Naled

(CAS No: 300-76-5)

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 naled 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 L Portengen, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands)*.

In December 1999, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts, covering the period of 1964-1966 until December 1999, and using the following key words: naled, dibrom, and 300-76-5. Reviews published in the 'Handbook of pesticide toxicology' (Gal91) and by the American Conference of Governmental Industrial Hygienists (ACG99) were also used. Data of unpublished studies were generally not taken into account. Exceptions were made for studies that were summarised and evaluated by international bodies such the Food and Agricultural Organization/World Health Organization (FAO/WHO) (WHO78) and the Health Effects Division (HED) of the US Environmental Protection Agency (EPA) (Hum99), as part of its hazard identification assessment review. The final search was carried out in Toxline and Medline in May 2002.

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 literature search in Toxline and Medline in April 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	naled
synonyms	:	phosphoric acid 1,2-dibromo-2,2-dichloroethyl dimethyl ester; dimethyl 1,2-dibromo-2,2-dichloroethyl phosphate; bromchlophos; Dibrom; Bromex
molecular formula	:	$C_4H_7Br_2Cl_2O_4P$

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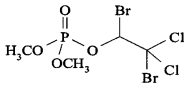
structural formula : 

CAS number : 300-76-5

3 Physical and chemical properties

molecular weight	:	380.78
boiling point	:	at 0.07 kPa: 120°C
melting point	:	26.5-27.5°C (pure)
flash point	:	-
vapour pressure	:	at 20°C: 0.3 Pa
solubility in water	:	poorly soluble (at 20°C: 0.2 g/100 mL)
Log $P_{octanol/water}$	:	1.38
conversion factors	:	not applicable

Data from ACG99, Gal91, NLM02, Rob99.

Pure naled is a white solid, while the technical form is 60% pure and is usually obtained as a liquid that has a slightly pungent odour. Naled is completely hydrolysed within 48 hours at room temperature in the presence of water. It is degraded by sunlight and should be stored in lightproof containers (ACG99).

4 Uses

Naled is used to control mites, sucking pests, and some other insects in a wide variety of crops. It is also used for the control of public and animal health pests including mosquitoes. Naled is available as a 4% dust and 96% emulsifiable concentrate.

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

* at: http://www.ctb-wageningen.nl/geel.html.

5 Biotransformation and kinetics

In cows and rats, oral doses of ^{32}P-labelled naled were rapidly excreted in the urine and faeces (>90%). Metabolism of naled occurs via debromination to yield 2,2-dichlorovinyl dimethyl phosphate (dichlorvos), hydrolysis to yield dimethyl phosphate and bromodichloroacetaldehyde, and demethylation to yield desmethyldichlorvos and monomethylphosphate (Cas62). In addition, the dichlorvos metabolite dichloroacetaldehyde might be formed (Hum99, Rob99).

6 Effects and mechanism of action

Human data

Naled was reported to have caused dermatitis in several publications. Contact sensitisation-type dermatitis was reported in women picking flowers sprayed with a mixture of naled (11%), captan (6%), and dicofol (2.4%). Results of patch tests gave strong evidence that naled had caused these effects (Edm67). In another case, contact dermatitis was reported in an aerial applicator who had used naled (Mic70). Technical-grade naled also was a skin irritant in adult white male volunteers (n=8-16) in a modified Draize skin irritancy test (5% w/v in ethanol), a 21-day continuous closed patch test (1% w/v), and a 21-day open patch test (at concentrations >10% w/v) (Phi72).

Animal data

Irritation and sensitisation

Naled caused dermal irritation in a modified Draize test with New Zealand white rabbits and is also a severe eye irritant (Phi72, Hum99). The chemical was weakly positive in a guinea pig maximisation test after induction and challenge with a 0.2% solution in distilled water. However, a 2% solution was extremely allergenic (Mat85).

Acute toxicity

Mice exposed to an air concentration of 1500 mg/m^3 naled for 6 hours did not show adverse effects (Tom94). However, EPA reported 4-hour inhalation LD_{50}s

of 200 and 190 mg/m^3 for male and female rats, respectively (EPA99). No further details were provided in either of the studies.

Acute inhalation LC_{50} values and dermal and oral LD_{50} values in test animals are summarised in Table 1.

