California Environmental Protection Agency
James M. Strock, *Secretary for Environmental Protection*

State of California
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OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
Steven A. Book, *Interim Director*

M E M O R A N D U M

TO: Larry L. Nelson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1220 N Street, Room A-413
Sacramento, CA 95814

FROM: Richard J. Jackson, M.D., M.P.H., Chief
Hazard Identification and Risk
Assessment Branch

DATE: June 11, 1992

SUBJECT: Review of Draft AB 2161 Documents on Malathion, Chlorpyrifos, and Bensulfuron Methyl

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Please find enclosed the Hazard Identification and Risk Assessment Branch's technical review of the Department of Pesticide Regulation's (DPR) draft dietary risk assessments prepared under AB 2161 for bensulfuron methyl (Londex^{tm}), malathion, and chlorpyrifos. We understand that prior to the completion of our review, DPR finalized the three documents. Nevertheless, these comments still apply to these and future documents prepared by DPR under AB 2161.

In general, the documents present the basic information necessary to develop dietary risk assessments for the three pesticides. We make the following recommendations for improving these documents:

- The risk assessment portions should be clearly separated from the risk management portions in these documents. If necessary, two documents should be issued.

- Organization of the three documents seems inconsistent and in some cases confusing. Organizational improvement of these documents would probably be accomplished by conforming to DPR's "Guidelines for Dietary Risk Assessment". Some changes on the draft reports may have already been made in DPR's final version of the three dietary risk assessments, but these documents have not been reviewed and compared to the draft reports.

- Cholinesterase inhibition is a toxic endpoint for risk assessment determination and should be identified in all applicable dietary risk assessment documents.

- Since multiple exposures to cholinesterase inhibitors in food are not taken into account in DPR's dietary health risk assessments, we recommend that additional uncertainty factors be applied to determine margins of safety, or that an analysis of the impact of not accounting

for multiple cholinesterase inhibitor exposure on the overall margins of safety of these pesticides.

- Although a brief discussion of uncertainties is included in these documents, only those that DPR believes would "overestimate" risks are presented. Uncertainties that would "underestimate" risk should also be included. Discussion of uncertainties should be science-based without risk management consideration.

- All dietary risk assessments should include a risk analysis of pesticide levels at the food tolerance since these are the legally allowed levels for pesticides in food. Such analyses should be conducted separately from those in which actual residue data are used.

- Current margin of safety determinations for dietary risks of pesticide exposure do not include exposure from non-dietary sources. Exposures from drinking water, treated structures, and surfaces such as lawns occur. Some margin of safety for non-food exposure must be included.

Further concerns and recommendations are presented in the attached comments. If you have any questions concerning this review, please contact me or Dr. Michael J. DiBartolomeis at 8/571-3063.

Attachment

cc: Steven A. Book, Ph.D.
Michael J. DiBartolomeis, Ph.D.
Anna M. Fan, Ph.D.
Lubow Jowa, Ph.D.

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OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

M E M O R A N D U M

TO: Richard J. Jackson, Chief
Hazard Identification and Risk Assessment Branch

VIA: Anna M. Fan, Ph.D, Chief
Pesticide and Environmental Toxicology Section

VIA: Michael J. DiBartolomeis, Ph.D.,
Acting Chief, Pesticide and Food Toxicology Unit

FROM: Lubow Jowa, Ph.D.
Staff Toxicologist

DATE: May 1, 1992

SUBJECT: Review of three AB 2161 Draft Documents:
Malathion, Chlorpyrifos, and Bensulfuron Methyl

At the request of Dr. DiBartolomeis, I reviewed the three AB 2161 draft dietary risk assessments prepared by the Department of Pesticide Regulation. My comments are attached. If you have any questions please call me at 8//467-7327.

Attachment

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HAZARD IDENTIFICATION AND RISK ASSESSMENT BRANCH'S REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT DIETARY EXPOSURE ASSESSMENT DOCUMENTS FOR MALATHION, CHLORPYRIFOS, AND LONDAX^{tm}

The following is a review of the Department of Pesticide Regulation's (DPR) draft AB 2161 dietary exposure assessment documents for malathion, Londax^{tm}, and chlorpyrifos. The review addresses the major issues of concern inherent in all three documents. The substance of these issues is presented in Section 1.0, "GENERAL COMMENTS" of this review. However, specific comments were noted on individual documents in Section 2.0.

