8EHQ-0295-1047

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February 9, 1995

TSCA Document Processing Center (TS-790)
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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Attn: TSCA Section 8(e) Coordinator
401 M Street S.W.
Washington, D.C. 20460

Re Supplemental Submission to 8EHQ-0890-1047
TSCA Section 8(e) Notification of Substantial Risk
Hexamethoxydisilylethane

No CBI

Dear Sir

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (40 FR 11110, March 16, 1978), Dow Corning Corporation is submitting the following final report as a supplemental submission to our Notification of Substantial Risk of August 10, 1990 (8EHQ-0890-1047)

Chemical Substance:

8EHQ-90-1047

Hexamethoxydisilylethane
CASRN 18406-41-2

Manufacturer:

EPA-OTB
00081160LM

Dow Corning Corporation
2200 West Salzburg Road
Midland, Michigan 48686-0994

Follow up Support

Submitted Study:

A COMPARISON OF THE VAPOR INHALATION TOXICITY OF THREE BIS(TRIALKOXYSILYL)ALKANE COMPOUNDS

Dow Corning Corporation
February 6, 1995

Background:

On August 10, 1990, Dow Corning submitted a Notification of Substantial Risk under TSCA Section 8(e) concerning preliminary results obtained in an acute vapor phase inhalation toxicity study of DOW CORNING® X1-6145A Additive in rats. A copy of the final report was submitted to EPA August 21, 1990. In response to the Agency's request, Dow Corning provided additional followup to our initial notification (8EHQ-0890-1047) and has continued to submit new data on this chemical substance as such data was developed or became known to Dow Corning

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As additional followup to 8EHQ-0890-1047, we are providing EPA with a copy of a recent Dow Corning report comparing the vapor phase inhalation toxicity of hexamethoxydisilylethane (1,2- bis(trimethoxysilyl)ethane) with that of two structurally similar compounds, 1,2- bis(triethoxysilyl)ethane and 1,6- bis(trimethoxysilyl)hexane.

Executive Summary:

Acute and repeated short-term vapor inhalation toxicity studies in rats and dogs with 1,2- bis(trimethoxysilyl)ethane (hexamethoxydisilylethane) showed severe mucous membrane damage and epithelial necrosis of the cornea and upper respiratory tract at levels as low as 0.5 ppm, and microscopic changes in the respiratory tract tissue at subacute exposure concentrations down to 48 ppb. The four hour acute median lethal concentration (LC_{50}) was calculated to be 2.4 ppm (95% CL 2.1-2.9 ppm). By contrast, acute 4 hour inhalation exposures to two structurally similar compounds, 1,2- bis(triethoxysilyl)ethane and 1,6- bis(trimethoxysilyl)hexane, at concentrations of 26 and 3.2 ppm, respectively, produced no mortality and essentially no clinical signs of toxicity, macroscopic or microscopic tissue damage. The extreme vapor inhalation toxicity of 1,2- bis(trimethoxysilyl)ethane appears to be virtually eliminated by either substitution of methoxy-groups with ethoxy-groups or by extension of the connecting alkane chain length from $-(CH_2)_2-$ to $-(CH_2)_6-$.

Actions:

Dow Corning will continue to notify EPA of any further pertinent information that may be developed concerning hexamethoxydisilylethane. Dow Corning has ceased efforts to commercialize this substance and has taken action to insure that it is not present as an unintentional byproduct in other materials we make.

If you require further information concerning the toxicity of hexamethoxydisilylethane, please contact Dr. Robert G. Meeks, Manager, Dow Corning Product Toxicology Department, at 517-496-8629. If you require further information concerning this supplemental submission, please contact Dr. Rhys G. Daniels, Regulatory Compliance Specialist, Dow Corning Product Safety and Regulatory Compliance Department, at the address provided below or by telephone at 517-496-4222.

Sincerely,

Alvin E. Bey

Alvin E. Bey
U.S. Area Vice-President
Corporate Director HES

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DOW CORNING

TSCA SECTION 8(e) NOTIFICATION OF SUBSTANTIAL RISK

TOXICOLOGICAL STUDIES

TSCA CONFIDENTIAL BUSINESS INFORMATION CLAIMS

For purposes of Notification of Substantial Risk under Section 8(e) of the Toxic Substances Control Act (TSCA), the general **PROPRIETARY** designation on the attached toxicological study has been waived by Dow Corning Corporation

Submitter _____ Date _____

Rhys G. Daniels, Ph.D.
Regulatory Compliance Specialist
Health and Environmental Sciences
DOW CORNING CORPORATION

