



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

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TXR NO. 0050523

**MEMORANDUM**

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

DATE: February 26, 2002

SUBJECT: Cancer Reclassification of Thiabendazole

FROM: William L. Burnam *WLB*  
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TO: Lorilyn Montford  
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The CARC classified thiabendazole (TBZ) under the Agency's 1999 Draft Guidelines for Carcinogen Risk Assessment as "likely to be carcinogenic to humans" by the oral route (CARC report, February 24, 2000). This approach was based on a weight of the evidence analysis that indicated that TBZ was not mutagenic, but that it interfered with thyroid-pituitary homeostasis leading to increased TSH stimulation of the thyroid and thyroid tumors. Such effects are not expected at doses that do not affect thyroid and pituitary status. In accord with the draft guidelines and the EPA thyroid cancer policy (1998), the CARC recommended that the linear dose response default was not applicable. Instead, it should be replaced by the nonlinear, margin of exposure (MOE) approach.

Recently questions arose about the implications of the cancer classification of TBZ. As is stated in the draft cancer guidelines [section (2.6.2)], mode of action information may allow for more than one classification for a chemical. For instance, an agent may be a carcinogen by one route but not by another, like asbestos that may be carcinogenic via airborne exposure, but noncarcinogenic by the dermal route. Likewise, a chemical may be carcinogenic in one dose range but not carcinogenic below that level. However, the determination of a chemical not being carcinogenic at a certain human exposure level cannot be made at the hazard stage of the risk assessment. It can only be done after knowing expected exposure and, thus, is a determination made in risk assessment.

Information on the mode of action of TBZ leads to a conclusion that the chemical may be carcinogenic at "high" exposures where there is perturbation of thyroid-pituitary status. However, when exposure is "low", that is, below levels that disturb hormonal balance, there is no expected increase in cancer risk above background. The cancer classification of TBZ can be summarized as "likely at high doses but unlikely at low doses."

Several factors applicable to a determination of the significance of anticipated human exposures to TBZ are as follows:

1. The overall NOAEL for thyroid tumors and change in thyroid hormone levels is 10 mg/kg/day.
2. The EPA thyroid cancer policy states that rodents are much more sensitive than humans regarding the applicability of the mode of action. As a still conservative position, the Agency assumes that the interspecies uncertainty factor should not be the 10x default, but instead 1x.
3. An intraspecies variability factor is applicable to antithyroid compounds. Children are not known to be especially sensitive to thyroid-pituitary disruption, although it is recognized that once disruption occurs, the developing fetal brain is liable to decrements in mental functioning. Therefore, it is thought that a 10x factor is appropriate for antithyroid chemicals.

cc: Margaret Stasikowski  
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