ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorizarion Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect-level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15 364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste

sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ]Intermediate [ ] Chronic
Key to figure: 2
Species: rat

MRL: 0.002 [ ] mg/kg/day [x] ppm [ ] mg/m^3

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

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Schmidt et al. (1979) reported on a study where male Sprague-Dawley rats were exposed to atmospheres containing dichlorvos for 3, 7, or 14 days to determine its effect on acetylcholinesterase activity in the bronchi and the blood. Groups of 3 rats were kept in 0.55 m^3 gas cages and the dichlorvos atmosphere generated by suspended polyvinyl chloride strips impregnated with dichlorvos. These strips were hung in the cages 24 hours before the beginning of the experiment and the dichlorvos concentration determined by withdrawing a 10-liter sample of air and passing it through 2 wash bottles containing water. This water was then tested for its ability to inhibit a standard preparation of bovine erythrocyte membrane acetylcholinesterase. Comparison with known concentrations of dichlorvos in this assay allowed an estimate of dichlorvos concentration in the cage air to be made. Different sizes of dichlorvos strips were used to generate dichlorvos concentrations ranging from 0 to 56.64 mg dichlorvos/m^3. At the end of the exposure, blood samples were taken and the pulmonary and bronchial arteries were perfused to remove blood. The bronchial tree was scarified under a dissecting microscope, rinsed, and homogenized. Acetylcholinesterase activity was measured by automatic pH titration after the addition of acetylcholine iodide. Acetylcholinesterase activity was also detected histochemically by the thiolacetic acid method using neostigmine as a specific blocker. A NOAEL of 1.82 mg dichlorvos/m^3 (0.20 ppm) was identified for inhibition of erythrocyte acetylcholinesterase. This enzyme is always inhibited in cases of dichlorvos neurotoxicity.

APPENDIX A

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose	Bronchial AChE (% inhibition)	Erythrocyte AChE (% inhibition)
0 mg dichlorvos/m^3	0	0
0.83 mg/m^3 (0.09 ppm)	40	0
1.82 mg/m^3 (0.20 ppm)	46	0
4.32 mg/m^3 (0.48 ppm)	60	60
8.20 mg/m^3 (0.91 ppm)	90	80
16.32 mg/m^3 (1.80 ppm)	90	80
56.64 mg/m^3 (6.3 ppm)	85	100

Dose end point used for MRL derivation: 1.82 mg/m^3 (0.20 ppm) for inhibition of erythrocyte acetylcholinesterase.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ x (human blood-gas partition coefficient/animal blood-gas partition coefficient). Since the blood-gas partitioning coefficients of dichlorvos are unknown for humans or rats, a default value of 1 is being used for this ratio. Thus, $NOAEL_{[HEC]} = NOAEL_{[ANIMAL]} = 0.2$ ppm dichlorvos. Data were reported as μg dichlorvos per liter air; this value was converted to the recommended units for gases (ppm) by multiplying μg/L by 24.45 liters/mole (the standard value for the volume of a mole of contaminant at 760 mm Hg and 25 °C) and then dividing by the molecular weight of dichlorvos in grams per mole (220.98). The result is expressed as μg/g, which is equivalent to ppm.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No, exposure was continuous.

Other additional studies or pertinent information that lend support to this MRL:
This is the only acute inhalation study available for derivation of an MRL. Bronchial homogenate acetylcholinesterase showed significant inhibition at 0.09 ppm. The authors stated that lengthening the exposure period to 7 or 14 days produced similar results, but did not provide any data.

The Permissible Exposure Level (PEL) for dichlorvos established by OSHA is 0.1 ppm for a 10-hour workday. Practical insecticidal use concentrations for dichlorvos are 0.025 ppm.

