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California Environmental Protection Agency

State of California
Pete Wilson, Governor

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

MEMORANDUM

TO: Gary T. Patterson, Ph.D.
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1020 N Street
Sacramento, CA 95814-5624

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

DATE: December 1, 1994

SUBJECT: Risk Characterization Document for Dichlorvos

Thank you for the opportunity to review and comment on the draft risk characterization document for dichlorvos (DDVP). For the most part Office of Environmental Health Hazard Assessment (OEHHA) staff support the Department of Pesticide Regulation's (DPR's) conclusions on the DDVP health risk assessment.

We are concerned that majority of exposure levels to DDVP are not protective of human health. The groups at the highest health risk include: 1) most of the workers exposed to DDVP at work (MOS of 5-42) and in combination with home exposure (MOS of 2-12), 2) most residents from residential use of DDVP (MOS of 3-33), 3) children one to six years old from chronic exposure in the diet (MOS of 95), and 4) the general population from lifetime exposure to DDVP in the diet (carcinogenic risk of 4×10^{-5} to 7.7×10^{-5}).

A summary of OEHHA's technical and health-related concerns are listed below for the reviewed document. These concerns may also apply to other chemicals with similar toxicological issues (for future reference).

- The standard MOS of 100 for mortality is not adequate to protect an individual from lethal exposure to DDVP. An additional factor (OEHHA has used a 10-fold factor in previous risk assessments) accounting for the severity of the effect should be incorporated, thus increasing the MOS for protecting human health.

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- The choice of using a higher no-effect level (NOEL) (based on cholinergic signs and maternal mortality) instead of the available lower NOEL (based on brain cholinesterase inhibition) for potential risk from occupational and residential acute exposures to DDVP should be substantiated in the document.

- Multiple exposure to cholinesterase (ChE) inhibitors should be addressed more specifically in this document.

- In the absence of an adequate carcinogenicity study via inhalation route, it is a prudent risk assessment approach to assume that if a substance causes cancer when administered by ingestion, it will cause cancer when inhaled. DPR should make this assumption and assess carcinogenic risk resulting from inhalation exposure.

- The health risk assessment for DDVP is not complete without estimating total carcinogenic risk resulting from combined occupational and residential uses or activities involving exposure to this compound.

- It would be helpful if the document addressed structure-activity relationships among organophosphates for carcinogenic, neurotoxic, ChE inhibition and any other critical toxic effects.

- Adequacy of food tolerances should be assessed taking into account the carcinogenic potential of DDVP.

- An explanation for not characterizing seasonal exposure to DDVP should be provided within the body of the main document.

- Discussion of the significance of the results from mutagenicity tests should be included in the risk characterization document.

We would like to follow up with discussion on the current hazards (as indicated above) from exposure to DDVP and its implications on future actions, which should be taken in order to protect groups at risk.

If you have any questions regarding our review or would like further discussions, please call me or Dr. Michael DiBartolomeis at (510) 540-3063.

cc: Jolanta Bankowska, Ph.D.
Michael DiBartolomeis, Ph.D.
Robert Howd, Ph.D.
Charles M. Shulock

ATTACHMENT

REVIEW OF THE RISK CHARACTERIZATION DOCUMENT FOR DICHLORVOS

This report consists of three parts: background information, comments, and summary of conclusions and recommendations. The background information provides a brief summary of the characteristic features of dichlorvos toxicology and the Department of Pesticide Regulation's (DPR's) risk characterization document for this active ingredient. The Office of Environmental Health Hazard Assessment's (OEHHA's) comments generally refer to the specific technical or policy issues covered in the risk characterization document. The last part of our review summarizes the issues of importance and makes some recommendations for future actions.

BACKGROUND INFORMATION

Use

Dichlorvos (DDVP) is an organophosphorous insecticide used to control nuisance insects and other pests in or on structures such as homes, apartments, warehouses, office buildings, etc. It is also used on pests associated with livestock production or storage of agricultural commodities and in flea collars for pets. The direct food uses of DDVP include vegetables grown in greenhouses, livestock and processed food.

