THIOURACIL

This substance was considered by previous working groups, in 1974 (IARC, 1974) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

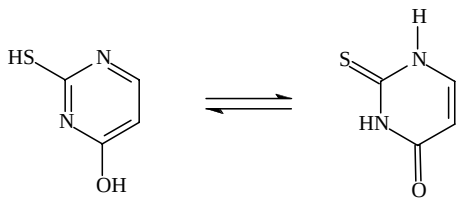
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 141-90-2
Deleted CAS Reg. Nos: 156-82-1; 4401-53-0; 4401-54-1; 107646-88-8; 107646-89-9
Chem. Abstr. Name: 2,3-Dihydro-2-thioxo-4(1*H*)-pyrimidinone
IUPAC Systematic Name: 2-Thiouracil
Synonyms: 4-Hydroxy-2-mercaptopyrimidine; 6-hydroxy-2-mercaptopyrimidine; 4-hydroxy-2-pyrimidinethiol; 2-mercapto-4-hydroxypyrimidine; 2-mercapto-4-pyrimidinol; 2-mercapto-4-pyrimidinone

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_4N_2OS$ Relative molecular mass: 128.15

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Prisms from water or ethanol (Lide & Milne, 1996)
(*b*) *Melting-point*: > 340 °C (decomposes) (Lide & Milne, 1996)
(*c*) *Spectroscopy data*: Infrared [prism (9400), grating (29954)], ultraviolet (2508), nuclear magnetic resonance [proton (9191)] and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).
(*d*) *Solubility*: Slightly soluble in water and ethanol; soluble in anhydrous hydrofluoric acid and alkaline solutions (Lide & Milne, 1996; Budavari, 2000)

1.1.4 *Technical products and impurities*

Trade names for thiouracil include Antagothyroil, Deracil and Nobilen.

1.1.5 *Analysis*

Methods have been reported for the analysis of thiouracil in biological fluids (blood, milk, serum, urine), tissues, incubation material, dried animal feed, feed additives and drugs. The methods include potentiometric titration, capillary zone electrophoresis with ultraviolet detection, flow injection analysis with chemiluminescent detection, micellar electrokinetic chromatography, thin-layer chromatography, high-performance thin-layer chromatography, high-performance liquid chromatography (HPLC) with atmospheric pressure chemical ionization mass spectrometry, reversed-phase HPLC with ultraviolet and electrochemical detection and gas chromatography with negative-ion chemical-ionization mass spectrometry (Saldaña Monllor *et al*., 1980; Moretti *et al*., 1986; Hooijerink & De Ruig, 1987; Moretti *et al.*, 1988; Centrich Escarpenter & Rubio Hernández, 1990; Watson *et al*., 1991; De Brabander *et al*., 1992; López García *et al.*, 1993; Moretti *et al.*, 1993; Vinas *et al*., 1993; Batjoens *et al*., 1996; Kriványková *et al*., 1996; Blanchflower *et al*., 1997; Le Bizec *et al*., 1997; Yu *et al*., 1997; Buick *et al*., 1998; Vargas *et al*., 1998; Esteve-Romero *et al*., 1999; Ciesielski & Zakrzewski, 2000).

1.2 Production

Thiouracil can be prepared by condensing ethyl formylacetate with thiourea (Budavari, 2000).

Information available in 2000 indicated that thiouracil was manufactured by six companies in China and one company in Switzerland (CIS Information Services, 2000).

1.3 Use

Thiouracil was introduced in 1943 as the first thionamide anti-thyroid drug. The usual dose was 1–2 g/day in divided doses. Owing to a high frequency of adverse reactions, especially agranulocytosis, its use was abandoned in favour of other, less toxic

drugs, such as propylthiouracil and methimazole (see monographs in this volume). Thiouracil is not currently used as a thyrostatic drug in humans (Astwood & VanderLaan, 1945; Stanley & Astwood, 1949).

Thiouracil also has been reported to be used as a chemical intermediate (IARC, 1974) and in metal plating.

