HAZARD ASSESSMENT REPORT

Dimethyl 2,2-dichlorovinyl phosphate

(Synonyms: Dichlorvos, DDVP)

CAS No. 62-73-7

Chemicals Evaluation and Research Institute (CERI), Japan

This report was prepared by CERI in collaboration with National Institute of Technology and Evaluation (NITE) under the sponsorship of New Energy and Industrial Technology Development Organization (NEDO).

Preface to the English Version of the Hazard Assessment Reports

For six years from April 2001 to March 2007, Chemicals Evaluation and Research Institute (CERI/Japan) was engaged in a project named “Chemical Risk Assessment and Development of Risk Assessment Methods” under "Comprehensive Chemical Substance Assessment and Management Program" funded by New Energy and Industrial Technology Development Organization (NEDO/Japan). Under this project, about 150 chemical substances were selected among those designated as Class-I Chemicals in the Law for Pollutant Release and Transfer Register and Promotion of Chemical Management (hereafter PRTR Law)[1)]. The selection criteria of these chemicals were their priorities for risk assessment based on their production levels and environmental/human health concerns.

CERI developed the hazard assessment reports of these selected chemical substances based on the review and evaluation of the environmental and human health hazard data obtained from the existing evaluation documents released by the regulatory agencies and international organizations as well as those from the published scientific literatures. The data review and compilation of the reports were conducted according to the guidelines[2)] and the guidance manual[2)] developed for this project. The proposed hazard assessment reports by CERI were reviewed by the experts in the relevant scientific fields from both inside and outside this project for accuracy, relevance and completeness. The final reports were published in Japanese after going through the deliberation by the “Council on Chemical Substances” under the Ministry of Economy, Trade and Industry (METI/Japan), which is responsible for regulation of chemical substances in Japan.

This project was the first attempt in Japan to develop comprehensive hazard assessments of chemical substances for application in risk assessment. In order to share the outcomes of the project globally, CERI independently selected the following seven chemical substances and developed the English version of the hazard assessment reports:

(1) Acetaldehyde
(2) Chlorobenzene
(3) Hydrazine
(4) *N*, *N*-Dimethylformamide
(5) Poly(oxyethylene) nonylphenyl ether
(6) 3,3’-Dichloro-4,4’-diaminodiphenylmethane
(7) Dimethyl 2,2-dichlorovinyl phosphate (Dichlorvos)

We hope that the hazard assessment reports from our project contribute to the risk assessment and management of chemical substances globally, and appreciate your feedback.

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1) Details of the PRTR Law, the list of designated chemical substances, and release data in Japan are available on Internet at: http://www.prtr.nite.go.jp/index-e.html.

2) Guidelines and the guidance manual in Japanese are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html. Also, the initial risk assessment reports in Japanese developed in this project which include calculations of margin of exposure based on the result of hazard assessment and exposure assessment, are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html.

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Summary

Dimethyl 2,2-dichlorovinyl phosphate (dichlorvos) is a colorless to amber liquid with a boiling point of 140°C at 2.7 kPa and a vapor pressure of 1.6 Pa at 20°C. Dichlorvos has a water solubility of 8 g/L at 20°C and is miscible with alcohols and toluene. Dichlorvos is used as agricultural chemicals, pesticides for households and infectious disease control to eliminate insects in stored products and crops (mainly greenhouse crops), and in buildings, aircraft, and outdoor areas. Sums of domestic production and import levels of dichlorvos for fiscal years 2000 and 2001 in Japan were 385 and 251 tons, respectively.

Considering from the uses of dichlorvos and the annual emission data for fiscal year 2001 in Japan (2001 PRTR data), dichlorvos is released mainly into air as household pesticides, into land as agricultural chemicals, and into public water as pesticides for disease control. It has been estimated that 57 tons of dichlorvos was released annually into air, 48 tons into water, and 426 tons into land in Japan.

Dichlorvos is hydrolized, particularly in basic conditions and biodegraded in aerobic and anaerobic conditions. Therefore, dichlorvos released into the environmental water is eliminated mainly by hydrolysis and biodegradation, but not by volatilization.

Many studies have been conducted to assess toxic effects of dichlorvos on organisms in the environment using indices including mortality, immobilization and growth inhibition. On acute toxicity of dichlorvos to freshwater algae, the 24 to 72-hr EC_{50} was 87.8 mg/L in growth rate for the alga. The acute toxicity of dichlorvos to invertebrates has been reported in crustaceae, freshwater water fleas and shrimps. The 48-hr EC_{50} (immobilization) in a water flea was 0.000144 mg/L and the 96-hr LC_{50} in a shrimp was 0.00719 mg/L. As the long-term toxicity of dichlorvos to the water flea, the 21-day NOEC value has been reported to be 0.000120 mg/L. The 96-day LC_{50} values in freshwater fish, fathead minnow, carp, Japanese killifish, guppy, bluegill, and trout, ranged from 0.17 to 11.1 mg/L. The long-term toxicity of dichlorvos has been reported in fish at an early life stage. The 28-day NOEC for growth was 0.070 mg/L in the larva of fathead minnow. Regarding the acute toxicity of dichlorvos to marine fish, the lowest 96-day LC_{50} was 0.122 mg/L in Atlantic herring.

The lowest value of toxicity in aquatic organisms is 0.000120 mg/L as the 21-day NOEC for reproduction in crustacea, water flea.

In humans and experimental animals, dichlorvos is rapidly absorbed through the gastrointestinal and respiratory tracts and skin, and easily metabolized by esterases that exist in most tissues. Dichlorvos exposed to rats is distributed in the kidney and adipose tissue at relatively high concentrations. Dichlorvos orally administered to pregnant rabbits transferred to fetuses in a short time. Dichlorvos is mainly metabolized by esterase to dimethyl phosphate and dichloroacetaldehyde. Dimethyl phosphate is excreted in the urine. Dichloroacetaldehyde is rapidly metabolized via two pathways to dichloroethanol glucuronide,

hippuric acid, urea and carbon dioxide, and excreted in the urine and expiration. Within 4 days after oral administration to rats, 39% of dichlorvos administered was excreted in the expiration, 13% in the urine, 3.4% in the feces and 16% in carcass.

Acute effects of dichlorvos on humans were weakness due to severe anemia, a severe reduction in plasma cholinesterase activity, severe toxic symptoms (anticholinergic symptoms) and delayed neurotoxicity (axonal degeneration neuropathy) in patients with helminthic infections who were given dichlorvos as vermifuge. Chronic and short-term toxicity in humans were effects on the gastrointestinal tract and central nervous system associated with a reduction in cholinesterase activity. Regarding carcinogenicity of dichlorvos, it has been reported that the relationship was found between the use of dichlorvos as pesticide and insecticide and the incidence of leukemia.

In acute toxicity of dichlorvos to experimental animals, the oral LD_{50} values were 61 to 275 mg/kg in mice and 17 to 110 mg/kg in rats. The LC_{50} values for inhalation exposure were 1.42 to 33.8 ppm in mice (4 hours) and 9.05 to 49.6 ppm in rats (1 hour). Acute toxicity symptoms with oral administration included a reduction of spontaneous activity, salivation, defecation, vomiting, poor coordination, opisthotonos, cyanosis, gasping, coma, tremor, and spasm, and also, salivation, lacrimation, proptosis, tremor and spasm were observed in inhalation exposure.

Dichlorvos induces severe irritation to the rabbit skin. Dichlorvos is considered to induce skin sensitization in guinea pigs.

Regarding repeated dose toxicity, oral, inhalation and dermal administration of dichlorvos caused reductions in brain, plasma and red blood cell (RBC) cholinesterase activities, excitement, enhancement in spontaneous activity and aggression, and a reduction in brain acetylcholine esterase activity. The NOAEL of dichlorvos for oral administration to beagle dogs is considered to be 0.05 mg/kg/day with the endpoints of reductions in plasma and RBC (males and females) and brain (males) cholinesterase activities. The NOAEL of dichlorvos for inhalation exposure to rats is considered to be 0.05 mg/m^3 with the endpoints of a reduction in brain cholinesterase activity.

In a three-generation reproduction study of rats, dichlorvos did not affect pregnancy rates of maternal animals, the number of litters, body weight of neonates and survival rates of offspring. Furthermore, no abnormality was observed in F_1 and F_2 litters. In studies of developmental toxicity, an oral administration (gavage) or inhalation exposure of dichlorvos to pregnant mice, rats and rabbits caused no changes in the number of viable fetus and anomaly of organs and skeleton in fetuses. But dichlorvos caused abnormal behaviors in open field and T-maze tests in weanling pups of rats and brain developmental disorders (myelination impairment in the callosum, reduction in acid phosphatase activity in glial cells and acetylcholinesterase activity in whole brain area) in rabbit newborns. These results show that dichlorvos has no reproductive toxicity and teratogenicity but suggests that it has developmental toxicity.

Regarding genotoxicity, dichlorvos showed positive results in many *in vitro* tests of bacterial gene mutation, DNA damage and DNA adduct formation. However, dichlorvos showed negative results in *in*

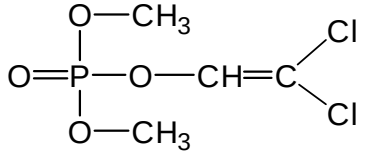
vivo tests of chromosomal aberration, dominant lethal and DNA adduct formation. Therefore, it is difficult to conclude genotoxicity of dichlorvos, because of the findings that dichlorvos showed genotoxicity in *in vitro* studies without metabolic activation but seldom exhibited genotoxicity in *in vivo* studies.

Regarding carcinogenicity of dichlorvos, oral administration of dichlorvos to mice resulted in a significant increase in forestomach papilloma. Monocytic leukemia and pancreas acinar cell adenoma were significantly increased in male rats. Breast fibroma and fibroadenoma were significantly increased in females. Based on the data summarized above, dichlorvos is considered to have carcinogenicity to experimental animals. Dichlorvos has been categorized as Group 2B (the agent is possibly carcinogenic to humans) by the IARC.

Contents

1. Identity of the substance

Dichlorvos is used as a chemical name in this document.

1.1 Chemical name	:	Dimethyl 2,2-dichlorovinyl phosphate
1.2 Class reference number in Chemical Substance Control Law[1)]	:	2-3224
1.3 PRTR[2)] Number (Law for PRTR and Promotion of Chemical Management)	:	1-350
1.4 CAS registry number	:	62-73-7
1.5 Structural formula	:	
1.6 Molecular formula	:	$C_4H_7Cl_2O_4P$
1.7 Molecular weight	:	220.98

2. General information

2.1 Synonyms

Dichlorvos, DDVP, 2,2-Dichlorovinyl dimethyl phosphate

2.2 Purity

Unknown (Commercial products)

2.3 Impurities

Unknown (Commercial products)

2.4 Additives/Stabilizers

There are four kinds of formulations as a pesticide, and following additives are used for each. formulation.

Oil solution: kerosene

Emulsion: kerosene, xylene, solvent naphtha

Smoke agent: fever agent, assistant heat agent

Transpiration agent: synthetic resin base material [a)] (oblong-shaped) (CERI/Japan, 2003a)

[a)]: Add about 20% dichlorvos

[1)] The Low Concerning the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc., Japan. Provisional translation is available on Internet at: http://www.safe.nite.go.jp/english/kasinn/kaiseikasinhou.html

[2)] Pollutant Release and Transfer Register

2.5 Current regulations in Japan[1)]

Law for PRTR and Promotion of Chemical Management:	Class-I designated chemical substance
Law Concerning the Examination and Regulation of Manufacture, etc. of Chemical Substances (Chemical Substance Control Law):	Designated chemical substance (Type II monitoring chemical substance)
Fire Service Law:	Dangerous goods class IV second oil division (The drug which includes drug containing oil / emulsion more than a constant ratio.) Dangerous goods class IV third oil division (The original agent and the drug which includes drug containing oil / emulsion more than a constant ratio.)
Poisonous and Deleterious Substances Control Law:	Deleterious substance
Pharmaceutical Affairs Law:	Deleterious medicine
Labor Standards Law:	Chemical substance related to the illness that appointed by Minister of Health, Labour and Welfare.[2)]
.Industrial Safety and Health Law:	Dangerous substance inflammable substance (The drug containing oil / emulsion more than a constant ratio.) Hazardous substance to be notified in terms of whose name.
Ship Safety Law:	Toxic substance
Civil Aeronautics Law:	Toxic substance
Port Regulation Law:	Toxic substance
Agricultural Chemicals Regulation Law:	Registration pesticide (Insecticide)
The Food Safety Basic Law:	Acceptable Daily Intake (ADI) 0.0033 mg/kg body weight /day
Food Sanitation Law:	Residual pesticide standard 0.1-0.5 μg/g (It is different by the crops)

[1)] As this document covers basic information on Japanese regulations (unofficial translations), you should confirm the details using it.

[2)] Follows are removed.

(1) The thing which contains less than dichlorvos 0.5g in one piece by an insecticide containing less than dichlorvos 5% and the insecticide which let paper or felt adsorb dichlorvos.

(2) The insecticide which contains less than 6% with complex compound with methyl dichloro vinyl calcium phosphate and dichlorvos (another name kalukurohosu), and the insecticide which let paper or plastic board adsorb complex compound with methyl dichloro vinyl calcium phosphate and dichlorvos. The thing which contains less than 0.35 g with complex compound methyl dichloro vinyl calcium phosphate and dichlorvos in one piece.

3. Physico-chemical properties

Appearance:	Colorless to amber liquid	(U.S.NLM:HSDB, 2003)
Melting point:	<-60°C	(Gangolli, 1999)
Boiling point:	140°C (2.7 kPa)	(Merck, 2001)
Flash point:	177°C (open cup)	(NFPA, 2002)
Ignition point:	No data	
Explosion limit:	No data	
Specific gravity:	1.415 (25°C /4°C)	(Merck, 2001)
Vapor density:	7.62 (air = 1)	
Vapor pressure:	1.6 Pa (20°C)	(IPCS, 2001)
Partition coefficient:	log Kow (*n*-octanol/water) =1.47 (measured), 0.60 (estimated)	(SRC:KowWin, 2003)
Dissociation constant:	No functional groups capable of dissociation.	
Mass spectrum:	Main mass fragments: m/z 109 (base peak = 1.0), 185 (0.18), 79 (0.18)	(NIST, 1998)
Soil adsorption coefficient:	Koc = 40 (estimated)	(SRC:PcKocWin, 2003)
Solubility:	Water: solubility 8 g/L (20°C)	(SRC:PhysProp, 2002)
	Alcohols: miscible,	(U.S.NLM:HSDB, 2003)
	Toluene: miscible	
Henry's constant:	5.81×10^{-2} Pa·m^3/mol (5.74×10^{-7} atm·m^3/mol) (25°C, measured)	(SRC:HenryWin, 2003)
Conversion factor:	(air, 20°C) 1 ppm = 9.19 mg/m^3, 1 mg/m^3 = 0.109 ppm	

4. Sources of release to the environment

4.1 Production, import, export and domestic supply

The production and import of dichlorvos in Japan was 385 tons in FY 2000 and 251 tons in FY 2001 (METI/Japan, 2002,2003).

Production, import, export and domestic supply levels of dichlorvos for 5 years from 1998 to 2002 in Japan are shown in Table 4-1 (Japan Plant Protection Association, 2001, 2002, 2003)。

Table 4-1 Production, import, export and domestic supply of dichlorvos[1)] (tons)

Agricultural year[2)]	1998	1999	2000	2001	2002
Production	343.6	585.8	603.6	580.3	488.3
Import	—	—	—	0.5	0.5
Export	30	—	12.0	—	—
Domestic supply[3)]	313.6	585.8	591.6	580.8	488.8

(Production, Export and import: Japan Plant Protection Association, 2001, 2002, 2003)

1) as a agrichemical containing dichlorvos

2) "1998 Agricultural year" means the period from October, 1997 to September, 1998.

3) Domestic supply = Production + Import - Export

4.2 Uses

Dichlorvos is a contact and oral insecticide with fumigant and penetrant actions. It is used for the protection of stored products and crops (mainly greenhouse crops), and for the control of internal and external parasites in livestock and insects in buildings, aircraft, and outdoor areas (IPCS, 1989). As a household and public health insecticide with fumigant action, dichlorvos has widespread use in the form of aerosol or liquid sprays, or as impregnated cellulosic, ceramic, or resin strips, especially against flies and mosquitoes. For the control of fleas and ticks on livestock and domestic animals (pets), impregnated resin collars are used. A granular form of an impregnated resin strip is used as an anthelmintic in domestic animals (IPCS, 1989).

Dichlorvos is mainly used as pesticides for households and for disease control in Japan (METI/Japan and MOE/Japan, 2003c). According to *Noyaku Yoran* (Annual Statitistic on Pests and Pesticides) (Japan Plant Protection Association, 2003), the following agrichemicals containing DDVP were used in Japan in 2002: insecticides of isoxathion-DDVP [1)] emulsion (30%) [1)], diazinon-DDVP emulsion (25%), diazinon-DDVP-MEP emulsion (5%), fenpropathrin-DDVP smoking agent (granule) (10%), hexythiazox-DDVP smoking agent (formulation) (17%), hexythiazox-DDVP emulsion (50%), phosalone-DDVP emulsion (40%), machine oil-DDVP emulsion (5%), CVP-DDVP emulsion (25%), DDVP smoking agent (18%), DDVP smoking agent (30%), DDVP fumigant (16%), DDVP emulsion (50%) and DDVP emulsion (75%); fungicides of DDVP-quinoxaline smoking agent (10%).

4.3 Releases

4.3.1 Releases under PRTR system

According to "Total Release and Transfers for the FY 2001 (hereafter 2001 PRTR Data)" under the PRTR system (METI/Japan and MOE/Japan, 2003a), 1 ton of dichlorvos was released into air, 46 kg into public water, 3 tons was transferred as wastes and 140 kg was released into sewer from the business institutions required to report their releases and transfer. In addition, it is estimated that 1 ton of dichlorvos was released from the business institutions in the business categories designated under the PRTR system but were exempted from notification, and 426 tons from the business categories outside the scope of the PRTR system. No estimation was made for the amounts of releases from households and those from mobile

1) dichlorvos

sources. However, according to the 2002 recruitment information for public comments to estimation methods of the amount of releases exempted from notification, the amounts of releases from pesticides for households and for disease control are estimated as 55 and 48 tons, respectively (METI/Japan and MOE/Japan, 2003c).

a. Release and transfer from the business categories within the scope of PRTR system

The amounts of releases into the environmental media (air, water and land) and transfer by the designated industries summarized from the 2001 PRTR Data are shown in Table 4-2. METI, Japan and MOE, Japan (2003a) do not provide the amounts of releases by environmental media for the estimations of releases from the business institutions exempted from notification. The ratio for each environmental medium of the releases estimated for the business institutions exempted for notification is calculated based on the assumption that ratios of releases into the air, water and land were the same as those obtained by notification (NITE/Japan, 2004).

Table 4-2 Releases and transfer of dichlorvos to environmental media by industries (tons/year)

Business Category	By Notification					Notification Exempted			Total amount of releases by notification and by estimation	
	Release			Transfer		Release (estimated)[1)]				
	Air	Water	Land	Sewer	Wastes	Air	Water	Land	Total release[2)]	ratio (%)
Research institutes for natural sciences	－	－	－	－	－	1	＜0.5	0	＜0.5	61
Chemical industry	1	＜0.5	0	＜0.5	3	－	－	－	1	38
Advanced educational organizations	－	－	－	－	－	＜0.5	＜0.5	0	＜0.5	2
Food industry	＜0.5	0	0	0	0	－	－	－	＜0.5	0
Total[2)]	1	＜0.5	0	＜0.5	3	1	＜0.5	0	2	100

(NITE/Japan, 2004)

1) Based on the assumption that ratios of releases into the air, water and land were the same as those of the releases obtained by notification, the amounts of releases from the business institutions exempted from notification were estimated.

2) The total may not correspond with the sum of rounded values in each column of the table.

－: Not notified or estimated

The release and transfer of less than 0.5 tons was mentioned as "<0.5" without exception.

Based on the production levels and the emission factor in manufacturing sites of dichlorvos in 2001 (Japan Chemical Industry Association, 2002), the amount of releases into the air was estimated to be 1 ton per year, and less than 0.5 tons into water (NITE/Japan, 2004). Therefore, based on the 2001 PRTR Data, the releases of dichlorvos from the business categories within the scope of PRTR system is considered to occur equally during the manufacturing and the use processes.

[1)] Dichlorvos contents are shown in parentheses.

b. Releases from the non-designated business categories, households, and mobile sources

Based on the 2001 PRTR Data and the METI/Japan and MOE/Japan (2003c) Public Comment Draft, the amounts of release from the non-designated business categories are summarized in Table 4-3.

Based on the 2001 PRTR Data, it is estimated that 426 tons of dichlorvos was released into the environment as an active ingredient of agricultural chemicals from the business categories outside the scope of the PRTR system (METI/Japan and MOE/Japan, 2003a). In release estimation of this category with application of dichlorvos as agricullural chemicals, all amount is assumed as released to the land. The amounts of dichlorvos releases from households and mobile sources are outside the scope of estimation required under the PRTR system (METI/Japan and MOE/Japan, 2003a).

However, according to the METI/Japan and MOE/Japan (2003c) Public Comment Draft, it is estimated that 48 tons of dichlorvos was released into the environment as pesticides for disease control from the business categories outside the scope of the PRTR system. Pesticides for disease control are mainly applied to street gutters for domestic wastewater, therefore, dichlorvos is considered to be released into public water. It is estimated that 55 tons of dichlorvos was released into the environment as household pesticides. Most of household pesticides are aerosol type and, therefore, dichlorvos is assumed to be released into the air with little release to the water and the land (METI/Japan and MOE/Japan, 2003c). Although these data are for FY 2002, and the period is one year after that of the 2001 PRTR data, it is assumed that the amounts of releases in FY 2001 were equivalent to those in the FY2002.

Table 4-3 Releases of dichlorvos from the non-designated industries and households into environmental medium[1)] (tons/year)

	Air	Water	Land
Non-designated business categories	0	48[1)]	426 [2)]
Households	55[1)]	0	0
Total	55	48	426

1) (METI/Japan and MOE/Japan, 2003b)
Although these data are for the Fiscal Year 2002, it is assumed that the amounts of releases in the FY 2001 were equivalent to those in the FY 2002.

2) The distribution to air, water and land was considered from the use and the physicochemical property (NITE/Japan, 2004)

4.3.2 Releases from other sources

No reports on dichlorvos releases from other sources were obtained in this investigation.

4.4 Estimated routes of releases

Considering the information on the uses of dichlorvos and the 2001 PRTR data and the METI/Japan and MOE/Japan (2003c) Public Comment Draft 2002, dichlorvos is released mainly from households and the business categories outside the scope of the PRTR system, i.e., releases into the air as household pesticides, into the land as agricultural chemicals, and into the public water as pesticides for disease control from the business categories outside the scope of the PRTR system. The main release route is through emissions

during the use of products containing dichlorvos.

As the scenario of dichlorvos releases in Japan, it has been estimated that 57 tons of dichlorvos is released annually into the air, 48 tons into water, and 426 tons into land. Releases into the environment after processing of wastes at waste disposal facilities are not considered for estimation of the amount transferred as wastes and that transferred into sewers.

5. Environmental fate

5.1 Stability in the atmosphere

a. Reaction with OH radical

The reaction rate constant of dichlorvos with OH radical is 9.41×10^{-12} cm^3/molecule-sec (25°C, estimated value) in the tropospheric air (SRC: AopWin, 2003). On the assumption of OH radical concentration of 5×10^5 to 1×10^6 molecule /cm^3, the half-life was calculated as 1 to 2 days.

b. Reaction with ozone

The reaction rate constant of dichlorvos with ozone is 3.58×10^{-20} cm^3/molecule-sec (25°C, measured value) in the tropospheric air (SRC: AopWin, 2003). On the assumption of ozone concentration of 7×10^{11} molecule /cm^3, the half-life was calculated as 10 months.

c. Reaction with nitrate radical

No reports on reaction of dichlorvos with nitrate radical were obtained in this investigation.

d. Direct degradation by sunlight

Dichlorvos absorbs ultraviolet radiation. The maximum absorbance was 0.0246 at 295 - 305 nm and the absorption coefficient was 54 L/mol·cm. Photolysis rate constant of dichlorvos is 2.65×10^{-5} sec^{-1} and when dichlorvos is applied to a glass plate as a thin lamina (0.67 μg/cm^2), dichlorvos was rapidly degraded (half-life: 7 hours) (Chen et al., 1984).

