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

OFFICE OF PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

13/October/1999

MEMORANDUM

Subject: Comparison of Rohm & Haas's 70% Oxyflurofen (GOAL Technical Herbicide) to Makhteshim-Agan's 97% Oxyflurofen (Galigan, EPA Reg No. 11603-EO)
PC Code: 111601

From: John C. Redden, M.S.; Byron Backus, Ph.D.; Deborah McCall
Technical Review Branch, Registration Division (7505C)

Through: William Dykstra, Ph.D., & Melba Morrow, D.V.M.
Registration Branch 1, Health Effects Division (7509C)

To: Donald Stubbs, Chief
Herbicide Branch, Registration Division (7505C)

Registrant: Makhteshim-Agan of North America Inc.
551 Fifth Ave., Suite 1100
New York, NY 10176

ACTION:

Technical Review Branch (TRB) performed a "preliminary review" of Makhteshim-Agan's Tier I toxicity data for 97% Oxyflurofen (Galigan) product. Then, TRB compared the results of Tier I toxicity data for both technical products of Rohm & Haas (GOAL 70%) and Makhteshim-Agan's technical product (Galigan 97%) to determine if a registration decision could be made for Makhteshim-Agan. Currently, Rohm & Haas holds the only technical Oxyflurofen registration and Makhteshim-Agan has completed the necessary data citation requirements.

BACKGROUND

(1)

Makhteshim-Agan Chemical Manufactures Ltd. is seeking a registration decision for its new Oxyfluorfen Technical. This new technical has been through a refined manufacturing process so that many of the impurities have been reduced or removed. Consequently, the active ingredient has increased in concentration from 70% to 97%.

Makhteshim-Agan Chemical has previously requested a "Me-Too" registration for this new technical citing the Rohm & Haas data. The Product Chemistry Team of the TRB on 13/May/1999 determined the two products were <u>not</u> substantially similar because the two technicals differed by more than ± 3% in their certified limits (CFR 158.175). [The two technicals differ by more than 25% in certified limits; this is a significant increase in the concentration of the a.i. when compared to the registered product.]

Makhteshim-Agan rebutted TRB's decision by stating that in removing and reducing impurities, the technical would be less toxic. The Health Effects Division was consulted on September 16, 1999, and the Toxicology Science Advisory Council (TOX-SAC) visited this issue and their committee made a determination that Tier I toxicity data would be required to address toxicity concerns of the purer product. An Agency memorandum entitled, *Policy for Determining Toxicology Data Requirements for Enriched Isomer Technical Chemicals*, (April 1999; Mike Ioannou HED & Bill Burnam HED) will be used as the template to evaluate the toxicological data requirements. The Toxicologists in RD and HED concluded there were 3 possible toxicological outcomes for the purer technical: 1) the new technical could be more toxic because impurities could have blocked the receptor sites in the body thereby potentially changing the toxicity profile; 2) the new technical could be equivalent in toxicity; or 3) the new technical could have a different toxicity.

Although the case under consideration is not that of an enriched isomer, the circumstances are similar as the concentration of active ingredient has increased. The document referenced above explains the toxicology data requirements for a food use technical as follows:

> "Routinely, for food use technicals (including mixed isomer technicals), the following studies are required: acute toxicity battery, 90-day feeding study in the rat, developmental toxicity studies in two species (rat and rabbit), a two-generation reproduction study (rat), two chronic toxicity studies (rat and dog), two carcinogenicity studies (rat and mouse), a rat metabolism study, and the mutagenicity battery; (other studies such as the neurotoxicity battery, developmental neurotoxicity, and immunotoxicity studies might be required on a case-by-case basis)."

For an enriched isomer (and now a technical with an increased concentration) the following are required: **acute toxicity battery, 90-day feeding study in the rat, a developmental toxicity study in the rat, and the mutagenicity battery.** The following guidance should be followed when conducting these studies:

> "These studies should be carried out in the same species and strain of animals and in the

same testing laboratory as the original (mixed isomer) studies, if at all possible. The additional studies on the mixed isomer technical could be used to support the enriched isomer technical if side by side comparisons of the acute toxicity, developmental toxicity, 90-day toxicity, and mutagenicity studies for both, the mixed isomer technical and the enriched isomer technical result in similar toxicity...If data from the enriched isomer technical indicate significantly higher toxicity (quantitatively or qualitatively) than the mixed isomer technical, then all the studies required for a food use chemical should be conducted."