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), about 1800 technicians and metal-plating machine operators working in the manufacture of instruments and related products were potentially exposed to thiouracil in the USA.

1.4.2 *Environmental occurrence*

Thiouracil occurs in seeds of Brassica and Cruciferae (Budavari, 2000).

1.5 Regulations and guidelines

No data were available to the Working Group.

2. Studies of Cancer in Humans

No information was available specifically on thiouracil.

2.1 Cohort studies

Dobyns *et al*. (1974) followed up 34 684 patients treated in England and the USA for hyperthyroidism between 1946 and 1964, 1238 of whom had been treated for at least 1 year with unspecified anti-thyroid drugs. No malignant thyroid neoplasm was found within 1 year of treatment. By 1968, more cases of thyroid neoplasm were found at follow-up among patients initially treated with anti-thyroid drugs (4 malignant tumours and 18 adenomas in 1238 patients) than among those initially treated with ^{131}I (19 malignant tumours and 41 adenomas in 21 714 patients) or (partial) thyroidectomy (4 malignant tumours and 14 adenomas in 11 732 patients). The authors suggested that more neoplasms were found in the drug-treated patients because subsequent thyroidectomy was more frequent in this group (30% of drug-treated patients, as compared with 0.5% of those initially treated with ^{131}I and 1.2% of those treated with primary thyroidectomy), which provided more opportunity for identification of neo-

plasms. [The Working Group noted that rates could not be calculated because person–years were not provided, and the ages of the groups were not given.]

Ron *et al*. (1998) updated the report of Dobyns *et al.* (1974) and followed-up 35 593 patients treated for hyperthyroidism between 1946 and 1964 in 25 clinics in the USA and one in the United Kingdom. By December 1990, about 19% had been lost to follow-up, and 50.5% of the study cohort had died. A total of 1374 patients (1094 women) had been treated with anti-thyroid drugs only, 10 439 (7999 women) with ^{131}I and drugs, 10 381 (8465 women) with thyroidectomy and drugs, 2661 (2235 women) with a combination of the three types of treatment and the remainder by other means. The drugs used during the study period were chiefly thiourea derivatives and iodine compounds. One year or more after the start of the study, the standardized mortality ratio (SMR) in comparison with the general population for the patients treated with anti-thyroid drugs only was 1.3 (95% confidence interval [CI], 1.1–1.6) for deaths from all cancers, which was chiefly due to significantly more deaths from oral cancer (4.2; 95% CI, 1.3–9.7; five cases) and brain tumours (3.7; 95% CI, 1.2–8.6; five cases). The excess risk for death from brain cancer persisted after exclusion of cases prevalent at the time of entry into the study. No deaths from thyroid carcinoma were recorded. The SMR for all cancers was approximately 1.0 in patients treated with ^{131}I or surgery (with or without anti-thyroid drugs), but the SMR for thyroid cancer was fourfold higher (3.9; 95% CI, 2.5–5.9; 24 cases observed) among patients who had been treated with ^{131}I with or without drugs. The authors noted that the group treated with drugs only was small; the type, quantity and dates of drug use were generally not available; and many patients had cancer before entry into the study, suggesting that some, but not all, of the excess could be attributed to the selection of patients with health problems for drug therapy. [The Working Group noted that the expected number of deaths from thyroid carcinomas was not reported, although it would almost certainly have been less than 1.0. Results were given separately for patients treated only with drugs and not for those given drugs with other treatment.]

2.2 Case–control studies

Ron *et al*. (1987) conducted a study of 159 cases of thyroid cancer and 285 population controls in Connecticut, USA, between 1978 and 1980. The use of anti-thyroid medications was not associated with an increased risk [relative risks not shown].

In a study carried out in northern Sweden between 1980 and 1989, 180 cases of thyroid cancer and 360 population controls were evaluated (Hallquist *et al*., 1994). Use of anti-thyroid drugs (two cases and two controls) was associated with a relative risk of 2.0 (95% CI, 0.2–21).

