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

006011

JUL 20 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Response by Registrant to EPA Comments Regarding a 90-Day Nose-Only Inhalation Study in Fischer 344 Rats with Chlorpyrifos (Dow Study No. K-044793-007) - EPA Identification No. 64-404; Caswell No. 219AA, Toxicology Branch Project No. 7-0237.

FROM: Alan C. Levy, Ph.D.
Toxicologist, Review Section V
Toxicology Branch/HED (TS-769C)
Alan C. Levy 6/30/87

TO: Dennis Edwards (PM 12)
Registration Division (TS-767C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V (TS-769C)
Quang Bui 6/30/87

and

Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)
7/19/87

Registrant: Dow Chemical Company

Action Requested: Review registrant's response to EPA's comments regarding a 90-day nose-only inhalation study in rats with Chlorpyrifos.

RECOMMENDATIONS: The three Toxicology Branch concerns, as stated in the memo from W. Teeters to D. Edwards dated 1/27/87, have been satisfactorily responded to by the registrant.

The study is now classified: Core Minimum.

006011

Primary Reviewer: Alan C. Levy, Ph.D.
Review Section V/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head
Review Section V/HED (TS-769C)

1. Study Type: 90-Day Inhalation

Study Title: Chlorpyrifos: 13-Week Nose-Only Vapor Inhalation Exposure Study in Fischer 344 Rats.

EPA Identification Numbers:

EPA Identification: 464-404
EPA Accession: 400139
EPA Record:
Shaughnessy: 059102
Caswell: 219AA
Tox. Branch Project: 7-0237
Document:

Sponsor: Dow Chemical Company

Testing Laboratory: Toxicology Research Laboratory, Dow Chemical Company

Study Number: K-044793-077

Study Date: November 13, 1986

Study Authors: R. A. Corley et al.

DISCUSSION:

Each of the reasons given in the Agency letter to Dow Chemical Company in reference to their 90-day nose-only inhalation study in rats with Chlorpyrifos for classifying the study is addressed by first stating the Agency concern, then giving the registrant's response, followed by the Agency comment on the response.

1. Agency Concern: A thorough detailed description of the exposure equipment and data developed during chamber distribution studies must be submitted.

Registrant's Response: "A diagram of the vapor generating system used in this study is shown in Figure 1."

