7-31-97

DATE STAMPED: 07/31/97

MEMORANDUM:

SUBJECT: Hazard Identification Committee Report of Bensulide.

CASRN: 741-58-2
PC Code: 009801
Caswell: 357

FROM: George Z. Ghali, PhD.
Executive Secretary, Hazard Identification Committee
Health Effects Division (7509C)

Thru: Clark Swentzel
Chairman, Hazard Identification Committee
Health Effects Division (7509C)

To: Jim Tompkins, PM 25
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on July 10, 1997 to evaluate the existing and/or recently submitted toxicology data in support of bensulide re-registration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and duration, and assess/reassess the reference dose for this chemical.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity-carcinogenicity study in rats **(83-5)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, subchronic studies in rodents and non-rodent species **(82-1a and 82-1b)**, a 21-day dermal toxicity study in rats **(82-2)**, an acute oral neurotoxicity study in rats **(81-8ss)**, an acute delayed neurotoxicity study in hens **(81-7)**, a battery of mutagenicity studies **(84-2)**, and a series of acute toxicity studies **(81-1 through 81-6)**.

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Individuals in Attendance

Hazard Identification Committee members present were David Anderson, Karl Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Nancy McCarroll, John Redden, Jess Rowland, Clark Swentzel (Chairman, Hazard Identification Committee, HED), and William Sette (for Kathleen Raffaele).

Hazard Identification Committee members in absentia were Melba Morrow and Kathleen Raffaele.

Scientific reviewer(s) (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated.

Raymond Locke _____

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I. TOXICOLOGY PROFILE:

Bensulide (Betasan) is an organophosphorus herbicide registered for use on certain vegetables, ornamental or shade trees, ornamental shrubs and vines, and ornamental lawns and turf. It is applied by variety of application methods. The mode of toxic action to non-target organisms, i. e. mammals, is via the inhibition of cholinesterase and accumulation of acetylcholine at the nerve synapses, resulting in classic symptoms of organophosphate poisoning.

A. Carcinogenicity:

Based on the toxicology data available, the Hazard Identification Committee determined that bensulide did not alter the spontaneous tumor profile in rats and mice under the testing conditions. Therefore, it was recommended that bensulide be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure. This weight of the evidence judgement is largely based on the absence of significant tumor increases in two adequate carcinogenicity studies in rats (MRID Nos.: 43919602, 44161101, 44161102, 44161103, and 44206301) and mice (MRID Nos.: 44161102, 44161103, 44161104, 44161105, and 44206301).

This classification is also supported by the lack of mutagenic activity (MRID Nos. 00153493, 41902601, 41902602, 42479201, and 43273901).

It should be noted, however, that designation of an agent as being in **"Group E"** or **"Not Likely"** is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

B. Reproductive and Developmental Toxicity:

1. Reproductive Toxicity:

In a 2-generation reproduction study, bensulide (92.4%) was administered to Sprague-Dawley rats at dietary levels of 25, 150, or 900 ppm (2.3, 13.2 or 80.8 for F0 females and 2.6, 15.4, or 93.2 mg/kg/day for F1 females). The parental systemic NOEL was ≥900 ppm (82.8 mg/kg/day), the highest dose level tested. The parental LOEL for red blood cell cholinesterase inhibition (47%) in dams was 150 ppm (15.4 mg/kg/day; F1 females); the NOEL was 25 ppm (2.6 mg/kg/day). The parental LOEL for inhibition of brain cholinesterase (51-68%) was 900 ppm (80.8 mg/kg/day for F0 females and 93.2 mg/kg/day for F1 females); the NOEL was 150 ppm (13.2 mg/kg/day for F0 females and 15.4 mg/kg/day for F1 females). The

LOEL for reproductive toxicity was 900 ppm (93.2 mg/kg/day for F1 females), highest dose level tested, based on reduced F2 pup survival; the NOEL was 150 ppm (15.4 mg/kg/day), (MRID No. 43948701, HED Doc. No. 000000).

