US EPA ARCHIVE DOCUMENT

Memorandum

Date: 27 April 1982

Subject: EPA Reg. No. 476-2109 ASPON TECHNICAL
Caswell #845A

From: B. T. Backus
IRB/TSS

To: Mr. William Miller
Product Manager 16

Registrant: Stauffer Chemical Co.
1200 South 47th St.
Richmond, CA 94804

Active Ingredient:
0,0,0,0-tetrapropyl dithiopyrophosphate.....90.0%
Inert Ingredients:.....10.0%

Background:

The registrant has submitted Acute Oral LD50, Acute Dermal LD50, Primary Dermal and Eye Irritation, Dermal Sensitization and 3 Mutagenic studies, as part of the data required to support reregistration.

Comments and Recommendations:

1. The Acute Oral LD50, Dermal and Eye Irritation, and Sensitization studies are acceptable.

2. In the Dermal LD50 study there is no report as to mortalities by sex, and animals were tested only at one dosage level (2000 mg/kg) at which 40% mortality occurred. While the comparatively considerable time between exposure and occurrence of mortalities (up to 10 days) suggests a dermal LD50 of above 2000 mg/kg, there is no reasonable confidence that this is actually so. The study should be extended to include other dosage levels (including one at which no more than 10% mortality occurs), and reporting should include mortality by sex.

3. No Inhalation LC50 studies (or a rationale for their not being required) were received.

4. The mutagenic evaluations of Aspon, involving both direct and activated assay in five Salmonella typhimurium revertant strains, as well as the forward mutation assay in mouse lymphoma cells, were well-conducted studies which satisfy the requirements (Aspon Pesticide Registration Standard, p. 54) for a sensitive sub-mammalian point mutation test and a mammalian in vitro point mutation test respectively. The assay for morphological transformation of BALB/3T3 cells was also a well-conducted

study, which, in the opinion of this reviewer, adequately satisfies the requirements for an in vitro cytogenetics test (p. 54, Aspon Pesticide Registration Standard). While the study was not designed to detect chromosomal changes and/or abnormalities, these frequently accompany cellular transformation. Note also that there is some ambiguity in that an in vitro mammalian cytogenetics study is not included in the the types of tests indicated for mutagenicity studies in FR43, #163, Aug. 22, 1978, p. 37388, although an in vivo cytogenetics test in mammals is.

5. No primary DNA damage test (sister chromatid exchange - SCE - or unscheduled DNA synthesis) was received, although the Forward Mutation Assay protocol (pages 9 and 11) indicates an SCE cytogenetic assay procedure. The reporting of results from the Forward Mutation assay (p. 12) states that data from the forward mutation assay is often available for evaluation far in advance of the results of the cytogenetic assay. The Agency should receive a clarification as to whether an SCE assay is, in fact, forthcoming.

Labeling:

1. "Atropine by injection is antidotal" should be revised to something like: "Atropine by injection is antidotal only if symptoms of cholinesterase inhibition are present."

2. The Statement of Practical Treatment for IF SWALLOWED should be revised to something like (Aspon Pesticide Registration Standard, p. 149):

   IF SWALLOWED: Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not give anything by mouth to an unconscious or convulsing person. Get medical attention.

3. The Statement of Practical Treatment for IF ON SKIN should be:

   IF ON SKIN: Wash with plenty of soap and water.

   (although not necessary, we can accept the additional wording: Remove contaminated clothing and shoes. Get medical attention if irritation occurs. Wash clothing before re-use.).

4. The Statement of Practical Treatment for IF IN EYES should be:

   IF IN EYES: Flush with water for 15 minutes. Get medical attention if irritation persists.

5. The recommended Statement of Practical Treatment for IF INHALED is:

   IF INHALED: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. Get medical attention.

6. The Hazards to Humans and Domestic Animals statement should be:

CAUTION: Harmful if swallowed or absorbed through skin. Avoid contact with skin, eyes or clothing. Wash thoroughly after handling.

This may require modification, depending on the results of the Acute Inhalation LC50 study and further data submitted regarding the dermal LD50 hazard potential.

Review:

The following studies were conducted on the registered product, containing 90% Aspon. Studies were conducted at the Stauffer Chemical Company, Richmond Toxicology Laboratory, Richmond, CA under Laboratory Report No. T-10330. Studies were received at EPA 3-4-82 and are in Acc. 246892.

1. Acute Oral LD50 - Rat. Laboratory Report T-10330; dated 11-19-81.

Procedure: Groups of 10 M SD rats received oral dosages of 1995, 2512, 3981 or 5000 mg/kg. A group of 20 M received a dosage level of 3162 mg/kg. Groups of 10 F SD rats received oral dosages of 316, 501, 562, 631, 708, 794, 1000, 1259, 1585, 1995, 2500 or 5000 mg/kg. For purposes of administration material was diluted with corn oil and apparently different concentrations were administered to rats at the rate of 10 ml/kg body weight. Animals were observed for 14 days.

Results: Mortality:

Dosage Level mg/kg	Mortalities/Animals Dosed M	F
316	-	0/10
501	-	0/10
562	-	4/10
631	-	5/10
708	-	3/10
794	-	10/10
1000	-	9/10
1259	-	8/10
1585	-	9/10
1995	1/10	10/10
2500	-	10/10
2512	5/10	-
3162	20/20	-
3981	8/10	-
5000	8/10	10/10

Oral LD50 (M) = 2800 (2314-3388) mg/kg.
Oral LD50 (F) = 740 (623-879) mg/kg
Occurrence of "peaks" in mortality (3162 mg/kg for males, 794 mg/kg for females) may reflect differences in toxicity between different concentrations of this material in corn oil.
Symptoms: depression, tremors, ataxia, salivation, diarrhea, labored breathing, vocalizations, ano-genital staining, red facial stains (all typical of a cholin-

esterase inhibitor). Survivors were generally normal by day 5. Necropsies of mortalities: Red and irritated intestines, blackened kidneys, livers and spleens. Enlarged purple testicles noted in some males. Post-sacrifice necropsies: Animals surviving 14 days were unremarkable.

