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

MEMORANDUM ~~APR 14 1983~~ APR 15 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby (21)
Registration Division (TS-767)

THRU: William Burnam, Acting Chief
Toxicology Branch/HED (TS-767)

SUBJECT: Addendum to Memo of December 21, 1982: Review of Acute Studies and Subchronic Inhalation Study of Vorlex; Acc. No. 249736 CASWELL#175 & 573

Registrant: Nor-Am Agricultural Products
350 West Shuman Blvd.
Naperville, Illinois 60566

Background Information:

My memo of December 21, 1982 classified these studies as Supplementary Data primarily because these studies did not have a description of the experimental procedures employed. My memo of March 22, 1983 stated that, if the acute studies were upgraded, "Toxicology Branch will not object to the requested new use".

Recommendation:

It is recommended that studies 1-4 discussed below be upgraded to Core-Minimum. Although it is recommended that studies 5-6 below remain classified as Core Supplementary, the need for further testing should be waived and the material labeled as a Toxicity Category I eye irritant. Toxicology Branch does not object to the requested new use of Vorlex on utility poles.

Review of Data:

(Note: The results for each of these studies were presented in my memo of December 21, 1982, attached. Recently submitted information consists only of a more complete description of the study procedures; thus the results presented in my original memo remain unchanged. Presented below are the experimental procedures used in 6 of the acute studies).

1) Acute Oral Rats. Conducted by Schering AG, Berlin, Germany, April 12, 1979, Protocol No. 496/78, and submitted by Nor-Am.

Five male and five female Wistar/SPF rats per dose level were administered a 2% formulation of Vorlex technical at doses of either 0, 0.1, 0.2, 0.4, 0.6 and 0.8 g/kg by gavage after starvation for 18-20 hours.

Observation of animals occurred 3 times on day 1 and daily for the following 21 days. Body weights were recorded on days 1 and 22. Method of sacrifice on day 22 was not reported. Gross necropsies were conducted on all sacrificed animals.

2) Acute Dermal, Rabbits. Conducted by Schering AG, Berlin, Germany, May 11, 1979, Protocol 1/79 and submitted by Nor-Am.

Three male and 3 female New Zealand white rabbits per dose level were treated dermally with either 0, 0.4, 0.5, 0.6, 0.8 or 1.0 ml/kg of Vortex technical. Test material was applied to a shaven area 10 x 15 cm and kept under occlusive conditions for 24 hours.

Observations were conducted 3 times on day 1 and daily for the following 21 days. Body weights were recorded on days 1 and 22. The animals were sacrificed on day 22 (method not reported) and grossly necropsied.

3) Acute Dermal, Rats. Conducted by Schering AG, Berlin, Germany, April 11, 1979, Protocol No. 497/78 and submitted by Nor-Am.

Five male and five female Wistar/SPF rats per dose level were treated dermally with either 0, 500, 630, 750, 880, or 1000 mg/kg of Vortex technical with controls receiving 10 ml/kg of sesame oil. The test material was applied as a 10% (w/v) solution in sesame oil. The test site was a shaved area of skin 3.0 x 8.3 cm. The test material remained occluded on the skin for 24 hours after which it was removed with tap water.

Observations were conducted 3 times on the first day and daily for the remaining 21 days. Body weights were recorded on day 1 and 22. Animals were sacrificed (method not specified) on day 22 and grossly necropsied.

4) Acute Intraperitoneal, Rats. Conducted by Schering AG, Berlin, Germany, May 26, 1979, Protocol No. 94/79 and submitted by Nor-Am.

Five male and 5 female Wistar/SPF rats per dose level were dosed i.p. with 1% w/v solution of Vorlex technical in sesame oil at concentrations of 0, 0.15, 0.20, 0.25, 0.30, and 0.35 g/kg. Controls were administered 35 ml/kg of the vehicle.

Observations were conducted 3 times on the first day and daily for the remaining 27 days. Body weights were recorded on day 1 and 27. The animals were sacrificed on day 27 (method not specified) and grossly necropsied.

5) Eye Irritation, Rabbits. Conducted by Huntingdon, England, December 23, 1976 and submitted by Nor-Am. Study No. 6912/133D/76.