Toxicology

The most pronounced toxicological effects produced by DDVP are due to cholinesterase (ChE) inhibition. In acute experiments in laboratory animals the signs of DDVP exposure included diarrhea, salivation, lethargy, pupillary constriction, tremors, impaired neuromuscular functions, and death. Subchronic exposure to DDVP caused the inhibition of ChE in brain, erythrocytes (RBC), and/or plasma in humans, rats, mice, dogs, and cows. Signs frequently observed in laboratory animals included tremors, diarrhea, decreased body weight gain, increased frequency of salivation and urine staining in rats, and increased activity and urination in dogs. Exposed animals showed also significant decreases in RBC parameters (cell counts, hemoglobin, and hematocrit).

Chronic experiments in laboratory animals exposed to DDVP produced not only cholinergic effects such as inhibition of plasma, RBC, and brain ChE activities but also other non-oncogenic and oncogenic effects. Other non-oncogenic effects included

hepatocellular lesions (vacuoles in the cytoplasm, cell swelling, prominence of cell membranes), reduced body weight, emesis, salivation, and ataxia.

Oncogenic effects in rats and mice were reported in feeding studies judged to be acceptable submissions by DPR. Observed effects included pancreatic adenoma, mononuclear leukemia, mammary gland carcinoma, fibroadenoma, and adenoma; forestomach papillomas and carcinomas; and pituitary adenomas.

DDVP was also reported to be genotoxic. It produced positive results in the tests designed to evaluate gene mutation and DNA damage. Possible adverse effects caused by DDVP also include neurotoxicity. Under the standard toxicity testing requirements for organophosphorous pesticides, there was nerve fiber and spinal cord degeneration in chickens treated with this chemical.

Exposure Assessment

The health risks from exposure to DDVP were assessed by DPR for occupational, residential, and dietary exposures under acute, chronic, and lifetime scenarios. Occupational exposures were determined for workers involved in warehouse fumigation, livestock applications, and structural applications. Residential exposures were calculated for structural pesticide use (use of liquid sprays, fogger, no-pest strips) as well as for pet owners (flea collars).

Dietary exposure analyses were performed for the general population and for 22 population subgroups by using the TAS computer programs for acute and chronic exposure estimation. These exposures were due to the use of DDVP on raw agricultural commodities, livestock, and processed foods.

Risk Appraisal

Assessment of the potential risk from occupational and residential acute exposure to DDVP was based on a corrected NOEL of 325 ug/kg-day established in rabbit inhalation developmental toxicity studies (see table 21 page 68). The NOEL was determined for mortality observed after two to three days of exposure. Risk from the acute dietary exposure was based on a NOEL of 500 ug/kg-day established for cholinergic signs (tremors, salivation, neuromuscular deficits) observed within 24 hours after a single dose by gavage.

Potential health risks from chronic occupational and residential exposures were determined based on a corrected NOEL of 25 ug/kg-day (equivalent of the tested dose of 50 ug/kg-day) established for brain ChE inhibition (10% ChE inhibition at the tested dose of 500 ug/kg-day) and reduced body weights in rats in a

two-year inhalation toxicity study. The assessment of health risks from chronic dietary exposure was based on a NOEL of 50 ug/kg-day established for brain ChE inhibition (22% ChE inhibition at 1000 ug/kg-day) and cholinergic signs in dogs fed DDVP in capsules for one year. It should be noted that effects in humans (33%-72% inhibition of plasma ChE) have been noted after subchronic exposure to doses in the range of 0.006 to 0.03 mg/kg-day (see table 2, page 23).

Carcinogenic risk from exposure to DDVP was calculated as the theoretical probability of excess cancer risk in a lifetime due to dietary exposure. It was based on the finding of mononuclear leukemia in feeding studies in rats and mice.

