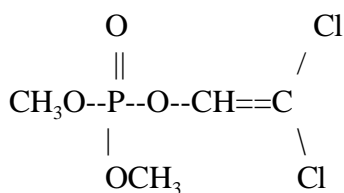


US EPA ARCHIVE DOCUMENT

Dichlorvos (DDVP):
Risk Assessment Issues for the FIFRA Science Advisory Panel
(July 8, 1998)



dichlorvos

I. INTRODUCTION

This document has been prepared by the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) for submission to and peer review by the FIFRA Scientific Advisory Panel for the purpose of resolving three issues important to the ongoing risk assessment of dichlorvos, an organophosphate pesticide: (1) whether certain populations, such as infants and children, may have special susceptibility to dichlorvos toxicity; (2) use of residue data from the Food and Drug Administration's surveillance data and Total Diet Study (TDS) data in the dietary exposure assessment; and (3) assessment of residential exposure from dichlorvos resin strips.

While this document is not intended to convey information for risk management decision-making purposes, the issues being presented to the Panel are pertinent, but not limited to, the broader issues which are being examined under the Environmental Protection Agency's Special Review program for pesticides. The Special Review Process is governed by 40 *CFR* Part 154. While there are additional concerns being addressed in the Agency's ongoing risk assessment for dichlorvos, the issues selected for presentation to the Panel represent the most challenging for the Agency.

Dichlorvos is an organophosphate insecticide registered for use in controlling flies, mosquitos, gnats, cockroaches, fleas, and other insect pests. The mechanism of pesticidal action of dichlorvos is inhibition of cholinesterase. At present, there are 154 product registrations for formulations containing dichlorvos. Formulations of dichlorvos include pressurized liquids, granulars, dusts, wettable powders, emulsifiable concentrates, total release aerosols, and impregnated materials. Dichlorvos is applied with: aerosol spray and fogging equipment; ground spray equipment; and through slow release from impregnated materials, such as resin strips and pet collars. The Agency has determined that the adverse effects caused by dichlorvos that are of primary concern to human health are cancer and those related to inhibition of cholinesterase activity.

The Agency has previously performed risk assessments which indicated risks of concern from occupational, residential, and dietary exposure to dichlorvos. Consequently, the Agency issued a proposal to cancel the registrations pertaining to those uses of dichlorvos that posed the greatest risks (Draft Notice of Intent to Cancel [PD 2/3], Federal Register of September 28, 1995). In its 1995 Notice, the EPA concluded that the risks outweighed the benefits for most uses of dichlorvos and, therefore, recommended a variety of measures to reduce those risks. Also in that notice, the Agency explained the steps involved in making its proposed decision to cancel certain uses of dichlorvos, including identification of the potential risks to humans, an assessment of the benefits from use of the chemical as a pesticide, and a proposed risk-management decision. Specifically, EPA concluded that dichlorvos poses carcinogenic risks of concern to the general population from dietary exposure, and risks of concern for cholinesterase inhibition to residents and to individuals mixing, loading, and applying this pesticide, as well as to those reentering treated areas. After careful consideration of the risks and benefits of using dichlorvos, EPA proposed cancellation of certain uses of dichlorvos and cancellation of other uses unless certain labeling modifications were made that would reduce risk.

The Federal Register Notice provided for a formal comment period, which closed on December 28, 1995. Comments were received, and are contained in a public docket identified as "OPP-30000/56." Major comments were submitted to the Agency by Amvac Chemical Corporation, the Japanese Resin Strip Manufacturer's Association, grower groups, and the general public. Some of the comments contained additional data pertaining to the risks posed by dichlorvos. In addition, the Agency has identified exposure and toxicity data pertaining to dichlorvos that have become available since publication of the PD 2/3. This information includes the following:

- additional information on the carcinogenicity of dichlorvos;
- a study conducted in human volunteers that measured blood cholinesterase inhibition following oral administration of dichlorvos;
- a 28-day delayed neurotoxicity study conducted in hens;
- a Pathology Working Group report on the hen study;

- data describing effects of dichlorvos on the brain size of developing guinea pigs;
- newer data and information pertaining to dietary, occupational and residential exposure to dichlorvos including use deletions, modifications to the technical label, updated information on percent crop treated, and additional sources of residue data;

In addition, the Agency now routinely uses the Exposure Factors Handbook (USEPA 1997) and Standard Operating Procedures (SOPs) for Residential Exposure Assessments (USEPA 1997) for residential exposure assessments. These two documents were not available at the time of the PD 2/3.

In addition to the newer data and information described above, statutory changes (the Food Quality Protection Act, August 1996) that have effectively modified the factors and considerations the Agency uses in assessing the risks of pesticides have taken place since publication of the PD 2/3 in 1995. Because of the new data and information and the recent statutory changes, the Agency plans to reassess the risks posed by dichlorvos.

The Agency is in the process of revising the dichlorvos risk assessment to incorporate new information as appropriate. At present, the Agency has reviewed the new information pertaining to the toxicology database of dichlorvos for hazard identification, dose-response assessment, and determination of potential special susceptibility of infants and children to dichlorvos. The Agency has reviewed new information pertaining to the dietary exposure assessment and performed a refined dietary exposure assessment. The Agency has also refined the residential exposure assessment for dichlorvos resin strips with new information and new methodologies that were unavailable when the PD 2/3 was published in 1995.

The Agency seeks guidance from the FIFRA Science Advisory Panel (SAP) with regard to specific aspects of the ongoing dichlorvos risk assessment. The Agency seeks guidance from the SAP on the following issues: (1) whether certain populations, such as infants and children, may have special susceptibility to dichlorvos toxicity; (2) use of residue data from the Food and Drug Administration's surveillance data and Total Diet Study (TDS) data in the dietary exposure assessment; and (3) assessment of residential exposure from dichlorvos resin strips. These issues are described in more detail below.

II. INFORMATION AVAILABLE TO AGENCY SINCE ISSUANCE OF PD 2/3

II.a. New Information Impacting Hazard Identification and Dose Response Relationships of Dichlorvos.

Amvac, the registrant of technical dichlorvos, submitted additional information on carcinogenicity of dichlorvos as a public comment to the Draft Notice of Intent to Cancel. This

information was reviewed by the Agency and considered by the Carcinogenicity Peer Review Committee of the Office of Pesticide Programs. The cancer potency estimate (Q_1^*) has been revised according to the recommendations of the Carcinogenicity Peer Review Committee.

In 1997, Amvac conducted a toxicology study of dichlorvos using human volunteers. The human study measured blood cholinesterase activity in human volunteers following oral ingestion of dichlorvos. This study has been reviewed by the Agency and was considered in the hazard identification and dose response assessment.

A 28-day delayed neurotoxicity study in hens was finalized and submitted to the Agency. The hen study showed lesions of concern in the central nervous system. To address the Agency's concern, the registrant convened a review by the Pathology Working Group (PWG) to re-examine the data from the hen study. (The PWG is an external peer review composed of expert pathologists.) The Agency has reviewed this report (Sette, 1998a).

A literature search was conducted by the Agency on the toxicity of dichlorvos and chemicals that may be converted into dichlorvos in plants or animals (e.g., naled and trichlorfon). In one publication identified by the Agency, brain hypoplasia was observed in the offspring of adult female guinea pigs that had been treated with dichlorvos during a certain period of gestation. In several articles, a similar finding was reported in newborn guinea pigs and in piglets following prenatal administration of trichlorfon. Decreases in neonatal cerebellum and total brain weights were reported in a number of these studies. After reviewing these publications, the Agency concluded that the open literature findings could not be dismissed and that additional data in the guinea pig are needed to confirm the developmental toxicity potential of dichlorvos. It should be noted that the developmental effects in neonatal guinea pigs reported in the open literature and discussed above were not seen in developmental (test species rat and rabbit) or reproduction (test species rat) toxicity studies submitted to the Agency for dichlorvos. (Also, at least one literature article indicates that the effects on brain weight and size seen in guinea pig pups following administration of trichlorfon during gestation could not be reproduced in the offspring of rats.) However, based upon the results of the literature studies, the Agency has recommended that a standard developmental toxicity study in guinea pigs be submitted with certain protocol modifications to assess the findings.

II.b. New Information Impacting Exposure Assessment.

The Agency received comments to the PD 2/3 regarding the use practices of dichlorvos. This information has been reviewed and is being considered to revise previous dietary and residential exposure assessments for dichlorvos.

Since publication of the PD 2/3 in 1995, Amvac (the registrant of technical dichlorvos) has voluntarily canceled the use of dichlorvos in tobacco warehouses and in commercial transportation vehicles. (The 6(f) notice was published in the Federal Register on April 7, 1995.) The registrant has made changes to the technical label for dichlorvos to comply with the 6(f)

notice and to improve personal protective equipment for workers.

II.b.i Residential Exposure. When the Agency assessed the risks of dichlorvos during its Special Review of the substance, the Agency did not routinely use the Residential Standard Operating Procedures (SOPs) for estimating exposure. These SOPs were developed by the Agency and submitted to the SAP for review after publication of the 1995 PD 2/3. These residential SOPs are now used for conducting exposure assessments.

In 1997, the Agency's Office of Research and Development published an updated version of the *Exposure Factors Handbook*, which contained activity pattern data from a national survey of homeowner activity. Data from the *Exposure Factors Handbook* have been used to re-evaluate some dichlorvos exposure scenarios.

II.b.ii Dietary Exposure. Dietary exposure estimates have been refined with residue data from USDA's PDP monitoring program, FDA surveillance data and FDA Total Diet Study (TDS) data. PDP data were not available and FDA surveillance data and TDS data were considered to be too limited for use in exposure assessment at the time of the PD 2/3.

Dietary exposure to dichlorvos residues may occur as a result of use on or at a variety of sites, including mushroom houses, bulk-stored and packaged or bagged nonperishable processed and raw food, commercial food processing plants, groceries, direct animal treatment, and livestock premise treatment.

In addition to registered uses of dichlorvos, naled (an organophosphate insecticide) provides an additional source of dietary exposure from dichlorvos. Naled is metabolized to dichlorvos by plants. As a result, the Agency felt it appropriate to characterize the total risk from dichlorvos even though naled itself is not under Special Review. Total dietary exposure to dichlorvos from use of naled and dichlorvos was estimated.

EPA plans to refine the risk estimates using residue data from USDA's PDP monitoring program, FDA surveillance data, FDA Total Diet Study data, and a revised cancer potency estimate (Q_1^*).

III. TOXICITY OF DICHLORVOS: HAZARD IDENTIFICATION

The toxicological endpoints used for risk assessment for dichlorvos are cancer and cholinesterase inhibition. (The studies and data used in the identification of the hazards posed by dichlorvos are described below.) The toxicology data supporting both of these endpoints have been evaluated by internal EPA Office of Pesticide (OPP) Health Effects Division (HED) peer review committees. In addition, the carcinogenicity data for dichlorvos have been evaluated by both internal Agency and external scientific peer review committees. Further, OPP's cholinesterase policy was reviewed by the FIFRA Science Advisory Panel (SAP) on June 3, 1997.

III.a. Carcinogenicity.

The carcinogenicity of dichlorvos has been evaluated by the Office of Pesticide Program's Carcinogenicity Peer Review Committee (CPRC), the FIFRA Science Advisory Panel (SAP), and the Agency Carcinogenicity Assessment Group (CAG).

