Dichlorvos; CASRN 62-73-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Dichlorvos

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	11/01/1993
Inhalation RfC (I.B.)	yes	06/01/1994
Carcinogenicity Assessment (II.)	yes	10/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Dichlorvos
CASRN — 62-73-7
Last Revised — 11/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Plasma and RBC ChE inhibition in males and females; brain ChE inhibition in males **1-Year Dog Feeding Study** **AMVAC Chemical Corp., 1990**	NOAEL: 0.05 mg/kg-day LOAEL: 0.1 mg/kg-day	100	1	5E-4 mg/kg-day

*Conversion Factors and Assumptions — None

I.A.2. Principal and Supporting Studies (Oral RfD)

AMVAC Chemical Corporation. 1990. MRID No. 41593101; HED Doc. No. 008178. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

In a chronic feeding study (AMVAC Chemical Corp., 1990), groups of beagle dogs (4/sex/dose) were administered dichlorvos by capsule for 52 weeks at dose levels of 0, 0.1, 1.0 and 3.0 mg/kg-day. The 0.1 mg/kg-day dose level was lowered to 0.05 mg/kg-day on day 22 due to the inhibition of plasma ChE noted after 12 days on test material. Capsules were prepared weekly based on the most recently recorded body weight, and stored refrigerated and protected from light. Animals received food and water ad libitum.

No deaths occurred. Ataxia, salivation and dyspnea were observed in one male in the high-dose group on 1 day in Week 33. The study investigator believed these signs were due to a slight overdose with dichlorvos. Formulation and dosing records could not confirm that an overdose occurred. Mean cumulative body weight gain was decreased in males in the high-dose group during Week 1 to Week 7. At termination, mean cumulative body weight gain was comparable among groups. Plasma ChE was decreased in males (21.1%) and females (25.7%) at Week 2 in the 0.1 mg/kg-day. In order to achieve a NOEL, the dose was dropped to 0.05 mg/kg-day at Day 1 of Week 4. After Week 2, plasma ChE was only significantly decreased in males (39.1 to 59.2%) and females (41.0 to 56.7%) in the mid-dose group and in males (65.1 to 74.3%) and

females (61.1 to 74.2%) in the high-dose group at all other later time intervals. RBC ChE was decreased in males (23.6%) and females (50.1%) at Week 6 in the low-dose group. This is believed to be the residual effect on RBC ChE of the initial higher dose of 0.1 mg/kg-day. Much lower levels were observed in this group after Week 6. After Week 6, RBC ChE was only significantly decreased in males (43.0 to 53.9%) and females (38.0 to 51.9%) in the mid-dose group and in males (81.2 to 86.9%) and females (79.2 to 82.5%) in the high-dose group at all other later time intervals. The percent inhibition did not appear to increase with time. Brain ChE was significantly decreased in males (approximately 22%) in the mid-dose group and in males (approximately 47%) and females (approximately 29%) in the high-dose group.

In the range-finding study (AMVAC Chemical Corp., 1990) for the chronic toxicity study, groups of beagle dogs were administered dichlorvos by capsule for 2 weeks at dose levels of 0, 0.1, 0.1 (10.0), 1.0 (5.0), 30 (15.0) and 60 mg/kg-day. Test Group 1 (1 male; 1 female) served as controls. Test Group 2 contained two groups of animals, each consisting of 1 male and 1 female. The first group received 0.1 mg/kg-day throughout the study. The second group received 0.1 mg/kg-day from Day 1 to 7 and 10 mg/kg-day from Day 8 to 24. Test Group 3 received 1.0 mg/kg-day from Day 1 to 14 and 5 mg/kg-day from Day 15 to 24. The male from Test Group 4 received 30 mg/kg-day throughout the study while the female received 30 mg/kg-day from Day 1 to 6, was not dosed on Days 7 and 8, and received 15 mg/kg-day from Day 9 to 15. Test Group 5 received 60 mg/kg-day throughout the study.

Death occurred in the 30 and 60 mg/kg-day groups. Toxic signs observed at these dose levels included: salivation, ataxia, emesis, miosis, cyanotic appearance, lacrimation, urine stains, soft feces (mucoid, red) and/or rough coat. Soft mucoid feces were noted at 1.0 mg/kg-day. At 5.0 mg/kg-day, emesis, tremors, alopecia, salivation, soft mucoid red feces and/or few feces were observed. The male in the 0.1 mg/kg-day group exhibited emesis. Body weight loss and decreased food consumption were noted in the 5.0 and 10.0 mg/kg-day groups. The blood urea nitrogen (BUN) was elevated in dogs in the 5.0 and 10.0 mg/kg-day groups. Plasma and RBC ChE were decreased in dogs in the 1.0 mg/kg-day group and at higher dose levels. Brain ChE was decreased in the female in the 0.1 mg/kg-day by approximately 16% and in all dogs at the higher dose levels. Brain ChE levels were not determined in the 1.0 mg/kg-day group until after the dose ChE level had been changed for at least 1 week. Therefore, brain ChE levels could not be accurately determined at the 1.0 mg/kg-day level.

In a subchronic feeding study (Shell Chemical Co., 1967a), groups of beagle dogs (3/sex/dose) were administered dichlorvos by capsule for 90 days at dose levels of 0, 5, 15 and 25 ppm (0, 0.125, 0.375 and 0.625 mg/kg-day). Twenty-one days after the start of the study, the 5 ppm group was increased to 50 ppm (1.25 mg/kg-day) and an additional 5 ppm group was added. Control animals received olive oil only.

Excitement and hyperactivity were reported among all the high-dose dogs and two of the mid-dose dogs. Dogs in the mid- and high-dose groups showed increased urinary output. No consistent decreases in RBC or plasma cholinesterase were reported, although the greatest decrease in the high-dose dogs was seen on day 54, when RBC ChE was 41.3%, the plasma ChE was 54.2% and the total ChE value was 47.8% of the control. The greatest decrease in the 25 ppm dogs was seen on day 74 when RBC ChE was 41.3% and total cholinesterase was 51% of the control. At terminal sacrifice, brain ChE activity was decreased to 32.8% of control at 50 ppm and to 88.6% of the control at 25 ppm. No changes were observed in the two lower doses. Based on decreases in brain and blood ChE activity, the LEL for systemic toxicity is 25 ppm (0.625 mg/kg- day). The NOEL for systemic toxicity is 15 ppm (0.375 mg/kg-day).

Based on the effects observed in these three dog studies, a weight of the evidence LEL for systemic toxicity can be set at 0.1 mg/kg-day based on plasma ChE inhibition in males and females and brain ChE inhibition in males. The NOEL for systemic toxicity is 0.05 mg/kg-day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for intraspecies-variability.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

1) 1-Year Feeding - dog: Principal study -- see previous description; core grade guideline (AMVAC Chemical Corp., 1990)

2) 2-Year Feeding/Oncogenicity - rat: Core grade supplementary for chronic feeding, minimum for oncogenicity (NTP, 1987)

Groups of Fischer 344 rats (60/sex/dose) were administered dichlorvos by gavage once daily 5 days/week for 103 consecutive weeks at dose levels of 0, 4 and 8 mg/kg-day followed by a 1 week observation period. The control group received corn oil. Five animals/sex/dose were used to monitor the systemic toxicity of dichlorvos by determining plasma and RBC ChE levels at 6 weeks and at 3, 6, 9, 12, 18 and 24 months. An additional five animals/sex/dose were used for brain and sciatic nerve histology.

