Dicrotophos

(CAS No: 141-66-2)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

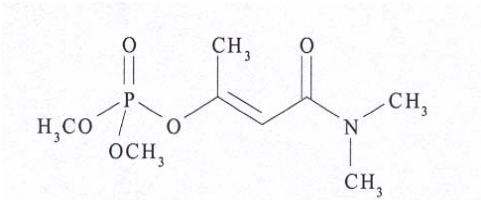
The present document contains the assessment of the health hazard of dicrotophos by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by E.Meijer, M.D. (Wageningen University and Research Centre,Wageningen, The Netherlands).

The evaluation of the toxicity of dicrotophos has been based on reviews published by the American Conference of Governmental Hygienists (ACG99) and in the 'Handbook of pesticide toxicology' (Gal91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in February 2000, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts, covering the period 1964-1966 until February 2000, and using the following key words: dicrotophos and 141-66-2. Data of unpublished studies were generally not taken into account. Exceptions were made for studies that were summarised and evaluated by the Health Effects Division (HED) of the US Environmental Protection Agency (EPA) as part of its human health risk assessment (Hrd99). No evaluation of dicrotophos has been published by the Food and Agricultural Organization/World Health Organization (FAO/WHO: Joint Meeting of the FAO Working Party of Experts and the WHO Expert Committee on Pesticide Residues (JMPR)).

In October 2002, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: J Soave (Health and Safety Executive, London, England).

An additional search in Toxline and Medline in May 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	dicrotophos
synonyms	:	phosphoric acid 3-(dimethlamino)-1-methyl-3-oxo-1-propenyl dimethyl ester; phosphoric acid dimethyl ester, ester with *cis*-3-hydroxy-*N*,*N*'-dimethylcrotonamide; dimethyl (E)-1-methyl-2-(dimethylcarbamoyl)- vinylphosphate; Bidrin®
molecular formula	:	$C_8H_{16}NO_5P$
structural formula	:	
CAS number	:	141-66-2

3 Physical and chemical properties

molecular weight	:	237.21
boiling point	:	400°C
melting point	:	not available
vapour pressure	:	at 25°C : 0.01 Pa
solubility in water	:	miscible
Log $P_{octanol/water}$	:	-0.49
conversion factors	:	not applicable

Data from ACG99, EPA99, NLM02, Rob99.

Dicrotophos is a yellow-brown liquid with a mild ester odour. Dicrotophos is somewhat corrosive to cast iron, mild steel, brass, and stainless steel. Eighty-five percent of the commercial grade consists of the E-isomer, which is amber in colour and more active to insects than the Z-isomer. Dicrotophos is available as 24% and 85% concentrates and as 40% and 50% emulsifiable concentrates. Dicrotophos is stable when stored in glass or polythene containers up to 40°C (ACG99, Gal91).

4 Uses

Dicrotophos is a systemic insecticide with a wide range of applications. The chemical is used to control aphids, spider mites, cotton flea hoppers, grasshoppers, etc. (Hrd99).

According to the database of the Dutch Pesticide Authorisation Board (CTB), dicrotophos is at present not registered for its use as an active ingredient in pesticides in the Netherlands.

5 Biotransformation and kinetics

Human data

Dimethyl phosphate was identified in a urine sample at a level of 5 mg/L in a severely intoxicated subject (Lor78). Hydrolysis of the vinyl-phosphate bond of dicrotophos or its oxidative metabolites to produce dimethyl phosphate is the predominant detoxifying reaction in humans (He93).

