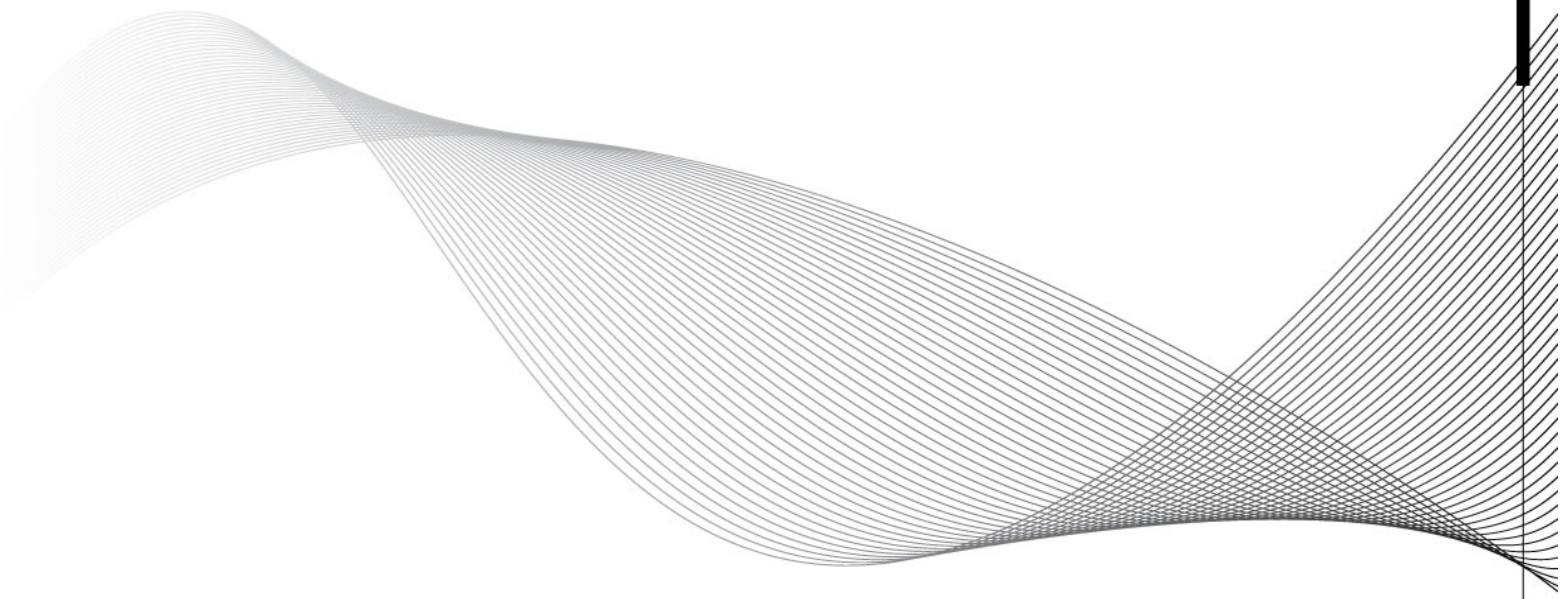
Social Europe



Recommendation from the Scientific Committee for Occupational Exposure Limits for 4,6-dinitro-o-cresol

SCOEL/SUM/60
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European Commission

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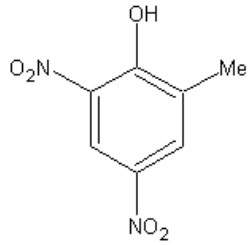
8 hour TWA	:	-
STEL (15 mins)	:	-
Biological limit value (BLV)	:	10 µg/ml (10 mg/l)in whole blood (average value, measured end of shift)
Additional classification	:	*Skin notation*

Substance Identity and Properties:

4,6-Dinitro-o-cresol $C_7H_6N_2O_5$

Structural formula:



