# Office of Environmental Health Hazard Assessment

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## MEMORANDUM

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**DATE:** August 27, 1998

**SUBJECT:** COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT PROPETAMPHOS

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We have completed our review of the draft risk characterization for propetamphos submitted for our review under SB 950 by the Department of Pesticide Regulation (DPR). Propetamphos, (E)-1-methylethyl-3[[(ethylamino)methoxyphosphinothioyl]oxy]-2-butenoate, is an organophosphate insecticide used for controlling cockroaches, flies, ants, ticks, moth, fleas, and mosquitoes. Propetamphos is a high priority active ingredient under the Birth Defect Prevention Act of 1984 (SB 950).

We conclude from our review that the draft RCD for propetamphos requires 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 a complete characterization of the risks posed by the use of propetamphos in California.

In reviewing the draft RCD for propetamphos, we considered the following information: 1) the draft propetamphos RCD (May 21, 1998); 2) the draft human exposure assessment for propetamphos prepared by the Worker Health and Safety Branch (August 9, 1996); 3) the

available toxicology summaries from DPR; 4) the analysis of acute exposure to propetamphos; 5) the analysis of chronic exposure to propetamphos; and 6) the results of our literature search.

Thank you for the opportunity to comment on the draft RCD for propetamphos. The comments are provided as follows. If you have any questions about our comments, please contact me or Dr. Michael J. DiBartolomeis at (510) 540-3063.

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## GENERAL COMMENTS

The draft risk characterization document for propetamphos includes summaries and critiques of the data available in DPR's registration database. There is a fair amount of repetition in summarizing the data, making the document unnecessarily hard to read. There are no appendices. The toxicological summary often included in RCDs was not appended to the draft propetamphos RCD. We found the inclusion of summary data tables helpful in accessing some of the more critical information.

### Literature Search

It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of propetamphos and its major breakdown products. 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 were identified, we recommend that this be made clear in the propetamphos RCD before it is finalized.

We conducted a literature search for propetamphos and its major breakdown products using the current 1998 on-line and CD-ROM based resources, including MedLine, ToxLine, BIOSIS, and the Integrated Risk Information System (IRIS). We would be happy to share the assembled information. In order to assist you in revising the draft RCD, we have cited selected published works at the end of this report that may be worth considering in your overall evaluation.

### Biotransformation and Pharmacokinetics

The sections on biotransformation and pharmacokinetics of propetamphos are difficult to follow because the location of the radiolabel on the chemical is not specified. However, it appears that the chemical was probably labeled only on the side-chain leaving group. Thus the moiety being followed in the distribution and excretion sections would be only the inactive side chain, which is of little interest following the initial hydrolysis. A discussion of the pharmacokinetics of phosphorylation reactions, including inhibition and reactivation of cholinesterase by propetamphos, would be more useful than a discussion of the rate of formation of $CO_2$ from the inactive side chain. We recommend that the revised RCD included a summary of the papers by Mason et al. (1993) and Dix et al. (1992) which address the aging of ChE and the pharmacokinetics of propetamphos. We also recommend including a discussion of the toxicodynamics of propetamphos, as well as the general principles applicable to organophosphate cholinesterase inhibitors in both the exposure assessment as well as the main risk characterization text.

**Acute Toxicity**

The draft RCD calculates margins of exposure (safety) well below 100 from exposure to propetamphos for both occupational and residential conditions, and for both adults and children. The draft exposure assessment utilizes average estimates for exposures. These margins of safety would be significantly smaller if upper-bound estimates for acute exposure were used as is scientifically valid and routinely done by risk assessors to obtain a range of exposure values inclusive of high-end exposures and to better characterize the uncertainty associated with using only mean estimates for exposure assessment. The draft RCD acknowledges that "the estimated MOEs for acute occupational exposures may not cover those individuals at the upper end of the exposure distribution curve." The same is true for the residential exposure estimates, and this should be stated also. We recommend including upper-bound estimates for acute exposures in addition to average estimates. If upper-bound estimates are not included, then an in-depth discussion of the quantitative impact of the use of average exposures rather than upper-bound exposures should be included in the uncertainty analysis section (see comment below on this issue). This approach and the results should also be discussed in the context of sensitive populations (see discussion of this issue below).