The health risk assessment document for DDVP used conventional criteria adopted by DPR and other regulatory agencies for describing safety. A margin of safety (MOS) of 100 or higher, and an excess individual cancer risk level of 1×10^{-6} were assumed to be sufficiently protective of human health for non-carcinogenic and carcinogenic effects, respectively. Based on the results of the risk characterization and these health criteria it can be concluded that significant health hazards exist for DDVP exposure in the following categories: 1) all the workers exposed to DDVP at work and in combination with home exposure, 2) most of the residents from residential use of DDVP, 3) children one to six years old from chronic exposure in the diet, and 4) and the general population from lifetime exposure to DDVP in the diet.

Tolerances

An acute exposure assessment using a residue level equal to the tolerances was conducted separately for the following commodities: tomatoes, radishes, poultry, eggs, beef, veal, pork, cucumber, lettuce, and milk. The MOSs for all the tolerances were greater than 100. This is the level considered by DPR to be sufficient for the protection of human health from exposure to non-carcinogens.

Summary of DPR's Conclusions

According to DPR, current exposure levels to DDVP present significant human health hazards for the following scenarios: 1) all of the workers exposed to DDVP at work and in combination with home exposure, 2) most of the residents from residential use of DDVP, 3) children one to six years old from chronic exposure in the diet, and 4) the general population from lifetime exposure to DDVP in the diet.

COMMENTS

In general, the health risk assessment for DDVP clearly reflects the scientific methods and policies adopted by DPR. The the "risk characterization" part of the document anticipates and addresses various risk assessment and health issues.

For the most part, scientific staff that reviewed the risk characterization document support DPR's conclusions about the health risks of DDVP as used in California. However, we have some comments and concerns about the continued use of this chemical, and about DPR's methodological approaches in this risk characterization document.

Protectiveness of MOS

Based on previous risk characterization documents, a margin of safety (MOS)of 100 is generally considered by DPR to be protective of public health when the NOEL is based on toxicology data from animal studies. However, U.S. EPA and OEHHA have identified that there are certain justifiable circumstances when a higher value (i.e., additional protection) should be used. Conditions when a higher value for a MOS (additional uncertainty factor applied to the NOEL) is commonly used include but are not limited to: 1) the use of a LOEL (in the absence of the NOEL) value for risk assessment, 2) extensive gaps in the toxicological data base, and 3) severity of toxic effects produced by a subject chemical. This approach is commonly used by U.S. EPA in establishing RfD and drinking water standards (MCLs)and by OEHHA when performing risk assessments (i.e., when developing reference exposure levels) for the protection of public and worker health.

The developmental toxicity study chosen by DPR for the acute risk assessment is an appropriate example of a situation where an additional uncertainty factor should be applied to the NOEL value to determine an adequately protective MOS. In the study conducted in rabbits, a corrected NOEL of 325 ug/kg-day was established by DPR on the basis of maternal mortality. DPR did not use any additional uncertainty factor (e.g., an added factor of 10 for a 1000 MOS) that would account for the severity of this effect (i.e., death) but such a use is highly recommended under the circumstances. As a result, MOSs already determined by DPR to be inadequate based on its default of 100, would be even less protective for this compound.

Choice of a NOEL for risk assessment

The choice of a NOEL for potential risk from occupational and residential acute exposure to DDVP was based on a NOEL of 650 ug/kg-day (corrected NOEL of 325 ug/kg-day) established in rabbit

inhalation developmental toxicity studies (see table 21 page 68 and page 49). The NOEL was determined for cholinergic signs and mortality observed after two to three days of exposure at the level of 3,250 ug/kg-day. However, brain ChE inhibition (44%) was observed at the level of 650 ug/kg-day. OEHHA's policy is to consider ChE inhibition of greater than 20%, particularly for brain ChE activity, to be a valid risk assessment endpoint for health risk evaluations. Therefore, staff conclude that the lower tested level of 130 ug/kg-day should have been considered as a NOEL for the risk assessment of DDVP. The choice of the higher NOEL for risk assessment (and the severity of the endpoint) instead of the lower value (but significant toxicological endpoint) must be sufficiently substantiated in the document.