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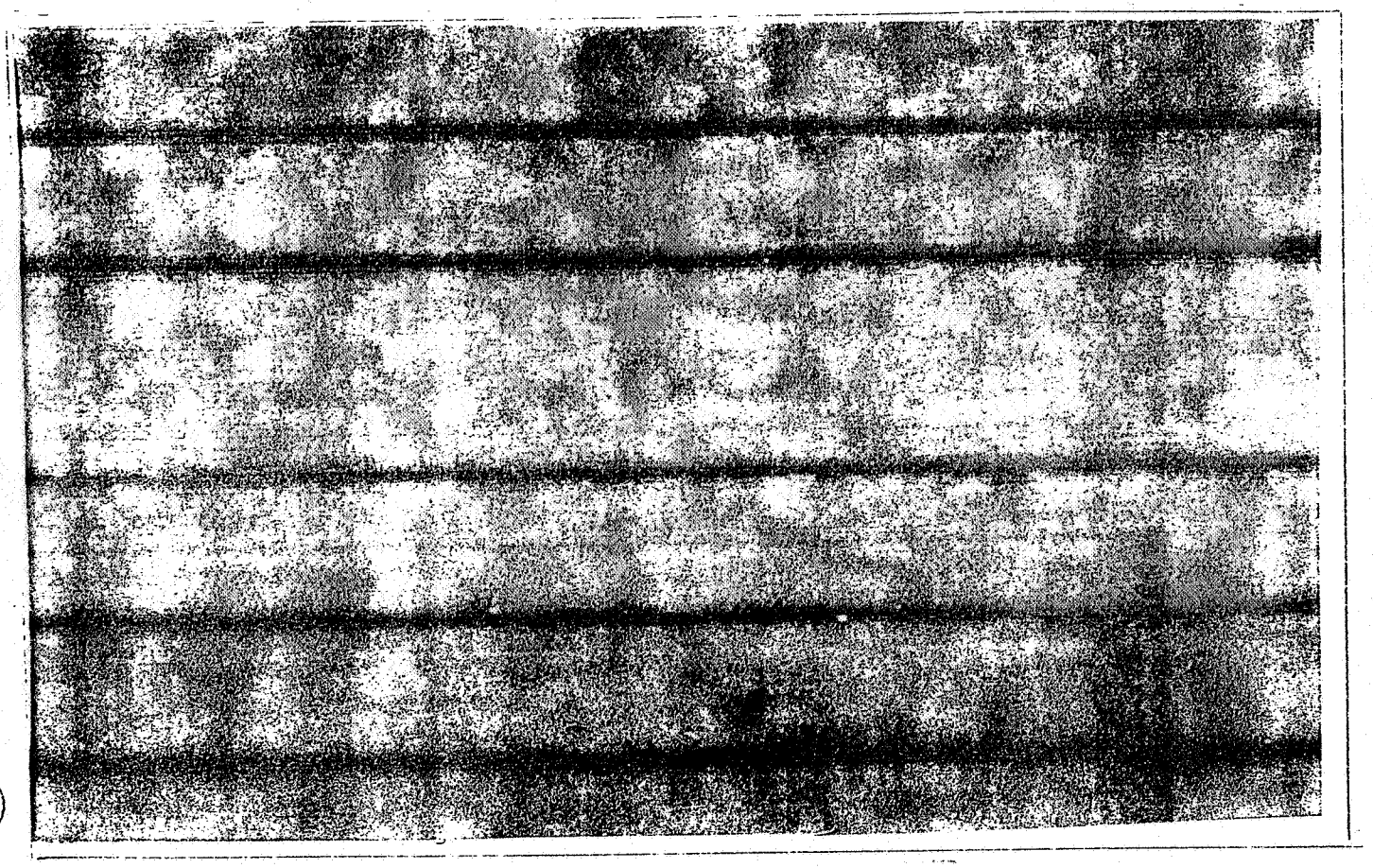
Pages 3,4, and 5 are not included in this copy of the review. The pages contain detailed test methodology submitted to the Agency by the Dow Chemical Company.

Detailed test method



Agency Comment: The registrant has provided a detailed description of the exposure equipment by diagram, text and photographs. A diagram and data regarding chamber distribution were submitted. Therefore, it is considered that the registrant has satisfactorily addressed the Toxicology Branch's concern.

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Page 7 is not included in this copy of the review. The page contains detailed test methodology submitted to the Agency by the Dow Chemical Company.

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Page 11 is not included in this copy of the review. The page contains detailed test results submitted to the Agency by the Dow Chemical Company.

2. Agency Concern: This was a completely negative study with no compound related effects noted. The NOEL in this study is 20.6 ppb. An HDT and LEL were not established.

Registrant's Response: The maximum attainable concentration was limited by the vapor pressure of the test material.

Agency Comment: The registrant's response is acceptable to the Toxicology Branch.

3. Agency Concern: The unusual aspect of this study is the lack of an effect on plasma, erythrocyte, or brain cholinesterase activity. This is remarkable since a whole-body inhalation study with 14 days duration at only 0.7 ppb concentration showed 15% depression of plasma cholinesterase in female rats. There are at least three possible explanations for this apparent discrepancy. One explanation, as suggested by Dow, is that oral and dermal exposure accompany whole body inhalation exposure under this situation. A second explanation can be that in this longer-term inhalation study (90 days vs. 14 days), accommodation to the cholinesterase depressant has occurred. However, plasma and erythrocyte cholinesterase activity in this study was not measured until termination of the study at 90 days. A third possibility is that the rats did not receive the reported concentrations. No details of the exposure equipment were submitted with this study although references were made to several published articles on the equipment and its use. Methodology in the report mentioned that "automated sampling of chamber air via solenoid valves was not possible due to absorption of chlorpyrifos to surface and to very low chamber concentrations." The relationship between the location in the chamber of the sampling port for the collecting impinger and the exposure ports was not reported. However, it was stated that chamber distribution studies verified that exposure concentration varied less than 15% between sampling and animal exposure ports, but no data were provided to support this statement.

