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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

006009

JUL 20 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Parathion, Light and Electron Microscopic examination of Tissue from the Eye of Rats Completing a Two-year Feeding Study

TO: David Giamporcaro RM-79
Special Review Branch
Registration Division (TS-767)

FROM: *[Signature]* Robert P. Zendzian PhD *7/1/87*
Pharmacologist
Toxicology Branch
HED (TS-769)

THROUGH: William Burnam *[Signature]*
Deputy Chief *7/7/87*
Toxicology Branch

Compound; Parathion

Tox Chem #637

Registration #057501

Registrant; Cheminova

MRID #40887-01

Tox Project #7-0645

Action Requested

Review the following report;

Report of results of findings of electron microscopy of retina, nervus opticus, mm. recti oculi med. and lat. and m. ciliaris., H.G. Liebich, B. Vollmerhaus & F. Sinowatz, Institut fur Tieranatomie der Universitat Munchen, Bayer Project T 1016770 Parathion (Chronic toxicology long-term study in rats) DEc 22, 1986; MRID 401887-01; In translation from the German.

Conclusion

Electron microscopy of tissue from the eyes of treated rats showed compound-related toxicity in the retina and the optic nerve of males and females at 32 ppm (HDT) [NOEL 8 ppm]. Extensive age-related abnormalities in the control rats were impossible to distinguish from those in the 2 and 8 ppm

groups.

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Discussion

Parathion has been shown to produce retinal degeneration, at a dose of 50 ppm, in a two-year rat feeding study. The effect was detected by both direct observation and light microscopy. Based on this observation and a history of effects on the eyes by organophosphate cholinesterase inhibitors reported from Japan, the Agency issued a data call in notice for special studies on the toxic effects of parathion on the eye (11/27/86).

Registrant notified the Agency of a modification of an ongoing chronic rat study which will add Electroretinographic (ERG) examinations and special light and electron microscopy of the eyes of several rats/sex/dose. The Registrant contended that this additional work would satisfy at least part of the data requirements of the Agency's Data Call In Notice of November 27, 1986. This submission and a previously submitted report by Rubin (1987) are the reports of the additional work. Together they verify that the toxic effects of parathion on the eye can be detected by these methodologies and provide evidence in a second study at somewhat lower dose of 32 ppm. However they do not satisfy the Agency's need to determine if toxic effects on the eye can be produced by shorter duration of dosing. The studies presented in the DCI of 11/27/86 are still required.

Attachments

DER

Memo, Katz to Zendzian re Parathion; Chronic Feeding Study in Rats; Light and Electron Microscopic Examination Data Bayer Project T 1016770, 6/22/87

Reference

Electroretinographic evaluation, G.A. Edwards, Monsanto, R.D. No. 693, July 23, 1986, Accession # 263986

Compound Parathion

Citation

Report of results of findings of electron microscopy of retina, nervus opticus, mm. recti oculi med. and lat. and m. ciliaris., H.G. Liebich, B. Vollmerhaus & F. Sinowatz, Institut fur Tieranatomie der Universitat Munchen, Bayer Project T 1016770 Parathion (Chronic toxicology long-term study in rats) Dec 22, 1986; MRID 401887-01; In translation from the German.

Reviewed by  = 1/187
Robert P. Zendzian PhD
Pharmacologist

Core classification Acceptable

Conclusion

Electron microscopy of tissue from the eyes of treated rats showed compound-related toxicity in the retina and the optic nerve of males and females at 32 ppm (HDT) [NOEL 8 ppm]. Extensive age-related abnormalities in the control rats were impossible to distinguish from those in the 2 and 8 ppm groups.

Materials

Information on the compound tested and rat strain utilized are to be contained in the Bayer final report of study [Bayer Project T 1016770 Parathion (Chronic toxicology long-term study in the rat)].

Experimental Design

Rats for this study were selected from the survivors of a 26 month feeding study in which they were fed 0 (control, 2, 8 or 32 ppm parathion in the diet.

