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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUL 16 1985

MEMORANDUM

SUBJECT: Trichlorfon RS - Studies submitted to Satisfy Data Requirements. Accession No. 257819.
ID No. 3125-9

Caswell No. 385
Chemical No. 057901

FROM: Irving Mauer, Ph.D., Geneticist
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TO: William Miller/G. Otakie, PM-16
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THRU: Jane E. Harris, Ph.D., Head
Section VI
Toxicology Branch
Hazard Evaluation Division (TS-769)

Registrant: Mobay Chemical, Kansas City, Missouri

Action Requested: Review the following studies on DYLOX, submitted April 22, 1985, to satisfy data requirements for the TRICHLORFON REGISTRATION STANDARD, Toxicology (technical, Table A):

1. Mobay Report No. 68783 - "Micronucleus Test on Mouse to Evaluate L 13/59 for Potential Mutagenic Effects." (Performed by B. Herbold, Bayer AG Institut fur Toxikologie, Report #8505, July 18, 1979.)

2. Mobay Report No. 68925 - "Dominant Lethal Study on Male Mouse to Test for Mutagenic Effects." (Performed by B. Herbold; Bayer AG Institut fur Toxikologie, Report #8745, November 15, 1979).

3. Mobay Report No. 69298 - "Studies of Embryotoxic and Teratogenic Effects on Rats Following Oral Administration." (Performed by L. Machemer, Bayer AG Institut fur Toxikologie, Report #8400, May 29, 1979.)

10 pages

TB Evaluation (TOXICOLOGY BRANCH: DATA REVIEWS - attached):

1. #68783 - Mouse Micronucleus Test (Bayer #8505): Inconclusive

2. #68925 - Mouse Dominant Lethal (Bayer #8745): Unacceptable

3. #69228 - Rat Teratology (Bayer #8400): This study was previously reviewed under Accession No. 244915 (see memo and DATA REVIEW, Mauer to Miller, dated June 3, 1983), with the following evaluation:

"This study was conducted according to recognized protocols and is graded CORE Minimum. However, due to the lack of maternal, fetal, or teratogenic effects at the highest level tested (100 mg/kg/day), additional teratogenic testing in the rat may be required to satisfy EPA regulatory data requirements."

TOXICOLOGY BRANCH: DATA REVIEW

CHEMICAL: Trichlorfon

Caswell: 385
EPA Chem. No. 057901

STUDY TYPE: Mutagenicity - Chromosome aberrations (Micronucleus Test) in the mouse

CITATION: "Micronucleus Test on Mouse to Evaluate L13/59 for Potential Mutagenic Effects"

ACCESSION NO./MRID NO.: 257819/na

SPONSOR/TESTING LAB.: Mobay/Bayer AG Institut fur Toxikologie (B. Herbold)

STUDY NO./DATE: Mobay #68783 (Bayer #8505)/July 18, 1979

TEST MATERIAL: L13/59 (technical trichlorfon), Batch #809831030 (98.1% ai)

Procedures:

Five male and five female NMRI mice per group (supplied by S. Ivanovas GmbH, Kisslegg/Algaü) were intubated twice with test substance (suspended in 0.5% Cremophor EL) 24 hrs apart at doses of 2 x 0 (emulsifier alone), 2 x 125 mg/kg or 2 x 250 mg/kg, or with 2 x 60 mg/kg of the reference mutagen, cyclophosphamide (as positive control), and sacrificed 6 hrs after the second dose. Dosage selection of test substance was based upon a preliminary test at acute oral levels of 2 x 125, 2 x 250, and 2 x 500 mg/kg, which showed that the middose "caused only slight drowsiness." Femoral bone marrow was prepared by referenced (standard) procedures for the scoring of micronuclei (MN) in 1000 polychromatic erythrocytes per animal (PCE) and the ratio of PCE's to normochromatic erythrocytes (NCE), the latter determination indicative of an effect on erythropoiesis. MN data were analyzed statistically by the non-parametric ranking test of Wilcoxon, with the level of significance set at $p < 0.05$.

