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MEMORANDUM

TO: Gary Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street
Sacramento, CA 95814-5624

FROM: Anna M. Fan, Ph.D., Chief
Pesticides and Environmental Toxicology Section

DATE: July 31, 1997

SUBJECT: Comments on DPR's Draft Risk Characterization Document for Propoxur

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Thank you for the opportunity to review and comment on the draft risk characterization document for propoxur. For the most part, staff of the Pesticide and Environmental Toxicology Section agree with the conclusions presented by the Department of Pesticide Regulation (DPR) in its document. A summary of our major comments and recommendations for your consideration in revising the draft risk characterization are listed below:

- In general, the conclusions stated in the draft risk characterization document for propoxur are supported by reasonable, objective scientific data and analysis.

- We agree with DPR's conclusion in the risk characterization document (and with the U.S. Environmental Protection Agency) that propoxur is a potential human carcinogen based on the evidence presented.

- The draft risk characterization provides an adequate discussion of the difference between oral and dermal exposures but does not address the potential for greater toxicity from inhalation exposures, particularly for acute effects. We suggest that inhalation exposures be assessed and incorporated into the risk characterization for propoxur.

Recycled Paper

- Expand and characterize more broadly the exposures to propoxur, including route-specific potency differences.

- The acute oral NOEL identified for risk appraisal in the risk characterization document does not accurately address the hazard posed by dermal exposure. A dermal NOEL can be estimated using pharmacokinetic data, working backward from a critical blood concentration to an applied dose by using estimates of dermal uptake rate and chemical half-life. The NOEL of 800 ug/kg-day as a combined exposure route toxicity estimate, rather than a dermal toxicity estimate, would be a reasonable substitute.

- Consideration of an additional scenario where acute exposure to propoxur could occur via a single bolus oral dose is also warranted. This is a likely scenario in a household environment with young children where hand-to-mouth behavior is common. An appropriate margin of safety estimation for the single bolus exposure would be based on a NOEL of 0.2 mg/kg.

- Discuss uncertainties pertaining to hazard identification, exposure analysis, and risk assessment.

- Address the possibility of the currently presented risk values as being underestimated because of chemical interactions and exposures to multiple cholinesterase inhibitors.

Please refer to the attached memorandum for a more detailed description of our comments. The comments were submitted for departmental approval in January 1997 and approved for section release in July 1997. We appreciate your patience during this time of competing priorities within the department. If you have any questions, please call me or Dr. Michael DiBartolomeis at (510) 540-3063.

cc: Michael J. DiBartolomeis, Ph.D.

ATTACHMENT

REVIEW OF THE RISK CHARACTERIZATION FOR PROPOXUR

This report consists of three parts. The background information in Part one provides a brief summary of the toxicology of propoxur and the Department of Pesticide Regulation's (DPR's) analysis and characterization of risks for this active ingredient. Part two provides our general and specific comments on toxicological and worker/public health issues related to the risk characterization, and it also includes some recommendations for enhancing the quality of the risk characterization document. The third part is a summary of our major comments.

BACKGROUND INFORMATION

Use

Propoxur is a general-use, non-systemic carbamate insecticide. It is used by commercial pest-control operators and homeowners against a wide variety of insects such as ants, cockroaches, flies, crickets, mosquitoes, wasps, ticks, and hornets in and around the home and office as well as commercial, industrial and institutional sites. For commercial use, propoxur is generally in the form of a wettable powder or emulsifiable concentrate. For homeowner use, propoxur is available as an aerosol, a ready-to-use liquid, or a granular or enclosed bait. For pet use, propoxur is available as an aerosol, a pet collar, and a dab-on.

Environmental Fate

The breakdown of propoxur in soil and water is accelerated by alkaline conditions. Data on hydrolysis submitted by the registrant was considered unacceptable. One published report indicated that at pH 8, the hydrolytic half-life of propoxur was 16 days. Bacterial degradation of propoxur was comparable under aerobic or anaerobic conditions with half-lives ranging from 80 to 210 days depending on soil type. Propoxur leaches readily from soils and may migrate from the location where it is applied. The risk characterization document concluded that propoxur is unlikely to become a persistent environmental contaminant.

Toxicology

Acute. Acute exposures to propoxur cause typical signs of acetylcholine poisoning resulting in both muscarinic (diarrhea, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, sweating) and nicotinic effects. Observed effect levels for humans are significantly lower than for other species. The acute no-observed-effect-level (NOEL) in humans for cholinergic signs resulting from a single bolus dose of propoxur is 0.2 mg/kg. In rats the lowest-observed-effect-level (LOEL) for cholinergic effects from a single dose is 2 mg/kg, and 4 mg/kg in dogs.