It is difficult to accept that there is such a difference between whole-body and nose-only exposure that exposure by the

latter method at a thirty fold concentration and six fold duration compared to the former method, is not as effective as the former in affecting cholinesterase activity of exposed animals. Any information that you can provide to explain the difference will be helpful.

Registrant's Response:

a) "We believe that whole-body exposure of rats is inappropriate for an inhalation toxicology evaluation of chlorpyrifos vapor and that our nose-only exposure study provides a well-defined inhalation administration. Contamination of fur during whole-body exposure could result in an oral and/or dermal exposure that would prevent a meaningful extrapolation to humans. A more detailed rationale appears in the Dow report submitted to the agency."

b) "This 13-week study was designed to evaluate subchronic persistent effects. Acute and 2-week chlorpyrifos inhalation exposure studies have been conducted by Dow and submitted to the EPA. These studies demonstrated that shorter term chlorpyrifos vapor inhalation exposure (nose-only) did not cause decreases in plasma cholinesterase. The chlorpyrifos concentration attained during the two-week study (12 ppb) was slightly less than during the 13-week study (20 ppb); this was largely due to our increased experience in generating and controlling the test atmosphere that was obtained prior to the 13-week study. A significant amount of accommodation would not have been missed with our series of nose-only exposure studies."

c) "Additional exposure methodology has been provided in the response to question number 1; this indicates that rats were indeed exposed to the intended concentrations."

"We have validated our nose-only exposure methodology by determining 4-hour LC50's of an odorless gas (carbon monoxide, CO) and a highly irritant gas (ammonia, NH_3) by nose-only and whole-body exposure in rats (Nitschke, 1985). The LC50 values for nose-only and whole-body exposure to CO were in very close agreement (Table 2). The LC50 values for rats nose-only exposed to NH_3 were in reasonable agreement, though somewhat higher then whole-body exposed rats (2.5 x in females). Nose-only exposure to lethal concentrations of ammonia represents an extreme test of the system. Rats that were nose-only exposed to chlorpyrifos tolerated the confinement and exposure very well."

"The inspired dose of chlorpyrifos in rats exposed to 20 ppb (assuming 100% absorption) is approximately 0.1 mg/kg/day (1 liter/g/min x 360 minute exposure x 20 ppb x 0.0144 microgram/liter/ppb). Based on McCollister et al., (1974), one would not expect a significant decrease in plasma cholinesterase activity in rats fed 0.1 mg/kg/day for 13 weeks. Therefore the nose-only exposure data is consistent with chlorpyrifos administered in the diet."

"In conclusion, in this 13-week nose-only inhalation study, the rats were exposed to chlorpyrifos vapor under well defined conditions at a concentration which approached the maximum theoretically obtainable concentration. Evaluations included cholinesterase activity (plasma, rbc and brain) and histopathology; these provided a sensitive index of potential subchronic effects."

Agency Comment: The Toxicology Branch accepts the registrant"s description and explanation concerning the nose-only exposure of chlorpyrifos to rats. Details of the exposure equipment are presented under the response to Agency Concern No. 1.

REFERENCES

"McCollister, S. B., Kociba, R. J., Humiston, C. G., and McCollister, D. D. (1974). Studies of the Acute and Long-term Oral Toxicity of Chlorpyrifos (O,O-Diethyl-O-(3,5,6-Trichloro-2-Pyridyl) Phosphorothioate). Fd. Cosmet. Toxicol., 12:45-60.

Nitschke, K. D. (1985). Comparison of LC50 Determinations Between Whole-body and Nose-only Exposures. Mammalian and Environmental Toxicology Research Laboratory Report, The Dow Chemical Company, Midland, MI."