13/OPP #37157

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

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OFFICE OF
PREVENTION, PESTICIDES AND
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MEMORANDUM

SUBJECT: Terbufos. HED Response to the American Cyanamid Rebuttal to the HED Chapter of the RED. Chemical ID No. 105001. DP Barcode No. D224857.

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THRU: William J. Hazel, PhD., Section Head
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TO: Richard Dumas, PM 61
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In a letter dated 3/21/96 American Cyanamid submitted a rebuttal to the HED chapter of the Terbufos RED. The package included an overview of use patterns, worker exposure profiles, and the dietary exposure and toxicology databases for the technical and the two granular formulations (Counter®15G and Counter®CR). An acute dietary exposure analysis was conducted using the Tier III "Monte Carlo" exposure model, and the results included in the rebuttal. A study was conducted to determine worker exposure from handling granular insecticides using the Lock'n Load® system versus open pouring. The registrant questioned the Agency's use of a toxicological endpoint based on plasma cholinesterase inhibition. Finally, American Cyanamid submitted a modified worker exposure estimate based on weighted use rates, a lower estimated dermal absorption, and additional correction factors for personal protective equipment (PPE).

The HED response to the American Cyanamid rebuttal is included herein, and includes input from HED reviewers in Toxicology Branch II (Alan C. Levy, memo dated 7/5/96), Occupational and Residential Exposure Branch (OREB, Bart Suhre and Mark Dow, memo dated 7/2/96), and Science Analysis Branch (SAB/DRES, Elizabeth Doyle, memo dated 7/11/96). A Toxicology Branch II review of acute oral (technical) and acute dermal (20CR and 15G formulations) studies, as well as the dust generation study, has been forwarded to SRRD under separate cover.

Conclusion/Recommendation

The registrant's requested change in the study/endpoint serving as the basis for the reference dose is denied. The Agency's dermal and inhalation worker exposure assessments, and concomitant risk, will

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not be changed in accordance with the arguments submitted in the American Cyanamid rebuttal package. The worker exposure assessment conducted for the draft HED chapter of the RED (dated 10/17/95) remains unchanged. The approach used in the registrant's acute dietary analysis is generally acceptable; however, the analysis should be repeated without using a percent crop treated correction factor for processed commodity residues. The results should be submitted to the Agency for evaluation. HED recommends the registrant consider use of the 99th percentile exposure level, since the submitted analysis included numerous refinements in the exposure estimates, and given the special consideration given to infants and children under FIFRA and FFDCA as amended.

DETAILED CONSIDERATIONS

The background information pertaining to each issue raised by the registrant will be discussed, followed by the HED response/comment.

I. Use of Plasma Cholinesterase Inhibition as an Endpoint for Risk Assessment

The registrant challenged the use of the plasma cholinesterase NOEL of 0.005 mg/kg/day obtained in a 28-day dog feeding study in calculating margins of exposure (MOEs) for worker dermal risk and acute dietary risk. The registrant argued that there is no direct correlation between the degree of plasma or RBC cholinesterase inhibition and the onset of clinical signs of neurotoxicity, in both subchronic and chronic studies conducted using other cholinesterase inhibitors and published in the literature. The registrant further correctly stated that there is a debate within the Agency regarding the use of plasma and/or red blood cell (RBC) cholinesterase endpoints in the absence of brain cholinesterase inhibition and/or clinical signs. An industry workgroup (Acute Cholinesterase Risk Assessment, ACRA) will address the topic in a submission to the Agency some time in late 1996.

The registrant cited a one-year dog study in which the NOEL for clinical signs of neurotoxicity was 0.09 mg/kg/day, and a recently submitted/reviewed 2-generation rat reproduction study in which the NOEL for plasma, RBC or brain cholinesterase inhibition was 0.04 mg/kg/day. In support of discounting the plasma cholinesterase endpoint from the 28-day dog study and using the RBC/brain cholinesterase endpoint from the 2-generation rat reproduction study, the registrant pointed out the 8-fold difference in the two species' sensitivity to terbufos-induced plasma cholinesterase depression, while sensitivity to terbufos-induced brain and RBC cholinesterase depression is similar across species. It was noted that the different routes of administration used in the studies, i.e capsule (bolus) dose in the dog and dietary admix in the rat, may have been a factor as well.

