



8EHQ-0694-13056

Contains No CBI

May 31, 1994

(A)

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460

ORIGINAL

94 JUN -2 PM 2:38

RECEIVED

ATTN: 8(e) Coordinator

Re: TSCA 8(e) CBI Submission Concerning Organosilane A-174

Dear Sir or Madame:

OSi Specialties has just become aware of a finding of adverse developmental effect for a product which it manufactures (gamma-methacryloxypropyltrimethoxysilane; CAS No. 2530-85-0; A-174). The study was sponsored jointly by Union Carbide and OSi Specialties, and is currently available only as an unaudited draft (draft report date 4/29/94). This study in rats provides evidence for an increase in the total incidence of malformations, with statistical significance achieved for visceral malformations. Increased incidences of certain skeletal malformations and variations was also found. These effects occurred only at overtly toxic doses to the dams, with a NOAEL for maternal and fetal toxicity observed at a gavage dose of 0.5 ml/kg/day.

This finding is not surprising given that A-174 rapidly forms methanol in acidic environments, and thus a large percentage of the gavaged dose likely formed methanol in the rat stomach. Methanol is well recognized as a developmental toxicant capable of producing the effects seen presently (USEPA, OHEA, Internal Report: Summary Review of Health Effects Associated with Methanol: Health Issue Assessment; 1987). Through the MSDS, users of A-174 are already alerted to the possibility that methanol production and toxicity is a possibility if accidental ingestion occurs. It should be noted that similar effects are not expected by the more possible industrial exposure routes (inhalation, dermal) since A-174 would not contact acidic media via these routes.



8EHQ-94-13056
INIT 06/03/94



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RECEIVED
6/20/94

OSi Specialties, Inc.

P.O. Box 100 • Sisseton, SD 57175

U.S. Environmental Protection Agency
Re: TSCA 8(e) CBI Submission Concerning Organosilane A-174
May 31, 1994
Page Two

A copy of the summary of the unaudited draft report has been attached for your files. We will update the 8(e) docket if the final report is materially different from this draft report, or if any other data pertinent to this issue are obtained.

Please contact me at (304) 652-3211 if you require additional information at this time.

Sincerely,



C. R. Thrash
Manager, Product Safety
and Regulatory Affairs

CRT:mrh
Attachment

A-174: Developmental Toxicity Study of
Gavage Administration to CD® Rats

SUMMARY

Timed-pregnant CD® rats were administered A-174 (gamma-Methacryloxypropyl-trimethoxysilane; CAS No. 2530-85-0) by gavage on gestational days (gd) 6 through 15. Twenty-five copulation plug-positive females/group were dosed with undiluted A-174 at dose volumes of 0.5, 2.0, or 5.0 ml/kg/day. An additional group of 25 timed-pregnant females received Milli-Q® (filtered) water (CAS No. 7732-18-5) at a dose volume equivalent to that used in the high dose group and served as the control group. Clinical observations were made daily (twice daily during dosing), and maternal body weights were measured on gd 0, 6, 9, 12, 15, 18, and 21. Maternal food consumption was measured at 3-day intervals throughout gestation, gd 0-21. Dams were necropsied on gd 21 and evaluated for body weight, liver weight, kidney weight, gravid uterine weight, and pregnancy status. Maternal liver and kidneys were retained in 10% neutral buffered formalin. All fetuses were dissected from the uterus, counted, weighed, examined for external malformations (including cleft palate) and variations and for determination of gender. Approximately one-half of the live fetuses in each litter were examined for visceral and craniofacial malformations and variations. The remaining fetuses in each litter were examined for skeletal malformations and variations after staining with alizarin red S.

The pregnancy rate was equivalent for all groups and ranged from 84 to 96%. Dose-dependent maternal toxicity was observed in dams from the 2.0 and 5.0 ml/kg/day groups. In the 5.0 ml/kg/day group, 2 dams died after completion of dosing, on days gd 16 and 19, respectively. Pertinent clinical signs in the high dose group included incoordination and abnormal gait (in 2 dams, 1 of which died), unkempt appearance, urine stains/urogenital area wetness, and red vaginal discharge. Unkempt appearance, urine stains/urogenital area wetness, and red vaginal discharge were also observed in animals from the 2.0 ml/kg/day group. Gestational body weights were reduced in the 5.0 ml/kg/day group throughout the treatment period and subsequent to treatment, on gd 18. Substantial reductions in body weight gain were noted in the high dose group for Days 6 to 12 and consequently, for the entire treatment period. Effects on food consumption correlated well with effects on body weight as food consumption was reduced in the high dose group throughout the treatment period. Reductions in weight gain and food consumption were also noted in the 2.0 ml/kg/day group for the first 3 days of the treatment period.

