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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of "13-Week Inhalation Study, Vorlex"
Accession #248402 and 249910; CASWELL Nos.: 175 and 573

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

FROM: Quang Q. Bui, Ph.D. *Quang Bui 08/03/84*
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Sponsor Registrant: Nor-Am Agricultural Products, Inc.
350 West Shuman Blvd.
Naperville, Illinois 60566

Background:

The applicant has submitted additional information requested relative to the deficiencies outlined in G. Burin's memo of 4/15/83 concerning the "13-Week Inhalation Study with Vorlex in Rats".

This memorandum summarizes and evaluates both sets of data submitted.

Recommendation:

This study is classified as Supplementary Data since a systemic NOEL could not be demonstrated at the dosage levels tested. "Nose only" exposure to Vorlex for 90 days results in statistically significant decreases in blood potassium and calcium and increase in water consumption in rats even at the lowest dose used (1 ppm). Since hematological, clinical chemistry, and systemic toxicity data of the test groups were statistically compared to those of the sham-treated control group, histopathological findings of the latter must be reported.

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Study Identification

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Study Title: Inhalation Study (12-13 weeks) in the Rat

Sponsor: Nor-Am Agricultural Products

Testing Laboratory: Schering AG, Berlin, Germany
Report No. 9678; 4/10/79

Data Review

I. Test Material: Di-Trapex (Vorlex):

Cis-dichloropropene [REDACTED]
Trans-dichloropropene [REDACTED]
Methyl mustard oil 19.9%
Dichloropropane [REDACTED]
Di-Trapex was used without further formulation.

II. Procedures

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

A copy of the procedures is appended.

The methods used are generally similar to the "1982 Pesticide Assessment Guidelines" for a subchronic inhalation study except as noted below:

Hematology and blood chemistry determinations should be made on at least 10 animals of each sex in each group while in this study only 5 animals/sex/level were studied.

Histopathological examinations of the sham-treated control group are not available.

III. Results

1. Physical measurements

Actual concentrations of the test atmosphere from the exposure chamber (nose only) were determined twice per run by gas chromatography and were equal to 0.99 + 0.05, 10.18 + 0.53, and 50.84 + 2.1 ppm. These values did not differ from the reported concentrations used (1, 10, and 50 ppm).

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2. Mortality

Five animals died during the course of the study: one each in the control, low and high dose, and two animals at the mid-dosage level. Necropsy of the dead animals did not reveal any compound-related effect. The cause of death of all five animals was cited as strangulation during blood sampling.

3. Clinical observations

The most relevant clinical observations are summarized as follows:

	<u>Group I</u> Control	<u>Group II</u> Sham-treated	<u>Group III</u> 1 ppm	<u>Group IV</u> 10 ppm	<u>Group V</u> 50 ppm
Conjunctivitis	15	19	20	20	20
Abdominal hypotension	-	-	2	2	17
Salivary and nose excretions	-	-	-	-	19
Neck enlargement (hematoma like)	-	-	1	-	-

(Data extracted from Table 5)

Instances of "abdominal hypotension" were found in all treated groups compared to none observed in either control group. The biological significance of which, however, remains unknown. Increased salivary and nasal discharge were observed in all animals of the highest dose group and were considered as compound-related. Conjunctivitis was observed with high frequency in all groups including the controls. Evaluation of individual animal ophthalmoscopic data revealed an incidence of conjunctivitis different from that reported in Table 5.

	<u>Group I</u>	<u>Group II</u>	<u>Group III</u>	<u>Group IV</u>	<u>Group V</u>
Conjunctivitis	5 (4M,1F)	7 (4M,3F)	7 (5M,2F)	7 (4M,3F)	10 (6M,4F)
Cornea, bubble inclusions	0	1	0	1	3

(Data extracted from "Addendum to Report", pp. 026-028.)

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Since a similar incidence of conjunctivitis and cornea with bubble inclusions were found in both the control and sham-treated control groups, these effects were not regarded by this reviewer as compound-related. The other clinical observations reported, however, could not be verified due to the lack of individual clinical finding data.

