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FYI

# Sumitomo Chemical America Inc.

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September 3, 1993

U.S. Environmental Protection Agency  
OPPT Document Control Officer  
East Tower, Room 201  
401 M St., S.W.  
Washington, D.C. 20460



FYI-93-000892  
INIT 09/08/93



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Attention: TSCA Section 8(e) Coordinator

Dear Sir or Madam:

Sumitomo Chemical America, Inc. (hereinafter SCAI) submits the following information on a "For Your Information" (FYI) basis. The study in question, conducted by Sumitomo Chemical, was a pilot study intended to assess the possible reproductive effects of methyl amyl ketone (MAK, 2-heptanone, CAS No 110-43-0), a chemical manufactured by SCAI, using methyl-3-methoxypropionate (MMP, CAS No 3852-09-3), as a reference chemical. MMP, in the present study, was demonstrated to cause numerous visceral and skeletal malformations in fetuses of pregnant rats treated at an oral dose of 1,000 mg/kg, the only dose of MMP tested in the study. It is especially noted that these effects included a heart defect, ventricular septal defect, or VSD, which is considered to be a potentially serious heart malformation. Specifically, the occurrence of VSD results in incomplete formation of the partition between the ventricles of the heart under certain conditions, thus allowing mixing of arterial and venous blood.

We believe that the various teratogenic effects, especially VSD, to be previously unknown and to possibly represent substantial risk within the meaning of TSCA Section 8(e), and therefore report them to the Agency under this FYI submission. Although the effect observed in a Reproductive Toxicity study may meet the "Substantial Risk" criteria for submittal in accordance with Section 8(e) of TSCA, SCAI does not manufacture, process or distribute in commerce the chemical in question, and therefore believes that they have no responsibility to submit a Section 8(e) notice under the Act. Nevertheless, the effect observed for the subject chemical was both serious and in SCAI's judgement not previously known. Therefore, SCAI believes that EPA is interested in these results.

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It should be noted that although MAK did not cause fetal malformations or variations of any kind at doses up to and including 1,000 mg/kg, the highest does used, ataxia was observed in the dams. The only fetal effect observed was a slight (6-8%) reduction in the rate of weight gain at 1000 mg/kg in the presence of maternal toxicity. These symptoms, including ataxia and reduced body weight gain, are not believed by SCAI to represent substantial risk findings; nevertheless, they are also included in this report as part of the FYI.

To elaborate, the terms "ataxia" and "ataxic gait" are broad descriptors that are used non-specifically for any apparent abnormality in locomotion and/or other neuromuscular effects related to presumed central nervous system or peripheral nervous system damage. Therefore, the use of this term and its application to TSCA section 8(e) reporting requirements necessitates interpretation with caution. Studies by Johnson et al. (1978, 1979) and Lynch et al. (1981) reported that no neurotoxic effects were observed in rats or monkeys exposed via inhalation of up to 1,025 ppm MAK for 6 hrs/day, 5 days/week, over 9-10 months. Because SCAI considers that ataxia in the absence of observations of other neurotoxic symptoms is of limited meaning, SCAI does not consider the observation of "ataxic gait" in the present study to be reportable. However, it is provided here for the purpose of completeness.

The summary of the above study is enclosed for the Agency's review. Please contact the undersigned at (212) 572-8210 if you have further questions.

Sincerely,

SUMITOMO CHEMICAL AMERICA, INC.



Ikuzo Ogawa  
Manager, Planning & Commercial Development  
Specialty Chemicals

IO/ah  
Enclosures

References:

Johnson, B.L., J.V. Setzer, T.R. Lewis, and R.W. Hornung. 1978. An electrodiagnostic study of the neurotoxicity of methyl n-amyl ketone. *Am. Ind. Hyg. Assoc. J.* 39: 866-872.

Johnson, B.L., W.K. Anger, J.V. Setzer, D.W. Lynch, and T.R. Lewis. 1979. Neurobehavioral effects of methyl n-butyl ketone and methyl n-amyl ketone in rats and monkeys: A summary of NIOSH investigations. *J. Environ. Pathol. Toxicol.* 2: 113-133.

Lynch, D.W., T.R. Lewis, W.J. Moorman, H.B. Plotnich, R.L. Schuler, A.W. Smallwood, and C. Kommineni. 1981. Inhalation toxicity of methyl-n-amyl ketone (2-heptanone) in rats and monkeys. *Toxicol. Applied Pharmacol.* 58 (3): 341-352.