Animal data

Following an oral dose of 1 mg/kg bw of ^{32}P-labelled dicrotophos to male and female rats, 45-51% of the radioactivity was excreted in the urine within 6 hours and 63-71% within 48 hours (Men65). After subcutaneous injection of ^{32}P-labelled dicrotophos into rats, 65% of the radioactivity was excreted after 6 hours and 83% within 24 hours (Bul64). The metabolic pathways are largely species independent. In mammals, including rats, mice, dogs, rabbits, and goats, dicrotophos undergoes demethylation to des-*O*-methyldicrotophos and hydrolysis to dimethyl phosphate and *N*-methylacetoacetamide. Hydroxylation of the *N*-methyl group followed by N-demethylation is also a metabolic pathway producing *N*-methyl-*N*-hydroxymethyl dicrotophos, monocrotophos, and *N*-hydroxymethyl monocrotophos (Bul64, Men65, Rob99). These N-demethylated metabolites are important from a toxicological point of view, since they are better inhibitors of acetylcholinesterase than dicrotophos (Rob99). Residues of dicrotophos are excreted almost entirely within 24 hours, as indicated by a rapid decrease in not-hydrolysed metabolites in urine or milk (Men65)

6 Effects and mechanism of action

Human data

Two case studies of dicrotophos intoxication have been reported, one case of an accidental and one case of an intentional poisoning. In both cases, subjects had typical cholinergic symptoms. In the first case, poisoning occurred in a 41-year-old male tractor driver who had recently made field applications of Bidrin to crops and who had been spraying the chemical inside his house to control mosquitoes, every day for 2 or 3 weeks. Symptoms were abdominal pain, nausea, vomiting, hypersalivation, and tremors. Plasma cholinesterase (ChE) and red blood cell acetylcholinesterase (AChE) activities were completely inhibited. Following several treatments with atropine and pralidoxime, he improved initially, but relapsed on the 6th hospital day and respiratory paralysis occurred. Following artificial respiratory support for 5 days, he was discharged on the 22nd hospital day. During the next several months, the cholinesterase activity returned to normal (Per69). The second case involves a 52-year-old male who accidentally drank a dicrotophos-containing turpentine solution. Clinical signs were lachrymation, salivation, bronchial secretion, pupillary constrictions, and a flaccid paralysis with prominent muscle fasciculation. Four hours after admission to hospital, both plasma ChE and red blood cell AChE were completely inhibited. He was treated repeatedly with atropine and pralidoxime chloride. Nevertheless, he had a relapse on the 10th day. At day 23 after intoxication, his red blood cell AChE level returned to normal limits; plasma ChE activity was about 65% of mean normal value. He was discharged 1 month after admission (War77).

Animal data

Irritation and sensitisation

Dicrotophos is irritating to the eyes but not to the skin. The compound is a strong dermal sensitiser (Hrd99).

Acute toxicity

A 4-hour LC_{50} of 90 mg/m^3 has been reported for dicrotophos in rats (NIO02). Dermal LD_{50} values were 43 and 42 mg/kg bw for male and female (Sherman) rats, respectively, in a non-occluded test (Gai69) while from another rat study, values of 876 and 476 mg/kg bw for males and females, respectively, were reported (Hrd99). In rabbits, a dermal LD_{50} of 168 mg/kg bw (sex not specified) was observed (Gal91). Oral LD_{50} values for male and female rats were 21 and 16 mg/kg bw, respectively (Gai69). Similar values (11 and 8 mg/kg bw for male and female rats, respectively) were found in another study (Hrd99). For mice, an oral LD_{50} of 11 mg/kg bw (sex not specified) was listed (NIO02). When dicrotophos was intravenously, intraperitoneally, or subcutaneously injected into mice, similar LD_{50} values of 9.5-11.2 mg/kg bw were observed (Gal91, NIO02).

In an acute neurotoxicity study with White Leghorn chickens, dicrotophos did not cause paralytic effects (leg weakness). The chickens were given atropine prior to administration of dicrotophos to protect them against the acute effects of the chemical (Gai69). The committee considers this study not relevant for assessment of potential delayed neurotoxicity. In an acute oral neurotoxicity study in rats, a LOAEL of 0.5 mg/kg bw/day was found, based on inhibition of plasma ChE, red blood cell AChE, and brain AChE on day 1. A NOAEL was not established. Neuropathological examination did not show abnormalities. No further details were provided (Haz98, Hrd99).