2. Developmental Toxicity:

In a developmental toxicity study in rats, bensulide (92.8%) was administered by gavage to Sprague-Dawley rats at the dose levels of 5.5, 23.0, or 95.0 mg/kg/day on gestation days 6-20. The NOEL/LOEL for maternal systemic toxicity were 23.0 and 95.0 mg/kg/day, respectively, based on tremors, decreased body weights, body weight gains, and food consumption, and increased liver/body weight ratio. The NOEL/LOEL for maternal plasma cholinesterase inhibition were 5.5 and 23.0 mg/kg/day, respectively, based on 48.4% decrease compared to controls; at 95.0 mg/kg/day, values were decreased 84.6% from control. The NOEL for maternal RBC cholinesterase inhibition was >95.0 mg/kg/day; at 95.0 mg/kg/day, values were 5.9% decreased from control. Developmental toxicity NOEL was >95.0 mg/kg/day, the highest dose level tested. Brain cholinesterase activity was not measured in the dams and none of the cholinesterase parameters was measured in fetuses (MRID Nos. 00146585, 92005018).

In another developmental toxicity study, bensulide (92.9%) was administered by gavage to New Zealand rabbits at dose levels of 5, 20, or 80 mg/kg/day on gestation days 7-19. Cholinesterase activity was not measured in either does or fetuses. The maternal toxicity NOEL/LOEL were 20 and 80 mg/kg/day, respectively, based on decreased body weight and body weight gain. The developmental NOEL was >80 mg/kg/day and the developmental toxicity LOEL was not determined (MRID No. 00152845, HED Doc. No. 000000).

3. Developmental Neurotoxicity:

Based upon the weight-of-evidence, the Hazard Identification Committee did not recommend that a developmental neurotoxicity study in rats be required for bensulide at this time. Although, bensulide is a neurotoxic chemical, there was no evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, observed in the developmental toxicity studies in rats and rabbits up to and including the dose levels sufficient to elicit maternal body weight decrements. Furthermore, although decreased brain weight was observed in the high dose males on the 2-generation reproductive toxicity study, no other subchronic or chronic study in rats, mice, or dogs identified any treatment-related findings in brain weight, nor was there any evidence of macroscopic or microscopic changes in nervous system tissues (including the acute neurotoxicity study in rats). In addition, delayed neuropathy was <u>not</u> observed in the acute delayed neurotoxicity study in hens up to the limit dose of 2000 mg/kg. However, this issue should be referred to the Committee on

Organophosphorus Data Requirements for further consideration.

C. **FQPA Considerations:**

Adequate data available on bensulide provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Bensulide. Therefore, an additional uncertainty factor for risk assessment purposes is not warranted.

This conclusion is based on the reproductive and developmental toxicity findings. In a two-generation reproduction study in rats, cholinesterase inhibition in the adult animals was observed at a dose which produced no evidence of toxicity in the offspring (the parental plasma cholinesterase inhibition NOEL was <2.3 mg/kg/day while the reproductive toxicity NOEL was 15.4 mg/kg/day, based on decreased viability in second generation pups at 93.2 mg/kg/day). In both the prenatal developmental toxicity studies in rats and rabbits, developmental toxicity was not observed up to the highest dose tested, although evidence of systemic toxicity was demonstrated in the maternal animals, including body weight decrements in both species and tremors, decreased food consumption, increased liver/body weight ratio, and plasma cholinesterase inhibition in rats.

D. **Mutagenicity:**

Four acceptable studies were available for review. The following are summaries and the committee's conclusion for these studies.

1. Gene mutations:

i) Salmonella typhimurium reverse gene mutation assay (MRID No. 00153493): The test is negative up to insoluble levels (≥1.0 μL/plate, equivalent to ≈1230 μg/plate) both in the presence and absence of S9 activation using strains TA1535, TA1537, TA98 and TA100.

ii) Mouse lymphoma L5178Y $TK^{+/-}$ forward gene mutation assay (MRID No. 43273901; Doc. No. 011409): The test was negative up to a cytotoxic nonactivated and S9-activated dose (≈30 μg/mL).