**Contains No CBI**

**Summary of A Pilot Teratology Study of 2-Heptanone  
Administered Orally to Rats**

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**Sumitomo Chemical Co., Ltd.  
Environmental Health Science Laboratory**

**August 17, 1993**

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**<MATERIAL & METHODS>**

2-Heptanone (purity: 99.8% or 99.7%) was administered orally at dose levels of 100, 250, 500 and 1000mg/kg to pregnant Crj:CD(SD) rats (12 to 13 dams per group) on days 6 to 15 of gestation. Methyl 3-methoxypropionate (MMP, purity: more than 99%) was administered orally at 1000mg/kg as a comparative control.

Dosing solutions for the 100, 250 and 500mg/kg groups of 2-heptanone were prepared by dilution of 2-heptanone in corn oil, and undiluted 2-heptanone or MMP was administered in the 1000mg/kg groups. Corn oil was administered as a negative control.

A dosing volume of 1 ml/kg body weight was used, except for the 1000mg/kg group of 2-heptanone, in which specific gravity of 2-heptanone (0.82) was taken into account. Doses administered to each animal were based on the body weight on day 6 of gestation.

Dams were observed daily for mortality and clinical signs. Maternal body weight was measured on days 0, 6, 9, 12, 15 and 20, and food consumption over a one day period on days 6, 9, 12, 15, and 20 of gestation. On day 20 of gestation, dams were sacrificed. The gravid uterus was weighed, the numbers of corpora lutea, implantations, live fetuses and dead embryos /fetuses were counted, and the time of death of each dead embryo /fetus was examined. Each live fetus was weighed, sexed and externally examined including the oral cavity. Approximately 1/2 of all fetuses from each litter were examined for skeleton and number of ossified sacrococcygeal vertebral bodies. The remaining live fetuses were examined for visceral organs.

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## &lt;RESULTS&gt; (Table)

1. There was no treatment-related maternal death in any of the groups.

2. In the 2-heptanone groups, ataxic gait was found in the 500mg/kg and higher groups, and bradypnea, lacrimation and prone position were found in the 1000mg/kg group.

Salivation was found in the 250mg/kg and higher groups of 2-heptanone and in the 1000mg/kg group of MMP. It was considered that this was attributable to the taste or irritation of the test substances.

3. Body weight gain during administration period was decreased in the 1000mg/kg group of 2-heptanone. Mean body weight and food consumption were not affected by the test substance.

In the MMP group, no effect was found on mean body weight, body weight gain and food consumption.

4. Autopsy findings on day 20 of gestation were not affected by both compounds.

5. Neither compounds affected the numbers of corpora lutea, implantations and live fetuses, the sex ratio and the embryonic/fetal mortality.

6. In terms of fetal growth, the live fetal body weight and the number of ossified sacroccosygeal vertebral bodies were decreased in the 1000mg/kg groups of 2-heptanone and MMP. They were decreased greater in the MMP group than in the 2-heptanone group.

7. In the 2-heptanone groups, there were neither treatment-related anomalies nor variations in external, visceral and skele-

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tal examinations.

On the other hand, in the MMP group, the incidences of fetuses with ventricular septal defect (malformation), wavy ribs (minor anomaly), 27 presacral vertebrae and thymic remnant in neck (variations) were increased. The incidence of 14th ribs tended to be high.

Thus, oral administration of 2-heptanone exhibited in toxic signs in dams such as ataxic gait at 500mg/kg and higher, and the decreased maternal body weight gain at 1000 mg/kg. Although fetal growth retardation was found, 2-heptanone revealed no embryo lethality and teratogenicity even at the maternal toxic dose level of 1000mg/kg.

MMP produced ventricular septal defect and remarkable fetal growth retardation, though it exhibited no maternal toxicity. Thus, MMP is teratogenic.

