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FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT(FIFRA)

SCIENTIFIC ADVISORY PANEL

Review of Notices of Intent to Hold
FIFRA Section 6(b)(2) Hearing on 2,4,5-T and Silvex

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel has completed review of the Notices of Intent by the Environmental Protection Agency (EPA) to hold hearings under the provisions of FIFRA Section 6(b)(2) to consider appropriate regulatory action for those uses of 2,4,5-T and silvex which were not included in the recent suspension orders. The review was completed in open meetings held in Arlington, Virginia, during the periods August 15-16, 1979, and September 20-21, 1979.

Maximum public participation was encouraged by the Scientific Advisory Panel to ensure an objective and adequate consideration of all relevant scientific issues relating to health and the environment. Public notice of the meeting was published in the Federal Register on July 27, 1979. In addition telephonic calls and special mailings were also sent to the general public who had previously expressed an interest in activities of the Panel.

Written statements relative to 2,4,5-T and silvex were received from Dow Chemical Company, and Michigan State University.

In addition, oral comments were received from Dr. J. R. Allen, University of Wisconsin Medical School; EPA technical staff; representatives of the Texas State Department of Agriculture; Dow Chemical Company; and the Environmental Defense Fund.

The FIFRA Scientific Advisory Panel wishes to recognize the excellent cooperation and assistance of numerous EPA technical staff throughout the review of 2,4,5-T and silvex. ~~The outstanding efforts of Mr. Mike Dellarco, Dr. John Preston, and Dr. Danny Spencer of the Office of Pesticide Programs were especially noteworthy.~~

In consideration of all matters brought out during the meeting and careful review of all documents submitted by the Agency and other parties, the Panel unanimously submits the following report:

In response to the Agency's request for advice concerning whether a FIFRA Section 6b(2) hearing should be held to resolve questions relative to the continued use of 2,4,5-T and Silvex on rice, rangeland, orchards, sugar cane, and certain non-crop sites, (1) the Scientific Advisory Panel does ~~not~~ NOT recommend that the Agency hold such a hearing at this time. After extensive review of the data we find no evidence of an immediate or substantial hazard to human health or to the environment associated with the use of 2,4,5-T or Silvex on rice, rangeland, orchards, sugar cane, and the non-crop uses specified in the decision documents.

The Scientific Advisory Panel has extensively reviewed the animal toxicity test data base for teratogenesis, carcinogenesis, and reproductive effects for 2,4,5-T, Silvex, and TCDD and has identified some additional data needs which should be addressed prior to final decision making relative to the safety evaluation of 2,4,5-T and Silvex. (2) The Scientific Advisory Panel recommends specifically that the full details be obtained and evaluated for the following three studies which were discussed briefly at the hearing:

1. The oncogenicity study on commercial 2,4,5-T being conducted in Germany in the Laboratorium Fur Pharmakologie Und Toxikologie. An oncogenic study has recently been completed on 2,4,5-T which was specially purified to contain a low concentration of TCDD. However, data is needed on the oncogenicity of commercial 2,4,5-T containing TCDD ($\leq$0.05 ppm).

2. The oncogenicity study recently completed at NCI with TCDD in both rats and mice; and

3. The reproductive toxicity study being conducted at the University of Wisconsin by Dr. Allen in which monkeys are being fed a diet containing TCDD at 25 ppt.

The Scientific Advisory Panel has also reviewed the available data regarding potential human exposure to 2,4,5-T and Silvex from use on rice, rangeland, orchards, sugar cane, and other non-crop applications and the monitoring data related to these uses and would characterize these as incomplete and preliminary in nature. (3) We therefore recommend that monitoring data be obtained regarding the levels of 2,4,5-T and Silvex and TCDD in milk, and that additional data be gathered regarding the levels of these agents in the tissues of range animals and that information be obtained regarding the levels of these agents in edible aquatic organisms.. In these additional monitoring studies special emphasis should be placed on TCDD levels rather than levels of 2,4,5-T and Silvex, per se.