Subchronic. Three subchronic toxicity studies were described in the draft risk characterization document, including a dietary-rat (14-week) study, a gavage-monkey (13 week) study, and a dermal-rabbit (13-week) study. DPR did not use the results of these studies to assess human health risks in the draft document.

Chronic Toxicity and Oncogenicity. Carcinomas of the urinary bladder were observed in both sexes of a group receiving 5,000 ppm (highest concentration administered) in a two-year rat chronic feeding study of 1984. Urothelial hyperplasia was also observed in the 1,000 and 5,000 ppm groups in this study. These findings were confirmed in a 1988 two-year carcinogenicity study in female rats.

In a 1982 carcinogenicity study in mice (concentrations up to 6,000 ppm), no adverse effects on the urinary bladder were noted. These findings were confirmed in a 1988 study of female mice. In a 1992 mouse study there was a dose-related increase in bladder epithelial hyperplasia, which was classified as minimal and diffuse at 2,000 ppm and 8,000 ppm. There was no indication of any carcinogenic effect in the urinary bladder in mice.

A chronic NOEL of 7 mg/kg-day for depression of body weight gain and hemolytic anemia was identified in a dog study. Chronic NOELs for uroepithelial hyperplasia were identified to be 8.23 mg/kg-day in male and 11.02 mg/kg-day in female rats.

Genotoxicity. DPR concluded that the results of the genotoxicity studies on propoxur are equivocal. Tests with or without activation in bacteria, yeast, and Chinese hamster ovary cells were negative. Propoxur did not cause chromosomal damage or unscheduled DNA synthesis in Chinese hamster tissue *in vitro;* it did induce increased frequencies of sister chromatid exchanges

and micronuclei in human lymphocyte cultures. In addition, a propoxur metabolite, 2-isopropoxy-phenylhydroxy methylcarbamate, and a nitrosoderivative of propoxur were found to be mutagenic.

Reproductive Toxicity. A two-generation rat reproduction study revealed no adverse reproductive effects. The parental NOEL was 7.3 mg/kg-day for body weight gain decrease and inhibition of brain and red blood cell cholinesterase activity. The developmental NOEL was 37 mg/kg-day for decrease in weight gain in pups after day four.

Neurotoxicity. A single dose LOEL of 2 mg/kg was identified in rats for cholinergic signs such as excessive chewing and reclining posture, as well as significant inhibition of brain cholinesterase activity. There was no NOEL identified for this effect.

Exposure Assessment

Human exposures to propoxur were evaluated for pest control operators (PCOs) and for selected groups of people exposed to propoxur through non-occupational activities. Exposures determined for the PCOs included applicators using aerosol (1%), bait (2%), and sprays (0.95% and 70WP). Non-occupational exposures to propoxur included "passive exposures" calculated for an infant (six to nine months), an adolescent (12 years), and an adult An "active exposure" was calculated for a dog groomer using 0.25% spray.

Exposure estimates for applicators included "absorbed cycle dosage" (exposure incurred by applicators as a result of their job activities performed in one location during 1.8 hours, the time necessary for completion), annual averaged daily dosage (AADD), and lifetime averaged daily dosage (LADD). Estimates of non-occupational exposures to propoxur included two-hour absorbed dosage, AADD, and LADD. The LADD was not calculated for infants and adolescents. Propoxur is not used on food crops and therefore DPR did not perform a dietary exposure analysis.

Risk Assessment Basis

The assessment of the potential risks from acute occupational and from acute non-occupational exposure was based on a two-hour human NOEL of 800 ug/kg-day for cholinergic signs. Margin of safety (MOS) calculations for potential annual and lifetime exposure were based on a dog NOEL of 7 mg/kg-day for hemolytic anemia. DPR's maximum likelihood estimate (MLE) of

excess lifetime risk of cancer was based on a $Q_1 = 0.003$ (mg/kg-day)$^{-1}$ calculated using the combined incidence of benign and malignant bladder tumors in male and female rats from the rat feeding study of 1988 (see page 40 of the draft risk characterization document).

Risk Assessment Results

According to the risk characterization, MOSs determined for both acute and chronic, occupational and non-occupational exposures are within the range of values "conventionally accepted as health protective."

