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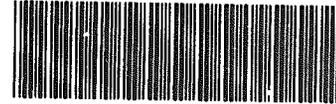
June 13, 1997

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Contains No CBI

Document Processing Center (TS-790)
(Attn: Section 8(e) Coordinator)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

Re: TSCA Section 8(e) Reportable Information



88970000204

Dear Sir or Madam:

Enclosed please find a completed TSCA Health & Safety Study Cover Sheet and audited draft report derived from a developmental toxicity study, conducted on behalf of the fragrance materials industry, entitled "Oral (Gavage) Developmental Toxicity Study of Musk Ketone in Rats." This submission is made in accordance with reporting responsibilities under Section 8(e) of the Toxic Substances Control Act, and is still under review by the sponsor. This submission is made within the fifteen day reporting time-frame provided by the statute. 15 U.S.C. § 2607(e).

The study evaluated the developmental toxicity of musk ketone at 3 dosage levels: 15, 45 and 150 mg/kg/day. The test article was not selectively toxic to development based on the study results, as it showed a maternal no-observable-adverse-effect-level (NOAEL) of 15 mg/kg/day and a developmental NOAEL of 45 mg/kg/day. The developmental findings indicated no gross external, soft tissue or skeletal malformations that could be attributed to the test article. However, at a dosage of 150 mg/kg/day, statistically significant ($p \leq 0.01$) decreases in fetal body weight and statistically significant ($p \leq 0.05$) increases in the litter averages for total and early resorptions, as compared to the concurrent control group incidences and historical experience, were observed.

Consistent with EPA's current interpretation of Section 8(e), the observed results would appear to be reportable; however, we believe that these findings do not present any real

June 13, 1997

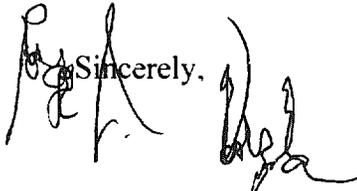
Page 2

indication of potential for "substantial risk of injury to health." In view of the perspective of the entire study, the seriousness of the noted effect is highly doubtful.

Developmental toxicity studies are designed to show some toxicity at the highest dose, but not to cause mortality or loss of the pregnancy, if possible. No abortions, premature deliveries or deaths occurred during the study. Only the highest dosage, 150 mg/kg/day, was associated with the noted statistically significant effects on fetal development. This finding is not considered to represent a selective toxic effect on development because it occurred only at maternally toxic dosages. It is well known that adverse maternal health contributes to adverse effects of growth, physical development and viability of the embryo and fetus.

Moreover, the statistically significant effects on development, noted in the rat study, are not significant in terms of the risk assessment of musk ketone under expected exposure conditions for humans. Musk ketone is used as a fragrance ingredient. Exposure of humans to musk ketone in cosmetic products has been conservatively estimated to provide a systemic exposure of 0.025 mg/kg/day. Thus, the exposure level of 45 mg/kg/day, the developmental NOAEL, represents an 1800-fold margin of exposure over that expected under conditions of actual use in humans. Accordingly, there is no basis to extrapolate any of the noted findings to conditions of exposure for humans.

Should you have questions or concerns regarding this submission, please feel free to contact me.

Sincerely,


Roger J. Marzulla

Enclosures

TSCA CBI STATUS:

CHECK IF THIS PAGE CONTAINS CONFIDENTIAL BUSINESS INFORMATION (CBI)

Clearly mark the confidential information with bracketing and check the box in the appropriate section (Contains CBI).
 Submit a sanitized cover sheet with CBI deleted. Mark the sanitized copy, "Public Display Copy" in the heading.

