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ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Date: April 2, 1973

Reply to Attn of:

Subject: AC 92100, amendment of 3/15/73.

To: Mr. Lee E. TerBush, Acting Chief
Coordination Branch
Registration Division

Pesticide Petition No. 3G1340

American Cyanamid Co.
Princeton, New Jersey

Petitioner submits toxicological data requested by CDB, (letter of W. H. Morgan, 2/21/73) which were required before a final judgement of safety of the temporary negligible residues tolerance of 0.05 ppm on corn grain, fodder and forage could be made (see review of W. E. Parkin, 2/6/73).

AC 92100, S-(tert-butylthio)methyl O,O-diethyl phosphorodithioate is an extremely toxic cholinesterase inhibitor with oral LD50 values for several mammalian species running from 1.3 to about 9.2 mg/kg; only small amounts applied to the skin and eyes of rabbits (0.5 and 0.1 ml respectively) causes quick death.

Three and six month progress reports on a two year rat chronic toxicity-carcinogenicity study indicated a ChE NEL of 0.25 ppm but a systemic NEL could not be clearly demonstrated at the lowest level fed of 0.25 ppm. The alarming systemic effect in this study was the induction of exophthalmos, cloudy corneas and ruptured eyes in some of the high dose females. Exophthalmos was noted in all treated groups of females (but not in any of the males). An 11 month status report of further eye observations is submitted with the amendment and is considered below.

Other data requested by Dr. Parkin were submitted. They include:

1. A completed six month dog feeding study;
2. an addendum to the hen demyelination study previously submitted;
3. a summary of eye effects in an on-going 18 month mouse feeding study.

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A requested cataractogenic study was deemed to be unnecessary (decided in conferences of Jan. 24 and Feb. 23, 1973 with representatives of American Cyanamid).

11 Month Status Report: Eye observations - 24 month rat feeding study

Summary

Groups of 60 male and 60 female rats were offered 0, 0.25, 1.0 or 4-8-4 ppm* AC 92100 in the diet and the condition of the eyes was determined, with special attention being given to the incidence of exophthalmos, corneal cloudiness and rupture of the eyeball. Observations were made at suitable intervals from week 11 to week 50.

Results

Female rats only were affected. There appeared to be a time and dose-related incidence of the appearance of exophthalmos; at the same time, we note that control rats also showed a similar but numerically reduced incidence of this syndrome.

TABLE NO. I

% of female rats affected with exophthalmia

WK	11	12	13	14	15	19	25	32	42
Control	0.0	0.0	0.0	0.9	0.0	1.8	9.1	10.9	9.1
0.25 ppm	0.0	0.0	0.0	6.0	22.0	4.0	26.0	14.0	18.0
1.0 ppm	0.0	0.0	0.0	2.0	64.7	19.6	58.8	25.5	10.2
4-8-4 ppm*	0.0	16.7	6.6	91.7	82.6	26.1	20.5	34.1	23.3

* Dose increased to 8 ppm on day 77, but reduced back to 4 ppm on day 105 due to severe toxicity.

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Thus, the high dose group showed severe involvement fairly early (91.7% at week 14), with the middle and low dose groups showing later and less severe reaction to insult. Interestingly, the control group showed a mild but definite increase in incidence of the exophthalmos.

Other ocular damage that could be related to treatment was confined to the high dose group, with seven occurances of corneal opacity; lower dose incidences were comparable to those of the controls.

Conclusions

The bell-shaped curve in each dose level, including controls, of percent occurance of exophthalmia vs. time indicates a transient effect of the compound which increased in severity with increased dose. This could represent an adaptation/healing mechanism, or it could represent an exacerbation of an otherwise mild epizootic in the rat colony. In any event, we cannot say that a no-effect level of toxicity has been demonstrated thus far in this study insofar as the eye is concerned.

The petitioner does make a good argument that the ruptured eyeballs and opacities may be due to cholinergic effects of AC 92100 on the lacrymal glands; if these are not able to produce normal eye moisture, of course, the eyes would become severely dried and injury would naturally result.

