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PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dicofol: Toxicology chapter of the RED for dicofol

Caswell No. 93 **PC code:** 010501

TO: Judith Loranger/Linda Propst, PM Team 73
Re-registration Division (7508W)
and
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RCAB/HED (7509C)

FROM: Whang Phang, Ph.D. 12/15/95
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THROUGH: James Rowe, Ph.D. James N. Rowe 12/18/95
Section Head
and
Stephanie Irene, Ph.D.
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Tox. Branch II has prepared a toxicology chapter of the RED for dicofol, and it is attached.

DICOFOL RED: TOXICOLOGY CHAPTER

B. HUMAN HEALTH ASSESSMENT

I. Hazard Assessment

Dicofol, 1,1-Bis(chlorophenyl)-2,2,2-trichloroethanol, is used as an acaricide, fungicide, and insecticide for terrestrial food, feed, and non-food crops. It also has indoor uses. The toxicology data requirements for this chemical, and the studies which satisfied the requirements are summarized in Table 1. The toxicological data base on dicofol is adequate to support registration eligibility.

Table 1. Required Toxicology Studies and Those which Satisfied the Data Requirements.

G. No.	Required Study Type	MRID No.	Satisfied
81-1	Acute oral-rats	40731204	Yes
81-2	Acute dermal-rats and rabbits	40731205	Yes
81-3	Acute inhalation toxicity	00256514 40731202	Yes
81-4	Primary Eye irritation	Bonin	Yes
81-5	Primary Dermal irritation	Bonin	Yes
81-6	Dermal Sensitization	40048506	Yes
82-1	90-day oral toxicity-rodent 90-day oral toxicity-dogs	40042044 470158014 (TRID #) 40042043	Yes Yes
83-1b	Chronic toxicity study in dogs	40997101	Yes
83-2a	Oncogenicity study in rats (NCI)	41037801	Yes
83-2a	Oncogenicity in mice (NCI)	41037801	Yes
83-5	Combined chronic/oncogenicity study in rats	41150001	Yes
83-3a	Developmental toxicity-rat	40042046	Yes
83-3b	Developmental toxicity-rabbit	40042047	Yes
83-4	2-generation reproduction-rats	41806601	Yes
84-2a 84-2b	Gene mutation In vitro cytogenetic assay CHO cell (Chromosomal aberration) In vivo cytogenetic assay-rat bone marrow cells	40042048 40042051 40044205	Yes Yes Yes
81-8	Acute neurotoxicity screening study	42633303	Yes
82-7	90-day neurotocicity screening study	42971401	Yes
85-1	Metabolism study in rats	00400420 43070103 43070104	Yes

Note: (1) The requirement for a developmental neurotoxicity study is reserved. (2) The registrant is currently conducting a special reproduction study to determine whether or not dicofol has any ~~hormonal effects~~. (3) ~~The available~~ dermal study, 4 weeks, used a formulation and is not included.

Acute Toxicity

The following table summarizes the acute toxicity values and categories for dicofol.

TEST	RESULTS	CATEGORY
Oral LD_{50} - Rat	587 mg/kg	III
Dermal LD_{50} - Rabbit	2 - 5 g/kg	III
Inhalation LC_{50} - Rat	>4.2 mg/L	IV
Eye Irritation - Rabbit	Moderate irritation	III
Dermal Irritation - Rabbit	Moderate irritation	III
Dermal Sensitization - Guinea pig	Not sensitizing	--

Acute oral toxicity testing in CRCD rats found an LD_{50} of 587 mg/kg. This was toxicity category III (guideline 81-1; MRID 40731204). An acute dermal toxicity test with CRCD rats found the LD_{50} was greater than 5.0 g/kg. This was toxicity category IV (guideline 81-2; MRID 40731205). An acute dermal toxicity test with New Zealand white rabbits found the LD_{50} was between 2 and 5 g/kg. This was toxicity category III (guideline 81-2; MRID 40731205).

An acute inhalation toxicity study with rats found the LC_{50} to be greater than 4.2 mg/L, the only dose tested. This was toxicity category IV (guideline 81-3; MRID 00256514). Another acute inhalation study with rats found the LC_{50} to be greater than 5 mg/L, toxicity category IV (guideline 81-3; MRID 40731202).

