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CIBA-GEIGY

EXPRESS MAIL
RETURN RECEIPT REQUESTED

8EHQ-1292-8530
CONTAINS NO CBI

September 30, 1992

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

RE.: TSCA Section 8(e) Notice: Cresyl Glycidyl Ether

Dear Madam or Sir:

CIBA-GEIGY Corporation claims no information in this letter or the enclosed study as Confidential Business Information.

In accordance with the Environmental Protection Agency's (EPA) March 16, 1978 policy statement on Section 8(e) reporting under the Toxic Substances Control Act and EPA's June, 1991 TSCA Section 8(e) Reporting Guide, CIBA-GEIGY Corporation wishes to bring to the attention of the EPA results of a 21-day inhalation study in rats with Cresyl Glycidyl Ether (CAS Registry No. 2210-79-9).

CIBA-GEIGY Corporation currently purchases this chemical domestically and markets it under the tradename, Araldite DY-023. It is a monofunctional epoxy resin reactive diluent, which is used to lower the viscosity of paints, coatings, etc..

The instant study was conducted in 1978 by the toxicology laboratories of CIBA-GEIGY Limited in Basel, Switzerland. CIBA-GEIGY Corporation recently received a copy of the study, and are now submitting it to EPA.

In a 21-day inhalation study with rats, male and female animals were exposed to concentrations of 0, 53 152, and 305 mg/m³. At the highest concentration employed, changes in body weight gain and food consumption were statistically significant compared to the control and six male and nine female animals died, with the first deaths occurring on day 6 of exposure.

The animals had acute congestion and occasional hemorrhaging in the myocardium, lungs, liver, kidney, adrenal, ovaries, and the brain. All rats displayed marked congestion of the nasal mucosa with purulent inflammation and ulceration and showed a depletion



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109 pgs



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of thymocytes in the thymus. Furthermore, 5 of 10 male rats showed reduced spermatogenesis. However, 3 of these 5 males died during exposure.

The 152 mg/m³ concentration caused similar acute effects as the 305 mg/m³ dose, although only 1 of 10 males appeared to have some spermatogenesis reduction. At the 53 mg/m³ concentration, the reduction in food consumption and body weight gain was still statistically significant.

Since there did not appear to be a NOEL at the lowest concentration used, the NOEL is less than 53 mg/m³. A copy of the study, entitled "TK 10'410, 21-Day Aerosol Inhalation Study in Rats," dated December 5, 1978, is enclosed.

CIBA-GEIGY Corporation will revise its Material Safety Data Sheet and label to reflect this new information and notify its workers and customers in accordance with the OSHA Hazard Communication Standard (29 CFR 1910.1200).

Please contact the undersigned if you need additional information.

Very truly yours,

A. Di Battista

Anthony Di Battista
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Toxicology, Regulatory Auditing & Compliance

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Enclosures

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SUMMARY AND ASSESSMENT

Test compound	TK 10'410
Batch No.	605 497
Test species	RAI f SPF rats (RA 25)
No. of animals per experimental group	10 males, 10 females
Route of exposure	inhalation (head exposure)
Concentration levels	0 mg/m ³ (Control) - group 1
	53 ± 4 mg/m ³ - group 2
$\bar{X} \pm SD$	152 ± 4 mg/m ³ - group 3
	305 ± 10 mg/m ³ - group 4
Duration of test	21 days
Follow up period	21 days (from control and group 3)
Starting date	11th January 1978
Termination date	22nd February 1978

Reaction to treatment may be summarised as follows:

At 305 ± 10 mg/m³

Reduction in food consumption during the first 15 days of the exposure period. Bodyweights were significantly decreased at various points during the exposure period.

Dyspnoe, exophthalmos, lateral or ventral position, bloating of the abdomen and ruffled fur were seen during the entire exposure period.

15 (6 males, 9 females) rats died during the exposure period. In all these animals acute congestion, and occasional haemorrhages in the myocardium, lungs, liver, kidneys, adrenals, pituitary, ovaries and brain were found.

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Furthermore, all rats displayed marked congestion of the nasal mucosa with purulent inflammation and ulceration. In 3 of these rats ulceration of the skin of the muzzle was also noted. All animals showed depletion of thymocytes in the thymus, 5 out of the 10 male rats showed reduced spermatogenesis and in 6 animals atrophy of the lymphoid tissue of the spleen was observed.

The organ weights, organ to body weight and organ to brain weight ratios of the animals sacrificed at termination of the treatment period were changed according to the lower body weights of those animals.

At 152 + 4 mg/m³

Reduction in food consumption and body weight gain during the first 8 days resp. the entire exposure period.

Dyspnoe, exophthalmos and ruffled fur were observed during the exposure period.