3. Studies of Cancer in Experimental Animals

Thiouracil was evaluated in a previous monograph (IARC, 1974). Because there have been no new studies on its carcinogenicity in animals, the most relevant studies from the previous monograph were analysed in greater depth. One study in which thiouracil was administered with a known carcinogen which had been published since the previous evaluation is summarized. Studies on the carcinogenicity of anti-thyroid chemicals, including thiouracil, in experimental animals have been reviewed (Doniach, 1970; Christov & Raichev, 1972; Paynter *et al*., 1988).

3.1 Oral administration

Mouse: Groups of 28 A, 29 C57 and 24 I mice [sex unspecified], 1–3 months of age, were fed diets containing thiouracil [purity not specified] at a concentration of 0.1% for various periods up to 81 weeks. Groups of 36 untreated A, 51 untreated C57 and 35 untreated I mice served as controls. In 69 treated mice of all three strains examined at various intervals, the author described thyroid follicular-cell hyperplasia from 40 days of treatment, which developed into follicular cystic or nodular lesions after 180 days. The author interpreted these lesions as non-malignant. In seven treated A strain mice, pulmonary foci very similar to the hyperplastic thyroid tissue were present (Gorbman, 1947). [The Working Group considered that, under current histopathological criteria, the thyroid and pulmonary lesions described in the study might be diagnosed as thyroid neoplasia and metastases of thyroid neoplasia.]

A total of 143 female C3H mice, approximately 10 weeks of age, were divided into two approximately equal groups; one was fed basal diet and served as controls, and the other received thiouracil in the diet at an initial concentration of 0.375%, increased later to 0.5%. The animals were killed at selected intervals or when moribund. The authors described the development of thyroid follicular-cell hyperplasia in treated mice during the first 12 months of the study but diagnosed no neoplasia. However, 10/23 mice treated for 362–464 days developed pulmonary metastases of thyroid tissue, which were interpreted by the authors as ‘benign metastasizing thyroid tissue’ (Dalton *et al*., 1948). [The Working Group noted that, under current histopathological criteria, the pulmonary lesions might be regarded as metastases of thyroid neoplasia.]

Groups of male and female C3H mice and an inbred strain designated TM [initial numbers not specified], 1 month of age, were fed a diet containing 0.3% thiouracil [purity not specified] for 17 months. Thiouracil produced ‘hepatomas’ in 12/13 male and 14/16 female C3H mice but not in 22 male or 22 female TM mice. In the control groups, hepatomas occurred in 2/32 male and 0/24 female C3H mice and in 0/20 male and 0/20 female TM mice (Casas, 1963).

Rat: Groups of 6–20 male and 7–15 female Stanford albino rats, of an average age of 55 and 45 days, respectively, were fed diets containing thiouracil [purity not

specified] at a concentration of 0.1% for various periods from 120 up to 312 days. Nodular hyperplasia (solitary or multiple nodules) of the thyroid was observed in 20/56 male rats examined at 169 days and in 17/55 female rats examined at 120 days. The nodular lesions were considered by the author to be benign (Laqueur, 1949). [The Working Group noted the lack of a control group.]

In a study of the combined effects of thiouracil and 2-acetylaminofluorene on the thyroid gland, 20 male and female Sherman strain rats, weighing 75–100 g [age not specified], were given thiouracil [purity not specified] in the drinking-water at a concentration of 0.05 or 0.1% for 245–884 days. Thyroid tumours occurred in 12/20 rats [not separated on the basis of dose], 11 of which had adenomas and one a carcinoma. In the group receiving thiouracil and 0.03% 2-acetylaminofluorene in the diet simultaneously and killed after only 22–45 weeks, the incidences of thyroid follicular-cell adenomas and carcinomas were 28/28 and 5/28, respectively (Paschkis *et al*., 1948). [The Working Group noted that there was no untreated control group.]

