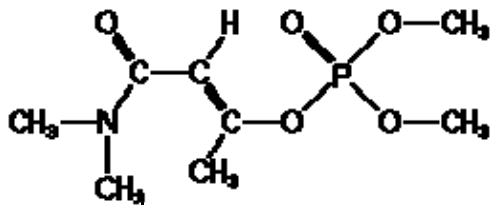
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PROPOSED

DICROTOPHOS (CAS Reg. No. 141-66-2)



PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels C AEGL-1, AEGL-2 and AEGL-3 C are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Dicrotophos is a restricted use organophosphate insecticide, the mechanism of action of which is inhibition of cholinesterase (ChE) resulting in toxic responses characterized by excessive cholinergic activity such as increased salivation, miosis, muscle fasciculations, tremors, and convulsions.

No information is available regarding the toxicity in humans following inhalation exposure to dicrotophos.

Inhalation data in animals are limited to conflicting lethality data for rats, poorly characterized exposure-response data for nonlethal effects, and inadequate information on the exposure concentration-duration relationship. Sachsse et. al. (1974) reported both 1-hour and 4-hour LC_{50} values of 90 mg/m^3 (95% confidence interval for 1-hour exposure was 62-129 mg/m^3) for groups of 9 male and 9 female rats exposed to dicrotophos (technical; 87.8% purity). A 1-hour exposure to 0.72 mg technical dicrotophos /L (720 mg/m^3) killed 4 of 5 rats while exposure to 0.48 mg/L (480 mg/m^3) was not lethal. Exposure for one hour to 0.86 mg/L (860 mg/m^3) of a 38.2% solution of dicrotophos killed 1 of 5 rats while 1-hour exposure to 0.81 mg/L (810 mg/m^3) was not lethal. Rats were observed for 2 weeks post exposure (U.S. EPA, 2005).

Information regarding the metabolism and disposition of dicrotophos following inhalation exposure are not available. Based upon data from alternate exposure routes, dicrotophos is extensively metabolized via demethylation, hydrolysis, and hydroxylation with metabolites exhibiting wide distribution. Elimination of dicrotophos in animals following oral, intravenous, intraperitoneal or subcutaneous exposure is rapid and primarily via the urine.

AEGL-1 values for dicrotophos are not recommended due to insufficient data.

Data were also insufficient to derive AEGL-2 values. The limited exposure-response data for rats, however, indicate that the exposure-response relationship for dicrotophos is steep; 480 mg/m^3 to 720 mg/^{3} for technical formulation and 810 mg/m^3 to 860 mg/m^3 for a 38% solution) for a 1-hour duration spanned a lethality rate from 0% up to 100%. Consistent with NRC (2003) guidelines, a 3-fold reduction of the AEGL-3 values would provide a justifiable estimate of the AEGL-2 values.

AEGL-3 values for dicrotophos are based upon very limited data. The 1-hour LC_{50} value of 90 mg/m^3 reported by Sachsee et al. (1974) served as the initial point-of-departure (POD). This value was adjusted to 78.9 mg/m^3 to adjust for reported 87.7% purity of the test article. Due to the steep exposure-response relationship for dicrotophos, a lethality threshold of 26.3 mg/m^3 for rats was estimated by a 3-fold reduction of the 78.9 mg/m^3 LC_{50} value.

Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). However, the variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse

effects. Plasma ChE levels are greater in humans than in rodents, and human plasma ChE activity represents a greater portion of blood ChE activity relative to animal species. Furthermore, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage. Therefore, the interspecies uncertainty factor was limited to 3.

The default intraspecies uncertainty factor of 10 was maintained for dicrotophos AEGL-3 values. The underlying mechanism of organophosphates is inhibition of cholinesterase by phosphorylation of the esteratic site of the enzyme. Cholinesterases in the blood and tissues are known to be instrumental in limiting the amount of organophosphate compounds reaching critical targets such as brain ChE and acetylChE at cholinergic synapses. Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans. Individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase and these individuals may exhibit greater sensitivity to some anticholinesterase compounds. Evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans (summarized in NRC, 2003). In the absence of chemical-specific data showing that dicrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained.

Data with which to assess the exposure concentration-duration relationship are not available; the same value for both a 1-hour and 4-hour LC_{50} implies that exposure time has little impact on the lethal response of rats to inhaled dicrotophos. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of definitive data, temporal scaling default exponents of $n = 3$ are typically applied when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points (NRC 2001).

The AEGL values for dicrotophos are summarized in Table S-1.