5.2 Stability in water

5.2.1 Abiotic degradation

The half-life values for hydrolysis of dichlorvos at 37.5°C were 77 hours at pH 5.4, 35 hours at pH 6, 7.7 hours at pH 7, and 5 hours at pH 8, showing a reduction against the increase in pH. The half-life values for hydrolysis of dichlorvos at pH 5 were 240 days at 10°C, 61.5 days at 20°C, 17.3 days at 30°C and 1.66 days at 50°C respectively, showing a reduction against the increase in temperature (Faust and Suffet, 1966). The hydrolysis products of dichlorvos were considered to be dimethyl phosphate and dichloroacetaldehyde (IPCS, 1989). It has been reported that hydrolysis of dichlorvos is enhanced in basic condition, and the degradation rates at room temperature in 96 hours were 19% at pH 6.2, 51% at pH 7.8, and 100% at pH 9.3, respectively (Lamoreaux and Newland, 1978).

Dichlorvos is formed by hydrolysis of trichlorfon (DEP), a pesticide. The hydrolysis half-life of

trichlorfon at 25°C was 46 days at pH 6.0, 2.8 days at pH 7.0, and 0.91 days at pH 8.0, showing a reduction against the increase in pH (Chapman and Cole, 1982).

5.2.2 Biodegradation

In an aerobic biodegradation study using activated sludge of artificial sewage water in a closed container, the degradation half-life of dichlorvos was 3.5 days at an initial concentration of 100 μg/L and at 20°C (Kawamoto and Urano, 1990). However, in a biodegradation study using microorganisms in sludge of sewage water, dichlorvos was degraded, under the accimatization of microorganisms These studies showed that biodegradation of dichlorvos depended on pH, temperature and dichlorvos concentrations. In a 7-day biodegradation study at an initial concentration of 250 μg/L and 29°C, dichlorvos was not completely degraded. Dichlorvos was hydrolyzed into dichloroacetaldehyde and dimethyl phosphate and further metabolized to dichloroacetic acid, 2,2-dichloroethanol and ethyl dichloroacetate (Lieberman and Alexander, 1983).

Biodegradation experiments of dichlorvos were conducted under several different aquatic environmental conditions. Based on the environmental monitoring data, the initial concentration of dichlorvos was set in the range of 0.5 to 2.0 μg/L and experiments were conducted in a closed container in dark condition. Pure water (pH 6.1), marine water (pH 8.1) and river water (untreated and filtrated, pH 7.3) were used. The temperature was set at 6 and 22°C to simulate winter and summer conditions and pH ranged from 6.1 to 8.1. In an experiment simulating winter conditions (6°C), dichlorvos still remained even after 180 days in pure water, while in river (untreated and filtrated) and marine (pH 8.1) water, dichlorvos was completely degraded in 81 and 34 days, respectively. In contrast, in an experiment simulating summer conditions (22°C), dichlorvos was completely degraded in 81 days in pure water, and 55 and 34 days in river water untreated and filtrated, respectively, however, in marine water, dichlorvos still remained even after 180 days (Lartiges and Garrigues, 1995).

In an anaerobic biodegradation study with anaerobic microorganisms, the 28-day degradation rate of dichlorvos was 30% or below at an initial concentration of 30 mg/L and microorganism-containing sludge concentration of 100 mg/L at 37°C. At an initial concentration of 3 mg/L, primary decomposition of dichlorvos (degradation level that agricultural chemical properties are lost) was achived completely within 7 days (Kameya et al., 1995). In an anaerobic biodegradation study in a closed container, the half-life of dichlorvos by anaerobic microorganisms cultured with artificial sewage water was 3.5 days at an initial concentration of 100 μg/L and at 20°C (Kawamoto and Urano, 1990).

Based on these results, dichlorvos is considered to be biodegraded in aerobic and anaerobic conditions.

5.2.3 Removal in sewage treatment

No reports on dichlorvos removal in sewage treatment were obtained in this investigation.

5.3 Behavior in the aquatic environment

Regarding volatility of dichlorvos from water into the air using Henry's constant, the half-life in a model river (water depth: 1 m; flow velocity: 1 m/sec; wind velocity: 3 m/sec) was estimated as 119 days (Lyman

et al., 1990). Considering the value of soil adsorption coefficient, Koc 40 (see Chapter 3), it is assumed that dichlorvos is hardly adsorbed to suspended solids in water and sediments. Dichlorvos has a water solubility of 8 g/L (20°C), and its vapor pressure is low (1.6 Pa at 20°C) and Henry's constant is also low (5.81×10^{-2} Pa·m^3/mol at 25°C) (see Chapter 3). Therefore, dichlorvos is assumed to be hardly released from the aquatic environment into the air.

Based on the information summarized above and in Section 5.2, it is assumed that dichlorvos released into the environmental water is eliminated mainly by hydrolysis and biodegradation. It is assumed that elimination from water by volatilization is not a main route.

5.4 Bioaccumulation

In a 168-hour bioaccumulation study with carp, bioconcetration factor (BCF) of dichlorvos was less than 0.5 (Abd-Allah, 1995). In a 24- and 168-hour bioaccumulation study in *Gnathopogon caerulescens,* the mean BCF was 0.8 (Tsuda et al., 1992).

It is considered that the bioaccumulation of dichlorvos is low.

6. Effects on organisms in the environment

6.1 Effects on aquatic organisms

6.1.1 Microorganisms

The toxicity studies of dichlorvos for microorganisms are summerized in Table 6-1.

The toxicity of dichlorvos to ciliate of protozoa has been reported and the 10-min LC_{100} in *Paramecium caudatum* was 30 mg/L (Rajini et al., 1989), and the 24-hr LC_{50} in *Tetrahymena pyriformis* was 3.91 mg/L (Mojzis et al., 1993).

Table 6-1 Toxicity of dichlorvos for microorganisms

Species	Temper-ature (°C)	Endpoint		Concent-ration (mg/L)	Reference
Protozoa *Parameciu caudatum* (ciliate)	ND	10-min LC_{100}	Death	30 (n)	Rajini et al., 1989
Tetrahymena pyriformis (ciliata)	25	24-hr LC_{50}	Death	3.91 (n)	Mojzis et al., 1993

ND: No data available; (n): Nominal concentration

6.1.2 Algae

The toxicity studies of dichlorvos for algae are summerized in Table 6-2.

In a growth inhibition study of dichlorvos in freshwater green alga (*Selenastrum capricornutum*), the 72-hr EC_{50} and the NOEC (biomass) were 38.4 and 11.5 mg/L, respectively, and the 24 to 72-hr EC_{50} and the NOEC (growth rate) were 87.8 and 24.0 mg/L, respectively (MOE/Japan, 2002). A growth inhibition study in *Scenedesmus* was reported; however, the exposure time and endpoints were not described (Ordog,

1979). In a 4-day photosynthesis inhibition study in Haptophyta of marine algae (*Isochrysis galbana* and *Pseudoisochrysis galbana*), 4-day EC_0 of dichlorvos for growth inhibition was 10 mg/L (Raine et al., 1990).

Table 6-2 Toxicity of dichlorvos for algae

Species	Method/ Condition	Tem-pera-ture (°C)	Endpoint		Concen-tration (mg/L)	Reference
Freshwater species						
Selenastrum capricornutum[1)] (green alga)	OECD 201 Static	23±2	72-hr EC_{50} 24 to 48-hr EC_{50} 24 to 72-hr EC_{50} 72-hr NOEC 24 to 48-hr NOEC 24 to 72-hr NOEC	Growth inhibition biomass growth rate growth rate biomass growth rate growth rate	38.4 79.6 87.8 11.5 24.0 24.0 (m)	MOE/Japan, 2002
Scenedesmus obtusiusculus (green alga)	Static	ND	ND	Growth inhibition	100 (n)	Ordog, 1979
Marine species						
Isochrysis galbana (haptophyta)	Static	Room temp-erature	4-day EC_0	Growth inhibition Photosynthesis rate	10 (n)	Raine et al., 1990
Pseudoisochrysis paradoxa (haptophyta)	Static	Room temp-erature	4-day EC_0	Growth inhibition Photosynthesis rate	10 (n)	Raine et al., 1990

ND: No data available; (m): Measured concentration; (n): Nominal concentration
1) Current scientific name: *Pseudokirchneriella subcapitata*

6.1.3 Invertebrates

The toxicity studies of dichlorvos for invertebrates are summerized in Table 6-3.

The acute toxicity of dichlorvos to invertebrates has been reported in freshwater crustacea, water fleas, scud, mosquito, midge, shell (snail) and oligochaete. Except one of oligochaete (*Lumbriculus variegates*), the LC_{50} and EC_{50} (immobilization) in oligochaete were less than 0.5 mg/L. In reliable studies with measured concentrations, dichlorvos showed that the 48-hr EC_{50} values of immobilization in water flea were 0.000144 and 0.000266 mg/L (Brooke, 1991; MOE/Japan, 2002). The 96-hr LC_{50} in Minaminuma shrimp was 0.00719 mg/L (MOE/Japan, 2002) and the 96-hr LC_{50} in one of freshwater pulmonate (*Physella virgata*) was 0.17 mg/L (Brooke, 1991). In addition, the LC_{50} values ranged 0.0158 to 0.0176 mg/L in insects and 0.0075 to 0.31 mg/L in shell (snail), which indicates strong effects of dichlorvos on these organisms similar to those on crustacea. However, one of oligochaete (*Lumbriculus variegates*) showed the sensitivity to dichlorvos quite different from other species with 96-hr LC_{50} of 2.18 mg/L.

In marine species, studies in crustacea and shell were reported. In most crustaceae, the effect concentration was 0.1 mg/L or less, showing strong effects on these organisms similar to freshwater

crustaceae. The lowest the 96-hr LC_{50} value was 0.000019 mg/L in midshrimp (Office of Pesticide Programs, 2000). However, the original article was not obtained and detailed results could not be confirmed.

The long-term toxicity of dichlorvos in *Daphnia magna* has been reported and the 21-day NOEC values for reproduction are 0.000120 mg/L (MOE/Japan, 2002), and 0.000109 mg/L and above (Brooke, 1991).

The long-term toxicity in marine species was reported in American lobster. The 23-day NOEC for death and behavior was 0.00063 mg/L (McHenery et al., 1996).

Table 6-3 Toxicity of dichlorvos for invertebrates

Species	Size/ Growth stage	Method/ Condition	Tem-pera-ture (°C)	Hardness (mg $CaCO_3$ /L)	pH	Endpoint	Concen-tration (mg/L)	Reference
Acute toxicity: Freshwater species								
Daphnia magna (crustacea) water flea)	<24 hours	OECD 202 Semi-static	20.2-20.5	30-40	7.9	48-hr EC_{50} Immobilization	0.000144 (m)	MOE/Japan, 2002
		Semi-static	21.2-21.8	176-186	8.2-8.4	48-hr EC_{50} Immobilization	0.000266 (m)	Brooke, 1991
		Static	ND	ND	ND	24-hr EC_{50} Immobilization	0.000233 (n)	Sturm & Hansen, 1999
		Static	20	250	8.2	48-hr LC_{50}	0.000085 (n)	Maas, 1982
Daphnia pulex (crustacea, water flea)	<24 hours	Static	15	40-50	7.2-7.8	48-hr EC_{50} Immobilization	0.00007 (n)	Johnson & Finley 1980
Ceriodaphnia dubia (crustacea, water flea)	<24 hours	Semi-static	20.4-20.6	180-187	8.3-8.4	48-hr EC_{50} Immobilization	0.000149 (m)	Brooke, 1991
	<48 hours	Static	25	ND	ND	48-hr LC_{50}	0.00013 (n)	Ankley et al., 1991
Simocephalus serrulatus (crustacea, water flea)	<24 hours	Static	15.6	ND	7.4-7.8	48-hr EC_{50} Immobilization	0.00028 (n)	Sanders & Cope, 1968
Macrobrachium lamarrei (crustacea, Oriental river prawn)	64 mm 1.2 g	Semi-static	ND	ND	ND	72-hr LC_{50}	0.0058 (n)	Mary et al., 1986
Neocaridina denticulate (crustacea, minaminuma shrimp)	1.9 ± 0.1 cm 0.1 ± 0.01 g	Semi-static	24.2-24.4	30-40	6.9-7.5	96-hr LC_{50}	0.00719 (m)	MOE /Japan, 2002
Gammarus fasciatus (crustacea, scud)	ND	Static	21.1	ND	7.1	96-hr LC_{50}	0.00040 (n)	Sanders, 1972

Species	Size/ Growth stage	Method/ Condition	Tem-pera-ture (°C)	Hardness (mg $CaCO_3$ /L)	pH	Endpoint	Concen-tration (mg/L)	Reference
Pteronarcys californicus (crustacea, one of giant salmonfly)	30-35 mm	Static	15.5	ND	7.1	96-hr LC_{50}	0.00010 (n)	Sanders & Cope, 1968
Aedes punctor (insect, one of mosquito)	4th instar larva	ND	20-23	ND	ND	24-hr LC_{50}	0.0158 (n)	Rettich, 1977
Culex pipiens fatigans (insect, one of mosquito)	4th instar larva	ND	ND	ND	ND	24-hr LC_{50}	0.0158 (n)	Yasuno & Kerdpibule 1967
Chironomus tentans (insect, midge)	3th instar larva	Static	23	ND	7.4-8.5	96-hr LC_{50}	0.0176 (n)	Ankley & Collyard, 1995
Anodonte cygnea (shell, ishigai)	Adult 92 mm 22.8 g	Static	22	ND	ND	7-day LC_{50}	0.31 (n)	Varanka, 1987
Lymnaea acuminata (shell, pond snail)	Adult 2.6 cm	ND	26-29	ND	ND	96-hr LC_{50}	0.0075-0.009 (n)	Tripathi & Agarwal, 1998
Physella virgata (shell, physidae)	0.10 g	Semi-static	21.6-22.8	51.9-79.8	7.2-7.5	96-hr LC_{50}	0.17 (m)	Brooke, 1991
Lumbriculus variegates (oligochaete, worm)	2 mg	Semi-static	21.3-22.6	51.9	6.4-8.0	96-hr LC_{50}	2.18 (m)	Brooke, 1991
Acute toxicity: Marine species								
Penaeus duorarum (crustacea, northern pink shrimp, kuruma prawn)	Adult	Static	26	Salinity concentration: 25‰	ND	48-hr EC_{50}	0.044 (n)	Butler, 1964
Palaemonetes vurgaris (crustacea, prawn)	31 mm 0.47 g	Static	20	Salinity concentration: 24‰	8.0	96-hr LC_{50}	0.015 (n)	Eisler, 1969
Crangon septemspinosa (crustacea, sand shrimp)	26 mm 0.25 g	Static	20	Salinity concentration: 24‰	8.0	96-hr LC_{50}	0.004 (n)	Eisler, 1969
Homarus americanus (crustacea, American lobster)	Larva Stage 5	Semi-static	10.3	Salinity concentration: 34‰	7.9	96-hr LC_{50} 96-hr EC_{50} 96-hr NOEC behavior 96-hr EC_{50} acetylcholinesterase inhibition	0.0057 0.0033 0.00156 0.0027 (a, n)	McHenery et al., 1991

Species	Size/ Growth stage	Method/ Condition	Tem-pera-ture (°C)	Hardness (mg $CaCO_3$ /L)	pH	Endpoint	Concen-tration (mg/L)	Reference
Metapenaeus monoceros (crustacea, speckled shrimp)	75 mm 2.5 g	Semi-static	23	Salinity concentration: 15‰	7.1	96-hr LC_{50}	0.794-0.980 (n)	Reddy & Rao, 1992
Pagurus longicarpus (crustacea, one of longwrist hermit crab)	3.5 mm 0.28 g	Static	20	Salinity concentration: 24‰	8.0	96-hr LC_{50}	0.045 (n)	Eisler, 1969
Tigriopus brevicornis (crustacea, harpacticoid copepod)	Nauplius	Static	20	Salinity concentration: 34.5-35‰	7.7-8.14	96-hr LC_{50}	0.00092 (n)	Forget et al., 1998
	Copepoda						0.0029 (n)	
	Brooding female						0.0046 (n)	
Americamysis bahia (crustacea, Mysid, shrimp)	<24 hours	Flow-through	ND	ND	ND	96-hr LC_{50}	0.000019 (n)	Office of Pesticide Programs, 2000
Crassostrea virginica (shell, American oyster)	ND	Flow-through	ND	ND	ND	96-hr LC_{50}	2.18 (n)	Office of Pesticide Programs, 2000
Anadara granosa (shell, ark shell)	ND	Semi-static	30	ND	ND	96-hr LC_{50}	1.79 (n)	Bharathi, 1994
Long-term toxicity: Freshwater species								
Daphnia magna (crustacea, water flea)	<24 hours	OECD 211 Semi-static	19.8-20.1	32.6-40.4	7.7-7.9	21-day NOEC Reproduction	0.000120 (a, n)	MOE /Japan, 2002
		OECD 202 Semi-static	20.4-22.8	163-231	8.1 8.6	21-day NOEC Reproduction	≧ 0.000109 (m)	Brooke, 1991
Long-term toxicity: Marine species								
Homarus americanus (crustacea, American lobster)	Larva Stage 4	Semi-static	10±1	Salinity concentration: ca. 34‰	Appr-oxim-ately 8.0	23-day LC_{50} 23-day NOEC	0.00125 0.00063 (n)	McHenery et al., 1996

ND: No data available; (a, n): The measured concentration of test substance was within ±20% of the nominal concentration, then, the nominal one is shown instead the measured one.
(m): Measured concentration; (n): Nominal concentration, Closed system: a test container and water bath are closed with a cover such as a lid, and a headspace is kept.

6.1.4 Fish

The toxicity studies of dichlorvos for fish are summerized in Table 6-4.

The acute toxicity of dichlorvos to freshwater fish has been studied in fathead minnow, carp, Japanese

killifish, guppy, bluegill, and trout. The 96-day LC_{50} values of these species ranged from 0.17 to 11.1 mg/L. Of the studies with a flow-through or semi-static system and those with estimation based on measured concentrations, the lowest value was 0.340 mg/L in carp (Verma et al., 1981).

In marine fish, the acute toxicity of dichlorvos to sheepshead minnow, Atlantic silverside, striped mullet and Atlantic herring has been reported The lowest 96-day LC_{50} was 0.122 mg/L in Atlantic herring (McHenery et al., 1991).

The long-term toxicity of dichlorvos has been reported in toxicity studies of early life stage from fertilized eggs to hatches in fathead minnow and Japanese killifish, and the 28-day NOEC for growth of larval fish was 0.070 mg/L in fathead minnow (Brooke, 1991) and the 40-day NOEC for death and growth was 0.375 mg/L in larva of Japanese killifish (MOE/Japan, 2002).

Table 6-4 Toxicity of dichlorvos for fish

Species	Growth stage	Method/ Condi-tion	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concen-tration (mg/L)	Reference
Acute toxicity: Freshwater species								
Pimephales promelas (fathead minnow)	30 days 11 mm 11 mg	Flow-through	21-23.5	60-64	7.3-7.5	96-rh LC_{50}	3.09 (m)	Brooke, 1991
	38-64 mm 1-2 g	Static	25	20	7.5	96-hr LC_{50}	4.0 (n)	Pickering & Henderson, 1966
Cyprinus carpio (carp)	Yolk sac fry 8 mm	Semi-static	20.0-23.2	60-88	7.2	96-hr LC_{50}	0.340 (n)	Verma et al., 1981
Oryzias latipes (Japanese killifish)	2.7± 0.085 cm 0.16± 0.01g	OECD 203 Semi-static	23.3-23.4	30-40	6.9-7.7	96-hr LC_{50}	11.1 (m)	MOE/Japan, 2002
Poecilia reticulata (guppy)	2-3 weeks	Static	25	250	8.2	96-hr LC_{50}	3.3 (n)	Maas, 1982
Lepomis macrochirus (bluegill)	38-64 mm 1-2 g	Static	25	20	7.5	96-hr LC_{50}	0.27 (n)	Pickering & Henderson, 1966
Oncorhynchus mykiss (rainbow trout)	0.28 g	Flow-through	ND	ND	ND	96-hr LC_{50}	0.75 (n)	Office of Pesticide Programs, 2000
Oncorhynchus clarki (cutthroat trout)	2.5 g	Static	12	205	6-9	96-hr LC_{50}	0.17 (n)	Mayer & Ellersieck, 1986
Salvelinus namaycush (lake trout)	4.2 g	Static	12	162	7.4	96-hr LC_{50}	0.183 (n)	Mayer & Ellersieck, 1986
Gambusia affinis (mosquitofish)	0.2 g	Static	17	40-50	7.2-7.5	96-hr LC_{50}	5.27 (n)	Johnson & Finley 1980
Tilapia mossambica (tilapia)	3-4 cm	Static	ND	ND	7.0-7.5	96-hr LC_{50}	1.42 (n)	Rath & Misra, 1979
Acute toxicity: Marine species								

Species	Growth stage	Method/ Condi-tion	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concen-tration (mg/L)	Reference
Cyprinodon variegates (sheepshead minnow)	29 mm	Flow-through	ND	ND	ND	96-hr LC_{50}	7.35 (n)	Office of Pesticide Programs, 2000
Fundulus majalis (striped killifish)	40 mm 0.92 g	Static	20	Salinity concentrat ion: 24‰	8.0	96-hr LC_{50}	2.30 (n)	Eisler, 1970
Menidia menidia (atlantic silverside)	50 mm 0.8 g	Static	20	Salinity concentrat ion: 24‰	8.0	96-hr LC_{50}	1.25 (n)	Eisler, 1970
Mugil cephalus (striped mullet)	84 mm 6.4 g	Static	20	Salinity concentrat ion: 24‰	8.0	96-hr LC_{50}	0.2 (n)	Eisler, 1970
Clupea harengus (atlantic herring)	Post-larva 26 mm 0.25 g	Static	10.3	Salinity concentrat ion: 34‰	7.9	96-hr LC_{50}	0.122 (a, n)	McHenery et al., 1991
Liza parsia (one of mullet)	85-120 mm 6.50-13.3 g	Static	27.5	Salinity concentrat ion: 10‰	6.0	96-hr LC_{50}	0.482 (n)	Mohapatra & Noble, 1992
Long-term toxicity: Freshwater species								
Pimephales promelas (fathead minnow)	Fertilized egg <24 hours	Flow-through	25.3	54.2	7.26	28-day NOEC Growth	0.070 (m)	Brooke, 1991
Oryzias latipes (japanese killifish)	Fertilized egg <24 hours	OECD 210 Flow-through	22.9-24.8	33.4-51.8	7.4-7.7	40-day NOEC Death, Growth	0.375 (a, n)	MOE/Japan, 2002

ND: No data available; (a, n): The measured concentration of test substance was within ±20% of the nominal concentration, and then, the nominal one is shown instead the measured one.
(m): Measured concentration; (n): Nominal concentration, Closed system: a test container and water bath are closed with a cover such as a lid, and a headspace is kept.

6.1.5 Other aquatic organisms

The toxicity to other species has been reported in larvae of Asian bullfrogs and Indian rice frogs. The 48-hr LC_{50} values were 10 and 9.7 mg/L, respectively, and there was no difference between them (Pan and Liang, 1993; Sreenivasan and Swaminathan, 1967).

6.2 Effects on terrestrial organisms

6.2.1 Microorganisms

No reports on the toxicity of chlorobenzene in microorganisms were obtained in this investigation.

6.2.2 Plants

After spraying dichlorvos solution (0.05%) at 50 L/ha, the percentages of abortive pollens in cabbage at 1, 2, 7 and 21 days after were 27%, 13%, 16% and 3%, respectively (Lal, 1975). After spraying 0.4% dichlorvos solution to leaves of bottlegourd, melon and watermelon, leaves were observed for 7 days after spraying, but no dead leaves were found in all species (Sood et al., 1972).

6.2.3 Animals

In a feeding study of dichlorvos in mallard ducks at 5-day and 16-day posthatch, the 8-day LC_{50} values were 1,317 ppm (5 days) and more than 5, 000 ppm (16 days), respectively. The 8-day LC_{50} values were 298 ppm in Japanese quail and 568 ppm in ring-necked pheasant (Hill et al., 1975), respectively. In a single local application study of dichlorvos to the abdomen of house flies and honeybees, the 24-hr LD_{50} values were 14.0 and 27.2 μg/g body weight, respectively (Deo et al., 1988).

6.3 Summary of effects on organisms in the environment

Many studies have been conducted to assess the hazardous effects of dichlorvos on organisms in the environment using indices including mortality, immobilization and growth inhibition.

In microorganisms, the 10-min LC_{100} in ciliate *Paramecium caudatum* was 30 mg/L, and the 24-hr LC_{50} in ciliate *Tetrahymena pyriformis* was 3.91 mg/L.

In a growth inhibition study of dichlorvos in algae, the 72-hr EC_{50} in *Selenastrum capricornutum* was 38.4 mg/L (biomass), and the 24 to 72-hr EC_{50} estimated from growth rate was 87.8 mg/L. The 72-hr NOEC in this species was 11.5 mg/L (biomass), and the 24 to 72-hr NOEC (growth rate) was 24.0 mg/L.