Multiple Exposure to Cholinesterase Inhibitors

As a matter of policy, multiple exposures to cholinesterase inhibitors from both occupational and dietary sources should be addressed in this and all health risk assessment documents for this group of chemicals. OEHHA's concerns relate mainly to the seasonal and chronic occupational and dietary exposures to organophosphates. The risk assessment documents for pesticides with cholinesterase inhibition activity do not fully address actual health risks unless they include scenarios that more closely approximate agricultural practices (and other occupational uses) where workers can be exposed to a number of cholinesterase inhibitors during one season.

The risk characterization document does not contain an evaluation of seasonal exposure of workers to DDVP. Seasonal exposure might be important and should be addressed in the body of the main document.

Evaluating exposures and assessing health risk separately for chemicals causing the same effects during the same period of time would underestimate risks. A worker may have an adequate MOS for cholinergic effects from the individual exposure to chemical A or chemical B, but the health risk from the combined exposure from A and B may be excessive.

Cholinergic effects and the related health risk from dietary exposure to the residues of a number of cholinesterase inhibitors should also be evaluated individually and for combined exposures to multiple chemicals with comparable mechanisms of actions.

OEHHA, as well as the Pesticide Exposure to Children Committee (PECC) and the National Academy of Sciences recommend that, in the future, efforts be made to evaluate and assess health risk from combined occupational and dietary exposures to multiple cholinesterase inhibiting pesticides. If it is currently not possible to assess the multiple exposure to cholinesterase

inhibitors, then at least the issue should be addressed, and the reasons for not performing this assessment should be clearly stated.

Carcinogenicity

DDVP produced numerous oncogenic and carcinogenic effects in rats and mice (see above under "Toxicology") in long-term feeding studies.

DPR has only one available chronic inhalation toxicity study in rats. This study was judged to be unacceptable by DPR staff due to deficiencies in study design and reporting; it did not meet FIFRA guidelines. As an "unacceptable" study, it should not be adequate on its own to draw conclusions either on chronic non-oncogenic or on oncogenic effects. However, DPR made an assumption based on this study that DDVP is not oncogenic (or carcinogenic) via inhalation. Consequently, life-time exposure and the resulting carcinogenic risk under occupational and residential scenarios (where inhalation is the primary route of exposure) were not determined.

According to Department of Health Services Guidelines for Chemical Carcinogen Risk Assessment and Their Scientific Rationale issued in November 1985 (page B-21) "In the absence of data with which to make an evaluation, it is prudent risk assessment policy to assume that if a substance causes cancer when administered by ingestion, it will cause cancer when inhaled, and vice versa". A health protective approach requires one to assume that DDVP is carcinogenic via inhalation route since there is clearly evidence supporting carcinogenicity in feeding studies. Furthermore, although the study was inadequate for quantitative evaluation, it did produced some signs of oncogenic activity that may be related to DDVP. For example, a slight increase in the incidences of pituitary adenomas and incidences of mammary and thyroid tumors was reported. The health risk assessment for DDVP is not complete without estimating oncogenic or carcinogenic risk via inhalation route resulting from occupational and residential activities.

Metabolism and Pharmacokinetics

DPR mentioned in its risk assessment document that DDVP is a metabolite of naled and trichlorfon. However, according to DPR's explanation, the potential for additional workplace exposure through the use of these two pesticides is unlikely "because of differences in use patterns and biotransformation." This explanation should be further expanded.

Discussion of metabolism and pharmacokinetics can play an important role in the weight of evidence in carcinogenicity

considerations in animal studies. In the case of DDVP, it is especially important to address the carcinogenic potential of naled and trichlorfon, two pesticides that are metabolized to DDVP. Summaries of Toxicology Data for naled (May 24, 1989) and trichlorfon (September 15, 1992) indicate that these two chemicals may have some oncogenic and/or carcinogenic potential. Naled caused mammary tumors in a chronic feeding study in rats and trichlorfon produced increases in renal neoplastic lesions such as renal tubular adenoma, alveolar/bronchiolar adenoma, and carcinoma and mononuclear cell leukemia.