S-1. AEGL Values for dicrotophos (mg/m^3)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	0.53	0.37	0.29	0.073	0.037	3-fold reduction of AEGL-3 values
AEGL-3 (Lethality)	1.6	1.1	0.88	0.22	0.11	Lethality threshold estimated as 3-fold reduction of 1-hr LC_{50} of 78.9 mg/m^3 (90 mg/m^3 reported adjusted for 87.7% purity of test article) ÷ 3 = 26.3 mg/m^3 in rats (Sachsse et al., 1974); UF=10x3

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

References

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan, W.A.M., Ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.

1. INTRODUCTION

Dicrotophos is a restricted use organophosphate insecticide. It functions as a cholinesterase (ChE) inhibitor. Approximately 550,000 pounds of dicrotophos are used annually in the United States, primarily on cotton in the southeast (U.S. EPA 2002). The physical/chemical properties of dicrotophos are summarized in Table 1.

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TABLE 1. Chemical and Physical Data for Dicrotophos

Parameter	Value	Reference
Synonyms	Phosphoric acid 3-(dimethlamino)-1-methyl-3-oxo-1-propenyl dimethyl ester ; phosphoric acid dimethyl ester, 3-(dimethoxyphosphinyloxy)-*N*,*N*-*cis*-crotonamide ; dimethyl 2-dimethylcarbamoyl-1-methoxyvinylphosphate ; dimethyl 1-dimethylcarbamoyl-1-propen-2-yl phosphate ; Bidrin® ; Carbicon® ; Ektaphos®	O'Neil et al., 2001; ACGIH, 2002
Chemical formula	$C_8H_{16}NO_5P$	O'Neil et al., 2001
Molecular weight	237.19	O'Neil et al., 2001
CAS Registry No.	141-66-2	
Physical state	Liquid	ACGIH, 2002
Solubility in water	Miscible	ACGIH, 2002
Vapor pressure	1 x 10^{-4} torr @ 20°C	ACGIH, 2002
Density	1.22 g/cm^3 @ 20°C	Sachsse et al., 1974
Boiling point/Melting point	400°C @ 760 torr	ACGIH, 2002
Conversion factors in air*	1 ppm = 9.68 mg/m^3 1 mg/m^3 = 0.10 ppm	

* Dicrotophos testing was with aerosols and, therefore, conversion to ppm was not applied

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data are available regarding human mortality following inhalation exposure to dicrotophos. Although a near-fatal poisoning following prolonged inhalation exposure was reported by Perron (1969), no exposure terms were available.

2.2 Nonlethal Toxicity

Data regarding inhalation exposure of humans to dicrotophos are not available.

2.3. Developmental/Reproductive Effects

Data on potential developmental/reproductive toxicity of dicrotophos in humans were not available.

2.4. Genotoxicity

No information regarding potential genotoxicity of dicrotophos in humans was available.

2.5. Carcinogenicity

No information regarding the carcinogenic potential of dicrotophos in humans was available.

2.6. Summary

No information regarding inhalation toxicity of dicrotophos in humans was available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1 Rats

A study on dicrotophos (Bidrin®) was conducted by Kettering Laboratory (1965) using groups of five male CD rats. Exposure levels were determined by measuring the weight of material added to the 30 liter chamber minus the amounts deposited on the walls of the apparatus, and dividing this by the total air volume supplied to the exposure chamber. Aerosol particle size was not determined. A 1-hour exposure to 0.72 mg technical dicrotophos /L (equivalent to 720 mg/m^3) killed 4 of 5 rats while exposure to 0.48 mg/L (equivalent to 480 mg/m^3) was not lethal. Exposure for one hour to 0.86 mg/L (equivalent to 860 mg/m^3) of a 38.2% solution of dicrotophos killed 1 of 5 rats while 1-hour exposure to 0.81 mg/L (equivalent to 810 mg/m^3) was not lethal. Rats were observed for 2 weeks post exposure.

Sachsse et. al. (1974) exposed groups of 9 male and 9 female rats (160-180 g; SPF) to dicrotophos (technical; 87.8% purity) for 1 or 4 hours. Post exposure observation was 7 days. A Cascade Impactor was used for sampling the test atmospheres and the aerosol concentrations and size determinations were determined using gravimetry (Mettler precision balance) and sampling membrane filters. The mass median aerodynamic diameter (MMAD) was 2-7 μm. The filters containing the pesticide were also analyzed using an automated cholinesterase-inhibition method. Both the 1-hour and 4-hour LC_{50} values were 90 mg/m^3. The 95% confidence interval for the 1-hour exposure was 62-129 mg/m^3. The exposure-response data used to determine these benchmarks were not provided in the published report.