Only minimal clinical signs were observed in the study. A significant decrease in both plasma and RBC ChE was observed in both test groups. Wide disparities were reported between cholinesterase values in male and female vehicle-treated rats (female plasma ChE values were 2

to 6 times higher than male values); however, the cholinesterase depressions were consistently lower in the treated animals than in the controls, indicating that cholinesterase depression was related to the administration of the test compound.

Based on the plasma and RBC ChE inhibition, the LEL for systemic toxicity is 4 mg/kg-day. A NOEL for systemic toxicity was not established.

3) 13-Week Feeding - rat: No core grade (NTP, 1987)

This study was conducted as the range-finding study for the 2-year rat feeding/oncogenicity study (NTP, 1983). Groups of Fischer 344 rats (10/sex/dose) were administered dichlorvos for 13 weeks at dietary levels of 0, 2, 4, 8, 16, 32 and 64 mg/kg-day.

All animals treated with 32 and 64 mg/kg-day died before study termination. At 16 mg/kg-day, 1 out of 10 males and 4r out of 10 females died. The one male death was accidental. When compared to the controls, body weight gains were -6%, +2%, +1% and +4% for the males and -7%, -2%, 0% and +2% for the females receiving 16, 8, 4 and 2 mg/kg-day, respectively. Clinical signs observed in the animals that died on study were trembling, diarrhea, wet fur around the mouth and convulsions immediately preceding death. No clinical signs or significant pathology were observed in animals which survived the study.

Based on mortality and clinical signs observed in this study, the MTD for the chronic rat study was selected at 16 mg/kg-day for males and 8 mg/kg-day for females. Since published information indicated that males were more sensitive than females, NTP approved doses of 0, 4 and 8 mg/kg-day for both sexes.

4) 3-Generation Reproduction - rat: Core grade supplementary (Shell Chemical Co., 1965)

Groups of Sprague-Dawley rats (15/sex/dose) were administered dichlorvos over three generations at dietary levels of 0, 0.1, 1, 10, 100 and 500 ppm (0, 0.005, 0.05, 0.5, 5 and 25 mg/kg-day). No maternal or reproductive toxicity were observed at any dose tested. Therefore, the NOEL for maternal and reproductive toxicity is greater than or equal to 500 ppm (25 mg/kg-day).

5) Developmental toxicity - rat: Core grade minimum (AMVAC Chemical Corp., 1991)

Groups of pregnant Sprague-Dawley rats (25/dose) were administered dichlorvos via gavage at dose levels of 0, 0.1, 3.0 and 21 mg/kg-day during gestational days 6-15. Maternal toxicity was observed at the highest dose tested. The signs of toxicity included tremors, prone positioning, hindleg splay, vocalization, labored respiration, ear shaking, ingesting of urine- marked bedding

and decreased water consumption. Based on these effects, the NOEL and LEL for maternal toxicity are 3 and 21 mg/kg-day, respectively. No developmental toxicity was observed at any dose tested. Therefore, the NOEL for developmental toxicity is equal to or greater than 21 mg/kg-day.

Other Data Reviewed:

1) 2-Year Feeding/Oncogenicity - mouse: Core grade minimum (NTP, 1987)

Groups of B6C3F1 mice (60/sex/dose) were administered dichlorvos by gavage (corn oil) 5 days/week for 103 weeks at dose levels of 0, 10 and 20 mg/kg-day for males and 0, 20, and 40 mg/kg-day for females followed by a 1 week observation period. Five animals/sex/dose were used for determination of plasma and RBC ChE levels at 6, 13, 24, 36, 52, 78 and 104 weeks. An additional 5 animals/sex/dose were used for brain and sciatic nerve histology at study termination. Significantly decreased plasma and RBC ChE was observed in males and females at all dose levels, although the cholinesterase values returned to normal in female mice on withdrawal of the test compound. The RBC ChE values of both control and treated animals varied too widely for a valid interpretation to be made of this effect.

Based on plasma ChE depression, the LEL for systemic toxicity is 10 mg/kg- day. The NOEL for systemic toxicity was not established.

2) 13-Week Feeding - mice: no core grade (NTP, 1987)

This study was conducted as the range-finding study for the 2-year mouse feeding/oncogenicity study (NTP, 1987). Groups of B6C3F1 mice (10/sex/dose) were administered dichlorvos by gavage (corn oil) at dose levels of 0, 5, 10, 20, 40, 80 and 160 mg/kg-day. All males and nine females receiving 160 mg/kg- day died prior to study termination. The only decrease in weight gain observed in males during the study was in the low-dose group (-23%). For females, the percentages of weight gain of the treated groups versus the control group were -11%, 0%, 0%, - 11% and +11% for the 160, 80, 40, 10 and 5 mg/kg-day groups, respectively. No toxic signs or significant pathology were observed in the animals that survived to study termination.

Based on mortality and clinical signs observed at the highest dose level, the maximum tolerated dose (MTD) for the chronic feeding/oncogenicity study was set at 40 mg/kg-day for males and 80 mg/kg-day for females. Doses of 0, 10 and 20 mg/kg-day for males and 0, 20 and 40 mg/kg-day for females were approved because it was expected that the effects of cholinesterase inhibition would be cumulative.

3) 2-Year Drinking/Oncogenicity - mice: Core grade supplementary (AMVAC Chemical Corp., 1989a).

Groups of B6C3F1 mice (50/sex/dose) were administered dichlorvos in the drinking water for 2 years at dose levels of 0, 58, and 94.8 mg/kg-day for males and 0, 56.2, and 102.3 mg/kg-day for females. Body weight gain and water consumption were decreased in both treated groups. There was a dose- related decrease in absolute and relative weight of the gonads of males. The absolute and/or relative weight of the pancreas was decreased in treated females. Other weight changes were apparent. Testicular atrophy was increased in males in the high-dose group.

4) 2-Year Drinking/Oncogenicity - rat: Core grade supplementary (AMVAC Chemical Corp., 1989b)

Groups of F344 rats (51/sex/dose) were administered dichlorvos in drinking water for 104 weeks at dose levels of 0, 140, and 280 ppm (Male: 0, 8.3 and 10.4 mg/kg-day; Female: 0, 17.5 and 21.8 mg/kg-day) followed by a 4 week recovery period. Animals in both treated groups exhibited chromodacryorrhea during the first 2 weeks of study. High-dose females had tremors and were hypersensitive to touch. During the last 3 months of the study, treated animals exhibited an increase in the incidence and severity of lacrimation. Mean body weight of high-dose males and low- and high-dose females was lower than controls during the last few months of the study. There was a decrease in the absolute and relative liver weight in high-dose males.

5) 80-Week Feeding/Oncogenicity - rat: Core grade supplementary (NCI, 1977)

Groups of Osborne Mendel rats (50/sex/dose) were administered dichlorvos for 80 weeks at dietary levels of 0, 150 and 326 ppm (0, 7.5 and 16.3 mg/kg- day). Test diets were discontinued after 80 weeks and treated animals and their matched controls were fed control diets until the termination of the study at 110 weeks. An additional 5 rats/sex/dose were used as matched controls. Another 60 male and 60 female rats being used as matched controls for other simultaneous bioassays were used as pooled controls for this study. The initial dose levels selected for this study were 150 and 1000 ppm. Because of serious toxicity observed in the 1000 ppm rats during the first 3 weeks of the study, the dose was reduced to 300 ppm for the remaining 77 weeks. The time weighted average doses were 150 and 326 ppm.