Classification : Muta. Cat. 3 ; R68, T+;R26/27/28, Xi ; R38-41, R43, R44, N ; R50-53

Synonyms: 4,6-Dinitro-ortho-cresol (IUPAC); DNOC; 2-methyl-4,6-dinitrophenol (CAS); 3,5-dinitro 2-hydroxytoluene; 2,4-dinitro-ortho-cresol ; 2,4-dinitro-6-methylphenol

CAS N° : 534-52-1

EINECS N° : 208-601-1

Molecular weight : 198.13

Melting point: 87.5°C

Boiling point: 312°C

Log P_{ow}: 2.564

Vapour pressure: 0.7×10^{-5} kPa at 20°C

Conversion factor: (20°C, 101kPa) 1 ppm = 8.24 mg/m^3 1 mg/m^3 = 0.12 ppm

1. Occurrence/use and analytical methods

DNOC is an odourless yellow crystalline solid with a bitter taste, which is soluble in alcohol, alkaline solution, acetic acid and most organic solvents, but poorly soluble in water. The vapour density is 6.8 times that of air and it has a lower explosive limit of 0.3 g/l.

DNOC has insecticidal, fungicidal, herbicidal and defoliant properties and has been used as a selective herbicide in the cultivation of grain, hops, vines and fruit. It is no longer authorised for use as a plant protection product in the European Union, however, and had been withdrawn from the market in all Member States by 2000. It has also been used occasionally as a fungicide, miticide, defoliant or deflorant. It was formerly used in the dyestuffs industry, and has been used as a slimming drug. DNOC is only produced synthetically. Commercially available preparations contain formulations of the alkali, ammonia, or amine salts of DNOC which are normally highly soluble in water. No production and use data are available.

DNOC in air is conventionally measured using the NIOSH method (NIOSH, 1984), while biological monitoring of DNOC in blood and urine has conventionally been carried out using a colorimetric procedure involving extraction with methyl ethyl ketone in the presence of sodium carbonate (Parker, 1949, NIOSH, 1978). Gas chromatographic and HPLC methods have also been used, for example for urine (Coye et al., 1986) and for serum (Diepenhorst et al., 1995) and provide higher resolution and greater sensitivity.

2. Health Effects

2.1. Toxicokinetics

DNOC is rapidly absorbed following inhalation, ingestion and via skin contact (Burkatskaya, 1963; Popov *et al*., 1971; Arustamyan, 1972). Skin absorption is more rapid when DNOC is applied in an oily formulation rather than in aqueous solution, peak plasma concentration is higher and occurs earlier (Fabreguettes, 1993, cited in WHO, 2000), indicative of a solvent effect on skin penetration. Biological monitoring of DNOC in blood has been used extensively in cases of acute accidental exposure in humans, as blood levels provide the most reliable indicator of the dose:response relationship for DNOC (DFG, 1998, WHO, 2000). Measurement of atmospheric levels of DNOC is less predictive of possible health effects because of the ready absorption of DNOC through the skin. Absorbed DNOC is preferentially bound to serum proteins and accumulation in blood may occur in man following repeated exposure (Thiele *et al*., 1981; Jastroch *et al*., 1978). Plasma levels increased daily in 18 sprayers exposed to DNOC over a spraying season, and at the end of the season ranged from 11 to 88 µg/ml (van Noort, 1960).

The major metabolic route in the rat and the rabbit following oral administration is by reduction to 6-amino-4-nitro-o-cresol (6-ANOC, 10 – 12% of administered dose) and, to a lesser extent, to 4-amino-6-nitro-o-cresol (4-ANOC), 4-ANOC conjugates and other minor metabolites (Leegwater *et al.*, 1982; van der Graaf & Leegwater, 1983). Ingebrigtsen and Froslie (1980) demonstrated rapid reduction to 6-ANOC followed by further reduction to diamino-o-cresol (DAOC) in an *in vitro* study in the presence of rat caecal contents, indicating a metabolic role for intestinal flora. No information is available on metabolic pathways following dermal or inhalation exposure.

