Iodine

MAK value	**not yet established, see Section IIb of the List of MAK and BAT Values**
Peak limitation	**–**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity	**–**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	–
Chemical name	iodine
CAS number	7553-56-2
Molecular formula	I_2
Molecular weight	253.809 g/mol
Melting point	114°C (CambridgeSoft 2005)
Boiling point	184.3°C (CambridgeSoft 2005)
Vapour pressure at 25°C	0.31 hPa (SRC 2005)
log K_{OW}[1)]	2.49 (SRC 2005)
1 ml/m³ (ppm) ≙ 10.531 mg/m³	**1 mg/m³ ≙ 0.095 ml/m³ (ppm)**

In 1958, in analogy to the Threshold Limit Value (TLV), a MAK value of 0.1 ml/m³ (1.1 mg/m³) was established for iodine. In 2000, the substance was classified in Peak Limitation Category I with an excursion factor of 1. Its sensitizing effects were evaluated in 1999.

This documentation is based on a report by the ATSDR (2004) and the documentation by the ACGIH (2001).

1) octanol/water partition coefficient

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1 Toxic Effects and Mode of Action

As a component of the thyroid hormones, iodine is essential for the human organism. The daily requirement in adults is given as 150 to 200 µg (ATSDR 2004).

Iodine is a strong oxidant. The substance is irritating to the eyes, skin and respiratory tract, and inhalation can lead to toxic pulmonary oedema. The absorption of iodine after dermal application is low. Initial effects after the ingestion of iodine for 7 or 90 days are observed in adults at doses of 0.46 mg/kg body weight and day and above. After the ingestion of large amounts of iodine, both hyperthyreosis (iodine Basedow) and symptoms of hypothyreosis are reported. Allergy of the skin to iodine is rare in humans.

In rats, the LC_{Lo} values after exposure for one hour are above 80 ml/m^3. After the intake of iodine with the drinking water for 100 days, the increase in the tetraiodine thyronine (T_4): triiodine thyronine (T_3) ratio in the plasma of rats is statistically significant at 1.25 (♀) or 12.5 (♂) mg/kg body weight and day and above.

There are no fertility studies available for iodine. For iodide, in a fertility study in rats with a small study size and inadequate documentation, a lowest observed adverse effect level (LOAEL) of 25 mg/kg body weight and day is given. The corresponding value in rabbits is 7.5 mg/kg body weight and day.

Iodine was not found to be genotoxic in the genotoxicity studies available.

In most of the epidemiological studies, no relationship between iodide intake and the occurrence of thyroid tumours was found.

In animal studies, both an excess of iodide administered with the drinking water and iodide deficiency were tumour-promoting in the thyroid gland. In a 2-year carcinogenicity study in rats, potassium iodide in the drinking water produced squamous cell carcinomas in the salivary glands of the lower jaw.

2 Mechanism of Action

As iodine is a strong oxidant, mainly oxidative damage is thought to be responsible for the local irritating effects. The effects on the thyroid can be explained by a disturbance in the thyroid hormone balance.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Inhaled iodine is rapidly absorbed, and almost 100% is retained. Even after the ingestion of water-soluble iodide salts, gastrointestinal absorption is about 100% (ATSDR 2004). For dermal exposure, the amount absorbed by sheep and miniature pigs is about 5% to 6% (Murray 1969; Wood et al. 1963). Of 0.5 ml aqueous iodine solution (> 70% $^{131}I_2$; < 30% ^{131}iodide; 0.1 mg $^{127}I_2$), which was applied to the skin

(2 × 1 inch; about 5 × 2.5 cm) for 2 hours, up to 0.2% iodide and I_2 was eliminated by humans with the urine (Harrison 1963).

While 30% to 60% of inhaled iodine is eliminated with the urine, and small quantities with bile, sweat, saliva or milk, about 20% to 30% is accumulated in the thyroid gland in order to be incorporated into hormones (ATSDR 2004).

3.2 Metabolism

In the body, iodine is rapidly reduced to iodide. The iodide actively absorbed from the plasma into the thyroid cells is first of all oxidized and incorporated in tyrosyl residues of thyroglobulin. Subsequently, via coupling reactions, thyroglobulin-bound T_3 and T_4 are formed. The thyroid hormones are released as a result of proteolytic degradation (ATSDR 2004).

4 Effects in Humans

4.1 Single exposures

While iodine vapour concentrations of 1.63 ml/m^3 caused irritation to the eyes after 2 minutes in 4 persons, exposure to iodine vapour in concentrations of 0.57 ml/m^3 for 5 minutes did not have this effect (no other details; NAS 1995).