(The experimental procedures were described in my memo of December 21, 1982.) A letter from the testing laboratory, dated February 15, 1983, indicated that the eyes were not washed following treatment and that only two animals were used because "It is contrary to our normal procedure to continue an eye test where undue suffering is likely to ensue or to expose further animals to a known severe eye irritant."

6) Eye Irritation of Methylisothiocyanate, Rabbits. Conducted by Huntingdon Research Centre, Huntington, England, December 23, 1976 (Report No. 6913/134D/76) and submitted by Nor-Am.

(The experimental procedures were described in my memo of December 21, 1982.) A letter from the testing laboratory, dated February 15, 1983, indicated that the eyes were not washed following treatment and that only two animals were used because "It is contrary to our normal procedure to continue an eye test where undue suffering is likely to ensue or to expose further animals to a known severe eye irritant."

Gary J. Burin 4/13/83

Gary J. Burin, Toxicologist
Review Section V
Toxicology Branch/HED (TS-769)

4/14/83

TS-769:th:TOX/HED:GJBurin:4-12-83:card 7

EPA Accession No's of Data Reviewed
Acute Tox → 248403
248402
Inhalation → 248404
Part. Breakdown → 2139-55

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

DEC 21 1982

MEMORANDUM

DEC 21 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby (21)
Registration Division (TS-767)

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Review of Acute Studies and Subchronic Inhalation Study of Vorlex; Acc. Nos.: 248402, 248403, 248404
CASWELL#175 & 573

Registrant: Nor-Am Agricultural Products
350 West Shuman Blvd.
Naperville, Illinois 60566

Background Information:

The studies reviewed in this memo were submitted subsequent to a meeting of August 31, 1982 between the registrants and EPA. At the time of that meeting, it was agreed that further analysis of applicator exposure was required before hazard evaluation could occur. Toxicology Branch will therefore postpone reconsidering it's original recommendation on the requested new use for Vorlex until Environmental Fate Branch can estimate applicator exposure. The following is a review of the recently submitted acute and subchronic studies.

Recommendation:

It is recommended that the studies be classified as follows:

1. Acute Oral, Rats. Supplementary Data. Oral LD_{50} is 538 mg/kg (Tox. Cat. III).

2. Acute Dermal, Rabbits. Supplementary Data. The dermal LD_{50} is 470 mg/kg in rabbits (Tox. Cat. II).

3. Acute Dermal, Rats. Supplementary Data. The dermal LD_{50} is 961 mg/kg (Tox. Cat. II).

4. Acute I.P., Rats. Supplementary Data. The i.p. LD_{50} is 259 mg/kg in rats.

5. Acute Inhalation, Rats. Core-Minimum Data. The LC_{50} is 11.0 g/m^3 (Tox. Cat. III).

6. Eye Irritation, Rabbits. Supplementary Data. Severe eye irritant (Tox. Cat. I).

7. Eye Irritation of Methyl Isothiocyanate, Rabbits. Supplementary Data. Severe eye irritant (Tox. Cat. I).

8. Eye Irritation Antidote Study, Rabbits. Supplementary Data. Sodium bicarbonate and cortisone ameliorate eye irritancy.

9. Skin Irritation, Rabbits. Invalid.

10. Subchronic Inhalation, Rats. Supplementary Data. A NOEL has not been established and individual animal data have not been submitted.

Review of Data:

1) Acute Oral, Rats. Conducted by Schering AG, Berlin, Germany, April 12, 1979, Protocol No. 496/78 and submitted by Nor-Am.

The experimental procedure for this study was not reported.

Results:

The LD_{50} for all animals was found to be 538 mg/kg. Observed reactions in treated animals considered to be related to treatment were blood stained snouts, diarrhea and "severe apathy". Gross observations considered to be related to treatment were renal damage (600 mg/kg), lung hyperemia and stomach ulcerations.

Core Classifications: Supplementary Data.

The oral LD_{50} is 538 mg/kg (Tox. Cat. III). May be upgraded if experimental procedure is submitted.

2) Acute Dermal, Rabbits. Conducted by Schering AG, Berlin, Germany, May 11, 1979, Protocol No. 1/79 and submitted by Nor-Am.

The experimental procedure for this study was not reported.