APPENDIX A

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 7
Species: rat

MRL: 0.0003 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Thorpe E, Wilson AB, Dix KM, and Blair D. (1972) Teratological studies with dichlorvos vapor in rabbits and rats. Arch. Toxikol. 30 29-38.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 15 pregnant Carworth E rats were exposed to atmospheres containing 0, 0.25, 1.25, or 6.25 mg/m^3 (0, 0.03, 0.14, or 0.69 ppm) throughout their 20-day gestation period. At the end of 20 days, the rats were sacrificed and the uteri removed for examination. The number of live fetuses, late fetal deaths, and resorption sites were noted, and live fetuses were weighed and examined for external malformations. Exposure of dams to all three concentrations of dichlorvos had no effect on the number of fetal resorptions, late fetal deaths, litter size, or mean weight per fetus. Some of the dams exposed to atmospheres containing 0.69 ppm dichlorvos were less active than controls. Exposure at 0.03 ppm had no effect on erythrocyte or brain acetylcholinesterase. Exposure at 0.14 ppm resulted in a 29% inhibition of erythrocyte and a 28% inhibition of brain acetylcholinesterase, while exposure at 6.25 mg/m^3 resulted in 88% inhibition of erythrocyte acetylcholinesterase and an 83% inhibition of brain acetylcholinesterase. Brain and erythrocyte acetylcholinesterase activities were inhibited 83% and 88% in dams in the high exposure (0.69) group, suggesting that acetylcholinesterase inhibition is not associated with teratogenicity. Measurement of acetylcholinesterase activities in the pups was not performed. A NOAEL of 0.03 ppm was established for the neurological effect of brain acetylcholinesterase inhibition.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose	Brain AChE (% inhibition)	Erythrocyte AChE (% inhibition)
0 ppm	0%	0%
0.03 ppm	0%	0%
0.14 ppm	28%	29%
0.69 ppm	83%	88%

Dose end point used for MRL derivation: 0.03 ppm for neurological effects of acetylcholinesterase inhibition.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ x (human blood-gas partition coefficient/animal blood-gas partition coefficient). Since the blood-gas partitioning coefficients of dichlorvos are unknown for humans or rats, a default value of 1 is being used for this ratio. Thus, $NOAEL_{[HEC]} = NOAEL_{[ANIMAL]} = 0.03$ ppm. Data were reported in the study as µg dichlorvos per liter air; this value was converted to the recommended units for gases (ppm) by multiplying µg/L by 24.45 liters/mole (the standard value for the volume of a mole of contaminant at 760 mm Hg and 25 °C) and then dividing by the molecular weight of dichlorvos in grams per mole (220.98). The result is expressed as µg/g, which is equivalent to ppm.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Rats were exposed for 23 hours a day; 0.03 ppm x 23/24 = 0.0288 ppm = 0.03 ppm.

Other additional studies or pertinent information that lend support to this MRL:
A NOAEL for developmental effects of 0.69 ppm dichlorvos was established in this study; however, the neurological NOAEL of 0.03 ppm was chosen for derivation of the MRL because it is more relevant to the principal toxicity of dichlorvos.

The Permissible Exposure Level (PEL) for dichlorvos established by OSHA is 0.1 ppm for a 10-hour workday. Practical insecticidal use concentrations for dichlorvos are 0.025 ppm.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1997
Profile status: Post-Public Comment, Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 16
Species: rat

MRL: 0.00006 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Blair D, Dix KM, Hunt PF, Thorpe E, Stevenson DE, and Walker AIT 1976 Dichlorvos - A 2-year inhalation carcinogenesis study in rats. Arch. Toxicol 35:281-294.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 50 Carworth E strain rats of both sexes were exposed to atmospheres containing 0, 0.05, 0.5, or 5.0 mg dichlorvos/m^3 (0, 0.006, 0.06, or 0.6 ppm) for 2 years for 23 hours per day as part of a carcinogenicity study. At the end of the study, the surviving rats were killed, blood was collected and half the brain was used to determine brain acetylcholinesterase. Plasma cholinesterase and erythrocyte acetylcholinesterase were also measured. In males treated at 0.006 ppm a NOAEL for brain and erythrocyte acetylcholinesterase was identified. Females at this dose had a 12% reduction in erythrocyte acetylcholinesterase, this is also a NOAEL, since erythrocyte acetylcholinesterase inhibition of 20% or less is not considered an adverse effect.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose	Brain AChE (% inhibition)	Erythrocyte AchE (% inhibition)
0 ppm	0	0
0.006 ppm	0 (M) 0 (F)	0 (M) 12 (F)
0.06 ppm	10 (M) 10 (F)	0 (M) 31 (F)
0.6 ppm	79 (M) 81 (F)	96 (M) 95 (F)

Dose end point used for MRL derivation: 0.006 ppm for brain and erythrocyte acetylcholinesterase inhibition in male rats.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ x (human blood-gas partition coefficient/animal blood-gas partition coefficient). Since the blood-gas partitioning coefficients of dichlorvos are unknown for humans or rats, a default value of 1 is being used for this ratio. Thus, $NOAEL_{[HEC]} = NOAEL_{[ANIMAL]}$ = 0.006 ppm. Data were reported as µg dichlorvos per liter air; this value was converted to the recommended units for gases (ppm) by multiplying µg/L by 24.45 liters/mole (the standard value for the volume of a mole of contaminant at 760 mm Hg and 25 °C) and then dividing by the molecular weight of dichlorvos in grams per mole (220.98). The result is expressed as µg/g, which is equivalent to ppm.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Rats were exposed for 23 hours a day; 0.006 ppm x 23/24 = 0.0058 ppm = 0.006 ppm.