An acute eye irritation study with rabbits found moderate irritation. This is toxicity category III (guideline 81-4; Bonin, 1985a). Rabbits treated with dicofol in a skin irritation study showed moderate irritation, which was toxicity category III (guideline 81-5; Bonin, 1985b).

A dermal sensitization study with guinea pigs did not find dicofol to be a sensitizer (guideline 81-6; MRID 40048506).

Subchronic Toxicity

In a subchronic oral toxicity study in dogs, groups of beagle dogs (6/sex/dose) received dicofol at dietary concentrations of 0, 10, 100, 300, or 1000 ppm (0, 0.29, 3.3, 9.9, or 26 mg/kg for males and 0, 0.31, 3.4, 9.8, or 27 mg/kg for females) for three months. The NOEL was 10 ppm (0.29 mg/kg/day). The LEL was 100 ppm (3.3 mg/kg/day), based on a decrease in cortisol release in response to ACTH administration, an increase in relative liver weights, and oligospermatogenesis in males. There were effects also on survival, testes, prostate, liver, gastrointestinal tract, and heart at the LEL and higher doses (guideline 82-1; MRID 40042043).

In a subchronic oral toxicity study in rats, groups of Crl:CD (SD) BR rats (10/sex/dose) received dicofol at dietary concentrations of 1, 10, 100, 500, and 1500 ppm for 90 days (0.07, 0.64, 6.49, 32.01, and 95.84 mg/kg/day for males and 0.08, 0.78, 7.84,

36.11, 105.91 mg/kg/day for females). Under the conditions of the study, dicofol produced a wide range of effects in both sexes of rats. At 1500 ppm dicofol produced death and clinical signs such as lethargy and ataxia prior to death. Reduced body weights and food consumption were seen in 500 and 1500 ppm rats of both sexes. Most of the other effects were associated with toxicity seen in the liver (*increased liver weights, enhanced hepatic MFO activity, and hepatocellular hypertrophy*), adrenals (*diffuse adrenal cortical cell vacuolation & decreased corticosterone levels*), thyroid (*hypertrophy of the thyroid follicular epithelium*), and stomach (*focal chief-cell hyperplasia in the fundic mucosa*). The effects on the liver and thyroid were seen in dose levels as low as 100 ppm and 10 ppm, respectively. The dicofol induced increase in liver enzyme activity in rats was also reported by Flodstrom et al. (1990). However, at 1 ppm, dicofol did not produced an effect in any of the parameters examined in this study. Based on the increase in the incidence of hypertrophy of the thyroid follicular epithelium, the LEL is 10 ppm (0.64 mg/kg); NOEL, 1 ppm (0.07 mg/kg). (TRID No. 470158014)

In a 90-day feeding study in mice, groups of Crl:CD^{R}-1 (ICR) BR mice (10/sex/group) received dicofol in the diet for 3 months at concentrations of 10, 125, 250, 500, and 1000 ppm (1.6, 18.2, 38.2, 84.4, and 178.4 mg/kg for males and 2.1, 29.3, 56.2, 108.0, and 188.4 mg/kg for females). Under the conditions of this study dicofol did not produce any compound-related effects in 10 ppm male or female mice. Dicofol produces dose-related effects on the body

weights, the liver (*increased liver weights, hepatic MFO activity, hepatocellular hypertrophy associated with necrosis and vacuolation*), kidney (*decrease in weight, granular and dilated kidneys, dilation and degeneration of cortical tubules of kidneys*), and the adrenal glands (*diffuse hypertrophy of adrenal cortical cells*) at dose levels as low as 125 ppm, 250 ppm and 500 ppm, respectively. The effects seen in 1000 ppm were more severe than any lower dose levels. Therefore, based on the decrease in body weights, increased hepatic MFO activity, and increase in liver weights, the LEL for subchronic toxicity of dicofol is established at 125 ppm (18.2 mg/kg); NOEL, 10 ppm (1.6 mg/kg). (MRID No. 40042044)

Chronic Toxicity and Carcinogenicity

In a one-year chronic toxicity study in dogs, groups of beagle dogs (6/sex/dose) were fed doses of 0, 5, 30, or 180 ppm (0, 0.12, 0.82, or 5.71 mg/kg for males and 0, 0.13, 0.85, or 5.42 mg/kg for females). The NOEL was 5 ppm (0.12 mg/kg/day in males and 0.13 mg/kg/day in females). The LEL was 30 ppm (0.85 mg/kg/day in females and 0.82 mg/kg/day in males), based on inhibition of ACTH-stimulated cortisol release in both sexes. There were increased mortality, increased alkaline phosphatase levels, increased liver weights, and hepatocyte hypertrophy in males and females at the high dose (guideline 83-1; MRID 40997101).