12 Month Status on Eye Observations, 18 Month Mouse Carcinogenicity

Summary

Groups of 75 male and 75 female mice each received dietary levels of AC 92100 of 0, 0.5, 2 or 8 ppm. The eyes of all males were examined as for the rat study above at twelve months.

Results

Male Mice Only

Group	Exophthalmos	Opacities	Rupture
Control	0.0%	3.5%	0.7%
0.5 ppm	0.0	3.0	1.5
2.0 ppm	1.4	4.3	2.9
8.0 ppm	10.8	13.5	9.5

Conclusions

Only the high dose males showed ophthalmic lesions that could be attributed to AC 92100.

Addendum to Neurotoxicity Study in Hens

This addendum was submitted to demonstrate that no histopathologic lesions were induced in spinal cords of treated hens. It is satisfactory.

Final Report, Six Month Feeding Study in Dogs

(This study was initially reviewed by Dr. Parkin in his memo of 2/6/72.)

Methods

4 Male and 4 female beagles per group were fed diets containing 0, 2.5, 10 or 40 micrograms/kg body weight per day, six days per week for 26 weeks. Animals were monitored at appropriate intervals for appearance, behavior, weight changes, and hematological and biochemical parameters initially, at 4, 12 and 26 weeks.

Hematology included clotting times, WBC's, RBC's, Differential counts, Hct., sed. rate, percent retics and Hb. Clinical chemistry included determination of serum BUN, Glucose, SGOT, SGPT and Alkaline phosphatase activity. Urinalysis included estimation of pH, Sp. Gr., albumin, glucose, ketones, bile and formed elements. Special studies included the determination of plasma and RBC cholinesterase activity at -1, initially, 4, 12, and 26 weeks; brain ChE activity was measured terminally. The delta pH method of Michel was used. A thorough ophthalmological examination was performed at 3 and 6 months using atropine.

Histopathological examination was done on the following organs and tissues:

adrenals*
aorta
bone (rib junction)
bone marrow
brain
cholecyst
epididymis
eye
gonad*
heart (with coronary* vessels)
intestine
  colon
  duodenum
  jejunum
kidney*
lens
liver*
lungs
lymph node
  mesenteric
mammary glands
nerve (with muscle)
pancreas
pituitary
prostate
salivary gland
skeletal muscle (with nerve)
spinal cord
spleen
stomach
  pyloric
  fundus
thymus
thyroid
urocyst
uterus
all gross lesions

* Organ weights obtained

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Results

One control male was terminated in extremis during the 23rd week. There were no changes in any of the parameters measured that could be attributed to AC 92100.

Conclusions

The no-effect level in this study is greater 40 micrograms/kg (highest level fed) (1.6 ppm in the diet) based on ChE inhibition and systemic effects.

Conclusions and Recommendations

AC 92100 induces exophthalmia and severe eye damage in rats and mice; this is probably a result of its potent ChE inhibiting properties. In the 11 month status report such eye damage was noted (in the females only) at all levels fed, but to a lesser extent, this was also seen in the controls. We are not unduly concerned about the appearance of exophthalmos in these rats; this is a very subjective observation, and, to our knowledge no other compound has been found that induces a true exophthalmia in rats. (which would be especially useful in thyroid research). Moreover, these findings are not repeated in the mouse or dog study.

The ChE NEL is therefore demonstrated to be 1.6 ppm based on ChE effects at the six month dog feeding study.

TB therefore recommends that the temporary tolerance of 0.05 ppm negligible residues of AC 92100 and its ChE-inhibiting metabolites in or on corn grain forage and fodder be established.

We defer to CB the question of transfer of residues into meat, milk and eggs.

David Ritter 4/4/73

David L. Ritter, Pharmacologist
Toxicology Branch
Registration Division

cc: Chemistry Branch
Ecological Effects Branch
Division Reading File
Branch Reading File
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