1.0 SUBMISSION TYPE <input type="checkbox"/> Contains CBI <input type="checkbox"/> 8(d) <input checked="" type="checkbox"/> 8(e) <input type="checkbox"/> FYI <input type="checkbox"/> 4 <input type="checkbox"/> OTHER: Specify _____ <input checked="" type="checkbox"/> Initial Submission <input type="checkbox"/> Follow-up Submission <input type="checkbox"/> Final Report Submission Previous EPA Submission Number or Title if update or follow-up: _____ Docket Number, if any: # _____ <input type="checkbox"/> continuation sheet attached										
2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e): optional for 8(d), 8(d) & FYI) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID N/A	2.3 FOR EPA USE ONLY								
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY <input type="checkbox"/> Contains CBI <p align="center"><i>Reported Chemical Name (specify nomenclature if other than CAS name):</i></p> CAS# <u>81 - 14 - 1</u> 1-[4-(1,1-dimethylethyl) - 2, 6-dimethyl-3, 5-dinitrophenyl] - Ethanone Purity _____ % <input checked="" type="checkbox"/> Single Ingredient <input type="checkbox"/> Commercial/Tech Grade <input type="checkbox"/> Mixture <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;"></td> <td style="width: 30%; text-align: center;"><i>Trade Name:</i></td> <td style="width: 30%; text-align: center;"><i>Common Name:</i> Musk ketone</td> </tr> <tr> <td></td> <td style="text-align: center;"><i>CAS Number</i></td> <td style="text-align: center;"><i>NAME</i> <i>% P/EIGHT</i></td> </tr> </table> Other chemical(s) present in tested mixture: N/A <input type="checkbox"/> continuation sheet attached				<i>Trade Name:</i>	<i>Common Name:</i> Musk ketone		<i>CAS Number</i>	<i>NAME</i> <i>% P/EIGHT</i>		
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	<i>CAS Number</i>	<i>NAME</i> <i>% P/EIGHT</i>								
4.0 REPORT/STUDY TITLE <input type="checkbox"/> Contains CBI Protocol 1318.003 Oral (Gavage) developmental toxicity study of musk ketone in rats Draft summary of study attached. <input type="checkbox"/> continuation sheet attached										
5.1 STUDY/TSCATS INDEXING TERMS [CHECK ONE] HEALTH EFFECTS (HE): <input checked="" type="checkbox"/> ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____										
5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes) <table style="width: 100%; border: none;"> <tr> <td style="width: 25%;">STUDY TYPE: <u>TERE</u></td> <td style="width: 25%;">SUBJECT ORGANISM (HE, EE only): <u>RATS</u></td> <td style="width: 25%;">ROUTE OF EXPOSURE (HE only): <u>GAVG.</u></td> <td style="width: 25%;">VEHICLE OF EXPOSURE (HE only): <u>CORN OIL</u></td> </tr> <tr> <td>Other: _____</td> <td>Other: _____</td> <td>Other: _____</td> <td>Other: _____</td> </tr> </table>			STUDY TYPE: <u>TERE</u>	SUBJECT ORGANISM (HE, EE only): <u>RATS</u>	ROUTE OF EXPOSURE (HE only): <u>GAVG.</u>	VEHICLE OF EXPOSURE (HE only): <u>CORN OIL</u>	Other: _____	Other: _____	Other: _____	Other: _____
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Other: _____	Other: _____	Other: _____	Other: _____							
6.0 REPORT/STUDY INFORMATION <input type="checkbox"/> Contains CBI <input checked="" type="checkbox"/> Study in GLP Laboratory <u>Argus Research Laboratories, Inc.</u> Report/Study _____ Date <u>May 28, 1997 (draft)</u> Source of Data/Study Sponsor (if different than submitter) <u>Research Institute for Fragrance Materials, Inc.</u> Number of pages _____ <input type="checkbox"/> continuation sheet attached										
7.0 SUBMITTER INFORMATION <input type="checkbox"/> Contains CBI Submitter: <u>Roger J. Marzulla, Esq.</u> Title: <u>Counsel</u> Phone: (<u>202-887-4001</u>) Company Name: <u>Fragrance Materials Assn.</u> Company Address: <u>1620 I Street, NW, Ste. 925 Washington, DC 20006</u> _____ Submitter Address (if different): <u>1333 New Hamp. Av., NW Washington, DC 20036</u> Technical Contact: <u>Emil A. Pfitzer, ScD</u> Phone: (<u>201-488-5527</u>) <input type="checkbox"/> continuation sheet attached										
8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS <input type="checkbox"/> Contains CBI See attached cover letter. <input type="checkbox"/> continuation sheet attached										

Submitter Signature: _____

Date: 6/13/97

* Continuation of answer to Question 4.0

TITLE: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF MUSK KETONE IN RATS

ARGUS RESEARCH LABORATORIES, INC., PROTOCOL NUMBER: 1318-003

I. SUMMARY AND CONCLUSION

A. Methods

Twenty-five Cr:CD@BR VAF/Plus@ (Sprague-Dawley) presumed pregnant female rats were assigned to each of four dosage group (Groups I through IV). The test article, musk ketone, or vehicle, Mazola@ Corn Oil, was administered orally (via gavage) once daily to female rats on days 7 through 17 of presumed gestation (DGs 7 through 17). Dosages of 0 (Vehicle), 15, 45 and 150 mg/kg/day of the test article were administered at a dosage volume of 5 mL/kg, adjusted daily on the basis of the individual body weights recorded before intubation. The rats were intubated once daily at approximately the same time each day.

The female rats were observed for viability at least twice each day of the study. The rats were also examined for clinical observations of effects of the test article, abortions, premature deliveries and deaths before and approximately one hour after dosage. These observations were also conducted once daily during the postdosage period (DGs 18 through 20). Body weights were recorded on DG 0 and daily during the dosage and postdosage periods. Feed consumption values were recorded on DGs 0, 7, 10, 12, 15, 18 and 20.