The acute toxicity of dichlorvos to invertebrates is reported in water flea and minaminuma shrimp. The 48-hr EC_{50} values (immobilization) in water flea ranges 0.000144 to 0.000266mg/L and the 96-hr LC_{50} in minaminuma shrimp was 0.00719 mg/L. The long-term toxicity of dichlorvos to *Daphnia magna* has been reported, and the 21-day NOEC values are more than 0.000109 mg/L and 0.000120 mg/L.

In marine species of crustaceae, the effective concentrations were 0.1 mg/L or less in most crustacea, showing strong effects on these organisms as well as freshwater crustaceae. As the long-term toxicity to American lobster, the 23-day NOEC for death and behavior was 0.00063 mg/L.

The 96-day LC_{50} values in fish ranged from 0.17 to 11.1 mg/L and the lowest value of the studies with flow-through or semi-static system and those with estimation based on measured concentrations was 0.340 mg/L in carp. The long-term toxicity of dichlorvos has been reported in toxicity studies of fish at early life stage. The 28-day NOEC for growth was 0.070 mg/L in larva of fathead minnow and the 40-day NOEC for death and growth was 0.375 mg/L in larva of medaka. Regarding the acute toxicity of dichlorvos to marine fish, the lowest 96-day LC_{50} was 0.122 mg/L in Atlantic herring.

The 48-hr LC_{50} values in larvae of Asian bullfrogs and Indian rice frogs were 10 and 9.7 mg/L, respectively.

In terrestrial plants, after spraying 0.4% dichlorvos solution to leaves of bottlegourd, melon and watermelon, no dead leaves were found in all species for 7 days. In terrestrial animals, studies in birds and insect have been reported, and in a single local application study of dichlorvos to the abdomen of house

flies and honeybees, the 24-hr LD_{50} values were 14.0 and 27.2 μg/g body weight, respectively.

Based on the data summarized above, The long-term NOEC values ranged from 11.5 to 24.0 mg/L in algae and were 0.000120 and 0.070 mg/L in crustacea and fish, respectively. The lowest value of toxicity in aquatic organisms is 0.000120 mg/L as the 21-day NOEC for reproduction in crustacea, water flea.

Although formal classification criteria is not used in this investigation, it can be considered that the acute toxicity values of dichlorvos to aquatic organisms, crustacea and fish are corresponding to the GHS acute toxicity hazard category I (very toxic).

7. Effects on human health

7.1 Kinetics and metabolism

a. Absorption

a-1. Inhalation exposure

In an inhalation exposure study of dimethyl 2,2-dichlorovinyl phosphate (dichlorvos) in male volunteers, 0.42 μg/mL of dichloroethanol, a specific metabolite of dichlorvos, was detected in the first urine sample of a volunteer who was exposed to dichlorvos at an extremely high concentration of 38 mg/m^3 (4.2 ppm) for 105 minutes. Therefore, it was indirectly evidenced that dichlorvos was absorbed through an inhalation route (Hutson and Hoadley, 1972b).

In an 8-hour inhalation exposure study of dichlorvos in 13 male volunteers, 0.32 to 1.39 μg/mL of dimethyl phosphate, a metabolite of dichlorvos, was detected in the urine samples of three subjects (Blair et al., 1975; Das et al., 1983). In this study, each volunteers wore goggles, a cap, a gas mask, a coat, gloves and shoes during exposure. In exposure, the volunteers were sprayed with 10 to 14 aerosol spray cans (230 to 330 g of dichlorvos) and 18 to 22 pints of 0.5% emulsion (corresponding to 40 to 50 g of dichlorvos).

In an inhalation exposure study of dichlorvos in 2 male volunteers, one of the subjects was exposed to dichlorvos at a concentration of 0.25 mg/m^3 (0.03 ppm) for 10 hours and the other at 0.7 mg/m^3 (0.08 ppm) for 20 hours. No dichlorvos was detected in the blood samples of the subjects immediately after exposure (detection limit: 1 μg/g) (Blair et al., 1975). The reason for no dichlorvos detection was considered that the exposure concentration of dichlorvos was low in this study and dichlorvos was rapidly degraded by esterase (ATSDR, 1997).

Sherman rats that were exposed by inhalation to the dichlorvos-saturated air (approximately 33 ppm) developed cholinergic neurological symptoms within 2 hours after exposure, which suggested that dichlorvos was absorbed in rats (Durham et al., 1957).

In the kidney of 2 of 3 male rats that were exposed by inhalation to dichlorvos at a concentration of 10 mg/m^3 (1.1 ppm) for 4 hours, 0.07 and 0.08 μg/g of dichlorvos were detected, respectively (Blair et al., 1975). Similarly, in a 4-hour inhalation exposure study of dichlorvos at a concentration of 90 mg/m^3 (10 ppm), dichlorvos was detected in the all organs and tissues examined of male mice and the blood, adipose tissue and lung of female mice (Blair et al., 1975).

In an inhalation exposure study of [vinyl-1-^{14}C]-dichlorvos in 3 pigs (20 kg; 1 female and 2 males) at

concentrations of 0.092 mg/m^3 for female and 0.114 mg/m^3 for male for 23 hour/day, for 24 days, neither dichlorvos nor demethylated dichlorvos was detected (the detection limit: 3 ng/g). Converting radioactivity in tissues to dichlorvos equivalent, the concentrations in the brain and subcutaneous adipose tissue ranged from 0.2 to 0.4 ppm and those in the liver from 2.4 to 2.6 ppm (Loeffler et al., 1976).

a-2. Oral administration

In acute toxicity studies of dichlorvos in Swiss mice at a single oral dose of 150 mg/kg (Mohammad et al., 1989) and in hybrid pigs at single doses of 100 to 560 mg/kg (Stanton et al., 1979), animals died within 9 and 15 to 30 minutes after the completion of administration, respectively, which evidenced that dichlorvos was rapidly absorbed via the oral route.

In a single oral administration study of [methyl-^{14}C]-dichlorvos dissolved in peanut oil at a dose of 3.6 mg/kg in male and female rats (6 each), 64.6% of given dichlorvos was collected from the urine, suggesting that dichlorvos was easily absorbed via the oral route. Also in a single oral administration study of [metyl-^{14}C]-dichlorvos at a dose of 22 mg/kg in male and female rats (6 each), similar results were obtained (Hutson and Hoadley, 1972a).

In a single oral administration study of [vinyl-1-^{14}C]-dichlorvos at a dose of 3.7 mg/kg in 2 male Syrian hamsters and 1.5 mg/kg in females, dichlorvos was rapidly absorbed and 11.9% to 21.8% of the radioactivity administered was collected from the urine (ATSDR, 1997).

In a single oral administration study of [vinyl-1-^{14}C]-dichlorvos mixed with polyvinyl chloride pellets at a dose of 40 mg/kg in 9 male Yorkshire pigs, 38.2% of given dichlorvos was absorbed in pigs and the rest was collected from pellets (Potter et al., 1973a).

a-3. Dermal application

In a single dermal application study of dichlorvos dissolved in xylene in monkeys at doses of 50, 75 and 100 mg/kg, neurotoxic symptom developed within 15 to 20 minutes after application, suggesting that dichlorvos was rapidly absorbed through the skin (Durham et al., 1957). Similar results were shown also in an acute toxicity study in Sherman rats; all deaths were observed within 20 minutes after administration (Durham et al., 1957). Based on these results, dichlorvos is considered to be rapidly absorbed through the skin (ATSDR, 1997).

b. Distribution

b-1. Inhalation exposure

In a 4-hour inhalation exposure study of dichlorvos in rats at a concentration of 10, 50, 90 mg/m^3 (1.1, 6, 10 ppm), dichlorvos concentrations detected in the blood (<0.2 mg/kg), liver, testis, lung and brain (<0.1 mg/kg) were extremely low or below the detection limit. In contrast, dichlorvos concentrations detected in the kidney and adipose tissue were high, 2.4 and 0.4 mg/kg, respectively. Dichlorvos was accumulated in the lung more highly than the trachea (Blair et al., 1975). In a 4-hour inhalation exposure study of dichlorvos in rats at a concentration of 10 mg/m^3 (1.1 ppm), dichlorvos was detected only in the kidney of male rats (0.08 mg/kg). In the kidney of male rats that were exposed by inhalation at a concentration of 50

mg/m^3 (6 ppm) for 2 and 4 hours, 1.7 mg/kg of dichlorvos was detected. Dichlorvos in the kidney was eliminated immediately after the withdrawal of exposure and the half-life was 13.5 minutes. Dichlorvos was eliminated from the blood within 15 minutes after exposure (Blair et al., 1975).

In a 24-day inhalation exposure study of [vinyl-1-^{14}C]-dichlorvos in pigs at concentrations of 0.15 mg/m^3, radioactivity was detected in various tissues including the blood, liver and lung. However, neither dichlorvos nor demethylated dichlorvos, was detected (Loeffler et al., 1976).

b-2. Oral administration

It is considered that dichlorvos that was absorbed through the digestive tract was metabolized in the liver and dichlorvos concentrations in tissues were rapidly reduced below the detection limit (Gaines et al., 1966).

In a single oral administration study of dichlorvos dissolved in sunflower oil in pregnant rabbits at a dose of 6 mg/kg on the delivery day, dichlorvos of 0.18 mg/L was detected in the fetal blood at 5 minutes after administration (Maslinska et al., 1979).

In an oral administration study of ^{32}P-dichlorvos in female cows at a dose of 1 mg/kg/day for 7 days and subsequently at a single dose of 20 mg/kg in gelatin capsule, ^{32}P (probably dichlorvos or demethylated dichlorvos) was detected in the organic solvent-soluble fraction of milk that was collected 30 minutes after the completion of administration (Casida et al., 1962).

c. Metabolism

Metabolic pathway of dichlorvos is shown in Figure 7-1.

Results from *in vivo* and *in vitro* studies confirmed that the liver is the main organ to metabolize dichlorvos (Casida et al., 1962; Gaines et al., 1966). in *in vitro* studies, most of ^{32}P-dichlorvos was metabolized to dimethyl phosphate in the blood, adrenal gland, kidney, lung and spleen, and other metabolites detected were demethylated dichlorvos, monomethyl phosphate and inorganic phosphate（Loeffler et al., 1976）. Metabolism of dichlorvos has been studied in humans (Hutson and Hoadley, 1972b), mice (Hutson and Hoadley, 1972a,b), rats (Casida et al., 1962; Hutson and Hoadley, 1972a; Hutson et al., 1971), Syrian hamsters (Hutson and Hoadley, 1972b), pigs (Loeffler et al., 1976; Potter et al., 1973a,b), goats (Casida et al., 1962), and female cows (Casida et al., 1962) using isotope-labeled dichlorvos in various administration routes. The results of these studies indicate that dichlorvos metabolism is similar in various animals (ATSDR, 1997; IPCS, 1989).

In an oral study of [vinyl-1-^{14}C]-dichlorvos in male rats, 42% of radioactivity was collected in metabolites within the first 24 hours. For 4 days after administration, 39% of the radioactivity administered was excreted in the expiration, 13% in the urine, 3.4% in the feces and 16% in carcass. At least 9 metabolites were detected in the urine. ^{14}C-labeled urinary metabolites were dichloroethyl-β-D-glucuronic acid, demethylated dichlorvos, hippuric acid, *N*-benzoylglycine and urea. Furthermore, 5% of radioactivity administered was detected in the liver and most of them were contained in protein fraction as ^{14}C-glycine and ^{14}C-serine (Hutson et al., 1971a,b).

Dichlorvos is metabolized via two pathways. In the first pathway, dichlorvos is hydrolyzed at a bond

between phosphate and vinyl group by type-A esterase that is not involved with glutathione, and dimethyl phosphate and dichloroacetaldehyde are formed. Dimethyl phosphate is excreted in the urine and dichloroacetaldehyde is rapidly metabolized to dichloroethanol (Wright et al., 1979). In the second pathway, catalyzed by glutathione *S*-transferase, dichlorvos is metabolized to demethylated dichlorvos and *S*-methyl glutathione, subsequently by type-A esterase, degrades to dichloroacetaldehyde and monomethyl phosphate. *S*-methyl glutathione is metabolized into methyl mercapturic acid and excreted in the urine. Of these two metabolic pathways, the hydrolysis pathway by esterase is considered to be the main route (see section 8.3.6e) (Wright et al., 1979).

Several *in vitro* studies of dichlorvos metabolism in the blood have been reported. In human serum, activation of type-A esterase with K_m value of 7.1 mM for dichlorvos degradation, which is different from paraoxonase, was found (Traverse et al., 1989). It has also been reported that K_m values of dichlorvos degradation are 4 mM in human serum (Reiner et al., 1980).

The vinyl group of dichlorvos is metabolized via two pathways. The first pathway is that dichloroethanol glucuronide is formed via dichloroacetaldehyde and dichloroethanol and the second one is that dichlorvos is dechlorinated via dichloroacetaldehyde and degraded, and then, carbon atom is used as the component of hippuric acid, urea and carbon dioxide (Hutson and Hoadley, 1972b).

In a 2-hour or 4-hour inhalation exposure study of dichlorvos in rats at a concentration of 50 mg/m^3, the half-life of dichlorvos in the kidney was 13.5 minutes (Wright et al., 1979). In an *in vitro* study with human whole blood, the half-life of dichlorvos was 8.1 minutes in males and 11.2 minutes in females, respectively (Blair et al., 1975).

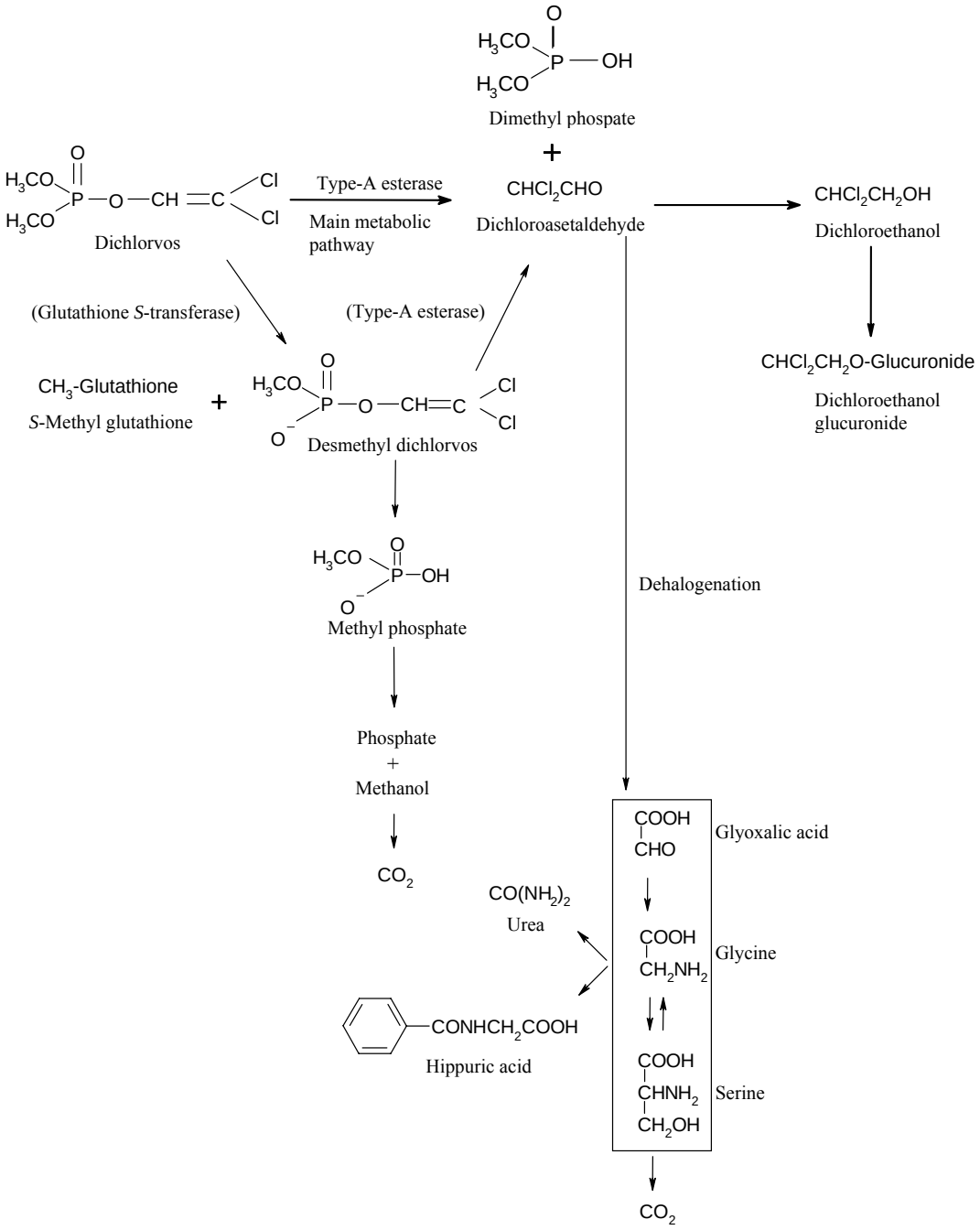


Figure 7-1 Metabolic pathway of dichlorvos (ATSDR, 1997, Recasting)

d. Excretion

In an oral administration study in male volunteers who were given orange juice containing 5 mg/kg of [vinyl-1-^{14}C]-dichlorvos, 27% of the radioactivity administered was excreted in the expiration as $^{14}CO_2$ within 24 hours after administration. In contrast, the radioactivity excreted in the urine was only 9%. The radioactivity in the urine was decreased with time and not detected 9 days after administration (Hutson and Hoadley, 1972b).

In a single oral administration study of ^{32}P-dichlorvos in rats at doses of 0.1 to 80 mg/kg, 66% to 70% of radioactivity administered was excreted in the urine and approximately 10% in the feces within 6 days after

dosing (Casida et al., 1962).

In a single oral administration study of [methyl-^{14}C]-dichlorvos dissolved in 0.5-mL peanut oil in mice at a dose of 0.5 mg and in rats at a dose of 1 mg, approximately 65% of the radioactivity administered was excreted in the urine and 15% in the expiration, respectively, in 4 days after administration (Hutson and Hoadley, 1972a).

In a single oral administration study of ^{32}P-dichlorvos in female cows at a dose of 20 mg/kg, 40% of the radioactivity administered was excreted in the urine and 50% in the feces, respectively. The radioactivity in milk within 2 hours after administration was significantly higher than the background value and the milk contained organic solvent-soluble radioactive substances (Casida et al, 1962). In a single oral administration study of [vinyl-1-^{14}C]-dichlorvos at a dose of 40 mg/kg in 9 male Yorkshire pigs, 4% of the radioactivity administered was collected from the urine, 5% and 6.6% from the feces and expiration, respectively (Potter et al., 1973b).

The percentages of radioactivity that was excreted in expiration, urine and feces within 24 hours after administration in a single oral administration study of [vinyl-^{14}C]-dichlorvos in humans, rats, mice and hamsters are shown in Table 7-1 (Hutson and Hoadley, 1972b).

Table 7-1 Radioactivity excreted in expiration, urine and feces within 24 hours after a single oral administration of [vinyl-^{14}C]-dichlorvos (%)

Species	Number of animals	Carbon dioxide	Urine	Feces
Humans	1	27 (8 hours after)	7.6	ND
Rat	3	28.8	9.8	1.5
Mouse	1	23.1	27.4	3.2
Hamster	2	33.5	14.7	2.9

Note: single oral administration; animals were males.
ND: No data available

e. Summary of kinetics and metabolism

The kinetics and metabolism of dichlorvos are similar among various mammals including humans with some differences in metabolic rate.

Dichlorvos is rapidly absorbed through the digestive and respiratory tracts as well as skin, and distributed in the kidney and adipose tissue at relatively high concentrations. It was reported in an oral study in pregnant rabbits that dichlorvos was transferred to fetuses in a short time.

Dichlorvos is metabolized by esterase that exists in most tissues. Dichlorvos is metabolized via two major pathwaysIn the first pathway, dichlorvos is hydrolyzed at a bond between phosphate and vinyl group by type-A esterase that is not involved with glutathione, and dimethyl phosphate and dichloroacetaldehyde are formed. Dimethyl phosphate is excreted in the urine and dichloroacetaldehyde is rapidly metabolized to dichloroethanol. In the second pathway, catalyzed by glutathione *S*-transferase, dichlorvos is metabolized to demethylated dichlorvos and *S*-methyl glutathione, subsequently by type-A esterase, degrades to dichloroacetaldehyde and monomethyl phosphate. Of these two metabolic pathways, the hydrolysis pathway by the esterases is the main route. Within 4 days after oral administration to rats, 39% of

dichlorvos administered was excreted in the expiration, 13% in the urine, 3.4% in the feces and 16% in carcass.

7.2 Epidemiological studies and case reports of dichlorvos

Epidemiological studies and case reports of dichlorvos are summarized in Table 7-2.

a. General population exposure

a-1. Acute effect

A woman aged 56 years who drank approximately 100 mg/kg of dichlorvos by mistake recovered in 14 days after the accident (Watanabe et al., 1976). A person who drank approximately 400 mg/kg of dichlorvos with suicidal intent died (Shinoda et al., 1972).

A Japanese woman aged 72 years who drank dichlorvos (75% toluene solution) with suicidal intent and died. From her stomach, 300 g of dichlorvos was detected. Necropsy findings included pale skin, bilateral conjunctival congestion, hemorrhage from the tracheal mucosa, hemorrhagic ulcer in the range of the dorsal tongue to upper pharynx, pale mucosa of the esophagus, stomach and duodenum, calcific stenosis of the pulmonary trunk, and severe pulmonary and renal congestion. A reduction in plasma cholinesterase activity (2 IU/L) was observed, but no miosis. Regarding the distribution of dichlorvos in organs and tissues, the concentrations in the spleen and heart were high, with concentrations of 3,340 and 815 μg/g, respectively, and that in the urine was low, 4.5 μg/g. The concentrations in the blood, brain, lung, kidney and liver were 29, 9.7, 81, 80 and 20 μg/g, respectively (Shimizu et al., 1996).

a-2. Short-term and chronic effects

In the case of an adult and a child were exposed to dichlorvos at a concentration of 0.8 mg/m^3 in a room, their plasma and RBC cholinesterase activities showed no abnormalities (Funckes et al., 1963; Gratz et al., 1963).

In the residences of 20 families, 0.5% dichlorvos solution as an insecticide for German cockroach was spread at average concentration of 0.189 g/m^2. The first 2-hour concentration in air was 548 μg/m^3 and the second 2-hour concentration was 183 μg/m^3. No dichlorvos nor dichloroacetic acid was detected in the urine of inhabitantsA slight reduction in serum cholinesterase activity was found in some of them, but cholinesteraseactivity of red blood cell (RBC) was not affected (Gold et al., 1984).

b. Examination by volunteers

In an oral administration study of dichlorvos in male volunteers, 107 subjects were given dichlorvos at single doses of 1 to 32 mg/kg, and 38 of them at repeated doses of 1 to 32 mg/kg/day for 2 to 7 days and at repeated doses of 1 to 16 mg/kg/day for 3 weeks. A reduction in plasma cholinesterase activity was observed at a single dose of approximately 6 mg/kg and 3-week repeated dose of 1 mg/kg/day. At single doses of approximately 1 to 3 mg/kg and above, a reduction in plasma cholinesterase activity was found and at single doses of approximately 4 to 12 mg/kg and above, a reduction in RBC cholinesterase activity was also observed. At repeated dose of 8 to 32 mg/kg/day, transient effects on the gastrointestinal tract and

central nervous system (anticholinergic-like symptoms) were found with a reduction in cholinesterase activity (Slomka and Hine, 1981).

In a 28-day oral adminisration study of dichlorvos in male volunteers (5 persons/dose) at doses of 1, 1.5, 2 and 2.5 mg/person/day, a reduction in plasma cholinesterase activity (30% respectively) was observed 2 days after the completion of administration at a dose of 2 mg and on administration day 20 at a dose of 2.5 mg (Rider et al., 1968).

In a 60-day oral administration study of dichlorvos in 10 male volunteers at a repeated dose of 1.5 mg/person/day, plasma cholinesterase activity was reduced by 40%, but recovered after the completion of administration period (Rider et al., 1967).

In an oral administration study of dichlorvos in male volunteers (6 persons/group, 21 to 45 years old), dichlorvos in gelatin capsule or capsule filled with cottonseed oil was orally administered at a dose of 0.9 mg/person, and placebo was orally administered to 2 control groups 3 times/day for 21 days. A reduction in plasma cholinesterase activity was observed in the dichlorvos-treated group (2 kinds of capsule) within 20 days after administration, and it took 13.7 days to recover to the 50% level. Cholinergic symptoms or reduction in RBC cholinesterase activity was not observed (Boyer et al., 1977).