1.0 GENERAL COMMENTS

It appears that the objective of these documents is to present risk assessments of acute and chronic dietary exposure to three food-use pesticides based on measured or threshold residue levels. Exposures to a nation-wide population, or to specific population subgroups, were computed using Exposure-1^{tm} and Exposure-2^{tm}. For malathion and chlorpyrifos, cholinesterase inhibition was used as an endpoint for evaluation of dietary health assessments. For Londax^{tm}, developmental toxicity and liver toxicity were chosen as the toxicological endpoints of concern for the acute and chronic exposure scenarios, respectively. DPR concluded that the computed margins of safety for all three pesticides were within acceptable limits for dietary risks.

1.1 Organization

Originally, substantial comments on the organization and content of these documents were prepared. However, sometime later, a revised addendum to the "Outline for Dietary Risk Assessment Document for Sections 3, 5, 24(c) and AB 2161" (January, 1992) was received and it was noted that all the comments regarding terminology and organization were addressed in this document. [NOTE: We never received a copy of the complete draft outline document (October 31, 1991) from DPR, only the final version]. Organizational improvement of the three existing AB 2161 documents may be accomplished by conforming to this outline.

In reference to these "guidelines", it is recommended that more specific guidance regarding content be provided in the outline. For example, each dietary health risk assessment document should include a purpose and scope. The purpose is important for the reader to comprehend why the document was generated, so that no misinterpretation

regarding the document's intent or purpose is made. The scope is important to understand how the document is organized. In the chlorpyrifos and malathion draft documents, there is an attempt to define the purpose, but the scope is virtually ignored. The draft Londax^{tm} dietary risk assessment document has neither purpose nor scope defined within. The inclusion of a scope would be helpful in all three documents.

1.2 Cholinesterase Inhibition

DPR's policy for using cholinesterase inhibition as a toxic endpoint for risk assessment determination is not defined in either the chlorpyrifos or malathion risk assessment documents. However, DPR's use of cholinesterase inhibition in these two documents can be summarized as follows:

1) It is DPR's position that cholinesterase inhibition by itself is not a suitable endpoint for hazard determination and risk assessment for acute and chronic exposures. This conclusion seems to be based on DPR's observation that no *proven* toxicity has been associated with the depression of the various forms of cholinesterase (brain, red blood cell, and plasma). Therefore, DPR concludes that clinical effects of cholinesterase inhibition should be the only suitable endpoints related to cholinesterase inhibition.

2) However, DPR occasionally may identify a no-observed-(adverse) effect-level [NO(A)EL] based on acute human studies having blood cholinesterase inhibition, with the understanding that the "true" NO(A)EL is likely to be higher.

3) In chronic dietary risk assessments, cholinesterase inhibition found in experimental animal studies may be used as an endpoint for margin of safety determinations, but only when brain cholinesterase is inhibited by at least 50% (a level at which reported cholinergic signs had occurred in animals).

At this time, OEHHA considers 20% inhibition of plasma, red blood cell (RBC), or brain cholinesterase to be a toxicological endpoint of concern for risk assessment (see 1991 DHS malathion risk assessment for example). However, OEHHA staff are currently reevaluating the science supporting this assumption. OEHHA asserts that DPR's limited application of cholinesterase inhibition for risk assessment is under-protective of health, particularly since

multiple exposures to cholinesterase inhibitors in food were not taken into account in these dietary health risk assessments.

We are also concerned about inconsistencies in DPR's application of its own assumptions. Examples of such inconsistencies can be found in the chlorpyrifos and malathion dietary risk assessment documents. In the malathion document, acute inhibition of cholinesterase without concomitant signs of clinical disease is not considered a toxicological endpoint of concern (see Section 2.3, Malathion). For chlorpyrifos, DPR identifies 50% depression of brain cholinesterase by chlorpyrifos as an adverse effect in rats and dogs even though no cholinergic signs were reported (Young and Grandjean, 1988; McCollister, 1971). The 50% inhibition of brain cholinesterase is supposed to be associated with cholinergic signs according to Bignami *et al.*(1975). Therefore, DPR has chosen to ignore the experimental results by deferring to Bignami *et al.* principle when it appears not to be applicable for chlorpyrifos-associated inhibition of brain cholinesterase. Adoption of the 50% level inhibition level of brain cholinesterase as a LOAEL in this case violates DPR's first assumption, that cholinergic signs must accompany the analytical determination. If DPR believes that cholinergic signs should have been seen when they were not, justification should be provided as to why these signs could not have been detected.