3.1.2 Summary of Lethal Toxicity in Animals

Lethality data for acute exposure of animals to dicrotophos are limited to conflicting 1-hour and 4-hour LC_{50} values in rats.

3.2. Nonlethal Toxicity

3.2.1. Rats

Studies on dicrotophos (Bidrin®) submitted in support of pesticide registration (U.S. EPA, 2005) provided cursory descriptions of incompletely characterized nonlethal exposures. In one study, rats (3/gender/group) were exposed to technical grade dicrotophos (Bidrin®) at concentrations of 0, 0.025%, 0.125%, or 0.25% (equivalent to 250, 1250, or 2,500 mg/m^3) by whole body inhalation for an unspecified duration (U. S. EPA, 2005 summary; no additional data provided). Clinical signs up to 164 hours post exposure included: sedation at 8 hours, hyperglycemia at 4 hours and normal at 24 hours post-treatment for the 0.025% group; sedation

at 8 hours, hypothermia at 4 hours and normal at 24 hours post-treatment in the 0.125% group; and sedation, ataxia, and salivation at 8 hours, hypothermia and hypoglycemia at 4 hours, and normal at 24 hours post-treatment in the 0.25% group.

As previously noted in Section 3.1.1 (Kettering Laboratory, 1965), there were no deaths among groups of five rats exposed for 1 hour to technical dicrotophos at 0.48 mg/L (480 mg/m^3) or to a 38.2 % solution of technical dicrotophos at 0.81 mg/L (810 mg/m^3). Animals exhibiting clinical signs (increased respiratory rate and volume, excessive salivation, defecation) reportedly recovered upon removal from the exposure chamber and no effects were observed over the 2-week post exposure period.

3.3. Developmental/Reproductive Effects

No information is available in the open literature regarding potential developmental and reproductive toxicity of dicrotophos following inhalation exposure.

3.4. Genotoxicity

Information regarding the genotoxicity of dicrotophos following inhalation exposure is not available.

3.5. Carcinogenicity

Information regarding the carcinogenicity of dicrotophos following inhalation exposure is not available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There is no information regarding the metabolism and disposition of dicrotophos following inhalation exposure. However, its metabolism has been examined in rats, mice, dogs, rabbits, and goats following oral, intravenous, subcutaneous or intraperitoneal administration (Lores et al., 1978; Wu et al., 1996; Menzer and Casida,1965; Bull and Lindquist, 1964; Tseng and Menzer, 1974). Dicrotophos appears to be extensively metabolized via demethylation, hydrolysis, and hydroxylation. The absorption of dicrotophos from the gastrointestinal tract is rapid and nearly complete. Following oral, intravenous, and intraperitoneal administration, dicrotophos and its metabolites are widely distributed (Wu and Gu, 1996; Menzer and Casida, 1965; Bull and Lindquist, 1964). Elimination of dicrotophos in animals following oral, intravenous, intraperitoneal or subcutaneous exposure is rapid and primarily via the urine.

Human data on dicrotophos metabolism and disposition are limited to metabolite elimination following an accidental poisoning by ingestion (Lores et al., 1978). Although dimethyl and diethyl phosphate metabolites were identified in the urine at levels of 5 ppm and <0.05 ppm, respectively, the amount of dicrotophos ingested was unknown. No other metabolites were characterized.

4.2. Mechanism of Toxicity

Being an organophosphate, dicrotophos inhibits acetylChE activity resulting in an excess of acetylcholine at neuronal synapses and myoneural junctions. Like other organophosphates, dicrotophos phosphorylates the esteratic subsite of the enzyme which, in turn, prevents the enzyme from deactivating acetylcholine (Taylor, 1985). The overall result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors).

4.3. Structure-Activity Relationships

The mode of action of organophosphates is inactivation of cholinesterase. Although all organophosphate ChE inhibitors have the same mode of action, their potency and physicochemical properties vary. The physicochemical differences will also affect environmental persistence and metabolic fate. In the absence of relative potency data, development of AEGL values for dicrotophos by analogy to other organophosphates would be tenuous.

4.4. Other Relevant Information

4.4.1. Species Variability

As an organophosphate cholinesterase inhibitor, the mode of action of dicrotophos (inhibition of acetylChE at neuromuscular junctions and in the CNS) will be the same across species and toxic responses will be qualitatively similar. Variability in toxicity would likely be a function of dosimetric factors and the extent of interaction of dicrotophos with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE.