Results:

No differences from the mean negative control value of 1.0 MN per thousand PCE were evident in either trichlorfon-treated group (1.50/1000 at the 2 x 125 mg/kg dose, 1.56/1000 at 2 x 250 mg/kg) and no depression of erythropoiesis was found, as indicated by similar ratios of PCE to NCE. The positive control group responded appropriately with a significant mean incidence of 18.8 MN/1000 PCE, in the absence of any effect on the PCE/NCE ratio.

Conclusions:

The author concluded that trichlorfon had no mutagenic effect at dose levels up to 2 x 250 mg/kg.

TB Evaluation:

The study is INCONCLUSIVE as a comprehensive assay to determine an effect on the induction of micronuclei in bone-marrow PCE, because an apparently insufficient dosage was administered orally. As reported here in the main study, no clinical or erythropioetic effects were found at the HDT (two doses of 250 mg/kg given 24 hrs apart); previous acute toxicity studies by the registrants reported LD_{50}'s in mice in the range of 950 mg/kg for males and 940 mg/kg for both sexes combined (see TRICHLORFON REGISTRATION STANDARD). No evidence is presented that a toxic dose was approached, even in the preliminary dose-selection test. That a mutagenic effect (increased MN) could be induced even in the absence of a depression of erythropoeisis was evident in the response of the cyclophosphamide-treated positive control group.

TOXICOLOGY BRANCH: DATA REVIEW

CHEMICAL: Trichlorfon

Caswell: 385
EPA Chem. No: 057901

STUDY TYPE: Mutagenicity - chromosome aberrations (dominant lethal test) in mice

CITATION: "Dominant Lethal Study on Male Mouse to Test for Mutagenic Effects."

ACCESSION NO./MRID NO.: 257819/na

SPONSOR/TESTING LAB.: Mobay/Bayer AG Institut fur Toxikologie

STUDY NO./DATE: Mobay No. 68925 (Bayer No. 8745)/November 15, 1979

TEST MATERIAL: L13/59 (technical trichlorfon), Batch No. 809831030 (98.4% ai)

Procedure:

Two groups of 50 male NMRI mice (supplied by S. Ivanovas GmbH, Kisslegg/Algau) were given either a single oral dose of 250 mg/kg test substance by intubation (suspended in 0.5% Cremophor EL) or the emulsifier alone, immediately following each was caged serially to single untreated females for a total of 12 matings of 4 days duration each. The single test dose was chosen on the basis of a preliminary acute test in females treated orally at 750 and 500 mg/kg, both of which "induced symptoms." Uteri were examined 14 days after mating to determine preimplantation and post-implantation losses, based upon counts of total, viable, and dead (deciduoma + resorptions + dead embryos) implants and corpora lutea. Implant data for dose and time periods were analyzed after transformation by ANOVA ($p < 0.05$) and F-tests, and frequency distributions between test and control groups compared by a non-parametric test.

Results:

Other than "mild drowsiness" one hour after trichlorfon administration (in an unstated number of animals), no clinically adverse effects were reported in treated males. Analysis of individual data for all mated females (in 12 Appendices to the

Report) revealed no differences between treated and control groups in fertilization ratio, pre-implantation loss, total implants, dead and/or viable implantations, or post-implantation loss (deciduomata + resorptions + dead embryos).

Conclusions:

The author concluded that 250 mg/kg trichlorfon had no adverse effects on treated males, their fertility, or on parameters of dominant lethality.

TB Evaluation:

This study is UNACCEPTABLE as a mutagenic evaluation of dominant lethals, since:

1. Only one dose was used, and that is considered insufficient to affect treated animals or reproductive processes.

2. No positive controls were run concurrently to determine transport to germ cells, or sensitivity of the animals to respond.