In the reports by the ATSDR (2004) and the ACGIH (2001), attention is drawn to suicide attempts by ingestion of iodine tinctures (about 40 mg iodine/ml) containing also NaI or NaI_3 besides molecular iodine (ACGIH 2001; ATSDR 2004). Eighteen persons ingested iodine doses of 17 to 120 mg/kg body weight and day; death occurred within 48 hours (ATSDR 2004). Of 1195 attempted suicides treated in Boston City Hospital, 327 had taken iodine in the form of Iodoform, Lugol's solution or iodide. Of these persons, a 60-year-old man, who had also ingested mercury dichloride, died (Moore 1938). There are no details available for the respective doses ingested.

4.2 Repeated exposure

The statement that the inhalation of an iodine concentration of 1 ml/m^3 in a factory in Massachusetts caused strong irritation, and 0.07 ml/m^3 did not produce this effect (no other details; ACGIH 2001), could not be confirmed from the original literature (Casarett 1975).

As regards the oral absorption of iodine or iodide, there are numerous studies with volunteers available. Case reports without exposure data are not described here; see the sources mentioned above and reviews (Backer and Hollowell 2000; Pennington 1990).

Table 1 summarizes exemplary data for repeated treatment with iodine at known exposure levels.

Table 1 Effects of iodine after repeated ingestion

Administration route, dose	Duration	Number of persons	Dose: findings	References
4 water disinfection tablets (tetraglycine hydroperiodide) releasing 8 mg free iodine per tablet about 0.46 mg I_2/kg body weight and day assuming a body weight of 70 kg	7 days	7	**0.46 mg I_2/kg body weight**: T_3 and T_4 in serum ↓, TSH and TSH-20 in serum ↑	Georgitis et al. 1993
500, 1500, 4500 µg NaI solution/day (about 7, 21, 64 µg NaI/kg body weight and day assuming a body weight of 70 kg); oral; daily dose in the form of two 0.5 ml aliquots of a NaI solution in distilled water; 1 mg ascorbic acid/ml	14 days	30 ♂ aged between 22 and 40 years	**7 µg I^-/kg body weight and above**: iodide concentration in serum and urine ↑ compared with day 1; excretion of iodide with the urine ↑; TRH-stimulated TSH ↑ **7 µg I^-/kg body weight**: NOAEL **21 µg I^-/kg body weight and above**: T_4 and free T_4 in serum ↓ compared with day 1, TSH in serum ↑; T_3 in serum and T_3-"charcoal uptake" unchanged compared with day 1	Gardner et al. 1988
250, 500, 1500 µg NaI solution/day (about 4, 7, 21 µg NaI/kg body weight and day assuming a body weight of 70 kg); oral; daily dose in the form of two 0.5 ml aliquots of a NaI solution in water; 5 mg ascorbic acid/ml	14 days	9 ♂ aged between 26 and 56 years, 23 ♀ aged between 23 and 44 years	**4 µg I^-/kg body weight and above**: excretion of iodide with the urine ↑ **7 µg I^-/kg body weight**: NOAEL **21 µg I^-/kg body weight**: T_4, free T_4 and T_3 in serum ↓ compared with day 1, TSH in serum ↑; TRH-stimulated TSH ↑	Paul et al. 1988

Table 1 (Continued)

Administration route, dose	Duration	Number of persons	Dose: findings	References
I_2 or NaI in phosphate buffer; 0.3, 1.0 mg iodine or I^-/kg body weight and day[a)]	14 days	6–7/dose group	**0.3 mg iodine or I^-/kg body weight**: 4/6 (67%): reported burning in the throat (physical examination without adverse findings); no statistically significant difference in T_3, T_4 and TSH in serum after 7, 14, 15 and 25 days compared with controls, NOAEL **1.0 mg iodine or I^-/kg body weight**: 5/7 (71%): reported burning in the throat (physical examination without adverse findings); TSH in serum after 15 days ↑ (after 7, 14 and 25 days difference not statistically significant compared with controls), no statistically significant difference in T_3 and T_4 in the serum after 7, 14, 15 and 25 days compared with controls, LOAEL	Robison et al. 1998
4 tetraglycine hydroperiodide tablets about 0.46 mg I_2/kg body weight and day	90 days	8	**0.46 mg I_2/kg body weight**: concentration of inorganic iodide in serum and urine ↑, TSH and TSH-20 in serum ↑ after 7 and 28 days, average thyroid volume ↑ (37%) (initial value after 7 months), T_3 and T_4 in serum normal, no hyperthyreosis or hypothyreosis	LeMar et al. 1995
54, 462.5 µg iodine/l in the drinking water (no other details); 0.9, 7.7 µg/kg body weight and day assuming a body weight of 30 kg and a consumed amount of 500 ml/day	7–15 years	51 (low dose group); 120 (high dose group); children aged 7–15 years	**0.9 µg iodine/kg body weight**: 15.4% with goitre (levels 0, 1a, 1b, 2 together), 0% with goitre level 2; NOAEL **7.7 µg iodine/kg body weight**: iodine in urine (in relation to creatinine) ↑, T_3 in serum ↓, free T_4 and TSH in serum ↑, 65% with goitre (levels 0, 1a, 1 b, 2 together), 20% with goitre level 2; LOAEL	Mu et al. 1987

