Office of Environmental Health Hazard Assessment

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MEMORANDUM

Winston H. Hickox
Agency Secretary

Gray Davis
Governor

TO: Gary Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
P.O. Box 4015
Sacramento, California 95812-4015

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

DATE: April 26, 2001

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S ADDENDUM TO NALED RISK CHARACTERIZATION DOCUMENT

The Office of Environmental Health Hazard Assessment (OEHHA) staff has completed the review of the Addendum to Naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) risk characterization document (draft RCD) prepared by the Department of Pesticide Regulation (DPR). We also took the opportunity to update the status of the risk assessment of Naled. Naled is an organophosphate insecticide that controls pests on raw agricultural commodities, in space treatment, on farm animal premises, on pets, and on ornamentals.

The package received by OEHHA consists of the Naled draft RCD (99-03) First Addendum dated January 22, 2001, and an Attachment A, Human Exposure Assessment for Naled, by Michael H. Dong and David E. Haskell, Worker Health and Safety Branch, DPR.

To assist in our review, we consulted our comments (dated August 31, 1998) on the DPR draft RCD of May 1998, DPR responses to those comments addressed in a memorandum to Anna Fan from Gary Patterson dated March 2, 1999, and Naled RCD dated November 11, 1999.

The reevaluation of exposure to Naled and the resulting Addendum to the RCD were triggered by the registrant's submission to DPR of new acute and subchronic toxicity studies, the availability of 1995 air monitoring data, and revocation by the U.S. Environmental Protection Agency of naled tolerances for milk, meat and eggs.

In the Addendum the risks from exposures to Naled were reevaluated by taking into account the following: revised dermal absorption factor of 35 percent instead of the previously used default value of 50 percent, additional new acute and subchronic toxicity studies, change in the exposure expression for localized skin effects (amount per surface area instead of the amount per body weight), change in benchmark for localized skin effects (10 instead of 100), change in the default factor for the extrapolation of no-observed-adverse-effect level (NOAEL) from lowest-observed-adverse-effect-level (LOAEL) for localized dermal effects in the subchronic dermal toxicity study (3 instead of 10), and additional exposure scenarios (assessing acute effects on the skin, reassessing dietary exposures and ambient air exposures).

Overall, the primary comments are as follows. More details on particular issues related to the Addendum and an update on the overall risk assessment of Naled are presented in the attachment.

1. The Addendum does not provide enough information for OEHHA to conduct an objective evaluation of the change made in the absorption factor (from 50 to 35 percent, versus OEHHA's recommendation of 100 percent) and more details should be included in this regard.

2. More substantiation should be provided for changing the default factor (change from 10 to 3) for the extrapolation of NOAEL from LOAEL for localized dermal effects in the subchronic dermal toxicity study.

Other than these, OEHHA does not object to the approaches and procedures used by DPR in updating its RCD for Naled. The new information does allow refinement of the risk estimates presented in the 1999 RCD for Naled. However, there are still some outstanding issues from our comments of August 1998 that have not been addressed. These issues are mentioned in the attachment.

Thank you for providing the document for our review. If you have any questions about our comments, please contact me or Dr. Michael DiBartolomeis at (510) 622-3170.

Attachment

cc: See next page

cc: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

Michael J. DiBartolomeis, Ph.D., Chief
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ATTACHMENT

COMMENTS ON THE ADDENDUM TO NALED RISK CHARACTERIZATION DOCUMENT

In response to a memorandum to Anna Fan from Gary Patterson, dated January 22, 2001, the Office of Environmental Health Hazard Assessment (OEHHA) provides review comments on the Department of Pesticide Regulation's (DPR's) Addendum to Naled Risk Characterization Document (RCD) of 1999 as presented below.

The package received by the OEHHA for review consists of the Naled draft RCD (99-03), First Addendum dated January 22, 2001 and an Attachment A, Human Exposure Assessment for Naled by Michael H. Dong and David E. Haskell, Worker Health and Safety Branch.

Background Information

Naled (1,2-dibromo-2, 2-dichloroethyl dimethyl phosphate) is an organophosphate used in California for control of insects and mites in a great variety of agricultural and nonagricultural settings. Major uses include applications on fruits, cotton, nuts, greenhouse ornamentals, and vegetables. Naled can be also used in aquatic areas (e.g. marinas and swamps), forests, dwellings (e.g. hotels), and indoor settings such as animal buildings, hospitals, factories, restaurants, warehouses, feedlots, and meat packing establishments.