4.4.2. Susceptible Populations

Individual variability in plasma ChE activity is well documented (NRC, 2003). This variability includes age-related differences (neonates are more susceptible than are adults), gender differences (females tend to have lower plasma and red blood cell ChE activity) and genetically determined variations in plasma ChE activity. This genetic variability (sometimes resulting in greatly reduced activity of plasma ChE) may impart deficiencies in ability to detoxify organophosphates such as dicrotophos. Additionally, polymorphic variability in A-esterases (i.e., paraoxonase/arylesterase) may also contribute to individual variability in organophosphate ester detoxification processes (NRC, 2003).

4.4.3. Concurrent Exposure Issues

Both concurrent exposure to other organophosphates and simultaneous exposure via other exposure routes would be of concern. Metabolism data in animals show that dicrotophos may enter the body and be bioavailable by dermal, oral and inhalation pathways.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were available.

5.2. Animal Data Relevant to AEGL-1

No animal data were located in the open literature to assess AEGL-1 severity responses following acute inhalation exposure to dicrotophos.

5.3. Derivation of AEGL-1 Values

Data are insufficient for derivation of AEGL-1 values for dicrotophos (Table 2).

TABLE 2. AEGL-1 values for dicrotophos

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are no human data regarding AEGL-2 severity effects from inhalation exposure to dicrotophos.

6.2. Animal Data Relevant to AEGL-2

Clinical signs of sedation, hyperglycemia, hypothermia, ataxia, and salivation at various post exposure times up to 164 hours following whole-body inhalation exposure of rats to 0.025%, 0.125%, or 0.25% (equivalent to 250, 1250, or 2,500 mg/m^3) were the only responses consistent with AEGL-2 severity effects (U.S. EPA, 2005). Although recovery from the effects was noted and the effects were consistent with AEGL-2 severity, no exposure terms were provided. There were no deaths among groups of five rats exposed for 1 hour to technical dicrotophos at 0.48 mg/L or to a 38.2 % solution of technical dicrotophos at 0.81 mg/L (Kettering Laboratory, 1965). Animals exhibiting clinical signs (increased respiratory rate and volume, excessive salivation, defecation) reportedly recovered upon removal from the exposure chamber and no effects were observed over the 2-week post exposure period.

6.3. Derivation of AEGL-2 Values

Limited data (see Sections 3.1.1 and 3.2.1) in rats suggested that very small increases in exposure levels (0.48 mg/L to 0.72 mg/L for technical formulation and 0.81 mg/L to 0.86 mg/L for a 38% solution) for a 1-hour duration spanned a lethality rate from 0% up to 100% (5 rats/group). The data imply a very steep exposure-response relationship between lethal and nonlethal responses. Consistent with NRC (2003) guidelines, a 3-fold reduction of the AEGL-3 values would provide a justifiable estimate of the AEGL-2 values (Table 3).

TABLE 3. AEGL-2 values for dicrotophos (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-2	0.53	0.37	0.29	0.073	0.037

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were available for derivation of AEGL-3 values for dicrotophos.

7.2. Animal Data Relevant to AEGL-3

Animal data relevant to derivation of AEGL-3 values are limited to free-standing LC_{50} values for rats (see Section 3.1.1). In the Kettering Laboratory (a965) study, there was 80% lethality (4 of 5 rats) following a 1-hour exposure to 0.72 mg/L (720 mg/m^3) technical-grade dicrotophos (Bidrin®) and 20% lethality (1 of 5 rats) following exposure to 0.86 mg/L (860 mg/m^3) of a 36% solution. Sachsse et. al. (1974) reported both 1-hour and 4-hour LC_{50} values as 90 mg/m^3. Neither of these reports provided the exposure-response data used to determine the reported lethality benchmarks.

7.3. Derivation of AEGL-3 Values

Lethality data from different sources are conflicting; the two reported 1-hour LC_{50} values exhibit a 7.2 to 9.5-fold difference. The 1-hour and 4-hour LC_{50} values of 90 mg/m^3 come from a well-described study that included detailed descriptions of the test apparatus as well as atmosphere generation and monitoring. The Sachsse et al. (1974) study utilized an adequate number of animals per test group (9 males; 9 females) and a 7-day post exposure observation period. The investigators noted that dicrotophos, along with two other enolphosphates tested (phosphamodin and monocrotophos) did not exhibit a concentration-time dependent relationship in lethal toxicity.