Severe signs of toxicity including tremors, rough hair coats, diarrhea, and poor appearance were reported in the rats receiving 1000 ppm. When the dose was reduced to 300 ppm, the appearance and behavior were similar among all animals. During the second year of the study, rough hair coats, epistaxis, hematuria, alopecia, dark urine, bloating and abdominal distension were observed. Effects were more pronounced in high-dose females. At study termination, the surviving animals were reported to be in poor physical condition. Body weight was consistently

lower in high-dose animals than in the low-dose and the matched controls (approximately 15% in males and 25% in females).

Based on decreased body weight gain, the LEL for systemic toxicity is 326 ppm (16.3 mg/kg-day). The NOEL for systemic toxicity is 150 ppm (7.5 mg/kg- day).

6) 94-Week Feeding/Oncogenicity - mouse: No core grade (NCI, 1977)

Groups of B6C3F1 mice (50/sex/dose) were administered dichlorvos for 80 weeks at dietary levels of 0, 318 and 635 ppm (0, 47.7 and 95.25 mg/kg-day). Five mice/sex/dose were used as matched controls. Test diets were discontinued after 80 weeks and treated animals and their matched controls were fed control diets until the termination of the study at 92-94 weeks. Another 100 male and 80 female mice being used as matched controls for other simultaneous bioassays were used as pooled controls for this study. The initial doses for this study were 1000 and 2000 ppm, but because of observed toxic signs, the doses were reduced to 300 and 600 ppm. Time-weighted averages were 318 and 635 ppm.

Severe signs of toxicity were reported during the first 2 weeks of the study. When the dosages were reduced to 300 and 600, the appearance and behavior of the treated animals were comparable to that of the controls for the first year of the study. Toxic signs reported included alopecia and rough hair in all groups, and bloating and abdominal distension in all groups except high-dose females. Body weight was decreased in the high-dose. The low-dose female group had the lowest survival rate (74%) in the study.

7) 2-Year Feeding/Oncogenicity - rat: Core grade supplementary (high mortality in the control and treated animals due to infection and actual concentration of dichlorvos in the diet ranged from 22% to 80%) (Shell Chemical Co., 1967b)

Groups of CD rats (Control: 40/sex; Test groups 25/sex/dose) were administered dichlorvos for 2 years at dietary levels of 0, 0.047, 0.46, 4.67, 46.7 and 234 ppm (0, 0.0024, 0.023, 0.23, 2.3 and 11.7 mg/kg-day). No toxicity was on food consumption, body weight, hematology, blood protein, urinalysis or terminal organ weights. Toxicity was demonstrated by a significant inhibition of cholinesterase activity at doses of 100 ppm and higher. Liver cell vacuolation occurred in rats receiving 100 ppm. These changes were accompanied by fatty livers in 500 ppm treated animals.

Based on cholinesterase inhibition and hepatocellular vacuolation, the LEL for systemic toxicity is 46.7 ppm (2.3 mg/kg-day). The NOEL for systemic toxicity is 4.67 ppm (0.23 mg/kg-day).

Data Gap(s): Rat Reproduction Study, Rabbit Developmental Toxicity Study

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

The principal study is of good quality. However, due to the change in the dosing regime, the study is given a medium to high confidence rating. Additional studies are supportive of the principal study but the database lacks a rabbit developmental toxicity study and adequate studies to fully address chronic and reproductive toxicity in the rat. Therefore, the data base is given a medium confidence rating. Medium confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 09/16/1986, 07/16/1987, 05/27/1992

Verification Date — 05/27/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Dichlorvos conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Dichlorvos
CASRN — 62-73-7
Last Revised — 06/01/1994

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Decreased brain colinesterase activity **Carworth Farm E Strain Rat Chronic Inhalation Study** **Blair et al., 1976**	NOAEL: 0.05 mg/cu.m NOAEL(ADJ): 0.05 mg/cu.m NOAEL(HEC): 0.05 mg/cu.m LOAEL: 0.48 mg/cu.m LOAEL(ADJ): 0.48 mg/cu.m LOAEL(HEC): 0.48 mg/cu.m	100	1	5E-4 mg/cu.m

*Conversion Factors and Assumptions — None required; exposures were essentially continuous for 2 years. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect, assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental animal species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = 0.05 x [b:a lambda(a)/b:a lambda(h)] = 0.05 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Blair, D., K.M. Dix, P.F. Hunt, E. Thorpe, D.E. Stevenson, and A.I. Walker. 1976. Dichlorvos: A 2-year inhalation carcinogenesis study. Arch. Toxicol. 35(4): 281-294.

Carworth Farm E strain (CFE) rats, 50/sex/group, were exposed whole body to atmospheres containing dichlorvos vapor for at least 23 hours/day, 7 days/week for up to 2 years. Test atmospheres were generated by bathing wicks saturated with technical grade dichlorvos (>97% pure) in a metered flow of dried, compressed air. The dichlorvos-laden air was diluted to the exposure levels required in this study as it entered 10-cu.m chambers that were operated at flow rates ranging from 2.49-2.80 cu.m/minute. Chamber concentrations, were sampled once daily and averaged 0, 0.05, 0.48, and 4.70 mg/cu.m (+/-20%). Food and water were available ad libitum. Dichlorvos tends to adsorb onto surfaces, can corrode some materials, and will hydrolyze rapidly to dichloroacetaldehyde in the presence of moisture (Blair and Rees, 1975). It is not clear whether chamber homogeneity and test atmosphere purity in normally humid inhalation chambers were confirmed during the study. Whole body exposures and around-the-clock studies such as this permit skin, hair, food, and possibly water to absorb test material and to become additional sources of exposure, doubling the dose of dichlorvos received by the animals (Stevenson and Blair, 1977; Blair et al., 1976). The animals were observed for clinical signs of toxicity, hematology, clinical chemistry (but no urinalysis), and blood and plasma cholinesterase activity. Brain cholinesterase activity was measured in rats surviving the study. Brain acetylcholine and choline were evaluated in three female rats from each exposure group. All animals on test were necropsied, and major organs, including the upper respiratory tract (number of sections unspecified), were examined histopathologically. Lower respiratory tract tissues from an unspecified number of male and female rats from the control and high-exposure group were prepared and examined by electron microscopy.

Observations in both sexes for toxic signs, organ weight, organ-to-body- weight ratios, and hematologic parameters revealed no changes attributable to exposure. Survival was inversely related to treatment. Clinical chemistry determinations for both sexes were unremarkable, except for unspecified increases in SGPT and SGOT levels in animals exposed to the high concentration only. Body weights were significantly decreased over corresponding control values for a large portion of the study in both males (up to 20%) and females (up to 14%) only at the highest concentration. Evaluations of brain acetylcholine and choline were unremarkable. Brain, plasma, and erythrocyte cholinesterase activities were decreased in a concentration-related manner in both sexes of animals exposed to the high and middle concentrations. Brain cholinesterase activity, the most toxicologically relevant of those monitored, was significantly depressed in both sexes (90% of control activity) in animals exposed to 0.48 mg/cu.m dichlorvos. This activity was not different between controls and either females (97% of control activity) or males (96% of

control activity) exposed to 0.05 mg/cu.m dichlorvos. The reductions in cholinesterase activity appear to have been asymptomatic.