Five male and five female rats were selected from each treatment group. "The animals used for the examination by electro microscopy were randomly selected from the clinically healthy and ophthalmologically normal rats intended for the ERG examination."

Animals were perfused in situ in order to fix the eyes and associated tissue before dissection. "For preparation the right eye together with the Harder's gland, the ocular muscles, fatty tissue and parts of the nervous opticus were removed--" The following tissues were prepared for light and EM examination.

A = m. ciliaris
B = sector of pars optica retinae
C = sector of pars optica retinae
D = sector of pars optica retinae
E = nervus opticus
F = m. rectus oculi med.
G = m. rectus oculi lat.

Results

Compound-related toxic effects were observed in the retina and the optic nerves of the high dose males and females. Copies of the Microscopic Finding Tables; Semithin Sections - Retina atrophy and Electron microscopic Finding Tables: Retina and Pigmentepithelium from the report are attached. These summary tables present the toxic effects on the retina of dosing with parathion. Copies of the Electronmicroscopic Finding Tables: Nervous opticus from the report are attached. These summary tables present the toxic effects on the optic nerve of dosing with parathion.

In relation to toxic effects the report states;

1. "The female rats in the test group administered a high dose of parathion (five animals - 32 ppm), on the strength of all the light and electron microscopic individual data, consistently exhibited the most marked retina alterations within the entire test series. Complete impairment of the functional efficiency of the retina may be assumed. The nervus opticus is also affected by these structural deformations to almost the same severe extent. Here too electron microscopy detected structural alterations in the axon and stratification of the myelin sheaths of substantial to severe degree. Massive impairment of conduction of the nervous stimuli may be assumed in four animals of five by morphological criteria. The external ocular muscles appear unchanged in their cytoplasmic structure from an electron microscopic viewpoint."

2. "Male rats after administration of parathion at the highest dose (five rats - 32 ppm) exhibited consistent marked to severe retina atrophy by light histology. Electron microscopy in addition detected more extensive degeneration in the area of the first and second neurons and the pigment epithelia. It may be seen as certain that retinal sensual perception was considerably impaired.

The alterations in the nervus opticus were slightly less extent. Moderate to severe myelin degeneration involves functional alteration within these nervous pathways.

The mm. recti oculi showed an unchanged ultra-structure by

electron microscopy. The myofibrils of the m. ciliaris were mostly moderately to slightly reduced by electron microscopy, only in one case was degeneration marked. If the test group is considered overall, moderate impairment of lens motility appears to be present."

"The structural changes in the eye detected by electron microscopy in the cases of the low and medium dose groups (2 ppm and 8 ppm) may not be attributed to the treatment; the reason is that the rats in these groups had reached an age, by the end of the chronic long-term study, which made it difficult to assess to what extent the described retina, muscle and nerve changes might be regarded as a result of the animals advanced ages, or as a result of treatment with parathion. The latter interpretation is supported by the sometimes considerable retina degeneration occurring in the control groups of both sexes."

Parathion

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Parathion; Chronic Feeding Study in Rats;
Light and Electron Microscopic Examination Data
Bayer Project T 1016770

TO: R. Zendzian, Ph.D.
Tox Branch/HED (TS-769C)

FROM: A. Katz *AKatz 6/22/87*
Tox Branch/HED

THROUGH: M. vanGemert, Ph.D. *M vanGemert 6/22/87*
Head, Section III
Tox Branch/HED (TS-769C)

Based upon an examination of the data provided in the report on the subject study, it appears that parathion treatment caused structural alterations which were detected by electron or light microscopy in the eyes of males and females at the highest dose tested (32 ppm). No discernible treatment-related changes were evident at lower doses (2 or 8 ppm). One major difficulty in evaluating effects of treatment in studies of this type is the confounding process of "spontaneous" degeneration associated with age in untreated rats.

Future studies of shorter duration (i.e., examination of younger exposed rats) may provide a more definitive basis for assessing specific treatment-related structural and functional alterations.