Table 1 Acute lethal toxicity data for naled.

exposure route (duration)	vehiculum	species (strain)	sex	LC_{50} or LD_{50}	reference
inhalation (4 h)		rat	male	200 mg/m^3	Hum99
(4 h)		rat	female	190 mg/m^3	Hum99
(6 h)		mouse	not specified	>1500 mg/m^3	Tom94
dermal	xylene	rat (Sherman)	male	800 mg/kg bw	Gai69
		mouse	not specified	600 mg/kg bw	NIO02
		rabbit	male	390 mg/kg bw	Hum99
		rabbit	female	360 mg/kg bw	Hum99
		rabbit	not specified	1100 mg/kg bw	Wei93
oral	peanut oil	rat (Sherman)	male	250 mg/kg bw	Gai69
	corn oil	rat	male	325 mg/kg bw	Hum99
	carboxymethylcellulose	rat	male	191 mg/kg bw	Hum99
	carboxymethylcellulose	rat (Sprague-Dawley)	male	85.1[a] mg/kg bw	Hum99
		rat	female	281 mg/kg bw	Brz69
	soya bean oil	rat (Sprague-Dawley)	female	160 mg/kg bw	Ber78
	corn oil	rat	female	230 mg/kg bw	Hum99
	carboxymethylcellulose	rat	female	92 mg/kg bw	Hum99
	carboxymethylcellulose	rat (Sprague-Dawley)	female	81.2[a] mg/kg bw	Hum99
		rat	not specified	430 mg/kg bw	Wei93
	polysorbate 80	mouse (CD-1)	male	375 mg/kg bw	Hal75
	polysorbate 80	mouse (CD-1)	female	360 mg/kg bw	Hal75
	soya bean oil	mouse (NAMRU)	female	222 mg/kg bw	Ber78

[a] Preliminary study to an *in vivo* cytogenetics assay.

In an acute neurotoxicity study, male and female rats (no numbers given) were given single oral (gavage) doses of naled of 0, 25, 100, or 400 mg/kg bw. Functional observational battery (FOB) and locomotor activity were assessed pre-treatment, and 30 minutes, 7, and 14 days after treatment. The high dose caused mortality, overt clinical signs of toxicity (e.g., orange/yellow material on body surfaces; red material around mouth/nose/eyes), and a transient decrease in body weight gain (days 0-7). Animals given 100 and 400 mg/kg bw showed marked effects in the FOB on the day of treatment. Convulsions, tremors, increased secretions, exophthalmus, respiratory changes, reduced muscle strength, slowed response to stimuli, and reduced total motor activity were observed. At 25 mg/kg on the day of treatment only, one female had tremors, 2 displayed exophthalmus, and one had reduced hind limb grip strength. No effects were observed 7 or 14 days after treatment at any dose level. The NOAEL for acute neurotoxicity was 25 mg/kg bw in males. Although no NOAEL could be identified for females, based on the minimal neurological findings in the main study and the lack of toxicity at doses of 5 and 25 mg/kg bw in the preliminary range-finding study (no details given), the NOAEL for female rats was set at 5 mg/kg bw (Hum99).

Adult domestic hens (n=40) were given an acute LD_{50} dose of naled (42 mg/kg), preceded by treatment with atropine sulphate and 2-PAM to protect from acute cholinergic effects. Animals were observed for neurotoxic signs for 21 days, re-dosed, observed for another 21 days, and then sacrificed for histological examination of central and peripheral nervous system tissue. Four treated and 2/10 control hens died during the study. All treated animals showed clinical signs of neurotoxicity (‘subdued’, unsteady), but did not display locomotor ataxia characteristic of delayed neurotoxicity. Axonal degeneration was increased in the spinal cord compared to controls, but it was less severe than that produced by the positive control. A second group of hens (number not presented) was treated with single doses of 8 and 42 mg/kg bw and sacrificed 24 hours later for determination of brain AchE and neurotoxic esterase activities. Brain AChE was markedly depressed (50% at 42 mg/kg bw), but neuropathy target esterase (NTE) activity was unaffected (no more data presented) (Hum99).

