UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

Subject: Hydroxymetabolites of Atrazine and Other Triazine Herbicides.
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Several representatives of HED met to discuss the data requirements for the hydroxymetabolites of atrazine and other triazine herbicides (W. Burnam (HED), R. Schmitt (DEB), K. Baetcke (TOXI), M. Copley (TOXI), H. Spencer (TOXI), and M. Metzger (DEB)). TOX stated that the toxicity of the hydroxymetabolites indicates that they should be included in the total toxic residue if they are found in plant and animal commodities. Furthermore, all metabolites with the intact triazine moiety are of concern. These conclusions apply to atrazine as well as to other triazine herbicides including simazine. Below we discuss specific issues related to atrazine regarding how more realistic risk estimates may be obtained.

Corn

Hydroxymetabolites of atrazine are found in corn (Plant Physiol. (1971) 47, 10-14). The most recent Dietary Risk Evaluation System (DRES) analysis showed that corn and corn products contribute approximately 8.4×10^{-6} to the total estimated atrazine carcinogenic risk of 4.4×10^{-5} (approximately 19% of the total dietary carcinogenic risk estimate, 39% of the risk estimated from foods excluding water)(see J. R. Tomerlin, 6/12/89). This DRES analysis accounts for percent crop treated and uses an

anticipated residue of 0.10 ppm for corn grain and corn processed fractions based solely on samples containing non-detectable residues. Only parent and chlorometabolites were determined in the field trial data used to determine this anticipated residue. Residue data are not available for hydroxymetabolites on corn. Additional summary data are available showing total radioactivity of 0.1 ppm in corn grain treated at an exaggerated rate with ^{14}C atrazine (long PHI). Since the risk from residues of atrazine in corn containing intact triazine ring is unacceptable, we require the following additional data for corn (either (a) or (b) below, not both) in order to develop anticipated residue information for a more definitive exposure assessment:

(a) A corn metabolism study utilizing uniformly ring-labeled ^{14}C atrazine in which atrazine is applied to corn (field and sweet) at the maximum application rate, and samples are obtained at the minimum PHI (see Subdivision O of the Pesticide Assessment Guidelines for commodities which must be analyzed and other information). Total radioactivity in corn samples should be determined, and the radioactive residue should be characterized to determine absolute amounts and percentages of parent, chlorometabolites, hydroxymetabolites, and other metabolites containing a triazine ring. The amount of total radioactivity, if any, associated with compounds not containing a triazine ring should also be determined. Samples of corn grain must also be obtained in this study and processed (both wet and dry milling) to determine and characterize residues in processed corn fractions. The data presented should utilize analytical methods with sufficiently sensitive LODs to allow unambiguous determination that the total estimated carcinogenic risk (combined for all commodities which may contain atrazine residues) is acceptable.

(b) Geographically representative field trial data for corn (field and sweet) utilizing maximum application rates and minimum PHIs, in which residues are measured of parent, chlorometabolites, hydroxymetabolites, and possibly other metabolites. DEB is currently reviewing an atrazine metabolism summary which the registrant states will show the nature of the residue for atrazine in plants (and animals) to be adequately understood. The specific metabolites which must be determined in field studies cannot be determined until the nature of the atrazine residue is adequately delineated. As indicated above, the residue data should utilize analytical methods with limits of detection (LODs) sufficiently sensitive to allow unambiguous determination that the total estimated carcinogenic risk (combined for all commodities which may contain atrazine residues) is acceptable.

We note that based on previously calculated anticipated residues for corn and corn processed fractions of 0.10 ppm, the calculated carcinogenic risk is 8.4 X 10^{-6}. Therefore, in order to be able to unambiguously determine a carcinogenic risk of 1 X 10^{-6}, an average LOD for corn and corn processed fractions of less than 0.01 ppm (0.10/8.4) is necessary (if detectable residues are found, the necessary LOD will depend on the percentage of each corn commodity consumed as provided in DRES). We note that the required LOD must be sufficiently sensitive so that it can be unambiguously determined that the combined carcinogenic risk from all commodities containing atrazine residues is acceptable. Additionally, we point out that submission of these data may continue to show unacceptable risk resulting from atrazine use on corn.