III.a.i. Background for Final Carcinogenicity Assessment

The background for dichlorvos carcinogenicity assessment is lengthy and somewhat complicated. What follows is a compilation of decisions made that has been taken, in some cases *verbatim*, from more complete decision documents that are referenced herein. Note that this section contains the conclusions that served as the basis for the cancer hazard assessment described in the 1995 PD 2/3.

First Cancer Peer Review.

In July 1987, the Office of Pesticide Program's Carcinogenicity Peer Review Committee (CPRC) classified dichlorvos as a Group B2 (probable human) carcinogen, based primarily on the results of studies involving mice and rats conducted by the National Toxicology Program (NTP). Since that time, EPA has re-evaluated the carcinogenic potential of dichlorvos and concluded that dichlorvos is a Group C (i.e., possible human) carcinogen. The issues and reasons for the earlier classification and revision in the classification are described below.

NTP Mouse Study. Dichlorvos was administered by gavage to B6C3F1 mice (60/sex/group) for 103 weeks (5 days/week) using corn oil as the vehicle (NTP 1986a). Doses were 0, 10, or 20 mg/kg/day for male mice and 0, 20, or 40 mg/kg/day for females. Administration of dichlorvos to female mice was associated with a statistically significant dose-related trend and statistically significant increase in: squamous cell forestomach papillomas; combined squamous cell forestomach papillomas; and carcinomas at the high-dose. The forestomach tumors were outside the historical control range. In male mice, an increase in squamous cell forestomach papillomas was associated with a significant dose-related trend, but was not statistically significant by pairwise comparison at either dose level. No other tumor types were identified in this study. No malignant squamous cell tumors were found in the historical controls.

NTP Rat Study. Dichlorvos was administered by oral gavage with corn oil as the vehicle to F344 rats (60/sex/group) for 103 weeks (five days/week) (NTP 1986b). The dosages were 0, 4, or 8 mg/kg/day. The study resulted in a statistically-significant increase in mononuclear cell leukemia in males by pairwise comparison at both dosage levels. The increase in leukemia also exhibited a statistically significant positive dose-related trend. There was an increased incidence of lung adenomas in high-dose male rats. In addition, dichlorvos administration was associated with a

statistically significant increased incidence of mammary gland adenomas and all mammary gland tumors at the low-dose only (by pairwise comparison) in rats. However, the incidence of lung adenomas and mammary gland tumors were within the historical control range.

On September 23, 1987, the FIFRA Scientific Advisory Panel (SAP) reviewed the CPRC's Group B2 cancer classification and concluded that dichlorvos should be classified as a Group C (possible human) carcinogen since: (1) only benign tumors were induced by dichlorvos; (2) they were not dose-related; and (3) dichlorvos was not mutagenic in *in vivo* assays (although it was mutagenic in several *in vitro* test systems with and without metabolic activation) (USEPA 1987).

Second Cancer Peer Review.

The CPRC met for a second time (September 29, 1987) to examine the issues raised by the SAP with respect to the classification of the carcinogenicity of dichlorvos (Hauswirth, 1988a). The Committee decided that the results of the NTP studies indicate that dichlorvos demonstrates sufficient evidence of carcinogenicity in the male rat and female mouse to confirm the initial classification of dichlorvos as a Group B2 carcinogen.

In reaching its decision, the committee concluded that the following results of the NTP bioassays indicate that dichlorvos demonstrates sufficient evidence of carcinogenicity in the male rat and in the female mouse:

- 1) a dose-response relationship of statistical significance was seen for pancreatic adenomas (which have the potential to progress towards malignancy) and mononuclear cell leukemia in male rats;
- 2) a dose-response relationship of statistical significance was seen in the female mouse for forestomach squamous cell papillomas which have the potential to progress to carcinomas;
- 3) the presence of some forestomach carcinomas (which are rare) was seen in the female mouse;
- 4) significant positive trend was seen for forestomach papillomas in male mice at a dose that did not achieve a maximum tolerated dose (MTD);
- 5) supporting evidence provided by a statistically significant increase in mammary tumors at the low-dose in the female rat which was associated with a significant trend; and
- 6) mutagenicity data was available indicating that dichlorvos is positive for mutagenicity *in vitro* in bacterial and mammalian cells both with and without metabolic activation.

The Committee thereby confirmed their initial classification of dichlorvos as a "B2 oncogen."

Third Cancer Peer Review.

The CPRC had a third meeting on June 2, 1988 to review the conclusions of an April 1988 meeting of the NTP Panel of Experts on the carcinogenic classification of dichlorvos (Hauswirth, 1988b). NTP scientists had resectioned the pancreas of all test groups in the rat bioassay. The additional sectioning of pancreata resulted in an increased number of tumors in the control animals, thus diminishing the statistical significance of this lesion. Based on this finding, the NTP scientists concluded that the evidence for carcinogenicity in male rats should be downgraded from “clear evidence” to “some evidence”. The CPRC considered the NTP's information and concluded that dichlorvos should remain classified as a Group B2 carcinogen, because:

- 1) the incidence of mononuclear cell leukemia in dichlorvos treated F344 rats was treatment-related;
- 2) although the results of longitudinal sectioning of the pancreas diminished the significance of the pancreatic acinar adenomas in male rats, the incidence of animals with multiple adenomas was still increased with dichlorvos treatment; and
- 3) dichlorvos is a direct acting mutagen.

The CPRC considered this as an interim classification until the following additional data had been reviewed: 1) the results of studies in which dichlorvos was administered in drinking water to Fischer 344 rats and B6C3F1 mice; 2) additional data on a chronic rat inhalation study; 3) additional *in vivo* mutagenicity data, and 4) additional historical control information on pancreatic acinar adenomas.

Fourth Cancer Peer Review.

The CPRC met for a fourth time on July 19, 1989 (Ghali, 1989). The purpose of this meeting was to: reconsider the NTP rat study in light of the recent NTP Panel of Experts report; evaluate new oncogenicity studies with dichlorvos administered by inhalation or in drinking water (see below); and consider other ancillary information. The conclusions of this Fourth CPRC review served as the basis for the cancer hazard assessment described in the 1995 PD 2/3 .

As mentioned earlier, the NTP scientists reexamined the pancreata of male and female rats using longitudinal sections which diminished the statistical significance of the pancreatic lesions. The NTP analysis of the combined data indicated a statistically significant difference between the treated and control groups with a positive dose-related trend using the logistic regression analysis. However, EPA scientists concluded that the increase in pancreatic acinar tumors was neither significant in the Fischer Exact test for pairwise comparison, nor positive in the Cochran-Armitage test for dose-related trend, which are typically used for testing dose groups having no survival disparities. The incidence of animals with multiple pancreatic adenomas was still increased with dichlorvos treatment and outside of the historical control range.

The CPRC also reevaluated an inhalation oncogenicity study in which 50 CFE rats/sex/dose were exposed to concentrations of 0.05, 0.5 or 5.0 mg/m³ of technical

dichlorvos 23 hours per day for 2 years. This study was reviewed for the dichlorvos Registration Standard and the Agency considered the study inadequate for evaluating the carcinogenicity of the chemical. The study was upgraded after the individual animal data were submitted to the Agency. The Agency concluded that administration of dichlorvos does not cause cancer following inhalation exposure.

Results from two separate carcinogenicity studies were conducted using administration of dichlorvos in drinking water. One study was conducted using rats (Fischer 344) and the other in mice (B6C3F1). In both studies, dichlorvos was administered via drinking water for 2 years. The CPRC considered both studies to be deficient in conduct and reporting, including incomplete histopathologic evaluation, absence of water consumption data, and failure to include individual animal data in the final report. As a result of these deficiencies, the studies are not amenable to statistical analyses. However, the studies are useful in identifying a qualitative trend in that dichlorvos treatment induced some tumors similar to those induced in the oral gavage studies. In the rat study, there appeared to be an increased incidence of mononuclear cell and lymphocytic leukemia in treated males, as well as mammary gland fibroadenomas in females. In the mouse study, there appeared to be an increased incidence of fibrous histiocytomas and thymomas in males.

The CPRC reclassified dichlorvos as a Group C carcinogen, in accordance with the Agency's Guidelines for Carcinogenic Risk Assessment. This downgrading from the previous classification as Group B2 was due to: (1) erosion of the evidence on the pancreatic acinar adenomas in male rats; (2) upgrading and consideration of the negative inhalation study in CFE rats; and (3) questions regarding the biological significance of the primary tumors in the NTP studies, i.e., leukemia in rats (variable tumors in historical controls) and forestomach tumors in mice and its relevance to man.

The CPRC also recommended not to quantify the cancer risk by a low-dose extrapolation model for the inhalation route of exposure. The primary basis for this recommendation was the upgrading of the 2-year inhalation study in rats which did not result in an increased tumor incidence. The recommendation was based on the following considerations: the quality of the oral cancer data; the route specificity of the target organs; the reliability and accuracy in estimating the target-dose; and the unlikelihood that exposure via the inhalation route would lead to the formation of a reactive metabolite.

III.a.ii. Current Carcinogenicity Assessment

This section contains the current position on the carcinogenicity of dichlorvos and includes a discussion of the additional information submitted to the Agency by the registrant.

Fifth Cancer Peer Review.

A fifth CPMC meeting occurred on March 27, 1996, after the publication of the PD 2/3. The CPMC met to consider new information provided by the registrant (Stewart, 1996). This information consisted of: a Pathology Working Group classification of the severity grades of the mononuclear cell leukemia observed in the dichlorvos treated male rats; studies on the mechanism of the forestomach tumors in female mice; and an *in vivo* cytogenetics assay in the bone marrow and spermatogonia cells of ICR mice.

The severity grades of the mononuclear cell leukemia per test group was as follows (50 animals per group): controls: 39, 4, 2, 5; low dose: 30, 5, 5, 10; high dose 29, 2, 9, 10 for severity grade 0, 1, 2, and 3 respectively, with grade zero being the least severe, and grade 3 the most severe. Statistical analysis of the data by HED indicated that administration of dichlorvos was not accompanied by a statistically significant increase in the severity of the mononuclear cell leukemia lesions with increasing dose.

In considering these data, the CPMC concluded that, although the severity of the mononuclear cell leukemia was not statistically significantly different between control and treated rats, and did not shorten the animals lifespan, these malignant tumors were caused by administration of dichlorvos.

Additionally, mechanistic studies were submitted in rebuttal to the Agency's use of forestomach tumors for cancer risk assessment. The mechanistic studies consisted of five experiments comparing the *in vitro* effects of dichlorvos to those of: 1-methyl-3-nitro-1-nitrosoguanidine (MNNG), which induces carcinomas in both forestomach and glandular stomach of the mouse and is known to alkylate DNA (IARC, 1987); and butylated hydroxyanisole (BHA) which is considered to act by increasing cellular proliferation (FASEB 1994). The registrant attempted to demonstrate that dichlorvos acted like BHA and not like MNNG. The hypothesis suggested here is that genotoxic agents induce unscheduled DNA synthesis, while nongenotoxic carcinogens induce replicative DNA synthesis and/or histopathological changes, including hyperplasia. The *in vivo* cytogenetics assay was negative, thereby allaying HED's concern for the heritable effects of dichlorvos.

With respect to the forestomach tumors, the CPMC concluded that the studies were inadequate to explain the mechanism of the tumor formation for the following reasons: (1) in the method development study, the prototype for the definitive study, there did not seem to be any difference in induction of replicative DNA synthesis whether BHA or MNNG was employed as the test agent, and BHA was designated "NT" not tested at some doses in the table submitted with the report (2) the protocols were not validated by repeated trials (3) in several of the studies only 3 animals/sex/dose were used with wide interanimal variation, and large standard deviations in the results, and (4) the methodology for performing the definitive studies was never explained, therefore it was very difficult for HED to assess the data.