2. Chromosomal Aberrations:

i) In vitro chromosome aberrations in human lymphocytes assay (MRID Nos. 41902601/42479201; Doc. Nos. 009077/010229): The test is negative up to a cytotoxic concentration (80 μg/mL) in both the presence and absence of S9 activation.

ii) In vivo bone marrow micronucleus assay (MRID No. 41902602;

Doc. No. 009077): The test is negative in C57BL/6JfCD-1/Alpk male and female mice up to the highest evaluated dose (400 mg/kg) when administered once by oral gavage. There were, however, no signs of overt toxicity or depression of erythropoiesis seen at 400 mg/kg. Higher levels (≥500 mg/kg) were lethal in preliminary studies.

3. Conclusions:

The available studies clearly indicate that bensulide is not genotoxic. Additionally, the negative mutagenicity studies support the lack of an oncogenic effect in the rat and mouse long-term feeding studies and also the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions). **Based on the overall results, there is no concern for mutagenicity.**

The submitted test battery satisfies the NEW mutagenicity initial testing battery guidelines; no further testing is required at this time.

E. Dermal Toxicity and Dermal Absorption:

In a 21-day dermal toxicity study (MRID 42162002), male and female specific pathogen-free Wistar-derived albino rats (Alpk:APfSD strain; 5/sex/dose; 6-8 weeks old) were dermally treated with bensulide (92.7%) over a 5 cm x 10 cm area of clipped dorso-lumbar skin at dose levels of 0 (sham control), 10, 100, and 1000 mg/kg/day (limit test dose), six hours a day.

There were no deaths, compound-related clinical signs, or significant changes in body weight or food consumption in any group. A small incidence of dermal trauma was apparently caused by the bandages. No abnormal hematology was seen, and the only clinical chemistry anomaly was a 43% decrease in plasma triglycerides in the high-dose (1000 mg/kg/day) males compared to controls; females were not affected. In the absence of other findings, this decrease is of unknown biological significance. There were no dose-related gross lesions or organ weight changes. Some scabbing of treated and untreated skin, due to bandage trauma, was observed in all groups. This observation correlates with several histopathologic findings of slight to minimal acanthosis, parakeratosis, and inflammatory infiltration in treated and untreated skin. A number of minimal to slight renal lesions were observed, but they are not clinically significant and may have represented artifacts. ***Therefore, the NOEL is > 1000 mg/kg/day (limit dose), based on the lack of any observed toxicity, and the LOEL was not determined.***

There were no dermal absorption data available on bensulide.

II. HAZARD IDENTIFICATION:

Based on comprehensive evaluation of the toxicology data available on bensulide, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route to route conversion, or variable durations extrapolation are also addressed.

Based on the exposure/use profile for bensulide, the Committee determined that the risk assessments indicated below are required.

A. Reference Dose (RfD):

Reference Dose (R_fD): 0.005 mg/kg/day.

Critical Study: Chronic toxicity study in the dog (83-1b), MRID Nos. 44066401, 44052704.

Executive Summary: In a chronic toxicity study in dogs, bensulide (92.4% a.i.) was administered to four dogs/sex/dose by feeding at dose levels of 0, 0.5, 4, or 30 mg/kg/day for 52 weeks. Analytical determinations demonstrated actual bensulide concentrations to be within ± 10% of theoretical values throughout the study. Additional analytical data (MRID 44052704) verified the adequacy of the homogeneity and stability of bensulide in the test diets.

In the 30 mg/kg/day treatment group, there was a 66-73% reduction in plasma cholinesterase activities, a 18.7-35.5% reduction in brain (pons) cholinesterase activities, and a 32-45% reduction in red cell cholinesterase activities. In addition, in the high dose females, mean body weight gains were 52% lower than the controls and histopathological changes were observed in the liver. Focal accumulations of pigmented Kupffer cells were observed in 2/4 females, and mild cytoplasmic vacuolation was noted in 3/4 females in the 30 mg/kg/day group. Absolute weights of the adrenal glands of males in the 30 mg/kg/day treatment group were 29% higher than the controls. In the 4 mg/kg/day treatment group, there was a 57-58% reduction in plasma cholinesterase activity, a 24% reduction in brain (pons) cholinesterase activities (males only), and a 34% reduction in body weight gain (females only). In the 0.5 mg/kg/day treatment group, there was a 19-31% reduction in plasma cholinesterase activity compared to the control. No animals died during the course of the study, and no treatment-related changes were observed in their appearance or behavior. Food

consumption appeared to be unaffected by treatment. No ocular, hematological, or urine abnormalities were detected during the study. No neoplastic tissue was observed in dogs in the treatment and control groups. ***The NOEL/LOEL are 0.5 and 4 mg/kg/day, based on the reduced body weight gains in females, reduced brain (pons) cholinesterase activities (24%) in males, and reduced plasma cholinesterase activities in both sexes (57-58%).***