Sugarcane

The most recently calculated carcinogenic risks resulting from atrazine use on sugarcane commodities is 1.1 X 10^{-5} assuming 30-40% crop treated and anticipated residues in whole cane of 0.13 ppm (approximately 25% of the total dietary carcinogenic risk, 51% of the total risk from food excluding water). The anticipated residue value is based on detectable residues of atrazine and its chlorometabolites. If residues of hydroxymetabolites and other metabolites containing the triazine ring were determined in sugarcane and sugarcane processed commodities, the calculated risk would likely increase. The registrant may wish to develop a monitoring program for sugarcane/sugarcane processed commodities in order to determine more realistic residues of atrazine likely to result from the proposed use (which must include determination of parent, chlorometabolites, hydroxymetabolites, and other potential metabolites containing the triazine ring). In this case, the LODs for the analytical methods used should be sufficiently sensitive so that the combined carcinogenic risk for all commodities containing atrazine residues can be unambiguously determined to be acceptable. A protocol for such a monitoring program should be submitted to DEB for review prior to initiation of the study. It should be pointed out that monitoring data for atrazine in sugar may continue to show residue levels in sugar which result in an unacceptable risk.

Milk and Red Meat

The most recent DRES dietary exposure assessment estimates that red meat, milk, and milk products account for a carcinogenic risk of 1.2 X 10^{-6} (approximately 3% of the total dietary risk, 6% of the risk from food excluding water). The estimate is based on feeding beef and dairy cattle diets containing feeds which are important nationally. The risk estimate may be modified when additional information regarding anticipated residues in corn commodities and other animal feeds are made available. In some

localities where dairy cattle are fed more highly contaminated feeds, risks could be substantially higher. These higher local risks should be considered when making risk/management decisions.

Since only residues of atrazine and its chlorometabolites were considered in red meat and milk, residues of the hydroxymetabolites and other metabolites containing the triazine ring must be considered. Additional data may be required for animal commodities and for major animal feed items in which hydroxymetabolites and other metabolites containing the triazine ring are determined. However, prior to further specification of any required data, DEB must review a metabolism data summary which has recently been submitted by Ciba-Geigy.

Conclusions and Recommendations

The carcinogenic risk resulting from dietary exposure to residues of atrazine and its chlorometabolites is approximately 4.4×10^{-5}. This risk results primarily from water (2.2×10^{-5}), sugarcane (1.1×10^{-5}), milk/red meat (1.2×10^{-6}), and corn (8.4×10^{-6})(DRES analysis, J. R. Tomerlin, 6/12/89). Hydroxymetabolites were not considered in this dietary exposure assessment. TOX has determined that the toxicity of the hydroxymetabolites (and other metabolites containing the triazine ring) indicates that they should be included in the total toxic residue if they are found in plant and animal commodities (meeting of 1/12/90 including representatives of HED, TOX and DEB). This conclusion applies to atrazine as well as to other triazine herbicides including simazine.

Based on the results of the dietary exposure analysis, DEB has concluded the following. First, either additional field trial/processing or radiolabel/processing studies are required for corn in which parent, chlorometabolites, hydroxymetabolites, and other metabolites containing the triazine ring are determined at sufficiently low LODs to allow unambiguous determination of acceptable carcinogenic risk (combined risk for all commodities containing atrazine residues). Secondly, the registrant may wish to initiate a monitoring study for sugarcane to show that carcinogenic risk resulting from atrazine application to sugarcane is less than the current estimate of 1.1×10^{-5}. However, since detectable residues have been found and percent crop treated data have been utilized, and since additional metabolites must be determined in the monitoring study, an unacceptable risk may also result from anticipated residues determined from this monitoring study. Finally, risks from milk and red meat must be reevaluated when additional information is obtained regarding anticipated residues in corn and other animal feeds. The contribution of hydroxymetabolites to the dietary exposure resulting from consumption of red meat and milk has not been determined. DEB must review a recently submitted overview of

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metabolism data for atrazine prior to specifying what additional data are required for milk and red meat as well as for animal feeds.

cc: M.Metzger (DEB), R. Schmitt (DEB), M. Copley (TOXI), H. Spencer (TOXI), W. Burnam (HED), Atrazine SF and Reg. Std. File, Simazine SF and Reg. Std. File, RF, E. Eldredge (PMSD/ISB), Circu (7)
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