

# The Toxicology of Iodate: A Review of the Literature

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Because it is more stable than iodide, most health authorities preferentially recommend iodate as an additive to salt for correcting iodine deficiency. Even though this results in a low exposure of at most 1700  $\mu\text{g}/\text{d}$ , doubts have recently been raised whether the safety of iodate has been adequately documented. In humans and rats, oral bioavailability of iodine from iodate is virtually equivalent to that from iodide. When given intravenously to rats, or when added to whole blood or tissue homogenates *in vitro* or to foodstuff, iodate is quantitatively reduced to iodide by nonenzymatic reactions, and thus becomes available to the body as iodide. Therefore, except perhaps for the gastrointestinal mucosa, exposure of tissues to iodate might be minimal. At much higher doses given intravenously (i.e., above 10 mg/kg), iodate is highly toxic to the retina. Ocular toxicity in humans has occurred only after exposure to doses of 600 to 1200 mg per individual. Oral exposures of several animal species to high doses, exceeding the human intake from fortified salt by orders of magnitude, pointed to corrosive effects in the gastrointestinal tract, hemolysis, nephrotoxicity, and hepatic injury. The studies do not meet current standards of toxicity testing, mostly because they lacked toxicokinetic data and did not separate iodate-specific effects from the effects of an overdose of any form of iodine. With regard to tissue injury, however, the data indicate a negligible risk of the small oral long-term doses achieved with iodate-fortified salt. Genotoxicity and carcinogenicity data for iodate are scarce or nonexistent. The proven genotoxic and carcinogenic effects of bromate raise the possibility of analogous activities of iodate. However, iodate has a lower oxidative potential than bromate, and it did not induce the formation of oxidized bases in DNA under conditions in which bromate did, and it may therefore present a lower genotoxic and carcinogenic hazard. This assumption needs experimental confirmation by proper genotoxicity and carcinogenicity data. These in turn will have to be related to toxicokinetic studies, which take into account the potential reduction of iodate to iodide in food, in the intestinal lumen or mucosa, or eventually during the liver passage.

## Introduction

SALT IS RECOGNIZED as the ideal carrier to supply deficient populations with the necessary iodine. This is usually achieved by adding 20 to 80 mg of iodine per kilogram salt in the form of a sodium or potassium salt of iodide or iodate. In impure salts or under humid and hot climatic conditions, iodide is easily oxidized to  $\text{I}_2$  and then lost by evaporation, while iodate is more stable (1). In 1991, upon a request from the Forty-Third World Health Assembly, the Joint FAO/WHO Expert Committee on Food Additives stated: "Potassium iodate and potassium iodide have a long-standing and widespread history of use for fortifying salt without apparent adverse health effects. In addition, no data are available indicating toxicological hazards from the ingestion of these salts below the level of the Provisional Max-

imum Tolerable Intake" (the limit being set at 1 mg iodine from all sources). The Committee concluded that "potassium iodate and potassium iodide should continue to be used for this important public health purpose" (2). Health authorities therefore usually recommend the addition of iodate (3). A recent survey has shown that of 38 countries in Europe and the former Soviet Union, 5 allow only iodate, 20 both iodate and iodide, and 13 only iodide (WHO Europe, unpublished data). The use of iodate has been the basis of major success in the elimination of iodine deficiency in many countries of the world.

Lately, however, a report prepared for the French authorities has expressed doubts as to the safety of iodate, since publications on adequate genotoxicity testing were lacking (4). This article attempts to review the published toxicology data on iodate. It includes a section on its metabolism. It will

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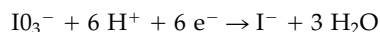
TABLE 1. PHYSICOCHEMICAL PROPERTIES OF THE TWO MOST COMMON IODATE SALTS

	<i>Potassium iodate</i>	<i>Sodium iodate</i>
Molecular weight	214.00	197.89
Density	White crystal 3.89	White crystal powder 4.28
Melting point	560° (decomp.)	decomp.
Solubility H <sub>2</sub> O	4.7% (0°); 32.3% (100°)	9% (20°); 34% (100°)
Ratio of iodine in the salt	59.3%	64.1%
Purity of commercial products	?	~99%

not deal with the problem of iodine-induced thyrotoxicosis because this is a problem of iodine supplementation in general, whether by iodate or iodide. We have been able to draw upon a previous short review (5), as well as on an unpublished report commissioned by the Austrian Ministry of Health and Consumer Protection (6). Moreover, we have scanned the literature by Medline, consulted textbooks and toxicology databases (Toxline, TOXNET: IRIS, EMIC, DART/ETIC, GENE-TOX, HSDB, RTEC) and looked at the regulatory status of iodate in the United States, in Europe, and in Switzerland.