In regard to the specific issues and questions posed by the Agency to the Panel regarding review of 2,4,5-T and Silvex, the Scientific Advisory Panel offers the following responses:

ISSUES ON TOXICOLOGY

Question 1. EPA has found that 2,4,5-T, Silvex, and TCDD are teratogens. Does the Panel agree:

RESPONSE: The Scientific Advisory Panel agrees with the

Agency that 2,4,5-T, Silvex, and TCDD are teratogens.

Question 2. EPA has found that 2,4,5-T, Silvex, and/or TCDD are fetotoxins. Does the Scientific Advisory Panel agree?

RESPONSE: The Scientific Advisory Panel agrees with the Agency that 2,4,5-T, Silvex, and TCDD produce reproductive (fetotoxic) effects.

Question 3. EPA has determined that TCDD exhibits fetotoxic effects and that a No Observable Effect Level (NOEL) has not been established for this effect. Does the Scientific Advisory Panel agree with this finding?

RESPONSE: The Panel agrees with the Agency that a NOEL has not been established for TCDD in chronic studies in monkeys. In contrast to the Agency position, the Panel concludes that a NOEL has been established for TCDD for both rats and mice. The Scientific Advisory Panel would like to point out in this regard that the Agency position is relatively close to that of the scientists from the Dow Chemical Company. The Scientific Advisory Panel believes that the dose of 0.001 ug/kg/day is for all practical purposes a NOEL (For the purposes of risk calculation; See Appendix I). It should be pointed out that a NOEL for reproductive effects has been established for commercial 2,4,5-T in all species tested including monkeys.

Question 4. EPA has found that TCDD is carcinogenic in test animals, and thus is a potential human carcinogen. Does the Scientific Advisory Panel concur with this finding?

RESPONSE: The Scientific Advisory Panel agrees with the Agency opinion that TCDD is carcinogenic in test animals and therefore may be a potential human carcinogen.

Question 5. EPA has found that TCDD is an extremely potent animal carcinogen. Does the Scientific Advisory Panel agree with this finding?

RESPONSE: Answered in question 4 above.

ISSUES ON EXPOSURE

Question 1. EPA believes that human exposure from the use of 2,4,5-T and Silvex on rice may be broad and substantial due to herbicide drift during and after application, and that more diffuse exposure is possible through the water environment and through crayfish, catfish and other food sources. How would the Panel characterize the exposure potentials and concerns for rice use? What questions do they have and how would they be answered by the proposed monitoring plan?

RESPONSE: The Scientific Advisory Panel agrees that exposure to 2,4,5-T and Silvex from use on rice may be possible through the water environment and through

edible aquatic organisms and other food sources. However, the Scientific Advisory Panel believes that insufficient data was presented or made available to the Panel in support of the argument that human exposure from spray drift and the water environment is likely to be broad or substantial. The questions regarding proposed monitoring have already been addressed. In addition to the need for more data on the concentrations of Silvex, 2,4,5-T, and TCDD in crayfish and catfish, monitoring data should also be obtained on soil sediments.

Question 2. EPA believes that drift from the use of 2,4,5-T/Silvex products on rangeland creates a lower, yet-still-real, potential for exposure due to lower population densities and distribution in range areas relative to rice growing areas. Sparsity of surface water and extreme depth of ground water in many areas would suggest a minimal exposure from aquatic sources used as food. However, beef monitoring shows low levels of dioxin in a limited number of samples from beef that grazed on 2,4,5-T treated range. How would the Panel characterize the exposure potential and concerns for the use of these chemicals on range? What unanswered questions do they believe the Agency should address in determining exposure potential?

RESPONSE: The Scientific Advisory Panel agrees with the Agency that there is a potential for exposure as a result of drift from the use of 2,4,5-T and Silvex products on rangeland and that the potential for exposure from this mechanism would be lower than that from use of the agents on rice. However, the Panel believes that the data made available to the Panel did not provide a convincing argument for the existance of an immediate or substantial hazard from the use of Silvex and 2,4,5-T on rangelands.