The CPRC concluded at their fifth meeting that dichlorvos should remain classified a Group "C" possible human carcinogen, with a linear low dose extrapolation based on the mononuclear cell leukemia in the male rat only, and not on the geometric mean of the two tumor types as previously calculated. The Committee also recommended risk assessment using the LED 10 value. The CPRC still contended that the forestomach tumors were related to administration of dichlorvos, but several members of the Committee questioned the relevance of such tumors to human health risks.

III.a.iii. Carcinogenicity Dose-response Assessment. The cancer potency value (Q_1^*) (mg/kg/day)⁻¹ for dichlorvos was calculated to be 2.72×10^{-1} (mg/kg/day)⁻¹ in human equivalents based on the incidence of mononuclear cell leukemia in male rats as compared to the previous Q_1^* of 1.22×10^{-1} used for the PD 2/3 based on the geometric mean of the mononuclear cell leukemia in male rats and forestomach tumors in female mice. The unit risk (slope) in human equivalents based on the LED 10 for mononuclear cell leukemia in male rats was calculated to be 2.58×10^{-1} (mg/kg/day)⁻¹.

III.a.iv. Route-to-Route Extrapolation for Cancer Risk Assessment. The OPP Reference Dose Committee concluded that extrapolating the results from the gavage studies to the dermal or inhalation routes of exposure is not appropriate for dichlorvos for purposes of cancer risk assessment (Ghali, 1993). This decision was based on the following considerations: (1) there was no dose-response relationship in the leukemia observed in male Fisher 344 rats (as per SAP conclusion); (2) the tumors observed in female B6C3F1 mice were contact site tumors, the relevance of which to humans is unknown, and the incidence of which, at all dose levels, including the concurrent controls, was outside the National Toxicology Program's control range; (3) the dynamics of absorption, distribution, metabolism and excretion do not favor retention of the chemical in animal tissues and makes it difficult to determine accurately the concentration at the target site; and (4) because the dermal absorption efficiency of dichlorvos is only 11%, it is not expected that topically applied doses would reach the target organ(s) in sufficient quantity to produce a carcinogenic response. Additionally, the 2-year inhalation study was negative for cancer. Therefore, extrapolation from oral data to dermal or inhalation routes is not appropriate for estimation of excess individual cancer risk following dermal or inhalation exposure to dichlorvos.

III.b. Cholinesterase Inhibition.

Cholinesterases (ChE) are a family of enzymes that are essential to the normal functioning of the nervous system. These enzymes are necessary for the transmission of nerve impulses. Inhibition of ChE activity can result in a number of cholinergic signs and symptoms in humans, depending on the extent and duration of exposure. These signs and symptoms include: headache;

dizziness; nausea; vomiting; diarrhea; increased urination; blurred vision; pinpoint pupils; increased salivation; labored breathing; muscle paralysis; slow heart rate; respiratory depression; convulsions; coma and even death. Cholinesterases have been identified in nearly every tissue of the body. For monitoring purposes, ChE activity is usually measured in blood plasma and red blood cells in humans, while ChE activity in laboratory animals are measured in plasma, red blood cells as well as brain tissue.

Organophosphate pesticides, such as dichlorvos, are known to inhibit ChE activity and some cause delayed neurotoxic effects. EPA has evaluated the available information and concluded that dichlorvos is a potent inhibitor of ChE. This determination is based on toxicological data using laboratory animals, human poisoning incidents, and limited human toxicity information, which are discussed below.

III.b.i. Laboratory Animal Data. Acute, subchronic and chronic laboratory studies using experimental animals have shown dichlorvos to be a potent ChE inhibitor, significantly reducing blood plasma, red blood cell and brain ChE. ChE inhibition has been demonstrated in several mammalian species following oral, inhalation, and dermal administration of dichlorvos. Only the primary studies selected for use in assessing risk from short-term, intermediate, and long-term exposures are discussed here.

III.b.ii. Data from Acute Toxicity Studies. Acute neurotoxicity studies have been conducted in both hens and rats. An acute neurotoxicity study in rats evaluated the neurobehavioral signs and the neuropathological effects following single exposures, but did not measure ChE inhibition (Lamb 1993). Groups of 12 male and female Sprague-Dawley rats were administered single oral doses of 0, 0.5, 35 or 70 mg/kg/day by gavage. At the mid and high-doses, administration of dichlorvos resulted in a variety of neurological and physiological changes (e.g., alterations in posture, mobility and gait, reduced or absent forelimb/hindlimb grasp, tremors). Most of these changes were observed about 15 minutes after administration of the substance. Several animals in the 70 mg/kg/day test group died. No signs of toxicity were apparent in any of the treated animals 7 days following administration of dichlorvos at all dose levels. Based on the study results, the NOEL for signs associated with ChE inhibition was established at 0.5 mg/kg/day.

Hen Delayed Neurotoxicity Study. An acute delayed neurotoxicity study in hens was resulted in cholinergic signs of ChE inhibition and neuropathic effects (Beavers et al. 1988). Ten birds were administered a single dose of 16.5 mg/kg/day by oral intubation. The test birds were given another oral dose at 21 days and observed for an additional 21 days. Dichlorvos-treated birds demonstrated signs of ChE inhibition shortly after dosing. These signs included: lethargy and depression; incoordination; limb weakness; wing drop; and reduced reaction to external stimulation. The birds were asymptomatic by day 3 after dosing. Administration of dichlorvos did not produce overt signs of acute delayed neurotoxicity, but neuropathic effects (peripheral

nerve lesions which are associated with paralysis) did occur in one hen. A NOEL was not shown for this effect in this one dose study.

Subacute Dog Study. Additional information about short-term exposure is provided by a range-finding study in which dogs (one male and one female for each dose) were administered dichlorvos by capsule for 2 weeks at the following doses: 0, 0.1, 1.0, 5.0, 10, 15, 30, or 60 mg/kg/day (AMVAC 1990). Plasma and red blood cell ChE levels were decreased in the 1.0 mg/kg/day and above test groups as early as six days after dosing. The degree of ChE inhibition increased with dose. During the first week following dosing, severe cholinergic signs were observed in animals at 30 and 60 mg/kg/day and death occurred at these doses during the second week of dosing. This study is not appropriate for short-term risk assessment because only a limited number of animals were treated at each dose and dichlorvos was administered repeatedly. Results from this study indicate, however, that short-term exposure to dichlorvos at low levels produces ChE inhibition in plasma, red blood cells and brain tissue, and contributes to the overall weight-of-the-evidence of the neurotoxicity of dichlorvos.

III.b.iii. Data from Subchronic Studies. *Rat 90-day Study.* A study performed in rats showed dichlorvos-induced ChE inhibition following subchronic exposure to dichlorvos (Kleeman 1988). Groups of 10 male and 10 female rats were administered doses of 0, 0.1, 1.5 or 15 mg/kg/day by oral gavage for 13 weeks (5 days/week). Observations recorded approximately 30 to 60 minutes postdose included salivation in 7 males and 4 females treated with 15 mg/kg/day. Urine stains were also seen in 7 males and 5 females at this dose. These observations were seen on certain days during weeks 6 through 12 for males and 8 through 12 for females. At week 7, plasma ChE activity was significantly reduced in mid- and high-dose male and high-dose female rats when compared to the controls. Mid- and high-dose male and female rats also demonstrated significantly reduced red blood cell (RBC) ChE activity when compared to the controls at 7 weeks. At the 14 week interval, plasma ChE activity was significantly reduced in high-dose males and females, while RBC ChE activity was significantly lower than controls in mid and high-dose animals. While RBC ChE activity was also reduced in the 0.1 mg/kg/day female test group at 14 weeks, ChE inhibition was not considered biologically significant since it was less than 10 percent below ChE activity in control animals. Brain ChE activity in high-dose female rats was 49 percent lower than in control females and this difference was statistically significant. Brain ChE activity in high-dose males was reduced 28 percent below control males, but the extent of this inhibition was not statistically significant. The results from this study support a NOEL of 0.1 mg/kg/day based on plasma and red blood cell ChE inhibition at doses of 1.5 mg/kg/day and above.

Rat 90-day Study with Neurotoxicity Battery. An additional subchronic study in rats evaluated neurobehavioral signs, neuropathological effects, and also measured ChE activity following oral administration of dichlorvos (Lamb 1993). Dichlorvos was administered by oral gavage to male and female rats at doses of 0, 0.1, 7.5, or 15 mg/kg/day (15 animals/sex/dose) for 90 days. There were no significant differences between the control and treated animals with respect to the functional observational battery or locomotor activity evaluations, nor were any neuropathological lesions attributable to dichlorvos. However, administration of dichlorvos was

accompanied by cholinergic signs (tremors, salivation, exophthalmos, lacrimation) approximately 15 minutes after dosing in the high-dose animals and, to a lesser extent, in the mid-dose animals. In general, cholinergic signs occurred during the first dosing week in high-dose animals and during the third dosing week in mid-dose animals, and persisted to study termination in both groups.

Plasma ChE inhibition was statistically significant at all time periods measured; however, RBC ChE inhibition was only statistically significant for high-dose males at week 3. ChE levels in RBC were reduced 23, 12, and 18 percent in the mid-dose males and 35, 8, and 11 percent in the high-dose males compared to controls during weeks 3, 7 and 13, respectively. In females, RBC ChE inhibition of 13, 38, and 33 percent at the mid-dose, and of 4, 42, and 35 percent at the high-dose were noted during weeks 3, 7, and 13, respectively. Brainstem and brain cortex ChE activity were also reduced from 11 to 12 percent in mid-dose animals and from 10 to 16 percent in high-dose rats as compared to controls. Inhibition of brain stem ChE activity was statistically significant in high-dose males only, while in the cerebral cortex ChE was significantly reduced for animals in the mid- and high-dose groups. The NOEL from this study was 0.1 mg/kg/day based on ChE inhibition (plasma, RBC, brain) and cholinergic signs occurring at 7.5 mg/kg/day.

Rabbit Developmental Toxicity Studies. A developmental toxicity study in New Zealand white rabbits produced signs of ChE inhibition at dose levels similar to those used in the rat subchronic studies (Tyl et al, 1991). Groups of 16 pregnant females were administered doses of 0, 0.1, 2.5, or 7.0 mg/kg/day by oral gavage on gestation days 7 through 19, inclusive. The doses were selected based on the results of a range-finding study conducted in the same strain of pregnant rabbits at dose levels of 0, 0.1, 1.0, 2.5, 5.0 or 10 mg/kg/day (8 per group, except for 7 in the 2.5 mg/kg/day group), in which there were statistically significant reductions in maternal plasma ChE and RBC ChE activity in a dose-related manner at all doses except 0.1 mg/kg/day. Profound treatment-related maternal mortality (5/8 animals died) and cholinergic signs occurred at 10 mg/kg/day. In the definitive developmental toxicity study, mortality was observed at 2.5 mg/kg/day (13 percent) and 7.0 mg/kg/day (25 percent). ChE inhibition was not measured; however, apparent anticholinesterase-related signs and symptoms were observed at the high-dose, including ataxia, prone positioning, tremors, excitation, salivation, diarrhea and difficulty in breathing. Based on the range-finding and definitive study results, the maternal toxicity NOEL and Lowest Observed Effect Level (LOEL) were demonstrated at 0.1 and 2.5 mg/kg/day, respectively. Developmental toxicity was not observed in this study. Consequently, the NOEL for developmental toxicity is greater than 7 mg/kg/day. The LOEL for developmental toxicity could not be determined.

