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- CERTIFIED MAIL -

October 15, 1993

8EHQ-93-12732
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Document Processing Center (TS-790)
Office of Pollution Prevention & Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington D.C. 20460

Attention: TSCA 8 (e) Coordinator

Dear Sir or Madam:

This is to advise you of a 28-day Subacute Inhalation Study of which we became aware on October 12, 1993.

The study on Fluorobenzene (CAS #462-06-6), conducted in Europe, was designed to evaluate the subacute toxicity in rats after administration by inhalation for twenty-eight consecutive days. Mean achieved atmospheric concentrations were 0.37, 1.50 and 6.25 mg/l.

No mortality and no treatment-related macroscopic abnormalities were observed. The observed effect of concern was the increased liver weight and histopathological findings of centrilobular hepatocyte enlargement in the liver and accumulation of eosinophilic material in the renal proximal tubular epithelium of high dose male rats.

The summary provided to us is attached. We will forward any follow-up information that we receive for your review.

If you have questions, please contact me at

Yours very truly,

RECEIVED
11-23-93

SafePharm Laboratories Ltd.

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Derby DE1 2BT England
Telephone Derby (0332) 782896
Telex 377079 SAFPHM G
Fax Derby (0332) 799018

Date 24 September 1993

Your ref.

Our ref. LJC/JAB-ADMIN-56

EINGEGANGEN
Leitung-LC
27. SEP. 1993
Er.....

FLUOROBENZENE:
TWENTY-EIGHT DAY SUB-ACUTE (NOSE-ONLY) INHALATION TOXICITY STUDY IN THE RAT
PROJECT NUMBER: 121/194

The above study is now complete, with the exception of full histopathology results, and a preliminary summary is given below. A full draft report will be prepared when histopathology examinations are completed.

The test material was administered by nose only inhalation to three groups, each of five male and five female Sprague-Dawley CD strain rats for twenty-eight consecutive days at target atmosphere concentrations of 0.4, 1.5 and 6.0 mg/l (the mean achieved atmosphere concentrations were 0.37, 1.50 and 6.25 mg/l). A control group of five males and five females was exposed to air only.

SUMMARY OF RESULTS

Mortality

There were no deaths during the study.

Clinical Observations

Incidents of red/brown staining of the external body surface were detected in all groups together with wetness of the fur. These are normal findings associated with the restraint procedure and are not indicative of toxicity.

...contd...

Clinical Observations (contd)

High dose animals however, showed signs of hunched posture and pilo-erection on removal from the chamber from Day 7 onwards. The incidence of these observations increased as the study progressed and by Day 24 all animals in this exposure group were showing hunched posture and pilo-erection both prior to exposure and on removal from the chamber. Possible respiratory pattern changes were also noted in individual animals from Day 10 to Day 17 but these were no longer apparent over the latter part of the study.

Intermediate dose animals showed similar observations to those in the highest exposure group with hunched posture and pilo-erection apparent from Day 21 onwards.

No clinically observable signs of toxicity were detected in the lowest exposure group.

Neurotoxicity Functional Observations

There was no evidence of significant neurotoxicity.

Bodyweight

No adverse effects on bodyweight gain were detected.

Food Consumption

No adverse effects on food consumption were detected.

Water Consumption

No overt intergroup differences were detected.

Haematology

No treatment-related effects were detected.

Blood Chemistry

No treatment-related effects were detected.

Fluoride Analysis

A substantial increase in fluoride levels was detected in the pooled teeth and sternum samples from all treatment groups in comparison with controls and a clear dose relationship was apparent.

...contd...

Urinalysis

No treatment-related effects were detected.

Necropsy

No treatment-related macroscopic abnormalities were detected.

Organ Weights

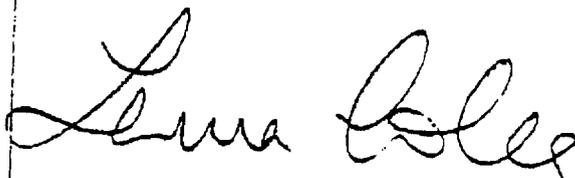
A statistically significant increase in absolute and relative liver weight was detected in intermediate and high dose males and relative liver weights were elevated for high dose females in comparison with controls. Kidney weights relative to bodyweight showed a statistically significant increase in high dose males with one value outside of the normally expected range.

No treatment-related effects were detected at the low dose.