Eight volunteers were exposed to dichlorvos by inhalation at concentrations of 0.73 to 1.18 mg/m^3 for 45 minutes in airplane in flight at 2,400 m altitude and showed no changes in dark adaptation function, airway resistance, plasma and RBC cholinesterase activities (Smith et al., 1972).

In an inhalation exposure study of dichlorvos in volunteers (26 males and 6 females) at a concentration of approximately 1 mg/m^3 for 2 to 7 hours in a chamber, a significant reduction in plasma cholinesterase activity was observed at 6 to 7 hours after exposure, however, no abnormalities were found in clinical observations, hematology, urinalysis, renal function, EEG, ECG, respiratory function and RBC cholinesterase activity (Hunter, 1970a).

In an inhalation exposure study of dichlorvos in male volunteers, 7 subjects were exposed to dichlorvos in the head and neck at concentrations of 1 to 52 mg/m^3 and 6 subjects only in the head at concentrations of 7 to 50 mg/m^3 for 10 minutes to 4 hours. Irritation to the throat, rhinorrhea and substernal discomfort were observed at the maximum concentration of 52 mg/m^3 for 65 minutes, however, no effects were seen in the pupil diameter and vision. A reduction in RBC cholinesterase activity was observed only in one subject with a correlation between plasma cholinesterase activity and exposed doses of dichlorvos. No change was observed in renal and pulmonary function and metabolic rate (Hunter, 1969, 1970b).

In a 6-month inhalation exposure study of dichlorvos in 14 volunteers at a concentration of approximately 0.09 mg/m^3 in a room where dichlorvos-impregnating resin vaporizers were installed one device/30 m^3, no change in plasma or RBC cholinesterase activity was found (Zavon and Kindel, 1966).

In an inhalation exposure study of dichlorvos in volunteers (26 families) in a house where dichlorvos-impregnating cloths were put around (mean maximum concentration of dichlorvos in the air: 0.13 mg/m^3) for one year and more, inhabitants showed no adverse effect on health or no reduction in plasma and RBC cholinesterase activities. With a condition to replace dichlorvos-impregnating cloths every month, only a slight reduction in plasma cholinesterase activity was found (Leary et al., 1971, 1974).

c. Effects from oral administration as drug

Dichlorvos was orally administered to 108 patients with helminthic infections at single doses of 6 and 12 mg/kg as an anthelmintic drug, and approximately 40% showed weakness due to severe anemia (decrease in hemoglobin concentration) and a severe reduction in plasma cholinesterase activity. However, RBC cholinesterase activity was only slightly to moderately reduced and no abnormalities were found in hematology, hepatic and renal function other than cholinesterase activity. There were no toxic symptoms except a slight headache in several patients (Pena Chavarra et al., 1969).

Dichlorvos was orally administered to 705 patients at single doses of 6 and 12 mg/kg as an anthelmintic drug and reduction in plasma and RBC cholinesterase activities was found at doses of 6 mg/kg and above, however, no abnormality was found in clinical observations, hematology, or hepatic and renal function (Cervoni et al., 1969).

In 2 patients who were given dichlorvos as an anthelmintic drug at high concentrations, severe toxic symptoms probably due to anticholinergic reaction developed, and after recovery severe axonal degeneration neuropathy was observed as a symptom of delayed neurotoxicity. One of the patients recovered within 12 months (Wadia et al., 1985).

d Occupational exposure

d-1. Acute effect

In the case of a worker was exposed to 1% dichlorvos mineral oil solution that ran out from a sprayer during pest control, worker developed contact dermatitis on the back skin, dizziness, dyspnea and weakness. Four days after exposure, a reduction in blood cholinesterase activity was found, however, no systemic symptoms were observed. The worker recovered without treatment, and cholinesterase activity was increased to 72% of the normal value within one month. Dermatitis was considered to be induced by the solvent (Bisby and Simpson, 1975).

A truck driver who transported 5% dichlorvos solution (solvent: 15% petroleum fraction, 80% trichloroethane) and had dermal exposure of dichlorvos in a traffic accident, had contact dermatitis for 2 months. In addition, the driver complained headache, slight rhinorrhea, burning pain in the tongue and bitter taste in the month. Blood cholinesterase activity, which was initially low, increased in 2 weeks after the accident, however, the values were within the normal range. The result of skin patch test with 0.1% and 1% dichlorvos dissolved with petroleum fraction showed negative. Based on these symptoms and a slight reduction in cholinesterase activity, dermatitis was considered to be induced by trichloroethane (Mathias, 1983).

d-2. Short-term and chronic effect

In 12 workers who were exposed to 4% dichlorvos aerosol for 16 hours/week during 2 to 4 months in tobacco warehouses, no change was observed in plasma and RBC cholinesterase activities (Witter, 1960).

Sixteen workers who replaced old dichlorvos sprayers with new ones indoors (5 days/week, for 3 weeks, dichlorvos concentration: 0.3 to 2.1 mg/m^3), showed a reduction in plasma cholinesterase activity but no toxic symptoms (Stein et al., 1966).

A worker who sprayed dichlorvos for pest control in a grain store (dichlorvos concentration in air: 1.9 to 3 mg/m^3) showed a reduction in blood cholinesterase activity (Sasinovich, 1970).

In 13 workers who sprayed dichlorvos aerosol (dichlorvos: 230 to 330 g) and emulsion (dichlorvos: 40 to 50 g) for one day in a house for pest control, the dichlorvos residue was detected after application on the back, the chest and a mask filter at the mean concentrations of 0.8, 0.4 and 11 mg/m^2, respectively. Dimethyl phosphate, a metabolite of dichlorvos, was detected in the urine, however, no abnormalities were found in blood biochemistry (including serum cholinesterase activity) and urinalysis (Das et al., 1983).

In the factory workers (11 males and 2 females) who were exposed to dichlorvos (mean: 0.7 mg/m^3, maximum: 3 mg/m^3) for 8 months in a dichlorvos formulation manufaturing plant, reduction in plasma cholinesterase activity was found within several days after the initiation of exposure, and the reduciton of RBC cholinesterase activity was observed later. The plasma and RBC cholinesterase activities recovered to the normal range one month after the exposure was discontinued. In health examination of the workers including other hematological parameters, no changes induced by the exposrue to dichlorvos were found (Menz et al., 1974).

e. Carcinogenicity

A survey by means of interview to investigate the relationship of pediatric cancers in children aged 15 years and less and insecticide use at home was conducted in Denver, U.S.A. Information on the use of insecticides at home was obtained from the parents of 252 children who were diagnosed with cancer from 1976 to 1983, as well as the parents of 222 children as control. The result suggested the relationship between the use of pest strips containing dichlorvos and leukemia (odds ratio of the pest strip-exposed group after birth until 2 years before diagnosis: 1.7, odds ratio of the pest strip-exposed group for at least 3 months of maternal gestation period: 3.0) (Leiss and Savitz, 1995).

A survey by means of interview to investigate the relationship of leukemia and use of pesticide and insecticide was conducted in 578 male Caucasian leukemia patients aged 30 years and above and 1,245 control subjects in Iowa and Minnesota States in U.S.A. from 1981 to 1984. The study results suggested the relationship between dichlorvos and leukemia (odds ratio: 2.0) (Brown et al., 1990).

There are some other studies which investigated the relationship of dichlorvos and cancer incidence, however, the observed effects were related to exposures to multiple chemicals not dichlorvos alone. Therefore, these studies are not referred in this assessment (Amoateng-Adjepong et al., 1995; Pogoda and Preston-Martin, 1997; Zhong and Rafnsson, 1996).

f. Summary of epidemiologicalstudies and case reports of dichlorvos

Acute effects of dichlorvos include debility due to severe anemia, a severe reduction in plasma cholinesterase activity in patients who were given dichlorvos as anthelmintic at single doses of 6 and 12 mg/kg, and severe toxic symptoms (anticholinergic-like symptoms) in high-dose patients, and delayed neurotoxicity (axonal degeneration neuropathy). A worker who was exposed to 1% dichlorvos solution during pest control developed dizziness, dyspnea and debility. Short-term and chronic effects are a

reduction in plasma cholinesterase activity induced by 3-week oral administration at a dose of 1 mg/kg/day and effects on the gastrointestinal tract and central nervous system (anticholinergic-like symptoms) associated with the reduction in cholinesterase activity induced by repeated dose of 8 to 32 mg/kg/day. As the effects to inhalation exposure, the plant workers who were exposed to dichlorvos (mean: 0.7 mg/m^3, maximum: 3 mg/m^3) for 8 months in a dichlorvos formulation manufacturing plant showed a reduction in plasma cholinesterase activity within several days after the initiation of exposure, and the reduciton of RBC cholinesterase activity was observed later. The activity recovered to the normal range one month after the exposure was discontinued. On carcinogenicity of dichlorvos, the relationship with leukemia has been reported between the use of pest strips containing dichlorvos and leukemia in children and between the use of dichlorvos as an anthelmintic drug and leukemia in male adults.

Table 7-2 Epidemiological studies and case reports of dichlorvos

Population Gender/number	Exposure condition	Dose	Results	Reference
A woman aged 56	Ingestion by mistake	Approximately 100 mg/kg	Recovered in 14 days after the accident	Watanabe et al., 1976
Unknown	Ingestion with suicidal intent	Approximately 400 mg/kg	Death	Shinoda et al., 1972
Japanese woman aged 72	Suicide	Dichlorvos (75% toluene solution) 300 g of dichlorvos was detected from the stomach	Necropsy: pale skin, bilateral conjunctival congestion, hemorrhage from the tracheal mucosa, hemorrhagic ulcer in the range of the dorsal tongue to upper pharynx, pale mucosa of the esophagus, stomach and duodenum, calcific stenosis of the pulmonary trunk, and severe pulmonary and renal congestion A reduction in serum cholinesterase activity: 2 IU/L (normal range: 206-459 IU/L), no miosis Dichlorvos distribution in tissues: Spleen 3,340 μg/g, heart 815 μg/g, urine 4.5 μg/mL, blood 29 μg/mL, brain 9.7 μg/g, lung 81 μg/g, kidney 80 μg/g, liver 20 μg/g	Shimizu et al., 1996
Adult, infant	Exposed indoors	0.8 mg/m^3	No abnormal changes in plasma and RBC cholinesterase activities	Funckes et al., 1963; Gratz et al., 1963
Residents of 20 families	Use of insecticide for German cockroach	1st 2 hours concentration: 548 μg/m^3 2nd 2 hours concentration: 183 μg/m^3 0.5% dichlorvos solution (mean concentration: 0.189 g/m^2)	No dichlorvos or dichloroacetic acid detected in the urine of inhabitants. A slight reduction in serum cholinesterase activity in several persons, no changes in RBC cholinesterase activity	Gold et al., 1984
Volunteer 107 males, 38 males	Single oral administration Repeated oral administration 2-7 days, 3 weeks	Single administration: 1-32 mg/kg Repeated administration: 1-32 mg/kg/day	At single doses of approximately 1 to 3 mg/kg and above, a reduction in plasma cholinesterase activity, at single doses of approximately 4 to 12 mg/kg and above, a reduction in RBC cholinesterase activity At repeated administration of 1 mg/kg/day for 3 weeks a reduction in plasma cholinesterase activity	Slomka & Hine, 1981

Population Gender/number	Exposure condition	Dose	Results	Reference
		1-16 mg/kg/day	At repeated administration of 8-32 mg/kg/day, transient effects on gastrointestinal and central nervous system associated with the reduction in cholinesterase activity	
Volunteer Male, 5 persons /dose	Repeated oral administration 28 days	1, 1.5, 2, 2.5 mg/person	2 mg/person: A reduction in plasma cholinesterase activity (30%) 2 days after the completion of administration 2.5 mg/person: A reduction in plasma cholinesterase activity (30%) 20 days after the completion of administration	Rider et al., 1968
Volunteer 10 males	Repeated oral administration 60 days	1.5 mg/person:	A reduction in plasma cholinesterase activity (40%) was observed, however, recovered after the completion of administration	Rider et al., 1967
Volunteer 24 males 21-45 years 6 persons/group	Repeated oral administration for 21 days, 3 times/day 0.9 mg of dichlorvos in (1) gelatin capsule or (2) capsule filled with cottonseed oil was administered Placebo was orally administered to 2 control groups (3) and (4)	0.9 mg	Groups (1) and (2): A reduction in plasma cholinesterase activity within 20 days after administration and it took 13.7 days to recover to the 50% level. No difference in recovery between two groups No cholinergic symptoms or a reduction in RBC cholinesterase activity	Boyer et al., 1977
Volunteer 8 persons	Inhalation exposure 45 minutes In airplane in flight at 2,400 m altitude	0.73 -1.18 mg/m^3	No changes in dark adaptation function, airway resistance, plasma and RBC cholinesterase activities	Smith et al., 1972
Volunteer 26 males 21-57 years old 6 females 19-25 years old	Inhalation exposure 2-7 hours exposure in a chamber	Approximately 1 mg/m^3	A reduction in plasma cholinesterase activity 6 to 7 hours after exposure No abnormalities in clinical symptoms, hematological examination, urinary test, renal function, EEG, ECG, respiratory function and RBC cholinesterase activity	Hunter, 1970a

Population Gender/number	Exposure condition	Dose	Results	Reference
Volunteer (1) 7 males 25-56 years old (2) 6 males	Inhalation exposure 10 minutes to 4 hours	(1) Exposure in the head and neck, 1-52 mg/m^3 (2) Exposure in the head only, 7-50 mg/m^3 Max concentration: 52 mg/m^3 (65 min) Max exposure time: 4 hours (13 mg/m^3)	52mg/m^3, exposure for 65 days: Irritation to the throat, rhinorrhea and substernal discomfort No effects on pupil diameter and vision A reduction in RBC cholinesterase activity was observed only in one volunteer, showing a correlation between plasma cholinesterase activity and exposed doses of dichlorvos. No changes in renal and pulmonary function and metabolic rate	Hunter, 1969, 1970b
Volunteer 3 males	Inhalation exposure 4 days 1-2 hours/day	0.3-0.9 mg/m^3 (mean: 0.5 mg/m^3) 0.9-3.5 mg/m^3 (mean: 2.1 mg/m^3)	Mean 2.1 mg/m^3, 2 h/day: A reduction in plasma cholinesterase activity	Witter et al., 1961
Volunteer 15 males 23-61 years old	Inhalation exposure 14 days, 6 times/day at 30 mins interval	0.14 -0.33 mg/m^3	No changes in airway resistance, vision and plasma cholinesterase activity	Rasmussen et al., 1963
	Inhalation exposure 11 weeks, 4 days/week, 8-10 hours interval/day	0.1 -0.6 mg/m^3	No changes in airway resistance, vision and plasma cholinesterase activity	
Volunteer 14 persons	Inhalation exposure 6 months dichlorvos-impregnating resin vaporizers were installed one device/30 m^3, cloths were replaced at shorter interval than usual	Approximately 0.09 mg/m^3 (indoor concentration 40 days after 4 sheets of resin vaporizers were installed)	No reduction in plasma and RBC cholinesterase activities	Zavon & Kindel, 1966
Volunteer 26 families	Inhalation exposure 1 year and more 8-10 sheets of ichlorvos-impregnating cloths were installed indoors	0.13 mg/m^3	No adverse effect on inhabitants' health or no reduciton in plasma and RBC cholinesterase activities In replacement of cloths every month, a slight reduction in plasma cholinesterase activity	Leary et al., 1971, 1974
Inpatient 108 persons	Single administration of dichlorvos (impregnated into resin and formed into a pellet) as an anthelmintic drug	6, 12 mg/kg	Many patients showed severe anemia, debility, a severe reduction in plasma cholinesterase activity, a slight reduction in RBC cholinesterase activity No toxic symptoms other than slight headache in several patients No abnormalities in hematological examination, hepatic and renal function	Pena Chavarra et al., 1969

Population Gender/number	Exposure condition	Dose	Results	Reference
Patient 705 persons	Single administration of dichlorvos (impregnated into polyvinyl chloride resin and formed) as an anthelmintic drug for parasite (whipworm, hookworm and roundworm) 2 hours before breakfast	6, 12 mg/kg	6 mg/kg and above: Reductions in plasma and RBC cholinesterase activities No abnormalities in clinical symptoms, hematological examination, hepatic and renal function	Cervoni et al., 1969
Patient 2 persons	Oral intake	Unknown (high concentration)	In 2 patients, severe toxic symptoms probably due to anticholinergic reaction developed and severe axonal degeneration neuropathy, delayed neurotoxicity, was observed after recovery. One of them recovered within 12 months.	Wadia et al., 1985
Worker	Dichlorvos was attached to some parts of the body	Condensed dichlorvos 3% solution, 120 mL	2 workers did not immediately wash out condensed dichlorvos attached to the body and died. Other workers who washed out dichlorvos developed toxic symptoms but recovered. Not lethal but serious case: a worker spilled out 120 mL of 3% dichlorvos solution and did not immediately washed out, and then, could not speak clearly and fell down 1 hour later, but recovered after treatment.	Hayes, 1963, 1982
Operator of pest control	Exposed to 1% dichlorvos mineral oil solution that ran out from a sprayer during pest control	1% dichlorvos mineral oil solution	An operator developed contact dermatitis on the back skin, dizziness, dyspnea and debility, 4 days later, showed a reduction in blood cholinesterase activity but no systemic symptoms. The operator recovered without treatment and cholinesterase activity was increased to 72% of the normal value within one month. Dermatitis was considered to be induced by the solvent.	Bisby & Simpson, 1975
Truck driver	During transport, touched dichlorvos by the skin in a traffic accident	5% solution (15% petroleum fraction, 80% trichloroethane)	Contact dermatitis, headache, slight rhinorrhea, burning pain in the tongue and bitter taste in the month Blood cholinesterase activity was initially low and increased 2 weeks later, however, the values were within the normal range. The result of skin patch test with 0.1% and 1% dichlorvos dissolved with petroleum fraction showed negative. Based on these symptoms and a slight reduction in cholinesterase activity, dermatitis was considered to be induced by trichloroethane.	Mathias, 1983
Cockroach exterminator 7-9 persons	18 mins, 4 hours Sprayed dichlorvos kerosene solution	0.3-0.6% kerosene solution 6 mL/m^2	Conjunctival congestion, sore throat, a reduction in cholinesterase activity	Ueda et al., 1959, 1960

Population Gender/number	Exposure condition	Dose	Results	Reference
Cockroach exterminator 4 persons	2 hours Sprayed dichlorvos kerosene solution in a room at 25°C	0.6% kerosene solution	Reductions in plasma and RBC cholinesterase activities	Ueda et al., 1959, 1960
Cockroach exterminator 11 persons	6 hours Sprayed dichlorvos kerosene solution in a room at 20°C	0.6% kerosene solution	A reduction in plasma cholinesterase activity but not RBC cholinesterase activity It was concluded that the reduction in cholinesterase activity was induced by long and continuous work. Conjunctival congestion and sore throat were induced by kerosene used as solvent.	Ueda et al., 1959, 1960
Worker 12 persons	2-4 months 16 h/week Used dichlorvos aerosol in tobacco warehouse	4%	No reduction in plasma and RBC cholinesterase activities	Witter, 1960
Worker 16 persons	3 weeks 5 day/week Insect protection	0.3 -2.1 mg/m^3: (room concentration)	A reduction in plasma cholinesterase activity No toxic symptom	Stein et al., 1966
Grain store worker	Pest control	1.9 -3 mg/m^3:	A reduction in blood cholinesterase activity	Sasinovich, 1970
Operator of pest control 13 persons	Sprayed dichlorvos aerosol and emulsion in 4 houses for one day for pest control	230-330 g (aerosol) 40-50 g (emulsion)	The remaining dichlorvos was detected in the back, the chest and a mask filter as the mean concentrations of 0.8, 0.4 and 11 mg/m^2. Dimethyl phosphate was detected in the urine, however, no changes were found in hematological examination (including serum cholinesterase activity) and urinary test.	Das et al., 1983
Plant worker 11 males, 2 females	8 months Exposed during manufacturing dichlorvos formulations	Mean: 0.7 mg/m^3, Max: 3 mg/m^3	A reduction in plasma cholinesterase activity was found within several days after the initiation of exposure, however, RBC cholinesterase activity was reduced later Plasma and RBC cholinesterase activities recovered to the normal range one month after the exposure discontinuation. In health examination including other hematological items, dichlorvos-induced changes were not found.	Menz et al., 1974
Children diagnosed with cancer 252 children	1976-1983 Surveyed the relationship between pediatric cancer and household insecticide, indoor insecticide, livestook insecticide and pest strips impregnating dichlorvos	Unknown	Odds ratio of pest strip use to leukemia (odds ratio: ORs) = 1.7,3.0 OR1.7 : Pest strip-exposed group after birth until 2 years before diagnosis OR3.0 : pest strip-exposed group for at least 3 months of maternal gestation period The use of household insecticide was related to the incidence of leukemia.	Leiss & Savitz, 1995

Population Gender/number	Exposure condition	Dose	Results	Reference
Male Caucasian aged 30 years and above 578 leukemia patients and 1245 control persons	1981-1984 Surveyed the relationship between use of insecticide and pesticide and leukemia	Unknown	Odds ratio of use of dichlorvos as insecticide to leukemia (odds ratio: OR) = 2.0 The use of dichlorvos was related to the incidence of leukemia.	Brown et al., 1990

7.3 Studies in experimental animals and *in vitro* studies

7.3.1 Acute toxicity

Acute toxicity data of dichlorvos to experimental animals are summerized in Table 7-3.

Oral LD_{50} values of dichlorvos were 61 to 275 mg/kg in mice (Anonym, 1974; Haley et al., 1975; Holmstedt et al., 1978; Issiki et al., 1983; Sasinovich, 1968, 1970; Takahashi et al., 1987; Ueda et al., 1960; Vrbovsky et al., 1959; Yamasita, 1960, 1962), and 17 to 110 mg/kg in rats (Durham et al., 1957; Gaines, 1969; Holmstedt et al., 1978; Narcisse, 1967; Sasinovich, 1968, 1970; Ueda et al., 1960; Vrbovsky et al., 1959). The LD_{50} s for inhalation exposure were 1.42 to 33.8 ppm in mice (13 to 310 mg/m^3, 4 hours) (MacDonald, 1982; Sasinovich, 1968, 1970; Ueda et al., 1960), and 9.05 to 49.6 ppm in rats (83-455 mg/m^3, 1 hour) (Kimmerle and Lorke, 1968; MacDonald, 1982; Sasinovich, 1968, 1970).

Acute toxic symptoms with oral administration included a reduction in spontaneous activity, salivation, defecation, vomiting, poor coordination, cyanosis gasping, coma, tremor and spasm and with inhalation exposure were salivation, lacrimation, proptosis, tremor and spasm (Ikeda et al., 1990).

Table 7-3 Acute toxicity of dichlorvos

	Mouse	Rat	Rabbit	Guinea pig	Dog
Oral LD_{50} (mg/kg)	61-275	17-110	ca 3-23	157	ND
Inhalation LC_{50}, (ppm, (mg/m^3))	1.42-33.8 (Male) (13-310) (4 hours)	9.05 (Female)- 49.6 (Male) (83-455) (1 hour)	ND	ND	22-316
Dermal LD_{50} (mg/kg)	206-395	75-900	107	ND	ND
Intraperitoneal LD_{50} (mg/kg)	22-41	15-18	ND	ND	ND
Subcutaneous LD_{50} (mg/kg)	13-33 (Male)	11-72	ND	28	ND
Intravenous LD_{50} (mg/kg)	8-10	ND	ND	ND	ND

ND: No data available

7.3.2 Irritation and corrosion

A study on irritation and corrosion of dichlorvos to experimenal animals is summarized in Table 7-4.

In a skin irritation study of 5% to 20% dichlorvos solution in male New Zealand White (NZW) rabbits, severe irritation of dichlorvos was confirmed (Arimatsu et al., 1977).

Table 7-4 Irritation and corrosion of dichlorvos

Species sex/number of animals	Test method Guidelines	Period	Dose	Results	Reference
Rabbit NZW Male	Skin irritation	ND	Application volume was unknown. 5-20% aqueous solution	Severe irritation	Arimatsu et al., 1977

ND: No data available

7.3.3 Sensitization

Studies on sensitization of dichlorvos to experimental animals are summarized in Table 7-5.

In a skin sensitization test using maximization test at concentrations of 0.05% and 0.5% (solvent unknown) in guinea pigs, 35% of the 0.5%-treated animals developed erythema. Dichlorvos was considered to have moderate sensitization (Fujita, 1985).

In a skin sensitization study using Ear/Frank test for 3 days, 0.1 mL of dichlorvos was applied to the lateral auricular skin of male guinea pigs and sensitization was judged to be negative (Kodama, 1968).