Comments: The Committee was aware that, at 0.5 mg/kg/day, sporadic statistically significant decreases in plasma cholinesterase were observed in males at 13 (24% decrease) and 26 weeks (22% decrease), but not at 52 weeks. Similarly, a statistically significant decrease (31% decrease) in plasma cholinesterase was observed in females at 52 weeks, but not at 13 or 26 weeks. The Committee also noted the large difference between this dose level of 0.5 mg/kg/day and those required to elicit statistically significant decreases in red blood cell cholinesterase (45% decrease; 30 mg/kg/day; males only) or brain (pons) cholinesterase (24% decrease; 4 mg/kg/day; males only) activities. In view of the inconsistency of the inhibition of plasma Chew observed in males and females at 0.5 mg/kg/day, as well as the large differences between this dose level and those required to elicit inhibition of either red blood cell or brain (pons) cholinesterase activities, the Committee believes that the biological significance of the sporadic decreases observed in plasma cholinesterase activity at 0.5 mg/kg/day is unknown.

Endpoint and Dose selected for use in risk assessment: NOEL/LOEL = 0.5/4.0 mg/kg/day, based on inhibition of plasma cholinesterase activity in both sexes and brain cholinesterase activity in males.

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. The use of a UF of 100 was justified based on the availability of a chronic toxicity study in a second species (MRID Nos. 43919602, 44161101) and a reproductive toxicity study in rats (MRID No. 43948701) in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group.

B. <u>Acute Dietary Exposure (one day)</u>:

Critical Study: Acute neurotoxicity study in the rat (81-8), MRID No. 43195901.

Executive Summary: In an acute neurotoxicity screening study, 22 CD rats/sex/group were administered single gavage doses of 0, 30, 100 or 300 mg bensulide (tech., 92.4% a.i.)/kg (males) or 0, 15, 50 or 150 mg/kg (females) in corn oil. Dose volumes were maintained at 5 mL/kg of body weight. Functional observational battery (FOB) and motor activity tests were conducted on 12 rats/sex/dose pretreatment, on the day of dosing (day 0) and days 7 and 14 post-

dosing. Plasma, erythrocyte and brain cholinesterase (Chew) activities were measured from 5 rats/sex at pretreatment, day 0 (6.25 and 6.75 hrs post-dosing) and day 15. Six perfused control and high dose rats/sex were evaluated for neuropathology.

At 150 mg/kg (females only), an increased incidence of diarrhea, flaccid abdominal and/or body tone (all 6/12 vs. 1, 2 and 2, controls) and pinpoint pupils (3/12 vs 0, controls) were observed on Day 0 in the FOB. At 300 mg/kg (males only), one death occurred on Day 1, preceded by clinical signs (salivation, lacrimation/ocular discharge, decreased respiration, hypothermia, and fur staining on muzzle and ventral surface). A second male exhibited abnormal respiration, tremors, hypoactivity, dehydration and fur staining between Days 1 -3. In the FOB, increased incidence of decreased arousal and locomotor activity (for both, 7/12 vs. 3, controls) were observed. A slight but statistically significant depression of body weight (-6.6%) was also observed on Day 7. No treatment-related effects on motor activity or macroscopic/microscopic neuropathology were reported.

