4,6-Dinitro-*o*-cresol
(DNOC)

CAS No. 534-52-1

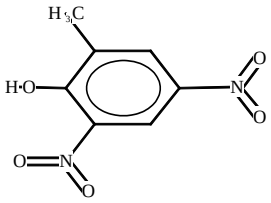

Figure 1: Structure of DNOC

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) the Minister of Health may gather information, conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether a substance is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html.

A State of the Science Report for a screening assessment has been prepared on 4,6-Dinitro-*o*-cresol (DNOC) (see Figure 1) on the basis that this compound was included in the Domestic Substances List pilot phase for screening as a substance likely to be prioritized on the basis for greatest potential for human exposure.

This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing Substances Division of Health Canada; the content of these documents was reviewed at several meetings of senior Divisional staff. The draft Report was subsequently externally reviewed for adequacy of data coverage and defensibility of the conclusions. The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca

Information identified as of June 2003 was considered for inclusion in this Report. The critical information and considerations upon which this Report is based are summarized below.

Identity, Uses and Sources of Exposure

Data submitted in a survey conducted in 2000 indicated that the importation of DNOC into Canada was in the range of 100–1000 tonnes/year (Environment Canada, 2001). Uses of DNOC are similar to those reported elsewhere (IPCS, 2000). While previously used as a pesticide, DNOC is no longer registered for this purpose in Canada, and therefore this use is not likely to be a continuing source of exposure (PMRA, 2000). The predominant current use of DNOC is in the plastics industry as a polymerization inhibitor (IPCS, 2000). Sources of exposure in the general environment are likely to be limited to fugitive releases from industrial sites and the combustion of fossil fuels. There is no indication that DNOC is present in consumer products.

Exposure Assessment, Hazard Characterization and Risk Evaluation

The upper-bounding estimate of exposure to DNOC for the general population is 0.06 µg/kg-bw per day for the 0- to 6-month (formula-fed) age group, based on very limited data from Canadian surveys of drinking water and soil (Ontario Ministry of Environment and Energy, 1994; City of Toronto Water and Wastewater Services Division, 2002a,b,c,d) and an estimated concentration of DNOC in air in Switzerland (Leuenberger et al., 1988) (see Table 1). No quantitative data on levels of DNOC in food were identified. Confidence in the database for estimating exposure is considered moderate, since there is information for conservative estimation of exposure through drinking water and air, the likely principal media of exposure. The levels of DNOC in drinking water were below the detection limit; thus, estimates based on the detection limit likely overestimate exposure. The concentration of DNOC in air was estimated from rain samples but is considered to be conservative, as it is higher than levels measured in automobile exhaust, a source of DNOC (Tremp et al., 1993).

A health assessment of DNOC was published by the International Programme on Chemical Safety (IPCS) in 2000 (see Table 2 for an overview of the toxicological database, in which confidence is considered to be high, in view of the wide range of toxicity studies available). Although IPCS did not select a critical study for use as a basis of a tolerable intake or guidance value, the Lowest-Observed-Effect Level (LOEL) identified in that review that is considered to be the critical effect level is 2.5 mg/kg-bw per day in a 90-day rat dietary exposure study, with resulting dose-related decreases in blood pyruvate and triiodothyronine levels (Den Tonkelaar et al., 1983). Although several lower effect levels were reported in the IPCS assessment, there was less confidence in these studies due to the fact that insufficient details were available; however, these lower values were generally within an order of magnitude of the effect level considered to be critical. Similarly, in very early clinical investigations of the potential application of DNOC in the treatment of obesity, effects associated with increases in basal metabolic rate were observed in individuals administered doses in the range of this critical value. DNOC was not carcinogenic in the only long-term study identified (Broadmeadow, 1991), and the weight of evidence for genotoxicity was considered to be equivocal by IPCS (2000), as positive results were observed in some but not all *in vivo* assays in which rodents were

administered doses generally greater than the critical effect level for non-neoplastic effects. Similarly, the results of modelling of *in vivo* and *in vitro* genotoxicity endpoints are also equivocal.

Comparison of the critical effect level with the upper-bounding estimate of exposure results in a margin of exposure of approximately 41 700. Based on the level of confidence in the available database and the conservative nature of this evaluation, including the use of an upper-bounding exposure estimate and lowest effect level, this margin is considered adequate to account for the uncertainties in the database.

