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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: April 15, 1999

MEMORANDUM

SUBJECT: TELONE II- Report of the Cancer Assessment Review Committee (CARC)

FROM: Sanjivani Diwan,
Executive Secretary,
Cancer Assessment Review Committee
Health Effects Division (7509)

TO: Lisa Nisenson
Chemical Review Manager
Special Review Reregistration Branch
Reregistration Division (7508W)
and
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THROUGH: William Burnam, Chairman
Cancer Assessment Review Committee
Health Effects Division (7509C)

PC Code: 029001

On March 10, 1999, the Cancer Assessment Review Committee (CARC) held an Ad Hoc meeting to discuss the additional mutagenicity and mechanistic data on Telone II (1,3-Dichloropropene; referred to as 1,3-D) submitted by the registrant.

Nancy McCarroll of the Toxicology Branch presented the results of new studies, the previously submitted mutagenicity data and findings from the open literature. The new studies consisted of in vitro and in vivo genetic toxicology studies and an in vivo cell proliferation/apoptosis/DNA

adduct mechanistic study. Based on the review of the newly submitted studies, the Ad Hoc Committee agreed with the reviewer that the results of these nonguideline studies do not support the registrant's claim that Telone II is non mutagenic. The Committee also reaffirmed that the previously submitted studies provided evidence that Telone II was mutagenic in bacterial, drosophila and mammalian cell studies There is confirmed evidence from the open literature of mutagenicity in bacteria as well as demonstration of both the in vitro and in vivo formation of mutagenic epoxides, and the induction in vivo of DNA strand breaks. Based on these findings the Committee concluded that Telone II presents a mutagenicity concern.

The registrant claims that Telone II does not present a carcinogenic hazard to humans because glutathione (GSH) conjugation is sufficient to conjugate and detoxify the administered dose; the Committee disagrees with this claim because tumors were observed at levels of Telone II that clearly did not deplete GSH. Following treatment of F344 rats and B6C3F1 mice with Telone II the GSH levels rebounded after initial decreases in rat liver and mouse lung GSH levels. Furthermore, conflicting evidence from several mammalian cell lines demonstrated no clear correlation between physiological levels of GSH and mitigation of mutagenicity. The negative mutagenicity was demonstrated in two mammalian cell lines that had either the highest or the lowest levels of GSH activity while cell lines clearly vulnerable to mutagenic attack had relatively high levels of GSH activity.

In conclusion, the registrant did not present compelling information to conclude that a mutagenic mode of action is not a plausible mode of action for Telone II induction of tumors. The registrant's claim for the "protective action" of GSH as a "mode of action" was not accepted by the Committee.

Based on all considerations, the Ad Hoc Committee did not see any need for changing the classification (classified as a Group B2) or the method of quantification (low dose extrapolation) for carcinogenicity. Furthermore, the Committee agrees that the mutagenic activity of Telone II is a plausible mode of action applicable to both oral and inhalation routes of exposure.

The details for the reviewed studies along with the Agency's comments on each study are presented in the attachment.

cc:
William Burnam
Kerry Dearfield
Vicki Dellarco
Yiannakis Ioannou
Nancy McCarroll
Esther Rinde

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