An inhalation developmental toxicity study in rabbits produced findings similar to those of the oral developmental toxicity study (Thorpe et al. 1972). Groups of 20 female Dutch rabbits were exposed to 0, 0.25, 1.25, or 6.25 $\mu\text{g/L}$ of dichlorvos for 23 hours per day, from day 1 of mating to gestation day 28. No cholinergic signs were noted at 0, 0.25, or 1.25 $\mu\text{g/L}$, but severe toxicity and mortality occurred after the 6th day of exposure to 6.25 $\mu\text{g/L}$. Cholinergic signs observed included anorexia, lethargy, muscular tremors, mucous nasal discharge and diarrhea. Sixteen of the 20 animals dosed at the high-dose level died or were euthanized because of

intoxication. There were statistically significant reductions in plasma, RBC and brain ChE activity at 1.25 and 6.25 $\mu\text{g/L}$, while at 0.25 $\mu\text{g/L}$ ChE activity was depressed less than 15 percent. The NOEL for this study is 0.25 $\mu\text{g/L}$ based on ChE inhibition in plasma, RBC and brain tissue. The NOEL of 0.25 $\mu\text{g/L}$ corresponds to approximately 0.14 mg/kg/day. In converting from $\mu\text{g/L}$ to mg/kg/day, EPA assumed that 100 percent of the dichlorvos vapor is absorbed by inhalation and also that the rabbit breathing rate is constant over time.

Hen 28-day Delayed Neurotoxicity Study. Additional information on neuropathological effects can be drawn from a 28-day delayed neurotoxicity study in hens, from which preliminary results were submitted to the Agency (Amvac, date unknown). This study was required based on the results of the acute study in hens discussed above. Groups of 21 hens were administered dichlorvos orally at doses of 0, 0.1, 0.3, 1.0, or 3.0 mg/kg/day for 28 days. Significant axonal degeneration in the spinal cord occurred following oral administration of 1 and 3 mg/kg/day, while at 0.3 mg/kg/day only minor effects were noted. In addition, significant (34 to 63 percent) brain ChE inhibition was seen at 1 and 3 mg/kg/day.

There were no overt signs of organophosphate-induced delayed neurotoxicity (OPIDN) as typically demonstrated by ataxia, loss of coordination, staggering gait, or loss of leg reflexes. There was no significant reduction in neurotoxic esterase in any of the dichlorvos treated birds. The study pathologist reported spinal cord lesions in a number of hens given 1 mg/kg and 3 mg/kg of dichlorvos at a grade level which she determined to be biologically significant. Subsequent re-read of the slides by a neuropathologist with specific expertise in OPIDN, as well as a Pathology Working Group determined by consensus that hens exposed to dichlorvos demonstrated a few scattered degenerating fibers which were also seen in the controls, and that these did not seem to involve a specific level of the spinal cord or have a consistent pattern of distribution. The pattern was contrasted with that seen in the positive controls, where more marked degeneration was seen in a pattern typically noted with OPIDN (i.e. upper cervical nucleus gracilis; lumbar-sacral spinocerebellar tract). Under the study conditions, there was no increase in neuropathological lesions when hens were treated for 28 days with dichlorvos at doses of 0.3, 1 or 3 mg/kg/day. The LOEL for brain cholinesterase inhibition was 0.3 mg/kg/day.

III.b.iv. Data from Chronic Studies. Both oral and inhalation toxicity data demonstrate that long-term exposure to dichlorvos results in plasma, RBC, and brain ChE inhibition.

Rat 2-year Study. In a chronic rat inhalation study, groups of 50 male and 50 female CFE rats per dose level were exposed to 0, 0.05, 0.48, or 4.7 mg/m^3 of dichlorvos for 2 years (Blair 1974). There was a statistically significant decrease in ChE activity in plasma, red blood cells, and brain in the mid- and high-dose groups (76, 72, 90 percent and 83, 68, 90 percent of control activity in mid-dose males and females; and 38, 4, 21 and 22, 5, 16 percent of control activity in high-dose males and females, respectively). Red blood cell ChE was reduced to 88 percent of control activity in females dosed at 0.05 mg/m^3 , but this decrease was not statistically significant. The NOEL was established at 0.05 mg/m^3 based on ChE inhibition in plasma, red blood cells and brain

tissue. The concentration of 0.05 mg/m³ corresponds to approximately 0.055 mg/kg/day, assuming a constant breathing rate in rats and 100 percent absorption of dichlorvos vapor.

Dog 1-year Study. Groups of 4 male and 4 female dogs were administered dichlorvos orally by capsule 7 days per week at doses of 0, 0.05 (0.1 for the first 3 weeks of study), 1.0 or 3.0 mg/kg/day for 1 year (Markiewicz 1990). Plasma ChE was inhibited (21.1 to 66.6 percent) in males and females in the 0.1, 1.0, and 3.0 mg/kg/day groups during week 2. The low-dose was consequently reduced to 0.05 mg/kg/day on day 22 due to the plasma ChE inhibition (26 percent in females) noted after 12 days of dichlorvos administration. Red blood cell ChE was only slightly decreased (less than 2 percent) in the 0.1 mg/kg/day group at week 2, while animals in the 1.0 and 3.0 mg/kg/day groups exhibited RBC ChE inhibition of 33 to 75 percent. Statistical analyses were not conducted prior to week 13. Statistically significant depression in plasma and RBC ChE occurred at week 13 in males and females in the 1.0 and 3.0 mg/kg/day groups. In addition, brain ChE was significantly reduced in males and females in the high-dose group and in the males of the mid-dose group at termination. Brain ChE activity was inhibited approximately 22 percent in males in the 1.0 mg/kg/day group and 47 percent and 29 percent, respectively, in males and females in the 3.0 mg/kg/day group compared to controls. Study results correspond to a NOEL of 0.05 mg/kg/day, based on plasma, RBC, and brain ChE inhibition.

Rat Reproductive Toxicity Study. A two-generation reproductive toxicity study was conducted in which Sprague-Dawley rats were exposed via drinking water to dichlorvos at concentrations of 0, 5, 20, or 80 ppm. In terms of mg/kg/day, these doses correspond to: 0.5, 1.9 or 7.2 mg/kg/day in males; and 0.6, 2.3, or 8.3 mg/kg/day in females (Tyl 1992). ChE assays (plasma, RBC and brain) were performed on males and females of both the F₀ and F₁ generations at terminal sacrifice. The data indicate that RBC ChE was inhibited in both males and females at all doses and in a dose-related manner. At the low-dose, RBC ChE activity was decreased 7 to 14 percent in males and 17 to 23 percent in females. RBC ChE inhibition was statistically significant for both males and females at all dose levels, except for the F₀ males at 0.5 mg/kg/day (7 percent inhibition). Plasma ChE inhibition was statistically significant for both males and females at the mid and high-dose levels. The plasma ChE inhibition for F₁ males at the low-dose (0.5 mg/kg/day) was also statistically significant (15 percent). In addition, brain ChE activity was inhibited in males and females of both generations at all dose levels. Statistically significant reductions occurred only at the mid and high-doses. The study results establish a NOEL of less than 5 ppm for RBC and plasma ChE inhibition (males - 0.5 mg/kg/day; females - 0.6 mg/kg/day).

III.c. Human Data.

III.c.i. Biomonitoring Data. EPA reviewed several studies in the scientific literature that measured ChE inhibition in humans following exposure to dichlorvos (Stewart 1993)¹. The studies only covered a few exposure scenarios, including occupant exposure to resin pest strips and workers reentering treated warehouses. Plasma and RBC ChE were inhibited, but only plasma ChE inhibition was statistically significant, with statistically significant RBC ChE inhibition

occurring only rarely. Interpretation of ChE inhibition results from this study is difficult because of methodological problems and utilization of outdated methods for measuring ChE activity.

III.c.ii. Toxicity Data. In addition to the studies discussed above, the registrant submitted results from three studies conducted in human volunteers after the publication of the PD 2/3. In the first study, fasted caucasian male subjects were administered a single oral dose of 35 mg dichlorvos, followed by a placebo dose of corn oil capsules then a second dose of 35 mg dichlorvos (Phase I). All doses were in a volume of 0.5 mL. Prior to dosing, all individuals were given thorough medical examinations and three baseline cholinesterase measurements were taken. A symptom form was kept for each volunteer to record any adverse physical signs or symptoms. RBC cholinesterase activity was monitored immediately prior to dosing, and on study days 1, 3, 5/6, and 7. Under the study conditions, RBC cholinesterase was not inhibited in phase I. The NOEL was 35 mg, equivalent to 0.5 mg/kg based on the absence of reduction of cholinesterase activity. When the same volunteers were administered 21 mg of dichlorvos daily for twelve or 15 days (Phase II), the LOEL was 21 mg, equivalent to 0.3 mg/kg/day, based on significant and persistent reduction of cholinesterase activity. A NOEL was not determined in this study.

The second study was a single blind oral study in which fasted male volunteers were administered dichlorvos in capsules daily at a dosage of 7 mg (equivalent to approximately 0.1 mg/kg/day) in corn oil for 21 days. Control subjects received corn oil as a placebo. Any adverse events suffered by the participants were recorded on "adverse events" forms. Baseline values for RBC cholinesterase activity for each participant were determined on days -14, -12, -10, -7, -5, -3, and immediately prior to dosing, and RBC cholinesterase activity was monitored on days 2, 4, 7, 9, 11, 14, 16, and 18. No toxicity was reported which could be attributed to dichlorvos administration. While there were significant decrements in RBC cholinesterase activity in dichlorvos treated subjects at some reporting periods, the overall mean reduction from pretreatment values did not exceed 16 percent at any time. The cholinesterase activity values used to calculate the individual means varied by up to 21 percent. From this study The LOEL for RBC cholinesterase inhibition was determined to be 0.1 mg/kg/day.

In the third study dichlorvos was administered in a single oral dose of 70 mg (equivalent to 1 mg/kg) to fasted young healthy male volunteers. Prior to dosing, baseline RBC cholinesterase activity was measured on study days -22, -20, -18, -15, -13, -11, -8, -6, -4, and immediately prior to dosing. The study subjects were medically supervised for clinical signs and body temperature changes for twenty four hours and for RBC cholinesterase inhibition for up to fourteen days post dichlorvos administration. Under the study conditions, no adverse clinical signs and no body temperature variations were reported. Mean RBC cholinesterase activity was statistically significantly inhibited, but the percent decrement was 12 percent or less on days 5/6, day 7, and day 14. No reduction in RBC cholinesterase activity was apparent at other reporting periods. The reduction in RBC cholinesterase is considered to be biologically meaningful. Under the study conditions, the LOEL for this study is 70 mg (equivalent to 1 mg/kg).

III.d. Prenatal Developmental Toxicity Studies in Guinea Pigs.

The OPP Hazard Identification Assessment Review Committee (HIARC) evaluated (May 7, 1998) a prenatal developmental toxicity study in guinea pigs that was published in the open literature (Mehl et al., 1994). In this study trichlorfon (125 mg/kg), dichlorvos (15 mg/kg, once or twice/day) and several other organophosphates (dimethoate, TOCP, Soman, and ethyl trichlorfon) were administered (route unspecified) to pregnant outbred albino guinea pigs (Ssc: AL, MOI:DHF) between day 42 and 46 of gestation. A dose of 15 mg/kg dichlorvos was considered the largest dose that could be given without causing cholinergic symptoms in the pregnant dams, but it was noted that the mother of the litter that received 15 mg/kg once in 24 hours had slight symptoms. Offspring were born between day 69 and 72 of gestation. Brain weights of pups were determined within 24 hours of birth. Brain regions dissected and weighed were: medulla oblongata; cerebellum; superior and inferior colliculi; hippocampus; and thalamus and hypothalamus. The brain regions were homogenized and analyzed for choline acetyltransferase, acetyl cholinesterase, and glutamate decarboxylase.