DOW CORNING CORPORATION, MIDLAND, MICHIGAN 48686-0994 TELEPHONE: (517) 496-4000

DOW CORNING

A COMPARISON OF THE VAPOR INHALATION TOXICITY OF THREE BIS(TRIALKOXYSILYL)ALKANE COMPOUNDS

Dow Corning Corporation
February 6, 1995

DOW CORNING CORPORATION, MIDLAND, MICHIGAN 48686-0994 TELEPHONE: (517) 496-4000

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REPORT NO.: 1995-10000-40092
AUTHORS: Simon L. Cassidy
Gary B. Kolesar
Waheed H. Siddiqui
DEPARTMENT: Health and Environmental Sciences
SUPERVISOR: R. G. Meeks
LOCATION: Midland, Michigan
DATE: February 6, 1995
TITLE: A COMPARISON OF THE VAPOR INHALATION TOXICITY OF THREE BIS(TRIALKOXYSILYL)ALKANE COMPOUNDS

ABSTRACT

Several bis(trialkoxysilyl)alkane compounds have been developed for use as adhesion promoters and hydrophobing treatments. These compounds show unique activity in certain electronic and industrial applications. One of the first materials used for these applications in this chemical class was 1,2-bis(trimethoxysilyl)ethane. Both acute and repeated short-term vapor inhalation studies in rats and dogs with this compound showed severe mucus membrane damage and epithelial necrosis of the cornea and upper respiratory tract at levels as low as 0.5 ppm, and microscopic changes in the respiratory tract tissue at subacute exposure concentrations down to 10 ppb. The 4 hour LC_{50} was calculated to be 2.4 ppm (95% CL 2.1-2.9 ppm). By contrast, acute 4 hour inhalation exposures to two structurally similar compounds, 1,2-bis(triethoxysilyl)ethane and 1,6-bis(trimethoxysilyl)hexane, at concentrations of 26 and 1.2 ppm, respectively, produced no mortality and essentially no clinical signs of toxicity, macroscopic or microscopic tissue damage. The extreme vapor inhalation toxicity of the 1,2-bis(trimethoxysilyl)ethane appears to be virtually eliminated by either substitution of the methoxy groups with ethoxy groups or by extension of the connecting alkane chain length from $-(CH_2)_2-$ to $-(CH_2)_6-$.

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FIGURE 1. GENERAL STRUCTURES OF BIS(TRIALKOXYSILYL)ALKANE COMPOUNDS

TABLES

1. Experimental Design Details of bis(trialkoxysilyl)alkane vapor inhalation studies.

2. Acute vapor inhalation toxicity data for Xi-6145A, AY43-082E and HMSH.

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INTRODUCTION

Several bis(trialkoxysilyl)alkane compounds have been developed for use primarily as adhesion promoters and hydrophobing surface treatments. These compounds show unique activity in certain electronic and other industrial applications. The general structure of currently used compounds of this type are shown in Figure 1; the variable structural features of significance are primarily the nature of the alkoxy groups (methoxy-, ethoxy-) and the length of the alkyl chain between the terminal trialkoxysilyl groups. The purpose of this report is to compare, summarize and discuss the results of vapor inhalation toxicity tests performed upon three members of this class of materials, and to assess the qualitative structure-activity relationship information these studies provide. this assessment may guide the future development and use of such compounds.

MATERIALS

The compounds studied in the Dow Corning Toxicology Laboratory include the following:

1,2-Bis(trimethoxysilyl)ethane (also known as Dow Corning X1-6145A Additive) 93-99% pure

1,2-Bis(triethoxysilyl)ethane (also known as DCTS AY 43-082E) with purity greater than 92%

1,6-Bis(trimethoxysilyl)hexane (also known on HMSH), purity > 97%

These three materials are clear, colorless liquids.

In addition, the material, 1,10-bis(trimethoxysilyl)decane (purity 99.3%), has been tested by Union Carbide Corporation. the results of this aerosol inhalation testing are briefly summarized in the Discussion Section of this report.

METHODS

1,2-bis(trimethoxysilyl)ethane (X1-6145A), 1,2-bis(triethoxysilyl)ethane (AY43-082E)and 1,6-bis(trimethoxysilyl)hexane (HMSH) were administered by vapor inhalation (whole body exposure) to rats and dogs. Both acute and subacute repeated exposure regimens were used to assess the vapor inhalation toxicity of X1-6145A, whereas AY43-082E and HMSH were tested only in acute, single exposure assays. The experimental details and reference for each study are summarized in Table 1.

RESULTS

Acute Exposures

The acute single exposure rat studies on X1-6145A (1, 3, 4) indicate that single 4-6 hour exposures to this material produced delayed clinical signs of toxicity (nasal discharge, oral breathing, abnormal respiratory noise and labored breathing) and reduced body weight gain at levels of 0.4 ppm and higher. At necropsy, gross macroscopic lesions were seen at levels of 1 ppm and above; these included primarily corneal opacity, nasal bleeding and congestion of the lungs.