The MLEs of theoretical excess lifetime individual cancer risks from occupational exposure to propoxur ranged from 1×10^{-6} to 6×10^{-6}. The 95th percentile theoretical excess lifetime individual cancer risks for occupational exposure ranged from 2×10^{-6} to 9×10^{-6}. The MLEs of theoretical excess lifetime cancer risks from non-occupational exposure to propoxur were below 1×10^{-6}. The 95th percentile theoretical excess lifetime individual cancer risks for non-occupational exposure were at or below 2×10^{-6}.

COMMENTS

General Comments

In general, the conclusions stated in the draft risk characterization document for propoxur are supported by reasonable and objective scientific data and analysis. The risk assessment documentation submitted for our review does not include any proposals for mitigation measures as is consistent with DPR's new policy. Nevertheless, OEHHA should receive a copy of any proposed mitigation measures to reduce propoxur exposures from DPR for review and comment when it is available.

Oncogenicity. The pesticide fact sheet issued in January 1995 by U.S. EPA states "EPA's most recent peer review of propoxur took place in 1991. At that time the agency confirmed that there was insufficient evidence to change the classification of propoxur from its B2 classification (probable human carcinogen). Using the tumor rates from the 1984 rat carcinogenicity study, the U.S. EPA calculated a unit risk estimate (Q1*) of 3.7×10^{-3}." U.S. EPA was considering a special review of propoxur because of its carcinogenic potential, but after cancellation of several product registrations and deletion of label uses for which U.S. EPA had concerns regarding carcinogenic risk, it decided not to subject propoxur to a special review.

DPR concluded in the risk characterization document that propoxur is a potential human carcinogen based on the evidence presented. The scientific support for this conclusion (page 39) includes the following: 1) significant increases in several tumor types across two species and sexes, 2) common occurrence of uroepithelial lesions (associated with the development of bladder tumors), and 3) evidence of tumorigenicity with two separate exposure routes. The weight-of-evidence supports the conclusion that propoxur is a potential human carcinogen. Therefore, we agree with DPR's conclusion.

The upper-bound potency estimate for propoxur presented in the risk characterization document is comparable to that derived by U.S. EPA (4.0×10^{-3} versus 3.7×10^{-3}) although the potency estimates were based on two data sets from different studies. The authors of the risk characterization did not use the data that U.S. EPA used because the calculated MLEs "were effectively zero." In other words, the MLEs were so low that the authors of the risk characterization document were concerned that the risk would be underestimated. The near-zero MLE was not a concern to

U.S. EPA because the MLE was not used in its cancer potency calculations.

Exposure Assessment. The draft risk characterization provides an adequate discussion of the difference between oral and dermal exposures, but the analysis and discussion of the potential for greater toxicity from inhalation exposures, particularly for acute effects, is not as well documented. The reason for this, as stated in the draft risk characterization, is because whole-body inhalation is likely to overestimate inhalation exposures in rats due to grooming of fur which could lead to significant oral exposures. This assumption could be better justified if deposition of the chemical on the coat or uptake by the fur were demonstrated specifically for propoxur. However, no such data were presented in the risk characterization (see specific comments, below).

Because carbamate pesticides, including propoxur, have a short mechanism of action related to rapid decarbamoylation of inhibited acetylcholinesterase (AChE) (decarbamoylation half-life of approximately 20 to 30 minutes), the acute toxicity of propoxur due to AChE inhibition would tend to be route-specific. In general, inhalation toxicity would depend on the dose rate, with high-concentration short exposures being most toxic and low-concentration, more prolonged exposures being less toxic (with equivalent total doses). Oral toxicity by gavage can be significantly less than that of a short-term inhalation exposure (because of slower oral absorption), while oral toxicity in the diet depends on the feeding pattern. In dogs, for example, dietary toxicity is usually similar to gavage because dogs tend to eat their food immediately and their stomach emptying time is short. In rats, dietary toxicity is much less than that by gavage. Dermal toxicity is usually less (perhaps by two or three orders of magnitude), because carbamates are often relatively hydrophilic and penetrate skin slowly.

