,5-T exposure to this group of workmen had no effect on their health. If 2,4,5-T had mutagenic significance, then one should see a change in the disease patterns of this group, and also see some significant chromosomal abnormalities in their serial chromosomal analysis.

Dr. Golberg raised the question of what realistic human exposures exist with the use of 2,4,5-T in our society. Data has been developed but was not available at this meeting showing that a several thousand-fold safety factor exists if one were to directly extrapolate animal data to man.

Considerable interest was expressed by the group in population monitoring to determine the distribution and concentration of 2,4,5-T and dioxin in humans. Dr. Kilian pointed out that it had been a relatively simple matter to enlist the aid of lactating mothers to cooperate with this type of study. Dr. Jack Moore related that he was familiar with animal work which indicated that TCDD was readily excreted in milk. It was the consensus of the group that fat biopsies of a large population group would not be practical since a considerable amount of tissue would be required for a part per trillion assay. However, a smaller human study group involving surgical biopsies or autopsy material would be possible.

The workshop recommended that:

1. Dr. Bleiberg be contacted to see if he has any additional information on porphyria since writing this paper;

2. Be looked at closely in order absenteeism and infectious disease patterns to evaluate evidence of possible effect on immune systems;

3. A larger study on distribution and concentration of 2,4,5-T and TCDD utilizing human milk as the sample tissue be considered;

4. A study utilizing adipose tissue from postmortem and surgical specimens be undertaken to determine if they contain 2,4,5-T and TCDD.

3. Other Toxicology

This workshop discussed acute and repeated dose toxicity, and absorption, excretion and tissue distribution of 2,4,5-T and TCDD. This was drawn from information presented in the Dow pre-hearing memorandum No. 2 and in two drafts of testimony (P. Gehring and J. Norris) in which studies conducted by The Dow Chemical Company as well as literature reports were discussed, including, for example, those of relevance from the 1971 American Chemical Society "Chlorodioxin" Symposium and work reported at the NIEHS Meeting in April, 1973.

Specifically referenced information was as follows:

Dow Pre-hearing Memorandum No. 2, corrected copy February 8, 1974 for 2,4,5-T:

Single dose toxicology: pages 9-10, pages 15-16.

Repeated dose toxicology: pages 16-19, pages 108-111.

Metabolism: pages 20-22, pages 32-37.

Metabolism from P. J. Gehring draft testimony: pages 3-20.

For 2,3,7,8-tetrachlorodibenzoparadioxin:

Single dose toxicology, draft testimony J. M. Norris: pages 3-11.

Repeated dose toxicology: page 22

Metabolism, P. J. Gehring draft testimony: beginning page 20 and from Dow pre-hearing No. 2, pages 111-113.

The acute and repeated dose toxicity information of 2,4,5-T was substantially that which is widely available. Much of the information on TCDD, however, is of recent date. In fact, Dr. George Fries, USDA; Dr. John Moore, NIEHS; and Dr. Alan Poland, University of Rochester presented data from current, ongoing investigations. Dr. Fries reported on a rat feeding study involving TCDD at dietary concentrations of 7 or 20 ppb (parts per billion) given over a period of over 42 days. He will present this paper at the National Meeting of the American Chemical Society beginning March 31, 1974 in Los Angeles, California.

Of particular importance to the workshop was the presentation by Dr. R. J. Kociba (Dow) of the results currently available from a 90 day study in which rats were given repeated oral dose daily by gavage of 1, 0.1, 0.01, or 0.001 micrograms TCDD per kilogram per day. Light and electron microscopic examination of the tissues is in the final stages. The most important findings were from the pathological examination in which there appears to be definite liver changes and minimal changes in the thymus seen in those animals maintained on the 0.1 micrograms/kilogram/day dose. Very minimal to minimal cloudy swelling in liver tissues (male rats only) was seen at the two lower levels, 0.01 and 0.001 micrograms/kilogram/day by light microscopy. Preliminary examination by electron microscropy indicate normal appearance of the liver cells, but with dispersion and a possible increase of the smooth endoplasmic reticulum

seen in both male and female rats. These hepatic alterations are similar to those reported with many other compounds and indicate a physiological adaptation on behalf of the liver to metabolizing foreign compounds.

The results of the metabolism studies for 2,4,5-T and TCDD (P. Gehring draft testimony) were reviewed by James Rose. It was emphasized that a "steady state" was indicated as having been achieved in the C-TCDD work in rats. Therefore, it is suggested that a steady state would have also been achieved during the 90-day study period reported by Dr. Kociba. Steady state in this instance is believed to mean that the body burden had been established at a maximum level and that the additional input of TCDD into the animal was matched by the rate of excretion.

There was a considerable amount of discussion about all the aspects of the single dose, repeated dose, and metabolism of both 2,4,5-T and TCDD. Insofar as possible, this discussion was directed toward evaluating the adequacy of the "other toxicology" irrespective of the other workshops on metabolism, teratogenicity, carcinogenicity, or mutagenicity.

The general concensus of the scientists in this workshop was that adequate data on 2,4,5-T was available on which conclusions for the safety evaluation of levels of exposure to residues which might be ingested due to their occurrence under practical conditions of use of the herbicide could be based. In the government regulatory sense, it was pointed out that negligible residues (less than 0.1 ppm) were indicated for any food crop use. Actually, results of "market basket" studies reported from the U.S. Department of Agriculture would indicate nil residues of 2,4,5-T occurring in the human food supply. Even so, the 90-day dietary feeding studies done in rats and dogs show a "no ill-effect" level of 10 mg/kg/day. Should the total diet of humans contain as much as 0.1 ppm of 2,4,5-T (a highly unlikely assumption), a safety factor of 5,000-fold exists for human consumption over that which caused no ill-effect in the total diet of rats and dogs.

One or two of the participants indicate that the results of long-term feeding and multi-generation studies of 2,4,5-T in rats would be desirable.

The workshop did not have sufficient qualitative and quantitiative data on the amount of TCDD that are occurring in the human food supply. This must be further defined by the analytical and residue chemists. Finalization of these analytical studies and those of the repeated dose toxicity studies on TCDD (90-days) are necessary before it will be possible to judge adequate margins for TCDD. These may well prove to be

sufficient. However, due to the very intricate toxicological and biological manifestations of this extremely toxic material, the workshop recommended that serious consideration be given to conducting longer term studies, i.e. 2 year dietary feeding studies and multi-generation studies in rats. It was reported that a 2 year study on TCDD may be in progress at the Illinois Institute of Technology. However, information relative to this study was not forthcoming in this workshop. It was recognized that much of the preliminary toxicological and pharmacological data essential for the proper planning of such studies has become only recently available. However, it is now believed that these essential data are in the hands of the toxicologists who should now be in a position to plan the protocols and proceed to organize the accomplishment of such long-term studies.

4. Carcinogencity/Mutagenicity

Dr. Legator gave a brief discussion on the relevancy of current mutagenic test systems. He pointed out that the relevancy of these tests were similar to other animal tests. Dr. Legator classified the current tests based on relevancy to man and ease of performing the test.

Test	Relevancy*	Ease of Performing*
In vitro bacterial test	10	1
Host-mediated	3	3
Specific locus	2	10
In vivo cytogenetics	2	3
Dominant lethal	2	4
Human cytogenetics	1	3-4
Body fluid analysis (blood, urine)/ bacterial system	Preferred Test	

* 1 = relevant or easy

10 = not relevant or difficult

Dr. Legator emphasized the necessity of using test systems employing metabolic activation and mentioned that the body fluid analysis technique could be used in the human.

Dr. Kilian agreed with Dr. Legator and referred to the old proposed FDA protocols on mutagenesis. Dr. Kilian briefly discussed the collaborative work with various laboratories to evaluate some of the current mutagenic test systems. Also some of these tests are being used to evaluate GRAS list compounds. Each test has its specific advantages and disadvantages and the investigator must select the most appropriate test for the specific purpose.

Dr. John Moore reported that NIEHS had conducted a dominant lethal test in rats with TCDD and it was negative. His group of workers does not consider TCDD to be a mutagen.

Dr. Robinson mentioned the dominant lethal test conducted with TCDD by Dr. Khera which was also negative. Also the host mediated and dominant lethal tests conducted with 2,4,5-T by Buselmaier which were also negative.

Dr. Alan Poland also reported sending TCDD samples to Dr. Bruce Ames for testing, using his tester strains of S. typhimurium; these test results were also negative.

Dr. Kilian reported that human cytogenetic and epidemiological studies had not revealed adverse effects in humans working in the production of 2,4,5-T. Dr. Kramer further defined the human cytogenetics studies as one study being conducted while the individuals were actively involved in the manufacture of 2,4,5-T and the second study was a follow-up on the original group two years later when they were not involved in the production of 2,4,5-T.

A brief discussion followed on the human exposure dose of TCDD. Dr. Gehring briefly summarized the comparative pharmacokinetics data on 2,4,5-T in man, rat and dog. Dr. Kilian pointed out that most carcinogens require metabolic activation and if TCDD is not metabolized there would be less potential for carcinogenesis. Dr. Gehring stated there would be no reason to suspect TCDD as a mutagen based on the rat data as the material is removable and there is no permanent association. Dr. Legator mentioned in vivo cytogenetics studies in man: dominant lethal, host mediated, and body fluid analysis if population is available. Dr. Robinson reiterated the tests and results that have been reported in the literature.