4. Body weight

The initial and final body weight of all groups were summarized in the following table

	Group I		Group II		Group III		Group IV		Group V	
	M	F	M	F	M	F	M	F	M	F
Initial body weight (grams)	224	164	231	163	221	167	222	161	221	168
Final body weight	368	242	314	209	308	217	292	207	270	196
Body weight gain	144	78	83	46	87	50	70	46	49*	28

(Data extracted from "Addendum to Report", p. 016-024.)

*Statistically different from Group II control at $p < 0.05$.

Decreased body weight gains were observed in males of the mid and high dosage levels with statistical significance found in Group V in comparison to the sham-treated control group (group II). Treated females gained weight comparable to controls except for those of the high dose group.

5. Food and water consumption

Food and water consumption are summarized as follows:

	Group I		Group II		Group III		Group IV		Group V	
	M	F	M	F	M	F	M	F	M	F
Food consumption (kg) ^a	1.29	0.98	1.25	0.93	1.16	0.97	1.13*	0.88	1.07**	0.8
Daily food consumption (grams) ^b	25.4	19.4	24.5	18.3	22.7	19.0	22.2	17.4	21.1	17.
Water consumption (kg) ^c	1.79	1.64	1.77	1.41	1.76	1.61*	1.75	1.69**	2.19**	2.0
Daily water consumption (ml) ^b	31.0	28.4	30.5	24.4	30.4	27.7	20.3	29.2	37.8	34.

(Data extracted from "Addendum to Report", pp. 005-014.)

- a = Over 51 days period.
- b = Calculated by this reviewer.
- c = Over 58 days period.
- * - Significantly different from control II at $p < 0.05$.
- ** - Significantly different from control II at $p < 0.01$.

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A dose related decrease in food consumption was noted in the males of treated groups with statistical significances found at the mid and high dose groups in comparison to group II control. No significant differences were observed in female food consumption. A dose-response increase in water consumption was evident in the females of the treated groups with statistical differences found at all dosage levels tested in comparison to group II control. Increased water consumption was also found in group V males ($p < .01$). However, water consumption in the females of the test groups were similar to that of control I except for the highest dosage group.

6. Hematology

The leucocyte and lymphocyte counts of group III males were statistically different at week 4 but equal to control values by week 8 and at study termination. Neutrophil count was decreased only in group IV males at week 8 and 12. Since these effects were not dose-related, they were not considered by this reviewer as compound-related.

7. Bone marrow, coagulation, and urinalysis

There were no meaningful differences among the control and test groups with respect to bone marrow analysis, coagulation studies, and urinalysis.

8. Clinical chemistry

Statistically significant differences to control group II were found at week 4 and 8 in the treated groups with respect to Na^+ , total protein, albumin, and gamma globulins. These effects were not regarded as compound-related due to the absence of a dose-response relationship. However, at study termination (week 12) several biologically and statistically significant differences were observed in the treated groups and tabulated as follows:

Clinical Chemistry (week 12)	Group I	Group II	Group III	Group IV	Group V
SGPT (U/L) males	12	28	11**	11**	15*
Potassium (mmol/L) males	6.25	6.68	5.64**	5.12**	5.26*
Calcium (mg/100 ml) males	10.43	9.28	8.84	8.24**	7.90**
females	9.60	9.36	8.44**	8.48**	8.08**

(Data extracted from "Addendum to Report:, pp. 93-113.)

*Significantly different from Group II control at $p < 0.05$.
 **Significantly different from Group II control at $p < 0.01$.

Potassium and SGPT concentration were significantly reduced in the males at all dosage levels tested including the lowest dose used (1 ppm) in comparison to the control II values. The SGPT levels of the test groups, however, were comparable to those of the control I. A dose related decrease in calcium was observed in both males and females of the test groups with significant differences found at 1 ppm. Serum alkaline phosphatase levels of both males and females at the highest dose level were also significantly increased ($p < 0.01$).

All other clinical chemistry determinations were not biologically different as compared to control II values.

9. Organ weights

With respect to organ weights, no significant differences to control groups were found at the lowest dose used (1 ppm). Compound related effects, if any, were probably characterized by increased adrenal weight in the females of the 50 ppm group.

10. Necropsy

Necropsy was performed on all animals of all groups and no compound-related effect was observed.