Update on the risk assessment for Naled

The human health risk assessment for Naled was conducted because of possible adverse effects identified in chronic, oncogenicity, and reproductive toxicity studies. DPR prepared a draft RCD for Naled in May 1998. OEHHA reviewed this document and provided comments in August 1998 (memorandum from Anna Fan to Gary Patterson dated August 31, 1998).

Major concerns addressed in these comments related to the oncogenic potential of Naled and its metabolites DDVP and dichloroacetic acid (DCAA) and Naled's potential for pre- and postnatal toxicity. We also pointed out that the document did not evaluate seasonal occupational and residential exposures.

Responses to our comments were provided in a memorandum to Anna Fan from Gary Patterson dated March 2, 1999. Overall, our suggestions for clarification, more discussion, and recommendation to assess seasonal exposures were accepted and reflected in the subsequent version of the RCD for Naled dated November 11, 1999.

However, potential oncogenicity of Naled and its metabolites/degradation products as well as the protectiveness of the current tolerances (e.g., a discussion as to whether application of an additional uncertainty factor should be considered under the Food Quality Protection Act) still remain two major areas to be addressed. While we may agree that the existing data are not sufficient to permit quantitative risk assessment for the oncogenic potential of Naled, we believe that Naled's potential oncogenicity should be taken into account by applying an extra uncertainty

factor in calculating margins of exposure (MOEs) from chronic exposures to Naled. We cannot disregard the evidence for tumor occurrence. We understand that these responses were considered in DPR's responses as either statistically insignificant or produced in inadequate studies (see DPR responses to OEHHA memorandum of August 31, 1998).

In the responses to our comments (memorandum to Gary Patterson from Lori O. Lim, February 26, 1999) and in the 1999 Naled RCDtwo reasons were given to justify the interpretation of the lack of pre- and post-natal developmental toxic effects of Naled. These are: 1) both developmental and maternal effects were produced at the same level of exposure, and 2) in the studies where positive developmental effects occurred at levels lower than those showing maternal effects, the positive results were not statistically significant and/or the studies were of poor quality. OEHHA staff believes that developmental effects should not be discounted on the basis that they were produced at the same level as maternal effects. These effects may be of lesser concern than those produced at levels lower than maternal toxicity, but could still have occurred independently from maternal toxicity and not as a result of it.The reason provided in the 1999 draft RCD (page 79) for not considering the effects of cumulative exposures to Naled and other organophosphate compounds is that there is currently no methodology to address this issue. We understand that it may take some time before appropriate methodology is developed and accepted, but in the meantime the health risk obviously increased by cumulative exposures to chemicals with the same mechanism of action. This should be addressed in DPR's report.

Another issue where OEHHA differs in its opinion from DPR is the default value used for absorption via the inhalation route. We believe that the default value for non-volatile and volatile chemicals should be 100 percent when there is no data to support a different value. Naled is a semivolatile compound and we recommend using 100 percent instead of the 50 percent used in the RCD for Naled. This particular unresolved issue would probably be revisited during the proposed review process of Naled as a Toxic Air Contaminant (TAC).

The 1999 RCD for Naled contains an Appendix G with Peer Review Comments and Responses. The Appendix includes the OEHHA comments (dated August 31, 1998) and responses to the comments from the Medical Toxicology Branch (memorandum from Lori O. Lim to Gary Patterson dated February 26, 1999, later on submitted to OEHHA in the memorandum to Anna Fan from Gary Patterson, dated March 2, 1999) and responses to the comments from the Worker Health and Safety Branch (WH&S) (memorandum to John S. Sanders from Michael H. Dong dated February 4, 1999). The responses from the WH&S on exposure related issues were not submitted to OEHHA. We identified them only after they were incorporated to the 1999 RCD.

Addendum to Naled draft RCD

The reevaluation of exposure to Naled and the resulting Addendum to the RCD were triggered by the registrant's submission to DPR's new acute and subchronic toxicity studies, the availability of 1995 air monitoring data, and revocation of naled tolerances for milk, meat and eggs.