Short-term toxicity

In a 13-week oral neurotoxicity study in rats, body weight and food consumption were decreased and plasma ChE, red blood cell AChE, and brain AChE were inhibited at 0.04 mg/kg bw/day and above. Neuropathological examination did not show abnormalities. A NOAEL was not established. No further details were provided (Haz98, Hrd99).

Long-term toxicity and carcinogenicity

In a 2-year feeding study, no mortality or changes in clinical chemical and haematological data were seen in Charles River albino rats (n=25/sex/group; controls: n=40/sex) given technical Bidrin at levels equivalent to 0, 0.05, 0.5, or 5 mg/kg bw/day. In the high-dose group, mean body weight and food intake were reduced in both males and females and tremors were occasionally observed. At

necropsy, gross examination did not show compound-related changes and no dose-related changes were noted in absolute and relative organ weights. Histological examination revealed a lower frequency of hepatocellular vacuolation in the 5 mg/kg bw/day group when compared to the other groups. There was no correlation between dose level and the frequency of neoplasms in the rats. A dose-related inhibition of plasma ChE, red blood cell AChE, and brain AChE was observed in both sexes. At week 78, mean plasma ChE activities were significantly inhibited at all dose levels in females (34 to 93%) and at the mid- and high-dose in males (55 and 80%, respectively). Red blood cell AChE activities were significantly depressed at 0.5 and 5 mg/kg bw/day in females (58 and 94%, respectively) and at the top dose only in males (81%). At termination, brain AChE activities were inhibited by 19, 35, and 88% in males and 4, 12, and 62% in females at 0.05, 0.5, and 5 mg/kg bw, respectively. The NOAEL was 0.05 mg/kg/day based on statistically significant brain and red blood cell AChE inhibition at 0.5 mg/kg bw/day and above (How67).

In another long-term dietary toxicity study using CD-1 rats, cholinergic signs of toxicity and increased white blood cell count were reported at levels equivalent to1.25 mg/kg bw/day and increased mortality at levels of 2.0 mg/kg bw. There was no evidence of carcinogenicity. A NOAEL for cholinesterase inhibition could not be established. The LOAEL was 0.02 mg/kg bw/day, based on inhibition of plasma ChE, red blood cell AChE, and brain AChE activity. The source of this study has not been mentioned and no further details were provided (Hrd99).

Beagle dogs (n=3/sex/group; controls: n=4/sex) were given dicrotophos in their diets at doses equivalent to 0, 0.004, 0.04, and 0.4 mg/kg bw, for 2 years. Starting at study week 52, a supplementary fifth group (n=2/sex) received dietary doses equivalent to 2.5 mg/kg bw for 52 weeks. Clinical signs were slight salivation in dogs given 0.004-0.4 mg/kg bw and more severe salivation and tremors in the 2.5-mg/kg bw group. Treatment did not cause mortality, effects on body weights, or changes in clinical chemical and haematological data. No abnormalities were seen upon gross and microscopic examination of organs. At week 104, a dose-related decrease in plasma ChE was observed, but this decrease was only statistically significant at 0.4 mg/kg bw (34%). Red blood cell AChE activities were significantly inhibited (49% in males and 42% in females) only at 0.4 mg/kg bw. Inhibition of brain AChE was much less and amounted to 29% in the 0.4 mg/kg bw. In the 2.5-mg/kg bw group, plasma ChE, red blood cell AChE, and brain AChE were inhibited by 60%, 100%, and 58%, respectively, at week