Short-term toxicity

No toxic effects were observed in rats and guinea pigs exposed to naled at a concentration of 19 mg/m^3, 6 hours/day, 5 days/week, for 5 weeks. At 42 mg/m^3, discomfort and inactivity were evident and cholinesterase activity (not further specified) was depressed (ACG99, WHO78). Exposure of rats (numbers and strain not given) to an aerosol of technical-grade naled at concentrations of 3.4, 7.2, or 12.1 mg/m^3, 6 hours/day, 5 days/week, for 3 weeks, caused a dose-dependent inhibition of brain and red blood cell acetylcholinesterase (AChE) and of plasma cholinesterase (ChE). Inhibition of cholinesterases started already at the lowest air concentration in both male and female rats (no more data presented) (Rit85). In a 13-week inhalation study, male and female Fischer 344 rats (no numbers given) were exposed to aerosols containing 0, 0.2, 1, or 6 mg/m^3 of naled, 6 hours/day, 5 days/week. Additional control and high-concentration groups recovered for 6 weeks. At 6 mg/m^3, brain and red blood cell AChE and plasma ChE were all inhibited (% not specified), and clinical signs consistent with cholinergic effects (tremors, salivation, nasal discharge, abnormal respiration, and anogenital staining) were observed. Only plasma ChE continued to be inhibited (% not given) after the 6-week exposure-free period. At 1 mg/m^3, plasma ChE (25-30% throughout the study) and red blood cell AChE (50-60% early in the study, 25-30% at 13 weeks) were still inhibited, but brain AChE activity was not different from the control group. The 13-week NOAEL for brain AChE inhibition in this study is 1 mg/m^3 and for plasma ChE and RBC AChE inhibition 0.2 mg/m^3 (Hum99).

In a 28-day dermal study, doses of 0, 1, 20, or 80 mg/kg bw/day of naled in carboxymethylcellulose were applied to the intact skin of male and female CD/Sprague-Dawley rats (no numbers given). The 2 highest doses produced severe skin irritation (erythema, oedema, necrosis, and exfoliation), reduced body weight gain, and inhibition of brain AChE, red blood cell AChE, and plasma ChE activities. At 20 mg/kg bw, these activities were decreased by 60%, 25%, and 50%, respectively. At the top dose, blood urea nitrogen was increased but creatinine, total protein, and albumin concentrations were decreased. Gross pathology revealed increased liver and adrenal weights (not specified) of females but histopathology did not show abnormalities. The NOAEL for dermal irritation, systemic toxicity, brain and red blood cell AChE, and plasma ChE inhibition was 1 mg/kg bw/day (Hum99).

Groups of male and female rats (species and numbers not given) were given technical naled in their diets at doses equivalent to 10, 20, and 40 mg/kg bw for

28 days and to 40, 80, and 160 mg/kg bw for 29-94 days. Significant growth depressions and reduced food intake were observed at the 2 top doses. At 160 mg/kg bw, there were tremors in some animals but no mortality occurred. No abnormalities in haematology or clinical chemistry and no gross or microscopic changes were found. Cholinesterase activities were not reported (WHO78). In a 28-day oral (gavage) study, rats (n=10/sex/group) were given doses of naled (purity: not presented) of 0, 0.25, 1, 10, or 100 mg/kg bw/day. Feeding 100 mg/kg bw/day produced mortality and marked cholinergic signs of toxicity. At 10 mg/kg bw/day, mild cholinergic signs and marked inhibition of plasma ChE and brain AChE (50%) were observed. Feeding of 1 mg/kg bw/day resulted in a small decrease (15%) in plasma ChE activity only. The NOAEL for brain AChE inhibition in this study is therefore 1 mg/kg bw/day (no more details presented) (Hum99). Rats tolerated a dose of 28 mg/kg bw/day for 9 weeks without visible signs of poisoning and with only moderate inhibition of plasma ChE and brain AChE. No further details were given (Brz69). Rats given approximately 5 mg/kg bw/day of technical naled in the diet for a period of 12 weeks did not show signs of toxicity. Further details were not available (Tom94, Wei93).

In a 90-day neurotoxicity study, male and female Sprague-Dawley rats (number not presented) were given naled (purity: 94.4%) at doses of 0, 0.4, 2.0, or 10.0 mg/kg/day by gavage. Neurological parameters were measured by both the FOB and locomotor activity. Minimal neurological effects (tremors of forelimb, hind limb, whole body) were recorded in 3 out of 10 females at the high dose, but no other clinical effects were observed. The 90-day neurotoxic NOAEL was 2.0 mg/kg bw (Hum99).