Structure - Activity Relationships

It would be helpful if the document addressed structure-activity relationships among organophosphates for carcinogenic, neurotoxic, ChE inhibition and any other critical toxic effects.

Tolerance Assessment

Tolerance evaluation performed for DDVP took into account only non-oncogenic toxicological endpoints. The results of this evaluation together with an indication of a MOS sufficient for the protection of human health should be accompanied by the appropriate interpretation. This interpretation should clarify the limited value of this "sufficient protectiveness" which might not include protection against carcinogenic effects from dietary exposure to DDVP. When only non-oncogenic effects are considered, analyses made for carcinogenic pesticides, indicating safe dietary exposures and protective tolerances may be misleading.

DDVP tolerances should also be assessed based on the carcinogenic potential of this compound.

Mutagenicity

Discussion of the significance of the results from mutagenicity tests should be included in the risk characterization document.

Actual Versus Calculated Health Risk

On the whole, estimates calculated by DPR for non-oncogenic risks from occupational and residential exposures, and also from life-time dietary exposure to DDVP do not allow sufficient margins of safety according to DPR's criteria.

MOSs for acute occupational and residential exposures range from 3 (home-use fogger, child) to 36 (structural pest control operator)(see table 22 on page 70). An exception is the estimate of MOS of 1100 for the pet owner. MOSs for chronic occupational

and residential exposures range from 4 (Pest strip, child) to 42 (warehouse worker)(table 22 on page 70). Exeptions are estimates of 125 (structural, resident) and 500 (pet owner). DPR's MOSs for potential acute and chronic combined occupational, residential, and dietary exposures are even lower. They range from 2 (livestock applicator) to 33 (structural pest control operator) for the combined acute exposures and from 4 (livestock applicator) to 28 (warehouse worker) for the combined chronic exposures (table 24, page 72).

Actual health risk from exposure to DDVP may be much higher. This especially applies to the non-oncogenic risks from the DPR categories labeled "acute" and "acute combined" (occupational, residential and dietary exposures) to DDVP and also to the carcinogenic risk estimates for the lifetime dietary exposure (4 $x10^{-5}$ to 7.7 x 10^{-5}) which currently do not factor in exposures from occupational and residential activities involving use of DDVP.

The risks from the acute exposures would be five to ten times lower in comparison with the current estimates depending on the value of a NOEL used as a basis for MOS calculation (see also "Choice of a NOEL for risk assessment on page 4).

Mitigation Measures

There are no mitigation measures recommended in the document. Previous risk characterization documents for active pesticide ingredients have usually included such a section. If there are no mitigation measures currently available to decrease the health risks from exposure to DDVP, it should be clearly stated. Also, if mitigation measures are not practical or feasible, the report should address implications of continued use for health protection.

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

A summary of OEHHA's technical and health concerns are listed below. These comments apply specifically to the risk characterization document for dichlorvos, but may also apply to risk assessment for other chemicals in general.

- The standard MOS of 100 for mortality is not adequate to protect an individual from lethal exposure to DDVP. An additional factor (OEHHA has used a 10-fold factor in previous risk assessments) accounting for the severity of the effect should be incorporated, thus increasing the MOS for protecting human health.

- The choice of using a higher no-effect level (NOEL) (based on cholinergic signs and maternal mortality) instead of the

available lower NOEL (based on brain cholinesterase inhibition) for potential risk from occupational and residential acute exposure to DDVP should be substantiated in the document.

- Multiple exposure to cholinesterase (ChE) inhibitors should be addressed more specifically in this document.

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- It would be helpful if the document addressed structure-activity relationships among organophosphates for carcinogenic, neurotoxic, ChE inhibition and any other critical toxic effects.

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- An explanation for not characterizing seasonal exposure to DDVP should be provided within the body of the main document.

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