Study Classification: Core Minimum Data (no individual body weight data, no individual necropsy reports, five instances of necropsies not being performed because of cannibalism; however, study adequately defines the hazard potential of this product by this exposure route).

Product Classification: Tox. Cat. III

2. Acute Dermal LD50 - Rabbit. Laboratory Report T-10330; dated 11-19-81.

Procedure: 10 Stauffland albino rabbits (of which at least 4 were M and 4 were F), 1.17-1.96 kg, received a 24-hr occluded dermal exposure to a dosage level of 2000 mg/kg, with subsequent 14-day observation.

Results: 4/10 subjects (no breakdown as to sex) reported as dying (one on day 3, 2 on day 6, 1 on day 10). All survivors normal by day 7. Necropsies showed intestinal irritation-related effects in 3/4 subjects dying.

Study Classification: Core Supplementary Data. With 4 subjects dying at 2000 mg/kg there is insufficient probability that the product has a dermal LD50 of above 2000 mg/kg to assign that product to toxicity category III by this exposure route.

3. Primary Dermal Irritation - Rabbit. Laboratory Report T-10330; dated 11-19-81.

Procedure: 0.5 mls was placed on one intact, one abraded site on each of 6 rabbits, with 24-hr occluded exposure.

Results: PDIS = 0.92. Maximum values of erythema or edema seen were 1.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. IV

4. Primary Eye Irritation - Rabbit. Laboratory Report T-10330; dated 11-19-81.

Procedure: 0.1 ml was placed in one eye of each of 9 rabbits, with 3 eyes being flushed with water starting 20-30 seconds after test material instillation. The remaining 6 eyes were unwashed.

Results: No apparent irritation at 24, 48, 72 hrs or 4 days. All scores were zero.

Study Classification: Core Guidelines Data

Product Classification: Tox. Cat. IV

The following studies were conducted at the In Vitro Toxicology Health Center, Stauffer Chemical Co., Farmington, CT 06032. Studies were received at EPA 3-4-82 and are in Acc. 246892.

5. Mutagenic - Ames (Mutagenicity Evaluation in Salmonella typhimurium). Report No. T-10786; dated 8-20-81.

   Procedure: Aspon technical in DMSO was evaluated, with triplicate plating, for mutagenic activity in five Salmonella typhimurium tester strains, both with and without a mammalian liver S-9 metabolic activation preparation. There were positive controls in all systems.

   Results: Average number of revertants/plate with both direct and activated mutagenicity testing for all dosage levels of Aspon were similar to negative controls and were considerably below positive controls.

   Study is acceptable.

6. Mutagenicity - Mammalian Cell Line (Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test. A Forward Mutation Assay). Report No. T-10787; dated 1-13-82.

   Procedure: Aspon technical was evaluated for ability to induce mutation at the TK (thymidine kinase) locus in L51784 mouse lymphoma cells (normally TK+/-) by direct assay and in the presence of Aroclor 1254 induced rat liver metabolic activation.

   Result: No evidence of increased rate of mutation from TK+ to TK-.

   Study is acceptable.

7. Mutagenicity - Mammalian Cell Line (Morphological Transformation of BALB/3T3 Cells). Report No. T-10788; dated 11-16-81.

   Procedure: Aspon technical was evaluated for its ability to induce morphological transformation in BALB/3T3 cells at a dose range of 0.00125-0.0200 ul/ml (reduction in clonal survival had been seen at 0.006 ul/ml and above) with direct application. 3-methylcholanthrene at 4 ug/ml was positive control.

   Results:

DOSE	Total Foci (15 flasks)	Survival %	Total Foci ÷ % Survival
Medium control	25	100*	25
Solvent/vehicle control	39	100	39
Positive control	61	100*	61
0.00125 ul Aspon/ml	42	89	47.2
0.00250 ul Aspon/ml	24	85	28
0.00500 ul Aspon/ml	24	79	30.4
0.01000 ul Aspon/ml	9	52	17.3
0.02000 ul Aspon/ml	14	13	107.7

Although the figure seen of total foci ± % survival of 107.7 in the 0.02000 ul Aspon/ml is disturbing, this may well be because of the relatively small number of surviving cells, and is probably within statistical probability for no mutations being induced. The figures, particularly for the 3 middle dosage levels of Aspon, are reassuring.

Study is acceptable.

The following study was conducted by Wil Research Laboratories, Inc. 3154 Exon Avenue, Cincinnati, OH 45241. Study was received at EPA 3-4-82, and is in Acc. 246892.

8. Sensitization - Guinea Pig. Project No. WIL-81271; client study no. T-10749. Study dated 2-9-82.

   Procedure: 0.5 ml of a 10% v/v test material in ethyl alcohol solution was applied to a skin site 3 times/week for a total of 10 applications on each of 10M, 10F guinea pigs. After a 2 week rest period subjects were challenged at a new skin site with 0.5 ml of 10% v/v test material in ethyl alcohol, with scoring at 24 and 48 hrs later.

   Results: One female died during initial series of applications (presumably unrelated to the test material). Of the 19 remaining subjects, none gave evidence of sensitization.

   Study Classification: Core Minimum Data (no positive control)

   Product Classification: Not a sensitizer.

Byron T Backus 04/26/82

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