In all groups, histopathology revealed a range of lesions commonly found in aging CFE rats, none of which appeared to be compound related. The respiratory tract also exhibited minor changes in all groups, including controls, that were not correlated with exposure. Electron and light microscopic examinations of the lungs also failed to reveal any pattern of changes that could be correlated with exposure. Based on alterations in brain cholinesterase activity, the LOAEL is 0.48 mg/cu.m, and the NOAEL is 0.05 mg/cu.m.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — A UF of 10 is used for the protection of sensitive human subjects. A UF of 3 is used for interspecies extrapolation. A single factor of 3 is used for consideration of both the lack of a multigenerational reproductive study and chronic data in a second species. Concern for the latter was ameliorated as the in vivo half life of dichlorvos is brief and chronic oral studies of dichlorvos show that cholinesterase inhibition does not increase with a regime of repeated exposures. Too, this same effect is noted in oral studies with dichlorvos in several species, including humans. The total UF is 100.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

The effects on applicators and residents following fumigation of houses with dichlorvos were investigated by Gold et al. (1984). Applicators were exposed to average levels of 0.21 mg/cu.m for an average duration of approximately 25.5 minutes. Residents were exposed to an average of about 0.21 mg/cu.m for an average duration of about 15.8 hours. Data on two applicators showed decreases in plasma cholinesterase activity of 21 and 59%, respectively. The changes in erythrocyte cholinesterase activity were inconsistent but suggestive of a decrease in one applicator. Some of the 20 exposed residents complained of headache. The mean plasma cholinesterase activity for the residents 24 hours after application of dichlorvos was only slightly reduced (-7.9%) compared with preexposure levels. The mean erythrocyte cholinesterase activity was not significantly reduced, although individual decreases ranged from 5.3-37.5%.

In a limited occupational study, six formulators and reactor workers in a pesticide manufacturing plant were exposed for 20 days to an average air concentration of 0.1 ppm dichlorvos (Ember et al., 1972). The text of this study claims that plasma cholinesterase activity and vitamin A levels decreased in five workers and that there was only a small recovery in these values after a 13-day period of nonexposure.

Case studies of accidentally exposed humans demonstrate the acute toxicity of dichlorvos. Children exposed to vapors of insecticides containing dichlorvos (in combination with other pesticides and chemicals) experience symptoms typical of organophosphate poisoning related to the cholinesterase inhibition caused by these chemicals (Low et al., 1980). Signs of poisoning include giddiness, headache, drowsiness, sweating, cold and clammy skin, abdominal pain, nausea, vomiting, and constricted pupils. Measurements of plasma cholinesterase show a substantial decrease in activity. It has been suggested that exposure to vapors of household insecticides (containing dichlorvos in addition to other pesticides and chemicals) may produce delayed severe blood effects (Reeves et al., 1981). Six children between the ages of 2 and 12 years developed aplastic anemia or acute lymphoblastic anemia within 0.5-28.0 weeks following known exposure to an insecticide containing dichlorvos and propoxur. The 7-month-old sibling of one of the patients had transient neutropenia 2 weeks after house fumigation. Because of the mixed exposure and the possibility of other confounding factors, it is difficult to assess the potential role of dichlorvos in the observed hematological effects.

Oral dosing of human volunteers also results in rapid depression of plasma cholinesterase activity, and in some cases, in decreased erythrocyte cholinesterase activity. Groups of five men were fed 1.0, 1.5, 2.0, or 2.5 mg doses of dichlorvos daily for 28 days (Rider et al., 1967). Cholinesterase activity was 71% of controls at the end of the 28 days in the group receiving 2.0 mg/day and was 70% of controls at the end of 20 days in the group administered 2.5 mg/day. No significant effect on erythrocyte cholinesterase activity was observed, and there were no clinical symptoms of exposure in the men. One hundred and seven male volunteers were administered oral doses of dichlorvos ranging from 0.1-16.0 mg/kg. A group of 44 males received only a placebo pellet (Slomka and Hine, 1981). Similar numbers of treated and control subjects reported clinical symptoms consisting of stomach rumbling, nausea, and diarrhea. There were no effects on any laboratory parameters except cholinesterase activity. The extent of depression of cholinesterase activity measured at 24 hours postadministration increased with dose and reached a maximum of approximately 80% at a dose of about 6 mg/kg. Erythrocyte cholinesterase activity also decreased with increasing dichlorvos administration, but the decrease was less than that observed in the plasma. Daily administration of the same doses to the volunteers resulted in such a dramatic rate of decrease in plasma and erythrocyte cholinesterase activity that the experiment was terminated in most subjects in less than 7 days. An attempt to gradually increase the dose in the subjects produced similar results, and, at the highest dose administered (16 mg/kg), the experiment was terminated after only 5.5 days.

Walker et al. (1972) exposed beagles, cats, and New Zealand white rabbits continuously for 8 weeks to levels of dichlorvos vapor simulating normal use. The animals, bearing cortical electrodes for EEG recordings, were housed in a kennel and exposed to dichlorvos vapor as it evolved under ambient conditions from dichlorvos-impregnated resin strips that were hung in the kennel. Exposure concentrations, monitored occasionally during the study, ranged from 0.05-

0.30 mg/cu.m. No effects on general health, behavior, plasma and erythrocyte cholinesterase activities, or EEG patterns were found.

Thorpe et al. (1972) exposed primiparous female Dutch rabbits (20/group) and pregnant CFE rats (15/group) throughout pregnancy to dichlorvos vapors from gestation days 1-28 for rabbits and days 1-20 for rats. The exposure, test atmosphere generation, and analytical procedures were the same as those employed in the 2-year chronic study. The animals were exposed at least 23 hours/day at actual chamber concentrations targeted at 0, 0.25, 1.25, and 6.25 mg/cu.m. Concentrations in the high-level chamber spiked on 3 separate days to levels between 7 and 8 mg/cu.m. Some rats exposed to the highest concentration appeared less active, and 80% of the rabbits exposed to the highest concentration exhibited signs of toxicity (anorexia, lethargy, tremors, nasal discharge, and diarrhea) and subsequently died. The remaining groups were not subjected to these spikes, and the dams of both species appeared to be free of clinical signs during exposure to 0.25 or 1.25 mg/cu.m. A second rabbit study, conducted at concentrations of 0, 2, and 4 mg/cu.m, also suffered from a 1-day concentration spike to 6.6 mg/cu.m in the highest exposure group, resulting in mortality (6/20). Five of the six rabbits in the highest exposure group that died during the second study were lost after the spike. Brain, plasma, and erythrocyte cholinesterase activities were depressed significantly in maternal rats exposed to 1.25 and 6.25 but not 0.25 mg/cu.m. These activities were also reported depressed in dams exposed to 1.25 mg/cu.m dichlorvos. No other signs of maternal toxicity were clearly related to exposure in animals exposed at or below 1.25-2.00 mg/cu.m. Fetuses of both species showed no compound-related skeletal or soft-tissue abnormalities. No differences were observed in litter size, resorptions, or mean fetal weight between control and exposed groups for either species. A NOAEL of 1.25 mg/cu.m, based on the lack of brain cholinesterase inhibition, is identified for maternal toxicity. A NOAEL of 6.25 mg/cu.m is identified for fetotoxicity.