#### Physical and Chemical Properties of Iodate

Iodic acid, together with chloric and bromic acid, belongs to the class of oxohalogen acids with the general formula HOXO<sub>2</sub> (where X denotes a halogen atom). Upon dissociation the halogenate anion XO<sub>3</sub><sup>-</sup> is formed. Halogenate salts are stable under most conditions, but due to their oxidative properties they may react rapidly and even explosively with easily oxidisable substances, such as carbon-containing organic compounds. Their oxidative properties, in particular, will have to be taken into account in the discussion of their mutagenic and carcinogenic potential. The principal chemical properties of the two most commonly used salts of iodic acid are compiled in table 1 (7,8). Iodate may undergo several redox reactions, of which the major one may be written as:



The standard redox potential of 1.085 V decreases to 0.672 V at pH 7, and to 0.648 V at the physiological pH of 7.4. Table 2 shows that both chlorate and bromate are of similar oxidative potency, whereas that of iodate is lower by one third (8).

In considering the toxicology data of this review it is important that one keeps in mind the following weight equivalents: 100 mg of iodine equals 137.9 mg of iodate, 168.6 mg potassium iodate, and 156.0 sodium iodate.

#### Iodate in Human Food

Salt is not the only foodstuff to which iodate is added. For decades, bakeries in the United States and elsewhere have used iodates (and even bromates) as conditioners for dough, which exposed the American people to higher doses of iodine than is ordinarily the case by iodized salt (9). Other dough conditioners are preferred now, and this is one of the reasons why the iodine intake of the American population has recently dropped from rather high to low normal values

(10,11). Iodate is added with the purpose of oxidizing sulfhydryl groups of flour proteins and thereby improving the rheological properties of the dough. By oxidizing sulfhydryl groups, iodate is reduced already during mixing of the dough and it reaches the consumer as iodide (12). Therefore, the decade-long use of iodate in American bakeries without obvious adverse effects is no proof of its long-term safety. However, the rapid reduction to iodide in dough (and possibly in other foodstuff) may minimize human exposure and contribute to the safety of iodate. Along these lines Wiechen and Hoffmann (13) studied iodination of cheese by iodide and iodate lakes. In contact with ripening cheese a reduction of iodate to cheese-bound iodine species occurred, precluding iodine to penetrate a cheese loaf incubated in a salt bath. Human food is a complex organic mixture containing antioxidants, radical scavengers and oxidizable functional groups; the fate of iodate added to this mixture is difficult to guess with the data presently at hand. The scant data lets one infer that—once added to food—iodate may be rapidly reduced to iodide. Analysis of the different iodine species in model meals prepared from iodate-containing ingredients with and without cooking (which might additionally promote reduction) should allow a better risk assessment.

#### Human Exposure at Recommended Doses of Iodate

The recommended level of iodine is between 20 and 80 mg per kilogram of salt (equaling 28 to 110 mg iodate per kilogram of salt). Given a maximal daily salt intake of 15 g, this results in a low human exposure of at most 440 to 1700 μg of iodate per day (9–34 μg/kg per day assuming body weights of 50 to 70 kg). Much higher exposures may take place if—in the case of a nuclear disaster—radioprotection is attempted with iodate instead of iodide tablets (14). The dose for adult persons in such an emergency is 100 mg of iodine (138 mg iodate) daily over several days.

TABLE 2. REDOX POTENTIALS IN VOLT OF IODATE, BROMATE AND CHLORATE AT DIFFERENT pH VALUES

	<i>pH 0</i>	<i>pH 7</i>	<i>pH 7.4</i>
Iodate	1.085	0.672	0.648
Bromate	1.423	1.01	0.986
Chlorate	1.451	1.038	1.014