The development of AEGL-3 values for dicrotophos is based upon very limited data. Because the effects of dicrotophos are expected to be additive, the 1-hour LC_{50} value was used rather than the 4-hour value or assuming linearity by the use of both the1-hour and 4-hour values. The 1-hour 90 mg/m^3 (78.9 mg/m^3 adjusted for 87.7% purity of test article) served as the initial point-of-departure (POD). The LC_{50} values reported by Sachsee et al. (1974) indicated greater toxicity than did those from the studies summarized by the U.S. EPA (2005). A lethality threshold of 26.3 mg/m^3 for rats was estimated by a 3-fold reduction of the 78.9 mg/m^3 LC_{50} value. Although data for dicrotophos are extremely limited, this approach is justified as previously described in Section 6.3. Additionally, other organophosphates exhibit a steep exposure-response relationship (for example; for methyl parathion, the lethality rate in rats increases from 20% to 90% with only a 1.5-fold increase in dose) thereby providing justification for this approach.

Uncertainty factor application for dicrotophos AEGL development followed that for other organophosphate anticholinesterases (nerve agents, parathion, methyl parathion) with justifications being similar. Specifically, the uncertainty factor for interspecies variability is 3 and the uncertainty factor for individual variability remains at the default value of 10.

Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). However, the variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. It has been reported that plasma ChE activity in humans is twice that of mice and four times that of rats (Cohen, 1971). It is important to note that human plasma ChE represents a greater portion of blood ChE relative to animal species (Wills, 1972; Osweiler et al., 1985; Cohen et al., 1971); specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE (Osweiler et al., 1985). Furthermore, baseline RBC ChE activity is higher in humans relative to animal species (Ellin, 1981) which provides an additional protective advantage.

There are several arguments in support of retaining the default intraspecies uncertainty factor of 10 for dicrotophos. The underlying mechanism of organophosphates is inhibition of cholinesterase by phosphorylation of the esteratic site of the enzyme. Cholinesterases in the blood and tissues are known to be instrumental in limiting the amount of organophosphate compounds reaching critical targets such as brain ChE and acetylChE at cholinergic synapses (Parkinson and Ogilvie, 2008). Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans (Cashman et al., 1996). This variability is relevant considering that the magnitude of the interaction of organophosphates with A-esterases may alter the aforementioned protective effect of these esterases. Yamasaki et al. (1997) reported that individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. Morgan (1989) noted that about 3% of individuals possess genetically determined low levels of plasma cholinesterase and that these individuals may exhibit greater sensitivity to some anticholinesterase compounds. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans (Shanor et al., 1961; Wills, 1972; Yokoyama et al., 1998) and animals (Mioduszewski et al., 2000, 2001, 2002a,b). In the absence of chemical-specific data showing that dicrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained.

Data with which to assess the exposure concentration-duration relationship are not available. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of definitive data, temporal scaling default exponents of $n = 3$ are typically applied when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points (NRC 2001).

The AEGL-3 values for dicrotophos are shown in Table 4 and their derivation is presented in Appendices A and C.

TABLE 4. AEGL-3 values for dicrotophos (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	1.6	1.1	0.88	0.22	0.11

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for dicrotophos are shown in Table 5. The only inhalation toxicity data available are those for rats. The AEGL-3 values were based upon lethality thresholds estimated by a 3-fold reduction of a 1-hour LC_{50} value for rats; justified by an apparently steep exposure-response curve. Because the reported lethality values varied considerably, the more conservative values were used for AEGL-3 derivation. Definitive exposure-response data for AEGL-1 and AEGL-2 tier severity were not available. Due to the steep exposure-response relationship of cholinesterase inhibition by other organophosphate compounds and limited data for dicrotophos, theAEGL-2 values were estimated as a 3-fold reduction of the AEGL-3 values. AEGL-1 values are not recommended.

TABLE 5. AEGL values for dicrotophos (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.53	0.37	0.29	0.073	0.037
AEGL-3 (Lethality)	1.6	1.1	0.88	0.22	0.11

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidelines for dicrotophos are limited to an ACGIH TLV-TWA and a MAC (Table 6).

TABLE 6. Extant Standards and Guidelines for Dicrotophos (mg/m^3)

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.53	0.37	0.29	0.073	0.037
AEGL-3	1.6	1.1	0.88	0.22	0.11
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]					
REL-TWA (NIOSH)[f]					
REL-STEL (NIOSH)[g]					
TLV-TWA (ACGIH)[h]					0.05
TLV-STEL (ACGIH)[i]					
MAK (Germany)[j]					
MAK Spitzenbegrenzung (Germany)[k]					
Einsaztoleranzwert (Germany)[l]					
MAC-Peak Category (The Netherlands)[m]					0.25

[a] ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA, 2008) The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual>s ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b] EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC, 1985) is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c] OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA, 2007) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d] OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit) (OSHA, 2007) is defined analogous to the ACGIH-TLV-STEL.