Question 3. Little is known about the potential for dietary exposure to Silvex and/or TCDD from the uses of Silvex on food crops, except for apples on which Silvex residues have been detected. Given the nature of the contaminant TCDD, EPA has reason for presuming that exposure to food consumers and the environment is possible from these uses. What are the Panel's views on the potential for ingestion exposure from these uses?

RESPONSE: Although there is information on the use patterns of Silvex in orchard crops, the Scientific Advisory Panel believes sufficient residue data is not currently available for a definitive opinion on dietary exposure to Silvex.

Question 4. The Agency believes that TCDD and 2,4,5-T move in water from rice to other environmental compartments thereby increasing exposure to widely diffuse populations. Does the Scientific Advisory Panel concur with this?

RESPONSE: The Panel agrees with the Agency that it would be possible for 2,4,5-T to move in water from rice to other environmental compartments and to thereby increase exposure to widely diffuse populations. However, we believe such movement would be unlikely for TCDD.

Fields

GENERAL ISSUES

Question 1. Do the residues (2,4,5-T, Silvex and TCDD) in water, sediment, aquatic organisms and/or the potential for exposure from herbicide drift, in light of the toxicological attributes of these compounds, suggest to the Scientific Advisory Panel the possibility of significant risk?

RESPONSE: No. (See recommendation (1).)

Question 2. Can the Scientific Advisory Panel assess whether the residues being found in the rice areas are due to the rice use or to other previously permitted uses?

RESPONSE: The Panel is not aware of data sufficient to answer this question (See recommendation (3).)

Question 3. Do the exposure potentials in range use, in light of the toxicological characteristics of these compounds, suggest

to the Scientific Advisory Panel the possibility of significant risk?

RESPONSE: No. (However, see recommendation (3).)

In consideration of the potential toxicity of TCDD, (4) the Scientific Advisory Panel recommends that efforts should be made to further reduce level of chemical TCDD in ~~reduce the level of chemical TCDD in~~ commercial preparations of 2,4,5-T and Silvex.

APPENDIX I

THE FIFRA SCIENTIFIC ADVISORY PANEL EVALUATION OF THE ONCOGENICITY, FETOTOXITY AND EXPOSURE CHARACTERISTICS FOR 2,4,5-T, SILVEX AND TCDD

Introduction

In our opinion the major health and environmental issues relative to possible regulatory action by the Agency center around the potential of commercial forms of 2,4,5-T and Silvex contaminated with TCDD to pose carcinogenic, teratogenic and reproductive risks to persons as a result of (1) exposure during mixing and application, or (2) direct exposure to the spray as a result of living in the immediate area of application. In contrast, the major concern relative to TCDD, essentially free of 2,4,5-T or Silvex, arises from the degree to which this agent concentrates in portions of the human food chain. The primary concern of the Scientific Advisory Panel is the potential carcinogenic, reproductive, and teratogenic risk from use of commercial 2,4,5-T and Silvex contaminated with TCDD. The potential for these same risks from TCDD essentially free of 2,4,5-T and Silvex is of secondary concern, as is the potential risk posed by 2,4,5-T or silvex essentially free of TCDD.

Commerical 2,4,5-T

Oncogenicity

Seven studies of variable quality have been carried out in mice to examine the oncogenicity of commercial 2,4,5-T contaminated with TCDD.