Less pronounced congestion and purulent inflammation with ulceration of the nasal mucosa were seen in the muzzle in 6 out of 10 rats. The nasal changes proved to be reversible after a recovery period of 21 days. Of this recovery group only one out of 10 rats showed in the muzzle remnants of a partially re-epithelized ulceration, foreign body reaction and chronic inflammatory infiltration at the base. One male rat only showed arrest of spermatogenesis in one testicle. The experimental significance of this finding is doubtful since unilaterally inhibited spermatogenesis is known to occur spontaneously in rats.

At 53 + 4 mg/m³

Reduced food consumption and body weight gain of male rats between days 3 and 10. Dyspnoe, exophthalmos and ruffled fur were observed.

It can be inferred from the observations made during the above study that the "no observable effect level" is below 53 mg/m³ air for male and female rats.

December 5, 1978

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Compound: TK 10'410

TEST MATERIAL

Identification: TK 10'410
Received: November 25, 1977
Description: yellow liquid
Batch No. 605497

METHOD

Species RAI f SPF rats (RA 25)

Husbandry (except for the exposure period) air conditioned rooms (15 air changes/hours)
temperature $22 \pm 1^\circ\text{C}$
relative humidity $50 \pm 5\%$ (animal room)
groups of 5 animals per cage
(typ 3 Macrolon cages)

Food pelleted standard diet, Nafag No. 890
ad libitum

Water tap water, ad libitum

No. of animals per group 10 males, 10 females

Initial body weight 166 - 204 g

Age 5 to 6 weeks

Preparation TK 10'410, used as a concentrate
Control: tap water

Frequency of exposure once/day (6 hours), 15 treatments
(except week-ends)

Duration of test 21 days

Follow up period 21 days

Compound: TK 10'410

Route of exposure Inhalation, according to the method of Sachsse et al. (1973, 1976)*. The animals were kept separately in PVC tubes which were positioned radially around the exposure chamber.

Aerosol generation TK 10'410 was injected with the help of a "Perfusor" (B. Braun, Melsungen/Germany) at rates of 0.33, 0.94 and 1.65 ml/hr. into an air stream discharged into the exposure chamber through a spray nozzle under a pressure of 2 atm. at a rate of 10 l/min.

Control: the rats were treated with 1.65 ml/h of tap water under the same conditions as described above.

Determination of concentration + particle size distribution In the vicinity of the animals throughout the exposure time.

Concentration Gravimetrically on selectronfilters, pore size 0.2 μ m and 50 mm in diameter (Schleicher and Schuell, Feldbach/Switzerland), airflow 10 l/min., 5 times a day.

Size distribution Gravimetrically with a 4 stage Cascade Impact on selectron filters, pore size 0.2 μ m and 25 mm diameter (Schleicher and Schuell, Feldbach/Switzerland), airflow 17.5 l/min., twice a day.

Groups and Concentrations

Group	Animals		Animal Numbers		Concentration mg/m ³ , $\bar{x} \pm$ SD gravimetrically determined
	male	female	male	female	
1	10*	10*	1-10	41-50	0
2	10	10	11-20	51-60	53 \pm 4
3	10*	10*	21-30	61-70	152 \pm 4
4	10	10	31-40	71-80	305 \pm 10

*) 10 (5 males, 5 females) rats of each concentration for a 21-day recovery period.

*) K. Sachsse, L. Ullmann, G. Voss and R. Hess: Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Proceedings of the Europ. Soc. for the Study of Drug Toxicity Vol. XV, pp. 239-251, Zurich, June 1973.

K. Sachsse, L. Ullmann, K. Zbinden: Toxikologische Prüfungen von Aerosolen im Tierexperiment, "Chemische Rundschau" 29 (1976), Nr. 38, Seite 1

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Compound: TK 10'410

Observations and Records

Mortality	daily
Symptoms	daily
Food consumption	twice weekly
Body weight	daily, except weekends
Eye examination	Ophthalmic inspections were performed weekly
Temperature and humidity control in the test chamber	daily

Statistical Analysis

for others than Laboratory Investigations:

For each time point and parameter a uni-variate statistical analysis was conducted. Due to the routine manner of the analysis system parameter free methods were applied. Each treated group was compared to the control group in respect of dispersion and displacement*. In addition a trend test** was applied considering all groups.

for Laboratory Investigations:

Student's "t" test and the analysis of variance were employed to assess the significance of difference between concentration groups and controls whenever indicated.

Clinical Laboratory Investigations

Haematologic and blood chemistry measurements were carried out by standard methods on 32, respectively 33 randomised rats from the control and three concentration groups at the end of the treatment period.

*) Y. Lepage, Biometrika (1971) 58: pp. 213-217

**) H. R. Jonckheere, Biometrika (1954) 41: pp. 133-145

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Compound: TK 10'410

To reduce the biologic variability due to circadian rhythms, blood sampling for haematology and blood chemistry was between the hours of 8.00 and 9.00 a.m. For blood chemistry measurements food was withheld for 18 hours prior to blood removal.