Makhteshim-Agan's agent told RD that Tier I toxicity data had been previously developed on the new technical and he could have it formatted and sent to OPP quickly. Due to competing priorities in HED with the FY 2000 work plan TRB agreed to give the data a "preliminary review" (in conjunction with HED) and then make a *snapshot* comparison with the Rohm & Haas 70% data to decide if the Makhteshim-Agan technical could be registered. The Makhteshim-Agan data will be comprehensively reviewed during the re-registration process for Oxyfluorfen occurring in FY 2000. It is important to emphasize that the data were evaluated only in a preliminary manner. In the future, when these data are examined in detail other studies could be required to address efficiencies in the database.

COMPARISON

The Tier I toxicity data for the Makteshism-Agan 97% Oxyflurofen were screened by the acceptability criteria and found to be acceptable. The "preliminary review" of this toxicity data was done by the Technical Review Branch in RD. Please note it is Agency policy to report all NOELs and LOELs as NOAELs and LOAELs. The comparison of the Tier I data between Rohm & Haas and Makteshism-Agan technicals are given as a TOX 1-liner in Table 1.

CONCLUSION

The data for the two technicals are similar in toxicity. Therefore, a "Me-Too" registration decision can be granted.

TOX-1 liner: Rohm & Haas data had been previously Peer Reviewed by OPP.

October 1999 -

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS 870.1100 § 81-1 Acute Oral Toxicity; Species Rat	LD_{50} > 5.0 g/kg; Toxicity Category IV; No deaths, toxic signs consisted of bright-yellow stained anal-genital region, salivation, soft feces, yellow-stained muzzle. No effect on body weight and no necropsy findings; Acceptable; MRID No. 4160100.	LD_{50} > 5.0 g/kg; Toxicity Category IV; No mortality or clinical signs were noted during the study. All rats had normal body weight gains. No abnormalities were noted at necropsy. Acceptable; MRID No: 44712010.
OPPTS 870.1200 § 81-2 Acute Dermal Toxicity; Species Rabbit	LD_{50} > 5.0 g/kg; Toxicity Category IV; No deaths, no toxic signs, no effect on body weight, and no necropsy findings; Acceptable; MRID No. 41601002.	LD_{50} > 2000 mg/kg; Toxicity Category III; No animals died during the study. No clinical abnormalities and no skin irritation were observed. All animals had normal body weight gains. No abnormalities were noted at necropsy; Acceptable; MRID No.: 44712011.

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS 870.1300 § 81-3 Acute Inhalation Toxicity; Species Rat	LC50 > 5.1 mg/L; Toxicity Category IV; MMAD = 1.6 - 2.9 µm, no deaths, no toxic signs, and no necropsy findings; Acceptable; MRID 42000001.	LC_{50} > 3.71 mg/L (nose only); Toxicity Category: IV; Clinical abnormalities during exposure included wet fur and/or increased respiratory rate. Hunched posture, piloerection, staining on fur on head/snout, ptosis, and/or increased respiratory rate were noted on all rats upon chamber removal. Wet fur and ptosis disappeared within one hour after completion of exposure. With the exception of staining on the fur that persisted through the end of the study, all rats recovered by day 2. All rats had normal body weight gains with the exception of one female that did not gain weight during the second week of study. No abnormalities were noted at necropsy. Acceptable; MRID No.: 44712012.
OPPTS 870.2400 § 81-4 Primary Eye Irritation; Species Rabbit	Slight irritant; Toxicity Category III; In the washed and unwashed eye, conjunctival effects (redness, discharge and chemosis) were observed at 1 - 72 hours, but disappeared by day 7. Washing eyes did not reduce the duration or severity of conjunctival effects. No iritis or corneal opacity; Acceptable; MRID 41601004.	Slight irritant; Toxicity Category IV No corneal opacity was noted in any rabbit. Four rabbits had iritis one hour after test material instillation. Within one hour after test material instillation, all rabbits exhibited conjunctivitis. By 24 hours, no positive reaction was noted for any rabbit; Acceptable; MRID No. 44712013.
OPPTS 870.2500 § 81-5 Primary Dermal Irritation; Species Rabbit	Toxicity Category IV; Erythema and edema at 1, 24, and 48 hours, but clearing at 72 hours. PDIS. at 72 hours = 0.0; Acceptable; MRID No. 41601003.	Slight irritant; Toxicity Category IV; PDIS = 0.2 (Slight irritant). One hour after patch removal, very slight erythema (maximum score of 1) was noted on 2/6 rabbits that persisted through 48 hours with resolution by 72 hours. Yellow staining was noted at all treatment sites; Acceptable; MRID No.: 44712014.