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<Table>

Dose Levels(mg/kg/day)	Control	2-Heptanone				MMP
	0	100	250	500	1000	1000
No. of Animals						
No. of Copulated	13	13	13	13	13	13
No. of Non-pregnant	1	1	0	1	1	0
No. of Dead	0	0	1 <sup>a)</sup>	1	1	4
No. of Pregnant Alive	12	12	12	11	11	9
<hr/>						
Clinical Signs						
Abnormal Respiratory Sound	—	○	—	○	○	○
Salivation	—	—	○	○	○	○
Lacrimation	—	—	—	○	○	○
Ataxic Gait	—	—	—	○	○	○
Bradypnea	—	—	—	○	○	○
Prone Position	—	—	—	—	○	○
Attachment of Reddish Material Around Vagina	—	—	○	—	—	—
Body Weights						
Body Weight Gains	—	—	—	—	—	—
Gravid Uterine Weights	—	—	—	—	↓ <sup>b)</sup>	—
Terminal Body Weights <sup>c)</sup>	—	—	—	—	—	—
Food Consumption	—	—	—	—	—	—
Autopsy Findings						
Esophagus: Cystic Formation	—	—	—	⊙	—	—
Thymus : Intracapsular Hemorrhage	—	—	—	⊙	—	—
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Litter Data						
No. of Corpora Lutea	18.5	17.3	17.9	18.5	17.5	18.1
No. of Implantations	14.7	15.6	15.8	15.2	16.0	16.1
% of Embryonic Deaths	4.5	5.9	8.5	9.0	6.8	4.1
Sex Ratio (male/alive)	40	41	54	58*	51	49
Body Weights of Fetus ♂	3.80	3.80	3.72	3.77	3.50**	2.98**
♀	3.58	3.58	3.55	3.59	3.38**	2.86**

\* : [Significantly different from control group (P<0.05) ]

\*\* : [Significantly different from control group (P<0.01) ]

— : [No abnormal sign] or [Not significantly different from control group]

○ : Clinical sign observed

⊙ : Autopsy finding observed

a) : Moribund sacrifice

b) : Significantly decreased during days 9 to 15 of gestation

c) : Body weight on day 20 of gestation minus gravid uterine weight

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(Continued)

No. of Examined for External Abnormalities	168	176	173	152	164	139
No. with Malformations	0	1	0	0	0	0
Cleft palate		1(0.6)				
No. of Examined for Skeletal Abnormalities	88	89	89	81	85	72
No. with Malformations	0	0	0	0	0	0
No. with Minor Anomalies	0	0	0	0	0	6
Wavy Ribs Curvature of Humerus						6(8.3)* 1(1.4)
No. with Variations	13	12	11	8	14	41
27 Presacral Vertebrae		2( 2.2)			1(1.2)	3( 4.2)*
Cervical Ribs					1(1.2)	5( 6.9)
Thoracic Vertebral Bodies						1( 1.4)
:Not-ossified						10(13.9)*
:Bipartite		1( 1.1)			2( 2.4)	4( 5.6)*
:Displacement						2( 2.8)
Lumber Vertebral Bodies						3( 4.2)*
:Not-ossified						
:Bipartite		1( 1.1)				
Sacrococcygeal Vertebral Bodies						
:Not-ossified						1( 1.4)
14th Ribs	13(15.1)	11(12.4)	11(12.4)	8(9.9)	12(14.1)	29(40.3)
Ossification <sup>d)</sup>						
♂	7.9	7.8	7.9	7.8	7.5*	6.0**
♀	7.6	7.6	7.7	7.7	7.5	5.5**

\* : [Significantly different from control group (P<0.05) ]

\*\* : [Significantly different from control group (P<0.01) ]

Figures in the parenthesis indicate incidence(%)

d): No. of ossified Sacrococcygeal vertebral bodies

(Continued)

No. of Examined for Visceral Abnormalities	82	86	84	71	79	67
No. with Malformations	2	3	0	0	5	12
Ventricular Septal Defect	2( 2.4)	3( 3.5)			5(6.3)	11(16.4)*
Interruption of Aortic Arch						1( 1.5)
Aberrant Right Subclavian Artery						2( 3.0)
Double Descending Aorta						1( 1.5)
No. with Minor Anomalies	2	1	2	2	3	0
Abnormal Bifurcation of Pulmonary Artery	2( 2.4)	1( 1.4)	2( 2.4)	2( 2.8)	3( 3.8)	
No. with Variations	30	21	24	24	18	32
Thymic Remnant in Neck		1( 1.2)	3( 3.6)	1( 1.4)	3( 3.8)	16(25.9)*
Raised Area in Liver					1( 1.3)	
Tortuosity of Ureter	27(32.9)	19(22.1)	20(23.8)	22(31.0)	14(17.7)	12(17.9)
Dilation of Ureter	12(14.6)	7( 8.1)	12(14.3)	18(25.4)	3( 3.8)	10(14.9)
Persistent Left Umbilical Artery		1( 1.2)		1( 1.4)		1( 1.5)

\* : [Significantly different from control group (P<0.05) ]

\*\* : [Significantly different from control group (P<0.01) ]

Figures in the parenthesis indicate incidence(%)