Table 1 (Continued)

Administration route, dose	Duration	Number of persons	Dose: findings	References
0.5–1 mg I_2/l in the drinking water for disinfection (1 mg the first 6 years, then 0.5 mg); about 0.004–0.014 mg I/kg body weight and day assuming a body weight of 70 kg and a consumed amount of 500 ml to 1 I/day	a few months to 15 years	750 prison inmates (♂ and ♀)	**0.004–0.014 mg I_2/kg body weight**: T_3 and T_4 in serum, intake of radioactive iodine via the thyroid gland: no unusual findings	Thomas et al. 1978

Abbreviations: T_3: triiodine thyronine, T_4: thyroxine, TRH: thyrotropine-releasing hormone, TSH: thyroid-stimulating hormone, TSH-20: TSH concentration 20 minutes after intravenous administration of TRH;

[a)] The authors state that 25% of elemental iodine was present in the form of I^-. On the first two treatment days the test persons in the higher dose group were therefore given 1.3 mg total iodine/kg body weight and day. From the third day of treatment onwards, the dose was corrected and the persons received 1 mg total iodine/kg body weight and day (of which 0.75 mg I_2/kg body weight).

After the ingestion of iodine for 14 days, dose levels of 0.01 mg/kg body weight and day (Gardner et al. 1988; Paul et al. 1988) or 0.3 mg/kg body weight and day (Robison et al. 1998) were given as the no observed adverse effect level (NOAEL) for systemic effects. In children, a NOAEL of 0.9 µg/kg body weight and day was determined after exposure to iodine for several years (Mu et al. 1987). Initial effects after exposure for 7 or 90 days were observed in adults at dose levels of 0.46 mg/kg body weight and day and above (see Table 1; Georgitis et al. 1993; LeMar et al. 1995; Robison et al. 1998). For children, the LOAEL after several years of iodine ingestion was given as 7.7 µg/kg body weight and day (Mu et al. 1987).

In reviews, it is assumed that most persons are able to tolerate a daily intake of 1 mg iodine (about 0.014 to 0.017 mg/kg body weight and day, assuming a body weight of 60 to 70 kg). This daily dose, however, does not take into account sensitive groups (such as thyroid patients suffering, for example, from thyroiditis, hyperthyroidism, hypothyroidism or goitre, or persons taking medication containing iodine such as amiodarone, an agent for cardiac arrhythmia) (ATSDR 2004; Backer and Hollowell 2000; Pennington 1990).

4.3 Local effects on skin and mucous membranes

Iodine was found to be strongly irritating to the skin and eyes (ACGIH 2001; see Section 4.1).

4.4 Allergenic effects

In 1999, iodine was classified as not sensitizing to the skin and airways. In humans, allergic skin reactions can occur, although these are rare in view of the frequent contact possibilities. Data for airway sensitization could not be evaluated, as information about exposure levels was not available (supplement "Iod" 1999, available in German only).

Since then, no further studies have been carried out.

4.5 Reproductive and developmental toxicity

No increase in the size of the thyroid gland was found in any of the 181 children of 177 prison inmates who had ingested drinking water containing iodine concentrations of 0.5 to 1.0 mg/l 24 to 225 days before giving birth. The drinking water had been treated with elemental iodine for disinfection. Congenital anomalies in 11 children were not attributable to the intake of iodine (Stockton and Thomas 1978; Thomas et al. 1978).

4.6 Genotoxicity

There are no studies available.

4.7 Carcinogenicity

There are no studies available for the inhalation of iodine.

In most epidemiological studies, no relationship was found between iodide intake and the occurrence of thyroid tumours. In a retrospective analysis of medical records in Tyrol (about 1 million inhabitants), an area with iodine deficiency in which goitre occurs endemically, an increase in the incidence of thyroid tumours after the introduction of iodized table salt (1960–1970: incidence 3.1; 1990–1994: 7.8) was observed. Investigation of a total of 439 patients with thyroid tumours revealed that during this time the prevalence of papillary tumours increased relative to that of follicular tumours. The prevalence of other advanced tumour stages decreased, which indicates an improvement in diagnosis (ATSDR 2004). There is no evidence for a plausible exposure–effect relationship between dietary iodide supplementation and the occurrence of thyroid tumours in areas with iodine deficiency.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

An LC_{Lo} value of 137 ml/m³ was given for rats after exposure for one hour. Observed effects were lacrimation, sleepiness and a decrease in body temperature (no other details; NIOSH 2004). In another investigation, also after exposure for one hour, an LC_{Lo} value of 80 ml/m³ was determined for the same species (no other details; NAS 1995).