Table7-5 Sensitization of dichlorvos

Species sex/number of animals	Test method Guidelines	Period	Dose	Results	Reference
Guinea pig Hartley	Maximization method	Sensitization 1 week after, induction the 2nd week after the last sensitization	0.05, 0.5% Intradermal sensitization: 0.1 mL Patch sensitization: 0.2 mL Induction: 0.1 mL	Slight or marked erythema in 35% of the 0.5%-treated animals Judged to be moderate	Fujita, 1985
Guinea pig Male 5 animals	Stevens Assay [1)] (ear/flank test)	3 days	Sensitization: 0.1 mL/day 3 days Induction: 0.2 mL	Negative	Kodama, 1968

[1)] Ear/flank test: 0.1 mL of substanse solution was applied to the lateral auricular skin of guinea pigs for 3 days. On 7thday, test substance was prepared at several step concentrations and 0.2 mL of test substance solution was applied to the skin (diameter: 1 cm) for induction. The level of erythema 24 hours after was assessed (cited from page 245 of "New dermal physiology and safety"

7.3.4 Repeated dose toxicity

Studies on repeated dose toxicity of dichlorvos to experimental animals are summarized in Table 7-6.

a. Oral administration

In a single oral (gavage) administration study of dichlorvos at 0, 40 mg/kg and an 18-day oral administration (gavage) study at 0, 10 mg/kg/day in male NMRI/Han mice (14 animals/group), the histopathological examination of testis was conducted at 9, 18, 27, 36, 54 and 63 days after the initiation of administration. In the rats of the dichlorvos-treated groups in both studies, seminiferous tubules

and Sertoli cell damage, spermatogenesis impairment, increased and swollen Leydig cells were observed (Krause and Homola, 1972, 1974).

In a 10-week oral administration (via drinking water) study of dichlorvos in male and female $B6C3F_1$ mice (10 animals/sex in control group, 12 animals/sex in treated groups) at concentrations of 0, 25, 50, 100, 200 and 400 mg/L water, no abnormalities were observed in all treated groups (Konishi et al., 1981).

In a 10-week oral administration (via drinking water) study of dichlorvos in male and female $B6C3F_1$ mice (10 animals/sex/group) at 0, 400, 1,600, 3,200, 5,000 and 10,000 mg/L, suppression of body weight gain was observed at 1,600 mg/L water and above , and death at concentrations of 5,000 mg/L and above (Konishi et al., 1981).

In a 13-week oral administration (gavage) study of dichlorvos in male and female $B6C3F_1$ mice (10 animals/sex/group) at doses of 0, 5, 10, 20, 40, 80 and 160 mg/kg/day for 5 days/week, 5 of 10 males at 80 mg/kg/day, all of 10 males and 9 of 10 females at 160 mg/kg/day died. However, no abnormalities were found in clinical observation and histopahological examination (U. S. NTP, 1989).

In a 12-week oral administration (gavage) study of dichlorvos at 0, 30 mg/kg/day in rats, decreases in hemoglobin, hematocrit and corpuscular hemoglobin concentration were found (Ellinger et al., 1985).

In an oral administration (gavage) study of dichlorvos in male Wistar rats (16 animals/group) on days 4 and 5 after birth at 0, 20 mg/kg/day or from day 4 to 23 after birth at 0, 10 mg/kg/day, the histopathological examinaiton of testis was conducted in two rats of each dose group at 6, 12, 18, 26, 34 and 50 days after birth, and slight decreases in seminiferous epithelium and Sertoli cells were observed. These changes were recovered by 50 days after the completion of administration (Krause et al., 1976; Xing-Shu, 1983).

An 8-week oral administration (gavage) study of dichlorvos at 0, 5 and 10 mg/kg every other day was conducted in male Wistar rats (5 months old, 5 animals/group). Dichlorvos-treated rats were assigned into 5 groups and the histopathological examinaiton of seminiferous tubules was performed every 4 weeks. From 4 to 8 weeks after administration, a decrease in seminiferous tubular cells was observed. These changes recovered 8 weeks after the completion of administration (Fujita, 1985).

In a 90-day oral feeding study of dichlorvos (purity: 90%) at doses of 0, 5, 20, 50, 200, 500 and 1,000 mg/kg diet (corresponding to 0, 0.4, 1.5, 3.5, 14.2, 35.7 and 69.9 mg/kg bw/day) in female Sherman rats (juvenile, 10 animals/group), no toxic symptoms developed. Reductions of cholinesterase activities in plasma and RBC were observed at doses of 14.2 mg/kg/day and above (Durham et al., 1957).

In a 13-week oral administration (gavage) study of dichlorvos in male and female F344 rats at doses of 0, 2, 4, 8, 16, 32 and 64 mg/kg/day (5 days/week), suppression of body weight gain was observed in females at doses of 8 and 16 mg/kg/day, and death in males at doses of 32 mg/kg/day and above and females at doses of 16 mg/kg/day and above. However no abnormalities were found in histopathological examination (U.S. NTP, 1989).

In a 15-week oral feeding study of dichlorvos (purity: 93%) at doses of 0, 0.1, 1, 10, 100 and 1,000 mg/kg diet in male and female SD rats (15 animals/sex/group), a reduction in RBC cholinesterase activity was observed at doses of 100 mg/kg diet and above and suppression of body weight gain, reductions in plasma and brain cholinesterase activities at 1,000 mg/kg diet. However no abnormalities were found in hematology, serum protein, urinalysis and histopathological examination (Witherup et al., 1964).

In an oral administration (gavage) study of dichlorvos at doses of 0, 3.5 and 7 mg/kg/day for 4 months and at doses of 0, 0.7 and 1.4 mg/kg/day for 12 months in rats, suppression of body weight gain, a decrease in food consumption, increases in many organ weights, and reductions in brain, plasma and RBC cholinesterase activities were observed at 1.4, 3.5 and 7 mg/kg/day, and toxic symptoms at 7 mg/kg/day (Sasinovich, 1970).

In a 2-year oral feeding study of dichlorvos (purity: 93%) at doses of 0, 0.1, 1, 10, 100 and 500 mg/kg diet (corresponding to 0, 0.0025, 0.025, 0.25, 2.5 and 12.5 mg/kg bw/day) in male and female SD rats (4 to 5 weeks, 40 animals/sex/group), reductions in plasma and RBC cholinesterase activities and hepatic steatosis were observed at doses of 2.5 mg/kg/day and above, and a reduction in brain cholinesterase activity at 12.5 mg/kg/day. However no abnormalities were found in hematology, blood biochemistry and urinalysis, anesthesia time, behaviors, survival rate, body weight gain, food consumption and organ weight (Witherup et al., 1967,1971).

In a 90-day oral administration (gavage) study of dichlorvos (purity: 93%) at doses of 0, 0.3, 1, 1.5 and 3 mg/kg/day in male and female dogs (3 animals/sex/group), reductions in plasma and RBC cholinesterase activities were observed at doses of 1 mg/kg/day and above, exciting status, enhancement in spontaneous activity and aggression at doses of 1.5 mg/kg/day and above, and a reduction in brain cholinesterase activity at 3 mg/kg/day. However no abnormalities were found in hematology and histopathological examination, survival rate, body weight gain, hepatic and renal function, and organ weight (Hine, 1962).

Dichlorvos was orally administered (gavage) to male and female Beagle dogs (6 to 7 months, 4 animals/sex/group) at doses of 0, 0.1, 1.0 and 3.0 mg/kg/day for 52 weeks. Serum cholinesterase activity was affected on administration day 12 at 0.1 mg/kg/day, and the dose was reduced from 0.1 to 0.05 mg/kg/day after administration day 22. As a result, no abnormalities were found in survival rate, body weight and pathological examination. However, reductions in serum and RBC cholinesterase activities were observed in males and females at doses of 0.1 mg/kg/day and above, and a reduction in brain cholinesterase activity in males at doses of 1.0 mg/kg/day and above and females at 3.0 mg/kg/day. No reduction in cholinesterase activity was observed at a reduced dose of 0.05 mg/kg/day (AMVAC Chemical corp., 1990). Based on the data summarized above, the LOAEL is considered to be 0.1 mg/kg/day with the endpoints of reductions in serum and RBC cholinesterase activities (male and female dogs) and the NOAEL as 0.05 mg/kg/day in this assessment.

In a 2-year oral feeding study of dichlorvos (purity: 93%) at doses of 0, 0.1, 1, 10, 100 and 500 mg/kg diet (corresponding to 0, 0.002, 0.008, 0.08, 0.8 and 6.4 mg/kg bw/day) in male and female dogs (3 animals/sex/group), a reduction in RBC cholinesterase activity was observed at doses of 0.08 mg/kg/day and above, and changes in hepatocytes in females, a reduction in plasma cholinesterase activity at doses of 0.8 mg/kg/day and above, an increase in liver weight in males and females and changes in hepatocytes in males at 6.4 mg/kg/day. However, no abnormalities were found in clinical observation, survival rate, body weight gain, food consumption, hematology and blood biochemistry and urinalysis (Jolley et al., 1967; Witherup et al., 1971).

In an oral feeding study of dichlorvos at doses of 5 to 80 mg/kg diet (corresponding to 1 to 16 mg/kg bw/day) everyday or at doses of 8 and 20 mg/kg diet twice a day in Rhesus monkeys (32 animals), plasma

and RBC cholinesterase activities were reduced approximately 20% at all doses. No toxic symptom was observed. The plasma cholinesterase activity was recovered within 3 weeks after the completion of administration and RBC cholinesterase activity within 50 to 60 days (Hass et al., 1972).

In a 30-day oral feeding study of dichlorvos at doses of 0, 1, 4 and 16 mg/kg/day in pigs aged 35 days, reductions in plasma and RBC cholinesterase activities were observed at doses of 4 mg/kg/day and above (Stanton et al., 1979).

In a 78-day oral feeding study of dichlorvos at doses of 0, 200 and 500 mg/kg diet in 2 lactating female cows, a severe reduction in RBC cholinesterase activity was observed in the maternal cows at 500 mg/kg diet (corresponding to 4.5 mg/kg bw/day). Their milk contained dichlorvos at concentrations of less than 0.08 mg/L, but calves showed no abnormality in cholinesterase activity. Cholinergic symptoms were observed in the maternal cows at a single dose of 27 mg/kg, but disappeared immediately (Tracy et al., 1960).

b. Inhalation exposure

In a inhalation exposure study of dichlorvos in CF-1 mice and CFE rats for 5-day (7 hours/day) at concentrations of 0, 50 to 80 mg/m^3, death was observed in mice at a concentration of 80 mg/m^3 (Stevenson and Blair, 1969).

In a inhalation exposure study of dichlorvos in mice (100 animals), rats (50 animals), rabbits (22 animals) and cats (13 animals) for 40-day (2 hours/day) at concentrations of 0, 16.5, 45 and 160 mg/m^3, no changes were found in respiration, body weight gain, blood biochemistry including blood cholinesterase activity, and pathological examination of all species including rabbit, except transient miosis in rabbits (Vashkov et al., 1966).

In a inhalation exposure study of dichlorvos in mice, rats and guinea pigs for 28-day (23 hours/day) at 0 and 0.03 mg/m^3, no changes were observed at necropsy of all species. In a 5-day inhalation exposure study of dichlorvos in mice, rats and guinea pigs at 0, 0.14 to 0.15 mg/m^3, a reduction in plasma cholinesterase activity was observed in male mice and guinea pigs, and a reduction in brain cholinesterase activity in male mice and female rats (Brown et al., 1968).

In a 12-week inhalation exposure study of dichlorvos in pregnant mice (20 animals), guinea pigs (6 animals), sheep (7 animals), cows (39 animals) and female cows aged less than 3 years at 0, 0.09 to 0.14 and 2.1 mg/m^3, no toxic symptoms or death were found in all species. The pregnant mice developed normal newborns. No abnormal serum esterase activity was found in cows (Henriksson et al., 1971).

An inhalation exposure study of dichlorvos in male and female CFE rats (5 weeks old, 50 animals/sex/group) for 104-week (23 hours/day, 7 days/week) at concentrations of 0, 0.05, 0.5 and 5 mg/m^3 (actual concentrations, male and female: 0, 0.05, 0.48 and 4.7 mg/m^3) was conducted. A reduction in RBC cholinesterase activity was observed in females at concentrations of 0.05 mg/m^3 and above, reductions in plasma and brain cholinesterase activities in males and females at concentrations of 0.48 mg/m^3 and above, body weight loss and a reduction in RBC cholinesterase activity in females at 0.48 mg/m^3 and in males and females at 4.7 mg/m^3. However, no changes in bronchial and alveolar ultrastructure were observed in males and females. At all concentrations, no changes in brain acetylcholine and choline concentrations were

found (Blair et al., 1976). Based on the data summarized above, the NOAEL is considered to be 0.05 mg/m^3 for the endpoint of the reduction in brain cholinesterase activity in this assessment.

Three inhalation exposure studies of dichlorvos at concentrations of 0, 0.11 and 1.1 mg/m^3 for 4 months, or at 5.2 mg/m^3 for 2 months or at 8.2 mg/m^3 for 45 days in rats were conducted. A reduction in cholinesterase activity and a decrease in blood glucose were observed at concentrations of 5.2 mg/m^3 and above, and toxic symptoms and death (2/8) found at 8.2 mg/m^3 (Sasinovich, 1968).

In a 2-week inhalation exposure study of dichlorvos in rats and monkeys, dichlorvos was sprayed in a breeding room once. The dichlorvos concentration in air was initially 6.0 mg/m^3 and reduced to approximately 0.1 to 0.2 mg/m^3 2 or 3 days after. In this study, no toxic symptoms were developed in rats and monkeys. The plasma and RBC cholinesterase activities were reduced by 50%, but recovered after the completion of exposure. In a 1-week inhalation exposure study of dichlorvos in rats and monkeys at a concentration of 2.2 mg/m^3, a reduction in cholinesterase activity was observed in both species, showing no species difference (Durham et al., 1957).

In a inhalation exposure study of dichlorvos in guinea pigs for 5-day (7 hours/day) at 0, 90 to 120 mg/m^3, no abnormalities were found (Stevenson and Blair, 1969).

In an 8-week inhalation exposure study of dichlorvos in rabbits, cats and dogs (8 to 10 animals/group) at concentrations of 0.05 to 0.3 mg/m^3, no abnormality in clinical observation, behavior, plasma and RBC cholinesterase activities and EEG was found in all species (Walker et al., 1972).

In a inhalation exposure study of dichlorvos in rabbits and cats at concentrations of 0.8 to 1.3 mg/m^3 for 4-month (4 hours/day), reductions in serum and RBC cholinesterase activities were found in rabbits but no reduction was observed in cats (Sasinovich, 1968).

In a inhalation exposure study of dichlorvos in monkeys (2 animals/group) at concentrations of 0, 0.7, 1.2 to 3.3, and 7.5 to 18 mg/m^3 for 4-day (2 hours/day), no changes in plasma and RBC cholinesterase activities were found at a concentration of 0.7 mg/m^3. A slight reduction in plasma cholinesterase activity was found at concentrations of 1.2 to 3.3 mg/m^3, miosis and reductions in plasma and RBC cholinesterase activities (40% to 70%) at 7.5 to 18 mg/m^3 (Witter et al., 1961).

In a 3-month inhalation exposure study of dichlorvos in male and female Rhesus monkeys (4 animals/sex/group) at concentrations of 0 and 0.05 mg/m^3, reductions in plasma and RBC cholinesterase activities were observed, however, no abnormalities were found in clinical observation, behavior, hematology and blood biochemistry (except the above enzyme activities). Also, nerve conduction velocity and muscular evoked potential showed no change (Coulston and Griffin, 1977).

In an 85-day inhalation exposure study of dichlorvos in cows with 20% dichlorvos-impregnating resin pieces, a reduction in RBC cholinesterase activity was observed. However, no abnormalities were found in clinnical observation (Horvath et al., 1968).

In a 22-day inhalation exposure study of dichlorvos in horses (5 animals/group) at a concentration of 17 mg/m^3, a reduction in RBC cholinesterase activity was observed (Tracy et al., 1960).

c. Dermal application

In a dermal application study of dichlorvos (purity: 96%) in male rats (12 to 48 animals/group) at doses

of 0 and 21.4 mg/kg/day for 90-day (5 days/week), no abnormality was found in the skin and testis at 21.4 mg/kg/day with histopathological examination (Dikshith et al., 1976).

In an 8-day dermal application study of dichlorvos (purity: 94%) in male and female guinea pigs (5 animals/sex/group) at doses of 0, 25, 50 and 100 mg/kg/day, dose-dependent reductions in plasma and RBC cholinesterase activities were observed at doses of 25 mg/kg/day and above. Plasma and RBC cholinesterase activities recovered to the normal level within 1 and 2 weeks after the completion of administration, respectively (Brown and Roberts, 1966).

In a dermal application study of dichlorvos (mixed with xylene) in 3 cynomolgus monkeys at doses of 0, 50, 75 and 100 mg/kg/day for 5 days/week until animal death (animals died after the 8th, 10th and 4th administration, respectively), all monkeys showed toxic symptoms. Reductions in plasma and RBC cholinesterase activities were observed at 75 mg/kg, and especially RBC cholinesterase activity was severely affected (Durham et al., 1957).

In a dermal application study of dichlorvos in female cows at a dose of 5 mg/kg/day (on administration 7 and after: 10 mg/kg/day, administration period: unknown), a reduction in serum cholinesterase activity was observed at 5 mg/kg, and toxic symptoms developed at the increased dose of 10 mg/kg. The milk of the maternal animals contained no dichlorvos (Majewski et al., 1978).

In a 21-day dermal application study of dichlorvos in female cows (juvenile, 2 animals/group) at doses of 0 and 1,800 mg/animal/day, no abnormal change in RBC cholinesterase activity was observed (Tracy et al., 1960).

d. Neurotoxicity

Studies on neurotoxicity of dichlorvos to experimental animals are summarized in Table 7-7.

It is generally known that organophosphorous compounds induce eurotoxicity. Ataxia and a reduction in neurotoxic esterase (NTE) activity were also reported (Aldridge and Johnson, 1971; Johnson, 1978). In contrast, several studies showed no delayed neutotoxicity in oral and dermal administration studies of dichlorvos in female chickens (Aldridge and Barnes, 1966; Aldridge and Johnson, 1971; Durham et al., 1956; Johnson, 1969, 1975a, b, 1978, 1981; Lotti and Johnson, 1978).

In a 10-day intraperitoneal administration study of dichlorvos in male rats at a dose of 3 mg/kg/day, hyperplasia of mitochondria in spinal nerve cells and myelin degeneration were observed (Ali et al., 1979a; Hasan et al., 1979).

In a 10-day intraperitoneal study of dichlorvos in male rats at doses of 0.6 to 3 mg/kg/day, a dose-dependent increase in brain lipid peroxide and an increase in lipofuscin deposition in Purkinje cells in the cerebellar cortex were found (Hasan and Ali, 1980).

In intraperitoneal administration studies of dichlorvos in rats at a dose of 3 mg/kg/day for 10 and 15 days, decreases in dopamine, norepinephrine and serotonin in several parts of the brain and a significant increase in serotonin in the spinal cord were confirmed (Ali and Hasan, 1977; Ali et al., 1979b,1980).

In a 3-month oral feeding study of dichlorvos at doses of 1.25 to 4.0 mg/kg diet in male and female CFY rats, plasma, RBC and brain cholinesterase activities were not changed, but increases in EEG activity and central hyperexcitability were observed in male rats (Desi, 1983). In a 10-day administration study of

dichlorvos in rabbits at doses of 4 to 8 mg/kg/day (administration route unknown), a change in ratio of brain phospholipid to protein, an increase in oxygen consumption and phospholipid accumulation in myelin were found (Maslinska et al., 1984).

In a 16-day administration study of dichlorvos in rabbits at a dose of 9 mg/kg/day (administration route unknown) from day 6 after birth, a reduction in cholinesterase activity in the cerebral blood vessel wall, perivascular astrocyte dysfunction and a change in vascular endothelial cells were observed (Dambska et al., 1984).

In a single dermal application study of dichlorvos in female chickens at 0 and 100 mg/kg, a slight ataxia was observed at 2 weeks after administration and NTE activities in peripheral nerves, spinal cord and brain were significantly reduced (Caroldi and Lotti, 1981). In addition, a similar study reported that ataxia was not observed but a severe reduction in brain NTE activity and a slight one in spinal cord NTE activity (Johnson, 1978).

In a 90-day oral (gavage) and dermal administration study of dichlorvos (purity: 99.9%) in female chickens (white leghorn), cholinergic-like symptoms including salvation and spasm, and death were observed at oral doses of 6 mg/kg/day and above. At dermal doses of 1 mg/kg/day and above, similar symptoms to those in the oral administration developed and ataxia and death were observed at doses of 1.7 and 3.3 mg/kg/day. No organophosphate-induced delayed neuropathy was observed (Francis et al., 1985).

In a single dermal application study of dichlorvos in male Wistar rats at 0 and 200 mg/kg, platelet NTE activity at 24 hours, 10 days and 21 days after administration, cerebral, cerebellar and brain-stem NTE activities at 24 hours and 21 days after administration and rod-holding time of rotor rod test at 21 days after administration were significantly reduced (Sarin and Gill, 2000).

In an 8-week dermal application study of dichlorvos in male Wistar rats at 0 and 6 mg/kg/day, significant decreases in hemolysate acetylcholinesterase activity and platelet cytochrome oxidase activity at 2 weeks after administration, a significant increase in acid phosphatase activity at 4 weeks after administration, and significant decreases in brain acetylcholinesterase, cytochrome oxidase and glucose-6-phosphate dehydrogenase activities and a significant increase acid phosphatase activity at 8 weeks after administration were confirmed (Sarin and Gill, 1998a).

In an 8-week dermal application study of dichlorvos in male Wistar rats at 0 and 6 mg/kg/day, a significant reduction in NTE, Paraoxon (organophosphorous pesticide)-resistant carboxylesterase, and acetylcholinesterase activities were observed in the cerebral cortex, cerebellum and brain stem. Spontaneous motion and stereotype time in an open field test, rod-holding time in a rotor rod test and active avoidance response were significantly reduced and aggressive behavior was significantly enhanced (Sarin and Gill, 1998b).

In a single dermal application study of dichlorvos in male Wistar rats at 0 and 200 mg/kg, a significant reduction in brain and platelet NTE activity was observed at 2, 7, 15 and 21 days after application. Significant increases in brain calmodulin (CaM) activity was observed from 7 days after application, in Ca^{2+}/CaM-dependent protein kinase and cAMP-dependent protein kinase activities from 15 days after application and in cyclic-AMP concentration from 21 days after applicaiton. Rod-holding time in rotor rod test at 21 days after administration was significantly reduced (Choudhary et al., 2001).

e. Summary of Repeated dose toxicity

Dichlorvos enhanced excitement, spontaneous motion and aggression, induced cholinergic-like symptoms and reduced brain, plasma and RBC cholinesterase activities and brain acetylcholinesterase activity with oral administration. Similar changes were also observed in inhalation exposure and dermal application studies. Testicular toxicity by oral administration was also reported. In studies to investigate neurotoxicity induced by dichlorvos in chickens and rats, cholinergic-like symptoms including salvation and spasm, ataxia, suppression of motion and response (significant reductions in spontaneous motion, stereotype time, active avoidance response and rod-holding time in a rotor rod test) enhancement in aggressive behavior and reductions in brain and platelet NTE activities were observed.

The NOAEL of dichlorvos for oral administration is determined as 0.05 mg/kg/day based on the results of the 52-week oral administration study in which dichlorvos was administered to male and female beagle dogs via gavage, and reductions in plasma and RBC (males and females) and brain (males) cholinesterase activities were observed. The NOAEL of dichlorvos for inhalation exposure is considered to be 0.05 mg/m^3 based on the results of the 104-week inhalation exposure study in which male and female CFE rats were exposed to dichlorvos, and reductions in brain cholinesterase activities were observed.

