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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reevaluation of Classification of Carcinogenicity of Assure Following Science Advisory Panel (SAP) Review of Data.

FROM: John A. Quest, Ph.D. JAQuest 2/10/88
Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Robert Taylor, Product Manager #25
Fungicide Herbicide Branch
Registration Division (TS-767)

The Peer Review Committee met on January 13, 1988, to examine the issues raised by the Science Advisory Panel (SAP) with respect to the classification of the carcinogenicity of Assure.

A. Individuals in Attendance

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

Theodore M. Farber Theodore M. Farber

William Burnam William L Burnam

Robert Beliles Robert Beliles

Richard Hill Richard Hill

Esther Rinde Esther Rinde

John Quest John A. Quest

Richard Levy Richard A Levy

Marion Copley Marion Copley

Kerry Dearfield Kerry Dearfield

Judith Hauswirth Judith W. Hauswirth

1

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

Whang Phang 2/11/88

Marcia van Gemert

C. J. Nelson 2/11/88

3. Peer Review Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with overall conclusions of the Committee.)

Anne Barton

Reto Engler

Diane Beal

B. Initial Peer Review Meetings on Assure:

The Toxicology Branch Peer Review Committee previously met twice, once on November 4, 1986 and again on August 25, 1987, to evaluate information relevant to the oncogenicity of the selective post-emergent herbicide, Assure. The relevant findings of the Committee from these meetings were as follows:

1. Assure produced an elevated incidence of hepatocellular adenomas and carcinomas combined ($p < 0.05$) in high dose (320 ppm) male CD-1 mice. The observed incidences were 7/70 or 10%, controls; 10/69 or 14%, 2 ppm; 7/69 or 10%, 10 ppm; 8/69 or 11%, 80 ppm; and 15/70 or 21%, 320 ppm. The high dose level of Assure exceeded a MTD level. There was no evidence for the appearance of liver hyperplasia in treated animals, but some evidence for a reduction in the latency period for time to tumor appearance was noted. The Committee considered Assure to be a weak oncogen based on this information.

2. No other compound-related oncogenic responses were observed in female CD-1 mice (ovarian stromal tumors occurred but these were ruled out on the basis of historical control data), or in male or female CR-SD rats (a positive trend for liver carcinomas was seen in females but this effect was also ruled out using historical control data).

3. Assure was not mutagenic in several short-term tests, and no structurally-related compounds of toxicological interest were identified in several data base searches.

In compliance with the Agency's Guidelines for Carcinogen Risk Assessment, the Peer Review Committee believed the finding of elevated liver tumors (adenomas and carcinomas combined) in male CD-1 mice to be sufficient to conservatively classify Assure as a weak Category C oncogen.

C. Science Advisory Panel Meeting on Assure:

The above findings were presented to the EPA's Scientific Advisory Panel (SAP) on December 15, 1987, by Dr. Whang Phang of the Toxicology Branch. The SAP concluded that the data did not support the classification of Assure as a Category C oncogen. They indicated that with the exception of the increase in male mouse liver tumors at a dose exceeding the MTD, all of the data supported classification of the chemical in Category E (no evidence of oncogenicity). They further believed that even if the high dose liver tumor data was accepted, greater statistical rigor (i.e., "p" value of less than 0.01 rather than a "p" value of less than 0.05) was needed to determine significance for variable tumor endpoints such as male mouse liver tumors.

D. Follow-Up Peer Review Meeting on Assure:

In light of the SAP review of the Assure oncogenicity data, the Toxicology Branch Peer Review Committee reevaluated the oncogenicity classification of Assure. The following conclusions were reached at the meeting that was held on January 13, 1988.

1. The Committee agreed with the SAP that Assure could be viewed as not fitting into the group C oncogenicity category. That is, several findings, as noted by Dr. Phang in his presentation to the SAP, appeared to diminish the biological relevance of the observed increase in liver tumors (adenomas plus carcinomas combined) in male CD-1 mice. These included the knowledge that the observed tumor types are common and occur with high and variable spontaneous background rates in male mice. Furthermore, in the Assure study, tumors occurred at low incidence and with marginal statistical significance in treated animals, and were seen only at the high dose level where the survivability of the animals was compromised and the MTD level was exceeded. The finding of individual hepatocyte necrosis in a 90-day toxicity study of Assure in male mice at doses of 100, 316 and 1000 ppm also suggested that the highest dose level tested in the chronic study (i.e., 320 ppm) exceeded an MTD level. Additional information on the extent and severity of these lesions is being requested from the registrant.

2. The Committee did not agree with the conclusions of the SAP that Assure be categorized as a Category E oncogen, since Assure was considered to have produced a possible weak positive oncogenic response in at least one adequately performed animal study.

3. The Committee believed that the liver tumor data in CD-1 mice could in fact be considered inadequate for decision making purposes because of major qualitative limitations (e.g., the only response observed was an increase in combined benign and malignant tumors in the male mouse liver at the highest dose level tested which exceeded an MTD level) and quantitative limitations (e.g., the response occurred at a low incidence and at a marginal level of statistical significance).

E. Conclusion of Peer Review Committee:

The Committee concluded that Assure would probably be best categorized in Category D (not classifiable as to human oncogenicity), because limitations in the data from an adequately performed mouse study precluded an accurate interpretation of oncogenic risk. No new animal studies are required. As noted above, this classification of Assure as a Category D oncogen differs from the recommendation of the SAP to place Assure in Category E, due to the presence of the marginal but evident liver tumor response that was observed in the male CD-1 mice.

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