All rats were sacrificed by carbon dioxide asphyxiation on DG 20, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The number of corpora lutea in each ovary was recorded. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions.

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- a. Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in APPENDIX C (PROTOCOL AND AMENDMENT).

Each fetus was weighed and examined for sex and gross external alterations. Approximately one-half of the fetuses in each litter were examined for soft tissue alterations. The remaining fetuses in each litter were eviscerated and examined for skeletal alterations.

B. Results

No abortions, premature deliveries or deaths occurred during the study. All rats survived until scheduled sacrifice.

Increased incidences of dried feces and perioral substance occurred in the 45 mg/kg/day dosage group; these two adverse clinical observations, as well as urine-stained abdominal fur, excessive salivation, dehydration, red substance (presumably blood) on forepaws and tremors occurred in significantly increased numbers ($p \leq 0.01$) in the 150 mg/kg/day dosage group rats, and one or two 150 mg/kg/day dosage group rats also had chromorrhinorrhea or chromodacryorrhea. Effects were first observed on gestation days (DGs) 13 and 7 in the 45 and 150 mg/kg/day dosage groups, respectively. Urine-stained abdominal fur, perioral substance, dehydration and dried feces continued to occur in a few 150 mg/kg/day dosage group rats during the postdosage period (DGs 18 to 20).

Dosage-dependent, statistically significant ($p \leq 0.05$ to $p \leq 0.01$) reductions in weight gains and absolute (g/day) and relative (g/kg/day) feed consumption values for the entire dosage period (calculated as DGs 7 to 18) occurred in the 45 and 150 mg/kg/day dosage groups. These effects of the test article were most severe on DGs 7 to 10, when significant weight loss ($p \leq 0.01$) occurred in the 150 mg/kg/day dosage group. These two dosage groups had significant increases ($p \leq 0.05$ to $p \leq 0.01$) in body weight gains and absolute and relative feed consumption values after completion of the dosage period (DGs 18 to 20), rebound phenomena that commonly occur in these types of studies. Despite these rebound phenomena, body weight gains and absolute and relative feed consumption values for the entire period after initiation of dosage (DGs 7 to 20) and for the entire pregnancy (DGs 0 to 20) were reduced or significantly reduced ($p \leq 0.05$ to $p \leq 0.01$) in the 45 and 150 mg/kg/day dosage groups. Body weights were generally significantly reduced ($p \leq 0.05$ to $p \leq 0.01$) on DGs 8 through 20 in the 45 and 150 mg/kg/day dosage groups.

Pregnancy incidences were comparable in the four dosage groups, and there were adequate numbers of litters with live fetuses for evaluation.

The 150 mg/kg/day dosage was associated with increased postimplantation loss [evident as significant increases ($p \leq 0.05$) in the litter averages for total and early

resorptions, a tendency for increased late resorptions and percentage of resorbed conceptuses per litter, and increased numbers of dams with any resorptions or with all conceptuses dead or resorbed] and significantly reduced ($p \leq 0.01$) fetal body weight. The values for the various parameters identifying postimplantation loss generally exceeded the historical ranges of the Testing Facility but were not sufficiently severe to result in statistically significant or biologically important differences in live litter size. No dosage-dependent, statistically significant or biologically important differences occurred in the litter averages for corpora lutea, implantations or percent male fetuses. Two 150 mg/kg/day dams had litters consisting of only resorbed conceptuses. There were no dead fetuses. All placentas appeared normal except those of a 150 mg/kg/day dosage group dam that had peripartum bleeding, which appeared pale.

All gross external, soft tissue and skeletal malformations and variations in the fetuses were considered unrelated to the test article.

Analytical studies identified that the concentrations of the test article used in this study were prepared accurately, and that the two lowest concentrations were stable stored at room temperature for eight days.

C. Conclusion

The maternal no-observable-adverse-effect-level (NOAEL) for musk ketone is 15 mg/kg/day. The 45 and 150 mg/kg/day dosages were toxic to the dams resulting in adverse clinical observations and reductions in maternal body weight gains, body weights and absolute and relative feed consumption values.

The developmental NOAEL for musk ketone is 45 mg/kg/day. The 150 mg/kg/day dosage was associated with increased postimplantation loss (total and early resorptions) and reduced fetal body weight.

Based on these data, musk ketone is not selectively toxic to development. Adverse effects on embryo-fetal development (postimplantation loss and reduced fetal body weight) occurred only at the higher of two dosages that were toxic to the dams.

Mildred S. Christian, Ph.D., ATS Date
Executive Director of Research

Alan M. Hoberman, Ph.D., DABT Date
Director of Research

Robert M. Parker, Ph.D., DABT Date
Senior Scientist and Study Director

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