Picric acid

(CAS No: 88-89-1)

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

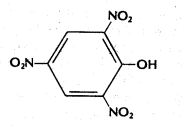
The present document contains the assessment of the health hazard of picric acid by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. and MM Verberk, Ph.D. (Coronel Institute of the Academic Medical Center, Amsterdam, the Netherlands).

Literature was retrieved from the databases Medline, Embase, and Chemical Abstracts starting from 1966, 1988, and 1970, respectively. HSEline, Cisdoc, Mhidas, and NIOSHTIC (covering the period 1985/87 until 1998) as well as Poltox (Toxline, Cambridge Scient. Abstr., and FSTA; covering the period 1990-1995), data bases available on CD-ROM, were also consulted. The following key words were used: picric acid, 2,4,6-trinitrophenol, and 88-89-1.

Data considered to be critical were evaluated by reviewing the original publications. The final literature search was carried out in May 1998.

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

2 Identity

name	:	picric acid
synonyms	:	2,4,6-trinitrophenol; trinitrophenol; 2-hydroxy-1,3,5-trinitrobenzene; carbazotic acid; picronitric acid; phenol trinitrate; nitroxanthic acid
molecular formula	:	$C_6H_3N_3O_7$
structural formula		
CAS number	:	88-89-1

3 Physical and chemical properties

molecular weight	:	229.1
boiling point	:	explodes above 300°C
melting point	:	122-123°C
flash point	:	150°C (closed cup)
vapour pressure	:	at 20°C: <0.01 kPa
solubility in water	:	slightly soluble
Log $P_{octanol/water}$	:	1.33
conversion factors (20°C, 101.3 kPa)	:	not applicable

Data from ACG99, NLM01.

Picric acid consists of colourless to pale yellow, odourless, intensely bitter crystals. Apart from heating, it may explosively decompose on shock or concussion or friction (NLM01).

4 Uses

Picric acid is used in explosives, matches, in leather industry, electric batteries, etching copper, manufacture of coloured glass and textile mordant, as a laboratory chemical, and as medicinal ointment. (ACG99, NLM01).

5 Biotransformation and kinetics

Wyman et al. studied the kinetics of picric acid in male rats (Fischer 344; n=4) by oral or intravenous administration of doses of ^{14}C-labelled picric acid of 100 and 50 mg/kg bw, respectively. Following intravenous injection, the amount of radioactivity excreted in urine and faeces was approximately 60 and 9% of the dose administered, respectively, during the first 24 hours, and increased to approximately 86 and 17%, respectively, after 48 hours. After an initial blood distribution period of 2 hours, radioactivity was eliminated following first-order kinetics with an elimination rate constant (k_{el}) of 0.052 h^{-1} and a plasma half-life of 13.4 h. Following oral administration, absorption of picric acid from the gut into the blood continually increased during a period of one hour, which was followed by elimination from the blood in a biphasic fashion. Comparison of

oral and intravenous blood elimination curves showed a quite limited bioavailability following oral administration with a large amount of picric acid remaining in the gut (gut absorption coefficient: k_a = 0.069 h^{-1}). Analysis of the distribution of radioactivity 24 hours after oral administration showed that, apart from the gut (contents + wall), urine, and faeces (containing ca. 26, 51, and 6% of the radioactivity administered, respectively), the blood was the principal depot (ca. 6%). Retention in the blood is, in part, the result of binding to plasma protein. Of the tissues assayed, the highest concentrations of radioactivity (per gram tissue) were found in (in decreasing order) the spleen, kidneys, liver, lungs, and testes. The lowest concentrations of radioactivity were found in the brain and adipose tissues. The radiolabel excreted in the urine during the first 24 hours following oral dosing consisted of 60% unchanged parent compound, 19% picramic acid (2-amino-4,6-dinitrophenol), 15% *N*-acetylisopicramic acid, 4.7% *N*-acetylpicramic acid, and 2.4% (3) unidentified metabolites (Wym92).

6 Effects and mechanism of action

Human data

Referring to literature published in the period 1900-1960, Grant stated that dusts or fumes of picric acid had caused irritation of the eyes, and that this may be aggravated by sensitisation. Accidental squirt of a picric acid solution in the eye may cause corneal injury. He further stated that ingestion of picric acid may induce strange visual effects. Experimental ingestion of 300 mg of picric acid was reported to cause a transient yellowish appearance in the subjects. Although this dose was thought to be too small to cause this kind of effects, larger, systemic toxicity-inducing amounts were said to colour all tissues yellow, including the conjunctiva and aqueous humor, and to cause yellow-tinted vision (Gra86).

Human data from several industrial, case, and experimental reports on skin effects from contact with solutions, cremes, and dusts containing picric acid or picrates, as reviewed by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Gre99), indicate that picric acid has a sensitising potential.

Apart from skin sensitisation, effects on the nose (bleeding; swelling and excoriation of mucosa; yellow discoloration of vestibules), skin (staining) and hair (discoloration), and palpable cervical glands were reported in (some of the) 71 male and female employees engaged in working with explosives in a factory

in the US, for 1 to 15 months. The concentrations of ammonium picrate at the sites of 'milling' and 'preforming' ranged from 0.009 to 0.19 mg/m^3 (Sun45). Harris et al. reported an outbreak of haematuria involving many of the personnel aboard US warships stationed in Japan. All evidence indicated that it was caused by picric acid, which was dumped in large quantities near an anchorage. It contaminated the harbour water and, consequently upon distillation of the sea water, the fresh water supply used by the personnel (Har46). NIOSH stated that ingestion of 2000 to 5000 mg of picric acid may induce — amongst others — headache, vertigo, nausea, diarrhoea, haematuria, and albuminuria. 'High' doses (not specified) would cause destruction of erythrocytes, haemorrhagic nephritis, hepatitis, yellow colouring of all tissues (including conjunctiva and aqueous humor), and yellow-tinted vision (NIO81).

Animal data

A solution of picric acid injected into the corneal stroma of the eyes of rabbits was stated to cause injury even when this solution was neutralised to a pH range of 7 to 9 (Gra86).

Several studies in guinea pigs, as reviewed by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Gre99), showed that picric acid has a sensitising potential.

From giving male and female Fischer 344 rats (n=3/sex/dose) single oral (gavage) doses of picric acid (in water) ranging from 50 to 800 mg/kg bw, Wyman et al. determined LD_{50} values of 290 and 200 mg/kg bw in males and females, respectively (observation time: 14 days). In a separate experiment in male animals, blood gas analysis showed severe acidosis to be the cause of death (Wym92). Single oral doses of 120 and 500 mg/kg bw were reported to be lethal in rabbits and cats, respectively. Dogs died from respiratory paralysis at a single subcutaneous injection of 100-125 mg/kg bw. Autopsy showed yellow staining of the subcutaneous fat, lungs, intestines, blood vessels, swelling of the liver, and glomerulitis. Doses of 50 mg/kg bw caused transitory kidney changes (NRC82). Senezuk et al. reported that picric acid did not induce methaemoglobinaemia in Wistar rats after a single injection of 0.4 mM/kg bw (92 mg/kg bw) (Sen76).

To study possible systemic effects, Sunderman et al. performed an experiment in which 4 rabbits and 8 guinea pigs had been placed inside a factory building

where milling and preforming operations were taking place. In this environment, the levels of exposure to ammonium picrate dusts were monitored to range from 0.009 to 0.19 mg/m^3. The dimensions of the dust particles were not reported, they were probably total dusts. Some of the animals were killed after a 6-week exposure period and the rest after a 1-year exposure period. Histological examination of 2 rabbits after a 6-week exposure period showed glycogen infiltration and periductal fibrosis of the liver. Guinea pigs that died 3 weeks after exposure revealed low grade subacute inflammation of the nasal mucosa. Some hyaline degeneration occurred in the heart tissues, and the lungs were somewhat congested (Sun45). The committee faces problems in interpreting this study: it is not clear whether the effects were induced by exposure to a mixture or to a single agent. Moreover, the unaccounted dimensions of the dust particles, the large range of exposure levels, and possible exposure by oral intake and skin contact hamper an assessment.

There are conflicting reports on the mutagenicity of picric acid. Whong and Edwards reported that picric acid was not mutagenic in the *S. typhimurium* plate-incorporation assay, with or without metabolic activation, in strains TA1535, TA100, TA1537, TA1538, and TA98 (Who84), while Kawai et al. found positive results in a pre-incubation assay using strains TA98 and TA100 both in the absence and presence of induced rat liver S9 (no other strains were tested) (Kaw87). In other tests in which strains TA1535, TA100, TA1537, TA1538, and TA98 were used, results were mainly positive when tested in the presence of a metabolic activation system in the frame-shift strains TA98, TA1535, and TA1538 while results were negative when tested without metabolic activation (Goc81, Haw83, Won77, Wym79). Picramic acid (2-amino-4,6-dinitrophenol), a metabolite of picric acid, induced both base pair substitution and frame shift-type mutations, only without activation by the rat liver preparation (Won77, Wym79). Testing in *E. coli* strain B/Sd-4 (probably without metabolic activation), resulted in mutagenic responses (Dem51).

Picric acid did not induce chromosome aberrations in the root tips from bulbs of *Allium cepa* (Lev48).

Both positive and negative results were obtained upon testing in *D. melanogaster*. Picric acid was found mutagenic in explanted gonads of *D. melanogaster* (Had49). After bathing eggs in aqueous solutions of picric acid, no sex-linked lethals were found (Aue47), but in a review, this study was considered to be inadequately performed since less than 1000 chromosomes were tested (Lee83). Woodruff et al. reported that picric acid was found

negative by 3 laboratories after feeding picric acid to males in the sex-linked recessive lethal mutation assay using *D. melanogaster*. Following injection, clearly negative (at 400 ppm), clearly positive (at 1500 ppm), and less clear-cut results (using a combination of 1000 and 1500 ppm) were obtained in the respective laboratories. Combining the data from these 3 laboratories, picric acid was concluded to be positive. Following injection, the results in the reciprocal translocation test were negative (Woo85). Gocke et al. found a statistically significant ($p \leq 0.05$) increase in the frequency of sex-linked dominant lethals after feeding (1.25 mM) picric acid (Goc81).

In vivo, 2 oral or intraperitoneal doses (administered with a 24-hour interval) of up to 458 and 91.6 mg/kg bw, respectively, did not cause an increase in the frequency of micronuclei in polychromatic erythrocytes obtained from bone marrow of mice (NMRI; n=2/sex/group) sacrificed 30 hours after receiving the final dose (Goc81). However, the committee considers this study inadequate since only 4 animals were exposed per dose and only one time point of evaluation was used.

The committee did not find data on long-term toxicity, carcinogenicity, and reproduction toxicity.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for picric acid in the Netherlands is 0.1 mg/m^3, 8-hour TWA, with a 'skin' notation (SZW01).

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

8 Assessment on health hazard

Twenty-four hours following intravenous injection to rats, 60 and 12% of the radioactivity administered were excreted in urine and faeces, respectively. After an initial blood distribution period of 2 hours, radioactivity was eliminated following first-order kinetics with a plasma half-life of 13.4 h. Following oral administration, bioavailability was quite limited with ca. 26% of the radioactivity administered remaining in the gut 24 hours after dosing. When orally dosed, picric acid and its metabolites picramic acid, *N*-acetylisopicramic acid, and *N*-acetylpicramic acid accounted for ca. 60, 19, 15, and 5% of the radioactivity excreted in the first 24-hour urine.

There are very few human and experimental animals data available on the effects of exposure to picric acid. Data from human industrial, case, and experimental reports which were confirmed by guinea pig studies showed that picric acid is a skin sensitising compound.

The committee did not find adequate data on the toxic effects of picric acid following exposure by inhalation or on the effects following repeated exposure (including carcinogenicity and reproduction toxicity).

Based on oral LD_{50} values of 200 and 290 mg/kg bw in rats, the committee considers picric acid as harmful when ingested. Effects observed were, amongst others, acidosis, yellow staining of tissues, swelling of the liver, and glomerulitis.

Picric acid was mutagenic in bacteria and in *Drosophila*. However, since the committee did not find adequate mutagenicity and genotoxicity data from *in vitro* assays in mammalian cell systems and *in vivo* assays, it cannot draw a definite conclusion on the (potential) mutagenicity/genotoxicity of picric acid.

The committee considers the toxicological database on picric acid too poor to justify recommendation of a health-based occupational exposure limit.

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

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Annex

Occupational exposure limits for picric acid 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	-	0.1	8 h	administrative	S	SZW02
Germany						
- AGS	-	0.1[c]	8 h		S	TRG00
	-	0.1[c]	15 min			
- DFG MAK-Kommission	-	-			S, sens, [d]	DFG02
Great Britain						
- HSE	-	0.1	8 h	OES		HSE02
	-	0.3	15 min	STEL		
Sweden	-	-				Arb00b
Denmark	-	0.1	8 h		S	Arb00a
USA						
- ACGIH	-	0.1	8 h	TLV		ACG02b
- OSHA	-	0.1	8 h	PEL	S	ACG02a
- NIOSH	-	0.1	10 h	REL	S	ACG02a
	-	0.3	15 min	STEL		
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] Measured as the inhalable fraction of the aerosol.

[d] Classified in carcinogenicity category 3B, i.e., listed among substances for which *in vitro* or animals studies have yielded evidence of carcinogenic efects that is not sufficient for classification in one of the other categories. Further studies are required before a final decision can be made. A MAK value can be established provided no genotoxic effects have been detected.