In the Addendum the risks from exposures to Naled were reevaluated by taking into account several factors. These are: revised dermal absorption factor of 35 percent instead of the previously used default value of 50 percent, additional new acute and subchronic toxicity studies, change in exposure expression for localized skin effects (amount per surface area instead of the amount per body weight), change in the benchmark for localized skin effects (10 instead of 100), change in the default factor for the extrapolation of no-observed-adverse-effect level (NOAEL) from lowest-observed-adverse-effect level (LOAEL) for localized dermal effects in the subchronic dermal toxicity study (3 instead of 10), and additional exposure scenarios (assessing acute effects on the skin, reassessing dietary exposures and ambient air exposures). Our comments on these issues are provided below.

New dermal absorption factor

In previous versions of RCD for Naled, doses absorbed from dermal exposure were calculated using the absorption default value of 50 percent. The registrant, AMVAC, submitted new studies on the dermal absorption of Naled as a part of the overall comments on the draft RCD (Jones, 1999; Davies, 2000). The dermal absorption factor of 35 percent was established (Dong, 2000 a, b) based on *in vivo* dermal absorption data on Naled in the rat.

Insufficient information is provided in the Addendum to us to evaluate objectively the quality and appropriateness of using this study and the absorption factor of 35 percent as the basis for risk assessment recalculations. We suggest that more details on the subject study and its evaluation be provided within the revised RCD. DPR review of the study (Dong, 2000 b) can also be included as a part of the Appendix G on Peer Review Comments and Responses.

Adjustment of the No-Observed-Effect Level (NOEL)/NOAEL for skin irritation

The NOEL for skin irritation) used in the 1999 RCD was 1 mg/kg-day (Rausina and Zimmerman, 1986). This NOEL was established in a 21-day dermal toxicity study in rats (12/sex/group) exposed to Naled at the levels of 0, 1, 20 or 80 mg/kg-day five days per week. In the new study rats (5/sex/group) received 21 dermal application of Naled at the levels of 0, 5, 10 or 40 mg/kg-day in a 28day period. We agree that the NOAEL of 5 mg/kg-day established in the latter study is more accurate and appropriate for risk assessment since the interval between the NOAEL and the Lowest-Observed-Effect Level (LOAEL) is only two-fold (5 and 10 mg/kg-day) compared to twenty-fold (1 and 20 mg/kg-day) in the first study.

Change in skin exposure expression

For localized skin effects, the report has revised the exposure expression to the amount of Naled per surface area instead of the amount of active ingredient per body weight as presented in the RCD. The underlying assumption in translating estimates from the subchronic dermal studies with rats expressed in mg/kg body weight to $\mu g/cm^2$ was: average body weight for a rat, 200 g, whole body surface area 325 cm^2, and applied surface area 32.5 cm^2. Consequently the NOAEL of 5 mg/kg-day for subchronic localized effects (Moxon, 2000) was translated to 1.5$\mu g/cm^2$. This NOAEL was further adjusted to 44 $\mu g/cm^2$ by accounting for the dosing regimen of five days per seven days (61.5$\mu g/cm^2$ x 5/7).

OEHHA supports the procedure described above. Expressing dermal exposure in $\mu g/cm^2$ instead of mg/kg-day seems appropriate.

Change in benchmark for localized skin effects

Dermal irritation as a toxicological end point was evaluated in the 1999 RCD by using a benchmark of 100 for an uncertainty factor. This benchmark consisted of interspecies and intraspecies uncertainty factors of ten (10 x 10). Application of the interspecies uncertainty factor of ten is based on the assumption that humans are more sensitive than experimental animals to chemical exposure.

The Risk Characterization part of the Addendum (page 25) provided a comprehensive discussion to show that the uncertainty factor for interspecies extrapolation is not necessary for dermal irritation. The ten-fold intraspecies uncertainty factor was retained for systemic effects after dermal exposure. The arguments provided by the report in support of eliminating the interspecies uncertainty factor for evaluating skin irritation from dermal exposures are convincing.

Change in default factor for the extrapolation from the LOAEL to the NOAEL

In the 1999 RCD, a default factor of ten was used to calculate the NOAEL from the LOAEL in the subchronic dermal toxicity study (Rausina and Zimmerman, 1986). In the Addendum, a factor of three was adopted to extrapolate from the LOAEL to NOAEL. The reason provided for this change was that the observed dermal effects at the LOAEL were mild. This justification seems to be subjective and the revised RCD would benefit if more substantiation were provided. DPR may consider applying a factor of six to extrapolate from the LOAEL to NOAEL when the observed effects at the LOAEL are mild (OEHHA, 1999). This and other issues related to uncertainty factors used in the derivation of acute reference exposure levels (RELs) were broadly discussed in the Air Toxic Hot Spots Program Risk Assessment Guidelines (OEHHA, 1999) reviewed by the Scientific Review Panel (SRP).