Groups of 8 to 10 guinea pigs (male and female animals) were exposed to gaseous iodine in concentrations of 0.5, 0.86, 3.1, 4.4 or 7.3 ml/m³ (about 5.5, 9.5, 34.1, 48.4 or 80.3 mg/m³) for one hour. During exposure and for one hour afterwards, the airway resistance, pulmonary compliance, time constant (mathematical product between airway resistance and pulmonary compliance), respiration rate, tidal volume and respiratory minute volume were determined every 5 minutes. The values determined before the exposure of each animal were taken as control values. After exposure for one hour, a concentration-dependent statistically significant increase in airway resistance and a decrease in the minute volume compared with the control values occurred at concentrations of 0.86 ml/m³ and above. The decrease in the respiration rate was dose-dependent and statistically significant after exposure for one hour at 3.1 ml/m³ and above. The increase in the time constant and tidal

volume was dose-dependent and statistically significant at 4.4 ml/m^3 and above. The decrease in pulmonary compliance was statistically significant at 7.3 ml/m^3. At concentrations of 0.5 ml/m^3, no statistically significant changes were observed after exposure for one hour. The author concluded that gaseous iodine has a strongly irritating effect on the upper respiratory tract at the low concentrations (0.86 ml/m^3 and above), but affects also the lower respiratory tract at the high concentration of 7.3 ml/m^3 (Amdur 1978).

In the dog, 14 mg iodine/kg body weight applied intratracheally as fume led to acute pulmonary oedema within 4 hours (Luckhardt et al. 1920).

5.1.2 Oral administration

For the dog, 8 to 12 g iodine was lethal ($LD_{Lo,}$ toxicity dose, low", that is the lowest dose at which effects are observed, 800 mg/kg body weight, assuming a body weight of 10 kg; Flury and Zernik 1935).

5.1.3 Dermal application

There are no studies available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a study not described in greater detail, TC_{Lo} values ("toxicity concentration, low", that is the lowest concentration at which effects are observed) of 1.38 or 3.1 mg/m^3 (0.13 or 0.28 ml/m^3) were given for the exposure of rats for 13 weeks (24 hours/day). At concentrations of 3.1 mg/m^3 (0.28 ml/m^3) and above, changes in the parameters of functional liver and kidney tests and endocrine changes not described in greater detail occurred. At concentrations of 1.38 mg/m^3 (0.13 ml/m^3) and above, changes in motor activity and aggressive behaviour were observed (no other details; NIOSH 2004).

5.2.2 Oral administration

Groups of 6 male and 6 female Sprague Dawley rats were given 0, 1, 3, 10 or 100 mg iodine or sodium iodide/l drinking water for 100 days (about 0, 0.125, 0.375, 1.25 or 12.5 mg/kg body weight and day, assuming a daily water intake of 50 ml and a body weight of 400 g). The control group, given untreated drinking water, consisted of 12 male and 12 female animals. Blood samples were taken on day 10 and at the end of the treatment period. The haematocrit value, the haemoglobin level in blood, the

activities of aspartate and alanine aminotransferase, the concentrations of total cholesterol and urea nitrogen in serum, and the concentrations of triglycerides and the T_3 and T_4 levels in plasma were determined. The body weights and the relative weights of the thyroid gland, brain, liver, kidneys, heart and testes were determined. After 10 days of treatment with iodine and with iodide, there was a statistically significant and dose-dependent increase in the plasma T_4 concentrations in male and female rats. After 100 days of treatment with iodine, the increase in the $T_4 : T_3$ ratio was statistically significant at 12.5 mg/kg body weight and day in males and at 1.25 mg/kg body weight and day and above in females. Iodide on the other hand, caused a statistically significant increase in the $T_4 : T_3$ ratio only in the female rats after 100 days of treatment with 12.5 mg/kg body weight and day. In the males given 1.25 mg/kg body weight and day and more, iodide produced a statistically significant increase in the relative thyroid weight compared with that in the controls. All the other parameters investigated were not affected by the treatment (Sherer et al. 1991). The NOAEL was determined to be 0.375 mg iodine/kg body weight and day.

5.2.3 Dermal application

There are no studies available.

5.3 Local effects on skin and mucous membranes

There are no studies available.

It may be assumed, however, that iodine has a strongly irritating effect on the skin and eyes in animals.

5.4 Allergenic effects

In the supplement on the sensitizing effects of iodine, two experimental studies with guinea pigs are described in which iodine was found to be a weak contact allergen. No studies of respiratory sensitization have been carried out (supplement "Iod" 1999, available in German only).