In addition, it has been suggested that exposed individuals (including experimental subjects) may accommodate to the initial toxic effects of cholinesterase inhibitors so that tolerance to the toxicity of such pesticides is achieved after repeated exposure (EPA, 1990). This may explain why the chronic NO(A)EL for chlorpyrifos(1 mg/kg-day) is higher than the acute NO(A)EL of 0.5 mg/kg-day. If this were true, the changes in physiological homeostasis leading to such a chemical tolerance may be considered an adverse effect in itself. From a scientific perspective, it would be difficult to advance this theory with the available data. On the other hand, it would be difficult to justify risk assessment of a pesticide based on a NO(A)EL for chronic exposure that is higher than a NO(A)EL for acute exposure for the same toxicological endpoint.

- DPR should review the appropriateness of using chronic cholinesterase inhibition for risk assessment when inhibition levels are less than seen with acute evaluations.

- We recommend that until further data are generated, DPR use the lower NO(A)EL based on an acute study for

cholinesterase inhibition for repeated exposures, and apply appropriate uncertainty factors.

Another concern is that in both the malathion and chlorpyrifos dietary risk assessment documents, the calculated margins of safety for acute exposures are approximately ten which is just within DPR's range of acceptable exposures. However, this is assessed for exposure to one pesticide residue. It is likely that individuals consuming a variety of products will be exposed to more than one cholinesterase-inhibiting pesticide. What should adequate margins of safety be for assumed exposures from multiple cholinesterase inhibitors? The concomitant acute effect of cholinesterase inhibition from a variety of sources may require greater margins of safety.

- This uncertainty in evaluating cholinesterase inhibitors should be addressed in all applicable dietary risk assessments.

1.3 Calculation of Exposure Values

DPR should present exposure levels on both detected residue levels and at established tolerances. Tolerances are the legally allowable levels of pesticides in foods, and therefore population groups can be assumed to be potentially exposed to these levels. To determine whether these legal limits are health protective, it would be necessary to conduct risk assessments for exposures to established tolerance levels for each pesticide.

DPR used two different approaches to determine average values for residues on commodities. In the chlorpyrifos dietary risk assessment document, arithmetic means were used. However in the malathion document, geometric means were used. The use of arithmetic means is not justified unless it is reasonably certain that a normal distribution exists. From a cursory review of the chlorpyrifos database, it does not appear that the data are normally distributed. It is likely that residue levels of other pesticides are not normally distributed, as well.

- DPR should perform a statistical analysis of the data, and if appropriate, the geometric mean approach used in the malathion document should be adopted for other pesticides reviewed under this program.

- DPR should provide exposure analyses on tolerance levels in foods and not just on detectable levels.

2.0 SPECIFIC COMMENTS

2.1 Londax^{tm} (Bensulfuron Methyl)

2.1.1 Executive Summary and Introduction

The major deficiencies of this document are primarily in logical development and in organization. For example, the authors present a summary of the risk assessment process in the EXECUTIVE SUMMARY, but fail to explain adequately the purpose of the risk assessment except to refer to the legislation in the executive summary. No statement of the reason of performing the risk assessment is given elsewhere in the document. Examining the dietary risk or potential dietary risk of the pesticide residue has a purpose (protection of public health) which could be stated up-front, even in terms of excerpting portions of the relevant legislation. The reader should not have to surmise the purpose of a document, and at a minimum, an explanation of the risk assessment process and the intent of these documents should be provided in the INTRODUCTION.

- The Executive Summary and Introduction should be expanded to address these concerns in the revised document(s).

- A section on the chemical and physical properties of the pesticide should be included either in the INTRODUCTION, or as a separate heading (this would be appropriate for all chemical health risk assessments). This information is helpful in considering how a chemical could be metabolized by the body or useful in predicting interactions with other toxic agents, if this should be a concern later.

2.1.2 Toxicology Profile

The following concerns should be addressed in the revised document:

An interpretive statement regarding the acute toxicities presented in TABLE 1, page 2, should be added to the document, along with a discussion of their relevance/nonrelevance to the overall risk assessment.

Part B, page 2. With regard to the effects of increased liver weight, cloudy liver color and centrilobular swelling, were these results statistically significant and at what dose? Do the results display a statistical trend? Why were liver/brain weight ratios the only criterion for identification of the NO(A)EL? These questions should be answered in the revised document.