Dogs were given dietary levels of 0.25, 0.75, 2.5, and 7.5 mg/kg bw/day for 89 days. No mortality or clinical symptoms of intoxication were observed. Haematology, urinalysis, liver and kidney function tests, and gross and microscopic examination did not reveal adverse effects. At 2.5 and 7.5 mg/kg bw/day, red blood cell AChE and plasma ChE activities were reduced in all animals. Plasma ChE was slightly inhibited at 0.25 and 0.75 mg/kg bw. The 13-week NOAEL for inhibition of red blood cell AchE was 0.75 mg/kg/day (no more details presented) (WHO78). In another study, naled in aqueous carboxymethylcellulose (0.5% w/w) was administered by gavage to male and female beagle dogs for one year at doses of 0, 0.2, 2, or 20 mg/kg bw/day. The 2 highest doses produced clinical signs of emesis, diarrhoea, and increases in mineralisation of the lumbar spinal cord in both sexes. Red blood cell count, haemoglobin levels, and haematocrit were decreased at these doses. At the high dose only, liver and kidney weights were increased but no histological changes

were found. At 2 mg/kg bw, brain AChE was inhibited by 5-17% (females only), red blood cell AChE by 43-58%, and plasma ChE by 24-48%. The 1-year NOAEL was 0.2 mg/kg bw for inhibition of brain and red blood cell AChE and for systemic toxicity (Hum99).

Laying hens given oral doses of 0, 0.4, 2.0, or 4.0 mg/kg bw/day of technical naled for 28 days did not display any treatment-related signs of clinical or delayed neuropathy. Brain AChE was inhibited at both 2.0 and 4.0 mg/kg bw/day (Hum99).

The results of the short-term toxicity studies in mammals are summarised in Table 2.

Table 2 Summary of short-term toxicity studies for naled in mammals.

exposure route	species	dose levels	exposure duration	critical effect[a]	NOAEL[b]	reference
inhalation	rat	19, 42 mg/m^3	5 w	BAChE RAChE	19 19	ACG99, Gal91, WHO78
	rat	3.4, 7.2, 12.1 mg/m^3	3 w	BAChE RAChE	<3.4 <3.4	Rit85
	rat (Fischer 344)	0, 0.2, 1, 6 mg/m^3	13 w	BAChE RAChE	1 0.2	Hum99
dermal	rat (Sprague-Dawley CD)	0, 1, 20, 80 mg/kg bw/d	28 d	BAChE RAChE	1 1	Hum99
oral	rat	10, 20, 40 mg/kg bw/d	28 d			WHO78
	rat	40, 80, 160 mg/kg bw/d	29-94 d	clinical signs	40	
	rat	0, 0.25, 1, 10, 100 mg/kg bw/d	28 d	BAChE	1	Hum99
	rat	28 mg/kg bw/d	9 w	BAChE	<28	Brz69
	rat	5 mg/kg bw/d	12 w	clinical signs	5	Tom94, Wei93
	rat (Sprague-Dawley)	0, 0.4, 2, 10 mg/kg bw/d	90 d	neurological	2	Hum99
	dog	0, 0.25, 0.75, 2.5, 7.5 mg/kg bw/d	89 d	RAChE	0.75	WHO78
	dog (beagle)	0, 0.2, 2, 20 mg/kg bw/d	1 y	BAChE RAChE	0.2 0.2	Hum99

[a] BAChE=brain AChE; RAChE=red blood cell AchE.
[b] mg/m^3 or mg/kg bw/day.

Long-term toxicity and carcinogenicity

In a 2-year oral (gavage) toxicity/carcinogenicity study, male and female Sprague-Dawley CD rats (no numbers given) were given (purity: not specified) in aqueous carboxymethylcellulose (0.5% w/w) at doses of 0, 0.2, 2, or 10 mg/kg bw/day. There was a dose-related reduction of cholinesterase activities. At 2 mg/kg/day, brain AChE was depressed by 24%, red blood cell AChE by 4-33%, and plasma ChE by 54-60%. No other treatment-related findings were observed. The incidence of neoplastic lesions in the treated animals was similar to that of the controls. No further details were provided. The NOAEL for inhibition of brain and red blood cell AChE was 0.2 mg/kg bw/day and for systemic toxicity 10 mg/kg bw/day (Bat84). Rats were daily given 100 mg/kg bw of technical naled (purity: 91%) in their diets for a period of 2 years. No adverse effects were observed. No further details were given (Tom94, Wei93).

In an 89-week carcinogenicity study naled in aqueous carboxymethylcellulose (0.5% w/w) was administered to male and female CD-1 mice by gavage at doses of 0, 3, 15, or 75 mg/kg bw/day. The high dose was reduced to 50 mg/kg bw after 26 weeks due to high mortality (10-13% after 26 weeks; 2% in controls). Body weight gain was reduced in male mice at the levels of 15 and 50/75 mg/kg bw/day. Cholinesterase activities were not determined. No treatment-related neoplastic findings were observed (Hum99).