No further results have since been published.

5.5 Reproductive and developmental toxicity

There are no studies available for the reproductive and developmental toxicity of iodine.

Prior to birth and during the lactation phase, groups of 9 female Long Evans rats were given food containing potassium iodide (500, 1000, 1500 or 2000 mg iodine/

kg diet; about 25, 50, 75 or 100 mg iodine/kg body weight and day, assuming a body weight of 400 g and a daily food intake of 20 g). The control animals were given an equivalent amount of potassium with their food. The females were mated with untreated males and the survival of the offspring was recorded. There was a statistically significant and dose-dependent decrease in the survival of the offspring at doses of 25 mg/kg body weight and day and above. Most of the offspring died 24 hours after birth and there was no milk in their stomachs. The treated dams consumed less food and their body weight gains were lower than in the control animals (not statistically significant). In another experiment, groups of 20 rats of the same species were given food containing potassium iodide (2500 mg iodide/kg diet; about 125 mg iodide/kg body weight and day, assuming a body weight of 400 g and a daily food intake of 20 g) continuously for 35 days before birth or with a 10-day interruption (mating period). As in the preceding study, control animals were given an equivalent amount of potassium with the diet. Investigations after 17 to 19 days of pregnancy and 24 to 48 hours after birth revealed that ovulation and implantation were unaffected by the treatment. There was a statistically significantly decrease in the survival of the offspring and the body weight gains of the surviving offspring. Histological examination of the mammary tissue in the dams showed that milk secretion was insufficient or greatly reduced. The authors assumed that a reduction in milk secretion could have been caused by a disturbance in the iodine metabolism (Ammerman et al. 1964). For the survival of the offspring, a LOAEL of 25 mg iodine/kg body weight and day was derived.

In a more extensive study, female animals of different species were given diets containing sodium or potassium iodide after mating with untreated male animals (2 to 10 days before giving birth). The control animals were given the equivalent amount of potassium or sodium with the diet. The duration of pregnancy, birth and lactation, and the survival period of the offspring were recorded. The following species were used: female Dutch and New Zealand White rabbits, Syrian hamsters, Long Evans rats and Hampshire Duroc swine. The following results were obtained: In rabbits, mortality occurred in the young at doses of 7.5 mg iodide/kg body weight and day and above. Histological examination of the mammary glands in this species did not reveal any unusual findings, unlike in the rats (see also Ammerman et al. 1964). Tremor was observed in around half of the treated animals and their heads were held to one side, the eyelids were swollen and lacrimation was evident; the authors did not attribute these findings to the iodide content of the diet, but had no other explanation for this. At the only dose given (2500 mg/kg food), the food consumption of the hamster dams was decreased and the body weights of the young at birth were reduced. The treated pigs were not affected by the iodide concentrations in the diet which were toxic to rabbits and rats. In the treated rats, parturition was prolonged. The greater sensitivity of rabbits was attributed to their habit of eating their faeces, which resulted in a higher iodine intake (Arrington et al. 1965). In rabbits, a LOAEL of 7.5 mg/kg body weight and day was derived for effects on fertility. There are no data available for maternal toxicity.

5.6 Genotoxicity

The results of in vitro studies of the genotoxicity of the substance are shown in Table 2.

In $TK^{+/-}$ mutation tests with L5178Y mouse lymphoma cells, iodine did not cause mutations in the absence of a metabolic activation system (Kessler et al. 1980). Iodine did not cause mutations or mitotic recombination or gene conversion in Saccharomyces cerevisiae XV185–14C and D5 at concentrations of 100 µg/ml (787 µM) and 12.5 µg/ml (98 µM), respectively (Mehta and von Borstel 1982).

There are no in vivo studies available for the genotoxicity of the substance.

Table 2 Studies of the genotoxicity of iodine in vitro

Test system		Concentration	Result		Remarks	References
			– m. a.	+ m. a.		
$TK^{+/-}$	L5178Y mouse lymphoma cells	22–340 µg/ml (173–2677 µM)	–	n. t.	solvent not specified, cloning efficiency at least 85% of that in controls	Kessler et al. 1980
mutation	Saccharomyces cerevisiae XV185–14C	100 µg/ml (787 µM)	–	n. t.	cytotoxicity	Mehta and von Borstel 1982
mitotic recombination, gene conversion	Saccharomyces cerevisiae D5	12.5 µg/ml (98 µM)	–	n. t.	cytotoxicity	Mehta and von Borstel 1982

n. t.: not tested, m. a.: metabolic activation, $TK^{+/-}$: $TK^{+/-}$ mutation test

5.7 Carcinogenicity

5.7.1 Short-term tests

In Balb/c-3T3 cells, iodine led to a statistically significant increase in cell transformations that was not concentration-dependent (at 170 µg/ml, 1339 µM; tested concentration range: 22–340 µg/ml, 173–2677 µM). The authors were of the opinion that this has no biological relevance. The "plating efficiency" was at least 50% of the control value (Kessler et al. 1980). The solvent was not specified.