52. The NOAEL was 0.04 mg/kg bw based on inhibition of brain and red blood cell AChE (Joh67).

Mutagenicity and genotoxicity

When tested at concentrations of 0.5, 5, 50, 500, and 5000 µg/plate, dicrotophos caused increases in mutation frequencies in the presence (at the 3 highest concentrations) and absence (at the highest concentration only) of a without metabolic activation system in *S. typhimurium* strain TA100 but not in strain TA98 (Bre84). Using several other strains of *S. typhimurium* constructed for the detection of mutagens causing base-pair substitutions or frame-shift mutations, only negative results were obtained. Tests were performed without metabolic activation only (Han75). Dicrotophos did not induce reverse mutations in *E. coli* WP2 (Dea72, Han75) and *S. marcescens* (Dea72), probably because of the low sensitivity of the methods used (Wil75). Tested without metabolic activation only, results in *E. coli* strains WP2, CM561, CM571, CM611, and WP12 were negative as well (Han75). In contrast, the chemical induced 5-methyltryptophan-resistant mutations in *E. coli* K12 at concentrations of 3-30 mM (Moh73) and streptomycin-resistant mutations in *E.coli* at levels of 30-300 mM (Wil75). Results in *E. coli* strains WP2 *uvrA* and WP67 were positive as well (tested without metabolic activation only) (Han75).

A significantly increased frequency of sister chromatid exchanges (SCE) was observed in cultured Chinese hamster ovary cells at a concentration of 0.3 mM dicrotophos (Nis81).

Dicrotophos also induced mitotic gene conversion in *S. cerevisiae* (Fah73).

The committee did not find data from *in vivo* tests.

The available data show evidence for mutagenicity in *in vitro*.

Reproduction toxicity

In a 3-generation reproduction study, weanling Long-Evans rats (10 males and 20 females/P0, F1b, F2a generation/dose group) were given Bidrin in the diet at concentrations equivalent to 0, 0.1, 0.25, 0.75, and 2.5 mg/kg bw/day. They were mated when 100-days old. Both parents and pups in the high-dose group exhibited cholinergic signs of toxicity (weakness, body weight loss, CNS effects). The fertility index and average numbers and sizes of litters were also

reduced in the high-dose group. A high mortality rate was observed among F1b pups in the 2.5 mg/kg bw/day group and this dose was not used beyond the F1b generation because of insufficient numbers. Significantly increased pup mortality was also observed at 0.25 in second-generation pups and at 0.75 mg/kg bw/day in all litters except F3a. However, pup weights were not affected, not even in the high-dose group. Gross pathological examination of tissues from parent rats or F3a weanlings at termination of the study did not reveal abnormalities in any of the dose groups. No changes were observed in relative organ weights of F3a weanlings and histological examination of tissues did not reveal abnormalities, with the exception of slight effects of lungs of males and females in the 0.25 and 0.75 mg/kg/day groups. The NOAEL for maternal toxicity was 0.75 mg/kg bw/day and for reproduction toxicity 0.1 mg/kg bw/day (Eis65).

In a teratology study, rabbits (n=18/group; controls: n=36) were given 0, 1.3, 4.0, and 8.0 mg/kg bw, on gestational days 6 through 18. Eight rabbits of the high-dose group were initially given 12 mg/kg bw, but because 3 animals died, the dose was reduced to 8 mg/kg bw/day. Most animals given this dose exhibited cholinergic signs of toxicity (salivation and tremors) and one rabbit died after 5 days of dosing, having shown severe clinical signs. Eventually, 14 rabbits survived until termination of the study on day 28. Rabbits in the lower dose groups were unaffected. There were no statistically significant differences in the number of pregnancies, resorption sites, litters, live fetuses and late fetal deaths, in the size and weight of fetuses, or in pup viability between any of the groups. No visceral abnormalities were found and there was no significant increase in skeletal abnormalities compared with the controls. In this study, the maternal NOAEL was 4 mg/kg/day and the developmental NOAEL 8 mg/kg/day (Dix73).