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS 870.2600 § 81-6 Dermal Sensitization; Species Guinea Pig	Equivocal; Buehler Method produced equivocal results at challenge in both naive and treated guinea pigs. The data do not support an interpretation of a positive response; Acceptable; MRID No. 41891802	NOT a dermal sensitizer. Well defined erythema and very slight erythema were noted at the intradermal induction sites of all test and vehicle control animals, respectively. Yellow staining was noted at all induction sites. The staining prevented accurate evaluation of the topical induction sites. However, no edema was noted on any test animals. No reaction was noted on the vehicle control animals after the topical induction. No reaction was noted on any test or vehicle control animals following challenge; Acceptable; MRID No.: 44712015.
OPPTS 870.3700 § 82-1(a) 90-day Oral Feeding Study; Species Rat	NOAEL ≤ 20 mg/kg/day (≤200 ppm) based on dose related effects: 1) yellow pigment in tubular epithelium and vascular degeneration of distal tubules (♀ only); Doses = 0, 20, 100 or 500 mg/kg/day (0, 200 1000 or 500 ppm); Supplementary; MRID 001176063.	NOAEL = 50 (M: 46.7; F:50.4) mg/kg/day; LOAEL = 150 mg/kg/day based on effects on kidney function and electrolytes; RBC parameters, liver & adrenals. At ≥ 600 mg/kg/day effects included increased pigment in renal cortical epithelium. Approximate Doses = 0, 50 150, 600, or 1,000 mg/kg/day (0, 500, 1500, 6000, or 10,000 ppm) MRID: 449331-01 meets the acceptance criteria for OPPTS 870.3100.

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS 870.3100 § 81-3(a) Developmental Toxicity Study; Species Rat	Maternal NOAEL = 18 mg/kg/day, Maternal LOAEL = 183 mg/kg/day based on decreased weight gain and food consumption, increased incidences of soft or scant feces, increased alkaline phosphatase and SGOT and mortality at high dose. Developmental NOAEL = 18 mg/kg/day; Developmental LOAEL = 183 mg/kg/day based on decreased fetal body weight, increased resorptions, and an increase in the incidences of left carotid artery arising from the innominate, bent bones of the forelimbs, and other ossification irregularities; these effects were confined to the mid-dose level, since there was a 100% litter loss in the high-dose groups as the result of maternal mortality and resorptions; Doses: 0, 18, 183, and 848 mg/kg/day (6-15 days of gestation); Minimum; MRID 418065-01.	Maternal NOAEL > 1000 mg/kg/day; Developmental NOAEL > 1000 mg/kg/day. CD rats of Sprague Dawley origin were dosed by gavage at doses of 0, 375, 750, 1000 mg/kg/day; MRID 449331-03 meets the acceptance criteria for OPPTS 870.3100.

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS 870.3100 § 81-3(b) Developmental Toxicity Study; Species: Rabbit	Maternal NOAEL = 10 mg/kg/day; Maternal LOAEL = 30 mg/kg/day based on anorexia, decreased body weight gain. Developmental NOAEL = 10 mg/kg/day; Developmental LOAEL = 30 mg/kg/day based on fused sternebrae. Doses: 0, 10, 30 and 90 mg/kg/day; Minimum; MRID No. 00094052.	Maternal NOAEL = 30 mg/kg/day; Maternal LOAEL = 90 mg/kg/day based on reduced food intake, fecal output, and variable body weight gain. One of the 90 mg/kg/day females found dead; two others, at this dose level, aborted in late gestation. Developmental NOAEL = 30 mg/kg/day; Developmental LOAEL = 90 mg/kg/day based on 3 litters with low litter mean weights, fetal delayed skeletal ossification and delayed development (fetal heads). Doses = 0, 10, 30, 90 mg/kg/day. Dose selection was based on a preliminary study (0, 5, 25 and 75 mg/kg/day; 75 mg/kg/day maternal weight loss & small fetuses). MRID 449331-02 meets the acceptance criteria for OPPTS 870.3100, but TRB notes the following: 1) Only 10 pregnancies in the control group and 11 in the high group; and 2) The dosage selection is barely adequate.