The major route of elimination is in the urine, with a half life in the rat of between 24 and 36 hours following oral administration of 0.4 mg/kg body weight (bw) (Leegwater *et al.*, 1982). A shorter half life of 6.5 hours has been reported in the rabbit (WHO, 2000). Excretion is

reported to be slower in humans (Pollard & Filbee, 1951), and half lives ranging from 4 days (van Noort, 1960) to over 6 days (Pollard & Filbee, 1951; Jastroch *et al*., 1978) have been reported in heavily exposed workers.

2.2. Acute toxicity

Information on acute toxicity in humans has been obtained from cases of high-level occupational exposure and from earlier therapeutic use as a slimming aid. DNOC causes uncoupling of oxidative phosphorylation, resulting in depletion of ATP and, ultimately, increased glycolysis and glycogenolysis, inhibition of lipogenesis and increased degradation of fatty acids (Gasiewicz, 1991). Early symptoms are elevation of the basal metabolic rate and a rise in body temperature accompanied by fatigue, excessive sweating, unusual thirst and loss of weight (Gosselin, 1984, de Bruin, 1976. Acute poisoning is rapid, with either death or almost complete recovery occurring within 24 - 48h (Hayes, 1963, Morgan, 1982).

The lethal dose in humans is reported to lie in the range of 350 to 3000 mg DNOC (DFG, 1976). A single oral dose of 75 mg (approximately 1 mg/kg body weight) is reported to have produced no toxic effects in five volunteers (Harvey, 1952, ACGIH, 1986), but data from earlier use as a slimming aid indicate that effects on basal metabolic rate (BMR) are likely at this level (Gasiewicz, 1991). Although the exposure data by air are limited in number and validity in most cases, exposure to a level of 4.7 mg/m^3 was reported to result in similar symptoms to those reported following ingestion (ACGIH, 1991). These symptoms were not observed when the air concentration was reduced to 2.5 mg/m^3. Reports of occupational poisonings following dermal contact with DNOC indicate ready absorption of DNOC through the skin.

In animals, reported LD50 values for DNOC range from 20 – 85 mg/kg bw orally in the rat, mouse and cat, 200 - > 2000 mg/kg by the dermal route in the rat, rabbit, mouse and guinea pig and 40 – 230 mg/m^3 by the inhalation route in rats or cats (as summarised in WHO, 2000). Signs of acute toxicity include hyperactivity, laboured respiration and convulsions, prior to death.

2.3. Irritation/corrosion and sensitisation effects

There are no substantiated reports of irritancy or allergenicity in humans, either dermal or in the respiratory tract. Patch testing of a substantial patient population having suspected allergic or non-allergic dermatitis with either 0.5% (n = 200) or 1% (n = 492) DNOC did not result in any treatment-related skin reactions (Lisi *et al*., 1986, 1987). Technical grade DNOC is however moderately irritating to rabbit skin (Driscoll, 1995a, cited in WHO, 2000) and is corrosive to the rabbit eye (Driscoll, 1995b, cited in WHO, 2000). It is also a skin sensitiser in the Guinea Pig Maximisation test (Driscoll, 1995c, cited in WHO, 2000).

Subacute, subchronic and chronic toxicity

There are a number of early reports of occupational intoxication following prolonged exposure to DNOC (e.g. Malter, 1949; Steer, 1951, Bidstrup & Payne, 1951; Heyndrickx *et al*, 1962, 1964, Prost *et al*, 1973; Jastroch *et al*., 1978). Reports of occupational poisonings following dermal contact with DNOC indicate ready absorption of DNOC through the skin. Symptomology was similar to that reported following acute exposure, including weight loss, fatigue, excessive sweating and development of yellow coloration of the skin and conjunctiva. Toxicity is enhanced in hot environmental conditions, reflecting DNOC's hyperthermia-inducing effects (Bidstrup & Payne, 1951) and fatalities have been reported

following prolonged exposure (Malter, 1949; Bidstrup & Payne, 1951). Cases of occupational intoxication declined markedly as recognition of the toxicity of DNOC increased, and under the use conditions pertaining in European agriculture prior to the removal of DNOC from the EU market, there were few reports of overt toxicity (WHO, 2000).