This route-specific toxicity complicates a risk assessment for pesticides or other environmental contaminants because a typical human exposure may be partly by the oral route (from hand-to-mouth behavior), partly by the inhalation route (for aerosolized or vapor-phase chemicals), and partly by the dermal route. It is not clear whether this pharmacodynamic effect is relevant for carcinogenicity and related chronic effects (e.g., hyperplasia) because the mechanism of carcinogenicity is not known for propoxur. However, in the rat dietary studies, the minimum effect level for tissue hyperplasia appeared to be 58 mg/kg-day, with a significant incidence of carcinogenicity only

at 184 mg/kg-day and above. When administered by inhalation, the minimum dose of propoxur causing tissue hyperplasia in rats was 12.7 mg/kg-day (Pauluhn, 1992).

Potential increased toxicity from inhalation exposures is only relevant if a significant part of total human exposures is by inhalation. The inhalation route was estimated to represent up to 12% of total exposure (Appendix A, Table 5), but the relative contributions for inhalation and dermal exposures were not broken out in some of the exposure tables, although it was stated that the route-specific information was available. Therefore, the significance of inhalation exposure cannot be fully determined by the information available in the document. If inhalation exposures were included, it is likely that the calculated MOSs would be lower and the theoretical excess lifetime individual cancer risks higher compared to what is presented in the risk characterization document. Therefore, we suggest that inhalation exposures be assessed and incorporated into the overall predicted risk characterization for propoxur.

Worker Health. Although the total use of propoxur appears to be relatively low when considering the number of pounds sold in California in 1993 (page 6), the 148 registered products containing this active ingredient would appear to facilitate combined exposures to multiple products. Risk values might be underestimated if all sources of exposure to propoxur are not considered.

Discussion of illness reports (see Appendix A, page 3) can logically be expanded to include an analysis of situations responsible for illnesses, to determine whether illness can be avoided. Consideration of providing a brief evaluation of these reports in the main part of the risk characterization document, in the context of the estimated MOS for propoxur, is warranted.

Exposure Scenarios. The acute exposure scenario applied to occupational and non-occupational risk assessment used 1.8 hours (occupational) and two hours (non-occupational) as the bases for absorbed dosage. For MOS calculations, this dosage was compared to the NOEL of 800 ug/kg-day. The NOEL was derived from a human study where an unknown number of volunteers were given five oral doses of 0.2 mg/kg propoxur at 30 minute intervals. Red blood cell cholinesterase activity was depressed to a "minimum of 60% of control levels," but returned to control levels within two hours. There were no cholinergic signs reported for subjects administered propoxur on an intermittent basis.

This acute oral NOEL might not accurately address the hazard posed by dermal exposure. A more accurate dermal NOEL might be estimated using pharmacokinetic data, working backward from a critical blood concentration to an applied dose by using estimates of dermal uptake rate and chemical half-life. Some judgment could also be introduced as to inhalation toxicity and pharmacokinetics for use in realistic exposure scenarios. However, we acknowledge that this might be considered undesirable on the basis of the limited available information. If so, the use of the NOEL of 800 ug/kg-day as a combined exposure route toxicity estimate, rather than a dermal toxicity estimate, would be a reasonable substitute.

Consideration of an additional scenario where acute exposure to propoxur could occur via a single bolus oral dose is also warranted. This is a likely scenario in a household environment with young children via hand-to-mouth behavior. An appropriate MOS estimation for the single bolus exposure would be based on a NOEL of 0.2 mg/kg.

Multiple Exposure to Cholinesterase Inhibitors. Current DPR risk assessment policy apparently does not allow for an evaluation of the contribution of risk from a single cholinesterase inhibitor to the overall risk of cholinergic effects incurred by people from exposure to multiple cholinesterase inhibitors. However, the results of such assessment might reveal excessive total risk for cholinergic effects for some people or in some activities. Consideration of this issue, at least qualitatively in the risk characterization document, is warranted.

Structure-Activity Relationships. The quality of the risk assessment would be enhanced if the document addressed structure-activity relationships of propoxur for carcinogenic, neurotoxic, and other critical toxic effects. The U.S. EPA recommended including such analyses regarding carcinogenicity in its recent "Draft Proposed Guidelines for Carcinogen Risk Assessment," Office of Research and Development, U.S. EPA, 1996. Because propoxur is classified as a potential human carcinogen, the recommendation seems to apply in this case.

Specific Comments

Main Document

Pages 1, 7 and 8. The risk characterization document states that propoxur is unlikely to become a persistent

at 184 mg/kg-day and above. When administered by inhalation, the minimum dose of propoxur causing tissue hyperplasia in rats was 12.7 mg/kg-day (Pauluhn, 1992).