Table 7-6 Repeated dose toxicity of dichlorvos

Species sex/number of animals	Route	Period	Dose	Results	Reference
Mouse *NMRI/H-an* Male 14 animals /group	Oral gavage	Single and 18 days Histopathological observation on 9, 18, 27, 36, 54, 63 days	Single dose: 40 mg/kg Repeated dose: 10 mg/kg/day	With single and repeated administration, damages of seminiferous tubules and Sertoli cell, spermatogenesis impairment, increase in swollen Leydig cells.	Krause & Homola, 1972,1974
Mouse $B6C3F_1$ Male and female 10/sex/ group	Oral (via drinking water)	10 weeks	0, 25, 50, 100, 200, 400 mg/Lwater	No abnormality	Konishi et al., 1981
Mouse $B6C3F_1$ Male and female 10-12/sex /group	Oral (via drinking water)	10 weeks	0, 400, 1,600, 3,200, 5,000, 10,000 mg/Lwater	1,600 mg/L and above: suppression of body weight gain 5,000 mg/L and above: death	Konishi et al., 1981
Mouse $B6C3F_1$ Male and female 7 weeks 10/sex /group	Oral gavage	13 weeks 5 days /week	0, 5, 10, 20, 40, 80, 160 mg/kg/day	80 mg/kg/day: death (5 males) 160 mg/kg/day: death (10 males and 9 females) No abnormality in general conditions and histopathological examination	U. S. NTP, 1989

Species sex/number of animals	Route	Period	Dose	Results	Reference
Rat	Oral gavage	12 weeks	0, 30 mg/kg/day	Decreases in hemoglobin, hematocrit and corpuscular hemoglobin concentration	Ellinger et al., 1985
Rat Wistar Male 16 /group Juvenile	Oral gavage	Days 4 and 5 after birth Days 4 to 23	Days 4 and 5 after birth: 0, 20 mg/kg/day Days 4 to 23: 0, 10 mg/kg/day	10 mg/kg/day: slight decreases in seminiferous epithelium and Sertoli cells in the histopathological examinaiton of testis in 2 rats per group 6, 12, 18, 26, 34 and 50 days after birth. These changes were recovered by 50 days after.	Krause et al., 1976; Xing-Shu, 1983
Rat Wistar Male 5 months 5/group	Oral gavage	8 weeks every other day	0, 5, 10 mg/kg/day	No increase in body and testis weight Decrease in seminiferous tubular cells 4 to 8 weeks after administration, and recovery after the completion of administration.	Fujita et al., 1977
Rat Sherman Female Juvenile 10/group	Oral (fed)	90 days	0, 5, 20, 50, 200, 500 , 1,000 mg/kg diet (corresponding to 0, 0.4, 1.5, 3.5, 14.2, 35.7 and 69.9 mg/kg/day)	14.2 mg/kg/day and above: reductions in plasma and RBC cholinesterase activities, no toxic symptom	Durham et al., 1957
Rat F344 Male and female 7 week old 10/sex/ group	Oral gavage	13 weeks 5 days /week	0, 2, 4, 8, 16, 32, 64 mg/kg/day	8 mg/kg/day: female; suppressed body weight gain 16 mg/kg/day: death (4 females) female; suppressed body weight gain 32 mg/kg/day: death (10 males and 10 females) 64 mg/kg/day: death (10 males and 10 females) No abnormality in histopathological examination	U. S. NTP, 1989
Rat SD Male and female 15/sex/ group	Oral (fed)	15 weeks	0, 0.1, 1, 10, 100, 1,000 mg/kg diet purity: 93%	100 mg/kg diet and above: reductions in RBC cholinesterase activities 1,000 mg/kg diet: suppressed body weight gain, reductions in plasma and brain cholinesterase activity No abnormality in hematological examination, serum protein, urinary test and histopathological examination	Witherup et al., 1964
Rat	Oral gavage	4 or 12 months	0, 3.5, 7 mg/kg/day or 0.7, 1.4 mg/kg/day purity: unknown	1.4 mg/kg/day and above: suppression of body weight gain, increases in many organ weight, and reductions in brain, plasma and RBC cholinesterase activities 7 mg/kg/day: toxic symptoms	Sasinovich, 1970
Rat SD Male and female 4 to 5 weeks 40/sex/ group	Oral (fed)	2 years male and female 5 rats per group was examined 6, 12 and	0, 0.1, 1, 10, 100, 500 mg/kg diet (corresponding to 0, 0.0025, 0.025, 0.25, 2.5, and 12.5 mg/kg/day)	2.5 mg/kg/day and above: reductions in plasma and RBC cholinesterase activities, hepatic steatosis 12.5 mg/kg/day: a reduction in brain cholinesterase activity No abnormality in anesthesia time, behaviors, survival rate, body weight gain, food consumption and organ weight, serum total	Witherup et al., 1967, 1971

Species sex/number of animals	Route	Period	Dose	Results	Reference
		18 months after the initiation of study.	purity: 93%	protein, A/G ratio, hematological and urinary tests	
Dog Male and female 3/sex/ group	Oral gavage	90 days	0, 0.3, 1, 1.5, 3 mg/kg/day purity: 93%	1 mg/kg/day and above: reductions in plasma and RBC cholinesterase activities 1.5 mg/kg/day and above: exciting status, enhancement in spontaneous motion and aggression 3 mg/kg/day: a reduction in brain cholinesterase activity No abnormality in survival rate, body weight gain, hepatic and renal function, and organ weight, hematological and histopathological tests	Hine, 1962
Dog Beagle Male and female 6 to 7 months 4/sex/group	Oral gavage	52 weeks	0, 0.1, 1.0, 3.0 mg/kg/day administration day 22 and after 0, 0.05, 1.0, 3.0 mg/kg/day (reason; serum cholinesterase activity was affected on administration day 12 at a dose of 0.1 mg/kg)	0.05 mg/kg/day: No abnormality 0.1 mg/kg/day and above: Male and female; reductions in serum cholinesterase activity and RBC acetylcholinesterase activity 1.0 mg/kg/day and above: Male; a reduction in brain acetylcholinesterase activity 3.0 mg/kg/day: Female; a reduction in brain acetylcholinesterase activity Endpoints: reductions in serum and RBC cholinesterase activities (male and female) NOAEL: 0.05 mg/kg/day (in this assessment)	AMVAC Chemical corp., 1990
Dog beagle Male and female 3/sex/group	Oral (fed)	2 years	0, 0.1, 1, 10, 100, 500 mg/kg diet (corresponding to actual consumption of 0, 0.002, 0.008, 0.08, 0.8, and 6.4 mg/kg/day) purity: 93%	0.08 mg/kg/day and above: reduction in RBC cholinesterase activity and changes in hepatocytes (female) 0.8 mg/kg/day and above: a reduction in plasma cholinesterase activity 6.4 mg/kg/day: increase in liver weight, change in hepatocytes (male) No abnormality in general conditions, behaviors, body weight gain, food consumption, hematological examination, serum alkaline phosphatase and transaminase activity, serum total protein, A/G ratio, and urinary tests	Jolley et al., 1967; Witherup et al., 1971
Rhesus monkey 32 animals	Oral (fed)	Everyday (period unknown) 10-21	0, 5-80 mg/kg diet (corresponding to 1-16	At all doses: reductions in plasma and RBC cholinesterase activities (80%), recovery of plasma cholinesterase activity within 3 weeks after the completion of administration and RBC	Hass et al., 1972

Species sex/number of animals	Route	Period	Dose	Results	Reference
		days (twice /day)	mg/kg/day) or 8, 20 mg/kg feed	cholinesterase activity within 50 to 60 days No toxic symptom	
Pig 35 days	Oral (fed)	30 days	0, 1, 4, 16 mg/kg/day	4 mg/kg/day and above: reductions in plasma and RBC cholinesterase activities	Stanton et al., 1979
Cow Female (lactating) 2 animals	Oral (fed)	78 days	0, 200, 500 mg/kg diet (corresponding to 0, 1.8, 4.5 mg/kg /day)	500 mg/kg: a severe reduction in RBC cholinesterase activity in the maternal animals no abnormal cholinesterase activity in calves Detection of dichlorvos atless than 0.08 mg/L in milk Cholinergic symptoms in the maternal cows at a single dose of 27 mg/kg	Tracy et al., 1960
Mouse CF-1 Rat CFE	Inhalation exposure	5 days 7 hours /day	0, 50 -80 mg/m^3:	80 mg/m^3: death (mouse)	Stevenson & Blair, 1969
Mouse Rat Rabbit Cat 13-100 animals	Inhalation exposure	40 days 2 hours /day	0, 16.5, 45, 160 mg/m^3 mixture of kerosene, xylene, freon and dichlorvos	Transient miosis in rabbits No abnormality in respiration, body weight and biochemical and pathological examinations in all species	Vashkov et al., 1966
Mouse Rat Guinea pig	Inhalation exposure	5 to 28 days 23 hours /day	0, 0.03, 0.14 - 0.15 mg/m^3/day	0.03 mg/m^3 (for 28 days): No changes at necropsy in all species 0.14 - 0.15 mg/m^3 (for 5 days): a reduction in plasma cholinesterase activity in mice (male) and guinea pigs (male) a reduction in brain cholinesterase activity in mice (male) and rats (female)	Brown et al., 1968
Mouse Guinea pig Sheep Cow Female cow aged less than 3 years 6-39/group	Inhalation exposure	12 weeks	0, 0.09-0.14, 2.1 mg/m^3 vapor	No death or toxic symptom in all species Mice developed normal newborns. no abnormality in serum cholinesterase activity in cows	Henriksson et al., 1971
Rat CFE Male and female 4 to 5 weeks 50/group	Inhalation exposure (systemic)	104 weeks 23 hours /day, 7 days /week	0, 0.05, 0.5, 5 mg/m^3 (corresponding to 0, 0.05, 0.48, 4.7 mg/m^3) purity: 97% and above vapor	0.05 mg/m^3 and above: Female; a reduction in RBC cholinesterase activity 0.48 mg/m^3 and above: Female; body weight loss Male and female; reductions in plasma and brain cholinesterase activities 4.7 mg/m^3: Male; a reduction in RBC cholinesterase activity	Blair et al., 1976

Species sex/number of animals	Route	Period	Dose	Results	Reference
				Male and female; body weight loss, no changes in bronchial and alveolar ultrastructure No changes in brain acetylcholine and choline concentrations at all doses Endpoint: a reduction in brain cholinesterase activity NOAEL: 0.05 mg/m^3 (in this assessment)	
Rat	Inhalation exposure (systemic)	45 days 2 months 4 months	0, 8.2 0, 5.2, 0, 0.11, 1.1 mg/m^3	5.2 mg/m^3 and above: a reduction in cholinesterase activity and a decrease in blood glucose 8.2 mg/m^3: toxic symptoms, death (2/8)	Sasinovich, 1968
Rat Monkey	Inhalation exposure (sprayed once in breeding room)	2 weeks	Initial concentration: 0, 6.0 mg/m^3, reduced to 0.1-0.2 mg/m^3 2-3 days after Mist	Decreases in plasma and RBC cholinesterase activities by 50% in monkeys, recovery after the completion of exposure. 2.2 mg/m^3: a reduction in cholinesterase activity, no difference between rats and monkeys No toxic symptom in rats and monkeys	Durham et al., 1957
Guinea pig	Inhalation exposure	5 days 7 hours /day	0, 90 -120 mg/m^3	No abnormality	Stevenson & Blair, 1969
Rabbit Cat Dog (dog: male and female) each 8/ group	Inhalation exposure	8 weeks	0, 0.05 -0.3 mg/m^3: vapor	No abnormality in general conditions, behavior, plasma and RBC cholinesterase activity	Walker et al., 1972
Rabbit Cat	Inhalation exposure	4 months 4 hours /day	0, 0.8 -1.3 mg/m^3	Reductions in serum and RBC cholinesterase activities in rabbits but not in cats	Sasinovich, 1968
Monkey 2/group	Inhalation exposure	4 days 2 hours /day	0, 0.7, 1.2-3.3, 7.5-18 mg/m^3: vapor	0.7 mg/m^3: No abnormality 1.2 -3.3 mg/m^3: slight eduction in plasma cholinesterase activity 7.5 -18 mg/m^3: miosis and reductions in plasma and RBC cholinesterase activities (40-70%)	Witter et al., 1961

Species sex/number of animals	Route	Period	Dose	Results	Reference
Rhesus monkey Male and female 4/sex/group (control group: 4 males and 1 female)	Inhalation exposure	3 months	0, 0.05 mg/m^3: vapor	Reductions in plasma and RBC cholinesterase activities No abnormality in general conditions, behavior, and hematological and biochemical examinations excluding cholinesterase No change in nerve conduction velocity and muscular evoked potential	Coulston & Griffin, 1977
Cow	Inhalation exposure	85 days	20%-dichlorvos-impregnating resin piece: vapor	a reduction in RBC cholinesterase activity No abnormality in general conditions	Horvath et al., 1968
Horse 5/group	Inhalation exposure	22 days	0, 17 mg/m^3	a reduction in RBC cholinesterase activity	Tracy et al., 1960
Rat Male 12-48/group	Dermal application	90 days 5 days /week	0, 21.4 mg/kg/day purity: 96%	21.4 mg/kg/day: No abnormality in skin and testis	Dikshith et al., 1976
Guinea pig Male and female 5/group	Dermal application	8 days	0, 25, 50, 100 mg/kg/day	25 mg/kg/day and above: dose-dependent reductions in plasma and RBC cholinesterase activity recovery of plasma and RBC cholinesterase activity to the normal level within 1 and 2 weeks after the completion of administration, respectively.	Brown & Roberts, 1966
Cynomolgus monkey 3 animals	Dermal application	Until death (4-10 days) 5 days /week	0, 50, 75, 100 mg/kg/day (mixture with xylene)	50 mg/kg/day and above: toxic symptoms and a severe reduction in RBC cholinesterase activity, change in oxic symptoms and a reduction in plasma cholinesterase activity	Durham et al., 1957
Cow Female	Dermal application	Period: unknown	0, 5, 10 mg/kg/day on administration 7 and after: 10 mg/kg/day	5 mg/kg/day and above: a reduction in plasma cholinesterase activity 10 mg/kg/day: toxic symptoms No detected in milk.	Majewski et al., 1978
Cow Female Juvenile 2/group	Dermal application (cows washed with water solution or emulsion)	21 days	0, 1,800 mg/animal	No abnormal change in RBC cholinesterase activity	Tracy et al., 1960

Table 7-7 Neurotoxicity of dichlorvos

Species sex/number of animals	Route	Period	Dose	Results	Reference
Rat Male	Intraperitoneal	10 days	0, 3 mg/kg/day	Hyperplasia of mitochondria in spinal nerve cells and myelin degeneration	Ali et al., 1979a; Hasan et al., 1979
Rat	Intraperitoneal	10 days	0, 0.6-3 mg/kg/day	A dose-dependent increase in brain lipid peroxide and an increase in lipofuscin deposition in Purkinje cells in the cerebellar cortex	Hasan & Ali, 1980
Rat	Intraperitoneal	10 days, 15 days	0, 3 mg/kg/day	Decreases in dopamine, norepinephrine and serotonin in several parts of the brain An increase in serotonin in the spinal cord	Ali & Hasan, 1977; Ali et al., 1979b, 1980
Rat CFY Male and female	Oral (fed)	3 months	0, 1.25-4.0 mg/kg feed	1.25 mg/kg and above: No change in plasma, RBC and brain cholinesterase activity Male: increases in EEG activity and central hyperexcitability	Desi, 1983
Rabbit Female	Administration route: unknown	10 days	0, 4-8 mg/kg/day	4-8 mg/kg/day and above: a change in ratio of brain phospholipid to protein, an increase in oxygen consumption and phospholipid accumulation in myelin	Maslinska et al., 1984
Rabbit	Administration route: unknown	16 days (from day 6 after birth)	0, 9 mg/kg/day	9 mg/kg/day: a reduction in cholinesterase activity in the cerebral vessel wall, perivascular astrocyte dysfunction and a change in vascular endothelial cells	Dambska et al., 1984
Chicken Female	Subcutaneous administration	Single administration	0, 100 mg/kg	100 mg/kg/day: slight ataxia 2 weeks after administration and severe reductions in NTE activities in peripheral nerves, spinal cord and brain In a similar study: severe reduction in brain NTE activity, slight decrease in spinal cord NTE activity, no ataxia	Caroldi & Lotti, 1981; Johnson, 1978
Chicken White leghorn Female	Oral gavage Dermal application	90 days	Oral: 0, 3-6 mg/kg/day and above Dermal: 0, 0.65, 1, 1.7, 3.3 mg/kg/day purity: 99.9%	Oral: 3-6 mg/kg/day: No ataxia or death 6 mg/kg/day and above: salvation and cholinergic symptoms spasm and death Dermal: 0.65 mg/kg/day: No ataxia or death 1 mg/kg/day and above: salvation and cholinergic symptoms spasm and death 1.7 mg/kg/day and above: ataxia	Francis et al., 1985

Species sex/number of animals	Route	Period	Dose	Results	Reference
				No organophosphate-induced delayed neuropathy (OPIDN)	
Rat Wistar Male	Subcutaneous	Single	0, 200 mg/kg	200 mg/kg: NTE activity: A significant reduction in platelet NTE activity 24 hours, 10 and 21 days after administration Significant reductions in NTE activities in the cerebrum, cerebellum and brain stem 24 hours and 21 days after administration Rotor rod test: A significant reduction in rod-holding time 21 days after administration	Sarin & Gill, 2000
Rat Wistar Male	Subcutaneous	8 weeks	0, 6 mg/kg/day	6 mg/kg: significant decreases in hemolysate acetylcholinesterase activity and platelet cytochrome oxidase activity 2 weeks after administration significant increase in acid phosphatase activity 4 weeks after administration, significant decreases in brain acetylcholinesterase, cytochrome oxidase glucose-6-phosphate dehydrogenase activities and a significant increase acid phosphatase activity in 8 weeks after administration, No significant difference in 2',3'-cyclic nucleotide phosphodiesterase	Sarin & Gill, 1998a
Rat Wistar Male	Subcutaneous	8 weeks	0, 6 mg/kg/day	6 mg/kg: significant reductions in Paraoxon (organophosphorous pesticide)-resistant carboxylesterase and acetylcholinesterase activities in the cerebral cortex, cerebellum and brain stem significant reductions in spontaneous motion and stereotype time in an open field test significant reductions in rod-holding time and active avoidance response n a rotor rod test, enhancement in aggressive behavior	Sarin & Gill, 1998b
Rat Wistar Male	Subcutaneous	Single	0, 200 mg/kg	200 mg/kg Determination 2, 7, 15 and 21 days after administration NTE activity: significant reductions in brain and platelet NTE activities 2, 7, 15 and 21 days after administration Rotor rod test: significant reduction in rod-holding time 21 days after administration Creatinine phosphokinase (CPK) activity: no significant difference Ca^{2+}/CaM-dependent protein kinase activity: significant increase from administration day 15 cAMP-dependent protein kinase activity:	Choudhary et al., 2001

Species sex/number of animals	Route	Period	Dose	Results	Reference
				significant increase from administration day 15 Calmodulin activity: significant increase from administration day 7 Cyclic-AMP concentration: significant increase on administration day 21	

7.3.5 Reproductive and developmental toxicity

Studies on reproductive and developmental toxicity of dichlorvos to experimental animals are summarized in Table 7-8.

a. Reproductive toxicity

a-1. Oral administration

In a three-generation reproduction study of dichlorvos (purity: 93%) via oral feeding at doses of 0, 0.1, 1, 10, 100 and 500 mg/kg diet (corresponding to 0, 0.0025, 0.025, 0.25, 2.5 and 12.5 mg/kg bw/day) in weanling male and female SD rats for 2 years, no abnormalities were found in pregnancy rate of maternal animals, and number of litters, body weight and survival rate of offsprings. At necropsy and histopathological examinations of F_1 and F_2 litters at 7 days of age, no abnormalities were observed at all doses (Witherup et al., 1965, 1971).

In a two-generation reproduction study of dichlorvos impregnated into polyvinyl chloride resin via oral feeding (dichlorvos concentration in diet: 0, 200, 250, 288, 400 and 500 ppm) in male and female pigs for 3 years from 6 months before mating, no abnormalities were found in number of litters, survival rate and growth of offsprings, hepatic and renal function, phosphorous and calcium in the femoral bone, hematological and histopathological examinations and urinalysis and necropsy. However, an increase in liver weight, reductions in blood and brain cholinesterase activities were observed (Collins et al., 1971).

b. Developmental toxicity

b-1. Oral administration

In an oral administration (gavage) study of dichlorvos (purity: 96%) at doses of 0, 5 and 60 mg/kg/day in female CF-1 mice from gestation day 6 to 15, no abnormalities were found in the number of viable fetus, and in the examinations of organs and skeleton (Schwetz et al., 1979).

In an oral administration (gavage) study of dichlorvos at doses of 0, 0.1, 3.0 and 21 mg/kg/day in female SD rats (25 animals/group) from gestation day 6 to 15, a decrease in water consumption, ingesting of urine, marked bedding, ear shaking, tremor, hindleg splay, vocalization, labored respiration and prone positioning were observed in maternal rats at 21 mg/kg/day. No abnormality was found in fetuses (AMVAC Chemical Corp., 1991).

In an oral administration (gavage) study of dichlorvos at doses of 0, 0.97, 1.46, 1.94 and 3.88 mg/kg/day in Wistar rats from gestation day 1 to the lactating period after delivery in maternal rats, and for

a lifetime after weanling in pups, no abnormalities were found in delivery, lactation, gestation period, delivery rate, clinical observation, and necropsy findings in maternal rats. In pups, an increase in horizontal activity and decreases in vertical activity and defecation frequency in open field test and increases in transmitting time and error frequency in T-maze test were found dose-dependently at doses of 0.97 mg/kg/day and above. A decrease in sleep score (sleep position) in open field test and reductions in brain and blood acetylcholinesterase activities were observed at doses of 0.97 mg/kg/day and above (Schulz et al., 1995). The LOAEL of this study for pups is considered to be 0.97 mg/kg/day in this assessment.

In an oral administration (gavage) study of dichlorvos in female NZW rabbits (15 to 26 animals/group, 10 groups, 168 animals in total) at doses of 0, 12 and 36 mg/kg/day from gestation day 6 to 18 or at doses of 0 and 62 mg/kg/day from gestation day 6 to 11 with 3 kinds of capsules, mortality was increased in maternal animals at 62 mg/kg/day, but, no abnormalities were found in mortality and the examinaiton of skeleton in fetuses (Carson, 1969).

In an oral administration (gavage) study of dichlorvos in rabbit newborns at a dose of 9 mg/kg/day from day 5 to 16 after birth, brain developmental disorders (myelination impairment in the callosum, reduction in plasmalogen reaction, acid phosphatase activity in glial cells and acetylcholinesterase activity in whole brain area) were found (Dambska and Maslinska, 1982).

b-2. Inhalation exposure

In an inhalation exposure study of dichlorvos in female Carworth E rats (15 animals/group) at concentrations of 0, 0.25, 1.25 and 6.25 mg/m^3 (actual concentrations: 0, 0.03, 0.14 and 0.69 ppm) from gestation day 1 to 20 for 23 hours/day, 7 days/week, the brain and RBC cholinesterase activities were significantly reduced in the maternal animals at 6.25 mg/m^3. No abnormalities were found in the numbers of dead embryos/fetuses and viable fetuses, and body weight, appearance, organs and skeleton of fetuses (Thorpe et al., 1972). In an inhalation exposure study of dichlorvos in female Dutch rabbits (20 animals/group) at concentrations of 0, 0.25, 1.25, 2 and 4 mg/m^3 (0, 0.03, 0.14, 0.22 and 0.44 ppm) from gestation day 1 to 28 for 23 hours/day, 7 days/week, the plasma, RBC and brain cholinesterase activities were significantly reduced in the maternal animals at doses of 1.25 mg/m^3 and above. The maternal death (6/20) and a significant decrease in body weight of the pups were found at 4 mg/m^3. No differences in the numbers of dead embryos/fetuses and viable fetuses, and body weight of the pups were found between the exposure and control groups. No abnormality was observed in the examinaitons of the organs and skeleton. Two dead fetuses of one maternal animal developed cleft palate. However, it was not considered as a sympton of developmental toxicity but due to the toxic effect of the maternal animal (Thorpe et al., 1972).

In an inhalation exposure study of dichlorvos in female NZW rabbits at a concentration of 4.06 mg/m^3 (0.44 ppm) from gestation day 6 to 18 for 7 hours/day, no abnormalities were found in the numbers of dead embryos/fetuses and viable fetuses, the incidence or distribution of resorptions, the body weight of viable fetuses, and no malformation was observed (Schwetz et al., 1979).

c. Summary of reproductive and developmental toxicity

Regarding reproductive toxicity, in a three-generation reproduction study of dichlorvos via oral feeding at doses of 0.0025 to 12.5 mg/kg/day in male and female rats, no abnormalities were found in pregnancy rate, the number of litters, and the body weight and survival rate of offsprings. Furthermore, at necropsy and histopathological examination of F_1 and F_2 litters at 7 days of age, no abnormalities were observed.

Regarding developmental toxicity, in an oral administation (gavage) study of dichlorvos at doses of 0.97 to 3.88 mg/kg/day in rats from gestation day 1 to the lactating period after delivery in maternal rats and for a lifetime after weanling in pups, no abnormalities were found in maternal rats, while in the pups at doses of 0.97 mg/kg/day and above, dose-dependent abnormal behaviors were observed in open field and T-maze tests. The LOAEL for pups is considered to be 0.97 mg/kg/day. In inhalation exposure studies, significant reductions in brain and RBC cholinesterase activities were found in the maternal animals at doses of 1.25 mg/m^3 and above, but no effects in the pups were observed.

