N,N′-DIETHYLTHIOUREA

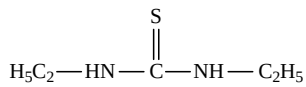
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 105-55-5
Deleted CAS Reg. No.: 27598-95-4
Chem. Abstr. Name: *N,N′*-Diethylthiourea
IUPAC Systematic Name: 1,3-Diethyl-2-thiourea
Synonyms: *N,N′*-Diethylthiocarbamide; 1,3-diethylthiourea

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_5H_{12}N_2S$ Relative molecular mass: 132.23

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White solid (R.T. Vanderbilt Co., 1997)
(*b*) *Boiling-point*: Decomposes (Lide & Milne, 1996)
(*c*) *Melting-point*: 78 °C (Lide & Milne, 1996)
(*d*) *Spectroscopy data*: Infrared [proton (3661), grating (28294)], ultraviolet, nuclear magnetic resonance [proton (190), C-13 (5207)] and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).
(*e*) *Solubility*: Very slightly soluble in water; soluble in ethanol; very soluble in diethyl ether; slightly soluble in carbon tetrachloride (Lide & Milne, 1996; R.T. Vanderbilt Co, 1997; Dialog Corp., 2000)

1.1.4 *Technical products and impurities*

Trade names for *N*,*N*′-diethylthiourea include Accel EUR, Nocceler EUR, Pennzone E, Thiate H and U 15030.

1.1.5 *Analysis*

A method for the isolation, identification and determination of thioureas, including *N*,*N*′-diethylthiourea, in rat plasma by high-performance liquid chromatography (HPLC) with ultraviolet detection has been reported (Kobayashi *et al*., 1981). Analysis of lubricating oil additives for *N*,*N*′-diethylthiourea by HPLC (Musha *et al*., 1985) and determination with iodine monochloride or by redox titration (Murthy *et al*., 1979; Verma, 1979) have also been reported.

1.2 Production

N,*N*′-Diethylthiourea can be made from ethylamine and carbon disulfide (Ohm, 1997).

Information available in 2000 indicated that *N*,*N*′-diethylthiourea was manufactured by three companies each in France and Japan and one company each in the Netherlands, the United Kingdom and the USA (CIS Information Systems, 2000).

1.3 Use

N,*N*′-Diethylthiourea is used mainly in the rubber industry as an accelerator for the vulcanization of several types of rubber with reactive cross-linking sites, including polychloroprene (neoprene), ethylene–propylene–diene and chlorobutyl rubber. The suggested concentration ranges from 0.5 to 1.0 %. Chlorinated rubber derivatives are used, among other applications, as resins in some paints (IARC, 1989). The use of thioureas is decreasing, and they are supplied preferably as polymer-bound granulates, which effectively prevent exposure to and inhalation of thiourea dust (Engels, 1993; Ohm, 1997; R.T. Vanderbilt Co., 1997).

1.4 Occurrence

1.4.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 2000), only about 230 painters or paint-spraying machine workers in the USA were potentially exposed to *N*,*N*′-diethylthiourea. According to the Finnish Register of Employees Exposed to Carcinogens, 13 workers including laboratory workers and surface treatment workers were exposed in Finland in 1997 (Savela *et al*., 1999).

1.4.2 *Environmental occurrence*

No data were available to the Working Group.

1.5 Regulations and guidelines

No data were available to the Working Group.

2. Studies of Cancer in Humans

Although workers in the rubber industry may be exposed to *N*,*N*′-diethylthiourea, no specific mention of this compound was found in epidemiological studies of the cancer risk of these populations.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, 6 weeks of age, were fed diets containing 125 or 250 mg/kg *N*,*N*′-diethylthiourea (> 99% pure) for 103 weeks. A control group of 19 males and 20 females was available. The mice were killed at 104 weeks and evaluated for neoplasms. A dose-related depression of mean body weight was observed in both male and female mice after week 30. The survival rate was comparable in treated and control groups, being 79–94% for males and 60–70% for females. There were no significant increases in the incidences of neoplasms, including thyroid follicular-cell neoplasms, associated with the administration of *N*,*N*′-diethylthiourea in males or females. However, there was a significant ($p < 0.01$) decrease in the incidence of combined hepatocellular adenomas and carcinomas in male mice treated at the higher concentration, which may have been related to the depression in body weight (National Cancer Institute, 1979).

Rat: Groups of 50 male and 50 female Fischer 344 rats, 6 weeks of age, were fed diets containing 125 or 250 mg/kg *N*,*N*′-diethylthiourea (> 99% pure) for 103 weeks. A group of 20 males and 20 females served as controls. The rats were killed at 104 weeks and evaluated for neoplasms. No evidence of a change in mean body weight was observed in either male or female rats, and the survival rates were comparable in treated and control groups, being 80–82% for males and 84–90% for females. The incidences of thyroid follicular-cell adenomas were 0/18, 0/45 and 6/48 males and 0/18, 4/46 and 9/46 females at 0, 125 or 250 mg/kg of diet, respectively. The incidences of thyroid follicular-cell carcinomas were 0/18, 1/45 and 11/45 males and 0/18, 1/46 and 8/46 females in these groups, respectively. The incidences of follicular-cell adenomas

and carcinomas combined were 0/18, 1/45 and 15/48 males and 0/18, 4/46 and 17/46 females, that in males and in females at the highest concentration being significantly ($p < 0.05$; Fisher exact test) higher than in the respective control groups. There was no significant increase in the incidence of tumours at other sites in male or female rats (National Cancer Institute, 1979).