Another teratology study was carried out in mice that received single intraperitoneal injections of 0, 1, 2, 4, or 7.5 mg/kg bw Bidrin on day 11 or 13 of gestation or daily injections on days 10-12. The animals were killed at day 19. No effects were observed on fetal resorption rate or fetal body weight at birth. At the top dose, maternal mortality was increased and fetal body weight decreased. No gross, soft-tissue, or skeletal abnormalities were seen. Prenatal exposure to Bidrin did not alter the development of AChE or choline acetyltransferase enzymes in fetal brain (Bus74).

Following incubation of White Leghorn chicken eggs for 24, 48, 72, and 96 hours, the eggs were treated with dicrotophos at levels of 250 μg to 2.0 mg per egg and observed for 48 hours. Treated embryos displayed general developmental retardation as well as unilateral retardation of the cranial sense

organs, the youngest embryos being most severely affected. Many embryos injected with dicrotophos after 24 hours incubation, and all but one injected at 48 or 72 hours, displayed notochordal folding, usually restricted to the cervical region. Most of these also showed deformities of the adjacent spinal cord. The incidence and severity of epiphyseal, lens, and vascular defects were greatest among embryos treated at 24 hours, whereas notochordal and both types of neural defects were greatest among those treated at 48 hours (Gar85). Injection of dicrotophos into yolk sac of hens' eggs after 4 days of incubation, resulted in achondroplasia with tibiotarsus deformities in the embryo (Mei80).

- *In vitro* studies

In vitro studies with tubular epithelial cell cultures (LLC-PK_1) have demonstrated that incubation of renal proximal tubular cells with dicrotophos is associated with H_2O_2 production, lipid peroxidation, and cell injury and that antioxidants which suppress lipid peroxidation and free radicals protect against this form of cell injury. The study shows that dicrotophos may generate reactive oxygen species which might be responsible for the toxic effects observed in human and rat kidneys (Poo99).

7 Existing occupational exposure limits

The current administrative occupational exposure limit (MAC) for dicrotophos in the Netherlands is 0.2 mg/m^3, 8-hour TWA, with a skin notation.

Existing occupational exposure limits in some European countries and the USA are summarised in the annex.

8 Health hazard assessment

The health hazard assessment of dicrotophos is based mainly on a toxicology review issued by the Health Effect Division of the United States EPA for reregistration eligibility. The toxicity profile in this review is obtained mainly from unpublished toxicology studies conducted for registration purposes by the chemical companies manufacturing or marketing the compound.

Workers can be exposed to dicrotophos through inhalation of aerosols or by direct skin contact with a formulation. The committee did not find quantitative data on absorption of dicrotophos through the lungs or the skin. The extent of absorption following oral intake of dicrotophos is at least 63-71% within 48 hours in rat, but the committee did not find data for other species. Following

absorption, the compound is extensively metabolised into breakdown products, e.g., dimethyl phosphate, which are mainly excreted in the urine. There is no evidence of accumulation of the compound in any of the tissues.

Case studies in humans show a high acute toxicity of dicrotophos following accidental exposures. Effects observed in these studies were typical cholinergic symptoms such as strong inhibition of red blood cell AChE and plasma ChE activity, excessive salivation, reversible nerve paralysis, and respiratory difficulty. The recovery of red blood cell AChE or plasma ChE activity following intoxication is slow and may take more than one month.

In experimental animals, dicrotophos is irritating to the eyes but not to the skin, and a strong dermal sensitiser. Based on the results of acute lethal toxicity studies in test animals, the committee considers the compound as very toxic after oral and dermal exposure. In contrast, the Health Effect Division (HED) of EPA considers dicrotophos much less toxic via the dermal route (Hrd99). Inhibition of plasma ChE, red blood cell AChE, and brain AChE has been reported in one 13-week and two 2-year feeding studies in rats and in a 2-year feeding study in dogs. These cholinesterases have approximately the same sensitivity for inhibition by dicrotophos in these species. The NOAELs for brain and red blood cell AChE in rats (2-year studies) were 0.05 mg/kg bw/day and <0.02 mg/kg bw/day, respectively, and in dogs (2-year study) 0.04 mg/kg bw/day.