A group of 35 male Sprague-Dawley rats, weighing on average 61 g [age not specified], was given thiouracil [purity not specified] in the drinking-water at a concentration of 0.2% for 24 months. A control group of 25 males was available. Two rats from each group were killed at 6, 14 and 18 months, and the remaining 26 treated and 17 control rats were killed at 2 years. Thyroid adenomas were diagnosed in approximately 65% of the treated rats, but the tumour incidence in the control group was not reported (Clausen, 1954). [The Working Group noted the limited information provided in the report.]

In a complex study of carcinogen interactions in various target organs, groups of 23–24 male and female Fischer 344 rats [age not specified] were fed diets containing thiouracil [‘checked for purity’] at a concentration of 83, 250 or 750 mg/kg for 104 weeks. A control group comprised 214 male and 214 female rats. At 725 days, the numbers of survivors were 191/214, 19/24, 21/24 and 4/24 males at 0, 83, 250 and 750 mg/kg, respectively, and 184/214, 21/23, 18/24 and 17/24 females, respectively. The incidences of malignant thyroid follicular-cell tumours over the study period were 5/214, 6/24, 14/24 and 5/24 males and 5/214, 2/23, 6/24 and 18/24 females in the four groups, respectively. No malignant liver or kidney tumours were found (Fears *et al*., 1989).

3.2 Administration with known carcinogens

Gerbil: Groups of 20 male and 11 female gerbils [age not specified but stated as equal across groups] were given diets containing thiouracil [purity not specified] at a concentration of 0.2% in combination with a subcutaneous injection of 23 mg/kg bw *N*-nitrosodiethylamine (NDEA) once a week for life. Additional groups of 20 males and 19 females received NDEA only, and 12 males and 12 females received the thiouracil diet only; a vehicle control group of 11 males and 10 females received 0.9% saline only. The average survival times were 37 weeks for males and 24 weeks for females given NDEA only, 54 weeks for males and 45 weeks for females given NDEA plus thiouracil,

79 weeks for males and 81 weeks for females given thiouracil only and 80 weeks for males and 69 weeks for females given saline. Thiouracil given in conjunction with NDEA inhibited the development of cholangiocarcinomas induced by NDEA alone, the incidences being 17/20 males and 16/19 females given NDEA only and 0/20 males and 0/11 females given NDEA plus thiouracil. Some cholangiomas were also observed, the incidences being 0/20 males and 0/19 females given NDEA only and 13/20 males and 4/11 females given NDEA plus thiouracil. The incidence of nasal cavity adenocarcinomas induced by NDEA was not influenced by thiouracil, and no tumours of any type were observed in the group given thiouracil alone (Green & Ketkar, 1978).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

In male Sprague-Dawley rats given a single intraperitoneal injection of 5 mg of [^{35}S]thiouracil, thyroid accumulation of the label began at 4 h and reached a peak at 10 h. The concentration gradient between thyroid tissue and plasma was 7.5 at 10 h and 156 after 48 h. Five ^{35}S-labelled compounds were detected in the thyroid by thin-layer chromatography: [^{35}S]sulfate, protein-bound ^{35}S, unmetabolized thiouracil and two unidentified metabolites (Lees *et al.*, 1973). Accumulation of [^{35}S]thiouracil in the thyroid of rats was also reported by Marchant *et al.* (1972).

Rapid placental transfer of [^{14}C]thiouracil was demonstrated in rabbits given a single intravenous injection of 0.01–0.03 mmol [1.3–3.8 mg] on days 31–33 of gestation and in dogs injected with a dose of 0.05 mmol [6.4 mg] on days 61–63 of gestation. An equilibrium was reached between maternal and fetal blood within 30 min, but the concentrations in maternal and fetal thyroid increased for 3 and 6 h after treatment in rabbits and dogs, respectively. The radiolabel in the fetal thyroid appeared to be associated with the parent compound (Quinones *et al.*, 1972).

After intraperitoneal injection of [^{14}C]thiouracil to pregnant Sprague-Dawley rats on day 10, 12, 14, 17 or 20 of gestation, placental transfer was found at all stages but was most pronounced at late stages of gestation (Sabbagha & Hayashi, 1969).