The results of these studies have not demonstrated a carcinogenic risk from commercial 2,4,5-T in this rodent species. A complete study of the carcinogenic potential of commercial 2,4,5-T contaminated with TCDD at $\leq$ 0.05 ppm has not yet been reported in rats. However, such a study has recently been completed by the Laboratorium for Pharmakologie und Toxikologie, Hamburg, Germany. The Scientific Advisory Panel was informed during the recent meeting that gross autopsy examination of these animals revealed no increase in tumors relative to the control groups. However, until the pathological examination is complete no definitive conclusion can be drawn relative to the oncogenic potential of commercial 2,4,5-T in rats. The Dow Chemical Company has recently completed a study of the oncogenicity of a specially purified sample of 2,4,5-T in rats. This sample of 2,4,5-T contained less than 0.0003 ppm TCDD. In this study there was no increase in tumors resulting from exposure to this purified preparation of 2,4,5-T fed at the maximum tolerated dose (30 mg/kg/day) or at lower doses (10 mg/kg/day and 3 mg/kg/day). Thus it appears that 2,4,5-T, which is essentially free of contaminating TCDD, is not oncogenic in rats. However, this study is of limited predictive value since the form of 2,4,5-T of concern to the Scientific Advisory Panel is commercial 2,4,5-T; in other words, 2,4,5-T contaminated with TCDD.

Chronic tests carried out using TCDD free of 2,4,5-T have demonstrated that TCDD is carcinogenic in rats and carcinogenic or tumorigenic in mice. Thus, since commercial 2,4,5-T contains TCDD as a contaminant ($\leq$ 0.05 ppm)

the lack of a carcinogenic response in rodents using commercial 2,4,5-T must be viewed with caution. The Scientific Advisory Panel is of the opinion that some carcinogenic risk to man is posed by exposure to 2,4,5-T contaminated with TCDD at the level present in the 2,4,5-T in current use. However, the data currently available indicate that this risk is not substantial.

In summary, the evidence currently available indicates there is not an immediate or substantial oncogenic risk to man from exposure to 2,4,5-T contaminated with TCDD at a level of $\leq$ 0.05 ppm.

Reproductive and Embryo Toxicity

Commercial 2,4,5-T produces fetal toxicity and is teratogenic in rats and mice. According to the data presented to the Scientific Advisory Panel during the August 15-16, 1979 meeting, the no effect level for embryo toxicity for commercial 2,4,5-T in various species when examined in conventional toxicity studies is as follows: rat, 25 mg/kg/day; mouse, 20 mg/kg/day; hamster, 40 mg/kg/day; and monkey, 40 mg/kg/day. However, a recent study conducted at the National Center for Toxicological Research revealed teratogenic effects in A/J mice at the lowest dose of commercial 2,4,5-T tested (15 mg/kg/day). It would appear, therefore, that there are strain differences in the no effect level for 2,4,5-T in mice.

Two three-generation studies of 2,4,5-T reproductive toxicity have been carried out in rats. One of these studies was carried out using commercial 2,4,5-T containing $\leq$ 0.05 ppm TCDD. No teratogenic effects, reproductive toxicity or fetal toxicity were observed

in any animals at the doses tested (3, 10 and 30 mg/kg/day). In contrast another three-generation study carried out using purified 2,4,5-T ($\leq$0.0003 ppm TCDD) reported a significant decrease in neonatal survival at 10 and 30 mg/kg/day but not at 3 mg/kg/day. However some effects suggestive of reproductive toxicity were noted at the intake level of 3 mg/kg/day in this study. The Scientific Advisory Panel believes that this three-generation study establishes for practical purposes a NOEL and recommends that this NOEL be used for subsequent evaluation of risk.

In summary, the Scientific Advisory Panel believes that these data suggest that a potential for reproductive risk and embryo toxicity exists for persons engaged in the mixing and application of commercial 2,4,5-T. However with use of protective clothing such as a one piece jump suit with long sleeves, gloves and, perhaps, respirators, risks should be reduced to an acceptable level. The potential for significant reproductive and teratogenic risk to persons living in the immediate area of the spraying operations does not appear to be substantial except as they may be directly exposed on a chronic basis.

The Panel has some reservations relative to the validity of the three-generation study in rats carried out by the Laboratory fur Pharmakologie and Toxikologie using commercial 2,4,5-T ($\leq$ 0.05 ppm TCDD), and recommends that an additional three-generation study in rats using commercial 2,4,5-T be carried out.

