Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for picric acid

SCOEL/SUM/92

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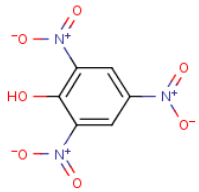
8 hour TWA	: not assigned (see Recommendations)
STEL	: not assigned
Notation	: skin sensitizer
BLV	: not assigned

Substance identification

Picric acid

$C_6H_2(NO_2)_3OH$



Synonyms: 2,4,6-Trinitrophenol; Phenoltrinitrate
EC: 201-865-9
Annex I Index No.: 609-009-00-X

Classification: E; R3 -R4 - T; R23/24/25

CAS No.: 88-89-1
MWt: 229.1
Conversion factor (20 °C, 101 kPa): does not apply

Physico-chemical properties
Picric acid is a yellow crystalline solid.
Solubility: soluble in hot water, alcohol, ether and chloroform.
Melting point: 122-123°C.
Boiling point: explodes above 300°C.
Flash point: 150 °C.

1. Occurrence/use and occupational exposure

Picric acid has been used as an explosive, in match and battery manufacturing, in the leather and textile industry, in the production of coloured glass and dyes. In the 20th century it was used as antiseptic component of medical ointments, applied for wounds, especially for burns. Picric acid is employed as component of clinical chemistry reagent, dyes and fixatives used in pathology, bacteriology and forensic laboratories.

Picric acid is marketed (Wyman et al, 1992; ACGIH 2001) and used typically in wetted form or as solution. Since dry picric acid is explosive, stringent handling procedures are followed. It is therefore unlikely that picric acid would pose a significant inhalation hazard (CHEMINFO, 2003).

2. Health significance

2.1. Toxicokinetics

2.1.1 Human data

No quantitative data are available regarding the absorption, distribution, metabolism and elimination of picric acid in humans.

No available data support the absorption of picric acid through intact skin. The only human case reported by Dennie et al. (1929; cited in DFG, 2000.) mentions systemic effects in a man, whose burns were treated with picric acid containing ointment, however the absorption of picric acid was not verified.

2.1.2. Animal data

Toxicokinetics of picric acid was studied by Wyman et al. (1992) in rats.

It was estimated that approximately 60 % of [^{14}C]picric acid administered to fasted rats by gavage (dose:100 mg/kg bw) would be absorbed from the gut in a 24-h period. Under physiologic conditions picric acid is present in the form of a charged picrate anion. Primary depots of radioactivity were blood, spleen, kidney, liver, lungs and testes. Retention of ^{14}C by lipophilic depots was negligible. In the blood picric acid is bound to plasma proteins.

Elimination of radioactivity from the blood after iv injection of [^{14}C]picric acid (50 mg/kg bw) appeared to follow first order kinetics. Plasma half-life was calculated as 13.4 hour. Following oral administration (100 mg/kg) the elimination curve was found to be biphasic. The relatively low rate of elimination at low concentration was attributed to plasma protein binding of picric acid, which resulted in retention of low levels of the compound for an extended period of time, in excess of that predicted by a the plasma half-life. ^{14}C radioactivity was measurable even after 14 days of administration (Wyman et al, 1992).

After iv or oral administration of [^{14}C] picric acid about 60% of radioactivity was excreted in urine and 12 % in the faeces at 24 h.

Approximately 60 % of the administered dose was excreted unchanged. The rest of picric acid was metabolized by reduction of the nitro groups to amines with subsequent conjugation by acetate. Metabolites identified in the urine were N-acetylisopicramic acid (N-acetyl-4-amino-2,6-diphenol): 14.8 %, picramic acid (2-amino-4,6,dinitrophenol): 18.5 % and N-acetylpicramic acid (4.7 %) (Wyman et al, 1992).

Dermal absorption: 50 ml of an alcoholic solution of picric acid was applied to the skin of a dog. 24 hours later picric acid was detectable in the blood (Dennie et al., 1929; cit. by DFG, 2000.).

2.1.3. Biological monitoring

Biological monitoring is not in use.

2.2. Acute toxicity

2.2.1. Human data

According to ACGIH TLV documentation (2001) systemic poisoning after absorption of picric acid in man caused headache, vertigo, nausea, vomiting and diarrhoea, yellow coloration of the skin and conjunctiva and occasionally darkened urine. High doses resulted in destruction of erythrocytes, gastroenteritis, hemorrhagic nephritis, and acute hepatitis. The doses and routes of exposure, however were not specified.

2.2.2. Animal data

Inhalation exposure

No data are available.

Oral exposure

The oral LD_{50} for rats is 200 and 290 mg/kg b.w. for females and males, respectively. The animals died in approximately 60 minutes following gavage. Symptoms were tremor and clonic-tonic convulsions. Results of blood gas analysis in male rats suggest the specific cause of death following acute exposure to picric acid was acidosis of mixed metabolic and respiratory type (Wyman et al. 1992).

Dermal exposure

In a limited study with a dog, it was shown that the substance applied as a solution in alcohol can be taken up via the skin (Dennie et al. 1929; cit. DFG, 2000), but no symptoms were mentioned.

2.3. Irritation and corrosivity

Based on pH value (1.3 for saturated solution) picric acid is a strong acid and it is expected to be corrosive or strong irritant (CHEMINFO 2003).

2.3.1. Human data

According to ACGIH TLV documentation (2001) picric acid dust or „fumes“ caused irritation of the eyes and corneal injury resulted from accidental contact of a picric acid solution with the eyes, as well as „yellow tainted vision“ in workers. No further details are given (references: Grant's Toxicology of the Eye, 1979 and ILO Encyclopedia, 1983).