More detailed information is necessary in this and subsequent toxicity study summaries where effects are mentioned without regard to the doses at which they appear. This information is useful for supporting the NO(A)EL designations for these studies.

Part F, page 4. It is unclear why minor histological changes to the liver of females were not sufficient to select a NO(A)EL for maternal effects. DPR should designate a NO(A)EL for this study as it does for other reproductive studies summarized in this document.

2.1.3 Hazard Identification/Dose-Response Evaluation

The following concerns should be addressed in the revised document:

In this section (pages 6 and 7), a developmental toxicity study used to determine the acute exposure NO(A)EL is identified and described (Haskell, 1984). Rats were given 0, 50, 500 and 2,000 mg/kg-day of Londax^{tm}. Increases in fetal variations were observed at the 500 mg/kg-day dose and above. The test material was reported not to be maternally toxic at these doses. Thus a NO(A)EL of 50 mg/kg-day was proposed.

Whereas the teratology study receives an extensive write-up, little information is provided about the chronic toxicity study selected for risk assessment in this section. The document states that a NO(A)EL of 19.9 mg/kg-day, based on liver effects, was observed in a chronic dog feeding study. The reader is referred to a more extensive description provided earlier. However, it is awkward to handle the chronic and acute toxicity description and selection in the stated manner. This section should have been combined with the toxicology profile into a toxicity assessment section, and therefore all the toxicity studies and the derived NO(A)ELs could be presented together.

With regard to the developmental abnormalities, it would be useful to compare the incidence in historical controls for that strain with these experimental results. This comparison is highly useful for interpreting the significance of any deviation in the anomaly rate. Were the historical occurrence data mentioned in the experimental report?

2.1.4 Risk Characterization

The following concerns should be addressed in the revised document:

A discussion of the carcinogenicity/noncarcinogenicity of Londax^{tm} is not included in this section. Since Londax^{tm} has not been associated with higher rates of tumor formation, this should be noted accordingly in this section to emphasize that the carcinogenic effect has not been demonstrated to be a concern for exposure to Londax^{tm}.

Although a brief discussion of uncertainties is included, and this section appears to correspond to the "Risk Appraisal" section in the other dietary risk assessment documents, it does not appear to be designated as such in this one. Not all assumptions made here are known to overestimate the risks. For example, there is no scientific basis to assume that the use of a teratology study would over-predict acute exposure. It is not known how many doses are required to influence the effects noted here, perhaps only one dose is necessary. Therefore, the use of the teratology study may not be overly conservative to predict possible effects from acute exposure to pregnant women.

2.1.5 Conclusions

Although there are data gaps, notably the lack of metabolism information, the compound has no significant toxicity found in the chronic studies. The data do not indicate that the compound is carcinogenic.

Overall, the risk assessment document could be improved by major reorganization and enhancement of certain sections to more clearly show the risk assessment rationale.

2.2 Chlorpyrifos

2.2.1 Executive Summary

As with the Londax^{tm} dietary risk assessment, the entire executive summary focuses too much on what a risk assessment is (which is not addressed in the text) and devotes too little attention to summarizing the entire document. For example, nothing about the toxic effects of chlorpyrifos is stated in this section. Also, it is more important to explain how the risk assessment is meeting the requirements of the AB 2161 legislation, than it is to explain what a risk assessment consists of. Finally, the meaning of margins of safety should be explained as part of the risk assessment process.

2.2.2 Introduction

The following concerns should be addressed in the revised document:

It should be stated on page 1 that actual risks are not quantified, but rather the doses from estimated exposures are compared with doses estimated to be safe.

The explanation of the mechanism of toxic action of chlorpyrifos is good, but it might be more appropriate for the TOXICOLOGICAL PROFILE section.

2.2.3 Pharmacokinetics

Summary, page 2. It should be mentioned how rapidly chlorpyrifos is absorbed or eliminated. This information would be important for understanding whether a toxic dose of chlorpyrifos can be accumulated in the organism.

2.2.4 Acute Toxicity

The following concerns should be addressed in the revised document:

No mention is made of depression of cholinesterase in acute animal studies. Was it reported at all? It is important to compare the animal cholinesterase response with that of the human after acute dosing.