Drs. Robinson and Emerson stated that there was a correlation between mutagenicity and carcinogenicity. Many scientists feel that carcinogenicity is the result of several mutational events within a

cell. Dr. Kramer mentioned "Down's Syndrome" and the abnormal karyotypes associated with it; also the Philadelphia chromosome. Dr. Legator pointed out that about three-fourths of the carcinogens require metabolic activation.

Dr. Kociba briefly discussed and showed slides of the multinucleated and enlarged hepatocytes of the rats which were treated with 1 g TCDD/kg for 13 weeks. These changes were similar to those of Buu Hoi and others. Dr. Kramer asked iffeta protein determinations were made and Dr. Kociba said no. Dr. Gehring briefly discussed what Dr. Golberg had said in reference to the hepatocytes - "that multinucleated cells are observed normally in aging rats". Dr. Emerson stated that the lesion was different from those induced by AAF and that multinucleated cells could be found in aging rats and in vitamin deficiencies of primates. Dr. Kramer suggested that the lesion may be reversible.

Dr. Moore read several sentences from Gupta's paper - "Besides these degenerative lesions, large multinucleated giant hepatocytes were also seen in liver of TCDD treated rats. The presence of these cells, increased numbers of mitotic figures and pleomorphism of cord cells suggest that a long term study should be done to assess the possibility of the development of hyperplastic nodules and/or neoplasm".

Dr. Gehring mentioned that in the Bionetics study the mice were treated with an estimated .7γg/kg/week for 7 - 28 days of age and then .2γg/kg of TCDD/week as a contaminant of 2,4,5-T for 17 months.

Dr. Moore referred to an article in press (Tox. App. Pharm.) that reported the LD_{50} of TCDD in C57BL mice as 114 ug/kg. The authors also reported similar hepatic lesions, as described by Gupta, et al, in a subacute study, and stated there was a need for long term studies to evaluate these changes. Dr. Gehring pointed out that the Bionetics study has done that.

Dr. Robinson mentioned the work of IIT on TCDD oral rat and mice studies. Dr. Emerson elaborated on the IIT studies by saying that the objectives of this program were to determine the chronic toxicity and carcinogenicity of chlorinated dibenzodioxins (including TCDD and hexachlorodioxin) and related compounds by skin application to mice and by oral administration to mice and rats. Dr. Emerson mentioned the 3 mouse carcinogenic studies in Europe on 2,4,5-T that were reported by the International Agency for Research on Cancer, 1973. Dr. Kramer asked if we needed inhalation studies on TCDD. Dr. Gehring said there was no evidence that TCDD was metabolized and that it was not volatile.

Dr. Legator stated that data now available is negative on the question of mutagenicity and carcinogenicity of 2,4,5-T and TCDD but additional tests can be added. There is not enough information available at this time.

In summary, it was generally agreed that data presently available do not suggest that 2,4,5-T is a mutagen or a carcinogen. Additional studies might possibly lend more confidence. The Bionetics study in mice was long-term. The TCDD contained in the 2,4,5-T amounted to approximately 0.7 micrograms/week for 1 month and 0.2 micrograms/week for 17 months without an increase in incidence of tumors. Long-term studies on TCDD in rats now in progress at IIT Laboratories should help clarify the hepatic lesions seen at high dose levels in subacute studies in mice and rats.

II. Chemistry

1. Environmental Impact

Several participants presented data from laboratory and field studies with TCDD, alone or in conjunction with 2,4,5-T and 2,4-D. The information presented herein was developed from notes taken during the workshop supplemented by published and unpublished reports of the individual studies as listed under references. Proposed answers to the assigned questions are outlined briefly at the end of this report on Workshop B.

Discussions during the workshop included attempts to define terms used to describe the relationship between concentrations of TCDD reported to be associated with different components of the ecosystems studied. Although agreement was not reached among all participants, the following definitions are hereby proposed for further consideration:

(a) Bioconcentration - the concentration of a chemical in or on an organism compared to its environment, due at least in part to physical adsorption on the organism.

(b) bioaccumulation - the accumulation of a chemical in an organism from its environment.

(c) biomagnification - the increase in concentration of a chemical in successive organisms in ascending the trophic food chain.

The terms used in the following reports are the terms used by those making the presentations and do not necessarily conform to the above proposed definitions.

Studies by Isensee and Matsumura were done quite differently but the data obtained were similar and generally supportive of each other. The general conclusion from Isensee's work with ^{14}C-TCDD was that the distribution ratio for the radioactivity in water/soil was about 1/10,000 and the ratio for organisms/water was about 10,000/1. The bioaccumulation ratio calculated for TCDD (based on ^{14}C count) was about 10 times less than for DDT in Isensee's experiments and about 10 to 100 times less than for DDT in Matsumura's studies. According to Matsumura, no evidence was obtained to indicate biomagnification of TCDD in the food chain.

Isensee's data were reported in part on page 34 of the EPA January 18 prehearing brief. His studies were conducted in a glass aquarium containing 4 liters of water and various amounts of Matapeake silt loam or Lakeland sandy loam in three distinct experiments. The soil was pretreated with ^{14}C-TCDD at nine levels ranging from 7.45 parts per million to 0.0001 ppm. The amount of TCDD per tank was 149 g in 20 g of soil in the first experiment, 63 g in various amounts of soil in the second experiment, and ranged from 10 to 0.01 g in 100 g of soil in the third experiment. The organisms were introduced into the tank in sequence as follows: Algae, duckweed, snails and daphnids for 28-29 days, then Gambusia (mosquito fish) for 3 days, then catfish for 6 days.

The following table taken from Isensee's manuscript represents the distribution of apparent TCDD in the various componetns, all based on ^{14}C-counting. Almost all the recovered radioactivity was associated with the soil, regardless of level added, indicating that soild would be the main reservoir for TCDD in the environment. The amount recovered in the water ranged from 0.05 to 3.61% of the amount added, with no apparent relation to the amount added.

The TCDD levels reported were all based on ^{14}C-counting. The nature of the radioactivity was examined by thin-layer-chromatography (tlc). About 86 to 94% of the recovered activity was found in a single mobile spot for each extract, with up to 6% at the origin and up to 10% as a streak between the origin and the mobile spot. The major spot for tissue and water extracts had a somewhat lower mobility compared to the standard TCDD (R_f 0.71), attributed by Isensee to the presence of soluble organic material. (However, it is possible that the 1% radioactivity found in the organisms and water compared to the soil represented soluble impurities or photodegradation products of TCDD rather than TCDD itself.) The levels reported for soil and water are shown on the following page of text, giving an average distributon ratio of 1/11,350 for water/soil.

Table III. Recovery of ^{14}C in Ecosystem Components.

Expt. no.	Soil conc. ppm	Percent of ^{14}C-TCDD originally added								
		Soil	H_2O	Algae	Duckweed	Snails	Daphnids	Gambusia	Catfish	Total
I	7.45	84.90	3.61	1.90	na[a]	0.44	0.16	0.06	na	91.07
II	3.17	97.79	1.51	0.67	na	0.23	0.02	0.04	0.20	100.46
II	0.53	95.09	0.30	0.12	na	0.04	nd[b]	0.02	0.04	95.61
II	0.29	88.45	0.11	0.06	na	0.02	nd	0.01	0.04	88.69
II	0.15	87.57	0.05	0.04	na	0.02	nd	0.01	0.02	87.70
III	0.10	85.44	0.31	0.26	0.03	0.21	0.01	0.11	0.47	86.83
III	0.01	86.73	0.32	0.28	0.04	0.15	0.01	0.07	0.53	88.13
III	0.001	87.59	1.32	0.55	0.04	0.18	0.01	0.06	0.47	90.22
III	0.0001	98.56	0.79	0.28	0.26	0.68	0.02	0.15	0.43	101.17

[a] not analyzed. [b] not detectable.

Experiment	ppm in soil	ppt in water	water/soil
I	7.45	1330	1/5,600
II	3.17	239	1/13,260
II	0.53	48	1/11,000
II	0.29	18	1/16,000
II	0.15	7	1/21,400
III	0.10	7.13	1/14,000
III	0.01	0.66	1/15,000
III	0.001	0.26	1/3,850
III	0.0001	0.05	1/2,000
		average	1/11,350

In experiment I at 7.45 ppm TCDD in soil, the apparent 1330 parts per trillion (ppt) TCDD in the water exceeded the solubility of TCDD in pure water (0.2 ppb or 200 ppt). This discrepancy may be due to increased solubility of TCDD in water containing dissolved organic matter from components in the ecosystem, or to adsorption of TCDD on colloidal particles in the sample of water which was counted, or because part or all of the dissolved ^{14}C-activity was not TCDD. A concentration of 3.17 ppm in soil gave 239 ppt TCDD equivalent in water (close to the solubility of TCDD in water). Experiment III was conducted using higher specific activity ^{14}C-TCDD than in Experiment I and II, and the lowest levels studied approached levels which might be encountered in soil treated with 2,4,5-T containing measurable levels of TCDD.