Other additional studies or pertinent information that lend support to this MRL:
This is the only chronic inhalation study available for the derivation of an MRL. The EPA used this study to derive an RfC of 0.0005 mg dichlorvos/m^3 for lifetime exposure to dichlorvos.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1997
Profile status: Post-Public Comment, Final
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ]Intermediate [ ] Chronic
Key to figure: 14
Species: rat

MRL: 0.004 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Teichert K, Szymczyk T, Consolo S, and Ladinsky H. (1976) Effect of acute and chronic treatment with dichlorvos on rat brain cholinergic parameters. Toxicol and Appl Pharmacol 35 77-81.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Male Sprague-Dawley rats were treated daily for 14 days with 4 mg/kg dichlorvos by gavage in corn oil. Dichlorvos purity was 99%. Control animals received corn oil only. Ten animals were used in the control group and 11 in the treatment group. At the end of the 14 day dosing period, the rats were decapitated, the brains removed, homogenized in 10 volumes of 0.3% Triton X-100, and centrifuged for 10 minutes. Aliquots of the supernatant were assayed for acetylcholinesterase activity by the hydrolysis of radioactive acetylcholine.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Brain Acetylcholinesterase Activity
(μmoles acetylcholine hydrolyzed/gram wet weight/hour)

0 mg/kg/day	4 mg/kg/day (from Table 1 of reference)
559.3 +/- 5.2	314.91 +/- 1.97

Dichlorvos treatment at 4 mg/kg/day over a 14-day period resulted in a 44% inhibition of brain acetylcholinesterase activity, which is considered a less serious LOAEL for neurological effects.

Dose end point used for MRL derivation: 4 mg/kg/day for a 44% inhibition of brain AChE activity.

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [x] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
If so, explain: No

Other additional studies or pertinent information that lend support to this MRL:
This is the only reliable study located for acute duration oral exposure to dichlorvos where doses ranging from 5 to 10% of the LD_{50} were administered on a daily basis and brain acetylcholinesterase (one of the targets for dichlorvos) was measured rather than erythrocyte acetylcholinesterase. Most of the acute duration oral studies for dichlorvos in rodent species were LD_{50} studies; representative LD_{50} values for the rat range from 56 to 97.5 mg/kg (Durham et al. 1957; Gajewski and Katkiewicz 1981; Ikeda et al. 1990). The 44% inhibition of brain acetylcholinesterase reported in this study is considered a less serious LOAEL; clinical signs were not reported in this study, but in another oral dosing study in Fischer 344 rats (NTP 1989) over an 11-day period, no clinical signs of organophosphate neurotoxicity were reported in animals receiving up to 16 mg/kg/day dichlorvos. The major limitation of the study used to derive the MRL is that because of its design, a dose-response relationship was not demonstrated.

The FAO/WHO Joint Meeting on Pesticide Residues has established an acceptable daily intake of dichlorvos for humans of 0.004 mg/kg/day (FAO/WHO 1967).

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 27
Species: human

MRL: 0.003 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Boyer AC, Brown LJ, Slomka MB, and Hine CH (1977) Inhibition of human plasma cholinesterase by ingested dichlorvos: effect of formulation vehicle. Toxicol. Appl. Pharmacol. 41 389-394.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Boyer et al. (1977) reported on a study designed to determine if different formulations would change the effect of dichlorvos on serum cholinesterase and erythrocyte acetylcholinesterase. Plasma cholinesterase and erythrocyte acetylcholinesterase were determined twice a week for 3 weeks in 30 male volunteers. Twenty-four men with the most stable activities were used in the study. Two treatment groups of 6 men each received 0.9 mg dichlorvos 3 times daily either in a premeal capsule filled with cottonseed oil or in a 3-ounce container of gelatin. Two other groups of 6 men each received placebo capsules or gelatin. The treated volunteers received 0.9 mg dichlorvos 3 times a day or 2.7 mg/day. The average weight of the volunteers was 81 kg, resulting in an average dose of 0.033 mg/kg/day. Dosing was started and carried out for a 21-day period during which plasma cholinesterase and erythrocyte acetylcholinesterase were measured twice a week by a pH titration method. Following the termination of dosing, plasma and erythrocyte activities were monitored twice weekly for seven weeks. Each individual's observation of cholinesterase activities was converted to a percentage of his pretrial average determinations. No clinical signs of neurotoxicity were noted in any of the subjects (tremor, pupillary response to light and skin moisture were assessed). A NOAEL of 0.033 mg dichlorvos/kg/day was observed for inhibition of erythrocyte acetylcholinesterase.