Dean and Thorpe (1972), using the same exposure methods as Blair and Rees (1975), evaluated the mutagenic potential (dominant lethal assay) of dichlorvos vapor in male CF1 mice. The animals were exposed to 30 or 55 mg/cu.m for a single 16-hour period or to 2.1 or 5.8 mg/cu.m continuously for 4 weeks prior to mating. The animals exhibited no impairment of fertility and no mutagenic effects, based on the lack of preimplantation losses or early fetal deaths. Dean and Blair (1976) were subsequently unable to induce dominant lethal mutations in mice of either sex, regardless of whether the mice were dosed orally (25 or 50 mg/kg) or by inhalation (2 or 8 mg/cu.m).

On the premise that inhibition of acetylcholinesterase activity may induce cholinergic responses in portal-of-entry tissues, Schmidt et al. (1979) exposed male Sprague-Dawley rats to dichlorvos at 0.20-56.64 mg/cu.m for 3-14 days and observed a concentration-related decrease in acetylcholinesterase activity in bronchial homogenates. Histochemical preparations of tracheal and bronchial tissue corroborated acetylcholinesterase activity, which was reduced in the tissues

even at the lowest level of exposure. However, the toxicological significance of those results is not clear because Pauluhn et al. (1987) could not provoke increases in lung resistance in Wistar rats after exposure to dichlorvos (1-4 hours at 183 mg/cu.m) without provocation by acetylcholine.

Pregnant CF1 mice and New Zealand rabbits exposed to 4.06 mg/cu.m for 7 hours/day on days 6-15 (mice) or days 6-18 (rabbits) showed no significant compound-related differences in reproductive or developmental parameters compared with controls (Schwetz et al., 1979). Parameters monitored included clinical signs; gestational and litter weights; number of corpora lutea; number and position of live, dead, and resorbed fetuses; and malformation of fetuses. A statistically significant (p < 0.05) decrease in gestational weight was observed in the exposed mice on day 16 only. There were no signs of toxicity in the dams. This study indicates 4.06 mg/cu.m to be a NOAEL for fetotoxicity.

Exposure of groups of CD-1 mice to 1.9, 3.0, or 4.6 mg/cu.m dichlorvos during a 4-day breeding period resulted in significant (p < 0.05) depression of plasma cholinesterase activity (Casebolt et al., 1990). An additional experiment exposed groups of mice to the same concentrations starting from 4 days prior to formation of breeding units and continuing through pregnancy. Despite the substantial decrease in plasma cholinesterase activity, no signs of toxicity were observed in the dams, and there was no effect on litter frequency, litter size, or length of gestation, indicating 4.6 mg/cu.m to be a NOAEL for fetoxicity.

D'Souza and Batra (1976) appear to produce partial sterility in male (partial loss of seminiferous tubules) and female (hyalinized ovaries and missing follicles and oocytes) offspring during a two-generation study on the effects of dichlorvos. Closer examination, however, reveals major procedural difficulties with this study. Female mice, their offspring, and their caging were all sprayed directly each week with dichlorvos. No estimates of dose were made. The test material was available to each mouse orally and dermally, as well as by inhalation. No effect levels can be assigned from this study.

Timmons et al. (1975) determined that the onset of estrous was significantly (p < 0.05) delayed in female rats exposed from birth to vapor from pesticide strips containing dichlorvos; onset of estrous was 42 days in the control group and 52 days in the exposed group. Exposure concentrations were not measured.

Dichlorvos is absorbed following inhalation, oral, and dermal exposure; however, the rapid metabolism of the chemical makes it difficult to quantify the extent of absorption (WHO, 1991). Excretion data indicate that at least 85% of an orally administered dose is absorbed. Tissue deposition appears to vary between different species. It has been reported to be found primarily in the kidneys of CFE rats (Blair et al., 1975) and in the ovarian tissue and blood of female

Sprague-Dawley rats (Timmons et al., 1975) exposed by inhalation. When radiolabeled dichlorvos is used, the label that is found in tissues is believed to be a metabolic breakdown product of the dichlorvos molecule and its incorporation into normal tissue constituents (Page et al., 1972; Potter et al., 1973). Metabolism of dichlorvos is very rapid in all species studied (Page et al., 1972; Hutson and Hoadley, 1972a,b).

Blair et al. (1975) reported that dichlorvos was rapidly degraded in blood and tissues of rats and mice that had been exposed to various concentrations of dichlorvos vapors. Dichlorvos could not be detected in any tissue examined from rats that were exposed continuously to either 0.05 or 0.50 mg/cu.m for 14 days. Parent dichlorvos was detected in the kidneys of rats exposed to 10 mg/cu.m for 4 hours and in most tissues of rats (although remaining highest in the kidneys) exposed to 90 mg/cu.m for 4 hours. Mild signs of toxicity (lethargy and pupillary constriction) were noted in rats exposed to this highest concentration. The distribution of dichlorvos in tissues of mice exposed to the highest concentration differed from rats as fat, lung, and testes had higher concentrations than did the kidneys. Dichlorvos disappeared from the kidneys of male rats with a half-life of approximately 13.5 minutes. In vitro assays with whole blood showed dichlorvos to have a half-life ranging from 1.5-31.0 minutes. The principal metabolic products of dichlorvos are dimethyl phosphate and dichloroacetaldehyde. The blood of two human volunteers exposed to dichlorvos vapor (0.25-0.70 mg/cu.m) for up to 20 hours contained no detectable test material, and the volunteers apparently exhibited no symptoms.

Two metabolic pathways have been proposed for dichlorvos, one glutathione- dependent and one glutathione-independent (Dicowsky and Morello, 1971). Gaines et al. (1966) demonstrated that significant detoxification of dichlorvos took place in the liver. Excretion studies with mice, rats, and hamsters (Hutson and Hoadley, 1972a,b), as well as swine (Potter et al., 1973), have shown that most of the label absorbed from an oral dose of dichlorvos is excreted in the urine and breath. In humans, as well as rats, mice, and swine, dimethyl phosphoric acid and dichloroacetaldehyde have been identified as the primary metabolites (Bradway et al., 1977; Das et al., 1983; Page et al., 1972; Hutson and Hoadley, 1972b; Riemer et al., 1981; Stevenson and Blair, 1977). Desmethyl dichlorvos, dichloroethanol, hippuric acid, and glutathione conjugates have also been detected (Page et al., 1972; Hutson and Hoadley, 1972a,b).