Apparent TCDD levels in the organisms reached as high as 2 ppm in daphnids in Experiment I at 7.45 ppm in soil vs. 1330 ppt in water. The organisms survived these very high concentrations, possibly because the 14C-activity was not TCDD or was TCDD adsorbed on the surface rather than absorbed into the organisms. This view is supported by the fact that the organism/water ratio of ^{14}C-activity was lower for catfish than for the smaller Gambusia (mosquito fish). This is the opposite to DDT in fish in natural systems where larger fish have higher residues; however, the exposure may not have been long enough in this study to

draw firm conclusions. At lower concentrations the relative amount in various species changed, indicating that there is a difference between bioconcentration and bioaccumulation. Raising the concentration in water two-fold resulted in a decrease in the apparent bioaccumulation ratio by half. (In all cases, the bioaccumulation ratios were calculated from the ^{14}C-activity in tissue on a dry weight basis compared to the ^{14}C-activity in water, emphasizing differences for tiny aquatic organisms which consist of up to 90% water.) (See Table II from Isensee, which follows.)

Table II. Bioaccumulation of ^{14}C-TCDD by Several Aquatic Organisms as Affected by Soil and Water Concentration

Expt. no.[a]	Soil conc. ppm	H_2O Conc. ppt	Algae	Duckweed	Snails	Daphnids	Gambusia	Catfish
			ppb					
I	7.45	1330	6,690 ± 960[b]	na[c]	1,820 ± 170	10,400 ± 480	1,380 ± 220	na
II	3.17	239	2,500 ± 120	na	2,780 ± 400	7,450 ± 30	2,200 ± 680	720 ± 130
II	0.53	48	390 ± 20	na	1,970 ± 690	70 ±	540 ± 250	110 ± 90
II	0.29	18	230 ± 20	na	290 ± 30	70 ±	420 ± 190	120 ± 5
II	0.15	7	130 ± 50	na	330 ± 80	70 ±	90 ± 20	80 ± 50
III	0.10	7.13	79.3 ± 12.5	30.7 ± 1.3	125 ± 23	163 ± 10	439 ± 76	103 ± 49
III	0.01	0.66	5.0 ± 1.0	3.3 ± 0.5	9.7 ± 1.4	17.7 ± 5.9	41.8 ± 4.5	18.4 ± 5.3
III	0.001	0.26	1.4 ± 0.2	0.3 ± 0.0	1.4 ± 0.2	4.7 ± 2.2	5.9 ± 2.7	1.2 ± 0.3
III	0.0001	0.05	0.1 ± 0.0	0.2 ± 0.1	1.2 ± 0.6	2.4 ± 1.1	1.2 ± 0.6	0.1 ± 0.0
			Bioaccumulation Ratio[d]					
I		1330	5,000	na	1,400	7,800	1,000	na
II		239	10,500	na	11,600	31,200	9,200	3,000
II		48	8,100	na	41,000	na	11,300	2,300
II		18	12,800	na	16,100	na	23,300	6,700
II		7	18,600	na	47,100	na	12,900	11,400
III		7.13	11,100	4,300	17,500	22,900	61,600	14,400
III		0.66	7,600	5,000	14,700	26,800	63,300	27,900
III		0.26	5,400	1,200	5,400	18,100	22,700	4,600
III		0.05	2,000	4,000	24,000	48,000	24,000	2,000

[a]TCDD of 2.8 uCi/mg specific activity used in experiments I and II; 460 uCi/mg specific activity used in experiment III. [b]Standard error of the mean for 3 replications (experiment I) and 2 replications (experiments II and III). [c]na - Not analyzed. [d]Concentration of TCDD in tissue (dry wt.) divided by concentration of TCDD in water.

* Solubility of TCDD in water to 200 ppt

The January 1974 prehearing brief submitted by EPA contained data derived from Isensee's study. Values cited were 0.08 to 0.44 ppm TCDD in various aquatic organisms exposed for 28-29 days or 3 days to water in contact with soil containing 0.1 ppm (100,000 ppt) TCDD. They calculated that treatment of rice with 2,4,5-T containing 0.1 ppm TCDD would result in 12 ppt TCDD in the top 1/4 inch of soil and 0.01 ppt in the water in contact with it. They extrapolated this to result in 140 ppt in fish within 3 days exposure to rice flood water. (This was based on the 1/14,000 concentration factor for water/soil at the 0.1 ppm level in soil rather than for the lower 1/2000 factor found at the more reasonable level of 100 ppt in soil.

Matsumura measured the uptake of radioactivity by a variety of organisms in a 200 ml mini-ecosystem to which he added the same ^{14}C-TCDD used by Isensee in Experiments I and II above. In one series of experiments the TCDD was added directly to water as a solvent solution along with the primary food organism such as algae and yeast. In a second series the solvent solution was evaporated as a thin film on the inner surface of a glass container in which the food organisms were grown prior to transferring them to the aquarium. In a third series the ^{14}C-TCDD solution was added to sand, the solvent evaporated, and the sand added to the aquarium. All studies were conducted for only 4 to 7 days under static conditions with single and mixed populations of organisms to compare the bioaccumulation ratios for TCDD, DDT, Y-BHC and mexacarbate (the active ingredient in ZECTRAN(R) insecticide).

In the first study, concentration factors for TCDD in organisms compared to water were 49 for daphnia in the presence of algae, 218 for ostracods in the presence of algae, and 121 for brine shrimp in the presence of yeast. However, the theoretical water concentrations of 32.4 and 16.2 ppb TCDD equivalent far exceeded the solubility of 0.2 ppb for TCDD in water so absorption of the TCDD on the food organisms must have occurred. In the second experiment with algae containg 162 ppb TCDD, the concentration factors were 2198 for Daphnia compared to water containing 0.4 ppb TCDD equivalent, and 107 for Ostracod in water containing 2.6 ppb TCDD equivalent.

In the third series of experiments using 1.62 ppm (ug/g) ^{14}C-TCDD on sand, he found 157 ppb TCDD equivalent in brine shrimp vs. 0.1 ppb in water, and 4,150 ppb in mosquito larvae vs. 0.45 ppb in water. Under the same conditions only 2 ppb was found in fish (silverside) and none was detected in water. In a two-step study with mosquito larvae followed by fish, the level in fish was 708 ppb TCDD equivalent compared to 3700 ppb in the mosquito larvae and 1.3 ppb in the water. This gave a concentration factor of 54 as compared to 306 for DDT (not 540 as cited

in the January 1974 prehearing brief submitted by EPA). Based on these experiments, TCDD has a bioaccumulation factor about 1/10 to 1/100 that of DDT for the organisms studied or about 1/10 of that found in Isensee's studies.

Matsumura stated during the workshop that we have no proof that TCDD is biomagnified, i.e. that its concentration increases as it goes up the food chain. However, he did find bioconcentration of the ^{14}C-activity in or on organisms compared to water under the conditions of the studies. He also found that the bioconcentration factor was 10 times less when he used lake sediment rather than sand in his mini-ecosystem. He also found 1-2% degradation of the TCDD in the presence of lake sediment and a variety of organisms. He plans to do more work on microbial degradation using higher specific activity TCDD and lower concentrations in the soil reservoir of his system.

Baughman and Meselson of Harvard reported finding 18 to 810 ppt TCDD in crustaceans and fish caught in rivers and near the coast of Vietnam not far from Saigon. The samples were collected in August and September 1970 and were kept frozen under liquid nitrogen until analyzed 2-1/2 years later using Baughman's repeat scan mass spectrometry technique.

Dow has requested samples of the fish and/or shrimp for confirmatory analysis using combined gas chromatography-mass spectrometry (GC/MS), but these requests have not yet been honored. Dow is interested in performing confirmatory analysis because it is possible that the TCDD reported to have been found in these samples may represent inadequate separation from high levels of interfering PCB's or DDE, or to the presence of tetrachlorodioxins other than the toxic 2,3,7,8-isomer referred to as TCDD. Such "dioxins" could originate from pentachlorophenol used in that region for treatment of aquatic areas. Analyses of Asiatic pentachlorophenol revealed high levels of "dioxin" compounds including TCDD whereas no TCDD has been detected in Dow pentachlorophenol.

Use of Herbicide Orange (Agent Orange) for defoliation in Vietnam was at 3 gal/A (approx. 13 lb 2,4,5-T acid equivalent per acre plus 13 lb 2,4-D ae/A, both as butyl esters). Captain Young stated that herbicides were applied as a spray released at 150 ft elevation at 130 (Knots Indicated Air Speed) with average particle size 250 microns and 98% of all particles greater than 50 microns in diameter. Thus most of the material was intercepted by foliage of the target forest area. Since TCDD is considerably more soluble in Herbicide Orange than in water, and esters of 2,4-D and 2,4,5-T are readily taken up by the waxy surface of leaves, most of the TCDD in the herbicide remained on the foliage where it was subject to photodegradation without ever reaching

the water. Young added that some areas may have received four or five applications over the years and a few spots may have been grossly contaminated when defoliant loads were dumped by pilots to escape enemy attack.

Leng has calculated that direct application of Herbicide Orange to a pond one foot deep would result in initial levels of 5 ppm 2,4,5-T plus 5 ppm 2,4-D as butyl esters. Such levels would be lethal to fish. If the 2,4,5-T contained 1 ppm TCDD (the specification level for Dow 2,4,5-T in the 1960's) the water would contain 5 ppt TCDD at the time of application. However, the dissolved TCDD could undergo photodegradation in the presence of dissolved organic hydrogen donors and could also be largely absorbed on the pond sediment resulting in much less than the calculated 5 ppt TCDD in the water. The chances seem slim that contaminated sediment from treated aquatic sites could end up in any one location to provide levels of TCDD sufficiently high to cause residues up to 810 ppt in fish or shrimp caught up to 30 kilometers from shore, as implied in reports on the work by Baughman and Meselson.