Effects noted in study and corresponding doses:

Effect of Dichlorvos on Cholinesterase Activity

Dose	Serum ChE (% inhibition)	Erythrocyte AChE (% inhibition)
0.033 mg/kg/day	38% (capsule)	0% (capsule)
	28% (gelatin)	0% (gelatin)

Dose end point used for MRL derivation: 0.033 mg/kg/day for inhibition of AchE activity.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
If so, explain: NA

Other additional studies or pertinent information that lend support to this MRL:
The reduction of serum cholinesterase observed in the study confirms that dichlorvos was absorbed by the volunteers under these conditions. No signs of clinical neurotoxicity were observed at any time in the volunteers. The dose given appeared to have been chosen expressly to not cause inhibition of erythrocyte acetylcholinesterase. This study was chosen for MRL derivation because it was the only one located that defined a NOAEL for humans for the end point of erythrocyte acetylcholinesterase inhibition.

The FAO/WHO Joint Meeting on Pesticide Residues has established an acceptable daily intake of dichlorvos for humans of 0.004 mg/kg/day (FAO/WHO 1967).

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Dichlorvos
CAS number: 62-73-7
Date: September 1996
Profile status: Post-Public Comment, Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 38
Species: dog

MRL: 0.0005 [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: AMVAC Chemical Corp. 1990 A 52-week chronic toxicity study on DDVP in dogs. Unpublished report dated August 6, 1990 submitted by AMVAC Chemical Corporation, Los Angeles CA. EPA-41593101.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): In a chronic feeding study, groups of Beagle dogs (4 per sex per dose, approximately 6–7 months old) were administered dichlorvos daily by gelatin capsule for 52 weeks at dose levels of 0, 0.1, 1.0, and 3.0 mg/kg/day. Observations included clinical signs, body weight, food consumption, ophthalmology, blood chemistry, necropsy, and histopathology. The 0.1 mg/kg/day dose level was lowered to 0.05 mg/kg/day on day 22 due to inhibition of serum cholinesterase noted after 12 days on dichlorvos (the authors were attempting to assure a no-effect level for serum ChE). Serum cholinesterase and erythrocyte acetylcholinesterase were measured throughout the study (3 times prior to treatment, and during weeks 2, 6, 13, 26, 39, and 52). At termination of the study, the brain was weighed and brain acetylcholinesterase was measured. Histopathology was performed on the brain (with brainstem), cervical spinal cord, lumbar spinal cord and the sciatic nerve.

Effects noted in study and corresponding doses: The main clinical observations were soft feces and emesis. Soft feces did not appear to be related to dichlorvos administration. One male treated at 3.0 mg/kg/day experienced emesis on 29 different days in the study. One male experienced ataxia, salivation, and dyspnea on one day during week 33, these classical symptoms of organophosphate toxicity were thought to be from an accidental overdose although this was not confirmed. Serum cholinesterase was unchanged in the 0.05 mg/kg/day groups for both sexes. At 1.0 mg/kg/day, serum cholinesterase was decreased by 52.9% in males and 51.8% in females. Erythrocyte acetylcholinesterase was decreased by 53.4% in males and 45.2% in females. At 3.0 mg/kg/day, serum cholinesterase was decreased 71.5% in males and 64.6% in females. Erythrocyte acetylcholinesterase was decreased 85.1% in males and 81.1% in females. Levels of inhibition did not increase over time of measurement (2–52 weeks). At termination of the study, brain acetylcholinesterase was decreased 22% in males at 1.0 mg/kg/day, but not in females. At 3.0 mg/kg/day, brain acetylcholinesterase was decreased 47% in males and 29% in females. No treatment-related changes were seen on histopathology for the following tissues: brain with brainstem, cervical spinal cord, lumbar spinal cord, optic nerve, thoracic spinal cord, and sciatic nerve.