### Metabolism and Kinetics of Iodate

In pioneering experiments, using  $^{128}\text{I}$  prepared by F. Joliot-Curie, Leblond and Süe (15) have shown that after intravenous injection of 750  $\mu\text{g}$  of iodate (an excessive iodine dose in this species) the rat thyroid gland accumulated radioactivity, albeit at a slower rate than when the  $^{128}\text{I}$  was injected in the form of iodide. In rats and rabbits given much smaller, physiological doses (0.750 to 1.0  $\mu\text{g}$  of iodine) orally or intraperitoneally, the tracer was equally available to the thyroid, whether originating from iodate or iodide (16). Tissue distribution of radioiodine in liver, kidney, brain, heart, muscle, small intestine, stomach, testes, submaxillary gland, skin, hair, and thyroid was identical from iodide and from iodate. After iodate injection, radioactivity in tissues (as well as in urine) was exclusively in the form of iodide (16,17). Large doses of iodate (1.4 to 15 mg iodine per kilogram) blocked the thyroïdal uptake of injected labeled iodide in rats, again suggesting that iodine from iodate is available to the thyroid (14,18). When added to animal feed, iodate increases the iodine content of eggs and milk respectively (19).

Iodate oxidizes iodide to  $\text{I}_2$  (which is volatile), thus increasing the instability of iodide. This interaction has important practical consequences: when iodized with a mixture of potassium iodate and iodide, bread loses 34% of its iodine over 1 week of storage, whereas with either iodide or iodate alone its iodine content remains stable (19).

In humans, Murray and Pochin (20) has confirmed that isotopic iodine from iodate is available to the thyroid when given orally, but the bioavailability was about 10% lower than that of iodide. Five milligrams of iodine weekly per os reduced the goiter prevalence among iodine deficient children equally well, whether given in the form of iodate or iodide tablets (21). This study does however not prove exact bioequivalence of the two iodine compounds because the iodine dose by far exceeded the physiologic requirement, which might have obscured minor differences in bioequivalence.

Thyroid slices incubated *in vitro* took up radioiodine from iodate, albeit at a slightly slower rate than from iodide (16,22). The radioiodine accumulating in the slices was all in the form of iodide. Iodate was partly transformed into iodide already in the incubation medium (22). After injection of large doses of iodate into rats, Leblond and Süe (15) found that iodate in blood was quantitatively reduced to iodide within 40 minutes. After intravenous administration of intermediate iodate doses to rabbits (1000  $\mu\text{g}$  of iodine) and rats (95  $\mu\text{g}$  of iodine) transformation in the blood into iodide was complete in less than 1 minute (16). When high retinotoxic doses (30 mg/kg) were injected intravenously into rabbits, iodate disappeared from the circulation and was transformed into iodide with a half-life of 14 minutes (17). *In vitro*, whole blood as well as extracts of liver, kidney, and brain reduced 84% to 99% of added iodate to iodide within 1 minute, while washed red cells and serum were clearly less efficient (16), confirming other experiments that used longer incubation times (23). Taurog et al. (16) has convincingly shown that the reduction of iodate is a nonenzymatic process and depends on the availability of sulfhydryl groups, e.g., in glutathione. Furthermore, this reaction is inhibited by N-ethyl-maleimide, a recognized glutathione-depleting agent (17).

One unresolved question is the form in which iodine from

iodate crosses the intestinal barrier into blood. Radioiodine-labeled iodate and iodide given by stomach tube to rats disappear equally fast from the gut *in vivo* (16). Everted rat intestine *in vitro* easily transports iodide, but is impermeable to iodate. It has been postulated that the permeability barrier resides in the intestinal mucosa (24). It is therefore assumed that iodate, when given in small doses, is reduced to iodide already within the gastrointestinal lumen or, at the latest, in the gastrointestinal mucosa, but this hypothesis has never been formally tested. When dogs are fed a dose of 200 mg/kg of potassium iodate in the form of gelatin capsules, their urine contains iodide as well as iodate (25). This suggests that in such excessive doses iodate does indeed cross the intestinal barrier.

In conclusion, iodine from iodate is available to the thyroid, whether given per os, injected intravenously or added to the incubation medium of thyroid slices. However, it is most likely that iodate is reduced to iodide and reaches the thyroid gland in this form. The potent nonenzymatic reduction mechanisms in whole blood, in many tissues, in flour, and in other food will greatly diminish general tissue exposure to iodate, but an exact risk assessment will have to be based on future toxicokinetic and pharmacokinetic studies.