Table 1: Upper-bounding estimates of daily intake of DNOC by the general population in Canada

Route of exposure	**Estimated intake (µg/kg-bw per day) of DNOC by various age groups**						
	0–6 months[1]		**0.5–4 years[3]**	**5–11 years[4]**	**12–19 years[5]**	**20–59 years[6]**	**60+ years[7]**
	Formula fed[2]	**not formula fed**					
Air[8]	1.4×10^{-2}		3.0×10^{-2}	2.4×10^{-2}	1.4×10^{-2}	1.1×10^{-2}	9.9×10^{-3}
Drinking water[9]	4.3×10^{-2}	1.6×10^{-2}	1.8×10^{-2}	1.4×10^{-2}	8.1×10^{-3}	8.5×10^{-2}	8.9×10^{-3}
Food[10]		NA[11]	NA	NA	NA	NA	NA
Soil[12]	4.0×10^{-4}		6.5×10^{-4}	2.1×10^{-4}	5.1×10^{-5}	4.2×10^{-5}	4.2×10^{-5}
Total intake	5.7×10^{-2}	3.0×10^{-2}	4.9×10^{-2}	3.8×10^{-2}	2.1×10^{-2}	2.0×10^{-2}	1.9×10^{-2}

1 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (EHD, 1998).

2 For formula-fed infants, intake from water is synonymous with intake from food. No data on concentrations of DNOC in formula were identified for Canada.

3 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (EHD, 1998).

4 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (EHD, 1998).

5 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

6 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

7 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

8 Leuenberger et al. (1988) estimated an ambient air concentration of 0.05 µg/m^3 using measured concentrations of DNOC from a rainwater sample (15 nM) taken at Dübendorf, Switzerland, in 1985 and using a reference rain/air partition coefficient (5.6×10^4). Canadians are assumed to spend 3 hours outdoors each day (EHD, 1998). Data available from which the critical data were selected included Tremp et al. (1993). In the absence of data, the estimated ambient air concentration (0.05 µg/m^3) was also used for indoor air. Canadians are assumed to spend 21 hours indoors each day (EHD, 1998). Ambient air was assumed to be representative of exposure to indoor air, since there was no indication of additional sources of DNOC in indoor environments.

9 The detection limit (0.4 µg/L) for DNOC in 19 samples of tap water from Toronto, Ontario, in 2002 was used as a surrogate for the level of DNOC in Canadian drinking water (City of Toronto Water and Wastewater Services Division, 2002a,b,c,d). Data available from which the critical data were selected included Hallberg (1989), City of Toronto (1990) and Spliid and Koppen (1998).

10 No quantitative data were identified for concentrations of DNOC in food items. A detection limit of 1000 µg/g was used for a study by Schmidt (1970) that measured for DNOC in potatoes. However, this value was not used in the intake estimate due to the age of the study and because DNOC is not expected to contaminate foods based on its application method. Data available from which the critical data were selected included DeVault (1985).

11 NA = not available.

12 The Ontario Ministry of Environment and Energy (1994) did not detect DNOC in 161 soil samples collected from Ontario. The method detection limit of 100 ng/g was used in the intake estimate as a surrogate for the level of DNOC in Canadian soil. Data available from which the critical data were selected included Webber (1994) and Migaszewski (1999).