Levels in blood are considered to provide the most reliable indicator of the dose:response relationship for DNOC (DFG, 1998, WHO, 2000), in particular because of the ready absorption of DNOC through the skin. Although the data from the early occupational poisoning cases are limited for the purposes of deriving a dose:response relationship, clear clinical symptomology and even death were associated with blood levels above 70 µg/ml (Steer, 1951, Jastroch *et al*., 1978). Harvey (1952) measured blood DNOC levels in volunteers given 75 mg DNOC every day for either 5 (three subjects) or 7 days (two subjects). Blood levels were measured daily, 4 hours after dosing, and in two of the volunteers receiving DNOC for 5 days levels rose to approximately 20 µg/ml, while in the third volunteer the level at the end of 5 days was approximately 40 µg/ml. In the two volunteers receiving DNOC for 7 days, the blood DNOC level in one rose to approximately 38 µg/ml, while in the other the level reached 48 µg/ml. The latter showed signs of DNOC toxicity (headache, lassitude and malaise) (Harvey, 1952).

Clinical biochemical changes indicative of liver and kidney damage have been reported in a number of the cases of occupational poisoning at elevated (> 40 µg/ml) blood levels of DNOC (e.g. Heyndrickx *et al.*, 1962, 1964, Prost *et al.*, 1973; Jastroch *et al.*, 1978, Thiele *et al.*, 1983). Jastroch and co-workers studied a group of 7 workers exposed to DNOC for periods ranging between 29 and 70 hours at a level of 2.5% in an agrochemical spray (Jastroch *et al.*, 1978). Atmospheric levels of DNOC in this study averaged 0.103 µg/m^3, well below the MAK value of 0.2 µg/m^3 pertaining at that time. They reported clinical symptoms and biochemical changes in 3 of these workers, with associated blood levels of 36 µg/ml, 36 µg/ml and 69 µg/ml respectively, while 2 workers with blood levels of 15 µg/ml and 11 µg/ml showed some elevation in aspartate aminotransferase (AST), which was already identified before spraying with DNOC. Clinical chemistry results were normal in the remaining 2 workers. More recently, Heuts (Heuts, 1993, cited in WHO, 2000) reported an absence of effect on liver function, as measured by several parameters, and no clinical symptomology in sprayers having < 0.5 µg/ml DNOC in blood. Although a threshold of 30 - 40 µg/ml (30 – 40 mg/l) for clinical symptomology of DNOC toxicity has been suggested (Jastroch *et al*., 1978, WHO, 2000), the small numbers involved in the Jastroch *et al* study and the low exposures involved in the Heuts study do not allow definite conclusions to be drawn about a possible Lowest-Observed-Adverse-Effect-Level (LOAEL) or a No-Observed-Adverse-Effect-Level (NOAEL) for DNOC in blood. However, it is generally assumed that a DNOC level of up to 10 µg/ml (10 mg/l) (DFG, 1998) or even 20 µg/ml (20 mg/l) (WHO, 2000) is unlikely to result in adverse health effects in humans.

A number of subacute, subchronic and chronic toxicity studies have been carried out in rats, mice, dogs and cats, via the oral or inhalation route (summarised in DFG, 1998, WHO, 2000). A dose level of 10 mg/kg DNOC in the diet (equivalent to 2.5 mg/kg bw/day) was considered to be a no effect level in a 90 day feeding study in the rat (den Tonkelaar *et al*, 1983), with some decrease in body weight, occasional deaths, increased blood urea nitrogen and decreases in T3 and T4 levels being seen at a dietary level of 100 mg/kg (equivalent to 5 mg/kg bw/day). In a 90 day study in dogs, the No Observed Adverse Effect Level (NOAEL) was considered to be 0.89 mg/kg bw/day (Til, 1980, cited in WHO, 2000).