### Government Regulatory Acts and Manufacturers' Recommendations

Toxicity of, and other hazards by, iodates as bulk chemicals are not rated particularly high by national regulatory agencies. The European Union considers iodates as nontoxic, with the labels R8 (risk of ignition) and S17 (safety measures against fire). In the United States, potassium iodate is not listed as hazardous by government regulations. As a food additive it is given GRAS ("generally recognized as safe") status (56); It may be added to flour at up to 0.0075% (75 parts per million based on the weight of flour) for baking bread or doughnuts. Low concentrations of various iodate salts, all considered equal from a regulatory standpoint, are permitted as mineral supplement for livestock. In Switzerland, moderate toxicity is assumed, the toxicity class 3 restricting the use of pure iodates by the public at large, but the scientific evidence for this classification is not available; it is most likely based on acute toxicity (median lethal dose [LD<sub>50</sub>]-values). Many countries, including Switzerland, have created a legal basis for the addition of iodate to salt for human and animal use (26).

Material safety data sheets, while extensively recognizing fire and even explosive hazards, keep a low profile on the toxic properties of the bulk substance. They mention irritating action on body surfaces, kidney failure or central nervous system damage as risks after chronic ingestion. The toxicology data section is, however, blank (57).

### Toxicity Reports on Iodates

#### *Human toxicity experience*

There are only few reports of accidental poisoning via the oral route, the most recent being on a 22-year-old man who drank a highly concentrated solution of potassium iodate; he developed nausea, vomiting, diarrhea, and marked loss of visual acuity. Ophthalmoscopic examination revealed extensive retinal damage with degeneration of photoreceptor

layers (27–31). The exact dose could not be established, but must have exceeded several grams (>100 mg/kg). Another case of iodate-induced blindness has occurred in China; the dose calculated amounted to 10 to 20 mg/kg (29).

More remarkable were parenteral intoxications by an antibacterial preparation called Septojod (Pregl's solution) in the 1920s. Several individuals developed blindness after systemic treatment for septicemia. In 1927, Riehm established that blindness resulted from damage to the pigment epithelium and that the toxic effects of Pregl's solution could be attributed to iodate (reviewed by Lewis [32]).

Except for iodine-induced thyrotoxicosis (a subject excluded from this review) the longstanding low-dose use of iodates as additive to bread or table salt has not produced evidence of human toxicity. Exposure to iodate, however, may have been inadequate because iodate might already be reduced to iodide during food preparation or in the gut (see previous section on Metabolism).

#### *Acute single-dose toxicity*

The oral LD<sub>50</sub> of iodates have been reported to be in the range of 500 to 1100 mg/kg for mice; iodides were three times more toxic than iodates (31,33). Parenteral median lethal dose (LD<sub>50</sub>) are in the range of 100 to 120 mg/kg in mice (reviewed by Webster et al. [34]). The lowest parenteral lethal dose in rabbits was 75 mg/kg. Mice apparently tolerated a single dose of 250 mg/kg (33). Oral administration of 200 to 250 mg/kg potassium iodate proved lethal in the dog. A surviving animal exhibited irreversible retinal degeneration (25). The cationic partner, i.e., sodium or potassium, does not modify toxicity (reviewed by Newton and Clawson [35]).

#### *Multiple-dose and chronic toxicity*

There is somewhat conflicting evidence of toxicity in animals exposed over 4 weeks to iodate dissolved in drinking water. In one study in mice marked toxic effects such as hemolysis and renal damage occurred from 300 mg/kg upward with a no observable effect level (NOEL) of approximately 120 mg/kg, while guinea pigs exposed via the same route tolerated nearly 300 mg/kg without apparent effects (31). The functional assessment of ocular toxicity in these experiments was not adequate, but histologic retinal degeneration was not seen. The authors did not determine the stability of iodate in the drinking solution. The NOEL in mice exceeded the maximal human exposure via iodized salt by a factor of approximately 400. Dogs exposed orally from 66 to 192 days with doses of 6 to 100 mg/kg per day apparently did not develop retinal damage because electroretinograms remained unchanged, although in some animals evidence of gastric toxicity and other minor abnormalities (indicative of hemolysis) were noted. The NOEL for retinal toxicity amounted to 300 times the highest human dose from iodized salt (25).

