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

JUL 28 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Second Peer Review of Paraquat

FROM: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Rpbert Taylor, Product Manager #25
Registration Division (TS-767)

The Peer Review Committee met on June 15, 1988, to reevaluate the classification of Paraquat and in particular to reconsider the squamous cell carcinomas in the head region of male Fischer 344 rats.

A. Individuals in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated):

Theodore M. Farber

William Burnam

Reto Engler

Lynnard Slaughter

Richard Levy

Marion Copley

John Quest

2. Scientific Reviewers (Non-committee members responsible for presentation of data; signature indicates technical accuracy of panel report):

Krystyna Locke

Edwin Budd

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee).

Anne Barton _____

Kerry Dearfield Kerry F Dearfield

Richard Hill _____

Robert Beliles Robert Beliles

Esther Rinde Esther Rinde

Diane Beal Diane C Beal

Judith Hauswirth Judith W. Hauswirth

4. Other Attendees:

Chris Rice (RD) was also present.

B. Material Reviewed:

The material reviewed consisted of: the Toxicology Branch Peer Review Memo on Paraquat 9/18/86. A reevaluation of the squamous cell carcinomas in male rats by EPL, and DER's in Japanese mouse and rat studies of 1982.

C. Evaluation of Data:

(1) Squamous Cell Carcinomas in the Head Region of Male Fischer 344 Rats.

The original review on Paraquat concluded that Paraquat showed some evidence of carcinogenicity in the male Fischer 344 rats since squamous cell carcinomas (an uncommon tumor) were seen in the head region (ear, nasal cavity, oral cavity and skin). The registrant contended that those tumor sites should not be combined. This argument was evaluated by an independent laboratory (EPL). EPL agreed that these sites of tumors should not be combined; at each site therefore there would be an insignificant increase in the particular tumor. The peer review Committee discussed this situation at length. It was concluded that these tumor sites normally should not be combined when the exposure to a chemical is by the oral route. However, there was also a strong remaining belief

among several committee members that in this particular case, the tumors are the likely result of topical exposure to Paraquat contained in the powdered diet. Paraquat is a topical irritant and thus the tumors in the nose, ears, mouth and skin around the head could well be the result of external exposure to Paraquat. However, it was also concluded that the tumors are not the result of exposure through the G.I. tract.

(2) Continued Chronic Toxicity/Oncogenicity Study in JCL:ICR Mice (Japan). Asahi Chemical Company, Japan, by Nippon Experimental Medical Research Institute, Japan, March 10, 1982.

Sixty mice/dose/sex were exposed to 0, 2, 10, 30 and 100 ppm Paraquat; 10 additional mice/sex/dose each were scheduled for a 26 and 52 week sacrifice. The DER (No. 006652) on this study was prepared by Dr. K. Locke on 3/9/88. In this study, the feed was pelleted. Under the study condition, 30 ppm was a NOEL, at 100 ppm the major effects were seen in hematological evaluations and in blood chemistry as well as changes in absolute and relative organ weights. Because of some inconsistencies the study was judged to be supplementary. However, overall the study appear to be conducted in an acceptable fashion. There were no compound related oncogenic effects. The dose selection in this study seem adequate and the doses are similar to the ones used in the mouse study evaluated previously (Peer Review of September 18, 1986).

(3) Combined Chronic Toxicity Study in JCL:Wistar Rats (Japan). Asahi Chemical Company, Japan, by Nippon Experimental Medical Research Institute, Japan, March 10, 1982.

Fifty rats/dose/sex were exposed to doses of 0, 6, 30, 100 and 300 ppm Paraquat; 6 additional rats/dose/sex each were used for 26 and 52 week sacrifices. Paraquat was administered in pelleted diet preparations. The NOEL for this study was defined to be 100 ppm for males and females. At 300, hematology parameters and blood chemistry were affected by Paraquat. In addition, mortality was increased at 300 ppm as well as absolute and relative organ weights (DER No. 006652). The dose selection in this study seemed adequate, moreover, the doses were consistent with those in the Fischer 344 rats. No neoplastic compound related effects were noted in this study. Both the oncogenicity and chronic portion of this study was judged to be acceptable (Core minimum).

D. Weight of the Evidence Determination:

The Committee considered the additional data and further evaluated the tumors observed in male Fischer 344 rats.

It was concluded that there was no evidence of carcinogenicity in male Wistar (Japanese) rats at 12 mg/kg/day (HDT), and no evidence of carcinogenicity in female Wistar (Japanese) rats at 15 mg/kg/day (HDT).

Furthermore, there was no evidence of carcinogenicity in female and male mice (JCL:ICR, Japanese) at 13 mg/kg/day (HDT).

From the previous Peer Review it was concluded that there was no evidence of carcinogenicity in male and female mice (SPF Swiss derived) at 15 mg/kg/day (HDT).

It was also concluded that there was no evidence in female Fischer 344 rats at 7.5 mg/kg/day (HDT) and there was, at best, equivocal evidence of carcinogenicity in male Fischer 344 rats at 7.5 mg/kg/day, however, it was also concluded that this equivocal evidence could not be associated with oral exposure but was probably the result of topical exposure.

Overall Paraquat was thus placed in Category E, according to the EPA Carcinogenicity Guidelines, when considering oral exposure. Since Paraquat is a restricted use pesticide and has significant toxicity against which the professional applicator has to protect himself or herself, it was concluded that the potential for oncogenic effects by excessive (irritating) topical exposure need not be explored any further. Moreover, Paraquat has a very low reference dose of 0.0045 mg/kg/day, and exposure limited by this RfD are not expected to elicit local/topical irritancy.