Autoradiographic analysis of the fate of about 0.07 mg of [^{14}C]thiouracil injected intravenously into pregnant NMRI mice in a late stage of gestation [gestational age not indicated] revealed accumulation in the fetal thyroid (Slanina *et al.*, 1973).

4.2 Toxic effects

4.2.1 *Humans*

When thiouracil was used as an anti-thyroid drug, a high frequency of adverse reactions was seen (VanderLaan & Storrie, 1955), including agranulocytosis.

4.2.2 *Experimental systems*

Thiouracil increased the iodide content of the salivary glands and decreased that of the thyroid of white male rats [strain not specified] fed a diet containing 0.035% thiouracil for 3 months (Hassanein & Almallah, 1978).

Male Fischer rats fed a low-iodine diet containing 0.25% thiouracil developed hyperplasia of the thyroid gland within 3 days, and the capsule of the gland increased to a substantial multilayered structure (Wollmann & Herveg, 1978).

Enlargement of the adipose tissue pads on the thyroid of male Fischer rats during ingestion of a diet containing 0.25% thiouracil for 10 days was probably due to an elevated concentration of circulating thyroid-stimulating hormone and not to a direct effect of thiouracil (Smeds & Wollman, 1983).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Perinatal thyroid deficiency induced by thiouracil (2 mg/kg of diet) given to pregnant rats [strain not specified] during the last 15 days of gestation and the first 15 days after parturition caused a chronic hypermetabolic state in both male and female offspring. In female rats, a mild hyperthyroid condition occasionally persisted (Davenport & Hennies, 1976).

The adrenal weights of 15-day-old Sprague-Dawley rats made hypothyroid by administration of 0.25% thiouracil in the diet of dams from the day of conception through lactation were reduced by 23%, but they showed no change in adrenal corticosterone secretion or corticosterone secretion per milligram of adrenal tissue. The corticotropin-releasing factor-like activity of the median eminence was reduced (Meserve & Pearlmutter, 1983). A similar response was observed in genetically hypothyroid (*hyt/hyt*) mice born to heterozygous dams, but the effect was not apparent until 30 days of age, i.e. after weaning, suggesting a role of maternal thyroid hormones in the maintenance of hypothalamic corticotropin-releasing factor (Meserve, 1987). A time-course study of corticosterone release after corticosterone stimulation in 15-day-old Sprague-Dawley rats made hypothyroid by dietary exposure of the dams to 0.25%

thiouracil from conception indicated that the hypothalamic response was attenuated and not ablated (Meserve & Juárez de Ku, 1993).

4.4 Effects on enzyme induction or inhibition and gene expression

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

In male CD rats given an intraperitoneal injection of 10–50 mg/kg bw thiouracil, in the absence of oxidizable substrates, irreversible inhibition of thyroid iodide peroxidase occurred. When iodine or thiocyanate was present, the inhibition was prevented, suggesting that the initial action of thiouracil is to block iodination by trapping oxidized iodide (Davidson *et al*., 1978).

Female Sprague-Dawley rats fed a diet containing 0.2% thiouracil for 14 days had increased (approximately threefold) NADH duroquinone (2,3,5,6-tetramethyl-1,4-benzoquinone) reductase activity and decreased (by ~ 20%) α-glycerophosphate dehydrogenase activity compared with controls (Ruzicka & Rose, 1981).

Chopra *et al*. (1982) studied the structure–activity relationships of the inhibition of hepatic monodeiodination of thyroxine to triiodothyronine by thiouracil and other related compounds in liver homogenates from male Sprague-Dawley rats. The results suggested that the thiourea moiety is insufficient to inhibit the conversion.

In rat liver microsomal systems, thiouracil at 0.5 or 1 μmol/L [64 or 128 μg/L] was a non-competitive inhibitor with respect to substrate and a competitive inhibitor with respect to cofactors of iodothyronine-5′-deiodinase (Visser, 1979). Inactivation of iodothyronine-5′-deiodinase by thiouracil required a substrate (Visser & van Overmeeren-Kaptein, 1981).