[e] IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH, 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f] NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH, 2005) is defined analogous to the ACGIH-TLV-TWA.

[g] NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH, 2005) is defined analogous to the ACGIH-TLV-STEL.

[h] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH, 2007) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i] ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit) (ACGIH, 2007) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[j] MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (DFG, 2007) is defined analogous to the ACGIH-TLV-TWA.

[k] MAK Spitzenbegrenzung (Kategorie II,2) [Peak Limit Category II,2] (DFG, 2007) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes, with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK. Cat. III indicates possible significant contribution to cancer risk.

[l] Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risks.

[m]MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration - Peak Category]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-Ceiling.

8.3. Data Adequacy and Research Needs

Inhalation toxicity data for dicrotophos are limited to widely varying LC_{50} values in rats and reports of nonlethal effects that lack exposure terms. Under the assumption that organophosphate ChE inhibitors operate by similar mechanisms, the data are marginally acceptable for estimating AEGL-3 and AEGL-2 values.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Dicrotophos

AEGL-1 values are not recommended (NR) for dicrotophos due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Derivation of AEGL-2 Values for Dicrotophos

Limited data (see Sections 3.1.1 and 3.2.1) in rats suggested that very small increases in exposure levels (480 mg/m^3 to 720 mg/m^3 for technical formulation and 810 mg/m to 860 mg/m^3 for a 38% solution) for a 1-hour duration spanned a lethality rate from 0% up to 100% (5 rats/group). The data imply a very steep exposure-response relationship between lethal and nonlethal responses. Consistent with NRC (2003) guidelines, a 3-fold reduction of the AEGL-3 values would provide a justifiable estimate of the AEGL-2 values.

10-min AEGL-2	1.6 mg/m^3 ÷ 3 = 0.53 mg/m^3
30-min AEGL-2	1.1 mg/m^3 ÷ 3 = 0.37 mg/m^3
1- h AEGL-2	0.88 mg/m^3 ÷ 3 = 0.29 mg/m^3
4-h AEGL-2	0.22mg/m^3 ÷ 3 = 0.073 mg/m^3
8-h AEGL-2	0.11 mg/m^3 ÷ 3 = 0.037 mg/m^3

Derivation of AEGL-3 Values for Dicrotophos

Key Study:	Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan,W.A.M., ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.
Critical effect:	Lethality threshold estimated from1-hour and 4-hour rat LC_{50} values of 90 mg/m^3 as the initial point-of-departure (POD). These values indicated greater toxicity than did those from the studies summarized by the EPA.(U.S. EPA, 2005). A lethality threshold of 30 mg/m^3 for rats was estimated by a 3-fold reduction of the 90 mg/m^3 LC_{50} values Because an additive effect is expected for the toxic response to this chemical, the 1-hour value was used as the POD. The final POD of 26.3 mg/m^3 reflects an adjustment for the 87.7% purity of the test article. Limited data (see Sections 3.1.1 and 3.2.1, Kettering Laboratory, 1965) in rats suggested that very small increases in exposure levels (0.48 mg/L to 0.72 mg/L for technical formulation and 0.81 mg/L to 0.86 mg/L for a 38% solution) for a 1-hour duration spanned a lethality rate from 0% up to 100% (5 rats/group). The data imply a very steep exposure-response relationship between lethal and nonlethal responses. Additionally, other organophosphates exhibit a steep exposure-response relationship (for example; for methyl parathion, the lethality rate in rats increases from 20% to 90% with only a 1.5-fold increase in dose) thereby providing justification for this approach.
Time scaling:	The 1-hour exposure duration was selected for the POD because the effects of an organophosphate are expected to be additive. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of definitive data, temporal scaling default exponents of n = 3 are typically applied when extrapolating to shorter time points and n = 1 when extrapolating to longer time points (NRC 2001).
Uncertainty factors:	Total uncertainty factor 30. <u>Interspecies</u>: 3; Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). The variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE in humans is twice

that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.

Intraspecies: 10; Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result in greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.