Dicrotophos has been found mutagenic in some *in vitro* assays. No *in vivo* studies have been reported. Two lifetime feeding studies in rats showed that dicrotophos was not carcinogenic to male and female rats. The committee concludes that the *in vitro* genotoxic effects of dicrotophos were thus not reflected in carcinogenicity.

The results of a reproduction study in rats showed a decrease in number of surviving pups at 0.25 mg/kg bw/day, indicating reproduction toxicity with a NOAEL of 0.1 mg/kg bw which is below the maternal NOAEL of 0.75 mg/kg bw/day. Teratology studies in rats and rabbits show that dicrotophos has no effect on prenatal development and did not increase fetal susceptibility at levels below maternal toxicity. Other published studies indicate that dicrotophos was teratogenic in birds but not in mice. It must be kept in mind that avian teratogenesis is a poor predictor of the same effect in mammals. Overall, the committee concludes that there is no evidence to consider dicrotophos as teratogenic for humans.

Based on the above data, the committee concludes that the mechanism of toxicity of dicrotophos in mammals is through inhibition of AChE activity in nerve tissue. The committee identifies inhibition of AChE in brain tissue as the

most sensitive adverse toxic effect of dicrotophos in animal studies, occurring at dose levels that are lower than those that cause other toxic effects. In human beings, for obvious reasons, brain AChE cannot be measured. Instead, red blood cell AChE, being the same molecular target for inhibition by organophosphorous pesticides as brain AChE, is used as a surrogate for brain AChE in assessing the human health risk of exposure to dicrotophos (Jey94). However, no data is available in the literature of effects of the compound on red blood cell AChE in human beings and, therefore, studies in test animals have to be used for the assessment of a health-based-recommended occupational exposure limit (HBROEL).

Because no short-term or long-term inhalation toxicity studies are available, the committee takes the 2-year feeding study in rats as a starting point in deriving a HBROEL. In this study, the NOAEL for brain AchE was 0.05 mg/kg/day. Since workers are exposed for 5 days a week, this NOAEL from a continuous feeding study (i.e., 7 days a week) is adjusted by multiplying with a factor of 7/5 resulting in a no-adverse-effect level (NAEL) of 0.07 mg/kg bw/day. For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall factor of 9, covering inter- and intraspecies variation are applied, resulting in a NAEL for humans of 0.002 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%, and applying the preferred-value approach, a health-based occupational exposure limit of 0.01 mg/m^3 is recommended for dicrotophos.

The committee recommends a health-based occupational exposure limit for dicrotophos of 0.01 mg/m^3, as an 8-hour time-weighted average (TWA).

Dicrotofos showed a high acute lethal dermal toxicity in rats. A ratio of the dermal LD_{50} and the calculated inhalation LD_{50} of less than 10 is proposed as one of the criteria for assigning a skin notation (ECE98). Since this criterion is met for dicrotofos, the committee recommends a skin notation.

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TRG00 TRGS900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2

War77 Warriner RA, Nies AS, Hayes WJ. Severe organophosphate poisoning complicated by alcohol and turpentine ingestion. Arch Environ Health 1977; 32: 203-5.

Wil75 Wild D. Mutagenicity studies on organophosphorus insecticides. Mutat Res 1975; 32: 133-50.

Annex

Occupational exposure limits for dicrotophos in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	0.25	8 h	administrative	S	SZW03
Germany						
- AGS	-	0.25			S	TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Arb02
Denmark	-	0.25	8 h		S	Swe00
USA						
- ACGIH	-	0.05[c]	8 h	TLV	S, A4[d]	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	-	0.25	10 h	REL	S	ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Measured as inhalable fraction of vapour and aerosol.

[d] Classified in carcinogen category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.