The general concensus of opinion among participants in the workshop was that it was unlikely that the residues found in Vietnamese fish and shrimp collected in 1970 were due to TCDD in the 2,4,5-T used for defoliation in that area during the 1960's. Further information should be obtained as to how the analyses were conducted, i.e. whole fish including heads, fins and viscera, and whether most of the alleged residue is associated with scales and skin or with fat of the fish, or with heads and tails of the shrimp as has been rumored recently. The samples should be made available for analysis in other laboratories, using slightly different methods, to confirm the nature and level of the residues claimed to have been found by Baughman.

Crummett reported on analyses for TCDD in samples collected by Dow in a rangeland area in Texas and in a rice growing area in Arkansas. No TCDD was found in catfish caught in a pound draining an area of about a million acres of rangeland. According to Bovey (USDA, Texas), the area had been treated with about a million pounds of 2,4,5-T since 1949. The GC/MS methods had a sensitivity of 1 to 2 ppt TCDD and a detection limit of 6 ppt in these fish.

Similarly, no TCDD was found in catfish and bass collected in a 200 acre pond adjacent to a 6000 acre rice field where 2,4,5-T had been used for many years and where the water had been recycled over the field each year. The lower limit of detection for TCDD was 8 ppt in these fish due to background interference from high levels of DDE and PCB's. No TCDD was detected in sediment from the pond (detection limit 1 ppt) nor in water from the pond (detection limit 250 parts per quadrillion).

Samples of human milk from women in the rice growing area in Arkansas were also analyzed. No TCDD was detected with a sensitivity of 1 to 2 ppt based on recovery studies on cow's milk with much interference due to high levels of DDE and PCB's..

Page 36 of the EPA prehearing brief reported finding 6 to 41 ppt TCDD in fat and 1 to 5 ppt in liver of calves, goats and sheep fed immediately after application of 2,4,5-T to rangeland. According to information obtained from EPA, the animals grazed for 38 days prior to slaughter in an area treated with 2,4,5-T at 0.5 lb/A. The 2,4,5-T contained 0.05 ppm TCDD. Leng calculated that measurable residues of TCDD are not likely to occur in fat and still less in liver of these animals. As shown below, the maximum theoretical residue of TCDD would be 117 ppt in fat if all the grass eaten contained the maximum calculated residue of 4 ppt TCDD for the entire 38 days, and all the ingested TCDD reamined in the fat on the animals.

In reality, most grass would contain less than the maximum residue, the TCDD content of the grass would decrease with time after application, much of the TCDD ingested would be excreted during the 38 days, and only part of the retained TCDD would be in the fat. This view is supported by data from independent analyses by Dow and EPA of fat and liver from cattle fed 50 to 900 ppt TCDD with 100 to 1800 ppm 2,4,5-T continuously in the total diet for 28 days. According to the EPA data (table following p. 36 of the January 1974 EPA prehearing brief) the levels of TCDD found in fat were about 2.1 times the level in the diet and were lower in liver. Therefore, ingestion of less than 4 ppt TCDD in the grass (12 ppt on a dry weight basis) would result in less than 25 ppt in the fat of the animals. Dow values for TCDD in fat were considerably less than those found by EPA at levels of 50 or 150 ppt TCDD in the diet and were much higher than EPA values at 450 and 900 ppt TCDD in the diet, indicating that EPA had more background interference and poorer recoveries than Dow.

EPA also reported finding up to 397 ppt TCDD in shrews trapped in rights-of-way treated with 2,4,5-T. Additional information obtained recently from EPA indicated that residues found in four samples of shrews ranged from 54 ppt to 397 ppt (average 202 ppt) from areas treated with 2,4,5-T at 10, 16 or 8 lb/A. No information was provided as to how the material was applied, nor the dates of treatment and sampling, nor the nature of samples analyzed. Further inquiries will be made to obtain full details of how the animals were exposed and how the analyses were conducted.

Dow will pursue obtaining monitoring samples from EPA for confirmatory analyses by the combined GC/MS procedure.

Captain Young reported on studies conducted in a U.S. Air Force test site (Test Area C-52A, Eglin Air Force Base Reservation, Florida). Massive amounts of herbicide were applied undiluted by air during 1962-70 to an area of approximately one square mile. In 1962-64, Herbicide Purple (Agent Purple) was used. It contained n-butyl ester of 2,4-D and mixed butyl and isobutyl esters of 2,4,5-T, and is estimated to have contained as much as 40 ppm TCDD. It was applied along the flight path on a 92 acre area at a total rate of 1894 pounds 2,4-D plus 2,4,5-T per acre. Another flight path in the 92 acre area was treated in 1964-66 with Herbicide Orange (Agent Orange) at a total rate of 1168 pounds 2,4-D plus 2,4,5-T per acre. Another 240 acre area received lower rates of Herbicide Orange and Herbicide White (picloram plus 2,4-D) in 1966-70.

The test site was very sandy (92% sand, 4% silt, 4% clay). Spring-fed ponds originated on the test grid and drained across the flight path into the adjacent plant and animal community. In 1970-71 samples of soil were analyzed for TCDD and none was detected by the methods available at that time (sensitivity 1 ppb rather than 1 ppm as given in a USDA summary report). Recent analyses of samples taken in June and October 1973 indicate levels of 10, 11, 30, and 710 ppt TCDD in the top 6 inches of soil from various locations in the site. Residues found at lower depths were probably due to contamination from the upper level during the sampling procedure. The highest level (710 ppt) was in a sample from the area that received 947 lb 2,4,5-T/A during 1962-64. Young estimated that initial residues may have been as high as 1 ppm TCDD in soil on one of the oldest flight paths treated at these high rates with Herbicide Purple in 1962-64. The 30 ppt level was at the intersection of flight paths receiving Herbicide Orange in 1964-66 and 1966-68.

Analysis of sediment from a bayhead near the test area revealed levels of 13 ppt near the 1962-64 flight path and 11 ppt in a pond adjacent to the intersection of the 1966-68 flight paths. The soil around the ponds also contained low levels of TCDD (10 and 11 ppt) but none was detected in aquatic organisms collected from ponds, bayheads, or streams draining the test area (limit of detection 10 ppt).

Livers of beach mice trapped in 1973 were reported to contain 300 to 540 ppt TCDD after an estimated 30 generations of exposure time in this area. Cotton rats trapped near ponds on the 1966-68 test area were reported to contain 210 ppt TCDD in the liver. Analyses of livers from mice and rats trapped about a mile from Test Area C-52A were reported as 20 ppt.

Photographs of the test areas in 1969 clearly showed the effects of the massive herbicide treatment but photgraphs in 1970-71 and in 1973 showed relatively complete recovery of the vegetation cover within a few

years. Samples of seed from panicum grass in the treated area are available for TCDD analysis to confirm the belief that this chemical is not taken up by plants from soil residues.

Young also reported on mass degradation studies where Herbicide Orange was incorporated below the soil surface at rates of 1000, 2000 or 4000 lb/A. The intitial TCDD level was about 148 ppb in sites receiving 4000 lb/A. The half life found for TCDD was only 88 days in the presence of massive amounts of 2,4-D and 2,4,5-T under the alkaline desert conditions of this study in Utah. This is considerably faster than the one-year half life found by Kearney et al. when only TCDD was added to soil at levels of 1, 10 and 100 ppm. It is likely that the TCDD was more evenly dispersed in the soil when added as a ppm solution in Herbicide Orange (butyl esters of 2,4-D and 2,4,5-T) and was cometabolized with these massive amounts of 2,4-D and 2,4,5-T in the soil. The soil was initially at a pH of about 8 but rapidly became acid when the esters were hydrolyzed to 2,4-D and 2,4,5-T by soil microorganisms. The degradation of TCDD is believed to occur via bacterial action.

Norris commented briefly on his work with TCDD in three species of fish (guppies, coho or silver salmon, and trout) and three aquatic invertebrates (a snail, a worm and mosquito larvae). The levels studied ranged from 0.056 to 10,000 ppt TCDD in water for 24 to 96 hours and observations were made for up to 80 days. The TCDD level in water with young salmon declined significantly with time. A 50 ppt solution decreased to 50% in 24 hr. and to 20% in 96 hr. The initial rapid loss is probably due to adsorption since a similar test without fish declined to 60% in 4 hr. Some volatilization may also have occurred.

The toxic response to TCDD in fish is delayed as it is in other animals. Initial response to the chemical did not occur for 5 to 10 days after the beginning of the exposure period and mortality often extended over the next 2 months. The levels of exposure were expressed in nanograms per gram of total body weight (ng/g) of the organism based on the amount of material in the container relative to fish biomass at the beginning of the experiment; this is not equivalent to total body burden in the fish.