Silvex

Oncogenicity

The carcinogenic testing of commercial Silvex has been less extensive than with 2,4,5-T. However, those few studies which have been carried out did not indicate an increase in oncogenicity as a result of chronic exposure to Silvex. Although no carcinogenic risk has been demonstrated with commercial Silvex, these data must be viewed with some caution because of the contamination of commercial Silvex with TCDD.

Reproductive and Embryo Toxicity

In contrast to commercial 2,4,5-T, very few studies of the reproductive toxicity of Silvex have been carried out. Those studies with commercial Silvex that have been carried out in rats and mice indicate that commercial Silvex is teratogenic in mice at high doses (400 mg/kg/day). Silvex is also fetotoxic in mice and rats and the no effect level in rats is 25 mg/kg/day.

Thus commercial Silvex does appear to pose some risks to reproduction and fetal viability. Much less information is available concerning the degree of exposure of humans to Silvex during mixing and spraying operations than is the case with 2,4,5-T. However, it should also be possible using proper protective clothing to reduce the reproductive and teratogenic risk from commercial Silvex to an acceptable level. Similarly there does not appear to be any

substantial risk to persons living in the immediate area of the spraying except from direct exposure on a chronic basis.

TCDD

Oncogenicity

Two major studies of the oncogenicity of TCDD have been reported. One study in rats has been carried out by the Dow Chemical Company and another in mice was performed by the Research Institute of Oncopathology in Hungary. A third study in mice and rats has recently been completed by NCI, but the results of this study were not yet available.

There was an increase in tumors of the liver, lung and hard palates/nasal turbinates in the rats fed of 0.1 ug/kg/day of TCDD in the diet. At a dose of 0.01 ug/kg/day there was an increase in hyperplastic nodules in the livers of the female rats. The EPA Carcinogen Assessment Group (CAG) has concluded that this increase in hyperplastic nodules at the dose of 0.01 ug/kg/day indicates that TCDD is also carcinogenic at this dosage level. The Scientific Advisory Panel concludes that there is a tumorigenic response at 0.01 ug/kg/day but has reservations as to whether hyperplastic nodules are precursors, per se, to hepatocellular carcinoma. (See Appendix II)

An increased incidence of liver tumors were produced in studies in male outbred Swiss mice in which TCDD was given by gavage at a dose of 0.7 ug/kg/week for one year. However, in this study there was no significant increase in tumor formation in animals given TCDD at 7.0 ug/kg/day although there was a decreased life span in the mice receiving this dose. There was also no increase in tumors in animals given TCDD at a dose of 0.007 ug/kg/week. Evaluation of this study by the Scientific Advisory Panel is difficult, since the type of liver tumor produced was not identified. Although the authors stated that the ratio of benign hepatomas to hepatocellular carcinomas was the same in the animals receiving the 0.7 ug/kg/week dose of TCDD as in the controls, it is not clear whether there was a significant increase in hepatocellular carcinomas in the treated animals.

The Scientific Advisory Panel concludes that there is a level of TCDD below which no oncogenic or tumorigenic effects were seen in either mice or rats. The dose level for tumorigenic response in the outbred strain of Swiss mice used in the Hungarian oncogenic study lies between 0.007 and 0.7 ug/kg/week. The Scientific Advisory Panel believes that the data available from this study are insufficient to reach a firm conclusion regarding whether there was a true oncogenic response in mice. In rats there was some controversy over which level of exposure to TCDD demonstrated an oncogenic effect. The Dow Chemical Company scientists stated that the level at which no oncogenic effects are seen lies between a dose of 0.1

and 0.01 ug/kg/day in the diet. The EPA Carcinogen Assessment Group concluded that the non-oncogenic dose lies between 0.01 and 0.001 ug/kg/day. Thus, there was agreement concerning the lack of an oncogenic response at the dose level of 0.001 ug/kg/day TCDD.