Thiouracil inhibited peroxidase in a microsomal preparation from the gastric mucosa of male Swiss mice (Banerjee & Datta, 1981).

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 reference)

Thiouracil did not induce DNA strand breaks in cultured mammalian cells in the only study in which thiouracil was tested alone for genotoxicity.

Table 1. Genetic and related effects of thiouracil

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA strand breaks, L5178Y mouse lymphoma cells *in vitro*	–	NT	1282	Garberg *et al*. (1988)

[a] –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL

Irradiation of *Escherichia coli recA*$^-$ cells in the presence of thiouracil resulted in greater cytotoxicity than in wild-type or *uvrA*$^-$ cells. Furthermore, thiouracil enhanced the incidence of mutations induced by ultraviolet A irradiation in *E. coli uvrA*$^-$, but not *recA*$^-$ cells, while irradiation of *Salmonella* cells with ultraviolet A in the presence of thiouracil led to increased expression of *umuDC* (Komeda *et al.*, 1997). Thiouracil enhanced the DNA-strand breaking effect of 334-nm ultraviolet radiation in purified bacterial DNA (Peak *et al.*, 1984).

4.6 Mechanistic considerations

Thiouracil belongs to a class of drugs used in the treatment of hyperthyroidism which act by interfering with thyroid peroxidase functioning, thus decreasing thyroid hormone production and increasing proliferation by increasing the concentration of thyroid-stimulating hormone. This is the probable basis of the tumorigenic activity of thiouracil in the thyroid of experimental animals.

The lack of adequate data on genotoxicity for thiouracil precludes a conclusion regarding the mechanism of carcinogenicity.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Thiouracil was used briefly in the 1940s as the first thionamide anti-thyroid drug.

5.2 Human carcinogenicity studies

No epidemiological data on use of thiouracil and cancer were found. However, two analyses were published of one cohort study conducted in the United Kingdom and the USA of the cancer risk of patients, mainly women, with hyperthyroidism who had been treated with anti-thyroid drugs. The earlier analysis showed more malignant thyroid neoplasms in patients receiving these drugs than in those treated with surgery or ^{131}I, but the excess may have been due to closer surveillance of the patients given drugs owing to more frequent use of thyroidectomy. In the later analysis, patients with hyperthyroidism treated only with anti-thyroid drugs had a modest increase in the risk for death from cancer, due chiefly to oral cancer and cancer of the brain. Neither report provided information on the type, quantity or dates of anti-thyroid drug use.

Two case–control studies of cancer of the thyroid showed no significant association with treatment with anti-thyroid medications.

5.3 Animal carcinogenicity data

Several early studies in mice showed that oral administration of thiouracil induced nodular thyroid follicular-cell hyperplasia, including some pulmonary metastases suggestive of thyroid neoplasia by current histopathological criteria. In one study in one strain of mice, thiouracil produced hepatocellular tumours. In one adequate study in rats, thiouracil produced thyroid follicular-cell adenomas and carcinomas. In one study in gerbils, thiouracil inhibited the progression of *N*-nitrosodiethylamine-induced cholangiomas into cholangiocarcinomas.

5.4 Other relevant data

Little is known about the disposition of thiouracil in humans. In rats and fetal rats, thiouracil accumulated in the thyroid. Thiouracil acts by inhibiting thyroid peroxidase, thus decreasing thyroid hormone production, and it increases proliferation by increasing the secretion of thyroid-stimulating hormone. This is the probable basis of its tumorigenic activity in the thyroid of experimental animals.

No data were available on the developmental or reproductive effects of thiouracil in humans. The only studies in experimental animals indicated altered adrenal function in young rats made hypothyroidal from birth.

In the only study in which thiouracil was tested for genotoxicity, it did not induce DNA strand breaks in cultured mammalian cells. It has not been tested for mutagenicity or clastogenicity.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of thiouracil.

There is *sufficient evidence* in experimental animals for the carcinogenicity of thiouracil.

Overall evaluation

Thiouracil is *possibly carcinogenic to humans (Group 2B)*.

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