In a chronic feeding/carcinogenicity study in rats, groups of CRL:CD® BR rats (60/sex/dose) received dicofol at dietary levels of

0, 5, 50, and 250 ppm (0, 0.22, 2.23, and 11.34 mg/kg/day for males and 0.27, 2.69, and 14.26 mg/kg/day for females) for 24 months. The NOEL for systemic toxicity was 5 ppm (0.27 mg/kg/day in females, 0.22 mg/kg/day in males). The LEL was 50 ppm (2.69 mg/kg/day in females, 2.23 mg/kg/day in males) based on changes of decreased food consumption, decreased body weight gain, reduced triglyceride levels, and increased hepatic mixed function oxidase activity, seen at or before 12 months. There were also histological changes: the liver showed centrilobular hepatocyte hypertrophy, vacuolation, and areas of necrosis in 50 and 250 ppm males and females, and the adrenal glands showed cortical cell vacuolation in 250 ppm males and females. No compound-related increases in tumor incidence were observed in this study (guideline 83-1; MRID 41150001).

Carcinogenic bioassays of dicofol were also carried out by the National Cancer Institute in rats and mice[1]. In the rat study, groups of Osborne-Mendel rats (50/sex/dose; control, 20/sex) were fed 0, 471, or 942 ppm (equivalent to 0, 23.6 or 47.1 mg/kg/day) in males and 0, 380, or 760 ppm (equivalent to 0, 19, or 38 mg/kg/day) in females for 78 weeks, followed by 34 weeks without treatment. Dose-related body weight depression was found in both sexes. No compound-related tumors were observed at either dose (MRID 41037801).

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[1] The dietary concentrations for the NCI rat and mouse carcinogenicity studies (discussed below) indicate time-weighted concentrations.

In the NCI mouse carcinogenicity study, groups of B6C3F1 mice (50/sex/dose; Control, 20/sex) were given dicofol at dietary concentrations of 0, 264, and 528 ppm in males (equivalent to 0, 39.6, and 79.2 mg/kg/day) and 0, 122, and 243 ppm (equivalent to 0, 18.3, 36.5 mg/kg/day) in females for 45 weeks, followed by 14-15 weeks without treatment. High dose females had decreased body weights. The incidences of hepatocellular adenomas and hepatocellular adenomas/carcinomas combined were significantly increased in males at both dose levels (39.6 and 79.2 mg/kg/day) (MRID 41037801).

Based on the increase in the incidence of liver adenomas and combined liver adenomas and carcinomas in male mice, the Carcinogenicity Peer Review Committee has classified dicofol as Group C-possible human carcinogen and has recommended that for the purpose of risk characterization the Reference Dose (RfD) approach be used for quantification of human risk (Phang and Rinde, 1992).

Developmental Toxicity

In a developmental toxicity study in rats, groups of pregnant Crl:COBS CD rats (25/dose group) received dicofol by gavage at doses of 0, 0.25, 2.5 and 25 mg/kg/day on gestation days 6-15. The maternal toxicity NOEL was 0.25 mg/kg/day. The maternal LOEL was 2.5 mg/kg/day as a result of salivation, reduced food consumption and weight gain, and increased relative liver weight accompanied by centrilobular hepatocyte hypertrophy. The developmental toxicity

NOEL exceeded 25 mg/kg/day (guideline 83-3; MRID 40042046). The lack of developmental toxicity seen in this study is also confirmed by the results of a published developmental toxicity study in normal and malnourished pregnant Wistar rats exposed to dicofol at 10 mg/kg/day on gestation days 4 to 15 (Lemonica et al., 1993).

In a developmental toxicity study in rabbits, groups of artificially inseminated New Zealand white rabbits (20/dose group) received dicofol by gavage at doses of 0, 0.4, 4, and 40 mg/kg/day on gestation days 7-19. The maternal toxicity NOEL was 4 mg/kg/day. The LEL was 40 mg/kg/day, based upon findings of abnormal feces, reduced food consumption and weight gain, and increased relative liver weight associated with hepatocyte cytoplasmic hyalinization and vacuolation. For the developmental toxicity, the NOEL and LEL were 4 mg/kg/day and 40 mg/kg/day, respecttively. The LEL was based one an increased incidence of abortions in the dams (guideline 83-3; MRID 40042047).