Dosing of the dams resulted in the exposure of: 19 pups receiving saline on days 42-45; 10 pups receiving trichlorfon on days 42-44 (125 mg/kg); and 4 pups each receiving dichlorvos at either 15 mg/kg/day on days 42-44 (3 pups), 15 mg/kg/12 hours on days 42-44, or 15 mg/kg/12 hours on days 44-46. No effects on body weight were found. Trichlorfon caused significant decreases in total brain weight (29%), and significant weight decreases of the: cerebellum; medulla; thalamus/hypothalamus; colliculi; and the cerebral cortex.

Dichlorvos, in both groups dosed twice/day produced significant decreases in total brain weight (12-14%) and significant decreases in cerebellum, medulla, thalamus/hypothalamus, and the colliculi. In the group given 15 mg/kg dichlorvos once daily, total brain weight decreases (6%) were not statistically significantly decreased, and only the thalamus/hypothalamus (19%) was significantly decreased. For dams given trichlorfon, RBC cholinesterase inhibition was 64% at 1 hour, with recovery at 24 hours. There were no significant decreases in brain levels of ChE, glutamate decarboxylase, or choline acetyltransferase.

Neither soman, a much more potent ChE inhibitor, nor TOCP, a potent NTE inhibitor, caused any affect on brain weight. Ethyl trichlorfon, a more potent ChE inhibitor and analogue of trichlorfon, caused a slight decrease in brain weights of offspring, and atropine given with trichlorfon did not prevent the decrease in brain weights (data not shown). The article mentions seven articles by a variety of labs in several countries in which decreases in brain weights of pups from trichlorfon have been noted in guinea pigs and pigs, but not rats. It has been shown that 1-10% of trichlorfon is metabolized to dichlorvos, which is generally regarded as the active moiety in its anthelmintic and ChE inhibitory properties.

After reviewing the open literature studies, the Agency concluded that the open literature findings could not be dismissed and that additional data in the guinea pig are needed to further assess the developmental toxicity potential of dichlorvos (Rowland, 1998). It should be noted that the developmental effects reported in the open literature and discussed above for the neonatal

guinea pig and piglet where not seen in developmental (test species rat and rabbit) or reproduction (test species rat) toxicity studies submitted to the Agency for dichlorvos. Also, at least one literature article (Arch. Toxicol. 1986, 59:30-35) indicates that the effects on brain weight and size seen in guinea pig pups following administration of trichlorfon during gestation could not be reproduced in the offspring of rats. However, based upon the results from the literature studies, the HIARC concluded that a standard developmental toxicity study in guinea pigs be submitted with certain protocol modifications to further assess the findings reported in the Mehl et al. Study.

III.e. Food Quality Protection Act (FQPA) Considerations and Selection of Toxic Endpoints for Risk Assessment

The Hazard Identification Assessment Review Committee (HIARC) of the Health Effects Division evaluated the toxicology data base of dichlorvos and selected the doses and toxicological endpoints for dietary and non-dietary exposure risk assessments. The HIARC also assessed the potential enhanced susceptibility to infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions of the meeting were recorded in a memorandum (G. Ghali, 1997). The toxicological endpoints selected for risk assessment are summarized in Table 1. The discussion and decision concerning the potential enhanced susceptibility of infants and children to dichlorvos are summarized below.

The initial concern for neuropathy due to “inconclusive” evidence of neuropathy in a hen study was mitigated a Pathology Working Group review which concluded that there were no treatment-related increases in neuropathological lesions in the spinal cord or cerebellum. However, an open literature study in guinea pigs which reported decreased brain weight in pups whose dam had been exposed to dichlorvos again raised the concern for potential enhanced susceptibility of infants and children. The HIARC recommended that a developmental toxicity study in guinea pigs should be conducted with protocol modifications which included examination of brain weight (Rowland, 1998).

Subsequently, the OPP FQPA Safety Factor Committee met to consider if the body of toxicological data warranted removal of all or part of the FQPA Safety Factor. The decision proved to be elusive. The discussion focused on the weight that should be given the guinea pig study found in the open literature. The study had several obvious deficiencies: it did not meet Agency guidelines, the route of exposure was not reported, the number of dams exposed was small, the number of pups was small, the relevance of guinea pigs to humans is uncertain, and none of the required guideline studies submitted to OPP reported or suggested this effect. On the other hand, the study did report serious adverse effects. The Committee was not able to reach consensus on the issue and raised the issue to a higher management level (Tarplee and Rowland, 1998).

After carefully considering all the factors, the decision was made to retain a FQPA safety factor of 3x. The reduction from 10x was made based upon the fact that the standard developmental and reproductive toxicity studies submitted to the Agency showed no indication of

increased susceptibility of rats, mice, or rabbits to *in utero* and/or postnatal exposure to dichlorovos and there are no data gaps with respect to the standard Subdivision F Guidelines requirements. The recommendation of the HIARC for a prenatal developmental toxicity study in guinea pigs to assess the findings of Mehl, et.al. was also considered in the decision-making process.

The FQPA Safety Factor will be applied to the acute and chronic dietary risk assessments, and to the residential exposure assessment for the general population, including infants and children.

III.e.i. Toxicological Endpoints Selected for Risk Assessment of Dichlorvos. Shown below (Table 1) are the doses and toxicological endpoints selected for various exposure risk assessments at the November 18, 1997 HIARC meeting discussed above.

Table 1. Doses and Toxicological Endpoints Selected for Risk Assessment of Dichlorvos.

| EXPOSURE SCENARIO | DOSE (mg/kg/day) and UF | ENDPOINT | STUDY |
|--------------------------------|-------------------------|---|---------------------|
| Acute Dietary | NOEL =0.5 | Red blood cell cholinesterase inhibition | Acute- Human |
| | UF=10 | Acute RfD = 0.05 mg/kg | |
| Chronic Dietary | NOEL = 0.05 | Plasma and RBC cholinesterase inhibition in both sexes and brain cholinesterase inhibition in males | 1-Year Dog |
| | UF = 100 | Chronic RfD = 0.0005 mg/kg/day | |
| Short-Term (Dermal) (a) | Oral NOEL= 0.5 | Red blood cell cholinesterase inhibition | Acute -Human |
| | UF = 10 | | |
| Intermediate-Term (Dermal) (a) | Oral LOEL= 0.1 | Red blood cell cholinesterase inhibition | Repeated Dose Human |
| | UF=30 | | |
| Chronic (Dermal) | None | The use pattern does not indicate a potential Long-Term dermal exposure; this risk assessment is not required | None |
| Inhalation (Any Time Period) | 0.00005 mg/L | Plasma, RBC and Brain cholinesterase inhibition. | 2-Year Rat |
| | UF=100 | | |

(a) Since an oral NOEL was selected for these exposure periods, a dermal absorption factor of 11% (determined from a dermal absorption study, MRID No. 41435201) should be used for these exposure risk assessments.

Shown below (Table 2) is a summary of the endpoints and uncertainty factors used in the PD 2/3 risk assessment, and those proposed for use now, based on current HIARC and FQPA Safety Factor Committee recommendations. Note that “acceptable” MOEs have changed from those stated in the PD 2/3 because of the analysis of additional data.

Table 2. Comparison of Hazard Endpoints currently identified for Risk Assessment and those used in PD2/3.

| Risk Assessment | Current Endpoint | Current Total UF (uncertainty factor) | Current “Acceptable” MOE or %RfD | PD2/3 Endpoint | PD2/3 “Acceptable” MOE or RfD |
|--------------------------|---|--|----------------------------------|--|-------------------------------|
| Cancer (dietary) | $Q_1^* = 0.272$ leukemia in male rats | | | $Q_1^* = 0.122$ average of leukemia (rats) and forestomach tumors (mice) | |
| Chronic (dietary) | NOEL 0.05 mg/kg/day from dog feeding study (ChE) RfD = 0.00017 mg/kg/day | 300 3x FQPA 10x intra-species 10x inter-species | below 100% RfD | NOEL 0.05 mg/kg/day from dog feeding study RfD = 0.0005 mg/kg/day | 10x intra 10x inter |
| Short-term dermal | NOEL of 0.5 mg/kg/day from Human study (ChE) | 30 3x FQPA 10x intra | MOE greater than 30 | NOEL was 0.5 mg/kg/day from Rat neurotox study | MOE greater than 100 |
| Intermediate-term dermal | LOEL of 0.1 mg/kg/day from Human study (repeated dose phase) (ChE) | 100 3x FQPA 3x use of LOEL 10x intra | MOE greater than 100 | NOEL was 0.1 mg/kg/day from rat neurotox and rabbit inhalation developmental | MOE greater than 100 |
| Inhalation | NOEL of 0.5ug/L (corresponds to 0.55 mg/kg/day) from rat inhalation carcinogenicity study (ChE) | 300 3x FQPA 10x intra 10x inter | MOE greater than 300 | NOEL was 0.1 mg/kg/day (converted from 0.25 ug/L) neurotox and rabbit inhalation developmental | MOE greater than 100 |

IV. EXPOSURE ANALYSIS

The Agency has refined its exposure analysis of dichlorvos since publication of the PD 2/3. These refinements were based on newer data and information pertaining to dietary, occupational and residential exposure to dichlorvos including use deletions, modifications to the technical label, updated information on percent crop treated, and additional sources of residue data. In addition, the Agency now routinely uses the Residential SOPs and the *Exposure Factors Handbook* for residential exposure assessments. These two documents were not available at the time of the PD 2/3. The refined exposure analysis is described below.

IV.a. Chronic Dietary (Food) Exposure Analysis

IV.a.i. Background. The dichlorvos PD2/3 proposed cancellation of dichlorvos use on bulk, packages, or bagged nonperishable processed and raw food (except for impregnated resin strips in silos) because dichlorvos posed carcinogenic risks of concern to the general population from dietary exposure. Since issuance of the PD 2/3, additional data are available to allow the Agency to further refine chronic dietary exposure estimates (S. Hummel, 4/9/98 and S. Hummel, 6/15/98). Based on these data and the new Q_1^* for dichlorvos, a new cancer risk estimate for the general population can be calculated.

Dietary (food) exposure to a pesticide depends on two components: the amount of pesticide residue on a commodity and how much of that commodity is consumed. In estimating dichlorvos residues on food for the PD 2/3, EPA relied on a variety of data for dichlorvos, including: tolerance levels (the legal maximum residue) and field trial data (measured residues resulting from actual application of dichlorvos). These estimated residues can be further refined by taking into account the effects of processing and cooking on treated foods, and by estimating the percent of the crop that is treated. The current dietary (food) exposure and risk assessment is based primarily on monitoring data (both regulatory enforcement data and statistically based sampling data) and dietary intake surveys.