At 50 mg/kg (females only), plasma cholinesterase was decreased on day 0 by 80% less than controls (not significant). At 100 mg/kg (males only), plasma Chew was decreased on day 0 by 53% (not significant). At 150 mg/kg (females only) on day 0, reductions were observed in plasma Chew (89% less than controls, $p<0.01$) and erythrocyte Chew (37% less than control, $p<0.01$) both of which showed partial recovery by day 15. However, a significant decrease (73% of control, $p<0.01$) in brain Chew for high-dose females was noted on day 15 which was not present at day 0 (18% less than controls, not significant). At 300 mg/kg (males only), Statistically significant Chew inhibition was observed only in the high-dose groups. On day 0, there were significant decreases in brain Chew (62% of control, $p<0.01$), plasma cholinesterase (19% of control, $p<0.01$), and erythrocyte cholinesterase (60% of control, $p<0.01$) for males of the high dose (300 mg/kg) group. At day 15, brain Chew was still significantly reduced (73% of control, $p<0.01$) but values for plasma and erythrocyte Chew had returned to normal.

The NOEL/LOEL are 100 and 150 mg/kg, respectively, based on minimal, transient clinical signs consistent with cholinesterase inhibition in females. The NOEL/LOEL for plasma cholinesterase inhibition are 15 and 50 mg/kg, based on 80% inhibition in females on Day 0. The NOEL/LOEL for RBC cholinesterase inhibition are 50 and 150 mg/kg, respectively, based on 37% inhibition ($p \leq 0.01$) in females on Day 0. The NOEL/LOEL for brain cholinesterase inhibition are 50 and 150 mg/kg, respectively, based on 18% inhibition in females on Day 0 and 27% inhibition ($p \leq 0.01$) on Day 15.

Endpoint and Dose Level Selected for Use in Risk Assessment: NOEL

= 15 mg/kg, based on 80% inhibition of plasma cholinesterase activity in females on Day 0 observed at 50 mg/kg/day.

Uncertainty Factor (UF): A UF of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

C. **Short Term Occupational or Residential Exposure (1-7 days):**

Critical Study: Developmental Toxicity study in rats (83-3a), **MRID No.** 00146585, 92005018

Executive Summary: In a developmental toxicity study, bensulide technical (92.8 % a.i.) was administered to 25 or 26 female Sprague-Dawley rats/dose in corn oil by gavage at analytically determined dose levels of 0, 5.5, 23.0 or 95.0 mg/kg/day from days 6 through 20 of gestation.

Bensulide technical exerted no effects on maternal gross pathology, fertility, or cesarian parameters. The maternal systemic NOEL/LOEL are 23.0 and 95.0 mg/kg/day (HDT), based on tremors, decreased body weight (range: 93-94% of control value) on days 12, 16, and 21 of gestation, decreased body weight gain during days 9-12 (25% control value) and 6-21 (76% of control value) of gestation, decreased (79% of control value) feed intake during days 13-16 of gestation, and decreased whole and corrected (reproductive tract subtracted) body weights (93% and 91% of control values, respectively) and increased liver/body weight ratio (112% of control value) at study termination. ***The maternal NOEL/LOEL for cholinesterase inhibition are 5.5 and 23.0 mg/kg/day, respectively, based on a 48% decrease in plasma cholinesterase activity in the absence of any other effects. The developmental NOEL ≥ 95.0 mg/kg/day, the highest dose level tested.***

Endpoint and Dose Level selected for use in risk assessment: NOEL = 5.5 mg/kg/day, based on inhibition of maternal plasma cholinesterase activity (48%) at 23.0 mg/kg/day.

Uncertainty Factor (UF): A UF of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

Comments: A 21-day dermal toxicity study in Wistar rats (MRID No. 42162002) was available. However since cholinesterase measurements were not performed, the Committee could not use this study in the risk assessment for this exposure category.

D. **Intermediate Term Occupational or Residential Exposure (one week to several months):**

Critical Study: 83-1(b), Chronic toxicity study in the dog (83-1b), MRID Nos. 44066401, 44052704.

Executive Summary: See Section A, above.

Endpoint and Dose Level Selected for Use in Risk Assessment: NOEL = 0.5 mg/kg/day based on inhibition of plasma cholinesterase activity in both sexes and brain cholinesterase activity in males at 4.0 mg/kg/day.

Total Uncertainty Factor (UF): A total uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

Comments: See Section A, above.

E. Chronic Occupational or Residential Exposure (several months to life time):

Critical Study: Chronic toxicity study in the dog (83-1b), MRID Nos. 44066401 and 44052704

Executive Summary: Same as for Intermediate Occupational or Residential Exposure (see Section C, above).