2.3.2. Animal data

100 mg picric acid was weakly and reversibly irritating to the rabbit eye in the Draize test (Sugai et al. 1990). Injection of a solution of picric acid into the corneal stroma of the rabbit eye caused damage even if the solution was quickly neutralized (ACGIH 2001).

2.4. Sensitisation

Some older animal experiments and human experiences point to a sensitising potential.

2.4.1. Human data

In workers exposed to ammonium picrate and picric acid edematous and papula-vesiculous changes of the skin were described in the area of mouth and nose (Schwartz, 1944.) or the forearms (Sunderman et al. 1945). The latter report excluded irritative reactions. Martonaro et al. (1966) found a small percentage of positive reactions in 306 men who were tested for sensitivity to picric acid prior to employment. However, the test described appeared to measure irritation rather than sensitization, as commented by CHEMINFO (2003)

Patients allergic to "para-compounds" also reacted to picric acid (Meltzer and Baer 1949; Rajka 1952; Schulz 1962). Tests in patients with contact dermatitis due to picric acid containing preparations used for the treatment of burns revealed positive reactions to picric acid (Aguirre et al. 1993; Cronin 1975; Serra-Baldrich and Camarasa 1991). Of 536 patients with dermatitis patch-tested with "common allergens" 2.3% reacted to 5% picric acid (Moriearty et al. 1978).

2.4.2. Animal data

Early sensitisation experiments with guinea pigs gave negative or inconclusive results (Landsteiner and Jacobs 1936). Sensitisation could be induced when the skin was pre-treated by 0,1% cantharidin solution before application of picric acid (Landsteiner and Di Somma 1940). One test with intradermal induction and epicutanous challenge was negative (Parker et al. 1983). In two split-adjuvant tests with guinea pigs positive results were obtained with picric acid (Maguire and Chase 1972; Chase and Maguire 1973). From the results, picric acid was concluded a weak allergen.

2.5. Repeated dose toxicity

2.5.1. Human data

Much of the human toxicity data for picric acid was collected during World War II, following isolated intoxications of munition workers, usually exposed to picric acid and picrates, mainly ammonium picrate (Wyman et al., 1992).

Inhalation exposure

In 71 male and female employees working for 1 - 15 months in an explosives factory, nose bleeding, swelling and excoriation of nasal mucosa, yellow discoloration of the skin and hair and palpable cervical glands were reported. The concentration of ammonium picrate dust in the air ranged from 0.009 – 0.19 mg/m^3 (Sunderman et al. 1945).

Wyman et al., (1992) mentions that in one individual inhalation of picrate dust produced weakness, muscle pain, anuria followed by polyuria, and temporary coma. No other details are given.

Oral exposure

In 1946 U.S. Navy personnel aboard ships developed hematuria, attributed to picric acid contamination (2-20 mg/l) of the drinking water (Harris et al., 1946.).

2.5.2. Animal data

Inhalation studies

No appropriate inhalation studies have been reported on animals.

Sunderman et al. (1945, cited in DECOS, 2002) placed rabbits and guinea pigs in an explosives factory building, where the concentration of ammonium picrate dust in the air ranged from 0.009 – 0.19 mg/m^3. Rabbits killed after a six weeks of exposure showed glycogen infiltration and periductal fibrosis in the liver. Guinea pigs that died after 3 weeks of exposure presented with low grade subacute inflammation of the nasal mucosa, some hyaline degeneration in the heart and somewhat congested lungs. It is hard to interpret these results, as the presence of other substances at the workplace was not excluded, the picrate dust was not characterized and ingestion may had contributed to the exposure of the animals.

Oral studies

No data are available on the repeated dose oral toxicity of picric acid in animals.

Dermal studies

No data are available on the repeated dose dermal toxicity of picric acid in animals.

2.6. Genotoxicity

2.6.1. In vitro

In 5 of 7 tests in Salmonella typhimurium with metabolic activation, picric acid was mutagenic mainly in frame-shift strains TA98, TA1537, TA1538 (Gocke et al. 1981; Haworth et al. 1983; Won 1977; Wyman et al. 1979; Yoshikawa et al. 1976). The main metabolite 2-amino-4,6-dinitrophenol (picramic acid) was also mutagenic (Won 1977; Zeiger et al. 1988). Tests without metabolic activation were negative. In an *in vitro* chromosomal aberration test a negative result and in an SCE-test a positive result were obtained (unpublished, NTP 1999).

2.6.2. In vivo

In several tests with Drosophila melanogaster for the induction of SLRL-mutations negative and positive results were obtained (Gocke et al. 1981; Woodruff et al. 1985). An *in vivo* micronucleus-test (two times 22.9, 68.7, 91.6 mg/kg b.w., i.p.; two times 229, 343, 458 mg/kg b.w., gavage) did not give evidence of a clastogenic effect (Gocke et al. 1981), however, only 4 mice were evaluated per dose level and only one time point of evaluation was used.

Overall, the genotoxic potential of picric acid was weak compared to other

nitroaromatic compounds (DFG, 2000).

2.7. Carcinogenicity

No human or animal carcinogenicity data for picric acid are available.

2.8. Reproductive toxicity

No human or animal data on reproductive toxicity are available

Recommendations

The available toxicological data on picric acid do not provide a scientific basis for the establishment of a health based OEL.

There is no information about the absorption of inhaled picric acid in humans or in animals, data on repeated dose inhalation exposure of humans are lacking, repeated dose inhalation animal experiments were not identified in the available literature. Furthermore, a weak genotoxic potential has been shown. Therefore, SCOEL concluded that no OEL values can be established so far.

There are no data to prove that picric acid can be absorbed via intact skin, therefore skin notation is not supported.

Animal experiments and human experiences point to a weak sensitising potential. Labelling the substance as sensitiser seems appropriate.

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