The Agency currently uses food consumption data derived from a USDA survey to estimate dietary exposure to pesticides. The USDA conducted a nationwide survey (1977-1978) of the food consumption patterns of 30,770 individuals for 3 days. Based on this survey, EPA can estimate the dietary exposure and risk for the U.S. population and 22 subgroups of the total population using a computer-based tool called the Dietary Risk Evaluation System (DRES). DRES multiplies the average daily consumption by residue information for each commodity to obtain the total dietary (food) exposure. EPA initially estimates dietary exposure based on the Theoretical Maximum Residue Contribution (TMRC). The TMRC assumes residues on crops are present at tolerance levels (the maximum residue limit allowed by law) and 100 percent of the crop is treated. When the risk estimated using the TMRC is considered too high, EPA uses additional data to refine the TMRC, including monitoring data, field trial data, processing data, and estimates of percent of crop treated. The Agency uses this additional information to calculate

the Anticipated Residue Contribution (ARC). When available, the ARC is used instead of the TMRC in estimating risk.

IV.a.ii. Sources of Dietary (Food) Exposure to Dichlorvos.

IV.a.ii.a. Use of dichlorvos. Dietary (food) exposure to dichlorvos residues may occur as a result of use on a variety of sites. These sites include mushroom houses, food or feed containers, bulk-stored, bagged or packaged nonperishable raw (RACs) food, and bulk stored, bagged or packaged nonperishable processed commodities, commercial food and feed manufacturing and processing plants, livestock (direct animal treatments), and livestock premise treatment. Tolerances and Food Additive Regulations exist for residues of dichlorvos in or on raw agricultural and processed products and on meat, milk, poultry and eggs.

IV.a.ii.b. Use of Naled and/or Trichlorfon. Naled and trichlorfon degrade to dichlorvos through plant metabolism. The Agency does not expect measurable dichlorvos residues from trichlorfon because all trichlorfon food uses have been canceled and associated tolerances revoked. Three factors will significantly affect dietary exposure to dichlorvos from registered uses of naled; these include, the pre-harvest interval (PHI), the condition and length of storage, and cooking and processing. Plant metabolism studies show that dichlorvos residues are formed 1 to 3 days after treatment with naled; however, dichlorvos residues decline to less than the limit of detection (0.01 to 0.05 ppm) 7 days after treatment. In general, registered uses of naled have PHIs of less than 7 days. Because of the short PHIs for naled products, measurable residues of dichlorvos may be present in the diet from naled treated food. As a result, the dietary (food) exposure assessment for dichlorvos includes residues of dichlorvos resulting from the application of naled.

IV.a.iii. Sources of Residue Data for Estimating Chronic Dietary Exposure to Dichlorvos. Sources of data to estimate the levels of residues to which the public is chronically exposed include: tolerance levels, controlled field trials, Food and Drug Administration (FDA) surveillance and compliance monitoring data, FDA Total Diet Study data (market basket survey based on a random sampling of residues on food in grocery stores), USDA Pesticide Data Program (PDP), and USDA/FSIS (Food Safety Inspection Service) livestock monitoring data (Hummel, 1998a). The estimated levels of residues can then be adjusted for the effects of processing using processing studies, including commercial processing studies, washing studies, cooking studies, and residue degradation studies. Of these sources, the Agency relied on tolerance levels and field trial data (adjusted for the effects of processing and cooking) to estimate dietary exposure to dichlorvos in the PD 2/3. For a variety of reasons, the other sources did not provide useful data (Hummel 1994a). In this updated assessment, field trial and monitoring data were used. No monitoring data were available for livestock commodities except milk. See Hummel memorandum of 4/9/98 for detailed discussion of data sources used in the current chronic dietary exposure assessment.

IV.a.iii.a. Field Trial Data. Data from controlled field trials which reflect currently registered uses are available for mushrooms and figs. Data from direct dermal treatments to cattle and poultry are discussed in the dichlorvos Registration Standard. Field trial data are also available for packaged or bagged food, use in food manufacturing and processing facilities, and for secondary residues in livestock commodities. EPA is including residue estimates for dried figs, even though these tolerances were revoked, because figs may be located in warehouses or areas where similar packaged, bagged, or bulk commodities are treated.

IV.A.iii.b. FDA Surveillance and Compliance Monitoring Data. The FDA Surveillance and Compliance Monitoring Program is designed to ensure that pesticide residues do not exceed established tolerances. Naled and dichlorvos are included in the FDA surveillance and compliance monitoring programs. However, dichlorvos is only detected using the Luke method on non-fatty foods, and only when "early eluter" column conditions are used (low column temperature). Thus, the number of samples analyzed for dichlorvos is low compared to the samples analyzed for other pesticides, although the number of analyses done by FDA that will detect dichlorvos have increased significantly in the last few years. FDA Surveillance and Compliance monitoring data were obtained from FDA for 1990 through 1996. From 1994 through 1996, FDA analyzed 1471 surveillance monitoring samples for dichlorvos. The limit of quantitation (LOQ) for dichlorvos in fruits and vegetables is approximately 0.01 ppm, and the limit of detection (LOD), approximately 0.003 ppm.

All residues reported were non-detectable, with the following exceptions: three samples of strawberries (which had low levels of detectable residues); one tomato sample from Mexico with a trace residue ($> \text{LOD}$, but $< \text{LOQ}$); one sample of garbanzo beans from S. Korea with a trace residue; and 0.03 ppm on one sample of cantaloupe from Honduras. The FDA monitoring data for berries were used in the updated dichlorvos dietary exposure analysis. Although the FDA monitoring data on other commodities were not used directly in the dichlorvos dietary exposure assessment, these data are consistent with and support the use of USDA PDP data (see below) for exposure assessment.

IV.A.iii.c. FDA Total Diet Study Data (TDS). The FDA Total Diet Study Program is designed to measure trends in pesticide residues. Since 1982, approximately four market baskets per year have been collected in a large city in one of four regions of the country. The region of the country in which the market basket samples are collected rotates so that samples are collected in all four regions over one year. FDA summarizes the data expressed as daily intakes for 8 age-sex groups (infants, young children, male and female teenagers, male and female adults, and male and female older persons). Each market basket has consisted of 234-265 individual food items prepared as ready to eat foods (washed and cooked). Individual foods are analyzed separately. Although the TDS includes sampling of meats and poultry, dichlorvos could not be analyzed in these commodities using the TDS analytical methods. The residue data on

which these calculations are based have not yet been published by FDA, but have been made available to EPA.

Historically, EPA has not used FDA Total Diet Study data for exposure assessment purposes because the number of samples is limited (approximately four samples per year of each of 234 - 265 individual food items since 1982) and because samples are only collected in large cities, and the treatment history is unknown. The TDS does not include minor crops. However, a total of 43 market basket surveys are now available for 1982 - 1996. Among the commodities collected in the TDS, there were approximately 35 non-fatty commodities analyzed which were similar to crackers and cereals, approximately 11 baked goods which were made from flour, sugar, and dried eggs, 4 coffee and 1 tea commodity, plus raisins, prunes, and cooked eggs. These are commodities that are or are produced from 'bulk stored' and 'packaged and bagged' commodities, and may have been treated with dichlorvos more recently than the wheat grain samples collected by USDA in their Pesticide Data Program.

By grouping the commodities (generally along crop group classifications), there were more than 100 samples per group of commodities analyzed. EPA has used extrapolation among members of crop groups in the past when using monitoring data. For example, monitoring data for oranges could be extrapolated to all citrus (tangerines, tangelos, grapefruit, lemons, and limes), provided the use pattern for citrus is the same.

Dichlorvos is not listed specifically as one of the pesticides recovered in the analyses for the FDA Total Diet Study. However, dichlorvos is known to be detected by the Luke method for non-fatty foods when low column temperatures are used in the analysis ("early eluter" conditions). All of the Total Diet Study samples were analyzed using temperature programming which would allow detection of "early eluters." Therefore, if dichlorvos were present, it would be detected. The LOD for dichlorvos in total diet samples is 0.001 ppm (personal communication, B. McMahon, FDA).

IV.A.iii.d. USDA Pesticide Data Program Data. The USDA Pesticide Data Program collects residue data primarily for fresh fruits and vegetables, plus wheat grain and milk. A few canned and frozen commodities have been tested. Samples are collected in terminal markets and large distribution centers. Sampling dates and sites are selected at random following a statistically designed sampling plan. Participating laboratories meet rigorous quality assurance/quality control (QA/QC) criteria including following good laboratory practices (GLP), a check sample program, and confirmation of residue findings. Sampling and analyses are done through a cooperative agreement with nine states and two USDA laboratories. These states represent about 50% of the population of the US and a large percentage of the fresh fruits and vegetables grown in the US. Food commodities collected in the PDP are prepared as normally would be done for consumption, washed and peeled, although not cooked. Canned and frozen commodities are not further cooked before analysis, although they may have been blanched or cooked in the canning or freezing process.

The USDA PDP analyzes for dichlorvos. The LOD for the analyses varied, depending on the laboratory conducting the analyses, and ranged from 3 ppb to 280 ppb. All samples analyzed for dichlorvos had non-detectable residues, except for one peach sample analyzed in 1992, which had a residue of 0.059 ppm; one green bean sample analyzed in 1994, which had a residue of 0.012 ppm; one grape sample analyzed in 1996, which had a residue of 0.003 ppm, which was below the LOQ; one milk sample analyzed in 1996, which had a residue of 0.003 ppm, which was below the LOQ; and one pear sample analyzed in 1997, which had a residue of 0.005 ppm, which was below the LOQ. PDP data were used in the dichlorvos dietary exposure assessment for commodities which could be treated with naled, and for milk. The PDP data on wheat grain were not used, because packaged and bagged commodities made from wheat grain could have been treated again with dichlorvos after the PDP samples would have been collected.

IV.a.iii.e. Processing and Cooking Study Data. Residues for raw commodities can be modified by processing factors to account for changes during commercial or other processing and cooking. Processing, cooking and decline (half-life) studies were available for cocoa beans, dry pinto beans, tomato juice, ground roasted coffee beans, raw hamburger meat, raw eggs, and raw whole milk. The resulting cooking factors were used to reduce the Agency's estimate of residues for these commodities and were translated to other commodities based on similarity of cooking time and temperature. Additional cooking studies were available and discussed in the Residue Chemistry Chapter of the Registration Standard. Half-lives of dichlorvos in various commodities ranged from 0 to over 1,000 hours. The reduction of dichlorvos upon cooking appeared to be related to the length of time and temperature used in cooking. Residues were adjusted based on these cooking factors to obtain the ARC.

IV.a.iv. Anticipated Residues for Dietary (Food) Exposure. See Hummel memorandum of 4/9/98 for a detailed discussion of calculation of anticipated residues.

IV.a.iv.a. From Use of Dichlorvos. For the updated dichlorvos dietary exposure assessment, FDA Total Diet Study data were used for residues resulting from the use of dichlorvos per se, where appropriate, by grouping similar commodities made from grain products, sugar, dried eggs, coffee and tea, and dried fruits.

Raw Agricultural Commodities. The following uses have been canceled: tomatoes, cucumbers, lettuce, and radishes. Therefore, these uses are not included in the exposure assessment.

Meat, Milk, Poultry and Eggs. Residues in livestock tissues, including milk and eggs, may result from consumption of dichlorvos treated livestock feeds, direct dermal treatments, livestock premise treatments, or from use as a drug in swine. Livestock metabolism studies done at exaggerated rates in ruminants and poultry have demonstrated that oral ingestion of dichlorvos by

cattle and poultry will not result in detectable residues. This conclusion can be extended to the drug use of dichlorvos in swine. Secondary residues in livestock from consumption of treated feed are expected to be so low that EPA is estimating these residues as zero. Data reflecting direct livestock treatments are discussed in the Residue Chemistry Chapter of the Dichlorvos Registration Standard. Data from direct dermal studies indicate that detectable residues are not expected, except in skin. Residues are non-detectable (<0.01 ppm) in cattle tissue and milk, and non-detectable (<0.05 ppm) in poultry tissues and eggs. For the PD 2/3 dietary exposure assessment, the Agency used one-half the limit of detection in both cases.

