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Office of Environmental Health Hazard Assessment

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MEMORANDUM

Peter M. Rooney
Secretary for Environmental Protection

Pete Wilson
Governor

TO: Gary T. Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief RA Howard for Anna Fan
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DATE: June 16, 1998

SUBJECT: Comments on the Department of Pesticide Regulation's Draft Risk Characterization Document for the Active Ingredient Naled

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We have completed a preliminary review of the draft risk characterization for naled prepared by the Department of Pesticide Regulation (DPR). Naled is an organophosphate insecticide that controls pests on raw agricultural commodities, in space treatment, on farm animals, on pets, and on ornamentals. In 1995, 711,000 pounds of naled were used in California. It is a high priority active ingredient under the Birth Defect Prevention Act of 1984 (SB 950) and also is a candidate for evaluation under the Toxic Air Contaminant Identification and Control Act of 1983 (AB 1807). It is our understanding that this draft risk characterization document (RCD) is being submitted for our review under SB 950 only, and our review addresses issues of relevance to the SB-950 program. We would be happy to provide a later review of a risk characterization/exposure assessment prepared for the AB 1807 program, but do not recommend that this document be submitted to the Scientific Review Panel as a health effects document under AB 1807 without significant revisions. It is our understanding that a modified version of the RCD will be submitted at a later date for OEHHA review under AB 1807.

We conclude from our review that the current draft RCD for naled is inadequate for the purposes of SB 950 without significant revision. Due to the short time period designated for our review in your memo, we are not able to provide detailed technical comments. Therefore, you should consider these as general major comments in revising the draft. If you would like a more detailed discussion of the RCD, we would be happy to meet with your staff to go over these points in greater depth.

The draft risk characterization document for naled includes a summary and critique of the data available in DPR's registration data base; the appendices include somewhat more detailed information. We found the inclusion of summary tables helpful in accessing some of the more critical information. It is not clear from the RCD whether there was a full literature search to identify relevant articles from the open literature on the toxicology and hazard of naled and its major breakdown products to incorporate into the RCD. We have initiated a literature search but due to the time constraints it is not completed at this time. Pertinent information published in the open literature, but not submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. If a complete search was conducted, and no relevant data are available from the literature, we recommend that this be made clear in the naled RCD before it is finalized.

The technical analysis is problematic. Because of the data base insufficiencies, the naled RCD appears to include more "scientific judgment" than has been used in risk characterization documents prepared previously under SB 950. Our concern is that adequate scientific rationale or support for some of the interpretations and conclusions presented in the draft document is not provided or is difficult to locate. For example, the contrasting results from oncogenicity testing of naled and its major metabolite dichlorvos (DDVP) were not adequately discussed nor assessed in the document (see below). Also, the rationale for the selection of the noncarcinogenic toxicity studies used in the risk assessment is not adequately presented which in this case might represent deficiencies in the organization of the document rather than the scientific content. In other cases, the summary of toxicological studies lacked the detailed information necessary to support the conclusions. Therefore, we recommend that the draft document be revised to include more discussion and support, or better organization, in addressing the various aspects of the hazard identification, exposure assessment, and risk characterization for naled.

The major metabolite and breakdown product of naled is DDVP which is carcinogenic. In laboratory animals, DDVP increased the incidences of mononuclear leukemia, pancreatic adenomas, mammary gland carcinomas, fibroadenomas and adenomas, forestomach papillomas and carcinomas, and pituitary adenomas. DDVP also increased tumor growth in rats given leukemia transplants. In January 1989, DDVP was listed under Proposition 65 as a chemical known to the state to cause cancer. However, the RCD concluded that the parent compound naled is not oncogenic based on the equivocal results from chronic gavage studies in rats, and the negative results in mice and dogs. Although the document also concludes that naled is not genotoxic in either *in vitro* or *in vivo* studies, we consider the positive and equivocal studies to be evidence that naled is possibly genotoxic. The draft risk characterization should include an assessment of occupational and residential lifetime carcinogenic risk for naled based on internal doses of DDVP produced as a result of naled metabolism and naled degradation or product contamination. An assessment of lifetime carcinogenic risk for naled based on DDVP residues in food from naled used as an insecticide should also be included.