There were no apparent treatment-related maternal necropsy findings. Gravid uterine weight appeared to be slightly (but not statistically significantly) reduced in the 5.0 ml/kg/day group. Absolute and relative liver and kidney weights were increased in dams from the 5.0 ml/kg/day group. Absolute liver and kidney weights appeared to be slightly increased in the 2.0 ml/kg/day group as well.

Two pregnant females which survived to scheduled sacrifice bore litters with only non-viable implants. However, there were no effects of treatment on the number of ovarian corpora lutea, or on the number of total, viable and

nonviable implantations/litter, or on percent preimplantation loss. There were no apparent effects of treatment on dams given 0.5 ml A-174/kg/day.

Fetal body weights/litter (for males, females and all fetuses) were reduced in the 5.0 ml/kg/day group. There were no increases in the incidences of individual external, visceral, or skeletal malformations that were attributable to treatment. Collectively, increases in the incidences of soft tissue malformations by category and of total malformations attained statistical significance in the high and mid dose groups. Due to the low frequency of occurrence of individual anomalies (in particular, malformations involving the circulatory system and palate closure), the toxicologic significance of the increase in soft tissue malformations is unknown. Increases in the incidence of total malformations in the 5.0 ml/kg/day group were partially due to skeletal alterations noted in 3 litters. These skeletal alterations included missing lumbar centra and arches, missing sacral centra and arches, rudimentary ribs (#1-#12), and extra cervical ribs (at arch #7). Increased incidences of several skeletal variations, including the presence of rudimentary ribs or bone islands on cervical arch #7 and increased incidences of unossified anterior arch of the atlas, poorly ossified squamosal, some poorly ossified or unossified metacarpals, some unossified metatarsals, poorly ossified sternebra #6 and unossified sternebra #6, were also noted at 5.0 mg/kg/day. In addition, a slight (but not statistically significant) increase in the incidence of dilated lateral ventricle(s) in the 5.0 ml/kg/day group was consistent with a general profile of delayed development.

In conclusion, gavage administration of undiluted A-174 to pregnant CD® rats during organogenesis resulted in clear evidence of maternal toxicity at 2.0 and 5.0 ml/kg/day. Consistent evidence of delayed development was noted in fetuses from the 5.0 ml/kg/day group, and toxicologically equivocal increases in the incidences of soft tissue malformations were noted at 2.0 and 5.0 ml/kg/day.

Based on the results of this study, the No-Observed-Effect Level (NOEL) for maternal toxicity was 0.5 ml/kg/day. The NOEL for developmental toxicity was also 0.5 ml/kg/day.



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

C.R. Thrash
Manager, Product Safety and Regulatory Affairs
OSi Specialties, Incorporated
P.O. Box 180
Sisterville, West Virginia 26175

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

AUG 16 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

13056 A



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contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: AUG 19 1994

NON-CAP

CAP

Submission number: 13056A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only	
entire document: <u>0</u> 1 2 pages <u>1,2</u>	pages <u>6,3,4</u>
Notes:	
Contractor reviewer: <u>DMC</u>	Date: <u>8/1</u>

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CHEMICAL DATA:
 Submission # 8EHO. 0694-13056 SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: Osi Specialties, Inc.

INFORMATION REQUESTED: FLWP DATE: _____
 0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TECH)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING RATIONALE)
 DISPOSITION:
 0639 REFER TO CHEMICAL SCREENING
 0678 CAP NOTICE

VOLUNTARY ACTIONS:
 0401 NO ACTION REPORTED
 0402 STUDIES PLANNED/UNDERWAY
 0403 NOTIFICATION OF WORKER/OTHERS
 0404 LABEL/MSDS CHANGES
 0405 PROCESS/HANDLING CHANGES
 0406 APP/USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

SUB. DATE: 05/31/94 OTS DATE: 06/03/94 CSRAD DATE: 06/20/94

CHEMICAL NAME: _____ CAS# 2530-85-0

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPI/CLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUR/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REOEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0229 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

TRIAL DATA: NON-CBI INVENTORY Ongoing Review Species Toxicological Concern Use Production
 YES (CONTINUE) YES (DROP/REFER) RAT LOW MED HIGH
 NO (DROP) NO (CONTINUE) REFER: 0.05% NOVEL for metformin + beta
 DETERMINE REFER:

COMMENTS: Non-COP gavage

*5ml/kg - 1/25 dose level, reduced GMI, increased absolute liver/body weight, and vaginal bleeding.
 2ml/kg - same except no liver. Absolute water time, increased absolute liver/body weight - reduced 1/25 at 5ml/kg, absolute water time, increased absolute liver/body weight - increased absolute liver/body weight.*