Julka et al. (1992) observed various alterations (decreased levels of glutathione and decreased activity of glutathione peroxidase, along with increases in enzymes that enhance the disposal of potentially toxic radicals) in brain tissues from rats exposed intraperitoneally to 5 mg/kg dichlorvos. These results may indicate that dichlorvos significantly disturbs the antioxidant defense system in the target tissue.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Although current test guidelines recommend more frequent measurement of the chamber atmosphere, the principal study was well-conducted for its time, used a sufficient number of animals (although only one species), and monitored appropriate endpoints. The whole-body, around-the-clock exposure protocol permitted auxiliary oral and dermal dosages of dichlorvos. In spite of the augmented dose received by the animals through ingestion, no demonstrable pathologic or cholinergic symptomatology was reported. Decreases in brain cholinesterase activity were observed and are an acknowledged target organ effect for organic phosphates. The database for this compound is relatively complete because the chronic oral studies used several species. Inhalation and oral reproductive and developmental studies are available. However, an inhalation-based assessment of its multigeneration reproductive toxicity was not found. Thus, the database is assigned a medium level of confidence. Consequently, the confidence in the RfC is medium.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 11/05/1992

Verification Date — 11/05/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Dichlorvos conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Dichlorvos
CASRN — 62-73-7
Last Revised — 10/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

NOTE: The carcinogen assessment for dichlorvos may change in the near future pending the outcome of a further review now being conducted by the CRAVE Work Group.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Significant increases in forestomach tumors in female and male B6C3F1 mice and leukemias and pancreatic acinar adenomas in Fischer 344 rats. Supporting evidence included observation of tumors at other sites in the rat and observation of mutagenicity for both dichlorvos and a major metabolite dichloroacetaldehyde. A structurally related material, dichloropropene, also induces forestomach tumors in rodents.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Sufficient. In a 2-year gavage study (NTP, 1986a), mice (60/sex/group) of the B6C3F1 strain were treated with dichlorvos at 10 and 20 (mg/kg)/day (males) or 20 and 40 (mg/kg)/day (females), 5 days/week for 104 weeks followed by a 1-week observation period. Corn oil was used as the solvent.

At 40 mg/kg the incidence of squamous papillomas of the forestomach of female mice (18/50) was statistically significantly increased compared with the vehicle control (5/49). There was a significant positive trend in both males and females. The incidence of carcinomas and squamous cell papillomas of the forestomach combined showed a significant trend for the high-dose females (19/50); it was also significantly elevated in a pairwise comparison. It is noteworthy that tumor incidence was elevated at a relatively low treatment dose.

Survival was unaffected by treatment. Based on a significant depression of plasma and RBC cholinesterase in treated mice of both sexes at all doses, dose selection appears to be adequate.

In a 2-year gavage study (NTP, 1986b), rats (60/sex/group) of the F344 strain were treated with 4 or 8 (mg/kg)/day once daily 5 days/week. Survival was unaffected by treatment. Dose selection was adequate based on plasma and RBC cholinesterase suppression.

In the males the incidence of pancreatic acinar adenoma was 16/50, 25/49, and 30/50 at 0, 4, and 8 mg/kg, respectively, which was statistically significantly elevated by pairwise comparison and showed a significant positive dose-related trend. The incidence of alveolar/bronchial adenoma of 3/49 in the high-dose males versus 0/50 in the controls was not significant on a pairwise basis but showed a positive dose-related trend. The incidence of leukemia (lymphocytic, monocytic, mononuclear or undifferentiated) was 11/50, 20/50, 21/50 for the males at 0, 4, or 8 (mg/kg)/day, respectively. These values were statistically significantly elevated at 4 and 8 mg/kg/day and also showed a significant dose-related trend. There was a statistically significant increase in lung tumors in the low-dose male rats.

In the females, the incidence (19/50) of mammary fibroadenoma was significant by pairwise comparison and the trend was also significant. When analyzed for all type mammary tumors (fibroma, fibroadenoma, carcinoma, adenocarcinoma or adenoma) the incidence was 11/50, 20/50, 17/50 for 0, 4, or 8 mg/kg, respectively. The mid-dose was significant while the dose-related trend was not. There was a statistically significant increase in mammary tumors in the low-dose female rats.

Four other chronic studies have been conducted on DDVP. A 2-year inhalation study was conducted by Shell Chemical Company (1967) wherein CFE rats (50/sex/dose group) were

exposed to DDVP vapors at nominal concentrations of 0.1, 1.0, 10, 100, and 500 ppm (measured concentrations of 0.047, 0.46, 4.67, and 234 ppm). This study was flawed by poor survival, tissue autolysis and inadequate number of tissues examined histopathologically. A 2-year rat study (Osborne-Mendel strain bred at Charles River Breeding Lab.) was conducted by NCI (1977) in which DDVP was fed to groups of 50/sex/dose at 0, 150, and 326 ppm. This study suffered from poor animal survival resulting from intercurrent infection in the animals. A 2-year mouse study (B6C3F1 strain obtained from Charles River Breeding Lab.) was conducted by NCI (1977) wherein DDVP was fed at 0, 318, or 635 ppm. The results were considered equivocal on the basis of insufficient numbers of control animals (dichlorvos controls were pooled with those from other studies). Lastly, in a 2-year inhalation study conducted by Shell Tunstall Laboratories, England (no date), rats were exposed to DDVP at 0, 0.05, 0.5, and 5.0 mg/cu.m. The results were considered equivocal.

II.A.4. Supporting Data for Carcinogenicity

DDVP was positive in mutation assays using S. typhimurium strain TA1530 and E. coli strains B/r, WP2-hcr, WP2, and Cm 881 (Moriya et al., 1978; Bridges, 1978) without metabolic activation. Results indicative of DNA interactions were obtained in the polA2 assay in E. coli (Rosenkranz, 1973) and for histidine and leucine mutants of Serratia marcescens (Dean, 1972). DDVP was mutagenic in the recessive lethal test using Drosophila (Hanna and Dyer, 1975), and in mouse lymphoma cells in culture without addition of hepatic homogenates (Litton Bionetics, 1985). It was negative in the mouse micronucleus test, in the sister chromatid exchange assay, and in the mouse dominant lethal test (Microbiological Associates, 1985). In addition, dichlorvos alkalates DNA (Segerbaeck and Ehrenberg, 1981).

Dichlorvos is structurally related to dichloropropene (a probable human carcinogen), which causes forestomach squamous cell tumors in rats and mice, lung tumors in mice and neoplastic nodules in the livers of rats.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 2.9E-1 per (mg/kg)/day

Drinking Water Unit Risk — 8.3E-6 per ug/L

Extrapolation Method — linearized multistage procedure, extra risk

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/L
E-5 (1 in 100,000)	1E+0 ug/L
E-6 (1 in 1,000,000)	1E-1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: forestomach, pancreatic, leukemia (see table)
Test animals: mouse and rat (see table)
Route: gavage
Reference: NTP, 1986a,b

---------------Dose--------------			
Administered (ppm)	Human Equivalent (mg/kg/day)	Tumor Incidence	Reference

mouse/B6C3F1, female. forestomach tumors (papilloma, squamous and squamous cell carcinoma)

0	0.0	5/49	NTP, 1986a
140	15.75	6/49	
280	31.50	19/50	

------- Dose --------		-------- Tumor Incidence ------		
Administered (ppm)	**Human Equivalent (ppm)**	**Pancreatic acinar adenoma**	**Leukemia**	**Reference**

rats/F344, male. pancreatic acinar adenoma; leukemia, all types

0	0	16/50	11/50	NTP, 1986b
80	80	25/49	20/50	
160	160	30/50	21/50	

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The oral slope factors (expressed as per (mg/kg)/day) are based on the tumors of the forestomach in B6C3F1 mice (1.1E-1), tumors of the pancreas in F344 rats (5.8E-1) and leukemia in the F344 rat (3.8E-1) individually. A geometric mean of these slope factors was taken as the final estimate [2.9E-1 per (mg/kg)/day] as all three were roughly equivalent and so that relevant data not be discarded.