Histopathological examination of the tissues indicated that irritative changes (exudate, epithelial necrosis/desquamation) in the eyes (cornea) and respiratory tract at 0.4 ppm and above. The most severe effects were seen in the upper respiratory tract (i.e. nasal cavities). No mortality occured at levels of 1 ppm or below.

Mortalities occured at acute exposure levels of 2.0 ppm and above with a calculated acute (4 hr) rat LC_{50} for X1-6145A of 2.4 ppm (3). By contrast, exposure of rats for 4 hours to the analogue compounds AY43-082E (7) and HMSH (8) to vapor concentrations (26 and 3.2 ppm respectively) close to their saturated vapor concentration did not produce any mortalities, clinical signs of toxicity or treatment-related pathological changes in the respiratory tract. These results are summarized in Table 2.

The severe respiratory tract toxicity seen in rats due to X1-6145A exposure may be due in part to the fact that the rat is an obligate nose breather. However, a two day (6 hr/day) vapor inhalation study in beagle dogs produced a similar pattern of respiratory tract and corneal epithelial damage and morbidity at an exposure level of 10 ppm (6). As in the rat studies, the respiratory tract lesions were most severe in the nasal passages.

Subacute Exposures

Two repeated exposure studies were attempted with X1-6145A in rats with intended study durations of 2 weeks at exposure concentrations ranging from 0.5 to 13 ppm (2,4). Repeated exposure to concentrations of 1 ppm or higher produced severe morbidity and mortality after only two 6 hour exposures. Rats exposed to 0.5 ppm were terminated *in extremis* after only 4 daily exposures.

The clinical signs of toxicity and the pattern of macroscopic and microscopic pathological lesions in the eyes (cornea) and respiratory tract (particularly the nasal cavity, trachea and bronchi) were essentially the same as those seen in the acute exposure studies described above.

A third subacute exposure (5) was performed using repeated daily (6 hr.) exposures of 0, 48, 96 and 203 ppb for 2 weeks (5 days/week)); in this study all animals survived to the end of the exposure period. Reduced weight gain and clinical signs of toxicity (rales, nasal discharge) were seen at 96 and 203 ppb. No macroscopic pathological lesions were observed at necropsy but histopathological examination revealed test material related changes in the respiratory tract (most severe in the nares, nasal cavity and pharynx and less so in the trachea and larynx) at all dose levels. These included inflammatory changes, squamous metaplasia, enlarged mucus goblet cells, erosions/ulcers and suppurative exudate.

DISCUSSIONS AND CONCLUSIONS

The results of both acute and subacute (up to 2 weeks) vapor exposures of 1,2-bis(trimethoxysilyl)ethane indicate that it severely damages mucus membrane tissue, specifically the eyes and upper respiratory tract, at levels of 0.5 ppm and above, and causes histopathological changes in respiratory tract tissue at subacute exposure levels of 48 ppb and above. This high vapor inhalation toxicity poses a severe potential human health hazard. A no observed effect level (NOEL) has not yet been established.

The results with 1,2-bis(triethoxysilyl)ethane and 1,6-bis(trimethoxysilyl) hexane indicate that replacement of methoxy groups with ethoxy-functionality or elongation of the alkane chain length from $-(CH_2)_2$ to $-(CH_2)_6-$ essentially abolishes the respiratory tract toxicity following acute inhalation exposure

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observed with the 1,2-bis(trimethoxysilyl)ethane. Some data suggests that methoxysilane compounds hydrolyse more rapidly than ethoxysilanes (9). This may explain their greater toxicity in terms of potential reactivity with the respiratory tract and/or formation of a toxic intermediate. Unpublished data obtained by this laboratory indicate that tetramethoxysilane and trimethoxysilane possess a higher acute inhalation toxicity than their ethoxy analogues. Elongation of the $(CH_2)_n$ chain length may simply reduce the molar quantities of alkoxy functionality available for reaction.

The results of several of the studies described in this report (1-4, 6-8) have been published in abstract form (10).

A subacute aerosol inhalation toxicity study of 1,10-bis(trimethoxysilyl)decane has also been reported (11). High mortality was observed together with multiple organ systemic toxicity (kidney, nervous system, male reproductive tract). However, in view of the fact that only one dose level was used (0.155 mg/litre), and the exposure was via aerosol generation, little useful comparative information can be derived from this study.