APPENDIX A

Effect of Dichlorvos on Acetylcholinesterase Activity

Dose (mg/kg/day)	Brain AChE (% inhibition)	Erythrocyte (% inhibition)
0	0	0
0.05	0	0
1.0	53.4 (M) 45.2 (F)	22 (M) 0 (F)
3.0	85.1 (M) 81.1 (F)	47 (M) 29 (F)

Dose end point used for MRL derivation: NOAEL of 0.05 mg/kg/day for erythrocyte and brain acetylcholinesterase inhibition

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: The EPA used this as the principal study to establish an RfD for dichlorvos of 0.0005 mg/kg/day.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1st review:_____
2nd review:_____

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exuosure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
(2) Exuosure Period Three exposure periods - acute (less than 15 days), intermediate (1.5-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference

to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a'NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote 'lb").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompames the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious

effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day .

(16) NOAEL In this example, 1% NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (ql*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

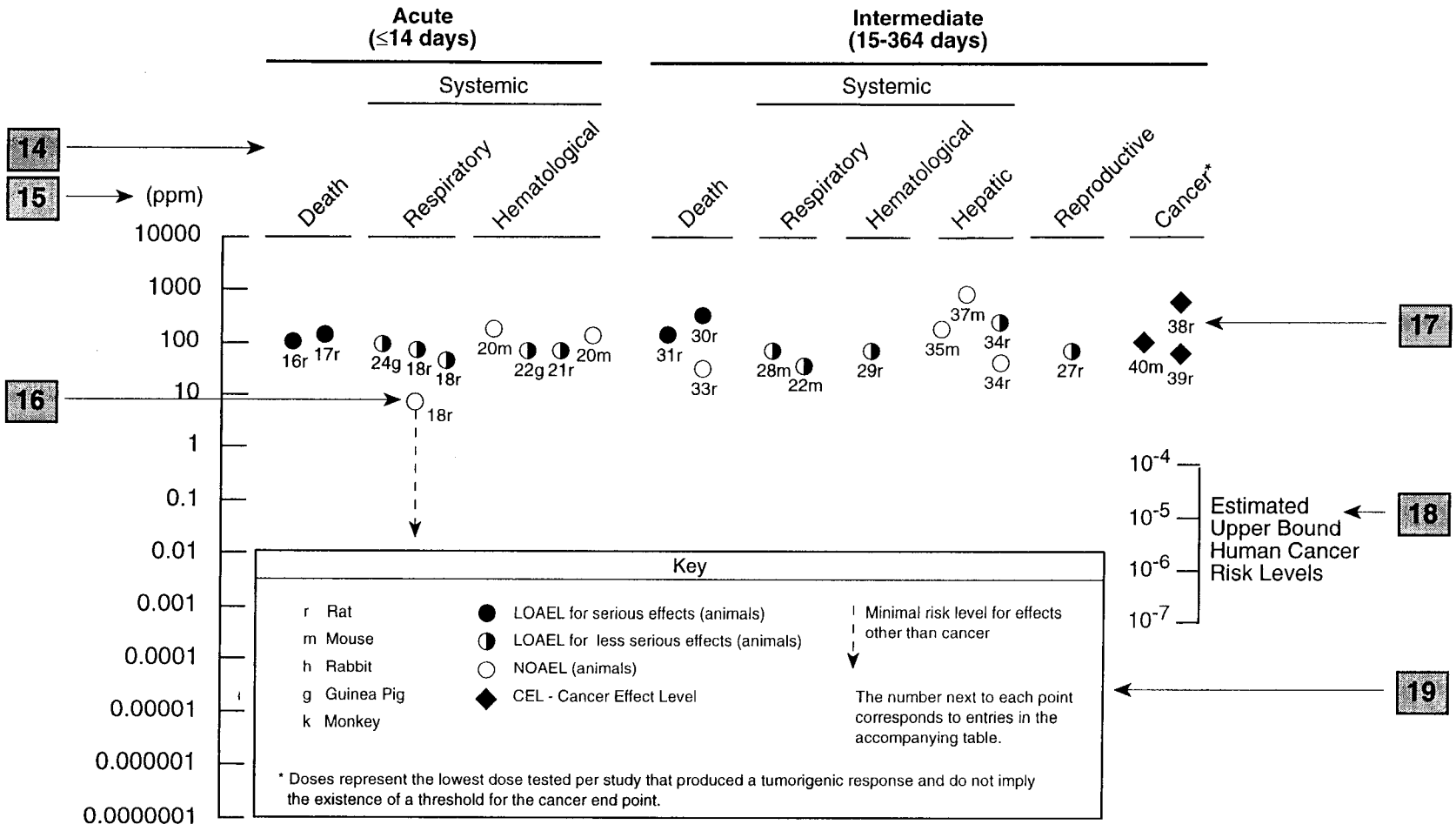
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement. represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography

APPENDIX C

LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL

TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram