2-Chloro-6-(trichloromethyl)pyridine (nitrapyrin)

(CAS reg no: 1929-82-4)
Health-based Reassessment of Administrative Occupational Exposure Limits

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

No. 2000/15OSH/032, The Hague, 7 March 2002

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. 2-Chloro-6-(trichloromethyl)pyridine (nitrapyrin); Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2002; 2000/15OSH/032.

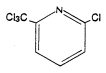
1 Introduction

The present document contains the assessment of the health hazard of 2-chloro-6-(trichloromethyl)pyridine 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 mrs MA Maclaine Pont, M.Sc. (Wageningen University, Wageningen, the Netherlands).

Literature was retrieved from the data bases Medline, Toxline, and Chemical Abstracts, covering the periods 1981 until May 2000, 1966 until May 2000, and 1937 until March 2000, respectively, and using the following key words: nitrapyrin, chloropicolinic, 6-chloropicolinic acid, 2-chloro-6-(trichloromethyl)pyridine, 1929-82-4, and 4684-94-0. Data considered to be critical were evaluated by reviewing the original publications. The final search has been carried out in December 1999.

In July 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	2-chloro-6-(trichloromethyl)pyridine
synonyms	:	nitrapyrin; α,α,α, 6-tetrachloro-2-picoline
molecular formula	:	$C_6H_3NCl_4$
structural formula	:	
CAS reg no	:	1929-82-4

Data from ACG99, How92.

3 Physical and chemical properties

molecular weight	:	230.9
boiling point	:	at 1.4 kPa: 136-137°C
melting point	:	62-63°C
vapour pressure	:	at 23°C: 0.4 Pa
solubility in water	:	insoluble
Log $P_{octanol/water}$	:	3.41 (experimental); 3.35 (estimated)
conversion factors (20°C, 101.3 kPa)	:	not applicable

Data from ACG99, Ric96, http://esc.syrres.com.

2-Chloro-6-(trichloromethyl)pyridine is a white crystalline solid with a mildly sweet odour (ACG99).

4 Uses

2-Chloro-6-(trichloromethyl)pyridine is used as a fertiliser additive to control nitrification and to prevent loss of nitrogen in soil (ACG99).

5 Biotransformation and kinetics

2-chloro-6-(trichloromethyl)pyridine

After oral administration of ^{14}C-2-chloro-6-(trichloromethyl)pyridine to one female dog, at least 80% of the radioactivity was excreted via the urine as *N*-(6-chloropicolinoyl)glycine. No half-life time was given (Red66). After feeding 2-chloro-6-(trichloromethyl)pyridine spiked with ^{14}C-2-chloro-6-(trichloromethyl)pyridine at 100 mg/kg diet for a number of days to rats, mainly 6-chloropicolinic acid and to a lesser extent *N*-(6-chloropicolinoyl)glycine were excreted. There are no quantitative data (Red67).

The committee concluded that the main metabolite of 2-chloro-6-(trichloromethyl)pyridine is 6-chloropicolinic acid, and that, depending on the species, a certain percentage is conjugated to glycine.

6-chloropicolinic acid

After oral administration of ^{14}C-chloropicolinic acid to rats, approximately 98% of the dose was excreted via the urine within 48 hours, with 1.5% and 1.3% eliminated via the faeces and expired air, respectively. The parent compound and its glycine conjugate accounted for 100% of the ^{14}C eliminated via the urine during the first 8 hours following administration. The half-life for elimination of chloropicolinic acid from the body was calculated to be 2.4 hours, and the half-life for clearance of ^{14}C from the blood was 1.1 hour (Ram74).

After 28 days of feeding 6-chloropicolinic acid to cattle at 100 mg/kg diet the compound could not be detected in fat and, therefore, does not accumulate in body tissues (Ken80).

6-Chloropicolinic acid was fed to cows first at 1 mg/kg food for 14 days, then at 10 mg/kg for 14 days, and finally at 100 mg/kg for 21 days. No residues were found in milk and cream (detection level 0.02 mg/kg). Since the cows ate 16.3 kg of feed daily, the intake of 6-chloropicolinic acid was calculated to be 3.4 mg/kg bw at the high dose level (Jen71). Also from this study, it can be concluded that the compound does not accumulate in fat.

Also in young pigs, no residues were detected in muscle, fat, or liver after feeding them with 10, 30, or 300 mg 6-chloropicolinic acid per kg food for 30 days. At the highest dose level, the kidneys contained 0.09-0.3 mg of the compound/kg organ tissue (Mul76).

6 Effects and mechanism of action

Human data

The committee did not find human data on the effects of exposure to 2-chloro-6-(trichloromethyl)pyridine.

Animal data

Acute toxicity

2-chloro-6-(trichloromethyl)pyridine

The following acute lethal toxicity data have been found for 2-chloro-6-(trichloromethyl)pyridine (Lew00, Mul76):

LD_{50} oral rat: 940, 1070, 1230 mg/kg bw
LD_{50} oral mouse: 710 mg/kg bw
LD_{50} oral rabbit: 713 mg/kg bw
LD_{50} dermal rabbit: 850 mg/kg bw.

6-chloropicolinic acid,

The following acute lethal toxicity data have been found for 6-chloropicolinic acid:

LD_{50} oral: male rats: 2830 mg/kg bw, female rats: 2180 mg/kg bw (Mul76).
LD_{50} oral: male mice: 1835 mg/kg bw, female mice: 1089 mg/kg bw (Dow86).

Repeated dose toxicity/carcinogenicity

2-chloro-6-(trichloromethyl)pyridine

A 94-day dietary feeding study in rats and dogs indicate a low order of chronic toxicity of 2-chloro-6-(trichloromethyl)pyridine. The following parameters were assessed: general appearance and behaviour, growth, food consumption, final body and organ weights, mortality, haematological, serum urea nitrogen and alkaline phosphatase determination, and gross and microscopic examination of tissues and organs. No adverse effects were observed in rats and dogs on daily level of 300 and 600 mg/kg diet, respectively. These levels correspond to a daily ingestion rate of 15 mg/kg bw for both species (unpublished studies from Dow Chemical Company from 1963, 1967, 1969, 1971, 1972, and 1974, summarised in Mul76 and ACG99).

2-Chloro-6-(trichloromethyl)pyridine was fed to groups of male and female rats at concentrations of 0, 30, 100, 300 or 1000 mg/kg diet, for 2 years. These dietary levels correspond with a daily ingestion of approximately 1.5, 5, 15, and 50 mg/kg bw. In the male rats fed 1000 mg/kg diet, a statistically significant reduction in mean body weight was recorded at 12 months, but decreases in body weight were not significant at 18 and 24 months.

In the female rats fed 30-1000 mg/kg diet, an increased incidence of bile duct hyperplasia was found (ACG99, no other details were available).

6-chloropicolinic acid

In 2-year feeding studies with 6-chloropicolinic acid, no adverse effects were observed in rats and dogs at 300 and 2000 mg/kg diet, respectively, in both the 90-day and 2-year feeding studies. These dietary levels correspond to a daily ingestion of 15 and 50 mg/kg bw for rats and dogs, respectively (studies from 1967 and 1970, summarised in Mul76, made available to the EPA in 1992).

Some data are available of a 2-year feeding study in mice. Groups of 70 male and 70 female B6C3F1 mice received doses of 6-chloropicolinic acid of 0, 100, 300, or 900 mg /kg bw/d. Ten mice per sex and per dose group were scheduled for interim sacrifices: one after 6 monhts and one after 12 months. The rest of the mice were scheduled for sacrifice after 24 months. Parameters examined included in-life body weight, feed consumption, palpation and clinical observations, mortality rates, clinical chemistry, haematology, final body and organ weights, gross pathology and histopathology. In the male animals of the high-dose group, body weights were decreased throughout most of the study and there were renal lesions evident at all sacrifices and consisting of a total or near-total loss of the normal vacuolation present in proximal tubular epithelial cells. In the female mice of this group, there was increased incidence of hepatocellular carcinomas of 12%. This increase did not show a statistical trend and was not significant in pairwise comparisons. It was slightly outside the control range (0 - 8%) found in mice in previous studies in the same laboratory, but within the range of control incidences (0 - 15%) for other laboratories using the B6C3F1 mouse. In addition, the incidence of total liver tumours in female mice of the 900 mg/kg-group was within historical control ranges of the same laboratory and was not statistically significant. The authors concluded that the biologic significance of this equivocal increase in hepatocellular carcinomas was questionable and may be a reflection of normal variability since there were no indications of a hepatotoxic effects. The authors concluded that 300 mg/kg bw is a NOAEL for male and female mice when given via the food during 2 years (Dow86). The committee noticed that detailed data on the study were lacking: although the study contained many tables, they were not present in the copy made available to the committee, and the committee did not succeed in retrieving them. The document did not contain information on the bile duct, whereas this was the target organ in

female rats after oral dosing of 2-chloro-6-(trichloromethyl)pyridine *(i.e.*, the parent compound). In this mouse study, the gall bladders were collected and preserved at necropsy. Therefore, presumably the gallbladders have been investigated and probably no effects have been found.

Mutagenicity and genotoxicity

2-Chloro-6-(trichloromethyl)pyridine was - in some cases weakly - positive when tested in *S. typhimurium* strains TA97, TA98, and TA100 with rat or hamster liver metabolic activation but negative when tested without metabolic activation. Testing with and without similar metabolic activation systems, results were negative in *S. typhimurium* strain TA1535 as well (Zei88).

The committee did not find data on other mutagenicity/genotoxicity tests and concluded that the mutagenic and genotoxic properties of 2-chloro-6-(trichloromethyl)pyridine should be investigated further.

Reproduction toxicity

2-chloro-6-(trichloromethyl)pyridine

Groups of pregnant Fischer 344 rats received daily oral doses of 0, 5, 15, or 50 mg 2-chloro-6-(trichloromethyl)pyridine/kg bw on gestation days 6-15. The high dose produced slight histological changes in the livers of pregnant females. There were no statistically significant differences in any of the reproductive or teratogenicity parameters (Ber88). The committee concluded that 2-chloro-6-(trichloromethyl)pyridine is not a reproductive toxicant in rats at dose levels up to 50 mg/kg bw/d, when given during organogenesis.

Groups of pregnant New Zealand white rabbits received daily oral doses of 0, 3, 10, or 30 mg 2-chloro-6-(trichloromethyl)pyridine/kg bw on gestation days 6-18. A significant depression in maternal weight gain and increased absolute and relative liver weights were observed at the high dose. At the low dose, the resorption rate was increased ($p<0.05$), but as these values fell within the range of the incidence of resorptions in historical control groups, and as the response was not dose-related, the apparent increase was not considered treatment-related by the authors. Treatment-related effects were limited to an increase in crooked hyoid bones at the high dose ($p<0.05$), with no effects observed in the lower treatment groups (Ber88). The committee concluded that when orally given during organogenesis, 2-chloro-6-(trichloromethyl)pyridine

was not teratogenic in rabbits but that it induced fetotoxicity at a maternally toxic dose of 30 mg/kg bw.

6-chloropicolinic acid

No adverse effects were seen on fertility, gestation, viability, lactation, body weights at weaning and mating and examination of fetuses for teratological effects in rats fed doses of 6-chloropicolinic acid up to 1000 mg/kg diet (the highest dose tested) in a 3-generation study with 2 litters per generation (unpublished study from 1967, summarised in Mul76).

7 Existing guidelines

The current adminstrative occupational exposure limit (MAC) for 2-chloro-6-(trichloromethyl)pyridine in the Netherlands is 10 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

After oral dosing, 2-chloro-6-(trichloromethyl)pyridine is rapidly excreted via the urine as 6-chloropicolinic acid. Studies with 6-chloropicolinic acid also show its rapid excretion in rats and the absence of accumulation in body tissues of cattle and young pigs.

From acute oral and dermal lethality data in rats and rabbits, respectively, the committee considers 2-chloro-6-(trichloromethyl)pyridine to be harmful if swallowed and when in contact with skin.

In a 94-day feeding study with 2-chloro-6-(trichloromethyl)pyridine, no effects were observed in rats and dogs given 15 mg/kg bw (ACG99, Mul76). In a 2-year feeding study with 2-chloro-6-(trichloromethyl)pyridine, an increased incidence of bile duct hyperplasia was found in female rats given 1.5 mg/kg bw (ACG99). However, 6-chloropicolinic acid, its major metabolite, did not induce this effect in rats and dogs given up to 15 and 50 mg/kg bw for 2 years, respectively, (Mul76), and probably also not in mice given up to 900 mg/kg bw for 2 years (Dow86). Therefore, the committee is of the opinion that the bile duct hyperplasia in female rats might be an incidental finding and is of questionable relevance. Apart from a questionable increased incidence of

hepatocellular carcinomas in female mice fed doses of 6-chloropicolinic acid of 900 mg/kg bw, for 2 years, no increases in the incidences of any tumour were reported following long-term oral administration of 2-chloro-6-(trichloromethyl)pyridine and 6-chloropicolinic acid.

2-Chloro-6-(trichloromethyl)pyridine was mutagenic when tested in an *in vitro* bacterial system (*S. typhimurium)*. No other information on the potential mutagenicity/genotoxicity was available.

2-Chloro-6-(trichloromethyl)pyridine (and 6-chloropicolinic acid) showed no reproduction toxicity after feeding pregnant rats and rabbits during organogenesis (Ber88).

The committee considers the toxicological data base on 2-chloro-6-(trichloromethyl)pyridine too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the present MAC level.

References

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Annex

Occupational exposure limits for 2-chloro-6-(trichloromethyl)pyridine in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	10	8 h	administrative		SZW01
Germany						
- AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG01
Great Britain						
- HSE	-	10	8 h	OES		HSE01
	-	20	15 min			
Sweden	-	-				Arb00b
Denmark	-	-				Arb00a
USA						
- ACGIH	-	10	8 h	TLV	C	ACG01
	-	20	15 min	STEL		
- OSHA	-	15[d]; 5[e]	8 h	PEL		ACG00
- NIOSH	-	10[d]; 5[e]	10 h			ACG00
	-	20[d]	15 min	REL		
European Union						
- SCOEL	-	-				CEC00

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

[d] Total dust

[e] Respirable dust