In a 104 week oral feeding study in rats at levels of 0, 2.5, 15 or 100 ppm in the diet, equivalent to a daily intake of 0.12, 0.75 and 5.03 mg/kg bw in females, and to 0.10, 0.59 and 4.12 mg/kg bw in males, there were no clinical signs of toxicity and no effects on

mortality or on body-weight (Broadmeadow, 1991, cited in WHO, 2000). Food consumption was slightly increased in high dose males compared with controls (+6%) from week 5 onwards. No significant changes were found in the haematological and biochemical parameters evaluated in the course of the study and there were no treatment-related histopathological changes). The NOEL was 0.59 mg/kg bw/day (Broadmeadow, 1991).

Inhalation studies provide the most relevant animal studies for consideration of an occupational exposure limit for DNOC. Subchronic inhalation studies in cats showed death in 2/3 animals exposed to 2.0 mg/m^3, 4h/day for 30 days, but only transient blood changes at 0.2 mg/m^3, 4h/day for 60 - 90 days (Burkatskaya, 1965b). Popov *et al*. (1971) found no effects in rats exposed to 0.001 mg/m^3 for an unspecified time throughout a 60 day period. No subacute, subchronic or chronic dermal exposure studies have been carried out in animals.

2.4. Reproductive toxicity

In a 2-generation reproductive toxicity study in rats (Coles & Brooks, 1997, cited in WHO, 2000), maternal body weight, food consumption and group mean litter weight were reduced at the highest dietary dose level of 100 mg/kg/day. The NOEL in this study was 30 mg/kg/day in diet, equivalent to a highest systemic dose of 2.4 mg/kg/ bw/day in F_1 males and 2.61 mg/kg/ bw/day in F_1 females. An oral developmental toxicity study in the rat at dose levels of 0, 5 and 25 mg/kg/day showed a slightly increased resorption rate at the highest dose level of 25 mg/kg/day. While this effect was not statistically significant, a NOAEL of 5 mg/kg bw/day in the rat can be derived (Dickhaus & Heisler, 1984, cited in DFG, 1998). A parallel study in the mouse using similar dose levels showed no treatment-related effects (Dickhaus & Heisler, 1984). In the rabbit a NOAEL of 10 mg/kg bw/day via either the oral or the dermal route was established, but higher oral dose levels resulted in external and/or visceral malformations, including microphthalmia and anopthalmia (Allen *et al*, 1990a, cited in WHO, 2000). Developmental toxicity was also evident via the dermal route, at dose levels of 30 mg/kg bw/day and above (Allen *et al*, 1990b, cited in WHO, 2000).

2.5. Carcinogenicity

A 104 week oral feeding study in rats at levels of 0, 2.5, 15 or 100 ppm in the diet, equivalent to a daily intake of 0.12, 0.75 and 5.03 mg/kg bw in females, and to 0.10, 0.59 and 4.12 mg/kg bw.
in males, showed no evidence of carcinogenicity (Broadmeadow, 1991, cited in WHO, 2000).