Norris et al. concluded that TCDD in water or food is toxic to fish and duration of exposure is less important than level of exposure. Irreversible effects were produced in young salmon exposed to TCDD in water at levels greater than 23 ng/g of fish and death resulted in 10-80 days. The critical exposure period may be somewhat less than 24 hours in static water toxicity tests in which TCDD concentrations may change

markedly with time. Small fish are more sensitive than large fish on an equivalent exposure level basis indicating adsorption on the surface may be the major route of uptake from water. Levels of 2.3 ppm TCDD in food markedly reduced growth of young rainbow trout in tests where 10 fish were exposed to 6.3 ug per tank per week for 6 weeks. However, no effect was noted in fish when the food contained 2.3 ppb (2300 ppt) TCDD.

Pupation of mosquito larvae was not affected at 0.2 ppb TCDD in water (its solubility) but this level reduced the reproductive success of the species of snail and worm studied.

As noted previously, all these studies were conducted at TCDD levels for in excess of what might be encountered in the environment from the use of 2,4,5-T containing 0.1 ppm TCDD. Norris estimated that levels of 0.0001 to 0.001 ppt TCDD might occur in streams shortly after aerial application of 2,4,5-T at 2 to 4 lb/A in Western forests.

Based on the above information, the following answers to questions presented to the workshop were suggested:

1. The reported finding of up to 800 ppt TCDD in Vietnamese fish and shrimp has little or no significance to current U.S. manufacture and use. Data reported by Young indicate that the residues found in 1973 are not derived from use of 2,4,5-T for defoliation in Vietnam during the 1960's.

2. The results of laboratory studies on "bioaccumulation" of TCDD indicate that TCDD is preferentially associated with soil in the natural environment, but that the very small quantities in water in contact with the soil may become bioconcentrated in/on aquatic organisms. However, the studies also indicated that the levels in/on the organisms would not exceed the levels in the soil source. Current U.S. manufacture and use is not likely to result in detectable residues of TCDD at the ppt level in water, fish, soil, crops, meat or milk. Care must be taken in interpreting analyses for TCDD in the presence of much larger amounts of DDE and PCB's in the samples.

3. There is little significant hazard to the non-human environment resulting from current U.S. 2,4,5-T manufacture and use. This conclusion is based on the lack of pathological effect noted in animals exposed to high

levels in the environment at Eglin Air Force Base as well as in the diet in exaggerated feeding studies along with 2,4,5-T in livestock. Calculations indicate that levels of TCDD which might occur in the environment from use of 2,4,5-T are far below those which might cause an untoward effect in animals, birds, fish, or other living organisms.

2. Analytical Methods

The workshop briefly discussed the following analytical methods; (1) analysis of 2,4,5-trichlorophenol, (2) analysis of 2,4,5-T acids and esters, (3) determination of 2,4,5-T acid in plant tissues and products, (4) determination of 2,4,5-T acid in animal tissues, (5) determination of 2,4,5-trichlorophenal in animal tissues, (6) TCDD in 2,4,5-trichlorophenol, 2,4,5-T acid, and 2,4,5-T esters, (7) TCDD in environmental samples and (8) other dioxins in 2,4,5-T acid and esters.

Participants in the workshop saw no problems with methods 1 and 2. A question was raised concerning methods 3, 4 and 5 as to whether these methods determine total 2,4,5-T acid and total 2,4, 5-trichlorophenol or if bound residues of these materials remained unextracted by the method. No problem was found with method 6. Considerable problems remained in the interpretation of the meaning of low part per trillion results in method 7, however. It was also generally agreed that method 8 was not completely developed due to lack of analytical standard of certain dioxins.

The workshop thus agreed that the two questions proposed by those who set up the work shop were the correct ones to which it should address itself. These were: (1) what is the ability of current methods used to determine bound residues of 2,4,5-T and 2,4,5-trichlorophenol? Those in attendance were in agreement that these methods determine total residues including "bound" residues in animal and plant tissues, (2) what are the criteria to be used in arriving at a determination of the valid level of detection for TCDD? This question was considered by a group of Analytical Scientists, December 13, 1973 in a meeting at the Environmental Protection Agency. The results of that meeting were summarized by Carrol Collier in a letter to the participants on January 25, 1974. He summarized the conclusions in seven points. The first five of these points were in agreement with the notes and recollection of the workshop participants who also participated in the December 13 meeting. However, points six and seven were not and Dow Chemical was instructed to respond to points six and seven in a letter to Collier.

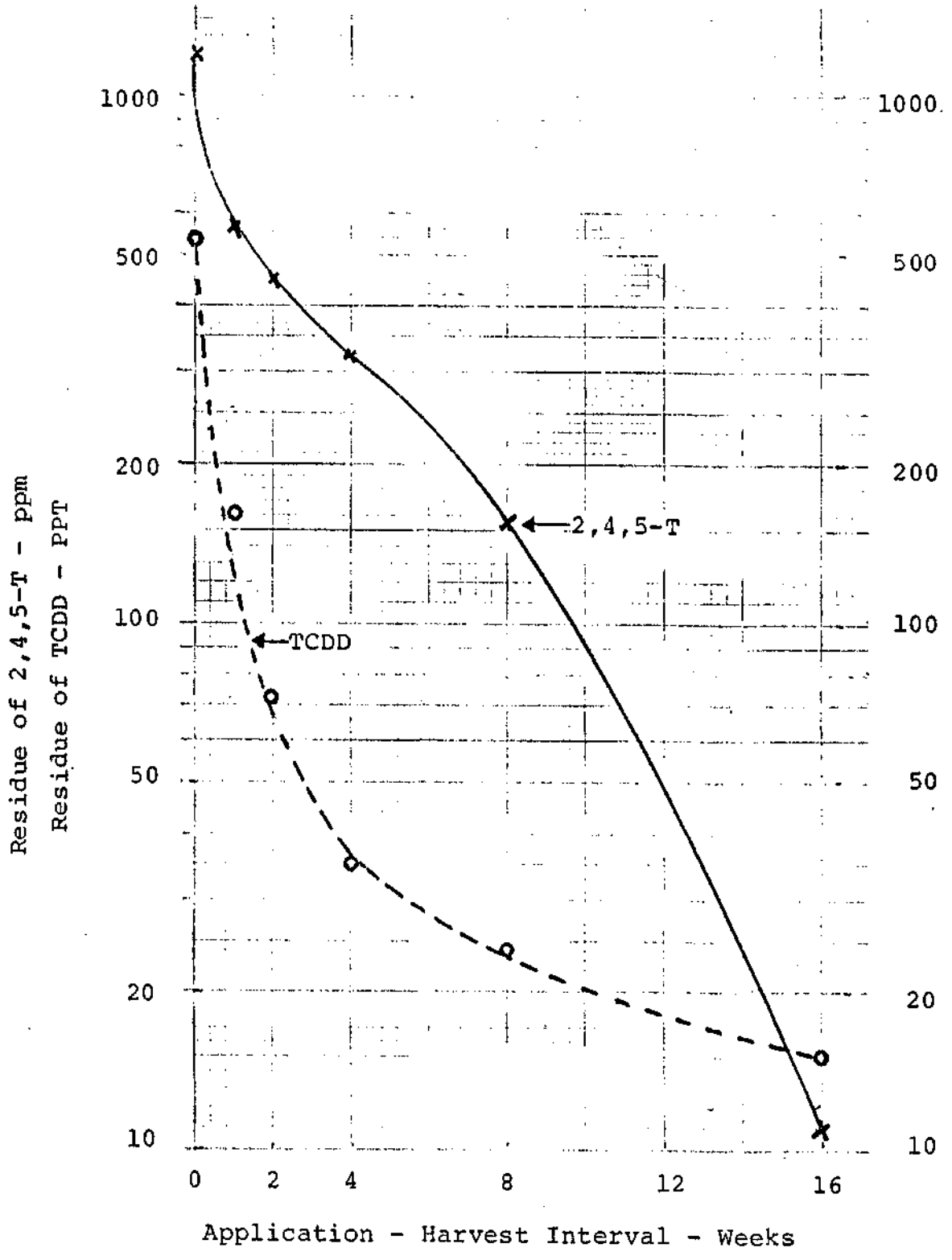
Present methods for determination of TCDD at low levels in environmental samples include: (1) gas chromatography/low resolution mass spectroscopy, (2) high resolution mass spectroscopy, and, (3) gas chromatography/high resolution mass spectroscopy. These methods are the most specific and sensitive methods known. But in spite of this, the exact meaning of small signals produced on the mass spectrometer is not clear. The reasons for this are: (1) control samples are not available, (2) ions having the same mass have been shown to arise from other materials present in the environment and, (3) interferences are easily picked up due to contamination. These reasons make interpretation of results at low parts per trillion levels very uncertain.

One way to increase the certainty of an analytical procedure is to have an alternative equally specific and sensitive technique. The participants in the analytical workshop had no such technique, although radio immunological assay was suggested as a possible solution into the problem. A second suggestion proposed to add more credibility to the analytical results was to have an exchange of samples between participating laboratories. In particular, the group suggested the Dow Chemical and Environmental Protection Agency exchange samples from the environment where the TCDD level was expected to be in the range of 0-20 parts per trillion.

A suggestion was made by Phil Kearney that TCDD levels in environmental samples be reported in groups or levels of data; for example, 0-10 parts per trillion, 10-50 parts per trillion, etc. This, it was thought, would be all that would be necessary to make judgements as to the meaning of levels in the environment.