The registrant believes that the use of plasma cholinesterase inhibition as an endpoint for risk assessment purposes is inappropriate, and that in the absence of clinical signs of neurotoxicity, brain cholinesterase inhibition should be used to define a no observable effects level (NOEL). The registrant proposes use of the NOEL of 0.04 mg/kg/day for brain and RBC cholinesterase inhibition obtained in the 2-generation rat reproduction study, rather than the currently used NOEL of 0.005 mg/kg/day for plasma cholinesterase inhibition obtained in the 28-day dog study.

The registrant plans to conduct an *in vitro* study to compare sensitivity to terbufos-induced plasma and RBC cholinesterase depression in the human, rat and dog. The registrant contends that this study will further support a less conservative safety factor (MOE) for acute dietary or worker risk assessments.

Stephanie Polek OPP
* I spoke with Jet

HED Response

The HED RfD/Peer Review Committee convened on 5/22/96 and 5/23/96 to reconsider the basis used in the assessment of the Reference Dose (RfD) for terbufos and to evaluate alternative toxicological endpoints as possible bases for the RfD (memo, G. Ghali, 7/1/96).

During the discussion, all of the available terbufos data concerning cholinesterase inhibition were taken into consideration, including a 6-month dog study dated 1973 in which both plasma and RBC cholinesterase were inhibited at 0.01 mg/kg/day; the NOEL for plasma and RBC cholinesterase inhibition was 0.0025 mg/kg/day. Given that this study demonstrated that RBC cholinesterase was inhibited at comparable or slightly higher dose levels than those required to cause plasma cholinesterase inhibition in the dog, the Committee recommended that the RfD for terbufos remain unchanged and be based on the three studies in dogs. The existing RfD for terbufos is based on a NOEL of 0.005 mg/kg/day with an uncertainty factor of 100 due to interspecies and intraspecies variation; this endpoint will continue to be used to calculate occupational risk.

II. Dermal Penetration

The registrant challenged the Agency's assumption of 100% dermal absorption for terbufos. The registrant proposed use of 15% dermal absorption for the 15G formulation, and 3% for the CR formulation, based on a comparison of the acute oral LD50 for the technical and the dermal LD50s for the 15G and CR formulations. Furthermore, the registrant stated that use of an oral 28-day dog study is not an appropriate toxicity study for identification of worker exposure endpoints. Consequently, the registrant has proposed to conduct a 28-day repeat-dose dermal toxicity study in rats using each end-use product, and will include analyses for plasma, RBC and brain cholinesterase activity.

HED Response

The registrant's arguments against the Agency's assumption of 100% dermal absorption were discussed by the tox reviewers and pertinent members of the Toxicology Endpoint Selection Committee (TESC). Based on the toxicity database for terbufos, including studies other than the acute oral for the technical and the acute dermal studies for the end-use products, toxicologists concluded that terbufos is highly absorbed and/or highly toxic via the dermal route. Therefore, the registrant's proposed estimates of lower dermal absorption will not be used in the Agency's assessment of dermal exposure and concomitant risk to workers.

III. Loader and Applicator Exposure to Terbufos

The registrant's rebuttal to the Agency's determination of exposure and concomitant risk to loaders and applicators included discussions of the % dermal absorption assumed, the lack of a protection factor for use of an apron during mixing/loading, the extrapolation from closed cab exposure to open cab applicator exposure for granular formulations, and inhalation exposure estimates for granular formulations. Finally, the registrant provided estimates of typical use rates for corn, sugarbeets and sorghum, and proposed that these more realistic rates be used in the risk assessment.

The registrant stated that realistic use rates for terbufos would be 1.1 lb ai/A (sugarbeets) and 0.74 lb ai/A (sorghum), and that 90% of applications would entail use of the typical rate, while maximum rates of 4.35 and 3.92 lb ai/A for sugarbeets and sorghum, respectively, would only be used approximately 10% of the time. The weighted average application rates were incorporated into the registrant's revised risk estimates.