One liners

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REGISTRATION STANDARDS PROGRAM
TOXICOLOGY

TRICHLORFON (TCF) 02-16-84
(Amended 3-12-84)

Caswell #385
Shaughnessy #057901

Antidotal - Mouse Chemagro Rpt.#467 (Dubois, 1955)	Technical (Dylox liq.)	090786 MRID# 00081186	Atropine sulfate (100 mg/kg) counteracts 3 x LD50.		
Acute oral LD50 - Rat Staszyc, Ann. Univ. Marie Curie D. 73:75 (undated)	Foschlor-50 (50% a.i.)	GS0104-153	[No LD50 determined; only one dose tested]		Invalid 003267
Acute oral LD50 - Rat MacDougall, 1962 (Chemagro report, CDL: 109105-A; 11/26/62)	Technical	MRID No. 00005494	[No protocol or data; LD50 stated as 560 mg/kg (females) and 630 mg/kg (males).]	III	001669 003267 Minimum
Acute oral LD50 - Rat Dubois, AMA Arch. Indust. Hlth. 11:53 (1955).	Technical	090786 MRID No. 00081186	LD50 = 450 mg/kg (sex not specified) [Same data as CDL: 20954-G] LEL (brain ChE) = 25 mg/kg.	II	001668/001669 Minimum 003267
Acute oral LD50 - Rat Williamson, USEPA Biol. Lab. Report, 9/27/74	VMI TCF Pour-On (8% a.i.)		[LD50 = 1.65 gm/kg for an 8% FP.]	III	Supple-mentary 003267
Acute oral LD50 - Rat Edson, 1960	50% WP	090786 GS0104-052	LD50 = 649 mg/kg a.i. (males only)	III	001669 Supple-mentary
Acute oral LD50 - Rat Gaines, 1960; 1969	Technical (10% aq. solution)	GS0104- -066/-067	LD50 = 625 mg/kg (males) LD50 = 500 mg/kg (both sexes)	III	001669 Minimum 003267
Acute oral LD50 - Mouse CDL: 20954-G, 3/5/75	Technical (?)	090786 GS0104-174	300 < LD50 < 500 mg/kg	II	001668 Minimum 003267
Acute oral LD50 - Mouse Two studies under CDL: 20954-G; also Chemagro Repts.# 777, 700	Technical	090786 GS0104-174	(i) LD50 = 940 mg/kg (both sexes) (ii) LD50 = 950 mg/kg (males)	III	001669 Minimum 003267

DISCUSSIONS

I. Experimental Acute Studies

Except for primary eye irritation (Toxicity Category I, e.g., MRID #GS0104-119-2, -3, -4, inter alia), trichlorfon technical exhibits moderate to low degrees of acute toxicity for other hazard indicators (Toxicity Categories II to IV) in experimental studies conducted with rodents, rabbits, dogs (and other laboratory species), as well as domestic (farm) animals.

Clinically demonstrable effects (including death) are referable to the well-known cholinergic (nicotinic/muscarinic) action of acetylcholine excess, occasioned by inhibition of cholinesterase enzyme activity, and common to all organophosphates.

Available acute oral toxicity studies in rats (MRID #00005494; GS0104052; GS0104174) report the LD_{50} for males in the narrow range between 625 and 649 mg/kg, slightly lower (560 mg/kg) in females, with two studies reporting combined values of 450 and 500 mg/kg (MRID #00081186; GS0104-066/-067). Trichlorfon appears to be less toxic to mice, 950 mg/kg for males and 940 mg/kg for both sexes combined (GS0104174). The consistency among individual studies satisfies the data requirements for acute oral toxicity, and no further studies are required at this time.

MRID#	CITATION
S0104173	Yasnova, G.P., Abbasov, T.G. and Tsaregorodtseva, G.N. 1971. [Pathomorphologic and histochemical changes in organs and tissues of calves following prolonged addition of organophosphorus insecticides to their feed.] Tr. Vses. Nauch. Issled. Inst. Vet. Sanit. 39:228-233 (Translated from Russian).
05007897	Yoder, J. Watson, M. Benson, W.W. 1973. Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. Mut. Res. 21:335-340.
S0104174	US-EPA. 1961. "Neguvon. Pharmacology and Toxicology Data. February 2, 1961." Submitted in support of Petition 7F0612 (EPA Accession # 090786).
S0104175	US-EPA. 1980. "Request for reconsideration of computer printout for trichlorfon (180198)." Memo, Jaeger to Frick, March 25, 1980.
S0104176	US-EPA. 1983. "Assessment of Teratogenic Potential of Trichlorfon in Mice and Rats," by K.D. Courtney, J. E. Andrews and J. Springer (Unpublished manuscript from the Health Effects Research Laboratory, U.S. - EPA, Research Triangle Park, NC).