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS # varies § 84-2(a) Mutagenicity Gene Mutation	Ames Assay; Positive in TA98, TA100, and TA1537 ate 2500 µg/plate with activation and at 6000 µg/plate without activation; Acceptable; Accession No. 247206.	Salmonella typhimurium/mammalian microsome mutagenicity assay; Negative. In two independently mutation assays Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 were exposed to concentrations ranging from 50 to 5000 µg/plate AG 510 technical (96%) (in the presence and absence of S9 activation); the test material was delivered to the test system in dimethyl sulfoxide. Compound insolubility at 5000 µg/plate +/-S9 in both assays, and at 1500 µg/plate in the second assay; however, no indication of cytotoxicity was observed in any strain at any dose level up to and including 5000 µg/plate +/- S9. No indication or evidence that AG 510 technical induced a mutagenic response in any strain at any nonactivated or S9-activated dose. MRID: 44933104 meets the acceptance criteria for OPPTS 870.5100 [§84-2].

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
		Salmonella typhimurium/mammalian microsome mutagenicity assay; In two independently performed microbial gene mutation assays, S.typhimurium strains TA1535, TA1537, TA 1538, TA98, and TA100 were exposed to concentrations ranging from (1st assay) 10 to 3333 µg/plate and (2nd assay) 17 to 5000 µg/plate AG 510 technical (96%) both +/- S9 activation. The study concluded that AG 510 was weakly mutagenic to strain TA 100 only "when tested in dimethylsulphoxide to the limit of its solubility" in the presence of S9 mix only. There was no indication or evidence that AG 510 technical induced a mutagenic response in any of the other strains at any dose level. MRID: None meets the acceptance criteria for OPPTS 870.5100 [§84-2].
OPPTS # varies § 84-2(b) Mutagenicity Structural Chromosome Aberration	Structural Chromosome Aberration: *In Vivo* Cytogenetic Assay/rat. Negative for cytogenetic chromosomal aberrations both with and without metabolic activation; Acceptable; Accession No. 247206.	Mouse Micronucleus; Negative; Groups of five male and five female mice (CD-1 outbred, Swiss origin)/sacrifice time were intraperitoneally injected with 2000 mg/kg (a limit dose) of AG 510 in aqueous 1% methyl cellulose at a standard volume of 20 ml/kg (concentration of the test material was 100 mg/ml). Toxicological signs included piloerection, gasping, hunched posture, lethargy, piloerection, ptosis and waddling. There was no evidence then that AG 510 induced a clastogenic or aneugenic effect at either sacrifice time. MRID: 449331-05. This study meets the acceptance criteria for OPPTS 870.5395 [§84-2].

Study	Rohm & Haas 70% Oxyflurofen USEPA, HED Review[1]	Makhteshim-Agan 97% Oxyflurofen[2]
OPPTS # varies § 84-4 Mutagenicity Other	Other Genotoxic Effects: Mouse Lymphoma Forward Mutation Assay. Positive mutagen in the presence of an activation system at the thymidine kinase locus of mouse lymphoma L51787Y (TK +/-) cells; Acceptable; Accession No. 247909.	DNA repair, rat hepatocytes; Negative. There is no indication that the test material, AG 510 technical, induced a genotoxic response at either dose or either sacrifice time. MRID: 44933106. This study meets the acceptance criteria for OPPTS 870.5550 [formerly §84-2].

1. Data for EPA Reg. No. 707-165 (70% a.i.) extracted from a memorandum entitled, *ID# 94WA005. Specific Exemption Request by the State of Washington for Use of Oxyfluorfen on Red Raspberries to Suppress Primocanes,* William Dykstra, Ph.D., February 22, 1994, and the HED TOX ONELINERS.

2. Data for the acute six pack was extracted from EPA Reg. No.: 011603-EO DP Barcode: D252072 Case No: 064230 Dennis McClain, Biologist *3/25/99*. The remaining data was supplied by the registrant, Agan Chemical Manufacturers Ltd. This data has not been reviewed by the Agency as of 9/28/99.