In estimating dermal exposure to mixer/loaders, EPA did not include a protection factor for the use of an apron, which is required on registered labels. The registrant contends that a protection factor of up to 90% could be used. Since open cab granular application data were not available from PHED V1.1, EPA calculated the open cab exposure by assuming a 98% protection factor for a closed versus an open cab scenario, and back-calculating from the closed cab data. This corresponds to a 50-fold increase in exposure for open cab applicators, which the registrant believes is overly conservative.

Based on a comparison of closed cab versus open cab PHED V1.1 data for liquid formulations, the registrant proposes use of a 3-fold protection factor for closed cab versus open cab application. The registrant provided EPA with proposed MOEs based on their assumptions/calculations.

The registrant also submitted a worker exposure study conducted at Purdue University and published in *Successful Farming*, 12/92, which demonstrated reduced worker exposure to granular pesticides using the Lock'n Load® closed handling system.

The registrant also provided revised estimates for inhalation exposure. First, the registrant contends that estimates should not be based on technical terbufos, but on the end-use products. In addition, the registrant conducted two dust generation studies in order to determine the potential for both formulations to produce respirable dust. The results indicated that the CR product produced only 0.4% dust, while the 15G formulation produced 3.4% dust. The dust from the CR and 15G products was analyzed, and found to contain 1.4% and 15% active ingredient, respectively. The registrant also contends that 10 microns is the size of dust particles which can be inhaled, while 4 microns is the size of particles which can be respired. Revised calculations for inhalation exposure MOEs were included in the rebuttal package. A waiver from the requirement of an acute inhalation toxicity study using the CR formulation was requested.

HED Response

The realistic use rates provided by the registrant are appropriate for determining risk for cancer or other chronic toxic effects. However, the Agency's policy for assessing worker risk resulting from short and intermediate term exposure is to use maximum label application rates combined with typical use practices and an average work day/cycle. Therefore, the Agency's worker risk assessment will not be revised to include weighted application rates for sugar beets and grain sorghum.

In preparing worker risk assessments, OREB generally calculates daily exposure assuming personal protective equipment (PPE) stipulated by the Worker Protection Standard (WPS), which includes long pants, long sleeves, coveralls and gloves for a TOX Category I pesticide such as terbufos. At this time there are no data in PHED V1.1 with which to assess the amount of protection afforded by an apron. In a paper published by the CA DPR (Thongsinthusak et. al., 1990), a range of protection to the covered areas was presented. For an apron, the range was 78-99%, with an assumed outlier of 48% protection. While it is true that an apron would reduce dermal exposure to thighs and chest, especially in cases involving accidental spills and splashes, the use of an apron will not significantly affect the Agency's total dermal exposure estimates as stated in the draft chapter of the HED RED.

The registrant believes that the Agency's 98% protection factor used for closed cab versus open cab application of granular formulations is overly conservative. Based on PHED V1.1 exposure data, it is apparent that dermal exposure to granular (dry) formulations is significantly different from exposure to liquid formulations. Therefore, use of the protection factor determined from liquid open cab versus closed cab application should not be translated to open vs. closed cab application of granular formulations. The Agency's risk assessment will not be revised to reflect the lower exposure estimate suggested by the Registrant for open cab application.

The published study demonstrating reduced worker exposure via the Lock'n Load® closed handling system did not provide quantitative results which could be used to derive additional protection factors. However, the Agency's assessment incorporated surrogate data from PHED V1.1 in which the Lock'n Load® delivery system was used.

The registrant's dust generation, or attrition, studies were examined by HED toxicologists and found to be acceptable in terms of methodology. However, for the purpose of the risk assessment, HED concludes that all particles in the subject dust generation studies, regardless of size, are assumed to result in inhalation exposure. The toxicologist further stated that the Agency's risk assessment could be adjusted for attrition and %ai in the dust, if these factors were not already taken into consideration in the exposure assessment. Since the exposure values determined from PHED are unit exposures, i.e. exposure per lbs ai handled, and since surrogate data from dust formulations were used in the Agency's worker exposure assessment, the attrition and %ai in the dust were already accounted for in the exposure assessment. Therefore, the Agency's inhalation exposure assessment will not be revised based on the results of the dust generation studies.