Results:

The dermal LD_{50} for all animals was found to be 470 mg/kg. Observed reactions considered to be treatment related were "apathy", salivation, "defensive movements" and miosis. All surviving animals showed a dark red to violet discoloration of the application sites leading to necrosis by day 7. Gross necropsy findings included discoloration of the liver and kidney of an unspecified number of animals.

Core Classification: Supplementary Data.

May be upgraded if experimental procedure is submitted. The dermal LD_{50} is 470 mg/kg (Tox. Cat. II).

3) Acute Dermal, Rats. Conducted by Schering AG, Berlin, Germany, April 11, 1979, Protocol No. 497/78 and submitted by Nor-Am.

The experimental procedure for the study was not reported.

Results:

The dermal LD_{50} for all animals was found to be 961 mg/kg. Observed reactions in the treated animals considered to be treatment related were vocalization, "apathy", and blood stained snouts. Gross necropsy findings considered to be related to treatment were pale discolorations of the kidney.

Core Classification: Supplementary Data

The dermal LD_{50} is 961 mg/kg. The study may be upgraded if the experimental procedure is submitted. Tox. Cat. II.

4) Acute Intraperitoneal, Rats. Conducted by Schering AG, Berlin, Germany, May 26, 1979. Protocol No. 94/79 and submitted by Nor-Am.

The experimental procedure for the study was not reported.

Results:

The intraperitoneal LD_{50} for all animals was 259 mg/kg. Observed reactions in the treated animals considered to be treatment related were ataxia, salivation, "apathy", and a rough coat. Gross necropsy findings considered to be related to treatment were discoloration of the kidney and residue in the abdominal cavity.

Core Classification: Supplementary Data.

The intraperitoneal LD_{50} is 259 mg/kg. The study may be upgraded if the experimental procedure is submitted.

5) Acute Inhalation, Rats. Conducted by Huntingdon Research Centre, Huntingdon, England, August 22, 1977 and submitted by Nor-Am. #130/77527

Technical Vorlex was introduced into a stainless steel chamber (0.37 m x 0.37 m x 0.37 m) at measured (actual) dose levels of 4.66, 9.64, 12.88 and 19.66 g/m^3. Five male and 5 female Sprague-Dawley descended albino rats were exposed at each dose level for one hour. Animals were observed during exposure and twice daily after exposure for 14 days. Animals were weighed on days 1, 3, 7, 10 and 14. All animals were necropsied the weight of the lungs measured.

Results:

The LC_{50} (1 hour) was 11.0 g/m^3 (11 mg/liter). Clinical observations in treated animals included decreased activity, eye irritation, vasodilation, dyspnea and convulsions. Necropsy observations included hemorrhage and congestion of the lung and distention of the stomach and small intestine with gas. Lung weights and lung to body weight ratios were increased in groups 3, 4 and 5.

Core Classification: Core-Minimum Data.

The LC_{50} (1 hour) was 11.0 g/m^3. Tox. Cat. III.

6) Eye Irritation, Rabbits. Conducted by Huntingdon Research Centre, Huntingdon, England, December 23, 1976 and submitted by Nor-Am. #6912/1330/76

One eye of each of two test animals was instilled with 0.1 ml technical Vorlex. The eyes may or may not have been washed after 24 hours. The eyes were examined and graded at 24 and 48 hours. The untreated eyes were used for control purposes. The study protocol and criteria for grading generally followed that of the Consumer Product Safety Commission (CFR 16, Section 1500.42).

Results:

Severe iritis and corneal opacities were observed in both animals. Due to the severity of the reactions, both animals were sacrificed on day 2. "Considerable" conjunctival swelling was observed in both animals.

Core Classification: Supplementary Data.

Only two animals were used and it could not be determined whether eyes were washed after treatment. The study results indicate a positive test for eye irritation with severe iritis, corneal opacity and conjunctival swelling occurring soon after treatment. Tox. Cat. I.

7) Eye Irritation of Methylisothiocyanate, Rabbits. Conducted by Huntingdon Research Centre, Huntingdon, England, December 23, 1976 (Report No. 6913/134D/76) and submitted by Nor-Am.

One eye of each of two albino rabbits was instilled with 0.1 ml of methylisothiocyanate (purity not specified). The eyes may or may not have been washed after 24 hours. The eyes were examined after 24 and 48 hours. The untreated eyes were used for control purposes. The study protocol and criteria for grading generally followed that of the Consumer Product Safety Commission (CFR 16, Section 1500.42).