In this document, it is stated on page 9, first paragraph, "... EPA RfD is 0.003 mg/kg-day based on inhibition of plasma cholinesterase activity in the dog study." (cited from an RfD tracking report). Recent examination of the IRIS database performed on 1/17/92 (the actual file was dated 3/01/88), revealed that the RfD (same value) was not based on a dog study, but on a subchronic human study performed for Dow Chemical in 1972. We reviewed this study in the DPR library:

1) Four human subjects were administered orally either 0, 0.014, 0.03, or 0.10 mg/kg-day of chlorpyrifos for up to 20 days.

2) Dosing for the highest exposure group was suspended after one subject was reported to have cold-like symptoms (runny nose and blurred vision). The investigators attributed these symptoms to a cold, nevertheless, they still suspended the dosing for that group.

3) The plasma cholinesterase activity was significantly depressed (up to 87% when compared with background levels) for this same exposure group.

This study is relevant for derivation of NO(A)ELs to be used for dietary risk assessment. The cold-like symptoms could be associated with depression of cholinesterase

levels, hence, this human study may show a relationship between depression of cholinesterase levels with clinical signs. A NO(A)EL can be designated from the lower doses used in the study at which no significant increase in cholinesterase inhibition was determined. We recommend that this study be incorporated into the dietary risk assessment.

2.2.5 Chronic Toxicity

The following concerns should be addressed in the revised document:

In the oral (dietary) subchronic dog study (page 3), how many dogs were used in the experiment? What were the dose levels? When did cholinergic signs occur? Important experimental information is lacking in the study descriptions.

We have difficulty in interpreting DPR's determination of NO(A)ELs from the various chronic studies. In the dog study a NO(A)EL for red blood cell and plasma cholinesterase is identified; in the rat dietary study, only the NO(A)EL for cholinesterase inhibition is given, without a specific designation of what type of cholinesterase was affected.

2.2.6 Teratogenicity

Page 9. In the gavage rat study, there was a statement that "no toxic developmental effects were noted". Were there *non-adverse* developmental effects? On what basis was this conclusion made?

2.2.7 Hazard Identification

Page 9. DPR states that a human study was used to avoid the use of an uncertainty factor. This statement is not appropriate. Human studies are often used because, when conducted appropriately, they are the best means to directly predict the result of chemical exposure in humans. The only reason human studies are not used more frequently in risk assessments is that they are frequently lacking, unethical to conduct, or inadequate for risk assessment purposes. Furthermore, the DPR approach for deriving margins of safety does not involve the use of uncertainty factors for interspecies differences, therefore this statement contradicts DPR's approach to risk assessment.

- Some other justification as to the appropriateness of using this human study for risk assessment should be included in the revised document.

It is premature to consider that 0.5 and 1.0 mg/kg-day are NO(A)ELs for acute and chronic exposures, when the

subacute study (Dow, 1972) clearly shows significant plasma cholinesterase depression at 0.1 mg/kg-day with concomitant clinical signs. Use of this study as the basis for risk assessment would affect the resulting margins of safety.

- The results of the Dow, 1972 study should be considered in the risk assessment prepared by DPR. A range of risks may be presented, and levels of uncertainty in the evaluation.

2.2.8 Exposure Assessment

The following concerns should be addressed in the revised document:

The rationale is not clear why margins of safety for certain population subgroups are not reported in the text. For Hispanic and Black subpopulations (important subpopulations for this state), margins of safety do not appear in the summary tables in the text (TABLES 3 and 4), but appear in the summary tables in the appendix. Summary tables should include margins of safety for all relevant subpopulations. Predicted exposure levels in these populations should also be included in the text.

The description of the surveillance monitoring programs administrated by DPR is helpful and should be included in other dietary risk assessment documents.

Page 11, first paragraph. "undetectable levels" should be "nondetectable."

2.2.9 Risk Appraisal

This section addresses uncertainties in the margins of safety determinations, but only for those estimates that DPR feels would result in an overestimate of risk. DPR should also address uncertainties that would tend to underestimate risk. For example, DPR's document does not address the problem of potential additive effects from exposure to multiple cholinesterase inhibiting pesticides. A discussion of uncertainty should include reference to this issue and other concerns that would underestimate risk.

2.2.8 Conclusions

The risk assessment of dietary chlorpyrifos exposure was based on reported acute cholinesterase depression in humans and for chronic cholinesterase depression in rat. The calculated margins of safety for both acute and chronic exposures were determined by DPR to be within acceptable risk management guidelines, although for the acute

exposures, the margin of safety for infants is 14, barely within an acceptable range.