For the updated dichlorvos dietary exposure assessment, there were no monitoring data available for meat commodities, but PDP data were available for milk. Ratios of residues found in livestock tissues in dermal metabolism studies to residues in milk were calculated. These ratios were then used with the PDP monitoring data in milk to estimate residues of dichlorvos in livestock tissues. With the exception of eggs, no change was made to the dietary exposure estimates in poultry commodities.

Bulk Stored, Packaged or Bagged Commodities, Food and Feed Handling Uses. The ARCs used in the PD 2/3 exposure assessment for packaged, bagged or bulk stored food were based on field studies submitted by Amvac (Hummel 1994b). Residue data were submitted for many commodities. For those commodities where data were not submitted, EPA translated residue data from similar commodities. For example, data on dry beans are translated to other legumes; data on wheat flour are translated to all flours and meals, etc. In addition, residue data were provided for corn and oats at various points during processing, and for flour, sugar, dried milk, dried eggs, shortening, and baking mix from a treated manufacturing facility. Bulk stored commodities are assumed to be uncovered when treated. Although pesticide labels state that bulk or unpackaged foods should be covered or removed before spraying, it is not possible to assess the effect of covering food since the type of material used in the cover is not specified and the manner in which food is covered would vary considerably. Therefore, food is assumed to be uncovered, which is likely to overestimate residues. Since the proportion of commodities stored in bulk vs. packaged/bagged is unknown, the ARCs are based on an average of the residues found in bulk and packaged/bagged food for any particular commodity.

FDA TDS data were used for the dichlorvos dietary exposure assessment on grain products and sugar, eggs, coffee and tea, and raisins and prunes. In the 43 samples of 126 commodities in which dichlorvos would be detected, only one sample had a detectable residue, one sample of rye bread at 0.01 ppm, which is below the LOQ of 0.03 ppm.

The Food Additive Regulation in 40 *CFR* 185.1900 for packaged or bagged nonperishable processed foods and the tolerance in 40 *CFR* 180.235 for nonperishable packaged, bagged or bulk raw food do not refer to specific commodities. Therefore, EPA has developed a list of commodities likely to be treated with dichlorvos that are covered by tolerances and/or Food Additive Regulations. Because these tolerances and Food Additive Regulations were established to cover residues resulting from use at different sites (for example, wheat could be treated in its raw form in a silo, later as flour, during processing into cake mixes, and finally as a stored

packaged commodity), cancellation of any one of the site-specific uses does not necessarily eliminate the risk of a commodity from dichlorvos treatment. EPA did not combine the residues from different sites in creating the ARCs, although the cumulative residues from treating a commodity at different sites were considered in the estimation of percent of crop treated for the PD 2/3; however, the Agency position has changed. Now we expect that sufficient time will pass between treatments that only the maximum residue from one type of treatment needs to be considered.

IV.a.iv.a. From Use of Naled. All naled tolerances in 40 *CFR* 180.215 were evaluated as a potential source of dichlorvos residues. Anticipated residues are based on either tolerance levels or field trials. Naled and dichlorvos residue estimates were reduced when data were available to account for the effects of washing, cooking, and processing. In addition, wide area application of naled in mosquito and fly control use could result in residues potentially on all crops in the Agency's Dietary Risk Evaluation System. Therefore, EPA included all these crops in its estimate of anticipated dichlorvos residues. Although it is possible that dichlorvos residues could occur on any raw agricultural commodity from this use of naled, it is unlikely that residues would be found on all commodities. As a result, this inclusion of residues of dichlorvos from all raw crops presents a possible source of overestimation of dietary exposure. As discussed earlier, EPA does not expect measurable residues from the use of trichlorfon because it has no tolerances or registered food uses (Hummel, 1998b). Changes in the dichlorvos dietary exposure analysis since the PD 2/3 are summarized in Table 3.

Table 3. Summary of Changes in the Dichlorvos Dietary Exposure Analysis since the PD 2/3

| Dietary Exposure Factors Considered in PD 2/3 Chronic Dietary Exposure Assessment | Factors Considered in Current Chronic Dietary Exposure Assessment |
|--|---|
| Uses: crop and greenhouse use food service establishments bulk stored raw & processed packaged & bagged raw & processed food handling uses food manufacturing establishments mushroom houses direct livestock treatment livestock premise treatment | Uses: crop uses canceled food service uses canceled other uses remain |
| Sources of dichlorvos: use of both dichlorvos and naled | Sources of dichlorvos: use of both dichlorvos and naled |
| Data used for dietary exposure: - field trials (not enough monitoring data for dichlorvos) - tolerance for unsupported crop uses - reduction in washing and cooking - cattle & poultry dermal studies | Data used for Dietary exposure: - monitoring data from FDA TDS & regulatory monitoring and USDA PDP (many more samples collected than before 1994) - zero for canceled unsupported crop uses - reduction in washing & cooking - PDP for milk & ratio to other livestock tissues - poultry dermal study |
| — | Added consideration of comments received in response to PD 2/3. Comments were received on the size of pallets stacks in warehouses, turnover of commodities in warehouses, and livestock residue estimates. |

IV.a.v. Percent of Crop Treated Information. In conducting a chronic risk assessment, EPA refines its estimate of dietary exposure based on percent of crop treated when such information is available. In the absence of this information, EPA assumes that 100 percent of the crop is treated. Where a range of percent crop treated estimates are supplied for this analysis, the upper end of that range is assumed. The Biological and Economic Analysis Division (BEAD) of OPP provided updated percent of crop treated information that were incorporated into the chronic dietary (food) exposure analysis as appropriate (Steinwand, 1998b).

IV.a.vi. Results of Chronic Dietary Exposure Analysis.

The results of the refined dietary exposure (DRES) analysis and comparison to those in the PD 2/3 are shown in Table 4 (Steinwand, 1998),

Table 4. Refined Dietary Exposure Estimates and Estimates from the PD 2/3.

| Chronic Dietary Risk Assessment | Current Estimate | PD2/3 Estimate |
|--|---|---|
| Cancer (US population) | Dichlorovos alone 3.4×10^{-7} Naled-derived Dichlorovos 1.8×10^{-7} Total Estimate = 5.2×10^{-7} | Dichlorovos alone 4.4×10^{-6} Naled-derived Dichlorovos 7.2×10^{-7} Total Estimate = 5.1×10^{-6} |
| Non-cancer (RfD) | Dichlorovos at 0.7% RfD for total US population 2.3% RfD for non-nursing infants <1 year old (highest exposure) Naled-derived Dichlorovos at less than 0.1% RfD for US and all population subgroups | All less than 100% - did not exceed level of concern |

IV.b. Occupational and Residential Exposure.

EPA completed a series of exposure assessments in August 1987 for the Registration Standard and PD 1. Many of the exposure assessments were based on limited data. Additional exposure data were submitted to the Agency prior to publication of the PD 2/3. These data were evaluated and used to revise the original 1987 exposure assessment for the following applicator exposure scenarios: crack and crevice; greenhouses, mushroom houses, dairy barns and milk rooms. In addition, data were available which allowed the Agency to estimate exposure from use of household aerosol and total release fogger products, from use in warehouse treatment, and for use on dairy cattle for the PD 2/3. EPA used a variety of data for estimating occupational and residential exposures.

The focus of this document are new approaches utilized for the assessment of resin strips in residential settings as this exposure scenario has several issues associated with it. The occupational and residential exposure assessments for the remaining use scenarios addressed in the PD2/3 remain unchanged and are not addressed herein. The revised residential exposure assessment is based on data from an air monitoring study used for the 1995 PD2/3 in conjunction with comments to the PD2/3 and new information from 1) Exposure Factors Handbook (USEPA 1997); 2) Standard Operating Procedures (SOPs) for Residential Exposure Assessments (USEPA 1997), and the use of an indoor air model (Multi-Chamber Concentration Exposure Model V2.4). These additional resources have undergone extensive levels of peer review (e.g., FIFRA SAP or EPA SAB). The major difference between the PD2/3 and the new approaches are the distribution of the exposure duration, the respiratory volume selected, and the further refinement of the exposed population. In all but one case, margins of exposure were unacceptable based on an uncertainty factor of 300. This case was for individuals exposed only during the time interval required for placement of a resin strip (i.e. only for the smallest exposure duration evaluated, 10 minutes). Independent of the distribution of the exposure duration, it is the Agency's position to use the chronic inhalation NOEL because this scenario could potentially be long-term given that the label states that strips are effective for 4 months and can be replaced after this time period or when effectiveness diminishes.

IV.b.i. Resin Strip Use (Residential Postapplication Exposure). The Agency has conducted exposure assessments for resin strip uses utilizing four different approaches (one is from the PD2/3 and others are new): 1) 90-day time weighted average; 2) percentile of time spent in proximity to resin strips; 3) time weighted average for various heating, ventilation, air conditioning (HVAC) descriptors; and 4) an indoor air Multi-Chamber Concentration and Exposure Model (MCCEM). All four approaches are based on data from an air concentration monitoring study from the literature [Collins, R.D. and D.M. DeVries (1973) Air concentrations and Food Residues from Use of Shell's No-Pest Insecticide Strip. Bull. Environ. Contamin. Toxicol. 9(4):227-233.]

In this study, air concentrations were monitored up to 91 days after placement of 10 inch dichlorvos-impregnated resin strips in 15 houses that used central air conditioning, window unit

air conditioners, or apparently had no air conditioning (or didn't use it during the study). Twenty minute air samples (samplers placed in dining room, volume = 40 L/sample) were collected on the following days: 1, 7, 14, 28, 56, and 91. Ten homes received 3 strips and the remaining 5 homes were treated with 4 strips (i.e., actual application rates ranged from 720 to 6790 ft³/strip with an average of 1833 ft³/strip -- at least one strip per home was in the kitchen). Air concentrations in this study ranged from 0.11 µg/L to the detection limit of 0.01 µg/L (½ of the LOD was used for all calculations where the value was ≤ LOD). At the 56 day after treatment interval, air concentrations were ≤ LOD in 12 of 15 samples. At the 91 day after treatment interval, all air concentrations were <LOD.

Method I: Chronic Time Weighted Average Method (Used for the 1995 PD2/3 Assessment).

The resin strip exposure assessment for the PD2/3 used a time weighted average air concentration of dichlorvos. Airborne concentrations of dichlorvos were measured on the day of pest strip installation and at 7, 14, 28, 56, and 91 days thereafter. A time weighted average concentration over 90 days was calculated based on these measured values. Assumptions used were: 1) an average 70 kg resident has a respiratory volume of 1.7 m³ per hour while performing light tasks and 0.44 m³ per hour while at rest; 2) an average 70 kg resident spends 15 hours/day in the home; 3) five of these hours are spent performing light tasks and the remaining 10 are spent at rest; 4) the daily respiratory volume is 12.9 m³ per day; 5) resin strips are changed every 90 days after which a new resin strip is used; and 6) residents are assumed to be exposed 365 days per year (Jaquith, 1987a and Jaquith, 1993).

Using this method, the time weighted average concentration over 90 days is 0.015 mg/m³. Daily exposure based on a respiratory rate of 12.9 m³/day and a 70 kg body weight is 2.5 x 10⁻³ mg/kg/day. The MOE calculated using this exposure level based on the current inhalation NOEL of 0.05 mg/kg/day in 20.