Results:

Severe iritis and corneal opacities were observed in both animals. Due to the severity of the reactions, both animals were sacrificed on day 2. "Considerable" conjunctival swelling was observed in both animals and in one animal the eye was completely closed.

Core Classification: Supplementary Data.

Only two animals were used and it could not be determined whether the eyes were washed after treatment. The study results indicate a positive test for eye irritation with severe iritis, corneal opacity and conjunctival swelling occurring within 48 hours after treatment. Tox. Cat. I.

8) Eye Irritation Antidote Study, Rabbits. Testing laboratory, date of test and study number not specified. Submitted by Nor-Am.

Solvent W2741 g ([redacted]) and solvent W27416 (20% methyl isothiocyanate, [redacted]) were applied to an unspecified number of animals. The amount of test solution applied was not stated. After 2 minutes, the eyes were treated as follows:

A. No Treatment
B. Rinse with 5% sodium biocarbonate
C. One drop of cortison enanthate
D. B & C
E. Cortison enanthate immediately after rinsing and every 30 minutes for 4 hours.

Results:

W2741 a produced reddening which was not noted after 60 minutes. W2741b without treatment produced slight or severe swelling and turbidity at every concentration tested. All treatments resulted in some amelioration of swelling although turbidity, once established, tended to persist.

Core Classification: Supplementary Data.

Amounts of test material applied and number of test animals per concentration were not stated. Other missing information includes date and location of the test. Prompt cortison or bicarbonate, alone or in combination appears to aid ocular recovery.

9) Skin Irritation, Rabbits. Testing laboratory, date of test and study number not specified. Submitted by Nor-Am.

Vorlex, methyl isothiocyanate and D-D were applied to rabbit ears. The number of animals, individual animal findings and criteria for grading of effects was not stated. Single applications of unspecified amounts of D-D and methyl isothiocyanate were made. .3 ml of Vorlex was applied daily for 8 weeks.

Results:

Although the available summary of these study stated that "no visible change" was produced in the skin treated with D-D or methyl isothiocyanate and that edema and hyperthermia was produced by Vorlex (subsiding after the 10th treatment), the results of testing of individual animals was not submitted.

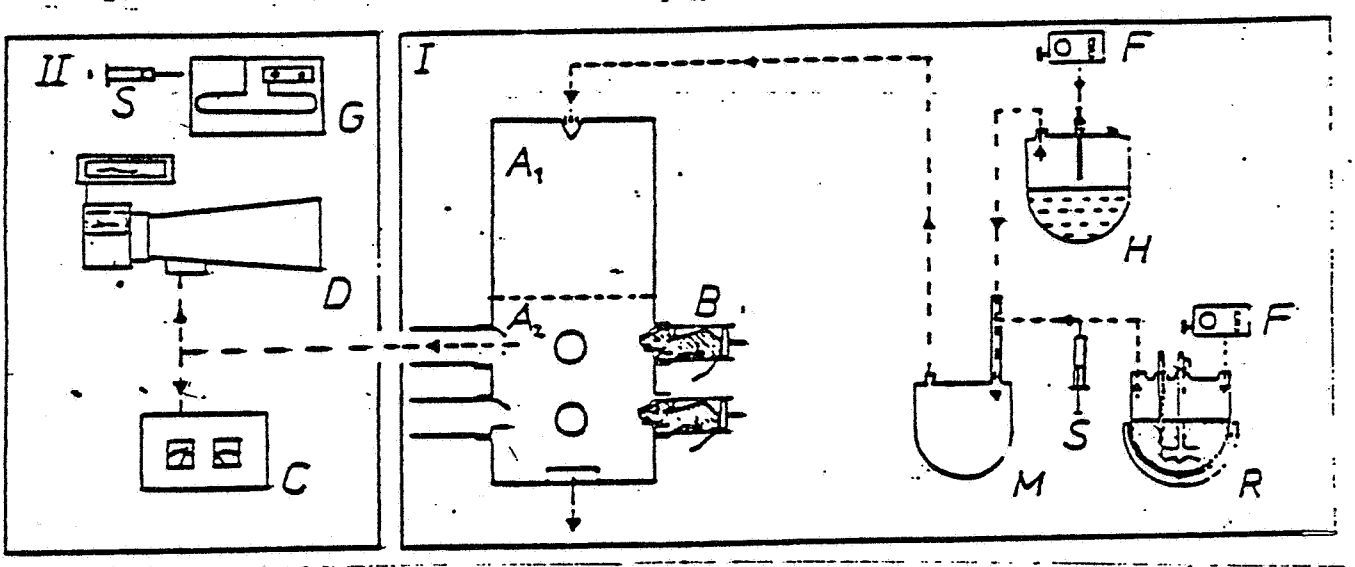
Core Classification: Invalid.