Reproduction

In a two-generation reproduction study, groups of Crl:CD BR rats received dicofol at dietary concentrations of 0, 5, 25, 125, or 250 ppm. The systemic and reproductive NOELs were 5 ppm (0.5 mg/kg/day). The systemic toxicity and reproductive LELs were 25 ppm (2.5 mg/kg/day) due to vacuolation of the ovaries of P2 females and vacuolation and hypertrophy of centrilobular hepatocytes in P1 and P2 males and females at this and higher doses. Adrenal gland

vacuolation and hypertrophy in parental females was found at the two higher doses. Dicofol effects on the offspring included reduced viability of pups, increased numbers of stillborn pups, pup deaths, total litter loss, and reductions in pup weight at the two higher dose levels. Vacuolation in the ovaries of P2 females was considered to be compatible with enhanced steroidogonic activity and thus an effect on reproductive physiology (guideline 83-4; MRID 41806601).

Mutagenicity

Dicofol at doses ranging from 5 to 5000 µg/plate did not cause mutations in an Ames assay (guideline 84--2a)(MRID 40042048). In addition, dicofol did not induce mutations in the in vitro Chinese hamster ovary cell HGPRT assay in which concentrations of 3.0 to 6.0 µg/ml without metabolic activation and 4.5 to 20 µg/ml with metabolic activation were tested (guideline 84-2a)(MRID 40042049).

There were no indications that dicofol at concentrattions ranging from 7.5 to 20 µg/ml (without metabolic activation) and 7.5 to 22.5 µg/ml (with metabolic activation) induced structural chromosomal aberrations in an in vitro cytogenetic assay using Chinese hamster ovary cells (guideline 84-2b)(MRID 40042051).

In an in vivo cytogenetic assay, groups of CRL:COBS-CD(SD) rats (30 males/dose) received dicofol at doses of 47.8, 191.2, and 478.0 mg/kg. Dicofol did not induce a clastogenic response in the

chromosomes of bone marrow cells of the test animals (guideline 84-2b)(MRID No. 40044205).

Since the initial battery of mutagenicity studies (discussed above) demonstrate no mutagenic activity, additional mutagenicity testing on dicofol is not required.

Neurotoxicity

In an acute neurotoxicity screening study, groups of Crl:CD^{R}BR VAF/Plus^{R} rats (10/sex/group) received dicofol by gavage once at doses of 0, 15, 75, and 350 mg/kg. Dicofol did not cause any histopathological changes in the central or peripheral nervous systems. Based on the decreases in body weights and reduced food consumptions, the LEL was 75 mg/kg; NOEL, 15 mg/kg (guideline 81-8)(MRID No. 42633303).

In a subchronic neurotoxicity study, groups of Crl:CD^{R}BR VAF/Plus^{R} rats (10/sex/group) received dicofol at dietary concentrations of 0, 5, 100, and 500 ppm, (0, 0.3, 5.6, and 27.8 mg/kg for males and 0, 0.3, 6.5, and 31.3 mg/kg for females). Dicofol did not cause any histopathological changed in the central or peripheral nervous systems. Based on the decreased motor activity and the increased liver weights, LEL was 100 ppm; NOEL, 5 ppm (0.3 mg/kg). A significant decrease in brain weight was also seen in 500 ppm males (guideline 82-7)(MRID No. 42971401).

Metabolism

Metabolism studies in male and female Sprague Dawley rats used a single oral dose of 50 mg/kg of ^{14}C-dicofol. The radiolabel was eliminated mainly in the feces and to a lesser extent in the urine. The parent compound was preferentially stored in adipose tissue. Also, when ^{14}C-dicofol was administered to female rats every day for 16 days at a dose of 0.5 mg/kg/day, the compound was eliminated mainly in feces and stored in adipose tissue (MRID No. 43070104). The metabolic pathways for dicofol were deduced, with the major one involving reductive halogenation to dichlorodicofol (DCD) and oxidation to dichlorobenzophenone (DCBP), dichlorobenzoic acid (DCBA), and dichlorobenzil (DCBH). This metabolic pathway is consistent with that proposed by Brown and Casida (1987). The analysis of metabolites revealed at most 0.2% of the radioactive residue was DDE which could be contributed by the presence of DDT (0.2%) and DDE (0.01%) in the test material. The data indicated that dicofol metabolized differently from that of DDT, which is metabolized to the purported carcinogen, DDE (guideline 85-1; MRID 00400420). This conclusion is also supported by the data of Brown and Casida (1987).