In general, however, the group felt that it was in no position to resolve this question at the level of 10 parts per trillion TCDD during the workshop. It suggested that we encourage the Environmental Protection Agency to ask the American Chemical Society to select a peer group to review the methods and determine the true level of detection for these methods.

Finally the workshop acknowledged that more work would need to be done to determine dioxins other than TCDD in 2,4,5-T acids and esters. Although estimates of these materials can be made, standards are not available and the precise structure of the material being measured is still in doubt. Efforts are being made by all participants to obtain standards and have them examined by Dow Chemical in relation to its products.



LEVELS OF TCDD AND 2,4,5-T(1) RESIDUE ON GRASS FROM APPLICATION OF 12 LB 2,4,5-T/A TEXAS (1969)

(1) ibid.

Graph of data on p. 28 in 1974 document by Fullerton.

3. Residues

In this session, we were primarily concerned with two questions:

1. What is the significance of low-level residue findings in fat?

2. What residues of 2,4,5-T and TCDD are likely to occur in human food as a result of registered uses of current 2,4,5-T manufacture?

A summary of the uses permitted by the label was given by the chairman. Data were then summarized by the chairman on residues of 2,4,5-T which have previously been reported, starting with sugarcane.

On growing sugarcane, two applications of 2,4,5-T at the rate of one pound/A gave an average of 10 ppm of 2,4,5-T immediately after the second application. This decreased to 0.05 ppm by harvest time, 24 weeks later. When sugarcane containing a residue was processed, the residue was distributed as follows: Stalks contained more than tops, the concentration in bagasse was greater than that in juice, syrup and molasses contained 5 and 12 times the concentration of the juice they were made from, and raw sugar contained less than the juice.

Next a summary of data of 2,4,5-T residues on grass was discussed (Getzendaner, M. E., "Fate of Herbicides in Forage Crops", Joint Session - Agronomy, Animal Science and Dairy Science, Southern Agricultural Workers, Atlanta, Georgia 2/6/73, slide 3). Specific residues averaged 100 ppm per pound per acre at time of application, and decreased with a half-life of 1-2 weeks. In the Texas experiment which comprised one of the experiments cited, grass was also analyzed for TCDD. This treatment was made in 1969 before the specification for TCDD in 2,4,5-T was lowered from 1 ppm to 0.1 ppm maximum TCDD. It is estimated that there was approximately 0.5 ppm of TCDD, in the 2,4,5-T used in the formulation. Preliminary data were given showing that one day after application of 12 pounds of 2,4,5-T per acre about 600 ppt of TCDD was on the grass. This decreased to about 200 ppt of TCDD one week after application, compared to 700 ppm of 2,4,5-T. Sixteen weeks after application there were residues of 10 ppm of 2,4,5-T and about 15 ppt of TCDD. It was emphasized that these are preliminary figures, and that the TCDD in the 2,4,5-T applied was much greater than the present maximum allowed. More samples need to be analyzed to get more precise data for this, but these data show the TCDD as well as 2,4,5-T disappears at a very rapid rate from grass after application.

A discussion of a milk residue study followed. (Bjerke, E. L., et al "Residue Study of Phenoxy Herbicides in Milk and Cream", J. Agr. Food Chem., 20, 963-967 (1972)). Three cows were given diets which contained 2,4,5-T at successive levels of 10, 30, 100, 300 and 1000 ppm, based on total feed weight, for two week periods. The 1000 ppm level was given for 3 weeks, then feed without 2,4,5-T for several weeks. The 2,4,5-T used in this study was found to contain about 0.5 ppm of TCDD, or about five times the maximum level permitted in 2,4,5-T manufactured today.

Average residues found in milk were 0.1 ppm of 2,4,5-T and 0.1 ppm trichlorophenol at the 300 ppm 2,4,5-T feeding level, and 0.4 ppm of 2,4,5-T and 0.2 ppm trichlorophenol from the 1000 ppm 2,4,5-T feeding level. These decreased in 3 days after withdrawal of 2,4,5-T from the feed to levels below the level of sensitivity of the method, 0.05 ppm.

Preliminary results on analysis of milk from the 1000 ppm 2,4,5-T feeding level, show about 50 ppt of TCDD. It was emphasized that these are preliminary data. These same animals had received increments of 2,4,5-T containing TCDD in the diet before the start of the 1000 ppm 2,4,5-T feeding adding up to 22% of the amount consumed during the 21-day feeding of 1000 ppm which would have made a contribution to this. Also, it must be remembered that the 2,4,5-T used contained about five times the concentration of TCDD as current production. Further, very limited numbers of samples have been analyzed.

Seven days after withdrawal of the chemicals from the feed, a level of 40 ppt of TCDD was recorded, while about 15 ppt of TCDD was found in a sample 60 days after withdrawal.

Discussion of these data, method of analysis and possibility of contamination in the laboratory followed. Dr. Kearney pointed out the critical nature of the data. Lynn stated the need to analyze samples at lower feeding levels which would more nearly reflect the levels of TCDD on grass sprayed in a pasture at rates actually used and with milk animals kept off for 6 weeks, as stated on the label, which would allow dissipation of the residue.

Dr. Bovey stated that on pastures for dairy animals, 2,4-D was usually used instead of 2,4,5-T.

Discussion of these data and consideration of the probability of TCDD being a residue in meat and/or milk from actual use patterns, led to the recommendation that we draw together information from the field people who know how 2,4,5-T is used and put that together with the data we have on residues to come up with a complete picture as to what the

potential is for TCDD residue in human food. Further, it was recommended that we try to find areas where 2,4,5-T is used in conjunction with dairy herds and get milk from the market there. Also recommended is that we try to get milk samples from EPA from a study they have conducted (Dr. Bovey) grazing cattle on rangeland sprayed with 2,4,5-T.

Dr. Bovey described a study of movement of 2,4,5-T in water which he had conducted on a 3 acre plot given multiple treatments with 2,4,5-T. 2,4,5-T was detected at only very low levels, the highest being 26 ppb. He concluded that the possibility of contamination of ground water was unrealistic. Even wash-off from a treated area would be very slight.

Discussion next centered on "residue data in tissues of beef animals and sheep given 2,4,5-T" in the diet (Jensen, D. J., Et al "Investigation for Bound Residues on Tissues from Cattle Fed 2,4,5-T" presented at the 165th National Meeting of American Chemical Society, April, 1973.

Animals were fed for 28 days with a constant level of 2,4,5-T in the diet. This was the same chemical which was used for the milk study, containing about 0.5 ppm of TCDD, roughly 5 times the amount permitted by the present specification on 2,4,5-T.

2,4,5-T data were reviewed briefly. At the maximum feeding level 2,4,5-T residues in muscle and fat were around 2 ppm, and about 8 ppm in liver. Levels were roughly proportional to the amount in the diet.

Dr. Jensen discussed the trichlorophenol data results. After 7-day withdrawals of 2,4,5-T from the diet the phenol did not disappear. A new test has been started feeding sheep the more realistic level of 300 ppm 2,4,5-T for 4 weeks followed by withdrawal for periods up to 56 days. The tissues are in hand and an analysis for 2,4,5-T and trichlorophenol, as well as TCDD is planned.

On analysis of liver from the cattle experiment, TCDD levels (single animal anaylses) were 13, 61, 150 and 360 ppt from feeding of 100, 300, 900 and 1800 ppm of 2,4,5-T in the diet. Half of the TCDD disappeared from the liver in 7 days. Fat from cattle on the 1800 ppm feeding level contained around 2000 ppt of TCDD. There is a big drop-off of TCDD level in fat in the first 7 days to about half of the level at 0-day withdrawal.

In the sheep experiment, composite samples of fat and liver from 3 animals after various periods of withdrawal of 2,4,5-T have been analyzed. Again a rapid drop-off of 7 days after withdrawal of 300 ppm 2,4,5-T containing 0.5 ppm of TCDD was seen - from about 170 ppt to 40 ppt. Little decrease has been observed from 7 days to 28 days withdrawal. In

livers at 0-days, a level of around 200 ppt was found, decreasing to about 70 ppt with 7 days withdrawal and to about 40 ppt with 28 days withdrawal.

Samples from a group of sheep slaughtered 56 days after withdrawal of the chemical from the feed are yet to be analyzed, and some values on individual animals as well as other tissues have yet to be completed.

Dr. Crummett reported that in fat heated to 160° C 3-15 hours, containing 1000 ppm of trichlorophenol, no TCDD was found with a limit of sensitivity of 50 ppb.

This concept was discussed at length with the final general agreement that formation of TCDD as a result of cooking fat containing 2,4,5-T or trichlorophenol does not pose a potential problem. With the experiment which has been done, it has been shown that there is a very low potential for TCDD to be formed in this way, especially in view of the low level of trichlorophenol in fat of cattle consuming 2,4,5-T.

Residue data on rice was reported. The rice had been given two applications of 2,4,5-T of 1.5 lb/A. Rice grain at harvest time had no detectable residue of 2,4,5-T with a method sensitive to 0.025 ppm, while the straw contained about 12 ppm of 2,4,5-T. These samples will be analyzed for TCDD. Rice samples from an area in which 2,4,5-T is used are being procured for analysis for TCDD, to determine if this crop can be a source of TCDD in human food.