The major concern of the Scientific Advisory Panel relative to the potential oncogenic risk from TCDD is whether TCDD accumulates in the human food chain. The data necessary to evaluate this risk must be derived from monitoring data for TCDD itself. The oncogenic risk from TCDD present as a contaminant in commercial 2,4,5-T and Silvex is best determined in those experiments in which commercial 2,4,5-T or Silvex contaminated with TCDD has been administered chronically to rats and mice.

The monitoring data obtained thus far does not suggest that TCDD derived from commercial 2,4,5-T and Silvex exhibits any tendency to accumulate in the human food chain in amounts which would pose a substantial risk. For example TCDD has been detected in some fat samples from cows grazed on rangeland immediately after spraying with commercial 2,4,5-T and sacrificed 2 weeks later. If one assumes that all beef fat in the U.S. contains TCDD at the level found in these studies (approximately 10 ppt) and if one assumes further that the average level of beef intake in the U.S. population is 6% of the diet; (1.5 kg food/day; 15% of beef is fat) and produces a 22% incidence of tumors at 0.1 ug/kg/day (Dow Study) a risk of 4×10^{-6} can be calculated. It should be pointed out that this is an extreme worse case calculation since the

present data indicate that only a small percent (approximately 7%) of beef fat samples from animals fed on ranges immediately after spraying with 2,4,5-T containing TCDD and that all beef eaten in the U.S. does not come from ranges sprayed with 2,4,5-T (only 2%). Thus, although it appears that there is some potential oncogenic risk from TCDD present in the food chain, on the basis of the current monitoring data, the risk is judged to be small.

Reproductive Toxicity

The results of the embryo toxicity studies indicate that the no effect level for TCDD in mice is 0.1 ug/kg/day (days 6-15 of gestation), in rats is 0.03 ug/kg/day (days 6-15 of gestation), and in monkeys is 0.02 ug/kg/3 times per week (days 20-40 of gestation).

In a three-generation reproductive study carried out in rats by the Dow Chemical Company clear cut embryo toxicity was seen at doses of 0.1 and 0.01 ug/kg/day of TCDD. At the dose of 0.001 ug/kg/day there was a decreased gestational survival in the F_2 generation but not in earlier or later generations. Postnatal survival in the group receiving 0.001 ug/kg/day was decreased in the F_{1a} generation and increased in the F_{1b} generation relative to the controls. An increase in dilated renal pelvis was also seen in the F_{1a} and F_{1b} generation in the animals receiving 0.001 ug/kg/day but not in later generations or at the 0.01 ug/kg/day dose. Although these effects at 0.001 ug/kg/day are suggestive of an embryo-toxic effect, the inconsistency of the effects from generation to generation and in relation

to the higher dose of 0.01 ug/kg/day (dilated renal pelvis) suggests that the 0.001 ug/kg/day dose is for all practical purposes a no effect level.

Long term studies in monkeys have shown reproductive toxicity from TCDD at levels of 50 ppt in the diet. Studies are currently underway at 25 ppt of TCDD in the diet, but results are not yet available. An intake of TCDD of 50 ppt in the diet is equivalent to approximately 0.002 ug/kg/day. If no reproductive toxicity is seen in the monkeys exposed to TCDD in the diet at 25 ppt, then the no effect level in the monkey will be similar to that seen in the rat, namely about 0.001 ug/kg/day.

The major concern of the Scientific Advisory Panel relative to the potential reproductive toxicity or teratogenic effects of TCDD is whether it accumulates in human food chains as previously noted for the oncogenic potential of TCDD. The reproductive toxicity and teratogenic potential of TCDD present as a contaminant in commercial 2,4,5-T and Silvex is best determined from experiments in animals exposed to commercial 2,4,5-T or Silvex contaminated with TCDD.