Table 2: Summary of health effects information for DNOC

Endpoint	Lowest effect levels[1]/Results
Laboratory animals and *in vitro*	
Acute toxicity	Lowest **oral LD_{50}** = 16 mg/kg-bw (Jongerius and Jongeneelen, 1991) (range: 16 mg/kg-bw to 100 mg/kg-bw) [Additional studies: Dow Chemical Co., 1940, 1950, 1992; Ambrose, 1942; Spencer et al., 1948; King and Harvey, 1953a; McGirr and Papworth, 1953; Burkatskaya, 1965b; Ben Dyke et al., 1970; Driscoll, 1995a] Lowest **dermal LD_{50}** = 187 mg/kg-bw (Arustamyn, 1972) (range: 187 mg/kg-bw to >2000 mg/kg-bw) [Additional studies: Dow Chemical Co., 1940, 1992; Spencer et al., 1948; Burkatskaya, 1965b; Ben Dyke et al., 1970; Jongerius and Jongeneelen, 1991; Driscoll, 1995b] Lowest **inhalation LC_{50}** = 40 mg/m^3 (Burkatskaya, 1965a) (range: 40 mg/m^3 to 230 mg/m^3) [Additional studies: King and Harvey, 1953b; Dey-Hazra and Heisler, 1981]
Short-term repeated-dose toxicity	Lowest **oral (diet) LOEL** (rat) = 7.24 mg/kg-bw per day: decreased body weight gain (6-week study) (Broadmeadow, 1988) [Additional studies: Dow Chemical Co., 1940, 1992; Spencer et al., 1948; Quinto et al., 1989; Takahashi et al., 1999] Lowest **inhalation LOEC** (cat) = 2 mg/m^3: mortality (30-day study) (Burkatskaya, 1965a)
Subchronic toxicity	Lowest **oral (diet) LOEL** (rat) = 2.5 mg/kg-bw per day: change in blood pyruvate and thyroid hormone levels (13-week study) (Den Tonkelaar et al., 1983) [Additional studies: Til, 1980; Kelly 1995] Lowest **inhalation NOEC** (cat) = 0.2 mg/m^3: "no severe adverse effects" (90-day study) (Burkatskaya, 1965a)
Chronic toxicity/ carcinogenicity	Lowest **oral (diet) non-neoplastic LOEL** (male rat) = 4.12 mg/kg-bw per day: increased food consumption (104-week study) (Broadmeadow, 1991) No increase in tumour incidences was observed at dose levels up to 5 mg/kg-bw per day in a 104-week study using rats exposed through the diet (Broadmeadow, 1991). [N.B.: It is not clear based on the secondary account of this study if the substance was tested up to the maximum tolerated dose.]
Genotoxicity and related endpoints: *in vivo*	**Positive**: mouse, bone marrow (micronuclei; 20 mg/kg-bw or 10 mg/kg-bw intraperitoneally [i.p.].after 1 year); rat, bone marrow (chromosomal aberrations; 7.5–30 mg/kg-bw i.p.); rat, hepatocytes (DNA unwinding; 1–9.3 mg/kg-bw i.p.); mouse (dominant lethal assay; 8–15 mg/kg-bw i.p.; and chromosomal aberration in F_1 embryo; 5–10 mg/kg-bw i.p.) (Nehéz et al.,[1] 1978, 1981, 1984; Grilli et al., 1991; Hrelia et al., 1994) **Negative**: rat and mouse, bone marrow (chromosomal aberrations; 4–16 mg/kg-bw oral and 3–12 mg/kg-bw i.p., respectively); mouse, bone marrow (micronuclei; 20 mg/kg-bw i.p.); rat, hepatocytes (unscheduled DNA synthesis; 28–70 mg/kg-bw oral) (Kirkland, 1984, 1986; Marzin, 1991c; Fellows, 1998)

[1] It was indicated in the IPCS (2000) review that studies by Nehéz et al. involved testing of a commercial product (Krezonit E) that contains 50% DNOC; therefore, results of these assays may relate to other components in the product.

Endpoint	Lowest effect levels[1]/Results
Genotoxicity and related endpoints: *in vitro*	**Positive**: *Proteus mirabilis* (DNA repair), *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 (mutagenicity), *Drosophila* (sex-linked recessive lethal), mouse lymphoma (mutagenicity), human lymphocytes (chromosome damage), Chinese hamster V79 cells (mutagenicity) (Adler et al., 1976; Nehéz et al., 1977, 1978; Muller and Haberzetti, 1980; Martin, 1981; Nishimura et al., 1982; Sundvall et al., 1984; Marzin, 1991a,b) **Negative**: *S. typhimurium* TA98, TA100, TA100NR, TA1535, TA1537 (mutagenicity), mouse lymphoma (mutagenicity), human lymphocytes (chromosome damage, sister chromatid exchange and unscheduled DNA synthesis), Chinese hamster ovary cells (chromosome damage) (Martin, 1981; Somani et al., 1981; Nishimura et al., 1982; Garner, 1984; Sundvall et al., 1984; Marzin, 1991a,b,d; Hrelia et al., 1994)
Developmental toxicity	Lowest **oral (gavage) LOEL** (rabbit) = 25 mg/kg-bw per day: external or visceral malformations or skeletal variations, including microphthalmia or anophthalmia and hydrocephaly or microcephaly (gestation days 6–18) (Allen et al., 1990a) [Additional studies: Nehéz et al., 1981; Dickhaus and Heisler, 1984] Lowest **dermal LOEL** (rabbit) = 30 mg/kg-bw per day: total resorptions in two females (gestation days 6–18) (Allen et al., 1990b)
Reproductive toxicity	Lowest **oral (diet) LOEL** (rat) = 1.73–2.24 mg/kg-bw per day: decreased group mean litter size in F_0 generation on days 14 and 21 of lactation (two-generation reproductive study) (Coles and Brooks, 1997)
Immunotoxicity	Highest **oral (diet) NOEL** (rat) = 20 mg/kg-bw per day (3-week study) (Vos et al., 1983)
Humans	
Clinical study	Increase in basal metabolic rate and symptoms of toxicity (sweating, lethargy, headache, altered sleep patterns) at 3 mg/kg-bw for "several" days. Slight increase in basal metabolic rate but no symptoms of toxicity were noted in one patient administered 0.5 and then 1 mg/kg bw/day for 39 days. (data presented for two subjects, total number examined unclear) (Dodds and Robertson, 1933) [Additional study: Plotz, 1936]

[1] LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOEC = lowest-observed-effect concentration; LOEL = lowest-observed-effect level; NOEC = no-observed-effect concentration.

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