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of animals, lifetime exposure, no effect on survival and adequate dose selection establishing greater confidence in the quantitative estimate.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA. 1987a,b,c,d,e, 1988a,b,c,d,c

The risk assessment for dichlorvos was reviewed by the OPP Peer Review Group and by the
FIFRA Science Advisory Panel.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 09/22/1988

Verification Date — 09/22/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA
contractor of the more recent toxicology literature pertinent to the cancer assessment for
Dichlorvos conducted in November 2001 did not identify any critical new studies. IRIS users
who know of important new studies may provide that information to the IRIS Hotline at
hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general,
at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Dichlorvos
CASRN — 62-73-7

VI.A. Oral RfD References

AMVAC Chemical Corporation. 1989a. MRID No. 41041801; HED Doc. No. 007543. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

AMVAC Chemical Corporation. 1989b. MRID No. 41041802; HED Doc. No. 007543. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

AMVAC Chemical Corporation. 1990. MRID No. 41593101; HED Doc. No. 008178. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

AMVAC Chemical Corporation. 1991. MRID No. 41951501; HED Doc. No. 009305. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

NCI (National Cancer Institute). 1977. Bioassay of Dichlorvos for Possible Carcinogenicity. NTIS PB-270937. 103 p.

NTP (National Toxicology Program). 1987. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dichlorvos in F344/N Rats and B6C3F1 Mice: (Gavage Studies): NTP TR 342. U.S. Dept. of Health and Human Services, Public Health Service. Pub. No. NIH 88-2598.

Shell Chemical Company. 1965. MRID No. 00050012; HED Doc. No. 007765 Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Shell Chemical Company. 1967a. MRID No. 00013550, 00050010; HED Doc. No. 007765. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Shell Chemical Company. 1967b. MRID No. 00059397, 000611333; HED Doc. No. 007765. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

Blair, D. and H.J. Rees. 1975. The generation and administration of atmospheres containing dichlorvos for inhalation studies. Am. Ind. Health. Assoc. J. 36(5): 385-397.

Blair, D., E.C. Hoadley and D.H. Hutson. 1975. The distribution of dichlorvos in the tissues of mammals after its inhalation or intravenous administration. Toxicol. Appl. Pharmacol. 31(2): 243-253.

Blair, D., K.M. Dix, P.F. Hunt, E. Thorpe, D.E. Stevenson and A.I. Walker. 1976. Dichlorvos: A 2-year inhalation carcinogenesis study in rats. Arch. Toxicol. 35(4): 281-294.

Bradway, D.E., T.M. Shafik and E.M. Lores. 1977. Comparison of cholinesterase activity, residue levels, and urinary metabolite excretion of rats exposed to organophosphorus pesticides. J. Agric. Food Chem. 25(6): 1353-1358.

Casebolt, D.B., S.L. Leary and L. Undeutsch. 1990. Effects of dichlorvos treatment on mouse reproduction. Lab. Anim. Sci. 40(1): 65-67.

Das, Y.T., P.K. Taskar, H.D. Brown and S.K. Chattopadhyay. 1983. Exposure of professional pest control operator to dichlorvos (DDVP) and residue on house structures. Toxicol. Lett. 17(1-2): 95-99.

Dean, B.J. and D. Blair. 1976. Dominant lethal assay in female mice after oral dosing with dichlorvos or exposure to atmospheres containing dichlorvos. Mutat. Res. 40(1): 67-72.

Dean, B.J. and E. Thorpe. 1972. Studies with dichlorvos vapor in dominant lethal mutation tests on mice. Arch. Toxikol. 30(1): 51-59.

Dicowsky, L. and A. Morello. 1971. Glutathione-dependent degradation of 2,2- dichlorovinyl dimethyl phosphate (DDVP) by the rat. Life Sci. 10(18): 1031- 1037.

D'Souza, A.V. and B.K. Batra. 1976. A study of the effects of DDVP (propoxure) on laboratory mouse. Curr. Sci. 45(10): 377-379.

Ember, M., L. Mindszenty, B. Rengei, L. Csaszar and M. Czina. 1972. Secondary vitamin A deficiency in organophosphate formulators and spray workers. Res. Commun. Chem. Pathol. Pharmacol. 3(1): 145-154.

Gaines, T.B., W.J. Hayes, Jr., and R.E. Linder. 1966. Liver metabolism of anticholinesterase compounds in live rats: Relation to toxicity. Nature. 209(5018): 88-89.

Gold, R.E., T. Holcslaw, D. Tupy and J.B. Ballard. 1984. Dermal and respiratory exposure to applicators and occupants of residences treated with dichlorvos (DDVP). J. Econ. Entomol. 77(2): 430-436.

Hutson, D.H. and E.C. Hoadley. 1972a. The comparative metabolism of (14-C- vinyl)dichlorvos in animals and man. Arch. Toxikol. 30(1): 9-18.

Hutson, D.H. and E.C. Hoadley. 1972b. The metabolism of (C14- methyl)dichlorvos in the rat and the mouse. Xenobiotica. 2(2): 107-116.

Julka, D., R. Pal and K.D. Gill. 1992. Neurotoxicity of dichlorvos: Effect on antioxidant defense system in the rat central nervous system. Exp. Mol. Pathol. 56: 144-152.

Low, P.S., T.E. Ngiam and S.H. Quak. 1980. Insecticide Baygon aerosol poisoning: A report of 5 cases. J. Singapore Paediatr. Soc. 22(1-4): 44-49.

Page, A.C., J.E. Loeffler, H.R. Hendrickson, C.K. Huston and D.M. DeVries. 1972. Metabolic fate of dichlorvos in swine. Arch. Toxikol. 30(1): 19-27.

Pauluhn, J., L. Machemer and G. Kimmerle. 1987. Effects of inhaled cholinesterase inhibitors on bronchial tonus and on plasma and erythrocytes acetylcholine esterase activity in rats. Toxicology. 46(2): 177-190.

Potter, J.C., A.C. Boyer, R.L. Marxmiller, R. Young and J.E. Loeffler. 1973. Radioisotope residues and residues of dichlorvos and its metabolites in pregnant sows and their progeny dosed with dichlorvos-14-carbon or dichlorvos- 36-chlorine formulated as PVC pellets. J. Agric. Food Chem. 21(4): 734-738.

Reeves, J.D., D.A. Driggers and V.A. Kiley. 1981. Household insecticide associated aplastic anaemia and acute leukemia in children. Lancet. 2(8241): 300-301.

Rider, J.A., H.C. Moeller and E.J. Puletti. 1967. Continuing studies on the anticholinesterase effect of methyl parathion, initial studies with gluthion, and determination of incipient toxicity level of dichlorvos in humans. Fed. Proc. 26(2): 427.

Riemer, F., C. Maruschke, E. Gensel, et al. 1981. Excretion of dimethyl phosphate and its thioderivatives after occupation exposure to selected organophosphorus pesticides. In: Industrial and Environmental Xenobiotics, Metabolism and Pharmacokinetics of Organic Chemicals and Metals, I. Gut, M. Cikrt and G.L. Plaa, Ed. Springer-Verlag, Berlin. p. 377-382.

Schmidt, G., M. Schmidt, M. Nenner and F. Vetterlein. 1979. Effects of dichlorvos (DDVP) inhalation on the activity of acetylcholinesterase in the bronchial tissue of rats. Arch. Toxicol. 42(3): 191-198.

Schwetz, B.A., H.D. Ioset, B.K.J. Leong and R.E. Staples. 1979. Teratogenic potential of dichlorvos given by inhalation and gavage to mice and rabbits. Teratology. 20: 383-388.