These results show that dichlorvos has no reproductive toxicity and teratogenicity but suggests that it has developmental toxicity.

Table 7-8 Reproductive and developmental toxicity of dichlorvos

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Reproductive toxicity					
Rat SD Male and female 30/group)	Reproduction study (3 generation) Oral (fed)	2 years	0, 0.1, 1, 10, 100, 500 mg/kg diet (corresponding to 0, 0.0025, 0.025, 0.25, 2.5, 12.5 mg/kg/day)	500 mg/kg and above: Dams: No abnormality in pregnancy rate or number of litters F_1 and F_2: No abnormality in body weight and survival rate of offsprings, and necropsy and histopathological examination at 7 days of age	Witherup et al., 1965, 1971
Rat Male and female	Reproduction study (3 generation) Oral (fed)	Unknown	0, 500 mg/kg diet and above	500 mg/kg: No abnormality in fertility of the maternal animals and growth of offsprings	Witherup et al., 1971
Pig Male and female	Reproduction study (2 generation) Oral (fed)	3 years from 6 months before mating	Dichlorvos impregnated into polyvinyl chloride resin (dichlorvos concentration in diet: 0, 200, 250, 288, 400 and 500 ppm)	Dams: No abnormality in the number of litters Fetus: No abnormality in survival rate and growth No abnormality in hepatic and renal function, phosphorous and calcium in the femoral bone, hematological and histopathological examinations and urinalysis An increase in liver weight, reduction in blood and brain cholinesterase activities	Collins et al., 1971

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Pig Male and female	Oral (fed)	37 months	0, 500 mg/kg diet	No reproductive toxicity	Collins et al., 1971
Developmental toxicity					
Mouse CF-1 Female	Oral gavage	Gestation day 6-15	0, 5, 60 mg/kg/day	Fetus: No abnormality in the number of viable fetuses, and organs and skeleton	Schwetz et al., 1979
Rat SD Female 25/group	Oral gavage	Gestation day 6-15	0, 0.1, 3.0, 21 mg/kg/day	21 mg/kg/day: Dams: A decrease in water consumption, ingesting of urine, marked bedding, ear shaking, tremor, hindleg splay, vocalization, labored respiration and prone positioning Fetus: No toxicity	AMVAC Chemical Corp., 1991
Rat Female	Oral gavage	Gestation day 8-15	0, 25 mg/kg/day	25 mg/kg/day: Dams: No description Fetus: Slight body weight loss No abnormality in organs and skeleton	Baksi, 1978
Rat Wistar Female	Oral gavage	From gestation day 1 to the lactating period after delivery (maternal animals), for a lifetime after weanling (newborns)	0, 0.97, 1.46, 1.94, 3.88 mg/kg/day	0.97 mg/kg/day and above: Dams: No abnormality was found in delivery, lactation, gestation period, delivery rate, general conditions, and necropsy results Fetus: Open field test Dose-dependent increase in horizontal activity and decreases in vertical activity and defecation frequency, and sleep score T-maze test Dose-dependent increases in transmitting time and error frequency Acetylcholinesterase activity Reduction in brain and blood acetylcholinesterase activity LOAEL for pups: 0.97 mg/kg/day (in this assessment)	Schulz et al., 1995
Rabbit NZW Female 10 groups 15-26/group 168 (total)	Oral gavage (3 different PVC placebo capsule)	Gestation day 6-18 0, 12, 36 mg/kg/day Gestation day 6-11: 62 mg/kg/day	0, 12, 36, 62 mg/kg/day (twice/day at doses of 15, 54, 93 mg/animal)	62 mg/kg/day: Dams: increase in mortality Pups no abnormality in skeleton	Carson, 1969

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Rabbit	Oral gavage	5-16 days	0, 9 mg/kg/day	9 mg/kg/day: Brain developmental disorders (myelination impairment in the callosum, reduction in plasmalogen reaction, acid phosphatase activity in glial cells and acetylcholinesterase activity in whole brain area)	Dambska & Maslinska, 1982
Rabbit NZW Female	Oral gavage	Organogenesis stage	0, 12, 34 mg/kg/day (PVC pellet)	Dams: 34 mg/kg/day; Toxic Pups: 12 mg/kg/day and above; No anomaly in major organs	Vogin et al., 1971
Rabbit NZW Female	Oral gavage	Gestation day 6-18	0, 5, 60 mg/kg/day (purity: 96%)	(No description of doses) No abnormality in the number of absorbed embryos and survival fetuses, body weight and organs and skeleton	Schwetz et al., 1979
Pig Female	Oral (fed)	From 21 days before mating to whole gestation period	0, 800 mg/animal (9% resin pellet)	Dams: No description Pups: No abnormality in the number of litters, body weigh of pups, number of viable or dead fetuses, weanling fetuses and body weight in weaning	Bazer et al., 1969
Pig Female	Oral (fed)	Before delivery 21-30 days	0, 4-13 mg/kg diet (resin pellet)	Dams: No description Pups: Dose-dependent increase in body weight	Bunding et al., 1972
Pig Female	Oral (fed)	30 days before delivery	0, 5, 25 mg/kg diet (pellet)	Dams: 5 mg/kg and above; Reduction in RBC, brain and myometrial acetylcholinesterase activities 25 mg/kg and above; Plasma and RBC cholinesterase activities were reduced to 80% and 90%, respectively. Fetus: Increase in hindbrain acetylcholinesterase activity	Stanton, et al., 1979
Pig Female 3 animals	Oral (fed)	Gestation day 41-70	0, 8.5 mg/kg diet	Dams: reduction in blood cholinesterase activity Pups: No abnormality	Wrathall et al., 1980
Mouse CF-1 Female	Oral gavage +inhalation exposure	Gestation day 6-15	Oral: maximum tolerated dose (no detailed description) Inhalation: 0, 4 mg/m^3	Dams: No description Pups: No abnormality	Schwetz et al., 1979

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Rabbit NZW Female	Oral gavage +inhalation exposure	Gestation day 6-18	Oral: 0, 5, 60 mg/kg/day Inhalation: 0, 4 mg/m^3	Dams: No description Pups: No abnormality	Schwetz et al., 1979
Mouse CF-1 Female	Inhalation exposure	Gestation day 6-15 7 hours/day Caesarian section on gestation day 18	0, 4.06 mg/m^3 (0, 0.44 ppm)	Dams: No description Fetus: No abnormality in the number of fetuses and body weight	Schwetz et al., 1979
Rat Carworth E Female 15/group	Inhalation exposure	Gestation day 1-20 23 hours/day 7 days/week Caesarian section on gestation day 20	0, 0.25, 1.25, 6.25 mg/m^3 (0, 0.03, 0.14, 0.69 ppm)	Dams: 6.25 mg/m^3; Significant reduction in brain and RBC acetylcholinesterase activities Fetus: No abnormality in the number of dead embryos/fetuses and viable fetuses, body weight, appearance, organs and skeleton	Thorpe et al., 1972
Rabbit Dutch Female 20/group	Inhalation exposure	Gestation day 1-28 23 hours/day 7 days/week	0, 0.25, 1.25, 2, 4 mg/m^3 (0, 0.03, 0.14, 0.22, 0.44 ppm)	Dams: 1.25 mg/m^3 and above; Significant reduction in plasma, RBC and brain cholinesterase activities 4 mg/m^3; 6/20 died Fetus: No abnormality in the number of viable and dead fetuses 4 mg/m^3; Significant decrease in pup body weight (toxicity on maternal animals) Two dead fetuses of the same material animal (cleft palate due to toxicity on the maternal animal)	Thorpe et al., 1972
Rabbit NZW Female	Inhalation exposure	Gestation day 6-18 7 hours/day Caesarian section on gestation day 14 for control and 19 for the treated	0, 4.06 mg/m^3 (0, 0.44 ppm)	Dams: No description Fetus: No abnormality in the numbers of dead embryos/fetuses and viablel fetuses, and the site and body weight of the viable fetuses	Schwetz et al., 1979

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Rabbit Dutch Female	Inhalation exposure	From mating to delivery 23 hours/day 7 days/week	0, 0.25, 1.25, 2, 4, 6.25 mg/m^3	Dams: Death at concentrations of 2 mg/ m^3 and above Dose-dependent reductions in plasma, RBC and brain acetylcholinesterase activities Fetus: No abnormality in the numbers of dead embryos/fetuses and viable fetuses, and body weight	Thorpe et al., 1972
Rat Sherman Female	Intraperitoneal	Single on gestation day 11	0, 15 mg/kg	Dams: Fetus: No abnormality in the numbers of fetuses, dead embryos/fetuses, and fetus body weight, omphalocele in 3/41	Kimbrough & Gaines, 1968

7.3.6 Genotoxicity

Studies on genotoxicity of dichlorvos are summarized in Table 7-9 and summary of these data is shown in Table 7-10.

a. *in vitro* studies

a-1. Mutation

Dichlorvos showed positive results in many reverse mutation assays in *Salmonella typhimurium* without metabolic activation (Hanna and Dyer, 1975; Moriya et al., 1978,1983; Shirasu et al., 1976). Also in studies with *Escherichia coli* WP2 *uvr*A (Hanna and Dyer, 1975) and WP2 *hcr* (Moriya et al., 1983) without metabolic activation, and *E. coli* B/r (Moriya et al., 1978) with/without metabolic activation, positive results were observed.

In a forward mutation assay of dichlorvos with streptomycin-sensitive *Escherichia coli* B strain at doses of 5 to 25 mmol/L for 1 to 10 hours, increases of mutation frequency were observed dose- and time-dependently (Wild, 1973,1975).

In a study with *Escherichia coli* WP2 strain, dichlorvos induced mutation at a dose of 5 mg/L (Green et al., 1976). However, in a study with Chinese hamster V79 cells, dichlorvos did not induce resistance mutation up to 1 mmol/L for 8-azaguanine and from 1.25 to 5 mmol/L for ouabain (Aquilina et al., 1984).

a-2. Chromosal aberration

In a study in human lymphocytes treated with dichlorvos at doses of 1 to 40 mg/L at a specified interval, cytotoxicity was observed at 5 mg/L and above, but chromosomal aberration was not detected (Dean, 1972b).

a-3. DNA damage

Dichlorvos was confirmed to bind to bovine thymus DNA *in vitro* (Lofroth, 1970; Segerback, 1981).

In DNA damage tests with *Escherichia coli*, dichlorvos showed positive results in DNA polymerase+ (*pol*A^+) strains at doses of 0.5 to 2 mg/mL and DNA polymerase- (*pol*A^-) strains at a dose of 6.4 mg/mL (Rosenkranz, 1973; Rosenkranz and Leifer, 1980), and in a study with Chinese hamster V79 cells without metabolic activation, DNA strand breaks were observed at a concentration of 0.2 (v/v) % (Green et al., 1974a). In a study with human epithelioid EUE cells at doses of 6.5 to 650 mmol/L, dichlorvos induced a dose-dependent unscheduled DNA synthesis (Aquilina et al., 1984; Benigni and Dogliotti, 1980a, b). However, in a study with human kidney T cells without metabolic activation at doses of 0.0001 to 1 mmol/L, DNA strand break was not observed (Bootsma et al., 1971).

In *rec* assays, dichlorvos induced base pair substitution and other DNA damage to *Proteus*, PG713 (rec^-) and PG273 (rec^+) at doses of 10 and 40 μmol/plate (Adler et al., 1976; Braun et al., 1982), and also in *Bacillus subtilis,* H17 (rec^+) and M45 (rec^-), dichlorvos showed positive results without metabolic activation (Shirasu et al., 1976).

In sister chromatid exchange tests in Chinese hamster ovarian (CHO) cells (Nishio and Uyeki, 1981) and Chinese hamster V79 cells (Tezuka et al., 1980), dichlorvos showed positive results without metabolic activation at doses on 0.03 and 0.1 mmol/L in the former study and 0.2 and 0.5 mmol/L in the latter study. In the latter study, an increase in polyploidy cells was observed at doses of 0.1 to 0.5 mmol/L (Tezuka et al., 1980). However, in a sister chromatid exchange study with human lymphocytes and fetal lung fibroblasts treated for 72 hours at doses of 2.5 to 10 mg/L, dichlorvos had no definite effect on sister chromatid exchange frequency (Nicholas et al., 1978).

a-4. Others

In a study with yearst *Saccharomyces cerevisiae* D4, dichlorvos induced dose-dependent gene conversions at concentrations of 5 to 40 mM without metabolic activation (Dean et al., 1972; Fahrig, 1973). In a cell transformation assay with Syrian hamstaer SA7 fetal cells, a significant increase in cell transformation frequency was observed at concentrations of 0.11 mmol/L and above (Hatch et al., 1986).

b. *in vivo* studies

b-1. Mutation

Host-mediated studies of dichlorvos were conducted in NMRI mice as follows: 1) an intraperitoneal study using *Salmonella typhimurium* (G46 his^-) and *Serratia bacterium* (a 21 leu^-) as indicators at a dose of 25 mg/kg (Buselmaier et al., 1972, 1973), 2) an oral study using *Salmonella typhimurium* (64-320) as indicator at a dose of 0.2 mg/animal (corresponding to 8 to 10 mg/kg) (Voogd et al., 1972), 3) an oral administration study using yeast D4 as indicator at doses of 50 and 100 mg/kg (Dean et al., 1972), and 4) a 5-hour inhalation exposure study with CF-1 mice using yeast D4 as indicator at a dose of 90 mg/m^3 (Dean et al., 1972). In all studies, dichlorvos did not induce mutations.

In an oral feeding study of dichlorvos at doses of 0.009, 0.048 and 0.09 mg/kg diet in *Drosophila melanogaster* (Kramers and Knaap, 1978) and inhalation exposure studies at concentrations of 0.0006 to

0.6 μmol (Sobels and Todd, 1979) and 0.035% (Jayasuriya and Ratnayake, 1973), no sex-linked recessive lethal mutation was observed.

In a multi-generation oral feeding study of dichlorvos at step concentrations (increased up to 0.75 mg/kg diet) in *Drosophila melanogaster* approximately for 18 months, autosomal lethal mutation frequency was increased (Hanna and Dyer, 1975). However, the validity of this test system itself has not yet been sufficiently confirmed (IARC, 1991).

b-2. Chromosal aberration

In an oral feeding study of dichlorvos at doses of 1 to 50 mg/kg diet in female *Drosophila melanogaster*, egg laying was not observed at doses of 10 mg/kg and above and the survival rate of eggs at 1 mg/kg was 45%. In a chromosome test in larva of *Drosophila melanogaster*, chromosomal aberration was found in the salivary gland at 1 mg/kg (Gupta and Singh, 1974).

No chromosomal aberration was observed in all of the following chromosomal aberration tests using mice, i.e., 1) a 7-week oral (via drinking water) study of dichlorvos in male Q mice at a dose of 2 mg/L (corresponding to 0.32 mg/kg/day) 5 days/week to examine chromosomes of the bone marrow, spermatogonia and spermatocytes (Degraeve et al., 1982,1984a; Moutschen-Dahmen et al., 1981), 2) a single intraperitoneal administrartion study in the same series mice at a dose of 10 mg/kg (Degraeve et al., 1984b; Moutschen-Dahmen et al., 1981), 3) a 21-day inhalation exposure study in male CF-1 mice at doses of 64 to 72 mg/m^3 for 16 hours/day or at a dose of 5 mg/m^3 for 23 hours/day to examine chromosomes of the bone marrow and spermatocytes (Dean and Thorpe, 1972a), and 4) a 2-day intraperitoneal study in Swiss mice at doses of 0.0075 nad 0.015 mg/kg/day to examine chromosomes of the bone marrow when sacrificed 6 hours after the last administration (Paik and Lee, 1977).

Of chromosomal aberration tests using hamsters, a 16-hour inhalation exposure study of dichlorvos in male Chinese hamsters at doses of 28 to 36 mg/m^3 and an oral administration study at a single dose of 15 mg/kg for males and 10 mg/kg for females showed no aberration (Dean and Thorpe, 1972a), while an intraperitoneal study in Syrian hamsters at doses of 3, 6, 15 and 30 mg/kg revealed a significant increase in aberration in the bone marrow (Dzwonkowska and Hubner, 1986).

In a micronucleus test of dichlorvos in Swiss mice at intraperitoneal doses of 0.0075 and 0.0015 mg/kg/day for 2 days, the incidence of micronucleus in the bone marrow cells was not increased (Dean and Thorpe, 1972).

No dominant lethal effect was observed in all of the following dominant lethal tests, i.e., 1) a single intraperitoneal administration study of dichlorvos at doses of 13 and 16.5 mg/kg and a 5-day oral administration study at doses of 5 and 10 mg/kg/day in ICR mice (Epstein et al., 1972), 2) a 7-week oral administration (via drinking water) study in male Q mice at a does of 2 mg/L (corresponding to 0.32 mg/kg/day) 5 days/week (Degraeve et al., 1982,1984a), 3) an oral administration study at single doses of 25 and 50 mg/kg and an inhalation exposure study at a concentration of 28 mg/m^3 until 11 weeks after weaning in female CF-1 mice which were mated at intervals of 5, 10 and 15 days (Dean and Blair, 1976), and 4) a 4-week inhalation exposure study in male CF-1 mice at concentrations of 30 and 55 mg/m^3 (3.3 and 6.1 ppm) for 16 hours 2.1 and 5.8 mg/m^3 for 23 hours/day (Dean and Thorpe, 1972b). However, in an

intraperitoneal administration study of dichlorvos in male Q mice at a single dose of 10 mg/kg, significant increases in the number of absorbed embryos before implantation were found at 2 and 5 weeks after mating (Degraeve et al., 1980; Moutschen-Dahmen et al., 1981).

In a DNA-binding assay in mice (Segerback, 1981) and rats (Wooder et al., 1977), dichlorvos showed negative results.

Wooder and Creedy (1979) showed in a single intraperitoneal administration study of dichlorvos in rats at a dose of 10 mg/kg that liver DNA was not damaged by dichlorvos (IPCS, 1989).

In a sister chromatid exchange test of dichlorvos with peripheral blood lymphocytes in male $B6C3F_1$ mice at intraperitoneal doses of 5, 15, 25 and 35 mg/kg, dichlorvos had no effect on sister chromatid exchange frequency (Klingerman et al., 1985).

c. DNA methylation

Dichlorvos is a phosphorylation reagent and an alkylating reagent (Wright et al., 1979). 4- Nitrobenzyl pyridine of typical nucleophilic reagents is methylated by dichlorvos but not by metabolites of dichlorvos (Bedford and Robinson, 1972). Phosphorus atom of dichlorvos is severely short of electrons, therefore, it is more vulnerable to nucleophilic reagents than carbon atom of methyl-group. DNA methylation activity of dichlorvos is reduced by the following two factors. The first factor is that mammal tissues (plasma, liver, etc.) have esterase Type A, which hydrolyzes phosphate and rapidly reduces concentrations of circulating toxic substances. The second factor is the fact that reaction rate of phosphate with acetylcholinesterase is several orders of magnitude greater than alkylation reaction to 4-nitrobenzyl pyridine, in case of dichlorvos, the rate ratio is 1×10^7 and desirable for phosphorylation of acetylcholinesterase (Aldridge and Johnson, 1977). Based on the above, in low exposure concentrations, *in vivo* methylation of DNA purine base by dichlorvos plays less important role compared with phosphorylation of acetylcholinesterase and other esterases and is negligible (Wooder et al., 1977; Wright et al., 1979).

Lawley et al. (1974) reported methylation of DNA and RNA by dichlorvos in a study with extracted nucleic acids and *Escherichia coli.* As a result of the study, 3-methyladenine, an important product of DNA methylation in *Escherichia coli* was not detected, however, in use of extracted DNA, 3-methyladenine was detected. In *Escherichia coil*, methylation level was low, suggesting a specific elimination of 3-methyladenine (IPCS, 1989).

In DNA and RNA extracted from *Escherichia coli* exposed to ^{3}H-dichlorvos, ^{3}H-labeled 7-methylguanine existed. Methylation activity of dichlorvos is low and 1/10 to 1/100 of mutagens with high methylation activity (Wennerberg and Lofroth, 1974).

In an intraperitoneal administration study of [methyl-^{14}C]-dichlorvos in mice at a dose of 1.9 μmol/kg (0.42 mg/kg), the methylation level at the *N-7* site of guanine in DNA that was extracted from soft tissues was 8×10^{-13} mol methyl/g DNA (Segerback, 1981; Segerback and Ehrenberg, 1981).

In a 12-hour inhalation exposure study of [methyl-^{14}C]-dichlorvos in male CFE rats at a concentration of 0.064 mg/m^3, methylation was not detected at the *N-7* site of guanine in DNA that was extracted from the lung, liver, heart, brain, testis and spleen and DNA and RNA from soft tissues (Wooder et al., 1977; Wooder

and Wright, 1981).

d. Summary of genoxicity

Dichlorvos is electron-withdrawing and has DNA methylation activity. Dichlorvos binds to DNA *in vitro* and induces DNA damage in microorganisms and mammalian cells. In many studies with microorganisms, dichlorvos induces mutations. However, dichlorvos showed negative results in *in vivo* DNA-binding assay, chromosomal aberration and dominant lethal tests. It is considered that dichlorvos is rapidly metabolized by type-A esterase *in vivo*. As the phosphate group is more electron-withdrawing than the methyl group and dichlorvos reacts to serum cholinesterase and acetylcholinesterase more than DNA in the blood and tissues, dichlorvos is not likely to induce genotoxicity *in vivo*. Therefore , dichlorvos shows *in vitro* genotoxicity without metabolic activation but seldom exhibit *in vivo* genotoxicity.