Additional exposure scenarios

In the draft RCD, localized effects were evaluated only after seasonal exposures. The Addendum document also includes an evaluation of acute effects on the skin. This was encouraged by a review of the currently available subchronic dermal toxicity studies and by the observation that skin irritation effects occurred after a few days of exposure. We support the addition of this evaluation.

Two other changes were provided for in the Addendum. The first is a reassessment of dietary exposures because of the U.S. Environmental Protection Agency's recent proposal to revoke Naled tolerances for milk, meat, and eggs. The second is a reassessment of ambient air exposures of residents to include the 1995 air monitoring data as well as the 1991 data evaluated in the RCD.

Both reassessments made the evaluation of Naled more current.

Conclusions on the current risks from exposure to Naled

According to the current revised risks from exposures to Naled, the MOEs for the following occupational and residential activities were below 100 for chronic effects and 10 for localized skin acute effects.

1. Acute exposure only for skin and systemic effects in homeowners using pet collars, and systemic effects only in homeowners and workers using backpack applicators, workers using pet collars, workers involved in sewage system injections.
2. Subchronic exposure for systemic effects only in mosquito control applicators.
3. Chronic exposure for systemic effects only in vegetable crop harvesters.
4. Acute and subchronic exposures for both skin and systemic effects in mixer/loaders, aerial application flaggers, airblast applicators, and backpack applicators following aerial application.
5. Acute, subchronic, and chronic exposures for both skin and systemic effects in greenhouse harvesters.

References

OEHHA, 1999. Air Toxic Hot Spots Program Risk Assessment Guidelines, Office of Environmental Health hazard Assessment, Oakland, CA.

Davies, D., 2000. Naled: *in vitro* absorption through human and rat epidermis. Central Toxicology Laboratory, Document number: CTL/JV1570/REG/REPT, AMVAC Chemical Corporation. DPR Volume 215-174 # 172831.

Dong, M.H., 2000a. Review of *in vivo* dermal penetration study of naled in the rat. Memorandum from Michael Dong to Kevin Solari, Pesticide Registration Branch. California Environmental Protection Agency, Department of Pesticide Regulation, Sacramento, CA.

Dong, M.H., 2000b. Review of *in vitro* absorption of naled through human and rat epidermis. Memorandum from Michael Dong to Kevin Solari, Pesticide Registration Branch. California Environmental Protection Agency, Department of Pesticide Regulation, Sacramento, CA.

Jones, B.K., 1999. Naled: *in vivo* dermal penetration study in the rat. Central Toxicology Laboratory. Document number: CTL/URO588/REG/REPT, AMVAC Chemical Corporation, DPR Vol. 215-173 #172830.

Moxon, M.E.(Central Toxicology Laboratory), 2000. Naled: 28-day dermal toxicity study in rats. Study # LR0584, Document # CTL/URO588/REG/REPT, AMVAC Chemical Corporation, DPR Vol. 215-188 #177307.

dpr

Department of Pesticide Regulation

Paul E. Helliker
Director

MEMORANDUM

Gray Davis
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Winston H. Hickox
Secretary, California Environmental Protection Agency

TO: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
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Oakland, CA 94612

FROM: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch

Gary T. Patterson

DATE: January 22, 2001

Rec'd 1/25/01
To MDIB

SUBJECT: Addendum to Naled Risk Characterization Document

Attached for your review is an Addendum to the Risk Characterization Document for the pesticide active ingredient naled. Since the completion of the Document in 1999, additional information became available which necessitated our reevaluation of the exposure to naled.

If you have specific questions or comments concerning the draft, contact Dr. Keith Pfeifer at (916) 324-3464. Please provide comments by February 28, 2001. If you can not meet this deadline, please notify me.

Michael,
I would like a timeline for this.

1. Pl assign
2. Meet c staff the next wk & decide initially if Feb 28 allows adequate time
3. Pl give me a timeline

Thanks!
Anna

cc. Keith Pfeifer w/o attachment

Received 1/30 B.
Deadline 2/13