11. Histopathology

Histopathological findings were reported for all animals of the group I (untreated control) and group V (50 ppm, highest dose used).

	<u>Control I</u>	<u>Group V</u>
Liver (lymphohistiocytic infilt.)	18/20	18/20
Liver (granuloma like lesion)	12/20	7/20
Pancreas, infiltration	1/20	4/20
Thymus, hemorrhage	4/20	8/20

(Data extracted from "Addendum to report:", pp. 176-179.)

Vorlex, at the dosage levels used, did not induce any histopathological changes in all organs investigated (33 organs in total). The increased adrenal weight observed in females of the highest dose group was not associated with histopathological alterations.

IV. Discussion and Conclusion

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Two control groups were used: untreated and sham-treated. Parameters of systemic toxicity (body weight, food and water consumption) hematology, and clinical chemistry were statistically compared to the sham-treated control group which, to this reviewer, was the most appropriate control group. However, those parameters should also be compared to the untreated control group. Similarly, histopathological examinations of both groups must be considered. It is unclear, however, why histopathological observations were not performed or reported for the sham-treated animals.

No treatment related gross pathological or microscopic alterations were noted in the tissues and organs of rats exposed to Vorlex at dosage levels up to and including 50ppm for 90 days. However, subchronic exposure to Vorlex may result in decreased food consumption and body weight gain as well as alterations in several clinical chemistry determinations (calcium, potassium, and SGPT).

Although liver and kidney pathological changes had been described with dichloropropene (main active ingredient of Vorlex; J. Amer. Ind. Hyg. Ass. 1977), no such findings were evident from the submitted data. However, significant reductions in serum potassium and calcium levels were observed among the treated animals in this study. The hypocalcemic effect was dose-related with statistically significant differences found even at the lowest dose used (1 ppm; females).

Many diseases are known to account for hypocalcemia and hypokalemia including dysfunction of the parathyroid gland and renal failure. In this reviewer's opinion, hypoparathyroidism may not be the primary cause in this study since the hypocalcemia observed was not associated with decreased serum protein levels in the treated groups. Renal failure which may alter the reabsorption process of calcium and potassium thus may be one of the main contributing factors. Decreased renal function may lead to hypocalcemia with the latter eventually results in osteomalacia which is hinted in this study by concurrent findings of significant increases in serum alkaline phosphatase in both males and females of the highest groups by week 12. Consequently, although renal and hepatic pathological changes were not found in this study, clinical chemistry determinations at least did allude to some functional changes in these organs.

Statistically decreases in SGPT were noted in all treated groups by week 12 in comparison to the sham-treated controls. These findings, however, were not considered as biologically significant by this reviewer since these SGPT values were comparable to those of the concurrent untreated control group and were well within the normal range for this enzyme. Statistical differences appeared to be due to an unexplainable significant increases in SGPT in the sham-treated animals by week 12. In rodents, increased SGPT levels are generally associated with hepatic diseases but this could not be ascertained in this study since histopathological data were not available for this group.

Although the increase in water consumption observed in the treated females was dose related with statistical significance found even at the lowest dosage tested, the biological significance of this finding remains uncertain.

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Hematologic and clinical chemistry parameters were determined from 5 animals/sex/group instead of at least 10 animals/sex/group (EPA, Pesticide Assessment Guidelines, pp. 92-102, 1982).

Clinical observations were reported in summary form and there were no individual observation data to confirm several findings (i.e. abdominal hypotension, nasal discharge,...).

Based upon the submitted data, a systemic NOEL could not be demonstrated (decreased calcium and potassium levels and increased water consumption at the lowest dose tested, 1 ppm).

V. Core Classification:

This study is classified as Core Supplementary Data for the following reasons:

- a) No systemic NOEL could be demonstrated from the dose levels selected.
- b) Histopathological data of the sham-treated control are not available.
- c) Hematologic and chemical determinations were performed on only 5 animals/sex/group.
- d) No individual clinical observations were presented.

RIN 3426-95

VORLEX REVIEW

Page _____ is not included in this copy.

Pages 9 through 16 are not included.

The material not included contains the following type of information:

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