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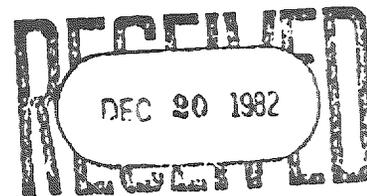


THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

December 9, 1982

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US Environmental Protection Agency
TSCA-8D1
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OPTS-84003A

Dear Sir or Madam:

As required by 40 CFR 716, we herewith submit copies of reports which meet the requirements of the referenced rule as Health and Safety Studies. As noted in the statement enclosed with the reports, some contain confidential business information.

The reports are separated into three categories for your convenience.

- Package 1. Reports which contain no Confidential Business Information.
- Package 2. Reports which contain Confidential Business Information.
- Package 3. Reports from which Confidential Business Information has been deleted. (Public File Copy of reports in Package 2).

Each report is marked with an identifying number at the top of the first page of the report, e.g., D-155. Use of this identification number in future correspondence regarding this submission will facilitate handling of questions.

In order to expedite the completion of our search and submission, no attempt was made to determine whether or not we manufactured or processed the chemicals which formed the subject of submitted reports. (40 CFR 716.6). Thus, submission of a report for any given material should not be construed as indicative of Dow's status as a manufacturer or processor of the material.

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Many of the submitted reports contain information which is not relevant to Health or Safety Studies of listed chemicals, e.g., references to unlisted chemicals, marketing or process data, account numbers, internal document identification codes or distribution lists. Such information has been deleted from all copies submitted.

The index required by 40 CFR 716.6(b) is enclosed. It lists the Dow identification number and title of each report submitted in CAS number order. Please note that the index contains Dow Confidential Business Information.

We have also included a reprint of a recently published article dealing with methylene chloride.

Very truly yours,



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D-158B

THE DOW CHEMICAL COMPANY
BIOCHEMICAL RESEARCH LABORATORY

TOXICOLOGICAL PROPERTIES AND INDUSTRIAL HANDLING HAZARDS OF

PROGRESS REPORT ON TETRACHLOROBENZENE: SKIN
ABSORPTION IN THE RABBIT, AND METABOLISM
IN THE RAT

FILE	
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SUB. BY	
REP'T. BY	W. N. Piper WNP
CHECKED BY	H. C. Spencer HCS
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LAB CODE LETTERS
AND REPORT NO.

INFORMATIVE SUMMARY WITH CONCLUSIONS - BASED ON THE SAMPLE RECEIVED. ADDITIONAL INFORMATION INCLUDING THE EFFECTS OF REPEATED EXPOSURE MAY BE REQUIRED AS SPECIFIC USES AND FORMULATIONS ARE DEVELOPED OR IF PROCESS CHANGES OCCUR.

SUMMARY

The skin absorption of tetrachlorobenzene has been studied in the rabbit, and the metabolism and excretion studied in the rat.

1,2,4,5-Tetrachlorobenzene could not be detected in blood plasma after 1 g/kg or 2 g/kg application to the skin. 1,2,3,4-Tetrachlorobenzene was present at a concentration of 0.7 to 1 µg/ml plasma up to 24 hours after a single skin application of 1 g/kg.

1,2,3,4-Tetrachlorobenzene is virtually 100 percent excreted in the feces of the rat within 24 hours after intra-peritoneal administration. Small quantities appear to be metabolized to the tri- and tetrachlorophenol.

DISTRIBUTION

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INTRODUCTION

1,2,3,4 and 1,2,4,5-Tetrachlorobenzene are intermediates in the synthesis of various chlorinated compounds.

Since personnel are being exposed to tetrachlorobenzene in the plant, studies on absorption, distribution and metabolism need to be conducted.

MATERIALS AND METHODS

Animals:

Rabbits were from the Dow colony (New Zealand albino strain) and weighed 2.75-3.35 kg.

Rats were from the Dow colony (Sherman strain) and weighed 230-250 g.

All animals used were males.