Table 3 shows initiation–promotion tests carried out with potassium iodide.

Table 3 Initiation–promotion tests to discover the tumour-promoting effect of potassium iodide

Author:		Kanno et al. 1992						
Species:		rat, only ♂, F344, 20 animals/group						
Administration route:		with the drinking water						
Concentration:		0, 12.5, 25, 50, 200, 65 000, 260 000 µg potassium iodide/l distilled water (about 0.7, 1.1, 1.6, 2.4, 7.4, 2171, 8571 µg I^-/kg body weight and day at an average body weight of 350 g). According to analyses by the authors, each rat ingested on average 12.1 g iodide-deficient food and 15.3 ml drinking water per day. When calculating the ingested dose, the drinking water and food were taken into account. Iodide-deficient diet: 21 ng iodine/g; purity of potassium iodide: > 99.5% In the literature it is reported that an iodine intake of 3 µg/rat and day (about 7.4 µg/kg body weight and day, assuming a body weight of 350 g) does not cause goitre. The dose of 7.4 µg/kg body weight and day was therefore used by the authors as a control. At the age of 6 weeks, the animals were given subcutaneous injections of 2800 µg *N*-bis(2-hydroxypropyl)-nitrosamine/kg body weight; the controls were given NaCl solution.						
Duration:		25 weeks, age at the start of exposure: 7 weeks						
Toxicity:		up to 2.4 µg I^-/kg body weight and day + *N*-bis(2-hydroxypropyl)-nitrosamine: serum T_4 ↓ 7.4 µg I^-/kg body weight and day + *N*-bis(2-hydroxypropyl)-nitrosamine and above: serum T_4 unchanged animals not treated with initiator: serum T_4 unchanged all animals: body weights, thyroid weights unchanged						
		Dose (µg I^-/kg body weight and day)						
		0.7	1.1	1.6	2.4	7.4 (control)	2171	8571
Survivors	NaCl	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)
(at end of test):	DHPN	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)	20/20 (100%)
Preneoplasms and tumours:								
Thyroid gland:								
neoplasms	NaCl	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)
	DHPN	12/20 (60%)	11/20 (55%)	6/20 (30%)	5/20 (25%)	0/20 (0%)	1/20 (5%)*	2/20 (10%)*

Table 3 (Continued)

adeno-matous goitre	NaCl	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)
	DHPN	8/20 (40%)	7/20 (35%)	2/20 (10%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	1/20 (5%)
adeno-matous nodule	NaCl	1/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)
	DHPN	no data	2/20 (10%)	12/20 (60%)	10/20 (50%)	2/20 (10%)	6/20 (30%)	6/20 (30%)

DHPN: *N*-bis(2-hydroxypropyl)-nitrosamine, T_4: thyroxine;
* $p < 0.03$ (combined Cochran-Armitage trend test) for dose levels above controls

Author:	Kanno et al. 1992
Species:	rat, only ♂, F344, 20 animals/group
Administration route:	with the drinking water
Concentration:	0, 200 000 µg potassium iodide/l distilled water (about 27.7, 6571 µg I^-/kg body weight and day at an average body weight of 350 g). According to analyses by the authors, each rat ingested on average 12.1 g food and 15.3 ml drinking water per day. When calculating the ingested dose, drinking water and food were taken into account. The control animals therefore ingested 27.7 µg I^-/kg body weight and day. Diet: 0.8 µg iodine/g, purity of potassium iodide: > 99.5% At the age of 6 weeks, the animals were given subcutaneous injections of 2800 µg *N*-bis(2-hydroxypropyl)-nitrosamine/kg body weight; the controls were given NaCl solution.
Duration:	25 weeks, age at the start of exposure: 7 weeks
Toxicity:	**KI + *N*-bis(2-hydroxypropyl)-nitrosamine**: slight decrease in serum TSH (not statistically significant) body weights, thyroid weights unchanged, serum T_4 unchanged

		Dose (µg I^-/kg body weight and day)	
		27.7 (controls)	6571
Survivors (at end of test):	NaCl	20/20 (100%)	20/20 (100%)
	DHPN	20/20 (100%)	20/20 (100%)
Preneoplasms and tumours:			
Thyroid gland:			
neoplasms	NaCl	0/20 (0%)	0/20 (0%)
	DHPN	1/20 (5%)	5/20 (25%)*
adenomatous goitre	NaCl	0/20 (0%)	0/20 (0%)
	DHPN	0/20 (0%)	1/20 (5%)
adenomatous nodes	NaCl	0/20 (0%)	0/20 (0%)
	DHPN	1/20 (5%)	3/20 (15%)