**Selection of NOEL for Chronic Toxicity**

From the one-year dog study a NOEL of 20 ppm (0.59 mg/kg-day) was identified and used in the draft propetamphos RCD for evaluating chronic occupational and residential exposure. According to the draft RCD, the NOEL is based on prolonged anestrus in females, reduced brain cholinesterase (ChE) activity, increased liver weights, and hepatic necrosis at the next higher dose of 100 ppm (3.03 mg/kg-day). However, we conclude that 0.59 mg/kg-day is a LO[A]EL, not a NOEL. Based on the scientific evidence, hepatotoxicity appears to be the critical toxic effect in this dog study; necrosis was observed at 3 mg/kg-day. At 0.59 mg/kg-day, significantly increased liver weights in male dogs were observed, establishing a dose-response for liver changes. In addition, inhibition of red blood cell ChE activity (55% and 71% of controls for males and females, respectively) was observed at 0.59 mg/kg-day. Furthermore, the revised October 31, 1995, version of the summary of toxicology data for propetamphos prepared by DPR (not included in the draft RCD) determined that the NOEL from this study is 4 ppm (0.13 mg/kg-day) propetamphos in the feed, presumably based on one or both of these endpoints. We determine that the NOAEL for this study is 0.13 mg/kg-day, in agreement with the DPR summary of toxicology data.

In another dog study (six month oral feeding), a NOEL of 0.09 mg/kg-day based on reduced brain ChE activity (64% of controls in male dogs) was identified. The two arguments (i.e., length of study and dose estimates not validated) for not selecting this lower NOEL for ChE inhibition for risk assessment were explained on page 37. The use of a six-month oral feeding study in dogs for chronic effects risk assessment can be scientifically justified. The fact that the concentrations of propetamphos in the feed cannot be confirmed is a concern, but not sufficient in itself to disregard the results. We conclude that 0.09 mg/kg-day is a scientifically acceptable NOEL to use for risk assessment.

After reviewing the available scientific information, we determine that 0.13 mg/kg-day is the most scientifically appropriate NOEL for the estimation of margins of safety for chronic exposure. This would agree with DPR's toxicological summary of October 31, 1995. The use of a NOEL of 0.59 mg/kg-day for reduced ChE activity rather than the NOEL of 0.13 mg/kg-day for the higher absolute and relative liver weights for the chronic exposure estimates underestimates risk by over four-fold. While the use of the NOEL of 0.09 mg/kg-day would result in lower margins of safety, the use of a slightly higher NOEL from a better-reported study would appear to be scientifically justified. Using the NOEL of 0.13 mg/kg-day, the lowest (mean) occupational MOE would be approximately 2 and the lowest (mean) residential exposure MOE for children would be approximately 10.

**Sensitive Populations**

No sensitive groups were identified in the draft RCD, although adverse reproductive effects were observed in a two-generation rat reproductive study at doses very close to the toxic threshold in dogs. In addition, the prolonged anestrus observed in the one-year dog study and the reduction in fertility and mating indices observed in the reproductive study may be related to endocrine effects. Increased sensitivity of females is further suggested by more pronounced inhibition of brain cholinesterase (ChE) in females than males in many of the subchronic experimental studies, and from the clinical differences in their susceptibility to propetamphos (Dix et al., 1992). We conclude based on the available scientific evidence that women should be considered a potential sensitive subgroup for this chemical, particularly during pregnancy. The observed endocrine effects are also likely to be more severe in the developing organism, and thus may require a higher margin of safety. We recommend consideration of this subpopulation in the risk appraisal in relation to the magnitude of risk in the general population, in relation to the use of averages for acute exposure (use of mean versus upper-bound exposure estimates), and with respect to the scientific uncertainty of evaluating exposure to only one organophosphate pesticide at a time.

**Exposure Assessment**

Level of Detail is Inadequate. The draft exposure assessment does not contain enough of the necessary scientific information to verify the results and assumptions made in deriving the potential exposure. For example, it is not possible to reproduce or confirm any of the calculations with the information provided. In addition, many exposure assumptions have not been justified (such as six hours of activity and 18 hours of rest per day for both adults and children, the adult inhalation rates, and the dislodgeable residue estimates). We recommend including scientific support for these assumptions when available, or when default assumptions are used, cite the risk assessment guidelines or other reference materials used as the source of the defaults.

One example where the science does not support the conclusions is related to the discussion of toxicity based on peak plasma levels of propetamphos following dermal and oral exposures. The draft RCD states that the use of an oral bolus administration is highly "conservative" for the estimation of exposure via the dermal route because the dermal dose acquired during a work-day would produce much lower peak plasma levels than the oral bolus,

and the toxicity would only occur when the plasma levels exceed critical levels in the target organs. When comparing dermal to oral absorption rates, it might be scientifically valid to apply a pharmacokinetically-derived correction factor to decrease the "apparent" toxicity when exposures are mainly dermal, when adequate data exist. However, this would not be based on the peak blood levels as indicated, because propetamphos is an irreversible cholinesterase inhibitor. The "plasma level" potency argument in the draft exposure assessment (pages 12 to 14) is not scientifically justified (nor scientifically valid). Another example is where the draft exposure assessment states that no aggregate exposure assessment (combined occupational and residential exposure) was carried out because "this exposure scenario was considered remote." This implies that no propetamphos applicators would have this termite treatment used in their own homes, which is still a possibility and worth consideration. A third example is the basis for assuming that one hour of extensive dermal contact during a Jazzercise® routine is equal to contact during a normal day's activities. This assumption has not been supported scientifically.