Endpoint and Dose Selected for Use in Risk Assessment: NOEL = 0.5 mg/kg/day, based on inhibition of plasma cholinesterase activity in both sexes and brain cholinesterase activity in males at 4.0 mg/kg/day.

Uncertainty Factor (UF): A UF of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

Comments: See Section A, above.

F. Inhalation Exposure (variable duration):

Critical Study: Acute inhalation toxicity in the rat (81-3), MRID No. 41646201

Executive Summary: In an acute inhalation toxicity study (MRID No. 41646201), groups of young adult specific pathogen-free (SPF) Wistar-derived Alpk:APfSD rats (5/sex/group) were exposed by the inhalation route (nose-only) to bensulide technical (92.7% a.i.) for four hours at the maximum stable concentration attainable (1.75 mg/L). Animals then were observed for 14 days.

Treatment-related clinical signs included reduced response to

sound (0/5M, 1/5F; day 1), shaking (1/5M, 0/5F; day 2), deep breathing (1/5M, days 2-4; 2/5F, day 5), lachrymation (3/5M, day 1; 4/5F day 1), increased salivation (5-2/5M, days 1-3; 5-1/5F, days 1-3), splayed gait (1/5M, 0/5F; days 2-3), and urinary incontinence (3-1/5M, days 3-6; 5-3/5F, days 2-6). The durations of hunched back (5-1/5M, days 1-5; 5-2/5F; days 1-6) and piloerection (5-2/5M, days 1-8; 5-1/5F, days 1-10) were prolonged over those seen in controls. No abnormal clinical signs were observed during days 11-15 post-treatment. There were no biologically significant differences between controls and bensulide-treated animals with respect to body weight or findings at gross necropsy. ***The LC_{50} for both males and females is > 1.75±0.102 mg/L. Bensulide technical is TOXICITY CATEGORY III based on data obtained in both males and females.***

Endpoint and Dose Level selected for use in risk assessment: 1.75±0.102 mg/L, the only dose level tested in this acute inhalation toxicity test.

Comments: The Committee recommended that the highest dose tested in the acute inhalation toxicity study be used with the assumption of 100% absorption via the inhalation route and estimates of expected inhalation exposure, to calculate the amount of bensulide expected to result from inhalation exposure. This amount should then be added to that expected from other routes of exposure to calculate the total amount of bensulide for use in risk assessment.

Uncertainty Factor (UF): A UF of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

cc: Stephanie Irene
Raymond Locke
Michael Metzger
Karen Whitby
Jess Rowland
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Hazard ID file
Caswell File

Appendix A **Acute Toxicity of Bensulide**

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral (Rat)	00097921	LD_{50} = 360 mg/kg (Males) 270 mg/kg (Females)	II
81-2	Acute Dermal (Rat)	41597501	LD_{50} > 2000 mg/kg (Males and Females; Limit Test)	III
81-2	Acute Dermal (Rabbit)	00097921	LD_{50} > 5000 mg/kg (Males and Females; Limit Test)	IV
81-3	Acute Inhalation (Rat)	41646201	LC_{50} = 1.75 mg/L (Males and Females)	III
81-4	Primary Eye Irritation (Rabbit)	41597502	Mild eye irritant, causing mild conjunctival irritation [slight redness (6/6 animals); slight to severe discharge (5/6); no corneal or iridial effects] clearing within three days.	III

81-5	Primary Skin Irritation (Rabbit)	00097921 92005012	Mild skin irritant; primary dermal irritation index = 0.5	IV
81-6	Dermal Sensitization (Guinea Pig)	00160075	Not a sensitizer	--
81-7	Acute Delayed Neurotoxicity (Hen)	43305601 43334302	Did not induce delayed neurotoxicity at the dose tested (2262 mg/kg).	--
81-8ss	Acute Neurotoxicity (Rat)	43195901	Neurotoxicity NOEL = 100 mg/kg, based on flaccid abdominal and/or body tone and pinpoint pupils in females at 150 mg/kg (LOEL). Cholinesterase inhibition NOEL = 15 mg/kg, based on 80% inhibition of plasma ChE activity in females at 50 mg/kg (LOEL)	--