Despite the lack of assessment of carcinogenic risk and the deficiencies in the exposure assessment, the calculated margins of exposure (safety) for noncarcinogenic health risks were "less than the benchmark" (i.e., not health protective) for several agricultural and nonagricultural uses. The tolerances for naled are not health protective for both nursing and nonnursing infants (oranges), children one to six years old (oranges and spinach), and females 13 to 19 years old (grapefruit). The current food tolerances are even less protective for children than indicated in the RCD, however, because special sensitivity of the developing organisms to neurotoxic effects from exposure to naled was not taken into account. We do not support the decision to not use an additional safety factor to account for pre- and post-natal sensitivity as would likely be required under the Food Quality Protection Act of 1996. Furthermore, these risk levels would be higher if cumulative effects from other cholinesterase inhibitors were to be considered.

The exposure assessment also appears to be incomplete. For example, the exposure assessment concludes that there is no seasonal occupational exposure. In the light of the broad agricultural use of naled on many commodities, especially on cotton, more scientific support for omitting an assessment of seasonal exposures is warranted. In addition, the exposure assessment does not account for the higher acute and subchronic toxicity of the breakdown product DDVP following occupational exposures to naled, even when separate measurements of naled and DDVP are available. Because it is known that DDVP is four to five times more toxic than naled, exposures to the two chemicals should not have been considered equivalent, and simply added, in calculating exposures to grape harvesters. Because the same data were used in estimating exposures for other conditions, such as greenhouse work, combined toxicity calculations [naled + (5 x DDVP)] would also have been appropriate in these cases.

The draft document includes only a limited discussion of the range and distribution of potential occupational exposures and the assumptions used are not adequately supported. At the maximal application rate and practical maximum daily use, there will still be a range of exposures due to differences in work practices, as shown in every exposure study. As noted in the draft document, there have been naled exposures in California associated with systemic effects and low cholinesterase levels. A risk characterization which does not associate these effects (and the probability of such effects) with the use practices and exposures seems to leave out a critical step in the total evaluation. Furthermore, the use of maximal application rates (pounds/acre) and amounts of daily usage (acres/day) does not constitute an adequate evaluation of the maximum likely exposures. In actual experiments, the measured exposures typically vary over 100-fold. Exposure estimates which do not acknowledge the range of likely exposures will provide no perspective on why some applicators become symptomatic, while others do not. Leaving out this level of detail in an exposure assessment does not serve its ultimate purpose of documenting the types of pesticides and application methods which constitute worker hazards.

The draft exposure assessment states that "Adverse effects occur only when plasma levels in the target organ exceed a critical level." This statement generally refers to a chemical which acts in a reversible manner; it is less relevant for a kinetically irreversible mechanism of action such as the organophosphate acetylcholinesterase (AChE) inhibitors. Effects of the di-O-methyl organophosphates like naled are cumulative over at least a couple of days. Although acute toxicity for a dermal exposure to a typical OP is certainly less than that for an oral exposure, the net effect is not based on peak plasma levels, but on magnitude and rate of AChE inhibition. The draft exposure assessment document and the conclusions should be revised to appropriately reflect the mechanism of toxicity of AChE inhibitors.

As noted previously, we conclude from our review that the current draft risk characterization document for naled is inadequate for the purposes of SB 950 without significant revision. In general, the assumptions and conclusions stated in the draft risk characterization document require more scientific support, additional analysis and more detailed discussion in order to provide the risk managers with a complete analysis of the risks posed by the use of naled in California.

If you have any questions, please contact me or Dr. Michael DiBartolomeis at (510) 540-3063.

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