DHPN: *N*-bis(2-hydroxypropyl)-nitrosamine, T_4: thyroxine, TSH: thyroid-stimulating hormone;
* $p < 0.03$ (combined Cochran-Armitage trend test)

Table 3 (Continued)

Author:	Takegawa et al. 2000		
Species:	rat, ♂ only, F344/DuCrj, only *N*-bis(2-hydroxypropyl)-nitrosamine: 20 animals, *N*-bis(2-hydroxypropyl)-nitrosamine and KI: 25 animals		
Administration route:	with the drinking water		
Concentration:	0, 1000 mg potassium iodide/l distilled water (0, 55.5 mg KI/kg body weight and day)		
	At the age of 6 weeks the animals were given subcutaneous injections of 2800 µg *N*-bis(2-hydroxypropyl)-nitrosamine/kg body weight.		
Duration:	82 weeks, age at the start of exposure: 7 weeks		
Toxicity:	**KI + *N*-bis(2-hydroxypropyl)-nitrosamine**: body weights and water consumption during the entire study ↓, absolute and relative thyroid weights ↑		
	Dose (mg KI/kg body weight and day)		
		0	55.5
Survivors (end of test)	DHPN	65%	44%
Preneoplasms and tumours:			
Thyroid gland:			
follicular cells:			
carcinomas	DHPN	2/19 (11%)	18/25 (72%)
invasive carcinomas	DHPN	1/19 (5%)	18/25 (72%)*
Remarks:	no increased incidences of preneoplasms and tumours in nose, lungs, liver, pancreas, colon, kidneys, spleen, pituitary gland, adrenal glands, testes, epididymis, preputial glands		

DHPN: *N*-bis(2-hydroxypropyl)-nitrosamine;
* statistically significant difference compared with control value ($p < 0.01$)

Two initiation–promotion experiments demonstrated the tumour-promoting effects of the administration of increased amounts of iodide and of iodide deficiency in the thyroid gland of rats (Kanno et al. 1992; Takegawa et al. 2000). Increased incidences of adenomatous nodules or neoplasms occurred after doses of 2171 µg I^-/kg body weight and day and above and 8571 µg I^-/kg body weight and day, respectively.

The tumour-promoting effects of iodide deficiency can be explained by the increase in serum TSH as a result of negative feedback mechanisms. As a mechanistic explanation for the tumour-promoting effects of increased potassium iodide doses, the authors postulate a relationship with the phenomenon of the escape from the Wolff-Chaikoff effect. The Wolff-Chaikoff effect is described as acute hypothyroidism induced by an increased iodine supply, characterized by a decrease in serum T_4, followed by an increase in serum TSH. The restoration of the euthyroid condi-

tion with a normalization of serum TSH is termed as an "escape" from the Wolff-Chaikoff effect (Kanno et al. 1992).

5.7.2 Long-term studies

There are no long-term studies available for iodine itself.

In a 2-year carcinogenicity study (see Table 4), in which rats were given **potassium** iodide with the drinking water in concentrations of 0, 10, 100 or 1000 mg/l

Table 4 Studies of the carcinogenicity of potassium iodide

Author:	Takegawa et al. 1998, 2000				
Species:	rat, F344/DuCrj, control group and high dose group: 60 ♂ and 60 ♀/group, low and middle dose group: 40 ♂ and 40 ♀/per group; interim necropsy of 5 ♂ and 5 ♀ animals in control group and high dose group after 3, 6, 12, 18 months				
Administration route:	with the drinking water				
Concentration:	0, 10, 100, 1000 mg potassium iodide/l distilled water (♂: 0, 0.6, 5.3, 53.0 mg/kg body weight and day, ♀: 0, 0.7, 6.7, 66.6 mg/kg body weight and day), purity of KI > 99%				
Duration:	2 years, age at the start of exposure: 5 weeks				
Toxicity:	**0.6 (♂) or 0.7 (♀) mg/kg body weight and day and above**: enlarged follicles in the thyroid gland				
	53.0 (♂) or 66.6 (♀) mg/kg body weight and day: at the age of 51 weeks and above: body weights ↓, incidence of lobular atrophy and ductular proliferation in the salivary glands of the lower jaw ↑				
	water consumption, haematology, histopathological examination of remaining organs (about 33 organs investigated): no unusual findings				
		Dose (mg KI/kg body weight and day)			
	♂	0	0.6	5.3	5.0
	♀	0	0.7	6.7	66.6
Survivors:	♂	82%	82%	60%	60%
	♀	88%	90%	90%	88%
Tumours:					
Salivary gland of the lower jaw:					
sqamous cell carcinomas	♂	0/40 (0%)	0/40 (0%)	0/40 (0%)	4/40 (10%)[a)]
	♀	0/40 (0%)	0/40 (0%)	0/40 (0%)	3/40 (7.5%)[a)]