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INFORMATION RETRIEVAL INDEX

Vapor Inhalation Toxicity - rat - dog
bis(trialkoxysilyl)alkane - hexabis

SIGNATURE OF AUTHOR(S)

This report constitutes pages 1-11, including Figure 1 and Tables 1 and 2.

Author: Simon L. Cassidy — Date: 6 Jan. 1995
Simon L. Cassidy, Ph.D., D.A.B.T.

Date: 1/6/95
Gary H. Kolesar, M.S., D.A.B.T.

Date: 1/6/95
Waheed H. Siddiqui, Ph.D.

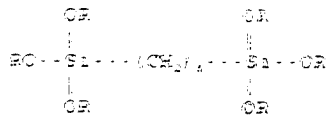
Reviewed By — Date: 1/30/95
R. O. Meeks, Ph.D., D.A.B.T.
Toxicology Manager
Health and Environmental Sciences

Typed by

Michelle L. Snook

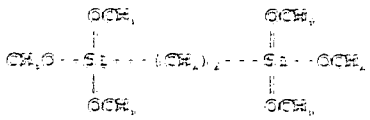
FIGURE 1

GENERAL STRUCTURE OF BIS(TRIALKOXYSILYL)ALKANE COMPOUNDS

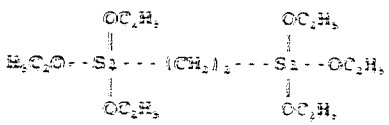


R = CH_3, C_2H_5, etc.

1,2-bis(trimethoxysilyl)ethane
(XI-6146A)



1,2-bis(triethoxysilyl)ethane
(AY 43-082E)



1,6-bis(trimethoxysilyl)hexane
(BYCSH)

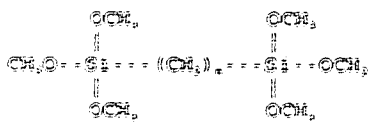


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TABLE 1 - EXPERIMENTAL DESIGN DETAILS OF BIS(TRIALKOXYSILYL)ALKANE VAPOR INHALATION STUDIES

Test Compound	Strain/ Species	No animals per exposure group	Intended duration (hr), length of study (days)	Vapor exposure concentration ppm * (mg/litre)	Method of vapor analysis	Gross Necropsy	Histopathology	Reference
XI-6145A	Sprague Dawley Rat	5 male, 5 female	Single 4 hr exposure	0, 80 ppm (0, 0.92) (Nominal)	None	X	Eyes, Respiratory Tract	1
XI-6145A	Sprague Dawley Rat	5 male, 5 female	6 hr/day, 5 days/week, 2 weeks	0, 2.0, 13.0	GC-FID	X	Respiratory Tract	2
XI-6145A	Fischer 344/N Rat	5 male, 5 female	Single 4 hr exposure	0.4, 2.6, 2.6, 5.7	FT-IR	X	Not done	3
XI-6145A	Sprague Dawley Rat	5 male, 5 female	(1) Single 6 hr exposure (2) 6 hr/day, 5 days/week 2 weeks **	0, 0.4, 0.9 and 1.9 (for both parts of the study)	GC-FID	X	16 Tissues	4
XI-6145A	Fischer 344/N Rat	10 male, 10 female	6 hr/day, 5 days/week, 2 weeks	0, 48, 96 and 200 ppm	FT-IR	X	17 Tissues	5
XI-6145A	Beagle Dogs	3 males	6 hr/day 2 days	10	IR	X	Eyes, Respiratory Tract	6
AY43-042E	Sprague Dawley Rat	5 male, 5 female	Single 4 hr exposure	1, 4, 8, 24 (Nominal)	None	X	Lung	7
KMCH	Sprague Dawley Rat	5 male, 5 female.	Single 4 hr exposure	3.15 (0.042) (Nominal)	None	X	Not done	8

KEY: GC-FID = Gas Chromatography - Flame Ionization Detection
IR = Infrared Spectroscopy
FT-IR = Fourier Transform - Infrared Spectroscopy

* = Measured values unless otherwise indicated
** = Two weeks of exposure were not completed due to high toxicity

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TABLE 2: ACUTE VAPOR INHALATION TOXICITY DATA FOR X1-6145A, AY43-082E AND HMSH

Test Material	Acute (4 hr) rat LC50 values (95% confidence limits)	Saturated vapor concentrations at room temp.	Vapor Pressure (mm/Hg at 25°C)	Molecular Weight
X1-6145A	2.4 ppm (2.1-2.9 ppm) 0.027(0.023-0.032) mg/litre	109 ppm	0.08	270.4
AY43-082E	>26 ppm (>0.38 mg/litre)	~40 ppm	0.03	354.5
HMSH	>3.2 ppm (>0.042 mg/litre)	~ 5 ppm	0.004	326.5