Mutagenicity and genotoxicity

Mutagenicity and genotoxicity assays comprised tests for the detection of gene mutations in bacteria and *in vitro* and *in vivo* cytogenicity and other *in vitro* genotoxicity assays.

- *In vitro* tests:
  - Gene mutation assays. Naled was tested positive for reverse mutations in the TA100 strain of *S. typhimurium* at concentrations of 0.5, 1, and 2 µM with and without metabolic activation. Supplementation of the S9 mix with reduced glutathion reduced the mutagenic activity of naled (Brau83). At concentrations up to 300 µg/plate, naled increased the frequency of reverse gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, TA1536, TA1537, and TA1538 and in *B. subtilis* strains TKJ5211 and TKJ6321. This activity was reduced when an induced rat liver S9 mix was added (Shi81). In a similar bacterial reversion-assay with *S. typhimurium*

strains TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli* strain WP2 *hcr*, no mutagenic activity was noted when tested with and without metabolic activation at doses up to 5000 µg/plate (Mor83). In assays performed without metabolic activation only, naled was positive only in *S. typhimurium* strain TA1535 after an overnight incubation of a saturated aqueous solution at 45ºC in a water bath before spot testing, and produced negative results in a set of other *S. typhimurium* LT-2 strains as well as in a set of isogenic *E. coli* WP2 strains (Han75). Naled at concentrations of 0.1, 1.0, 10, or 100 µg/plate did not induce reverse gene mutations in the β-lactamase gen in a recently developed assay with *S. typhimurium* (Hou98).

- Cytogenicity assays. Naled induced chromosome aberrations and micronuclei in an *in vitro* mouse culture. No further details were given (Sha88).
- Other genotoxicity assays. Naled was tested for DNA damage in a rec-type repair test with *P. mirabilis* strains. The chemical was negative at inhibitory concentrations of 10 and 40 µM/plate (Bra83).

- *In vivo* tests:

Male and female Swiss mice that were given naled as a single oral dose of 0, 55, 110, 220 (males), or 290 (females) mg/kg bw did not show an increased incidence of micronuclei in polychromatic bone marrow erythrocytes. Naled had no cytotoxic effect on bone marrow cells at these dose levels (Hum99). In another study, male and female Sprague-Dawley rats were given single oral doses of 0, 6.2, 21, or 62 mg/kg bw for males and of 0, 3.9, 13, or 39 mg/kg bw for females. Naled did not show clastogenic effects in bone marrow cells. No cytotoxicity was found at any dose level. No further details were given (Hum99).

Reproduction toxicity

In an oral (gavage) 2-generation reproduction study, Sprague-Dawley CD rats were given naled at doses of 0, 2, 6, or 18 mg/kg bw/day. Body weight gain was depressed at 18 mg/kg bw for F0 males and at all dose levels for F1 males. Reproduction indices were unaffected in both generations. Survival of pups was reduced at 18 mg/kg/day in F1 and F2b generations. A decrease in pup weight was also noted during lactation in both generations. No further details were provided. The NOAELs for parental and reproduction toxicity were 6 mg/kg bw/day (Hum99).

In an oral (gavage) teratology study, Sprague-Dawley rats were given naled at doses of 0, 2, 10, or 40 mg/kg/day on days 6-19 of gestation. Dams were sacrificed at day 20. At 40 mg/kg bw/day, maternal toxicity (clinical signs and reduced weight gain) was observed. Apart from a marginal increase in litters with 2 or more resorptions, no treatment-related developmental effects were found. This increase in resorptions occurred at a dose that was maternally toxic (40 mg/kg bw). No further details were provided. The NOAEL for maternal toxicity was 10 mg/kg bw and for developmental toxicity 40 mg/kg bw (Hum99). In another teratology study, naled was orally (gavage) administered to female rats (n=20/group) at doses of 25, 50, and 100 mg/kg (36% w/v formulation) on days 6-15 of gestation. A slightly higher number of fetuses with delayed ossification of the sternebrae were found in the high-dose group. However, these effects were not statistically significant and according to the authors, they were probably not related to treatment (Khe79). Artificially inseminated New Zealand rabbits were given oral (gavage) doses of naled of 0, 0.2, 2, or 8 mg/kg/day on days 7-19 of gestation. Does were sacrificed on day 29. No treatment-related maternal or developmental toxicity was reported. No further details were provided (Hum99).