Table 4 (Continued)

Thyroid gland:					
follicular cell adenomas	♂	0/40 (0%)	2/40 (5%)	0/40 (0%)	2/40 (5%)
	♀	0/40 (0%)	1/40 (2.5%)	2/40 (5%)	1/40 (2.5%)
follicular cell carcinomas	♂	0/40 (0%)	1/40 (2.5%)	0/40 (0%)	0/40 (0%)
	♀	0/40 (0%)	0/40 (0%)	0/40 (0%)	1/40 (2.5%)
C-cell adenomas	♂	5/40 (12.5)	3/40 (7.5%)	6/40 (15%)	7/40 (17.5%)
	♀	3/40 (7.5%)	1/40 (2.5%)	3/40 (7.5%)	0/40 (0%)
C-cell carcinomas	♂	1/40 (2.5%)	0/40 (0%)	0/40 (0%)	0/40 (0%)
	♀	0/40 (0%)	0/40 (0%)	0/40 (0%)	1/40 (2.5%)

[a)] not statistically significant when compared with value for the controls; statistically significant when ♂ and ♀ are analyzed together; according to authors no spontaneous squamous cell carcinomas of the salivary gland of the lower jaw in historical control animals

(♂: 0, 0.6, 5.3, 53.0 mg/kg body weight and day; ♀: 0, 0.7, 6.7, 66.6 mg/kg body weight and day), increased incidences of tumours of the salivary glands of the lower jaw were found in the treated animals (evaluation of male and female animals together). When males and females were evaluated separately, no statistical significance was obtained. Increased tumour incidences were not observed in the thyroid gland or in any other organ in the treated animals. The authors see a connection between the tumours in the salivary glands of the lower jaw and the potassium iodide intake. To support their assumption, they argued that contrast agents containing iodine produce "iodide mumps", which is accompanied by the swelling or inflammation of the salivary glands (lower jaw salivary gland, sublingual salivary gland, parotid salivary gland) (Takegawa et al. 1998).

6 Manifesto (MAK value/classification)

The main effects of iodine are irritation of the eyes and the respiratory tract. Another target organ of iodine is the thyroid gland.

There are no studies available for repeated inhalation of iodine in either humans or animals. In addition, the MAK value cannot be derived from the NOAEL for systemic effects from the studies with oral absorption of iodine or iodide as this does not take into account local irritation. Therefore, the previous MAK value for iodine has been withdrawn and the substance listed in Section IIb of the List of MAK and BAT Values. The Peak Limitation Category has likewise been withdrawn. The systemic NOAEL of 0.01 mg/kg body weight and day, assuming a body weight of 70 kg and a respiratory volume of 10 m^3, would correspond to a concentration of 0.07 mg/m^3. As a threshold value, this concentration, however, does not take into account the irritating effects of the substance or those groups of persons sensitive to iodine (see Section 4.2).

In humans, iodine is absorbed through the skin in only very low quantities. The substance is therefore not designated with an "H" (for substances which can be absorbed through the skin).

Iodine was not found to be genotoxic in vitro. There are no data available for the genotoxicity in vivo and carcinogenicity of iodine itself. In rats, both the excessive supply of potassium iodide (concentrations of 2.2 mg iodide/kg body weight and day and above) and iodide deficiency caused tumour promotion in the thyroid gland. The effects of iodine deficiency are not relevant for the workplace. In most epidemiological studies, no relationship was found between iodine intake and the occurrence of thyroid tumours. In a study in Tyrol, a region deficient in iodine in which goitre occurs endemically, increased incidences of thyroid tumours were observed after the introduction of iodized table salt. The investigation of a total of 439 patients with thyroid tumours revealed in addition to a shift in histological findings from papillary tumours to follicular tumours also the reduced prevalence of more advanced tumour stages. The latter observation might be attributed to an improvement in the diagnosis of thyroid tumours. There is no evidence for a plausible causal relationship between iodine food supplementation and the occurrence of thyroid tumours in iodine deficient areas. In a 2-year carcinogenicity study, potassium iodide in the drinking water resulted in squamous cell carcinomas in the salivary glands of the lower jaw in male and female rats. The dose level at which tumours occurred of 53 mg/kg body weight and day is higher than the NOAEL for systemic effects (0.01 mg/kg body weight and day) by a factor of 5000. There is therefore no reason to classify iodine in one of the categories for carcinogens.

There are no data available to justify classification of the substance in one of the categories for germ cell mutagens.

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