Modifying Factor: none applied

Calculation: 1-hr LC_{50} of 78.9 mg/m^3 (90 mg/m^3 adjusted for 87.7% purity) ÷ 3 = 26.3 mg/m^3
(26.3 mg/m^3)^1 x 1 hr = 26.3 mg·hrs/m^3
(26.3 mg/m^3)^3 x 1 hr = 18,191.4 mg·hrs/m^3

10-min AEGL-2
(C mg/m^3)^3 x 0.1667 hr = 18,191.4 mg·hrs/m^3
C^3 = 109,126.6 mg·hrs/m^3
C = 47.79 mg/m^3
C = 47.79 mg/m^3 ÷ 30 = 1.6 mg/m^3

30-min AEGL-2
(C mg/m^3)^3 x 0.5 hr = 18,191.4 mg·hrs/m^3
C^3 = 36,382.8mg·hrs/m^3
C = 33.14 mg/m^3
C = 33.14 mg/m^3 ÷ 30 = 1.1 mg/m^3

1- h AEGL-2
(C)^1 x 1 hr = 26.3 mg·min/m^3
C = 26.3 mg/m^3
C = 26.3 mg/m^3 ÷ 30 = 0.88 mg/m^3

4-h AEGL-2
(C)^1 x 4 hrs = 26.3 mg·min/m^3
C = 6.58 mg/m^3
C = 6.58 mg/m^3 ÷ 30 = 0.22 mg/m^3

8-hour AEGL-2
(C)^1 x 8 hrs = 26.3 mg·min/m^3
C = 3.29 mg/m^3
C = 3.29 mg/m^3 ÷ 30 = 0.11 mg/m^3

APPENDIX B: Time Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber=s Law or Haber=s Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically in the form of a linear regression analysis of the log-log transformation of a plot of C vs t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

The available data do not allow for empirical derivation of a temporal scaling factor (n) for dicrotophos. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, n, for the relationship $C^n \times t = k$ is not possible. In the absence of definitive data, temporal scaling default exponents of n = 3 are typically applied when extrapolating to shorter time points and n = 1 when extrapolating to longer time points (NRC 2001). Due to the paucity of data and the equivalent 1-hour and 4-hour LC_{50} values, a more protective approach was applied in which the 10-minute, 30-minute, and 1-hour AEGLs value were set equivalent to the 4-hour value rather than the default time scaling methodology. The 8-hour AEGL-3 was derived using n = 1 as per the default approach (NRC, 2001).

APPENDIX C: Derivation Summary Tables

Acute exposure guideline levels for Dicrotophos derivation summary

AEGL-1 VALUES FOR DICROTOPHOS (ppm)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
NR	NR	NR	NR	NR
Reference: Not applicable				
Test Species/Strain/Number: not applicable				
Exposure Route/Concentrations/Durations : not applicable				
Effects: not applicable				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: not applicable				
Modifying Factor: not applicable				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: not applicable				
Data Adequacy: Data are insufficient for derivation of AEGL-1 values for dicrotophos. Therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.				

1

AEGL-2 VALUES FOR DICROTOPHOS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.53	0.37	0.29	0.073	0.037
Reference. See AEGL-3 derivation				
Test Species/Strain/Number: See AEGL-3 derivation				
Exposure Route/Concentrations/Durations: NA				
Effects: AEGL-2 values derived by 3-fold reduction of AEGL-3 values				
Endpoint/Concentration/Rationale: Limited data (see Sections 3.1.1 and 3.2.1) in rats suggested that very small increases in exposure levels (480 mg/m^3 to 720 mg/m^3 for technical formulation and 810 mg/m to 860 mg/m^3 for a 38% solution) for a 1-hour duration spanned a lethality rate from 0% up to 100% (5 rats/group). The data imply a very steep exposure-response relationship between lethal and nonlethal responses. Consistent with NRC (2003) guidelines, a 3-fold reduction of the AEGL-3 values would provide a justifiable estimate of the AEGL-2 values.				
Uncertainty Factors/Rationale: See AEGL-3 derivation				
Modifying Factor: See AEGL-3 derivation				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: NA				
Data Adequacy: See AEGL-3 derivation				

2

1

AEGL-3 VALUES DICROTOPHOS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
1.6	1.1	0.88	0.22	0.11

Reference: Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan, W.A.M., ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.

Test Species/Strain/Sex/Number: SPF rats, strain not specified/9 males, 9 females per group

Exposure Route/Concentrations/Durations: inhalation, dicrotophos purity 87.7%; test group exposure concentrations not specified; MMAD 2-7 μm/ 1–hr or 4-hr exposure duration

Effects: lethality; 7-day observation period

Endpoint/Concentration/Rationale: 1-hr and 4-hr LC_{50} each of which were 90 mg/m^3; the 1-hr duration was chosen for the POD because an additive effect is expected. The lethality threshold was estimated as 3-fold reduction of the LC_{50} values (30 mg/m^3) justified by steep exposure-response relationship. The final POD, adjusted for 87.7% purity of the test article, was 26.3 mg/m^3

Uncertainty Factors/Rationale: 30

Interspecies: 3; Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). The variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE activity in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.