Tetrachlorobenzene Source and Purity:

Samples of 1,2,3,4 and 1,2,4,5-tetrachlorobenzene were obtained from B. L. Reber, and were analyzed by electron-capture gas-liquid chromatography and nuclear magnetic resonance. The results indicate that the samples are 94.9% 1,2,3,4 and 98.7% 1,2,4,5-tetrachlorobenzene.

Detection of Tetrachlorobenzene:

Gas-liquid chromatography, using an electron-capture detector, was found to be a very sensitive method for detection of tetrachlorobenzene. Amounts as small as 0.01 μ g have been detected.

The column used was alkaline carbowax 20 M on regular chromosorb (60-80 mesh), with a column temperature of 190°C and an injector temperature of 215°C.

RESULTS

Skin Absorption in the Rabbit:

Tetrachlorobenzene was applied to a 16cm² area of the shaved abdominal skin of the rabbit. The skin was covered with Saran wrap, and cloth was placed over the area to prevent the animals from removing the compound from the skin.

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Rabbits were placed on their backs in wooden stocks, and were denied access to food and water. Blood samples were taken by cardiac puncture over a 24 hour period, and 2.5 ml of blood plasma were extracted with 50 ml of isooctane. The extract was analyzed by gas-liquid chromatography.

1,2,3,4-Tetrachlorobenzene (1 g/kg) was present at a concentration of 0.7 to 1 µg/ml of plasma from 3 to 24 hours after application to the skin (Table 1).

Table 1
Skin Absorption of 1,2,3,4-Tetrachlorobenzene
in the Rabbit

<u>Treatment</u>	<u>Time (hr.)</u>	<u>µg 1,2,3,4-Tetrachlorobenzene per ml plasma</u>
Control	3	0
	6	0
	12	0
	24	0
1,2,3,4- Tetrachloro- benzene ^a	3	0.72
	6	0.54
	12	0.56
	24	1.03

^a
1 g/kg per 16cm² on skin abdomen.

Similar skin absorption studies were conducted with 1 g/kg and 2 g/kg of the 1,2,4,5 isomer. No 1,2,4,5-tetrachlorobenzene could be detected in blood plasma up to 24 hours after skin application.

These amounts of tetrachlorobenzene (1 g or 2 g/kg) produced hyperemia and slight edema of the skin.

Metabolism and Excretion in the Rat:

1,2,3,4-Tetrachlorobenzene (100 mg/kg, i.p. in peanut oil) was administered to a rat, and the feces and urine were collected over a 24 hour period. Feces and urine were extracted with 50 ml of isooctane, and the extracts were analyzed by gas-liquid chromatography. Virtually 100 percent of the tetrachlorobenzene was found in the feces in the 24 hour sample. No tetrachlorobenzene was detected in the urine.

Analysis of the fecal extract by mass spectrometry indicated that the rat metabolizes 1,2,3,4-tetrachlorobenzene to small quantities of trichlorophenol and tetrachlorophenol. The compound is metabolized to the tetrachlorophenol in rabbits(1).

In future studies, the fecal extract of isooctane will be acidified in an attempt to recover a higher concentration of the phenolic metabolites for analysis by mass spectrometry. Also, the bile duct will be cannulated, and bile will be collected, extracted with isooctane, and analyzed for tetrachlorobenzene.

The metabolism and distribution of the 1,2,4,5 isomer will also be studied.

SUMMARY

The skin absorption of tetrachlorobenzene has been studied in the rabbit, and the metabolism and excretion studied in the rat.

1,2,4,5-Tetrachlorobenzene could not be detected in blood plasma after 1 g/kg or 2 g/kg application to the skin. 1,2,3,4-Tetrachlorobenzene (1 g/kg) was present at a concentration of 0.7 to 1 µg/ml plasma up to 24 hours after skin application.

1,2,3,4-Tetrachlorobenzene is virtually 100 percent excreted in the feces of the rat within 24 hours after intraperitoneal administration. Small quantities appear to be metabolized to the tri- and tetrachlorophenol.

ACKNOWLEDGEMENTS

REFERENCE

1. W. R. Jondorf, D. V. Parke, and R. T. Williams, Biochem. J., 69:181-189 (1958).