The site of blood removal was the orbital sinus and a micro-haematocrit glass capillary tube was used.

Blood samples from each animal with the respective anticoagulant (EDTA for performing the complete blood count, 3.8 % Sodium Citrate for coagulation testing and Heparin for blood chemistry measurements) were aliquoted into individual vials.

No anaesthesia was used to restrain the animals. All blood collection was by manual restraint only.

The quantitative assay of all blood parameters was completed within an 8 hr. period under "Quality Control" conditions.

The quality control systems used in haematology and blood chemistry were as follows:

Haematology Reference Control: CH-60 Normal (Merz + Dade)
 CH-60 Abnormal " "
 4C Normal (Coulter)
 4C Abnormal " "
 PLACHECK-100 (TOA Medical)
 IL 282 CO-OXIMETER Control (Instrumentation Lab. Inc.)

Coagulation Reference Control: CI-TROL-1 (Merz + Dade)
 CI-TROL-2 " "
 CI-TROL-3 " "
 CONTROL PLASMA (Behringwerke)
 PATHOPLASMA-1 "
 PATHOPLASMA-2 "

Blood Chemistry Reference Control: MONI-TROL I (Merz + Dade)
 MONI-TROL II " "
 ENZA-TROL
 SERONORM (Nyegaard)
 LEDER-NORM (Cyanamid)
 LEDER-TROL "

Compound: TK 10'410

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RESULTS

Food Consumption and Body Weight Gain

There was a reduction in food consumption in the highest concentration group during the first 15 days of the exposure period. In the intermediate group it was reduced during the first 8 days of exposure, whereas in the low dose group it was reduced in males during days 3 to 8 only.

The body weights of the male rats of groups 3 and 4 were significantly ($p = 0.01$) decreased during the entire exposure period, whereas those of the male rats of group 2 were partially decreased ($p = 0.01$) at days 8, 9 and 10 of the test.

The body weights of the female rats of group 3 were significantly ($p = 0.01$) decreased at days 3 to 10 and 14 and 15 of the exposure period, those of the females of group 4 during days 2 to 10, whereas the female animals of group 2 only showed a significant decrease at day 9 of the exposure period.

During the recovery period the food intake and the body weight gain of the rats of group 3 was again comparable to that of the controls.

Toxic Symptoms

At the beginning of the exposure period the rats of all concentration groups showed dyspnoe, exophthalmos and ruffled fur. In addition the animals of group 4 showed lateral or ventral position and bloating of the abdomen.

During the observation period the rats of group 3 showed no toxic symptoms.

15 rats (6 males, 9 females) of group 4 died spontaneously during the exposure period.

Eye Examination

No ocular changes were seen.

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Compound: TK 10'410

Droplet Size Distribution

Droplet size distribution analysis of the chamber airborne droplets showed that 80 respectively 90 % were smaller than 7 micron in diameter (page 19).

Temperature and Relative Humidity (test chamber)

The values for the above mentioned parameters measured in the test chambers during the test period are shown in the table below:

Days	Group 1		Group 2		Group 3		Group 4	
	Humid. % RH	Temp. °C						
1	50	24	54	24	50	24	46	24
2	50	26	48	26	52	26	50	26
3	50	26	50	26	58	26	52	26
6	50	26	50	26	38	28	32	26
7	50	24	52	24	48	24	40	24
8	50	24	48	24	44	24	42	26
9	58	22	40	22	44	22	26	24
10	58	24	50	26	50	26	32	24
13	54	26	44	26	48	26	30	26
14	50	26	48	26	50	26	32	24
15	54	26	48	26	50	26	30	24
16	52	24	52	26	50	24	30	22
17	50	24	50	26	50	26	30	26
20	50	26	50	26	50	26	30	24
21	48	26	44	26	56	26	28	26
$\bar{x} \pm SD$	51/3.1	25/1.2	48/3.5	25/1.2	49/4.7	25/1.4	35/8.4	25/1.

Compound: TK 10'410

Clinical Laboratory Investigations

Haematology:

The observed haematological findings between treated rats and controls were generally unremarkable.

A slight increase in the haemoglobin concentration, packed cell volume and erythrocyte count was observed in the rats at the 305 mg/m³ concentration level. This is attributed to a slight degree of exsiccosis.

At the same concentration level a moderate shift in the differential leucocyte count occurred, i.e. a decrease in the percentage of polymorphonuclear neutrophils and increase in the percentage of lymphocytes.

Blood Chemistry:

In the assessment of blood chemistry values the findings were generally unremarkable and comparable to those of the controls.

An increase in the BUN, GOT, GPT and LDH level was observed in two out of three male rats (36 M and 37 M) at the 305 mg/m³ concentration level. Proportional changes in the electropherogram, i.e. a relative decrease of the alpha-1 and beta-2 globulin fractions was also observed in the animals at this level.

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