Another residue study reported was on wheat treated with 1 lb. 2,4,5-T per acre, in which no residue was found in grain 56 days after application.

Dr. Dutton reported on the fate of radioactive TCDD which had been added to soybean oil during the processing of the oil. About 50% of the radioactivity followed the oil through the processing. It can be removed down to the order of 3/10% by adding norite carbon black to the bleach step in the process. It is also removed by increasing the temperature of the deodorization process to 260°C.

A discussion followed on the question of whether TCDD might be found in food in the market. It was proposed we collect beef fat, as well as milk, from areas where 2,4,5-T is used, and analyze them for TCDD.

Dr. Young described some seed he has collected from areas in which TCDD is 25-30 ppt in the soil--no TCDD was found in the seed. He still has seed from plants growing in soil containing 710 ppt of TCDD, which are being analyzed now. This will give a good fix on the translocation of TCDD from soil to the seeds. He indicated that he has some sorghum samples collected from areas where 2,4,5-T had been placed at a 6" depth in the soil, at the rate of 1000 lb/A.

Further discussion on a market surveillance followed with ideas expressed as to how to proceed. It was concluded that a protocol should be developed at Dow after giving some thought to what we can expect to accomplish.

4. Sources of Dioxin

The workshop first considered to what extent TCDD is formed from the thermal stress of 2,4,5-T under environmental conditions. As has been previously reported (EPA, Dow-Langer), the apparent maximum amount of conversion of 2,4,5-trichlorophenol (or salts) to form 2,3,7,8-dioxin (TCDD) is between 0.1% and 0.3%, certainly less than 1% when heated under laboratory conditions.

The work of Buu-Hoi is not sufficiently described to be repeated and present indications are that 1% represents a maximum amount of conversion.

The apparent dioxins content of a material called "Toxic Fat" has been attributed to gross contamination by "bad" pentachlorophenol and tetrachlorophenol. Work by USDA and others has shown that pentachlorophenol is also a source of "dioxions". "The use pattern determines whether any of these contaminants will be as bad as 2,4,5-T".

The possibility of 2,3,7,8-dioxin formation from combustion of materials coated with various 2,4,5-trichlorophenoxy-containing compounds has been investigated. Recent work at Dow indicates that less than 0.0001% of any 2,4,5-T species is converted to 2,3,7,8-dioxin on combustion (i.e. less than 1 ppt 2,3,7,8-dioxin formed from each ppm 2,4,5-T burned).

Work at FDA and Dow which has subjected fat containing 1000 ppm of various 2,4,5-trichlorophenolics to "deep-fat frying" conditions found that after 14 hours, no 2,3,7,8-dioxin was detected, with a detection limit of 0.05 ppm.

We then considered to what extent other compounds bearing the 2,4,5-trichlorophenol moiety contribute to dioxins in the environment. USDA has investigated the photolysis of di- and trichlorophenols, both with and without a "photoactivator", riboflavin. They have identified both chlorinated phenoxyphenols and dihydroxybiphenyls, but have not detected "dioxins". This appears to suggest that the photolysis to form "dioxins" is slower than the photolytic decomposition of dioxins, especially in alcohol or water. Similar experiments which subjected 2,4-D and 2,4,5-T to metabolic conditions in soils (incubation) showed no detectable "dioxins".

Examination of 40 fish (107 determinations) from 2,4,5-T use areas showed no 2,3,7,8-dioxin detectable in 38 of these and "slight" positive responses from 2 samples which could not be repeated on resampling.

Examination of current Dow ronnel production showed no 2,3,7,8-dioxin with a detection limit of 0.01 ppm.

Examination of Dow pentachlorophenol showed no detectable 2,3,7,8-dioxin (0.05 ppm limit of detection). All current production 2,4,5-T materials (2,4,5-TCP, 2,4,5-T esters, Silvex esters) have less than 0.1 ppm. 2,3,7,8-Dioxin is detected (0.02 to 0.099 ppm) most often in 2,4,5-T esters. Different chemical conditions exist at several different steps for the different products and some processing conditions <u>can</u> lead to 2,3,7,8-dioxin but these condtions <u>can</u> be controlled. Dow employs good tight process quality control to keep 2,3,7,8-dioxin content in any products to less than 0.1 ppm.

The workshop then turned its attention to the question of contribution by other chlorophenols to "dioxins" in the environment. There appears to be no significant problem from pentachlorophenol, except for some uncertainty about the toxicity of hexachlorodibenzo-p-dioxins. Dow is currently investigating the identity of various "hexachloro-dioxins". Although there is no detectable 2,3,7,8-dioxin in Dow pentachlorophenol, it has been detected in several Asian pentachlorophenol samples. Similarly, heating pentachlorophenol with hydrocarbon oils and metal appears not to produce 2,3,7,8-dioxin, although some work is still in progress. (Crummett, Langer)

There is some <u>possibility</u> that anacrobic reductive dechlorination of hexa- or octachlorodibenzo-p-dioxin may give rise to "tetrachloro-dioxins". This should be investigated.

The following experiments were suggested.

1. Combustion of wood or grass which has been treated with 2,4,5-T should be done. Norris reported 100 ppm 2,4,5-T on "twigs" after spraying at 2 lbs/acre. One month later, this had declined to about 3 ppm. One should, therefore, burn wood which contains these residual amounts of 2,4,5-T. Kearney suggested that one should also examine whether any 2,3,7,8-dioxin so formed is primarily in the vapors or in the ashes.

2. Examination of "heating" products of pentachlorophenol should be done to determine extent of dechlorination. (Langer has some work in progress.)

3. Examination of various hexa-dioxins to determine identity. Dow has work in progress.

5. Statistics

The purpose of this workshop was to evaluate the statistical questions raised in the 2,4,5-T Advisory Committee dissenting opinion report and later expanded in Science, 174, 1971, pp. 1358-1359.

Specifically, two main criticisms were discussed:

1. The authors of the major 2,4,5-T studies did not "milk" the data by attempting to extrapolate the dose-response curves to "very low dose" levels in an effort to learn about expected teratogenic frequencies at these low levels.

2. Multiple t-tests and chi square tests were used in place of their nonparametric equivalents or one way analyses of variance.

Regarding the first criticism it was stated that to carry out this extrapolation required the assumption that the dose-response function is the same for lower doses as it is in the experimental region. This is not a reasonable assumption unless we know the mechanism by which the teratogenic responses occur. The probit, logit and one hit model all fit equally as well for most experimental data but give dose estimates orders of magnitudes apart when extrapolated to risks as low as 10^{-6}. Lower additional dose levels could perhaps have been used in some of the studies but we then get into the mega-mouse argument. Even if 100,000 animals show no difference from control this does not demonstrate a "safe" dose, it only shows 99% certainty that the true risk is less than 4.6/100,000.

The question was raised as to which is worse, extrapolating dose response functions assuming linearity, or applying somewhat arbitrary factors to the highest no-observed-effect levels in animals? No real answer was given (see recommendations).

Some concern was expressed about the size of the type II error when estimating no observed effect levels. It was felt that perhaps type II error should be considered when planning the experiments if no observed effect levels are important.

Regarding the second criticism, that the most appropriate statistical tests were not used to evaluate the data, it was pointed out that the criticism was somewhat self-contradictory. The author recommended that more "sophisticated" statistical methods such as multivariate analysis should have been used, but he also pointed out that the data is non-normal and generally discrete (frequency of teratogenic occurrences). With the present state of statistical methodology multivariate analysis of discrete data is not practical. Multivariate analyses are generally less robust against non-normality than their equivalent univariate methods.

Part of this second criticism is technically correct, however. Chi-square tests and t-tests were used when their nonparametric counterparts, Fisher's exact probability test and the Mann-Whitney U test (or Wilcoxon's test), would have been more appropriate. Multiple t-tests were used when a one way analysis of variance should have been done. However, when the data were reanalyzed using the other methods, the results were no different. In fact, the more appropriate tests will tend to show fewer statistical differences than the tests that were used.

The experimental design of the studies was discussed. It was felt that log or geometric spacing of the doses was the best choice of scale. It was suggested that sample sizes inversely proportional to expected response would enhance the power of the statistical testing for the small doses where it is most needed. From an intuitive point of view we would be learning more about the lower doses than the higher doses, which seems reasonable.

To summarize the workshop's feelings about the criticism, it was felt that the first criticism about extrapolation to lower dose levels was questionable, with our present knowledge of teratogenic mechanisms. The second criticism was felt to be technically justified but different methods would not affect the conclusions.

The workshop recommends that we obtain better estimates of baseline levels of anomalies both by pooling data when appropriate and through inter-laboratory data sharing; consider sample sizes inversely proportional to expected responses; and routinely perform dose response analyses, using for instance probit or logit models, in an effort to build up enough background information to consider establishing conservative "safe" levels using procedures such as Mantel-Bryan.

III Rule of Reason

At the Rule of Reason seminar on Friday March 8, 1974, the participants engaged in a general discussion of risks versus benefits. The following points were made:

1. Risks and benefits may be divided into the following categories:

(a) Voluntary vs. involuntary. For example, smoking vs. environmental impact of DDT.

(b) Controlled vs. Non-controlled.

(c) Public vs. private.

(d) Informed vs. uninformed.

(e) Vital vs. non-vital.