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Specific Comments

Main Document

Pages 1, 7 and 8. The risk characterization document states that propoxur is unlikely to become a persistent

Page 37. Consider replacing the first two paragraphs under "acute toxicity" with another paragraph after the existing third paragraph discussing the animal studies, with route-specific and time-dependent dose-response effects. Such a revision could specifically address the concept of lower toxicity with dermal exposures, and potential higher toxicity with inhalation exposures for later evaluation of exposure scenarios. This would also eliminate the need to provide an argument for not selecting to use human data (rather than the apparently preferred animal dermal data) to extrapolate dose-response data for human acute toxicity.

Page 40. The draft risk characterization states that the carcinogenic potency of propoxur was calculated using the linear multistage model. However, in Appendix B the computer printout shows computations based on the Weibull model. The printout for the linear multistage model should be provided in the appendix.

Page 42. The propoxur dermal absorption rate of 0.351% per hour used in this assessment (taken from Appendix A, pages 8 and 9) is based, according to the authors (J. Sanborn, personal communication) on the 0 to 4 hour urinary excretion rate in the human experiment of Feldmann and Maibach (1974). This procedure does not account for the dermal absorption and the urinary excretion lag times. One result of this procedure is that the maximum absorption dose rate, which is a critical factor in carbamate toxicity, might be significantly underestimated. Actual maximum dermal absorption rate is likely to be at least 1% per hour considering the observed 16% excretion in 24 hours and the dermal absorption lag times. Dermal absorption would also be faster through abraded skin. Changing the estimates to account for pharmacokinetics is fully justified by the available data.

The effect of dermal absorption rate and amount, compared to inhalation, on estimated route-specific toxicity is also important to predict total exposures to propoxur. If a dermal dose were absorbed at 1% per hour with 16% total absorption, and the same amount were available by inhalation over eight hours, with 50% uptake, the inhalation dose rate would be 6.25 times the dermal dose rate, and the total inhalation dose would be 3.125 times the dermal dose. If the dermal absorption rate were 0.351% per hour, then the inhalation dose rate would be 17.8 times the dermal dose rate (with a correspondingly greater toxicity by inhalation, compared to dermal exposure). The estimated dermal absorption rate greatly affects the proportion of total toxic dose equivalent delivered by inhalation in the mixed-route exposure expected from use of aerosol products.

Page 42. The statement that PCOs worked for six hours per day seems to conflict with Appendix A, which discusses four 1.8-hour cycles in an eight hour day.

Pages 43 to 44. We are aware of the historical context for assuming 50% respiratory uptake of propoxur for occupational exposures, and 100% uptake for all other contexts (taken from Appendix A, which is derived from earlier estimates; personal communication, James Sanborn). Nevertheless, independent calculations based on physicochemical properties of the chemical would be more scientifically objective for risk estimates and appear less internally inconsistent. A respiratory uptake value of between 50% and 70% would probably be reasonable, considering the high water solubility, moderate lipophilicity, and low vapor pressure of propoxur.

Pages 44 and 46. Assuming that it takes two hours to apply propoxur as an aerosol spray to two dogs is inconsistent with 1) the statement in Appendix A (page 10) that this task requires one to two minutes per dog, and 2) the 20 dogs per day rate in the dog-groomer study (Waggoner, 1991). A time period of 30 minutes, which would be associated with a NOEL of 200 ug/kg or a LOEL of 0.36 ug/kg, might better represent the available data. The estimated dose could then be corrected for partial inhalation and for slow dermal absorption of that fraction of the dose presumed to be dermal, which is not discussed. The effective NOEL for a dermal exposure would be much greater than the 800 ug/kg used here for acute effects, with an appropriate dose rate correction (i.e., 1% per hour or more). However, as discussed above, some inhalation exposure is likely when applying an aerosol spray to an animal. The effective NOEL of 800 ug/kg may be a good value for this combined-route absorption, but a discussion of the combined-route exposure would be helpful.