In two comparative disposition studies in rats which received orally equal doses of (0.5 mg/kg) dicofol and DDT, dicofol is consistently eliminated faster in the test animals. The tissue concentrations of radiolabel in fat, gonads, liver, adrenals, and muscle are not significantly different between dicofol- and DDT-

treated rats which were given (by gavage) multiple doses of dicofol or DDT (MRID No. 43070104). However, in another study, rats received a single oral high dose (50 mg/kg) of either DDT or dicofol; more DDT was found in fat and adrenals than dicofol (MRID No. 43070103). In the blood, the radioactivity level is consistently higher in dicofol-treated rats than that in DDT-treated ones (MRID No. 43070104).

Other Considerations

Reproductive effects in alligators: In a recent submission, the study of the effects of organochlorine contamination on the alligators in Lake Apopka, Florida, provided valuable information. The study is contained in the report on the Testimony to U.S. House of Representatives Subcommittee on Health and the Environment (Guillette, 1993). In 1980, the Tower Company, which was adjacent to Lake Apopka, had a chemical spill. One of the major products in the spill was reported to be Kelthane® (dicofol), which contained DDT at concentrations as high as 15% and its metabolites, DDD, DDE, and chloro-DDT. In summary, Guillette testified that, in his investigations, the alligator eggs and neonates from Lake Apopka differ from other Lakes in many significant ways. The following observations are most significant:

1. The embryos and the neonates within the first 10 days of life from Lake Apopka had high mortality rates.
2. The ratio of estradiol to testosterone was substantially

higher in the neonates from Lake Apopka than those from other lakes in FLorida (estradiol level was higher than the normal level while testosterone level was lower than the normal concentration).

3. The increase in estradiol level corresponded to the differences in the histological appearance of the gonads. "Females from Lake Apopka exhibit ovaries containing large numbers of polyovular follicles and polynuclear oocytes. Testes from males show poorly organized seminiferous tubules."(Guillette's testimony).
4. Alligator eggs from Lake Apopka were found to contain significant levels of DDE. When alligator eggs were experimentally injected with DDE, an abnormal testicular steroidogenesis was seen. Males produced elevated concentrations of estradiol and abnormally low levels of testosterone.

A published article by Heinz, Percival, and Jennings (1991) showed that there were elevated levels of several organochlorines in the alligator eggs from Lake Apopka collected in 1985. In those eggs, DDE was the most commonly found organochlorine, but dicofol was not detected. The absence of a detectable level of dicofol in the alligator eggs 5 years after the spill could not be considered as a convincing proof that dicofol was incapable of producing the hormonal effects noted in the alligators. It would be more convincing if there

were negative results derived from an experiment where alligator eggs were exposed to dicofol.

Reference Dose (RfD)

The reference dose for dicofol was determined to be 0.001 mg/kg/day, based on a long-term feeding study in dogs, in which the NOEL was 0.12 mg/kg/day. The LOEL, at 0.82 mg/kg/day, was based on inhibition of ACTH-stimulated cortisol release in both sexes. An uncertainty factor of 100 was used to account for inter-species extrapolation and intra-species variation (Ghali, 1994).

End point for less than life (LTL) time risk

The toxicological endpoints for the short- and intermediate-term occupational or residential exposure are 4.0 and 0.3 mg/kg, respectively. The short-term toxicological endpoint is derived from the NOEL of a rabbit developmental toxicity study (MRID No. 40042047) while the intermediate-term toxicological end point is derrived from a 90-day feeding study in dogs (MRID No. 40042043). No appropriate acute dietary end-point is identified. Currently no acceptable dermal absorption study is available, and 100% absorption by the dermal route is assumed.

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March 27, 1996

Docket Staff:

Please place this fax (Dicofol Toxicology Chapter for the RED) in the docket number **OPP 300415**. There should be 19 pages counting this page. Thank you very much.

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