Primarily, one must ask when is individual risk justified for public benefit. Example: the public risk of smallpox is now so low that the risk of individual inoculation is not justified. Applying this theory to the case, if rice cannot be grown without herbicides, as the Rice Institute contends, then the public benefit as well as the private benefit in using herbicides is great and the individual risk is low. Generally in speaking of risks, it is the involuntary risks which must be evaluated by decision makers since the individual cannot make that decision on his own. Voluntary risks are usually definable and assuming that the hazard can be understood by the user are not often the source of major controversy in technology assessment.

2. Alternatives must be evaluated in terms of benefits vs risks. From that evaluation, society can make value judgements. One method by which to do this is to consider the possible worst outcome of all alternatives and then to select the one alternative whose worst outcome is better than the

worst outcome of any other alternative. In making this evaluation, the public must be made aware of the nonexistence of absolute safety. The alternative of absolute safety in many instances would be worse than the risks of a certain alternative. Example: in the minds of many persons, the alternative of absolute safety would be worse than the risk of using chemical substances to produce food even with their implied risks. The public wants to know what the worst outcome could be and then it will make its judgements. Example: the worst that could happen to a truck going through town filled with gas is that it will crash and burn. If a circumferential highway is available, the truck should go around the town. If the truck is carrying vital provisions, and no route is available except through the center of town, the public must make its decision based on the worst outcome vs the benefit.

3. It was proposed that the upper limit of risk that should be accepted in any situation should be no greater than the risk of natural disease. But, 40 percent of the population is killed by heart attacks from too much fat in their diet. Yet a 40 percent figure as an upper limit of risk is too high. Query: what standard should we use as the tool to measure the upper limit of risk.

4. Risks and benefits were defined. A benefit confers an improvement in status. A risk confers a derogation in status in an area essential to life. Nonvital risks and benefits can be valued in the market place. It is easy to make judgements with skilled advice in vital risk areas. For instance, a doctor can decide when to give penicillin and when the patient should accept the risk of the side benefits of penicillin. The difficult question is the acceptance of vital risks for nonvital benefits. However, the public on an individual basis makes such judgements every day. For example, the nonvital benefits of driving are so great to the individual that he is willing to take vital risks. This is partly due to the fact that the risks can be easily visualized and the feeling on the part of the individual driver that such risks are controllable. In an area such as pesticides, the risks are not so easily visualized and the individual fears them more because he cannot control them. Morever, food is a nonvital benefit for the most part. It is only when an individual is starving that he would take a vital risk to eat; for example, eating food from a swollen can.

5. The DDT ban was partly based on a judgement that the risks of DDT were not as well known as risks of other substances and not as controllable by the individual.

6. In some instances, were functional alternatives available there would be no question but that the alternative would be used. Example: if there were an alternative to nitrate, it would be used without hesitation since the risks of nitrate are well known. The same applies to cyclamates. The only question which remains is cost benefit.

7. After weighing the risks and benefits, the decision maker is ultimately left with the prospect of making a value judgement. Society and its values are diverse. The judgement depends on where you stand: in rural society, weeds are bad, pulling them takes time, 2, 4, 5-T gets rid of them, and all of this increases beef production. The fact that it may decrease wildlife habitats is peripheral to this segment of society. A value judgement then become a question of trade offs among special interest groups. Consequently, it becomes much more difficult for the regulator to decide.

8. It is the obligation of a socially responsible agency to interpret the judgements of society as to what risk is acceptable for what benefit and then to respond to that interpretation. For instance, presently, the public will accept more air pollution when there is a gasoline shortage.

9. Coming up with the criteria to make judgements based on a rule of reason is difficult. Several approaches have been advanced:

A. Quality of life review--send proposed decision to interested agencies who will thrash out the impact given the interests they represent.

B. The market place--to the extent it is safe, leave the decision to the market place. This results in a personal translation of risk: how does this affect me.

C. Environmental dose commitment--the prediction of the probability of radiation getting into the environment and then the use of the Pier report to translate that into

the probability of causing cancer. In this way the regulator sets the magnitude of risk acceptable: the long term risk of cancer versus the immediate benefit of more nuclear power for man.

D. The probability approach--we can have cheaper rice with the use of herbicide which carries with it one chance in a million of a birth defect. Compared to the risks of birth defects from other substances, this fades into the background of importance. Although the probability of botulism from eating home canned food is 70 times greater than in eating processed food, much of the public is willing to assume that risk because of perceived benefits. They see the probability of botulism from eating home-canned food as very low, even though it is not, because the perceived benefits are high.

10. Unknown risks enter into decisions. First, quantify the facts you do know and then give that, along with the uncertainties involved, to the decision maker. Then the decision maker uses his judgement.

11. It is well known that the public makes conscious choices among varying hazards and nonvital benefits. If we could quantify the differences in risk the public is willing to take, we could make socially acceptable decisions based on this quantification. For example, the hazards of smoking during pregancy are better documented and more immediate than the hazards of smoking generally. If statistics on how many women give up smoking during pregnancy and then return to it after birth were available, we might be able to make one judgement on how individuals quantify differences in risk. If such information were available on a variety of issues, it would be possible to quantify acceptable risk and therefore make socially acceptable decisions for the public.

12. We could also quantify the benefit: how much death is a certain benefit worth? The examples are not widely applicable since those decisions which we know will result in death are not widespread. The public is willing to support the building of Golden Gate Bridge though they know at least 5 lives are likely to be sacrificed. However, the perceived benefit to millions of people is great and the immediacy of the risk is

more distant. Each individual feels that the lives sacrificed are not likely to be theirs or their family. The public is willing to take much greater risk when the risk is not perceived as a personal one.

Risks & Benefits of 2, 4, 5-T

A. Risks of 2, 4, 5-T

I Risks to Human Health

1. Toxicity factor (300 to 500 mg/kg acute oral 10 mg/kg chronic 90 day).
2. Chronic toxicity
3. residues in food
4. extra-sensitivity
5. teratogenicity
6. population at risk
7. metabolites
8. anxiety
9. economic cost

II Risks to the Environment

1. toxicity to fauna (acute and chronic)
2. phytotoxicity
3. habitat modification
4. increased erosion & runoff

5. mobility

6. aesthetics

7. alternative products

8. fire hazard (oak)

B. Benefits of 2, 4, 5-T

I Range Weed Control

1. increased food supply

2. aesthetics

3. wildlife habitats

4. elemination of harmful plants

5. secondary tsetse fly control

6. reduced evapotranspiration

7. water erosion

8. economic well-being of ranchers

9. reduced manpower requirements

II Rice Weed Control

1. increased food supply

2. reduced manpower requirement

3. economic advantage to growers

4. increased bird populations

III Utility & Rights-of-Way

1. lower cost vegetation management
2. cheaper, more dependable power and communication
3. lower personnel hazard
4. reduced erosion
5. habitat diversity
   a. faunal diversity
6. reduced fire hazard

IV Forestry Uses

1. increased commercial timber growth
2. lower production cost
3. [altered habitat]
4 increased personnel safety
5. fire protection

V Roadside Uses including Rail

1. less traffic hazard to man & deer
2. aesthetics
3. cheaper maintenance
4. reduced fire hazard
5. water erosion reduced
6. personnel safety

VI Miscellaneous Uses

1. general fire control
2. general flood control
3. general industrial vegetation control

Risks & Benefits of TCDD

I Risks to Man

1. acute toxicity 0.6 ug/kg (LD-50)
   a. dermal-chloracne
2. chronic toxicity (1×10^{-10} gm)
   a. enzyme inhibition?
   b. intracellular (endoplasmic vitriculum)
   c. liver
3. teratology
   a. potential - not proven
   b. rat [no effect level 3×10^{-8} gm]
      oral dose of 30 mg/kg
      1.25×10^{-7} pos.
      in other labs: no effect at 1×10^{-6} (various species & strains)
4. residues in food (fish)

II Environmental Risks

1. toxicity to fauna (inter & intra - specific variation, including teratogenicity)
2. bioccumulation
3. persistence (ingestion and retention within an organism)

4. phytoreproductive effects

5. mobility

6. conversion through fire

7. uncertainty due to limited scope of testing

Order of Benefits

1. Economic
   Food
   Timber
   Industrial factors

Alternatives

a. mechanics
b. other chemical combinations
c. nothing

Order of Risks

1. health

   a. occupational (mfg., trade, application)

   b. teratogenicity
      women of child bearing age.

2. Hazard to wildlife

Noted Reference Material:

Committee on Public Engineering Policy 1972 Perspecitives on Benefit-Risk Decision Making. (Washington: National Academy of Engineering) viii + 157 pp.

Birkhoff, George D.,
A Mathematical Approach to Ethics, Volume 4, Newman, The world of Mathematics, Simon & Schuster

Darby, William J., 1973 Acceptable Risk and Practical Safety: Philosophy in the Decision-Making Process. J. Am. Med. Assoc., 224: 1165-1168.

Environmental Studies Division 1973 The Quality of Life Concept: A Potential New Tool for Decision-Makers. (Washington: Environmental Protection Agency) xv + 397pp.

Environmental Studies Division 1972 Quality of Life Indicators. (Washington: Environmental Protection Agency) ii + 83 pp.

Panel on Chemicals and Health 1973 Democratic Representation (Washington: National Science Foundation) xi + 211 pp.