

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

MEMORANDUM

TO: Larry L. Nelson, Ph.D., Chief
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Department of Pesticide Regulation
1220 N Street
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FROM: Anna M. Fan, Ph.D., Chief 
Pesticide and Environmental Toxicology Section

DATE: September 17, 1993

SUBJECT: Review of a revised draft risk characterization for the pesticide active ingredient cycloate.

Thank you for sending us the second version of the risk characterization document on cycloate. We are pleased that the hazards of this chemical have been recognized by recommending basic changes in its usage. However, we still have some significant concerns about farm worker health and safety because of the risk of irreversible, degenerative alterations in the nervous system. The fact that several related pesticides can cause this effect has not been considered in this health risk assessment. Therefore it cannot be determined whether the mitigation of exposure to cycloate as discussed is sufficient to avoid the overall neurotoxic hazard. Detailed comments on this and other relevant issues are attached for your consideration.

We realize that risk assessment for every new active ingredient brings new challenges to you and us. We are happy to have the opportunity to work with you to fulfill our mutual goal of protecting the public from harmful effects of pesticides. In order to facilitate the review process and for us to gain additional insights on your approaches and information that we might have missed, it would be helpful if DPR could provide a response to our comments, including the basis for not taking into account any suggestions and recommendations that we may have. We are grateful for such comments on some of our past reviews.

If you have any questions regarding the attached, detailed review, please contact me or Dr. Michael DiBartolomeis at ATSS 571-3063.

cc: Jolanta Bankowska, Ph.D.
Robert Howd, Ph.D.
Michael DiBartolomeis, Ph.D.
James Stratton, M.D.

Attachment

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REVIEW OF A REVISED DRAFT RISK CHARACTERIZATION FOR THE PESTICIDE ACTIVE INGREDIENT CYCLOATE

BACKGROUND

The Office of Environmental Health Hazard Assessment (OEHHA) provided comments on an earlier draft risk characterization for cycloate in a memorandum to Dr. Larry Nelson from Dr. Richard Jackson dated February 21, 1992. Our main concerns centered around the potential hazards to the human nervous system from exposure to cycloate. Cycloate was found to cause neurotoxic effects in rats, mice and dogs in numerous tests including acute, subchronic, chronic and reproductive toxicity studies.

OEHHA still has significant concerns regarding the assumptions and conclusions of the revised risk characterization. They are summarized below under the relevant headings.

ACUTE EXPOSURE TO CYCLOATE

We feel that the NOEL of 220 mg/kg/day for the acute occupational and dietary exposure assessment is not the most appropriate one. This NOEL was based on the clinical observation of cholinergic signs in a rat neurotoxicity study. In the study by Sprague and Thomassen, 1979, an increased incidence of chromorhinorrhea at 400 mg/day served to establish the NOEL at 220 mg/kg/day.

Clinical signs of toxicity not accompanied by any other toxicological parameters such as biochemical or macroscopic or microscopic alterations are poor indicators of a dose-response relationship. They are subject to error-prone, subjective, human observations and should be used for risk assessment purposes only when there are no other more reliable dose-response determinants available in appropriate acute studies.

In this case, a more appropriate toxicity study is available. In a developmental study in rats (WIL Research Lab, 1985), the NOEL was established at 75 mg/kg/day. This NOEL was based on clinical signs (alopecia, salivation, and dried red material around the eyes and nares) accompanied by a 60% decrease in body weight gain observed during the first three days of treatment at 175 mg/kg/day. The better quality of this toxicological endpoint -- clinical signs and decrease in body weight gain rather than clinical signs only -- outweighs the advantage of having an observation after exactly one day rather than three days of treatment, in our opinion. We acknowledge the cumulative toxicity of this pesticide and the relatively high acute MOS even with this preferred lower value. The lowest acceptable NOEL should nevertheless have been used, to retain consistency with health-protective principles.

WORKER HEALTH AND SAFETY

One of the main purposes of risk characterization documents should be protection of worker health by assuring that exposure to a particular chemical will not result in an unacceptable increased risk of an adverse health effect. This goal cannot be achieved by evaluating risk from exposure to a single chemical if workers would be concurrently exposed to additional similarly-acting chemicals. As stated on page 43 of the Risk Characterization document, cycloate may be applied with another thiocarbamate herbicide, EPTC (S-ethyl dipropyl-thiocarbamate). This combined exposure must be considered to determine whether the proposed mitigation will protect against neurotoxicity. Exposure during the season to vernolate and other potential neuropathic chemicals (such as those which cause OPIDN) should also be evaluated because of the irreversible or slowly reversible nature of these effects.

The MOS for neuropathy from the combined exposure to these pesticides may not be adequate. Although the risk assessment of separate (partial) exposures responsible for the same toxic effect satisfies current requirements, it may be misleading in this case. OEHHA believes that a combined exposure evaluation will be necessary to determine whether workers are at risk from the cycloate-type neuropathy.

MITIGATION MEASURES

Because of the earlier conclusions that the margin of safety (MOS) was inadequate for several classes of applicators, new mitigation measures have been proposed. These measures, as stated in the Executive Summary pg. 2 and the Risk Mitigation document pg. 47, would require that cycloate be identified as:

"...a minimal exposure pesticide according to the California Code of Regulation Title 3 Section 6790. The additional protective clothing and equipment are specified in Section 6793 of that same regulation. Additionally, mixer/loaders would wear an apron and a half-face respirator while using a closed system. Applicators or incorporators would have additional respiratory protection within a closed cab. No open cab application or incorporation would be allowable".

These newly recommended mitigation measures, if feasible, would significantly increase previously calculated MOS's to levels that are acceptable for both seasonal and chronic exposures (to cycloate considered alone). These procedures are important enough to be clearly described within the text of the document. This is especially important for "the additional protective clothing and equipment" referred to. It appears that the regulations require workers to wear several layers of clothing and a respirator while operating a closed-cab tractor. Both feasibility and enforcement have not been addressed in the document. These points will be discussed in a separate memorandum.

OTHER COMMENTS

The NOEL for nasal effects from subchronic inhalation of cycloate is 0.0213 mg/kg/day in ~~this~~ version. It was 0.043 mg/kg/day in the previous version, based on the same study (Knapp and Thomassen 1984). An explanation should be provided for this change in the final document.

There is an apparent contradiction about the current availability of a skin sensitization study. Table 1 on page 15 indicates that such a test was performed and showed negative results, but page 3 of Appendix B says that "No studies on dermal sensitization had been reported for cycloate." This should be explained or corrected.

An absorption rate of 50% for respiratory intake needs convincing justification. The compounds studied in the referenced articles by Raabe et al. are mostly volatile hydrocarbons with significant lung:air partition under the equilibrium conditions of the studies. These compounds are not appropriate surrogates for cycloate, which has a relatively low vapor pressure. We agree with the registrant that a 100% pulmonary absorption factor should be used, unless relevant evidence for a lower value is provided.