DPR concludes that chlorpyrifos does not pose a significant dietary risk based on assessment involving cholinesterase inhibition levels in humans and animals. However, there are some conceptual problems because of the debate on using cholinesterase inhibition as both an indicator of exposure and of toxicity is ongoing. Cholinesterase inhibition from chronic, repeated exposures may present an added complication for risk assessment, that is, changes in physiological homeostasis may lead to chemical tolerance. There is some question on how to incorporate the concept of chemical tolerance to interpret cholinesterase inhibition outcome from chronic risk assessments.

Furthermore, we are concerned that human subacute study results were not evaluated and these results could impact significantly on the outcome of this assessment. Hence, the margins of safety computed in this document may not be adequately protective of public health.

2.3 Malathion

2.3.1 General

The major concern regarding the overall appearance of this document is that it is too abbreviated, particularly in the summary sections. The executive summary requires additional background explanation to aid the nontechnical reader. For example, what does it mean to derive the 95th percentile on the user-day (page 1)? Also, what is a "definitive" NO(A)EL (page 1)? This latter term seems to be used only in this document.

2.3.2 Introduction

This section is inadequate in the amount of relevant introductory information provided. A good introduction would describe the provisions of the AB 2161 legislation and risk assessment principles, and provide a scope for the document.

2.3.3 Toxicological Profile and Hazard Identification

The following concerns should be addressed in the revised document:

The basic explanation of the cholinesterase inhibition process is helpful and should be included in all documents in which cholinesterase inhibition is evaluated for risk assessment purposes.

Clarification is required in the description of the Moeller and Rider (1961) study on page 2. It should be noted that there were actually three experiments. In the first experiment, five adult males received malathion at 8 mg/day for 32 days, and no significant depression in plasma and red cell cholinesterase was seen. In the second experiment, 16 mg/day was given to another five adult males for 41 days, with no significant depression in either cholinesterases. In the final experiment, 24 mg/day was given for 56 days to another group of five adult males, significant depression in both red cell and plasma cholinesterase was observed after administration was terminated at a maximum of 25%.

In the acute section (page 2), the acute effects of malathion on animals are not mentioned. Although the human study may be the most appropriate for risk assessment, for comparative purposes, some mention should be made of acute studies performed in experimental animals.

Similarly, in the chronic study, although experimental studies on animals are mentioned, not a single one is addressed where cholinesterase inhibition activity was reported. Furthermore, there is no mention of studies which reported neurobehavioral effects, or studied genotoxicity, reproductive and other toxicological endpoints. It may not be necessary for the limited scope of this document to describe these studies in detail. However, brief summaries as to the toxicity profile of malathion can be presented in order to demonstrate that these effects were considered for the risk assessment. A toxicity summary is appended to this document and the reader could be referred to it for additional information.

The term "definitive NO(A)EL" appears in this section (page 2) only to describe the acute NO(A)EL, however there was also a reference to a chronic "definitive" NO(A)EL in the EXECUTIVE SUMMARY. Why is the chronic NO(A)EL listed here not designated "definitive?" It is not clear where this term originated and what it means in this context. Even according to the DPR rationale, the NO(A)EL from the acute study is not by any interpretation, <u>definitive</u>. DPR states that this NO(A)EL used is less than the "true" NO(A)EL, so how can it be definitive?

DPR has elected to use the highest dose administered 24 mg/day (0.34 mg/kg-day) as the NO(A)EL for the acute exposure assessment, because..."The acute toxicological endpoint of concern in animals and in humans is the occurrence of clinical signs associated with inhibition of ChE activity... Maximal inhibition did not result in clinical signs of toxicity ... The definitive acute NO(A)EL,

based on cholinergic signs is 0.34." (page 2). DPR implies that presence of cholinergic signs is the only valid criteria for designation acute NO(A)ELs, not cholinesterase inhibition. Cholinesterase inhibition appears to be a valid criterion only for chronic risk assessments.

We believe this policy is questionable based on the concept of chemical tolerance to cholinesterase inhibition, and that acute inhibition is more indicative of potential adverse effects than chronic inhibition. Therefore, the 0.22 mg/kg-day is the most appropriate NO(A)EL for both the acute and chronic exposure considerations, as was used in the Malathion Risk Assessment document prepared by DHS in 1991.