3.2 Administration with known carcinogens or modifying factors

Rat: In a study to assess the synergistic effect of three thyroid carcinogens, 2,4-diaminoanisole sulfate, *N*,*N*′-diethylthiourea and 4,4′-thiodianiline, groups of 20–21 male Fischer 344/Crj rats, 6 weeks of age, were fed a diet containing 200 mg/kg *N*,*N*′-diethylthiourea for 52 weeks alone or in combination with 2,4-diaminoanisole sulfate at 610 mg/kg and 4,4′-thiodianiline at 46 mg/kg of diet. After 52 weeks of treatment, the rats were killed, necropsied and evaluated for tumour incidences. *N*,*N*′-Diethylthiourea induced thyroid follicular-cell carcinoma in 1/21 (5%) rats and significantly ($p < 0.01$) increased the incidence of thyroid follicular-cell carcinomas produced by 4,4′-thiodianiline. *N*,*N*′-Diethylthiourea did not induce liver tumours or lung tumours after 52 weeks, but may have increased the incidences of these tumours caused by 4,4′-thiodianiline (Hasegawa *et al*., 1991). [From the study design, the Working Group considered that it was not possible to assess the synergistic effect of *N*,*N*′-diethylthiourea, if any, on the incidence of thyroid follicular-cell carcinomas induced by 4,4′-thiodianiline.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group.

4.2 Toxic effects

4.2.1 *Humans*

A 27-year-old man developed contact dermatitis to *N*,*N*′-diethylthiourea used to vulcanize a wet suit (Adams, 1982).

Contact dermatitis followed by depigmentation was reported in a 50-year-old man exposed to *N*,*N*′-diethylthiourea in a rubber attachment for a sleep apnoea device (Reynaerts *et al*., 1998).

4.2.2 *Experimental systems*

No data were available to the Working Group.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Effects on enzyme induction/inhibition and gene expression

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Male Sprague-Dawley rat microsomal systems were used to assess the induction of microsomal epoxide hydrolase and glutathione *S*-transferase A2 mRNAs. Treatment with an oral dose of *N*,*N*′-diethylthiourea at 160 mg/kg bw increased (by 7–10-fold) the mRNA levels of both enzymes at 24 h. The microsomal epoxide hydrolase and glutathione *S*-transferase A2 protein contents were induced approximately threefold after 3 days of oral treatment with 0.6 mmol/kg bw [80 mg/kg bw] per day *N*,*N*′-diethylthiourea (Kim *et al*., 1999).

4.5 Genetic and related effects

4.5.1 *Humans*

No data were available to the Working Group.

4.5.2 *Experimental systems* (see Table 1 for references)

N,*N*′-Diethylthiourea was not mutagenic to *Salmonella typhimurium* in an assay with preincubation with or without metabolic activation. It was mutagenic in mouse lymphoma L5178Y cells without metabolic activation. Sex-linked recessive lethal mutations were not produced in treated male *Drosophila melanogaster*. *N*,*N*′-Diethylthiourea transformed Syrian hamster embryo cells in culture.

4.6 Mechanistic considerations

No information was available on the mechanism of action of *N*,*N*′-diethylthiourea.

Table 1. Genetic and related effects of *N,N′*-diethylthiourea

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	10 000 µg/plate	Mortelmans *et al*. (1986)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		3000 ppm feed	Valencia *et al*. (1985)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		10 000 ppm inj	Valencia *et al*. (1985)
Gene mutation, mouse lymphoma L5178Y cells *in vitro*	+	NT	1500	McGregor *et al*. (1988)
Cell transformation, Syrian hamster embryo cells *in vitro*	+	NT	150	LeBoeuf *et al*. (1996)

[a] +, positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; inj, injection

5. Summary of Data Reported and Evaluation

5.1 Exposure data

N,*N*′-Diethylthiourea is used in the manufacture of some types of rubber and paint.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N,*N*′-Diethylthiourea was tested for carcinogenicity by dietary administration in one experiment each in mice and rats. Thyroid follicular-cell adenomas and carcinomas were induced in rats of each sex, but no increase in the incidence of tumours at any site was seen in mice.

5.4 Other relevant data

No data were available on the absorption, distribution, metabolism or excretion of *N*,*N*′-diethylthiourea. The only toxic effect seen in humans was contact dermatitis. No data were available on the reproductive or developmental effects of this compound.

N,*N*′-Diethylthiourea did not cause mutation in bacteria or insects. In single studies, it showed mutagenic activity in mouse lymphoma cells, in the absence of metabolic activation, and it transformed hamster embryo cells in culture.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *N*,*N*′-diethylthiourea.

There is *limited evidence* in experimental animals for the carcinogenicity of *N*,*N*′-diethylthiourea.

Overall evaluation

N,*N*′-Diethylthiourea is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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