2.6. Genotoxicity and germ cell mutagenicity

The genotoxicity of DNOC has been investigated in a number of *in vitro* and *in vivo* genotoxicity assays, as summarized by WHO (2000). DNOC has been shown to have mutagenic potential in bacterial mutagenicity systems (strains TA98 and TA100) both in the presence and absence of metabolic activation (Sundvall *et al*, 1984). Sundvall showed that the mutagenic response obtained in the Ames test was markedly reduced or abolished when the nitroreductase strains TA98NR and TA100NR were used, indicating involvement of nitroreductase. Relevant to this was the demonstration by Ingebrigtsen and Froslie (1980) that DNOC was rapidly reduced to 6-ANOC followed by further reduction to diamino-o-cresol (DAOC) in an *in vitro* study in the presence of rat caecal contents, indicating a metabolic role for intestinal flora. However, a more recent and better documented study (Hrelia *et al*, 1994) showed negative results in strains TA97, TA98, TA100 and TA102 with and without metabolic activation. The same study provided negative results in an UDS assay assessed by measuring 3H-TdR uptake by HPBL grown in the presence of three doses of DNOC and 10mM hydroxyurea and in an *in vitro* SCE assay using HPBL cultured with three doses of the substance with and without metabolic activation. DNOC gave a positive result in the mouse lymphoma HPRT test (Martin, 1981, cited in WHO, 2000).

DNOC has been reported to induce chromosomal aberrations both *in vitro* in human lymphocytes and *in vivo* in mouse bone marrow (Nehez *et al*., 1978; 1981; 1984; Hrelia, 1994). Other *in vivo* chromosomal aberration studies have, however, yielded negative results in rat and mice (Marzin, 1991, cited in WHO, 2000; Kirkland, 1984, 1986 (cited in WHO, 2000)), and it can be concluded overall that DNOC is not a clastogen. DNOC has also been reported to produce a low but statistically significant increase in recessive lethal mutations and chromosomal aberrations in *Drosophila melanogaster* (Muller and Haberzettl, 1980), but was negative in the dominant lethal test in D.melanogaster (Waters and Auletta, 1981, cited in Hrelia,1994).

Overall, although it has been suggested that some of the genotoxic effects may be attributable to impurities in the technical product rather than to the pure substance, DNOC has been classified as a category 3 mutagen in the 25th Adaptation to Technical Progress of Directive 67/548/EEC .

Recommendation

Consideration of the appropriateness of deriving a health-based occupational exposure limit for DNOC in air is complicated by the importance of the contribution of dermal exposure to total body burden of DNOC, as reported in many studies.. Additionally, there are no adequate inhalation studies in animals which would enable derivation of an air concentration which can be considered to be a clear NOAEL The data on concentrations in air resulting in systemic health effects in workers exposed to DNOC are not also considered adequate or sufficient for derivation of an atmospheric occupational exposure limit.

Biological monitoring of DNOC in blood has been used extensively in cases of acute accidental exposure in humans, as blood levels provide the most reliable indicator of the dose:response relationship for DNOC (DFG, 1998, WHO, 2000). A threshold of 30 - 40 µg/ml (30 – 40 mg/l) for clinical symptomology of DNOC toxicity has been suggested (WHO, 2000), based on reports from early occupational poisoning cases such as those of Jastroch et al (1978) and Steer (1951). While Jastroch and co-workers demonstrated a positive

relationship between DNOC levels in blood and the severity of effects, the small numbers involved in the study and limitations in the data do not allow definite conclusions to be drawn about a possible Lowest-Observed-Adverse-Effect-Level (LOAEL) or a No-Observed-Adverse-Effect-Level (NOAEL) for DNOC in blood. It is generally assumed that a DNOC level of up to 10 µg/ml (DFG, 1998) or even 20 µg/ml (WHO, 2000) is unlikely to result in adverse health effects in humans.

While recognising that the genotoxicity data on DNOC give rise to residual concern, SCOEL considers that a biological limit value (BLV) of 10 µg/ml DNOC in whole blood will be protective of the health of workers who might be exposed to the substance, despite the weakness of the database supporting this level. This is appropriately measured at end of shift, and is proposed as an average value rather than a ceiling limit.

SCOEL considers, however, that it is not possible to derive a scientifically-based occupational exposure limit in air. .

A "skin" notation is additionally recommended as percutaneous absorption is likely to considerably increase the total body burden. Although DNOC is a skin sensitiser in animals, there are no data which indicate that it has either a respiratory or a skin sensitising potential in humans, nor are there reports of irritancy to the respiratory tract.

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