Discussion of Uncertainty. The draft exposure assessment "Exposure Appraisal" (page 12) states that "risk assessment is filled with uncertainty, and the risk assessor tends to be very conservative when making the numerous assumptions that are inherent in the process." The text continues by providing two examples of "the most important factors that produce overestimates." The overall conclusion of the draft exposure assessment is that the exposure estimates are overestimated by "several fold." First, while the draft exposure assessment was prepared to "openly and honestly discuss the sources of uncertainty so that the risk manager can put them in perspective," it has not included a discussion of the examples of the numerous assumptions used in the assessment that might underestimate the exposure levels. Secondly, while difficult to do, no attempt was made to quantify the level of uncertainty for any of the factors. Nevertheless, the assessment uses words like "grossly overestimates actual doses," "high degree of conservatism," and "several fold" when describing the level of uncertainty. This results in an emphasis on the potential overestimation, but is not balanced by a discussion of the potential underestimation.

The presentation of scientific support for the assumptions and concepts presented in this section is minimal and not quantifiable. As a result, this section describing uncertainty, which is an important component of a risk characterization, is not justified with a scientific analysis of the existing data and data gaps and may bias the "risk manager" into believing only one perspective. We recommend that this section be deleted from the draft exposure assessment and that a more inclusive and scientifically neutral discussion of uncertainty for the exposure and risk assessment be included in the main RCD where uncertainty is discussed (page 36).

Populations at Risk. The populations at risk are not adequately defined in the draft exposure assessment.

Illness Reports. The relationship of exposures, as estimated in the draft exposure assessment, and the illnesses as separately documented in DPR's pesticide illness surveillance program and reported on page four of the draft RCD, is not clear. Information given by Koehler and Moye (1995) on airborne insecticide residue may be of significance. We recommend reviewing this paper and including a discussion about the relationship between exposures and documented illness reports in the revised RCD.

## SPECIFIC COMMENTS

Pages 3 and 7. On page 3 the draft RCD states that the registrant requested that "DPR assume 100% dermal absorption in lieu of [submitting] a dermal absorption study." On page 7 the draft RCD states that "no dermal absorption data were available for propetamphos, so a default assumption of 50% was used." These two statements are confusing and the rationale for selecting the 50% dermal absorption rate given on page 7 is misleading. The default assumption of 50% might be appropriate for propetamphos given its physical and chemical properties (which are derived from data). If so, this is the rationale for selecting the 50% absorption rate and not that the data were unavailable. It is misleading to support the decision to use a less than maximum default value by stating that data were unavailable when DPR has the authority to require the data, but waived it. This can be corrected by providing the scientific rationale for selecting the 50% default value on page 7 and not the maximum default of 100%, and then deleting the reference to the unavailability of data.

Pages 11 and 12. It would appear from the values for oral and dermal $LD_{50}$ in Tables 1 and 2 that the toxicity of propetamphos liquid concentrate is being reported in Table 2 in terms of the weight of formulation, not weight of the active ingredient. This should be made clear.

Page 20. The text identifies a NOEL of 0.59 mg/kg-day for ChE inhibition and increased liver weight (and other effects) from a one-year oral (feed) study in dogs. The October 31, 1995, summary of toxicological data for propetamphos identified a NOEL of 0.13 mg/kg-day for increased liver weight. As noted above, we conclude that the use of the lower NOEL is scientifically justified. Nevertheless, the inconsistency in the two reports with respect to this study needs to be resolved.

Page 20, Table 7. We recommend including the data for red blood cell and plasma ChE activities in the table, along with the brain ChE, because these values are discussed in the text and there were significant compound-related changes in these activities.

Page 27. In the acute inhalation study, the LOEL and $LC_{50}$ for the technical grade formulation appear high. According to the data presented, the concentrated product is less than one-tenth as toxic as the diluted product, the 18.9% liquid concentrate (Table 1 compared to Table 2), and the 50% emulsifiable concentrate (page 13, reference to Leuschner et al.). Similarly the concentrated formulation is less toxic than oral doses of the same technical grade product. Organophosphates are generally more potent by inhalation, not less potent. The obtained result is likely to be related to the difficulty of conducting inhalation exposures to a chemical at several thousand times its equilibrium vapor pressure (i.e., with aerosol droplets). For such studies, determination of the delivered concentration and dose is difficult. We recommend that the revised RCD include information on these aspects of the study to explain the apparent aberrant results rather than only presenting the data (Table 10).

Page 39, section V. It is appropriate that the risk characterization acknowledges that cumulative exposures to organophosphates that have similar mechanisms of action should be considered, but

that methodology for this is still under development. However, we recommend that a more prominent statement to this effect be included in the discussion on uncertainty as well as in the "Summary" and "Conclusions" as this is a major issue yet to be properly addressed.

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