2.3.4 Exposure Assessment

The basis for exposure assessment seems adequate. Malathion has an extensive residue monitoring program in all commodities. Besides the utilization of measurable residue values, a default methodology was used to estimate levels of malathion when detectable levels were not reported. Furthermore, if a processed food product had no detectable residues, but the raw agricultural commodity from which it was derived had measurable residues, the levels in raw agricultural commodities were also assume to be present in the processed food.

2.3.5 Risk Characterization

Margins of safety were calculated and listed for the exposures determined in the previous section. Although not all of the estimated margins of safety were presented in the text, all were within acceptable limits for the maximum exposed populations, under both acute and chronic conditions.

2.3.6 Risk Appraisal

In general, DPR states that the assumptions made during this assessment were made in the direction of overestimating exposures. No discussion is included of the uncertainties of the toxicological assessment. DPR believes that cholinergic signs would be the most sensitive toxicological endpoints in the malathion toxicity data base. However, since no cholinergic signs were reported in any of the studies from which DPR derived a NO(A)EL, DPR assumes that all evaluations based on NO(A)ELs for cholinesterase inhibition for malathion would be overly protective.

- DPR should clearly define its policy for using cholinesterase inhibition as a toxicological endpoint for risk assessment.

- In its analysis of uncertainty, DPR should include factors that would underestimate risk as well as overestimate risk.

The most sensitive effect described in the risk assessment is depression of cholinesterase activity in the blood. However, this is not considered by DPR to be a "true" toxic endpoint, but rather a useful value to assure that potential detrimental exposures are not reached. We believe that the malathion database is not extensive enough to make such definitive statements and this section should be modified to reflect this concern.

2.3.7 Conclusions

DPR's conclusions for malathion residues on food products are that for both acute and chronic exposures, the margins of safety are adequate. The basis for this conclusion is a study of cholinesterase depression in human experimental subjects. The human study is the most appropriate for the risk assessment of this compound, but we disagree with the manner in which the acute NO(A)EL was derived. Both the chronic and acute NO(A)ELs should be 0.22 mg/kg-day for malathion as was done in the 1991 DHS malathion risk assessment document.

3.0 RECOMMENDATIONS

The following recommendations apply in general to all dietary risk assessment prepared by DPR. Specific recommendations for the individual documents are listed in Section 2.0 above.

- DPR should separate risk assessment from risk management in these documents. If necessary, two documents should be issued. This is a problem with the SB 950 documents, and it should not carry over to the AB 2161 documents.

- Organization of the three documents is inconsistent and in some cases confusing. Organizational improvement of these documents would probably be accomplished by conforming to DPR's "Guidelines for Dietary Risk Assessment". [NOTE: OEHHA has received a copy of the final version (January 13, 1992) from DPR and is currently reviewing it for further comment].

- In reference to these "guidelines", it is recommended that more specific guidance regarding content be provided. For example, each dietary health risk assessment document should include a purpose and scope and discussion of risk assessment methods and assumptions.

- DPR's policy for using cholinesterase inhibition as a toxic endpoint for risk assessment determination should be defined in all applicable dietary risk assessment documents. Inconsistencies in applying the policy should be resolved.

- Since multiple exposures to cholinesterase inhibitors in food are not taken into account in DPR's dietary health risk assessments, we recommend that additional uncertainty factors be applied to determine margins of safety, or that an analysis of the impact of not

accounting for multiple cholinesterase inhibitor exposure on the overall margins of safety of these pesticides.

- DPR should review the appropriateness of using chronic cholinesterase inhibition for risk assessment when inhibition levels are less than seen with acute evaluations. For chlorpyrifos, we recommend that until further data are generated, DPR use the lower NO(A)EL based on an acute study for cholinesterase inhibition for repeated exposures, and apply appropriate uncertainty factors.

- DPR used two different approaches to determine average values for residues on commodities in the existing dietary risk assessments. DPR should perform a statistical analysis of the data, and if appropriate, the geometric mean should be used for all pesticides reviewed under AB 2161.

- We recommend that a section on the chemical and physical properties of the pesticide be included the dietary risk assessments.

- Although a brief discussion of uncertainties is included in these documents, only those that DPR believes would "overestimate" risks are presented. Uncertainties that would "underestimate" risk should also be included. Discussion of uncertainties should be science-based without risk management consideration.

- Summary tables in the main text should include margins of safety for all relevant subpopulations. Predicted exposure levels in these populations should also be included in the text.

- The use of the term "definitive NO(A)EL" needs clarification since there does not appear to be a scientific basis for using such a term.

- All other recommendations as noted above.

4.0 REFERENCES

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