Slomka, M.B. and C.H. Hine. 1981. Clinical pharmacology of dichlorvos. Acta. Pharmacol. Toxicol. 49(Suppl. 5): 105-108.

Stevenson, D.E. and D. Blair. 1977. The uptake of dichlorvos during long- term inhalation studies. In: Clinical Toxicology, W.A. Duncan and B.J. Leonard, eds. Excerpta Medica, Amsterdam. p. 215-217.

Thorpe, E., A.B. Wilson, K.M. Dix and D. Blair. 1972. Teratological studies with dichlorvos vapour in rabbits and rats. Arch. Toxikol. 30(1): 29-38.

Timmons, E.H., R.J. Chaklos, T.M. Bannister and H.M. Kaplan. 1975. Dichlorvos effects on estrous cycle onset in the rat. Lab. Anim. Sci. 25(1): 45-47.

Walker, A.I., D. Blair, D.E. Stevenson and P.L. Chambers. 1972. An inhalational toxicity study with dichlorvos. Arch. Toxikol. 30(1): 1-7.

WHO (World Health Organization). 1991. IARC Monograph on Evaluation of Carcinogenic Risks to Humans, Volume 53, Dichlorvos. p. 267-299.

VI.C. Carcinogenicity Assessment References

Bridges, B.A. 1978. On the detection of volatile liquid mutagens with bacteria: Experiments with dichlorvos and epichlorohydrin. Mutat. Res. 54(3): 367-371.

Dean, B.J. 1972. The mutagenic effects of organophorphorus pesticides on micro-organisms. Arch. Toxikol. 30(1): 67-74.

Hanna, P. and K. Dyer. 1975. Mutagenicity of organophosphorus compounds in bacteria and Drosophila. Mutat. Res. 28: 405-420.

Litton Bionetics. 1985. Accession No. 259602. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Microbiological Associates. 1985. Accession No. 259602. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Moriya, M., K. Kato and Y. Shirasu. 1978. Effects of cysteine and a liver metabolic activation system on the activities of mutagenic pesticides. Mutat. Res. 57(2): 259-263.

NCI (National Cancer Institute). 1977. Bioassay of Dichlorvos for Possible Carcinogenicity. NCI Technical Report Series No. 10.

NTP (National Toxicology Program). 1986a. Two-year mouse gavage study. Unpublished report prepared by Southern Research Institute, May 23. Study No. 05049. NTP, Research Triangle Park, NC.

NTP (National Toxicology Program). 1986b. Two-year gavage study of dichlorvos in rats. Unpublished report prepared by Southern Research Institute, May 23. Study No. 05049. NTP, Research Triangle Park, NC.

Rosenkranz, H.S. 1973. Preferential effect of dichlorvos (vapona) on bacteria deficient in DNA polymerase. Cancer Res. 33: 458-459.

Segerbaeck, D. and L. Ehrenberg. 1981. Alkylating properties of dichlorvos (DDVP). Acta Pharmacol. Toxicol. 49(5): 56-66.

Shell Chemical Company. 1967. MRID No. 00059397. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Shell Tunstall Laboratories, England. N.D. MRID No. 00063569. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

U.S. EPA. 1987a. Memorandum dated June 16. Weight-of-Evidence Evaluation for the Oncogenic Potential of Dichlorvos (DDVP).

U.S. EPA. 1987b. Memorandum dated July 10. Toxicology Branch Peer Review Committee Draft Document on DVVP.

U.S. EPA. 1987c. Memorandum dated July 21. Dichlorvos (DDVP) - Quantitative Risk Assessment.

U.S. EPA. 1987d. Memorandum dated September 25. Peer Review of Dichlorvos.

U.S. EPA. 1987e. Memorandum dated October 1. Report of the FIFRA Scientific Advisory Panel.

U.S. EPA. 1988a. Federal Register. 53(36): 5542-5549. Februrary 24.

U.S. EPA. 1988b. Memorandum dated March 16. Second Peer Review of Dichlorvos - Reevaluation follows the September 23, 1987 Science Advisory Panel Review.

U.S. EPA. 1988c. Memorandum dated May 11. Peer Review of DDVP (Dichlorvos).

U.S. EPA. 1988d. Memorandum dated June 27. Third Peer Review of Dichlorvos - Reevaluation following the April 18, 1988 meeting of the NTP Panel of Experts.

U.S. EPA. 1988e. One-liner: 03/17/1986. Toxchem No. 328-Dichlorvos. p. 1-7.

VII. Revision History

Substance Name — Dichlorvos
CASRN — 62-73-7

Date	Section	Description
03/01/1988	I.A.	NOAEL reevaluated-RfD changed
10/01/1989	II.	Carcinogen summary on-line
07/01/1992	I.A.	Withdrawn; new RfD verified (in preparation)
11/01/1993	I.A.	Oral RfD summary replaced; RfD changed
06/01/1994	I.B.	Inhalation RfC on-line
12/03/2002	I.A.6., I.B.6.,	Screening-Level Literature Review Findings message has

Date	Section	Description
	II.D.2.	been added.

VIII. Synonyms

Substance Name — Dichlorvos
CASRN — 62-73-7
Last Revised — 03/31/1987

- 62-73-7
- Astrobot
- Atgard
- Atgard V
- Bay-19149
- Bibesol
- Brevinyl
- Brevinyl E50
- Brevinyl Weedat 0002
- Canogard
- Cekusan
- Celcusan
- Chlorvinphos
- Cyanophos
- DDVF
- DDVP
- DEDEVAP
- Deriban
- Derribante
- Dichlorman
- 2,2-Dichloroethenyl phosphate
- 2,2-Dichloroethenyl Phosphoric Acid Dimethyl Ester
- Dichlorophos
- Dichlorovas
- 2,2-Dichlorovinyl Dimethyl Phosphate
- Dichlorovos
- Dichlorphos

- Dichlorvos
- Dimethyl 2,2-Dichloroethenyl Phosphate
- Dimethyl dichlorovinyl phosphate
- Dimethyl 2,2-Dichlorovinyl Phosphate
- Divipan
- ENT 20738
- Equigard
- Equigel
- Estrosel
- Estrosol
- Ethenol, 2,2-Dichloro-, Dimethyl Phosphate
- Fecama
- Fly-die
- Fly fighter
- Herkal
- Herkol
- Krecalvin
- Mafu
- Marvex
- Mopari UN NA 2783
- NCI-C00113
- Nerkol
- Nogos
- Nogos 50
- Nogos G
- No-Pest Strip
- NSC-6738
- Nuva
- Nuvan
- Nuvan 100 EC
- OKO
- OMS 14
- O,O-Dimethyl Dichlorovinyl Phosphate
- O,O-Dimethyl O-2,2-Dichlorovinyl Phosphate
- Phosphoric Acid, 2,2-Dichloroethenyl Dimethyl Ester
- Phosphoric Acid, 2,2-Dichlorovinyl Dimethyl Ester
- Phosvit
- SD1750
- Szklarniak
- Tap 9vp
- Task
- Task Tabs
- Tenac
- UDVF
- Unifos

- Unifos 50 EC
- Vapona
- Vapona II
- Vapona insecticide
- Vaponite
- Verdican
- Verdipor
- Vinyl alcohol, 2,2-Dichloro-, Dimethyl Phosphate
- Vinylophos

Integrated Risk Information System (IRIS)   U.S. Environmental Protection Agency
Chemical Assessment Summary   National Center for Environmental Assessment

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