If one assumes the worse case situation described previously in the evaluation of the oncogenic risk from TCDD in which TCDD is proposed to be present in the fat of all cows marketed in the U.S., the maximum intake would be approximately 2×10^{-6} ug/kg/day. Using a 0.001 ug/kg/day as the no effect level the safety factor would be approximately 500. As pointed out previously in the section on the oncogenicity of TCDD, this calculation represents an extreme exaggeration of exposure to TCDD. The Scientific Advisory Panel believes, therefore,

that the current monitoring data do not indicate that there is a substantial reproductive or teratogenic risk posed by the accumulation of TCDD in the human food chain.

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APPENDIX II

A Selected Review of the Histology
of the Dow TCDD Study (Tox. Appl. Pharm. 46, 279 (1978))

Drs. Donna Kuroda, Richard Kociba and I reviewed 3 representative microscopical sections each from control, 0.01, and 0.1 ug/kg/day level TCDD exposed female Sprague Dawley rats. These sections were selected by Dr. Kociba to demonstrate hyperplastic nodules and lesions designated hepatocellular cancers (see Table #5 R.J. Kociba et al. Tox. & Appl. Pharm. 46, 279 (1978)). Control sections were used for comparison.

Control animals, selected from timed sacrifices, showed a general presentation of the liver architecture. A natural incidence (spontaneous?) of extramedullary hematopoiesis, bile duct reduplication, and "hyperplastic nodules" was found by Dr. Kociba (Table 5) and demonstrated in the sections provided to me. Kociba and collegues considered a tissue mass to represent a hyperplastic nodule if a group of liver cells, with or without sinusoidal lining cells, formed a discrete population with cellular structure and/or tinctorial properties different from the surrounding parenchyma. These growths may or may not cause compression of surrounding parenchyma and may or may not have bile duct formation. Sharp demarcation from the surrounding parenchyma was observed.

In addition, there were both acute inflammatory exudates and granuloma-like lesions in the controls, not associated with the hyperplastic nodule. In addition there appeared to be an acute cholangitis. No

evidence of fibrosis was present.

Sections from the high dose exposure animals (0.1 ug/kg/day) showed some distortion of the hepatic parenchyma with cellular variability and thickening of the liver cell plates. Portal tracts were sometimes associated with dense collections of lymphocytes. Prominent were hyperplastic nodules and lesions characterized by Kociba and associates as hepatocellular carcinomata. These latter lesions showed more marked cellular differences from surrounding parenchyma and from hyperplastic nodules. In general, the liver cell nuclei were larger occupying a greater portion of the cell volume, the cell plates more disordered, formation of acinar and tubular forms were identified, and no formation of portal tracts were present in these lesions. These masses in one instance, arose in a hyperplastic nodule. No defined microscopical or gross evidence of invasion of the neoplastic cells into adjacent tissues was noted either at autopsy (according to Kociba) or by microscopy. Not infrequently fat was present in hyperplastic nodules but not in the "carcinomata".

The parenchyma adjacent to the carcinomatons and hyperplastic nodules showed some cellular irregularity, staining variation, and hyaline intracytoplasmic masses. No significant evidence of increased inflammatory exudates or fibrosis was noted, but bile duct reduplication was present.

The midrange dose shows hyperplastic nodules, the remaining changes were identical with the high dose, but these slides did not show a carcinoma. I believe that the group at Dow extensively and properly surveyed the evidence of hepatocellular disease following exposure of rats to TCDD. Autopsies on animals were conducted by pathologists and tissue sections were selected by them. Their microsopial review was extensive. Their nomenclature was defined and understandable. I personally would have been more conservative than they in designating carcinomata, so their result is a "worst case" designation. From these discussions and reviews, I am very comfortable with their evaluation for toxic injury and carcinogenesis. Additionally, I believe liver cancer was shown in the high dose level; might be questioned in the midrange level, but was not present in the low dose group.

S/ Edward Smuckler

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August 15, 1979
Survey conducted at
EPA Headquarters
Washington D.C.