Method II: Percentile of Time Spent in Proximity to Resin Strips for Four Populations. A National Human Activity Pattern Survey (NHAPS) reported time that various age groups of the population spent around pesticides, including bug strips (Tsang and Klepeis, 1996 as presented in USEPA, 1997). These data are presented in Table 16-33 ("Number of minutes spent in activities working with or near pesticides, including bug sprays or bug strips") of the Agency's Exposure Factors Handbook (USEPA 1997). Activity pattern data were reported for population groups including children 1-4 years old, children 5-11 years old, adult males, and adult females. Recommended daily respiratory volumes for these four population groups were also obtained from the Exposure Factors Handbook. The daily respiratory volumes were 8.7 m³/day (6 L/min) for both of the child categories and 15.2 m³/day (10.6 L/min) for adult males, and 11.3 m³/day (7.9 L/min) for adult females. Using these data, the potential respiratory exposures of residents of homes in which resin strips has been evaluated. Four categories of residents were assessed: adult males; adult females; toddlers, age 1-4; and small children, age 5-11. Estimates were derived using percentiles (50th, 75th, and 99th) of the time (minutes/per day) individuals spend either using or in the proximity of pesticides, including pest strips. For the purposes of this assessment

it was assumed that all of this time would be spent near resin strip products even though these data could be interpreted in other ways. Data from the Exposure Factors Handbook are summarized in Table 5.

Table 5. Estimated Minutes Consumers Spend Around or Using Pesticides.

| Group | Minutes Spent Around or Using Pesticides By Percentile ¹ | | |
|----------|---|------|------|
| | 50th | 75th | 99th |
| Male | 10.0 | 90 | >121 |
| Female | 10.0 | 35 | >121 |
| Age 1-4 | 10.0 | 15 | 20 |
| Age 5-11 | 7.5 | 30 | >121 |

¹For the 99th percentile, 120 minutes was used for calculation purposes.

Exposures were calculated by multiplying the air concentrations of dichlorvos at each of the measured time intervals for each house for each population by the appropriate respiratory volume (Jaquith, 1998). Similar calculations were also completed for the median, mean, maximum and minimum concentrations specific to each monitoring day of the study. These values were then divided by body weight; 70 kg for adult males, 60 kg for adult females, 15 kg for toddlers (1 to 4 years), and 22 kg for ages 5-11). This yielded a matrix of exposures by day by house by percentile for each of the four populations. The margin of exposure is based on an inhalation NOEL of 0.05 mg/kg/day for effects of cholinesterase inhibition. For illustrative purposes, exposures and MOE values based on the median air concentration on the day of resin strip installation coupled with the distribution of exposure duration values are presented in Table 6.

Table 6. Median Exposure and MOEs for Four Populations on the Day of Resin Strip Installation Based Percentile of Time Spent Around/Using Pesticides (Exposure Factors Handbook).

| Minutes Spent Around or Using Pesticides by Percentile | Male | | Female | | Child 1-4 | | Child 5-11 | |
|--|----------------------|-----|---------------------|-----|----------------------|-----|----------------------|-----|
| | Exposure (mg/kg/day) | MOE | Exposure (m/kg/day) | MOE | Exposure (mg/kg/day) | MOE | Exposure (mg/kg/day) | MOE |
| 50th percentile of activity ≤10 minutes | 0.00008 | 625 | 0.000066 | 758 | 0.0002 | 250 | 0.000102 | 490 |
| 75th percentile of activity 30-90 minutes | 0.00068 | 74 | 0.00023 | 217 | 0.0003 | 167 | 0.000411 | 122 |
| 99th percentile of activity >120 minutes | 0.00091 | 55 | 0.00079 | 63 | 0.0004 | 125 | 0.0016 | 31 |

Method III: Indoor Air Calculations Using Day 1 Dichlorvos Pest Strip Data (Averaged by HVAC Situation). This approach is based on an activity pattern duration variable (i.e., residential occupancy or time spent indoors is 16.4 hours/day which is considered a high confidence value) which is a "recommended" value from Table 1-2 (Summary of Exposure Factor Recommendations and Confidence Ratings) of the Exposure Factors Handbook (USEPA, 1997). Additionally, an alternative method for calculating exposure concentration values (i.e., average of day 1 empirical data from the same air monitoring study discussed above). This approach is essentially the same as used for Method II except the air concentration data are manipulated in a slightly different fashion and a different source for the exposure duration factor was used. In this assessment, averages are calculated from dichlorvos air concentration data delineated by HVAC situation (i.e., window, central, or no air conditioning) and these concentration data are assumed to be consistent throughout the treated residence. The parameters for this approach (body weight, respiration rate, etc.) are presented in Table 7 along with average air concentrations, exposures, and MOEs (Dawson, 1998).

Table 7. Average and Maximum Indoor Air Concentrations and MOEs for Four Populations on the Day of Resin Strip Installation based on HVAC¹ Descriptors.

| HVAC Descriptor | Ave. Air (ug/L) | Max. Air (ug/L) | Adult Male (mg/kg/day) | | | Adult Female (mg/kg/day) | | | Young Child (mg/kg/day) | | | Toddler (mg/kg/day) | | |
|-----------------|-----------------|-----------------|------------------------|-------|----------|--------------------------|-------|----------|-------------------------|-------|----------|---------------------|-------|----------|
| | | | Ave. | Max. | Max. MOE | Ave. | Max. | Max. MOE | Ave. | Max. | Max. MOE | Ave. | Max. | Max. MOE |
| None | 0.054 | 0.11 | 0.008 | 0.016 | 3 | 0.007 | 0.014 | 4 | 0.014 | 0.029 | 2 | 0.021 | 0.042 | 1 |
| Central AC | 0.050 | 0.08 | 0.007 | 0.011 | 4 | 0.006 | 0.010 | 5 | 0.013 | 0.021 | 5 | 0.019 | 0.031 | 2 |
| Window AC | 0.060 | 0.11 | 0.009 | 0.016 | 3 | 0.008 | 0.014 | 4 | 0.016 | 0.029 | 4 | 0.023 | 0.042 | 1 |
| All Types | 0.060 | 0.11 | 0.009 | 0.016 | 3 | 0.008 | 0.014 | 4 | 0.016 | 0.029 | 4 | 0.023 | 0.042 | 1 |

¹HVAC = Heating, Ventilation, Air Conditioning

Method IV: Indoor Air Calculations Using Multi-Chamber Concentration and Exposure Model, or MCCEM (V2.4). This approach is also based on an activity pattern duration variable (i.e., residential occupancy or time spent indoors is 16.4 hours/day which is considered a high confidence value) which is a "recommended" value from Table 1-2 (Summary of Exposure Factor Recommendations and Confidence Ratings) of the Exposure Factors Handbook (USEPA, 1997). Additionally, an alternative method for calculating exposure concentration values (i.e., chemical specific dissipation from the resin strip study coupled with MCCEM).

MCCEM is a model that has been used by EPA's OPPTS and OPP for several years to complete indoor air exposure assessments. Assessors using MCCEM can configure the model to produce time-weighted average air concentrations for a wide array of scenarios depending upon the inputs selected because it is a very flexible system. The major requirement for using MCCEM

is the development of a scenario specific source term (i.e., otherwise known as emission rate). Once the emission rate is defined, air concentration values over time (up to a year) can be incrementally calculated. The dilution aspects of the model are based on empirically derived data from actual houses. MCCEM outputs include both TWA and maximum [dichlorvos]_{air} (mg/m³) for the specific models selected. In this case, only the TWA values were used for the assessment.

Developing an MCCEM-based assessment is a several step process. The first step was to define the chemical use patterns. These are defined as follows:

Single Pest Strip: use of a single resin strip or treating one room of a house (i.e., 20 grams dichlorvos contained in a 100 gram resin strip based on a 20 percent ai level in the product); and

Multiple Pest Strips: use of four resin strips or treating an entire house (i.e., 80 grams dichlorvos contained in four 100 gram resin strips based on a 20 percent ai level in the product and the fact that the application rate is close to the maximum for a house with a volume of 217m³ -- the 1997 EFH recommended conservative house volume when 2 children's bedrooms and the kitchen are excluded as these areas are precluded from treatment by dichlorvos labeling).

The next step in the process was to define the kind of houses that were to be modeled. The "houses" selected for these calculations include the "generic house" option and an actual house included in the interzonal empirical database (i.e., house 6845A -- a two-story house in California with a high air exchange rate of 3.57 exchanges/hour based on evaluation in the summer season -- it is anticipated that this house would be a typical use situation where high air exchange is noted because the windows are open and insects get in requiring resin strip use). The generic house selected represents average volume and flow information that has been compiled from a large number of residences. The generic house GN001 was used for all assessments in both the summer (i.e., 0.18 air exchanges/hour) and fall (i.e., 0.45 air exchanges/hour). "The summer infiltration rate represents a conservative value for modeling purposes, whereas the fall infiltration rate represents a typical value (see MD Koontz and HE Rector, *Estimation of Distributions for Residential Air Exchange Rates*, Final Report March 1995 -- prepared for US EPA/OPPTS).

Another aspect of defining the modeled "house" is defining the number of zones to be modeled. For this assessment, zones were defined as follows:

Single Pest Strip: Two zone, generic house model is used (i.e., treated area and the rest of the house), house 6845A is also used for this scenario -- this house has three zones;

Multiple Pest Strips: single zone, generic house model is used (i.e., whole house is treated), house 6845A is also used for this scenario -- this house has three zones.

After the "house" to be modeled is selected, the next step is to define the duration of the model

calculations. In this case, because dichlorvos has a cholinesterase endpoint, a value of 16 hours was selected. This value also corresponds to the exposure duration exposure factor of 16.4 hours for residential occupancy (USEPA, 1997). A total of 960 calculations were completed for each model run (i.e., 16 hours x 60 minutes/hour x 1 model calculation/minute).

The final step for calculating exposure concentrations was to define emission rates (grams ai/hour) that reflect the use of the products. In this case, empirical data were available from the resin strip study to define a source term for the model (i.e., data indicates 90 percent or greater emission at 56 days after resin strip placement). Using a value of 56 days as the emission time based on the empirical monitoring data and the values of active ingredient included in both application scenarios described above, the following emission rates were calculated:

Single Pest Strip: 20 grams dichlorvos/(56 days x 24 hours/day) = 0.01488 grams ai/hour.

Multiple Pest Strips: 80 grams dichlorvos/(56 days x 24 hours/day) = 0.05952 grams ai/hour.

For illustrative purposes, exposures and MOE values based on the TWA air concentrations for house 6845A using single and multiple resin strips on the day of strip installation coupled with the distribution of exposure duration values are presented in Table 8 (Dawson, 1998).

Table 8. Exposures and MOEs for Four Populations in Calculated Using MCCEM.

| Scenarios for Ttwo-Story CA House (Summer Season) | Adult Males | | Adult Females | | Young Children | | Toddlers | |
|---|----------------------|-----|----------------------|-----|----------------------|-----|----------------------|-----|
| | Exposure (mg/kg/day) | MOE | Exposure (mg/kg/day) | MOE | Exposure (mg/kg/day) | MOE | Exposure (mg/kg/day) | MOE |
| Single Pest Strip | 0.00375 | 13 | 0.00326 | 15 | 0.00675 | 7 | 0.0091 | 5 |
| Multiple Pest Strip | 0.07923 | 0.6 | 0.06889 | 0.7 | 0.14269 | 0.4 | 0.20929 | 0.2 |

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