Table 7-9 Genotoxicity of dimethyl-2,2-dichlorovinyl phosphate

Test system		Species (Organisms) / Strain	Experimental condition	Concentration / Dose	Results[1)] -S9	Results[1)] +S9	Reference
in vitro	Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1536, TA1537, TA1538	Plate incorporation	20, 40 mmol	-	+	Braun et al., 1982
		Salmonella typhimurium TA98, TA100, TA1535, TA1536, TA1537, TA1538	Plate incorporation	5,000 μg/plate	+	ND	Moriya et al., 1983
		Salmonella typhimurium TA1535	Plate incorporation	5% solution 0.1 mL	+	-	Moriya et al., 1978
		Salmonella typhimurium TA1530, TA1535, LT2 his C117, his G46	Plate incorporation	5 μL	+	ND	Hanna & Dyer, 1975
		Salmonella typhimurium TA1535, TA1536, TA1537, TA1538	Plate incorporation	5% solution 0.1 mL	+	ND	Shirasu et al., 1976
		Escherichia coli WP2	Plate incorporation		-	ND	Dean, 1972a
		Escherichia coli WP2 uvrA	Plate incorporation	5 μL	+	ND	Hanna & Dyer, 1975
		Escherichia coli WP2 hcr	Plate incorporation	5,000 μg/plate	+	ND	Moriya et al., 1983
		Escherichia coli B/r	Plate incorporation	22.6 mmol/L	+	+	Moriya et al., 1978
		Escherichia coli B Sd-4 (streptomycin-independence)			+		Lofroth et al., 1969
	Forward mutation	*Escherichia coli* B (streptomycin-resistance)		5-25 mmol/L 1-10 hours	W+ (time- and concentration-dependent increase)	ND	Wild, 1973,1975
		Escherichia coli WP2		5 mg/L	+		Green et al., 1976
		Saccharomyces cerevisiae ade6	Plate incorporation	1.5-14 mmol	ND	+	Gilot-Delhalle et al., 1983

Test system		Species (Organisms) / Strain	Experimental condition	Concentration / Dose	Results[1)] -S9 +S9	Reference
		Chinese hamster CHO cells V79 cells		1mmol/L (8-azaguanine-resistance) 1.25-5mmol/L (ouabain-resistance)	- -	Aquilina et al., 1984
	rec assay	*Bacillus subtilis* H17rec$^+$, M45rec$^-$		10% solution 0.02 mL	+ ND	Shirasu et al., 1976
		Proteus mirabilis PG713(rec$^-$), PG273(rec$^+$)		10, 40 µmol/plate	+	Adler et al., 1976; Braun et al., 1982
	Chromosomal aberration	Human lymphocytes		1-40 mg/L	-	Dean, 1972b
	Gene conversion	*Saccharomyces cerevisiae* D4	Plate incorporation	5-40 mmol/L	+ ND (concentration-dependent increase)	Dean et al., 1972; Fahrig, 1973
	Cell transformation	Syrian hamster SA7 embryo cells		0.05-0.45 mmol/L	+ ND	Hatch et al., 1986
	Sister chromatid exchange (SCE)	CHO cells		0.03, 0.1 mmol/L	+ ND	Nishio & Uyeki, 1981
		Chinese hamster V79 cells		0.2, 0.5 mmol/L	+ ND	Tezuka et al., 1980
		Mouse lymphocytes			- ND	Klingerman et al., 1985
		Human lymphocytes, embryo lung fibroblasts cells treatment		2.5-10 mg/L 72 hours	-	Nicholas et al., 1978
	DNA damage	*Escherichia coli* (DNA strand break)		*pol*A$^+$: 0.5-2 mg/mL *pol*A: 6.4 mmol/L	+	Rosenkranz, 1973; Rosenkranz & Leifer, 1980
		Chinese hamster V79cells (DNA strand break)		0.2 (v/v)%	+ ND	Green et al., 1974a
		Human EUE cells (Unscheduled DNA synthesis)		6.5-650 mmol/L	+ ND (concentration-dependent increase)	Aquilina et al., 1984; Benigni & Dogliotti, 1980a,b
		Human kidney T-cells (single-strand break)		0.0001-1 mmol/L, 1-4 hours	- ND	Bootsma et al., 1971
	DNA binding	Calf thymus			+	Lofroth, 1970; Segerback, 1981
in vivo	Mutation (host-mediated assay)	Indicator organism: *Salmonella typhimurium* G46 his$^-$, *Serratia marcescens* a 21 leu$^-$ Host: NMRI Mouse	Intraperitoneal injection	25 mg/kg	-	Buselmaier et al., 1972, 1973

Test system		Species (Organisms) / Strain	Experimental condition	Concentration / Dose	Results[1)] -S9 +S9	Reference
		Indicator organism: *Salmonella typhimurium* (64-320) Host: NMRI Mouse	Oral administration	0.2 mg/animal (equivalent to 8-10 mg/kg)	-	Voogd et al., 1972
		Indicator organism: *Saccharomyces cerevisiae* D4 Host: NMRI Mouse	Oral administration	50, 100 mg/kg	-	Dean et al., 1972
		Indicator organism: *Saccharomyces cerevisiae* D4 Host: CF-1 Mouse	Inhalation exposure	90 mg/m^3 5 hours	-	Dean et al., 1972
	Sex-linked recessive lethal	*Drosophila melanogaster*	Oral administration (fed)	0.009, 0.048, 0.09 mg/kg diet	-	Kramers & Knaap, 1978
		Drosophila melanogaster	Inhalation exposure	0.035%	-	Jayasuriya & Ratnayake, 1973
		Drosophila melanogaster	Inhalation exposure	0.0006-0.6 μmol	-	Sobels & Todd, 1979
	Autosomal lethal	*Drosophila melanogaster* (multigeneration)	Oral administration (fed)	Gradually increasing concentrations of dichlorvos in the food medium (up to 0.75 mg/kg food) for about 18 months 18 months	+ The results of this study are not directly comparable with those from standard recessive lethal tests.	Hanna & Dyer, 1975
	Chromosomal aberration	*Drosophila melanogaster* Female (larvae)	Oral administration (fed)	1-50 mg/kg diet	+ (1 mg/kg diet) equivocal	Gupta & Singh, 1974
		Male Q Mouse (bone marrow, spermatogonia , primary spermatocyte)	Oral administration (via drinking water)	7 weeks (5 days/week) 2 mg/L (equivalent to 0.32 mg/kg/day)	-	Degraeve et al., 1982, 1984a; Moutschen-Dahmen et al., 1981
		Male Q mouse	Single intraperitoneal injection	10 mg/kg	-	Degraeve et al., 1984b; Moutschen-Dahmen et al., 1981
		Female and male Chinese hamster	Single oral administration	15 mg/kg (male) 10 mg/kg (female)	-	Dean & Thorpe, 1972a

Test system		Species (Organisms) / Strain	Experimental condition	Concentration / Dose	Results[1)] -S9 +S9	Reference
		Male CF-1 mouse (bone marrow, spermatocyte)	Inhalation exposure	64-72 mg/m^3, 16 hours or 5 mg/m^3, 21 days (23 hours/day)	-	Dean & Thorpe, 1972a
		Male Chinese hamster	Inhalation exposure	28-36 mg/m^3 (16 hours)	-	Dean & Thorpe, 1972a
		Swiss mouse (bone marrow)	Intraperitoneal injection	0.0075, 0.015 mg/kg/day 2 days	-	Paik & Lee, 1977
		Syrian hamster (bone marrow)	Intraperitoneal injection	3, 6, 15, 30 mg/kg	+	Dzwonkowska & Hubner, 1986
	Micronucleus	Male Swiss mouse (bone marrow)	Intraperitoneal injection	0.0075, 0.015 mg/kg/day 2 days	-	Dean & Thorpe, 1972
	Dominant lethal	ICR mouse	Oral administration	5, 10 mg/kg/day 5 days	-	Epstein et al., 1972
		ICR mouse	Single intraperitoneal injection	13, 16.5 mg/kg	-	Epstein et al., 1972
		Male Q mouse	Oral administration (via drinking water)	7 weeks (5 days/week) 2 mg/L (equivalent to 0.32 mg/kg)	-	Degraeve et al., 1982, 1984a
		Female CF-1 mouse	Single oral administration	25, 50 mg/kg	-	Dean & Blair, 1976
		Female CF-1 mouse	Inhalation exposure	28 mg/m^3 (from weaning until 11weeks)	-	Dean & Blair, 1976
		Male CF-1 mouse	Inhalation exposure	30, 55 mg/m^3 (3.3, 6.1 ppm) 16 hours	-	Dean & Thorpe, 1972b
		Male CF-1 mouse	Inhalation exposure	2.1, 5.8 mg/m^3 4weeks (23 hours / day)	-	Dean & Thorpe, 1972b

Test system		Species (Organisms) / Strain	Experimental condition	Concentration / Dose	Results[1)] -S9 +S9	Reference
		Male Q mouse	Single intraperitoneal injection	10 mg/kg	+	Degraeve et al., 1980; Moutschen-Dahmen et al., 1981
	Sister chromatid exchange (SCE)	Male $B6C3F_1$ mouse (Human peripheral lymphocytes)	Intraperitoneal injection	5, 15, 25, 35 mg/kg	-	Klingerman et al., 1985
	DNA binding	Mouse			-	Segerback, 1981
		Rat			-	Wooder et al., 1977
	DNA damage	Rat (liver)	Single intraperitoneal injection	10 mg/kg	-	Wooder & Creedy, 1979

1) +: Positive; -: Negative; w+: Weak positive; ND: No data available

2) CHO cells: Chinese hamster ovary cells.

Table 7-10 Genotoxicity of dichlorvos (Summary)

	Mutation	Chromosomal aberration	DNA damage
Bacteria	+	ND	+
Mold / Yeast/Plant	ND	ND	ND
Insects	-	+/-	ND
Culture cells	-	-	+
Mammals (*in vivo*)	ND	+/-	-

+: Positive; -: Negative; ND: No data available; +/-: equivocal

7.3.7 Carcinogenicity

Studies on carcinogenicity of dichlorvos are summarized in Table 7-11.

a. Oral administration

In a 103-week oral administration (gavage) study of dichlorvos (purity: 99%) dissolved in corn oil in male and female $B6C3F_1$ mice (8 week old, 50 animals/sex/group) at doses of 0, 10 and 20 mg/kg/day for males and 0, 20 and 40 mg/kg/day for females 5 days/week, increased incidence of forestomach papilloma was observed dose-relatedly in males (control: 1/50, 10 mg/kg/day: 1/50, 20 mg/kg/day: 5/50) and females (control: 5/49, 20 mg/kg/day: 6/49, 40 mg/kg/day: 18/50). In females, the incidence of forestomach papilloma of the 40 mg/kg/day-treated group was significantly higher than that of the control group (p=0.004) and 2 of 50 animals developed squamous carcinoma. Dichlorvos had no effect on the survival rate (U.S. NTP, 1989).

In a 103-week oral administration (gavage) study of dichlorvos (purity: 99%) in male and female F344 rats (7 week old, 50 animals/sex/group) at doses of 0, 4 and 8 mg/kg/day for 5 days/week, in males, pancreas acinar cell adenoma was observed in 16/50, 25/49 and 30/50 and monocytic leukemia in 11/50, 20/50 and 21/50 animals at doses of 0, 4 and 8 mg/kg/day, respectively, indicating significant

dose-relatedly increases. In addition, alveolar/bronchial adenoma was observed in 3/49 males at 8 mg/kg/day (control: 0/50), but no significant difference was found. In contrast, in females, the incidences of breast fibroma and fibroadenoma were significantly increased (control: 9/50, 4 mg/kg/day: 19/50, 8 mg/kg/day: 17/50). The incidences of total breast tumor (fibroma, fibroadenoma and carcinoma) were 11/50, 20/50 and 17/50 at doses of 0, 4 and 8 mg/kg/day, respectively. The incidence at 4 mg/kg/day was significant, but no dose-dependency was observed (U.S. NTP, 1989).

b. Inhalation exposure

In a 104-week inhalation exposure study of industrial dichlorvos (purity: 97% and above) in male and female CFE rats (5 week old, 50 animals/sex/group) at concentrations of 0, 0.05, 0.5 and 5 mg/m^3, suppression of body weight gain was observed in all exposure groups, but no significant increase in tumor incidence was observed. The survival rates at concentrations of 0, 0.05, 0.5 and 5 mg/m^3 were 11/50, 21/50, 15/50 and 32/50 in the 99 to 102-week exposed male groups and 22/47, 27/47, 26/47 and 34/47 in the 104-week exposerd female groups, respectively. In the study, the percentages of animals that underwent necropsy and histopathological examination were 20% to 32% of the surviving males and 22% to 38% of the surviving females (Blair et al., 1976) and the number of animals examined was small (IARC, 1991).

Other several studies reported carcinogenicity of dichlorvos by inhalation exposure, however, the data are not sufficient to evaluate carcinogenicity of dichlorvos due to the issues inclding low survival rates, a small number of tissues histopathologically examined, and histolysis (IARC, 1991; U.S.EPA, 2003).

c. Summary of carcinogenicity

Regarding carcinogenicity of dichlorvos, a significant increase in forestomach papilloma was found in B6C3F$_1$ mice at 40 mg/kg/day via oral route and monocytic leukemia and pancreas acinar cell adenoma were increased dose-dependently in male F344 rats at doses of 4 mg/kg/day and above. Similarly breast fibroma and fibroadenoma were significantly increased in females at doses of 4 mg/kg/day and above. Regarding carcinogenicity via inhalation route, no studies reliable enough for evaluation were available. Based on the data summarized above, dichlorvos is considered to be carcinogenic to esxperimental animals.

The evaluations of carcinogenicity of dichlorvos by the international and national organizations is shown in Table 7-12. The IARC has categorized dichlorvos as Group 2B (the agent is possibly carcinogenic to humans). The U.S. EPA classified dichlorvos in Group B2 (probable human carcinogen) in the IRIS and Group C (possible human carcinogen) in the Cancer Assessment Document, and estimated the oral slope factor for dichlorvos as 2.9×10^{-1}/(mg/kg)/day and the drinking water unit risk as 8.3×10^{-6}/μg/L based on the results of the oral administration studies in mice and rats (U.S. EPA, 2000,2003).

Table 7-11 Carcinogenicity of dichlorvos

Species	Test method Route	Period	Dose	Results				Reference
$B6C3F_1$ mouse Male and female 50/sex/ group 8 weeks	Oral gavage	103 weeks 5 days /week	Male: 0, 10, 20 mg/kg/day 0, 20, 40 mg/kg/day purity: 99%	Male (mg/kg/day)	0	10	20	U.S. NTP, 1989
				Forestomach papilloma	1/50	1/50	5/50	
				Female (mg/kg/day)	0	20	40	
				Forestomach papilloma	5/49	6/49	18/50* (squamous carcinoma: 2)	
F344 rat Male and female 50/sex/ group 7 weeks	Oral gavage	103 weeks 5 days /week	0, 4, 8 mg/kg/day purity: 99%	Male (mg/kg/day)	0	4	8	U.S. NTP, 1989
				Pancreas acinar cell adenoma	16/50	25/49*	30/50*	
				Monocytic leukemia	11/50	20/50*	21/50*	
				Female (mg/kg/day)	0	4	8	
				Breast fibroma and fibroadenoma	9/50	19/50*	17/50*	
				Breast tumor (fibroma, fibroadenoma and carcinoma)	11/50	20/50*	17/50	
$B6C3F_1$ mouse Male and female 50/sex/ group 8 weeks	Oral gavage	103 weeks 5 days /week	Male: 0, 10, 20 mg/kg/day 0, 20, 40 mg/kg/day purity: 99%	Male (mg/kg/day)	0	10	20	U.S. NTP, 1989
				Forestomach papilloma	1/50	1/50	5/50	
				Female (mg/kg/day)	0	20	40	
				Forestomach papilloma	5/49	6/49	18/50* (squamous carcinoma: 2)	
CFE rat Male and female 50/sex/ group 5 weeks	Inhalation exposure	104 weeks	0, 0.05, 0.5, 5 mg/m^3 Purity: 97% and above for industrial use	Suppression of body weight gain in all exposure groups, no significant increase in tumor incidence. Low survival rates, a small number of animals at necropsy				Blair et al., 1976

* Statistically significant difference

Table 7-12 Evaluations of carcinogenicity of dichlorvos by the international and national organizations

Organization/Source	Classification	Classification criteria
IARC (2003)	Group 2B	The agent is possibly carcinogenic to humans.
ACGIH (2003)	A4	Not classifiable as a human carcinogen.
The Japan Society for Occupational Health (2003)	Group 2B	The substance with less evidence (possibly carcinogenic to humans).
U.S. EPA (2003)	Group B2	Agent for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies
U.S. EPA (2000)	Group C	Possible human carcinogen
U.S. NTP (2002)	-	Not evaluated for human carcinogenicity.

7.4 Summary of effects on human health

Dichlorvos is rapidly absorbed through the digestive and respiratory tracts and skin, and easily metabolized by esterase that exists in most tissues. Dichlorvos is distributed in the kidney and adipose tissue at relatively high concentrations. It has been reported that in pregnant rabbits dichlorvos was transferred to fetuses in a short time after oral administration. Dichlorvos is metabolized by two pathways of which the hydrolysis pathway by esterase is the major route. In this pathway, dichlorvos is hydrolyzed at a bond between phosphate and vinyl group by type-A esterase into dimethyl phosphate and dichloroacetaldehyde. Dimethyl phosphate is excreted in the urine and dichloroacetaldehyde is rapidly metabolized to dichloroethanol. The metabolic pathway of dichlorvos is similar among various mammals including humans with some differences in metabolic rate. Dichlorvos in the kidney was eliminated immediately with the half-life of 13.5 minutes. Within 4 days after oral administration to rats, 39% of dichlorvos administered was excreted in the expiration, 13% in the urine, 3.4% in the feces and 16% in carcass.

Acute effects of dichlorvos in humans are weakness due to severe anemia, a severe reduction in plasma cholinesterase activity in patients who were given dichlorvos as anthelmintic at doses of 6 to 12 mg/kg. Severe toxic symptoms (anticholinergic symptoms) and delayed neurotoxicity (axonal degeneration neuropathy) were observed in high-dose patients. A worker was exposed to dichlorvos on the skin during pest control and developed dizziness, dyspnea and weakness. Chronic and short-term effects are effects on the gastrointestinal tract and central nervous system associated with the reduction in cholinesterase activity induced by repeated dose of 8 to 32 mg/kg/day for 2 to 7 days. In the plant workers who were exposed to dichlorvos by inhalation for a long period showed a reduction in plasma cholinesterase activity immediately after the initiation of exposure. However, the activity recovered to the normal range one month after the exposure and was discontinued. Regarding carcinogenicity of dichlorvos, it was reported that the use of dichlorvos was related to the incidence of leukemia.

In acute toxicity of dichlorvos to experimental animals, the oral LD_{50} values were 61 to 275 mg/kg in mice and 17 to 110 mg/kg in rats. The LD_{50} values for inhalation exposure were 1.42 to 33.8 ppm in mice (4 hours) and 9.05 to 49.6 ppm in rats (1 hour). Acute toxic symptoms in oral administration included a reduction of spontaneous activity, salivation, defecation, vomiting, poor coordination, opisthotonos, cyanosis, panting, coma, tremor, and spasm, and in inhalation exposure were salivation, lacrimation, proptosis, tremor and spasm.

Dichlorvos caused severe irritation to the rabbit skin. Dichlorvos is considered to have moderate sensitization effects.

In repeated dose toxicity to in experimental animals, reductions in brain, plasma and RBC cholinesterase activities, excitement, enhancement in spontaneous activity and aggression, and a reduction in brain acetylcholinesterase activity are found after oral administration. Miosis, reductions in brain, plasma and RBC cholinesterase activities are observed with inhalation exposure. In dermal application, toxic symptoms and a severe reduction in RBC cholinesterase activity are observed. Regarding neurotoxicity of dichlorvos,

salvation, spasm, cholinergic symptoms, ataxia, enhancement in aggressive behavior, reductions in brain and platelet NTE activities, significant reductions in spontaneous motion and stereotype time in an open field test, rod-holding time in a rotor rod test and active avoidance response are observed. The NOAEL of dichlorvos for oral administration is determined as 0.05 mg/kg/day with the endpoints in the results of the 52-week oral administration study in which dichlorvos was orally (gavage) administered to male and female beagle dogs and reductions in plasma and RBC (males and females) and brain (males) cholinesterase activities were observed. The NOAEL of dichlorvos for inhalation exposure is considered to be 0.05 mg/m^3 with the endpoint of a reduction in brain cholinesterase activity in 104-week inhalation exposure to male and female CFE rats.

Regarding reproductive toxicity, no abnormality was found in pregnancy rate of maternal animals, the number of litters, and the body weight and survival rate of offspring. Furthermore, at necropsy and histopathological examination of F_1 and F_2 litters aged 7 days, no abnormality was observed in a three-generation reproduction study of dichlorvos via oral feeding in rats. Among the studies of developmental toxicity, in an oral administration (gavage) study of dichlorvos in rats from gestation day 1 to the lactating period after delivery in maternal rats and for a lifetime after weanling in pups, no abnormality was found in maternal rats. However, in pups at doses of 0.97 mg/kg/day and above, dose-dependent abnormal behaviors were observed in open field and T-maze tests, and, therefore, the LOAEL for pups is considered to be 0.97 mg/kg/day. In inhalation exposure studies, significant reductions in brain and RBC cholinesterase activities were found in the maternal animals at doses of 1.25 mg/m^3 and above, but no effect on pups were observed. These results show that dichlorvos has no reproductive toxicity and teratogenicity but suggests that it has developmental toxicity.

Regarding genotoxicity, dichlorvos binds to DNA *in vitro* and induces DNA damages of DNA strand break and unscheduled DNA synthesis in microorganisms and mammalian cells. In many studies with microorganisms, dichlorvos induced mutations. However, dichlorvos showed negative results in *in vivo* DNA-binding assay, chromosomal aberration and dominant lethal tests. It is considered that dichlorvos *in vivo* reacts to serum cholinesterase and acetylcholinesterase more than DNA in the blood and tissues, and, therefore, dichlorvos is not likely to induce genotoxicity *in vivo*. It is consistent with the findings that dichlorvos shows genotoxicity in *in vitro* studies without metabolic activation but seldom exhibit genotoxicity in *in vivo* studies.

Regarding carcinogenicity of dichlorvos, with oral administration of dichlorvos, a significant increase in forestomach papilloma was found in $B6C3F_1$ mice. Monocytic leukemia and pancreas acinar cell adenoma were significantly increased in male F344 rats. Breast fibroma and fibroadenoma were significantly increased in females. Based on the data summarized above, dichlorvos is considered to be carcinogenicity to experimental animals. Dichlorvos has been categorized by the IARC as Group 2B (the agent is possibly carcinogenic to humans).

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ABBREVIATIONS

ACGIH : American Conference of Governmental Industrial Hygienists
ADH : Alcohol dehydrogenase
ALDH : Aldehyde dehydrogenase
ALP : Alkaline phosphatase
ALT : Alanine aminotransferase
ASAT : Aspartate aminotransferase
AST : Aspartate aminotransferase
ATSDR : Agency for Toxic Substances and Disease Registry
BCF : Bioconcentration Factor
BHK : Syrian hamster kidney culture cells
BOD : Biological Oxygen Demand
BUN : Blood urea nitrogen
CAS : Chemical Abstract Services
CAS Online : Chemical Abstract Services Online
CEPA : Commonwealth Environment Protection Agency
CERHR : Center for the Evaluation of Risks to Human Reproduction
CERI : Chemicals Evaluation and Research Institute, Japan
CHL : Chinese hamster lung cells
CHO : Chinese hamster ovary cells
CICAD : Concise International Chemical Assessment Document
Cmax : Maximum concentration of a compound in the blood, etc.
COD : Chemical Oxygen Demand
CPK : Creatinine phosphokinase
DDT : Dichlorodiphenyltrichloroethane
DOC : Dissolved Organic Carbon
EA : Environment Agency of Japan
EC : European Communities
EC_{10} : 10% Effect Concentration
EC_{50} : 50% Effect Concentration
ECB : European Chemicals Bureau
ECETOC : European Centre for Ecotoxicology and Toxicology of Chemicals
EEC : European Economic Communities
EHC : Environmental Health Criteria
EHI : Estimated Human Intake
EPA : Environmental Protection Agency (USA)
EU : European Union
EUSES : Europian Union System for the Evaluation of Substances
FAD : Flavin adenine dinucleotide
FAO : Food and Agriculture Organisation of the United Nations
GABA : g-Aminobutyric acid
GC : Gas chromatography
GGT : γ-Glutamyl transpeptidase
GLP : Good Laboratory Practice
hr : Hour
HSDB : Hazardous Substances Data Bank
IARC : International Agency for Research on Cancer
IC : Industrial Category
IC_{50} : Median Immobilisation Concentration or median Inhibitory Concentration (50%?)
ILO : International Labour Organisation
IPCS : International Programme on Chemical Safety
IRIS : Integrated Risk Information System
IUCLID : International Uniform Chemical Information Database (existing substances)
Koc : Soil adsorption coefficient Koc
Kow : Octanol/water partition coefficient
LC_{50} : Median Lethal Concentration

LD_{50} : Median Lethal Dose
LDH : Lactate dehydrogenase
LLNA : Local Lymph Node Assay
LOAEL : Lowest Observed Adverse Effect Level
LOEC : Lowest Observed Effect Concentration
LOEL : Lowest Observed Effect Level
MAO : Monoamineoxydase
MATC : Maximum Acceptable Toxic Concentration
MCH : Mean corpuscular hemoglobin
MCV : Mean corpuscular volume
METI : Ministry of Economy, Trade and Industry, Japan
MHLW : Ministry of Health, Labour and Welfare, Japan
min : Minute
MITI : Ministry of International Trade and Industry, Japan
MNLD : Maximum non lethal dose
MOE : Ministry of the Environment, Japan
MOF : Ministry of Finance, Japan
MOS : Margin of Safety
MTD : Maximum Tolerance Dose
NAT2 : *N*-Acetyltransferase
NCI : National Cancer Institute
NICNAS : Australia's National Industrial Chemicals Notification and Assessment Scheme
NIES : National Institute for Environmental Studies, Japan
NITE : National Institute of Technology and Evaluation, Japan
NMR : Nuclear magnetic resonance
NOAEL : No Observed Adverse Effect Level
NOEC : No Observed Effect Concentration
NOEL : No Observed Effect Level
NTE : Neurotoxic esterase
NTP : National Toxicology Program (USA)
NZW : New Zealand White
OECD : Organisation for Economic Cooperation and Development
OPIDN : Organophosphate-induced delayed neuropathy
OR : Odds ratios
ppm : Parts per million
$polA^-$: DNA polymerase$^-$
$polA^+$: DNA polymerase$^+$
pKa : Negative log of the acid dissociation constant
PRTR : Pollutant Release and Transfer Register
RBC : Radiation Biology Center
RAR : Risk Assessment Report
RC : Risk Characterisation
RfC : Reference Concentration
RfD : Reference Dose
RTECS : Registry of Toxic Effects of Chemical Substances
SCE : Sister chromatid exchange
SDH : Sorbitol dehydrogenase
SER : Smooth endoplasmic reticulum
SG : Syrian golden
SIDS : Screening Information Data Set
SLRL-test : Sex-linked recessive lethal test
SOD : Superoxide dismutase
TDI : Tolerable Daily Intake
TE : Toxic equivalent
TLV : Threshold Limit Value
Tmax : Time until a concentration reaches Cmax.
TOXLINE : Toxicology Literature Online
UV : Ultraviolet

v/v : volume per volume
w/w : weight per weight
WHO : World Health Organization
γ-GTP : γ-Glutamyl transpeptidase
δALS : δ-Aminolevulinic acid synthetase