Page 47. While the preponderance of exposure (by weight of chemical) should be dermal, as stated in the "acute toxicity" paragraph, acknowledgment of a greater toxic potential for inhalation exposure would be appropriate here. The statement that dermal exposure accounts for 99% of total exposure in most instances does not appear consistent with the exposure assessment in Appendix A. In Appendix A, Table 5, page 9, the only place (other than Table 7 which refers to a discontinued product) where a specific proportion can be determined, the percentages of total exposure by inhalation of the products "used routinely" in California are 3.3% and 12%, for the 1% aerosol and 70WP spray, respectively. An observation of 12% inhalation for the 70WP spray, multiplied by a 5- or 10-fold increase in relative

toxicity by inhalation (compared to dermal absorption) could result in 50% or more of the acute toxicity from the inhalation route. Therefore, most of the toxic effect could be from the small fraction of the dose by inhalation, since dermal absorption is so slow it contributes less to the toxic effects. Apparent inhalation exposures are common in reported illnesses from propoxur (S. Edmiston, "Human illnesses/injuries reported by physicians in California involving indoor exposure to pesticides containing chlorpyrifos, DDVP and/or propoxur 1983-1986," HS 1431, 1990). As noted above, inclusion of a quantitative assessment of the contribution of inhalation exposure to the total exposure is warranted by the scientific data.

Page 49. With reference to the last line on the page, the exposure to home-use pesticides depends on the frequency a house is sprayed for insect pests which would be related to lifestyle choices, including keeping household pets, rather than the length of time occupying a specific residence (in the risk characterization, this is assumed to be seven years). Consideration of other assumptions based on frequency of indoor pesticide application might be warranted here.

Page 50. The risk characterization cites a study in which 15 dog handlers who treated 20 dogs per day with flea dip control products (Waggoner) exhibited no signs of pesticide-related toxicity as support for not considering this pathway of exposure as significant. However, a California study of pesticide use by animal handlers (Ames *et al.*, 1989) documented reports of toxic symptoms from propoxur in this context. Review and evaluation of pesticide illness reports associated with propoxur (Edmiston, 1990) would provide additional information on this pathway of exposure to include in the risk characterization document.

Appendix A.

Pages 6 and 7, Tables 3 and 4. The exposure assessments cannot be interpreted with the minimal data provided. Of particular importance is the proportion of dose from the dermal route compared to the inhalation route in these exposures, which is not stated.

Page 8. First paragraph. Propoxur use in structures is stated as 2,535 pounds. According to page 2 and a separate communication with staff of the Worker Health and Safety Branch (Jim Sanborn, personal communication), this is the amount from the pesticide use reports, which represents use by structural pest control officers (there are no approved agricultural uses in California). The following statement, "This low level of use of

propoxur as a structural insecticide further decreases the probability of exposure to other cholinesterase-inhibiting insecticides used in this scenario..." was intended to relate only to use by professional pesticide applicators. It should not be overlooked, however, that the remaining propoxur uses, about 20,000 pounds, are applications in and around the home or office. While some proportion of these applications are exterior (e.g., for control of ants in the garden), all represent potential pathways for human exposures. Therefore, the majority of the potential exposures and uses of propoxur are not addressed in this use summation, despite the fact that the section is titled "Home Occupant and Worker Exposures." Since many of the illness reports (Edmiston, 1990) refer to use in just this situation, the exposure estimates might be understated. This possibility warrants further consideration.

Page 8. The derivation of the dermal absorption estimate and its potential use in risk assessment, should be discussed. As was noted above, it appears that the dermal uptake rate should be higher, that inhalation exposures should be considered, and that some quantitative estimate of relative toxicity by the two pathways should be provided.

Pages 9 and 11. As noted earlier, the use of two different inhalation exposure values, 50% for workers and 100% for all other contexts, seems inconsistent, despite the historical reasons for the dichotomy. A single value for exposure to aerosols (e.g., the average of these two numbers, 75%) would be more consistent.

SUMMARY OF MAJOR COMMENTS

- In general, the conclusions stated in the draft risk characterization document for propoxur are supported by reasonable, objective scientific data and analysis.

- We agree with DPR's conclusion in the risk characterization document that propoxur is a potential human carcinogen based on the evidence presented.

- The draft risk characterization provides an adequate discussion of the difference between oral and dermal exposures but does not address the potential for greater toxicity from inhalation exposures, particularly for acute effects. We suggest that inhalation exposures be assessed and incorporated into the risk characterization for propoxur.

- Expand and characterize more broadly the exposures to propoxur, including route-specific potency differences.

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- Consideration of an additional scenario where acute exposure to propoxur could occur via a single bolus oral dose is also warranted. This can easily happen in a household environment with young children via hand-to-mouth behavior. An appropriate MOS estimation for the single bolus exposure would be based on a NOEL of 0.2 mg/kg.

- Discuss uncertainties pertaining to hazard identification, exposure analysis, and risk assessment.

- Address the possibility of the currently presented risk values as being underestimated because of chemical interactions and exposures to multiple cholinesterase inhibitors.

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