Histopathology

Microscopic examination of control and high dose tissues has revealed centrilobular hepatocyte enlargement in the liver and accumulations of eosinophilic material in the renal proximal tubular epithelium of high dose male rats. It will therefore be necessary to examine liver and kidney sections from the low and intermediate dose groups. I would be most grateful if you could approve the additional histopathology, by fax, as soon as possible; the cost of this extra work will be £430.

Yours sincerely,



L.J. Coles B.Sc. (Hons)

DEPUTY STUDY DIRECTOR

This summary has been subject to some checking procedures during preparation but it has not been inspected by the Safepharm Quality Assurance Unit. We reserve the right to make any necessary amendment during production of the final report.

CHCATS DATA:

Submission # BEHQ-1093-12732(5) EU A

TYPE: INT SUPP FLWP

SUBMITTER NAME: Confidential

CHCATS TRIAGE TRACKING DBASE ENTRY FORM

INFORMATION REQUESTED: FLWP DATE:

- 0501 NO INFO REQUESTED
- 0502 INFO REQUESTED (TECH)
- 0503 INFO REQUESTED (VOL ACTIONS)
- 0504 INFO REQUESTED (REPORTING RATIONALE)
- DISPOSITION:
- 0670 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: 10/15/93 OTS DATE: 10/21/93 CSRAD DATE: 11/23/93

CHEMICAL NAME:

CASE
462-06-6

INFORMATION TYPE:

		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:

		P F C
0216	EPICLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECOAQUA TOX	01 02 04
0221	ENV. OCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQUEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0229	METAB/PHARMACO (ANIMAL)	01 02 04
0230	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:

		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEMPHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLAS'IO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PRODUSE/PROC	01 02 04
0251	MSDS	01 02 04
0259	OTHER	01 02 04

TRIAGE DATA:

NON-CRI INVENTORY

YES (CONTINUE)
NO (DROP)
IN FLAMING

ONGOING REVIEW

YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES

RAT

TOXICOLOGICAL CONCERN:

LOW
MED
HIGH

Subacute Inhalation

USE:

Toxicity

PRODUCTION:

REMARKS: Non-CRI
Subacute inhalation toxicity in the rat is low concern based on increased liver weight and centrilobular hepatocyte enlargement in the liver and accumulation of eosinophilic material in the renal proximal tubular epithelium.
Rats (5 males and 5 females) were each dosed (nose only) at mean concentrations of 0.37, 1.50, or 6.25 g/m³ for 28 consecutive days. No deaths occurred.
(over)

of eosinophilic material in the males. The liver and kidneys of

Centriobular hepatocyte enlargement and accumulations renal proximal tubular epithelium occurred in high dose low and intermediate dose rats were not examined.

Group	Sex	Age	Weight	Organ	Observations
1	Male	10 weeks	200g	Liver	Centriobular hepatocyte enlargement
1	Male	10 weeks	200g	Kidney	Renal proximal tubular epithelium
2	Female	10 weeks	180g	Liver	Centriobular hepatocyte enlargement
2	Female	10 weeks	180g	Kidney	Renal proximal tubular epithelium
3	Male	10 weeks	210g	Liver	Centriobular hepatocyte enlargement
3	Male	10 weeks	210g	Kidney	Renal proximal tubular epithelium
4	Female	10 weeks	190g	Liver	Centriobular hepatocyte enlargement
4	Female	10 weeks	190g	Kidney	Renal proximal tubular epithelium
5	Male	10 weeks	205g	Liver	Centriobular hepatocyte enlargement
5	Male	10 weeks	205g	Kidney	Renal proximal tubular epithelium
6	Female	10 weeks	185g	Liver	Centriobular hepatocyte enlargement
6	Female	10 weeks	185g	Kidney	Renal proximal tubular epithelium
7	Male	10 weeks	215g	Liver	Centriobular hepatocyte enlargement
7	Male	10 weeks	215g	Kidney	Renal proximal tubular epithelium
8	Female	10 weeks	195g	Liver	Centriobular hepatocyte enlargement
8	Female	10 weeks	195g	Kidney	Renal proximal tubular epithelium
9	Male	10 weeks	208g	Liver	Centriobular hepatocyte enlargement
9	Male	10 weeks	208g	Kidney	Renal proximal tubular epithelium
10	Female	10 weeks	188g	Liver	Centriobular hepatocyte enlargement
10	Female	10 weeks	188g	Kidney	Renal proximal tubular epithelium