Since the CR formulation is physically different from the 15G and other "typical" clay-based granulars, exposure from the CR formulation could be overestimated based on PHED data. Any further refinements in the Agency's inhalation risk assessment would require submission of chemical specific exposure data for the CR formulation. A waiver of the requirement for an acute inhalation toxicity study on the CR formulation was deemed appropriate by TOX.

IV. Acute Dietary Exposure Analysis for Terbufos

It is the registrant's belief that the acute dietary exposure assessment prepared in the draft chapter of the HED RED is overly conservative. In response to the Agency's assessment, the registrant has submitted a revised acute dietary exposure assessment, using the Monte Carlo approach, conducted by TAS. While the Agency's assessment was based on tolerance level residues and the 1977-78 Nationwide Food Consumption Survey, the TAS assessment used the USDA Continuing Surveys of Food Intake by Individuals (CSFII) of 1989 through 1992, as well as field trial data in which crops were treated at the maximum rate. Furthermore, the TAS assessment used mean residues from field trials, rather than tolerance levels, for blended commodities. Percent crop treated data were used in the TAS assessment. The Monte Carlo analysis was conducted for single serving commodities, instead of using tolerance level residues for all commodities. Rather than using absolute high-end exposure estimates, TAS calculated 95th percentile estimates, and compared these estimates to the established NOEL of 0.005 mg/kg/day for plasma cholinesterase inhibition (dog studies), as well as to the proposed NOEL of 0.04 mg/kg/day based on RBC/brain cholinesterase inhibition (2-generation rat reproduction study).

HED Response

The overall approach used by the registrant in the submitted Monte Carlo analysis is acceptable, with a few exceptions. While the assumption of blending/mixing of commodities in commerce is acceptable in defending use of point estimates from field trials, rather than the worst-case tolerance levels, the correction for percent crop treated should not be applied to such point estimates. The analysis submitted by the registrant underestimates the risk by lowering residues used for mixed/blended commodities beyond the intent of the guideline.

The use of 95th percentile to develop MOEs is flawed in three basic ways. First, the 95th percentile is reasonably used for unrefined acute analyses because of the built-in conservative nature of the exposure and hazard estimates. However, the analysis presented by the registrant is highly refined in that the exposure estimate uses the entire range of field trial residue data, includes percent crop treated information in the Monte Carlo assessment, and includes no high-end tolerance level residues. Second, the registrant's rationale that the 95th percentile is appropriate because the toxicity endpoint is cholinesterase inhibition is flawed--at the critical dose level (6-month dog study), both plasma and cholinesterase inhibition occurred, and furthermore, the Agency does not discount plasma cholinesterase inhibition as a toxic sign.

Third, the detailed tables provided in Appendix 3 of the Monte Carlo analysis show that the use of the 95th percentile exposure level was necessary to obtain an MOE of 100 for non-nursing infants and all infants (consumers only), even with the many refinements incorporated into the analysis. These two groups achieved acceptable MOEs (>100) at the 97.5th percentile of exposure when using the less conservative population of all possible subjects.

HED recommends that the registrant repeat the analysis, removing the percent crop treated refinement for processed commodity residues. The results should be submitted to the Agency for evaluation. Given that the acute dietary risk assessment is extremely refined in its estimation of dietary exposure, the registrant may want to consider use of the 99th percentile exposure level, especially in light of FIFRA and FFDCA as amended, which requires the Agency to pay special attention to exposure to infants and children, and given that unacceptable MOEs have been obtained for infants (all infants and non-nursing).

Attachments

cc (without attachments): Bill Hazel, Alan Levy and Mark Dow (7509C)
cc (with attachments): Chemical File; Amy Porter (7508W)
RDI:WJHazel:11/25/96