Intraspecies: 10; Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.

Modifying Factor: none applied

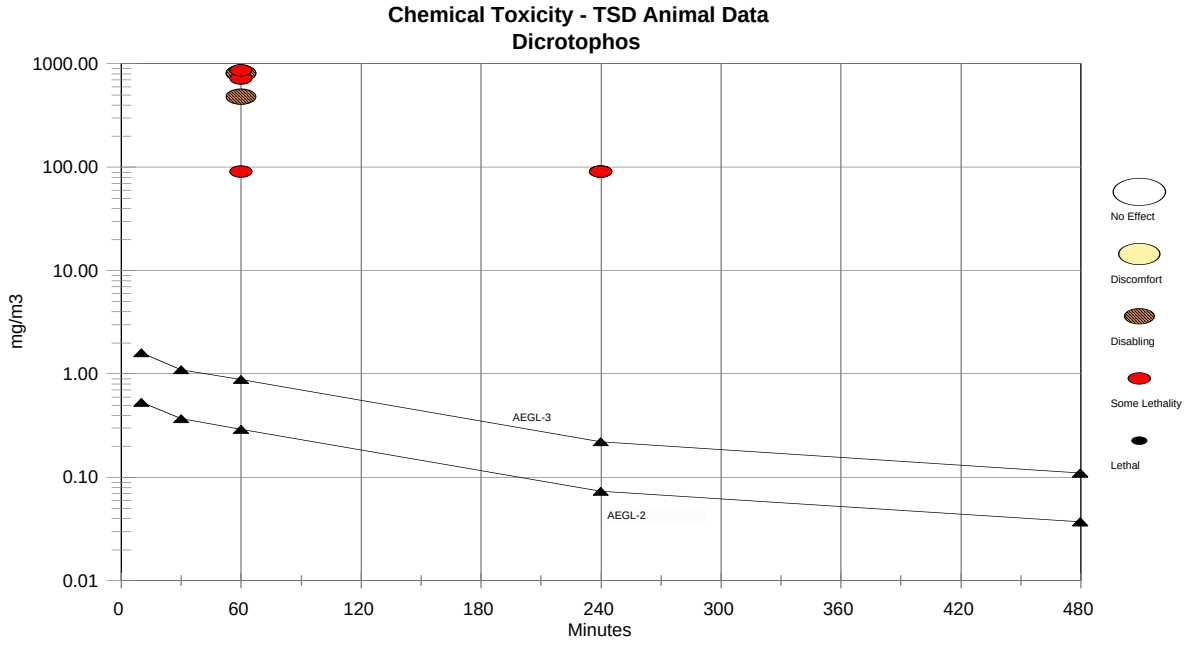
Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: $C^n \times t = k$, where n=1for extrapolation to 4-hr and 8-hr durations, and n=3 for extrapolation to 30-minute and 10-minute durations.

Data Adequacy: marginal; more definitive dose-response relationship data would allow for more defensible values.

2

APPENDIX D: Category Plot



AEGL-1 values are not recommended due to insufficient data.

Dicrotophos

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Partially Lethal, 3 = Lethal

Source	Species	Sex	# Exposures	mg/m^3	Minutes	Category	Comments
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				0.53	10	AEGL	
NAC/AEGL-2				0.37	30	AEGL	
NAC/AEGL-2				0.29	60	AEGL	
NAC/AEGL-2				0.073	240	AEGL	
NAC/AEGL-2				0.037	480	AEGL	
NAC/AEGL-3				1.6	10	AEGL	
NAC/AEGL-3				1.1	30	AEGL	
NAC/AEGL-3				0.88	60	AEGL	
NAC/AEGL-3				0.22	240	AEGL	
NAC/AEGL-3				0.11	480	AEGL	
rat	m	1	720	60	PL		4 of 5 dead (Kettering Lab report, 1965)
rat	m	1	480	60	2		no lethality; effects uncertain; 2-wk observ. (Kettering Lab report)
rat	m	1	860	60	PL		1 of 5 dead; 38.2% soln. (Kettering Lab report, 1965)
rat	m	1	810	60	2		no lethality; effects uncertain; 2-wk observ. (Kettering Lab report, 1965)
rat	m&f	1	90	60	PL		LC_{50} (Sachsse et al., 1974)
rat	m&f	1	90	240	PL		LC_{50} (Sachsse et al., 1974)