In an *in vivo*/*vitro* teratology study, naled was administered to pregnant Wistar rats either 4 or 24 hours prior to the delivery of embryos at day 10 of gestation. The rate of development of these embryos was monitored in an *in vitro* culture of Waymouth's medium and fetal calf serum and was found to be inhibited. No details were provided about the dose levels of naled used (Bea81).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for naled in the Netherlands is 3 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

The health hazard assessment of naled is mainly based on toxicology reviews issued by the Health Effect Division of the US EPA (Hum99) and by the FAO/ WHO (WHO78). The toxicity profile in these reviews is obtained mainly from unpublished reports of toxicology studies conducted for registration purposes by the chemical companies manufacturing or marketing the compound.

Absorption of naled into the body may occur via inhalation, skin contact, or oral ingestion. In the only experimental animal study reported, it is stated that following oral dosing, naled is rapidly metabolised into breakdown products, which are mainly excreted in the urine.

In humans, skin contact with naled may lead to severe irritation or to allergic dermatitis. No cases of mortality or systemic effects have been reported in humans manufacturing or using the chemical or its formulations.

In test animals, naled is irritating to the eyes and the skin, and a dermal sensitiser. Based on results of acute lethal toxicity studies in test animals, the committee considers the compound as very toxic via the respiratory route and toxic via the dermal and oral routes. The compound did not cause neurological changes indicative of acute delayed neurotoxicity. In some of the short-term toxicity studies in rats and dogs, liver or kidney damage or anaemia was reported at high dose levels. Most short-term toxicity studies in rats and dogs and the long-term/carcinogenicity study in rats showed inhibition of plasma ChE and of red blood cell and brain AChE. Plasma ChE and red blood cell AChE appeared to be somewhat more sensitive for inhibition by naled than brain AChE in these species. The inhalation NOAELs were 1 and 0.2 mg/m^3 for brain and red blood cell AChE inhibition, respectively, in rats (13-week study). The dermal NOAEL for both brain and red blood cell AChE inhibition was 1 mg/kg bw (28-day dermal study) in rats while 0.2 mg/kg bw was the oral NOAEL in both rats (2-year study) and dogs (one-year oral study).

Results of *in vitro* gene mutation tests with naled were conflicting and seem to be dependent on the test system used. Naled induced chromosome aberrations *in vitro,* but cytogenicity assays in mice did not show an increased incidence of abnormalities. Carcinogenicity studies in rats and mice did not show a treatment-related increase in tumour incidence. The committee concludes that the positive genotoxic effects of naled were thus not reflected in carcinogenicity. Effects on reproduction toxicity with rats were observed at doses that caused toxicity in parental animals, and were considered to be due to maternal toxicity by the committee.

Based on the above data, the committee concludes that the mechanism of toxicity of naled 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 naled 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 organophosporus pesticide as

brain AChE, is used as a surrogate for brain AChE in assessing the human health risk of exposure to naled (Jey94).

The committee has chosen the 13-week inhalation study in rats, producing a NOAEL of 0.2 mg/m^3 for inhibition of red blood cell AChE, as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall factor of 9 is established, covering the following aspects: intra-and interspecies variation. Thus, applying this factor and the preferred-value approach, a health-based occupational exposure limit of 0.02 mg/m^3 is recommended for naled.

The committee recommends a health-based occupational exposure limit for naled of 0.02 mg/m^3, as an 8-hour time-weighted average (TWA).

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 not met for naled*, the committee does not recommend a skin notation.

References

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ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 92.

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* The dermal LD_{50} in rats is 800 mg/kg bw; the inhalation LD_{50} calculated from the 4-hour LC_{50} of 200 mg/m^3 in rats (assuming a retention of 1.0 and a minute volume of 125 mL/min for a 200-g weighing rat) is ca. 60 mg/kg bw.

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Annex

Occupational exposure limits for naled 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	-	3	8 h	administrative	S	SZW03
Germany						
- AGS	-	3[c]	8 h		S	TRG00
	-	12	15 min			
- DFG MAK-Kommission	-	3[c]	8 h			DFG02
	-	6	15 min[d]			
Great Britain						
- HSE	-	3	8 h	OES		HSE02
	-	6	15 min			
Sweden	-	-				Swe00
Denmark	-	3	8 h			Arb02
USA						
- ACGIH	-	0.1[c]	8 h	TLV	S, sens, A4[e]	ACG03b
- OSHA	-	3	8 h	PEL		ACG03a
- NIOSH	-	3	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 the inhalable fraction.

[d] Maximum frequency per shift: 4, with a minimum interval between peaks of 1 hour.

[e] 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.