Insufficient information is submitted to evaluate these studies.

10) Thirteen Week Inhalation Study, Rats. Conducted by Schering AG, Berlin, Germany, April 10, 1979, Report No. 9678 and submitted by Nor-Am.

Ten male and 10 female SPF-originated Wistar rats per dose level were treated with nominal levels of 1, 10 or 50 ppm of technical Di-Trapex (19.9% methyl mustard oil i.e. methylisothiocyanat 24.2% cis-dichloropropene, 22.9% trans-dichloropropene, remainder 1,2 dichloropropane).

Equal numbers of animals were left untreated, or were exposed to filtered air in the inhalation chamber. Animals were exposed 6 hours/day for 5 days/week for 13 weeks. Exposure was by nose only; the design of the chamber was as follows:



Flow rates, temperature, humidity and actual concentrations periodically. The chamber volume was 60 liters. Clinical observations were recorded daily, body weights weekly, water consumption twice weekly, food consumption once a week, ophthalmoscopy at weeks -2 and 11. Hematology (PCV, MCH, MCV, RBC, WBC, reticulocyte, differential and thrombocyte counts) were conducted at weeks 4, 8 and 12 on 5 males and 5 females per group. Urinalysis (pH, specific gravity, protein, glucose, ketones, blood, urobilinogen and sediment examination) were conducted at weeks 4, 8 and 12 on all animals.

Blood chemistry for 5 males and 5 females per group (glucose, SGPT, AP, BUN, total cholesterol, total protein, protein electrophoresis) were conducted at weeks 4, 8 and 12. Na, K and Ca were quantified at week 12.

All animals were necropsied. Organ weights were recorded for liver, kidneys, adrenals, pituitary, heart, spleen, lymph nodes, brain, testes and ovary.

Histological examination was conducted on all animals in the untreated control and high dose groups for the following tissues: pancreas, liver, kidneys, heart, pituitary, stomach, diodenum, ileum, colon, uterus, mammary gland, skin, adrenals, urinary bladder, lungs, trachea, esophagus, ovary, testes, prostate, thyroid gland, artery, spleen, lymph nodes, cerebrum, cerebellum, medulla oblongata, spinal cord, peripheral nerve, skeletal muscle, bone, nose, eyes, larynx and bone smear.

Results:

(Mean values for actual concentrations were 0.99, 10.18 and 50.84 ppm.) Five animals died during the course of the study and all deaths were attributed to blood sampling. Clinical observations related to test compound exposure were abdominal hypotension, salivation and nasal discharge (affecting most animals in the high dose group. Two animals in both the low and mid dose groups showed abdominal hypotension). Conjunctivitis affected most animals, including controls, and was not considered to be treated related. Body weight gain was significantly reduced in high dose males, food was reduced for mid and high dose males, water consumption increased for all treated females and high dose males. No effects on hematology or urinalysis were found. A dose related decrease in calcium was noted which apparently affected males and females at all dose levels (significant at the $p < .01$ level for females of all groups and males at the mid and high). Although it is stated that other statistically significant clinical pathology changes are "without biological significance", the individual or group data by which such are statement can be supported have not been submitted. Individual and group gross and histopathology are also not submitted.

Core Classification: Supplementary Data.

Individual and group numerical values are not submitted for the majority of examined parameters. Gross and histopathology findings are not submitted by group or for individual animals. Based on decreased blood calcium at all dose levels, however, it is suggested that a NOEL has not been established.

Gary J. Burin

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TS-769:th:TOX/HEDGJBurin:12-14-82:card 1