The growth performance of calves and pigs receiving iodine in the form of iodate added to feed was evaluated up to the end of growth (36,37). Blood iodine levels were elevated at subtoxic doses of iodine, indicating adequate exposure. Iodine toxicity manifested itself as reduced performance. Because iron supplementation prevented it, this toxicity may have resulted from an apparent interference of

iodate or iodine respectively with iron uptake or utilization. NOELs for pigs were observed at 400 parts per million (ppm) calcium-iodate added to hog-mash; calves were more susceptible with a NOEL of only 25 ppm. The toxic signs were attributed either to iron deficiency or to general iodine toxicity.

All these studies are in part incomplete; nonetheless, they may be sufficient to derive adequate safety factors for overt organ toxicity by iodate (not iodine).

#### *Reproductive toxicity*

A formal program of testing for the reproductive toxicity of iodate does not exist. One milligram per kilogram given twice weekly to pregnant dams and to offspring over 14 months had no toxic effect in the rabbit (37–39). These doses are at least 10 times higher than the maximal human exposure from iodized salt. Doses retinotoxic to the rabbit dam, however, can apparently also cause irreversible damage to the retina of offspring (for review see Sugimoto et al. [40]). In order to ascertain the hypothesis that maternal NOELs are safe for the fetus, a better definition of the toxicokinetic behavior of small iodate doses such as those applied by iodized salt would be necessary for risk assessment.

#### *Oculotoxicity*

The tragic human experience with the antibacterial preparation Septojod (see Human toxicity experience section) stimulated research into the toxicological mechanisms of iodate. Oral exposure to iodate causes retinal damage only at doses exceeding the human exposure via iodized salt by two orders of magnitude (see preceding sections). All relevant mechanistic experiments have therefore been performed with parenteral (intraperitoneal, intravenous, intraarterial, and intraocular) exposures. Because overt retinal toxicity was the prime goal of such exposures, the authors did not determine the threshold-dose for ocular damage, i.e., innocuous doses, blood concentrations, and kinetics of iodate are unknown. In rats, 10 mg/kg sodium iodate administered intravenously as bolus visibly damaged the retinal pigment epithelium, inducing cell injury and a proliferative response (39,41). This must be near the threshold dose: Heike and Marmor (42) has shown by recording electroretinograms and studying the histomorphology of the eyes that 12.5 mg/kg intravenously did not produce retinal damage, whereas 20 mg/kg did; a formal dose-response curve was however not established. The retinal pigment epithelium is the primary target of iodate toxicity and this toxicity is associated with the oxidizing properties of iodate, because the damage threshold is lowered by other oxidizers (43) and raised by antioxidants, e.g., glutathione, given shortly before, or combined with, iodate. When given 30 minutes after an intravenous iodate bolus the retinal pigment epithelium, and subsequently the retina, can no longer be protected by glutathione (42). Many other phenomena have been described during investigation of the pathogenetic sequence outlined here. It appears that, in order to elicit retinotoxicity, the doses of iodate must exceed the capacity of endogenous radical scavenger systems (43). Here again, toxicokinetic data on the fate of low oral doses of iodates are needed for proper assessment of ocular risk.

### Genotoxicity

Data on the genotoxic and mutagenic activity of iodate are scarce, this in contrast to the related halogenate compounds chlorate and especially bromate. In a meeting abstract (44) it was reported that iodate did not induce mutations in *Salmonella typhimurium*, nor did it increase the frequencies of micronuclei in mouse bone marrow cells or in recessive lethal mutations in *Drosophila melanogaster*. By contrast, bromate induced a significant increase in the frequency of micronucleated cells, and chlorate proved to be mutagenic in bacteria and *Drosophila*. Because this abstract contains no experimental details, and since no raw data from the experiments could be retrieved (Gocke E., personal communication), we cannot assess the results properly. In the discussion section, we shall nevertheless try to judge their plausibility by taking into account the redox properties of iodate in comparison with those of bromate, sufficient genotoxicity data being available for the latter, as well as some recent comparative data on DNA damaging effects.

Another article reported that iodate exerted an antimutagenic activity towards aflatoxin B1-induced mutations in a Salmonella mutagenicity test, albeit only when assayed with strain TA 100, but not with TA 98 (45). The relevance of this finding is unknown.

A recent article (46) investigated cytotoxic and mutagenic activities of a number of oxyhalides in strains of *Escherichia coli* lacking either catalase (Cat<sup>-</sup>), or superoxide dismutase (Sod<sup>-</sup>), or both (Cat-Sod<sup>-</sup>). Unfortunately the authors tested only NaBrO<sub>3</sub>, but not iodate, for mutagenic activity. However, comparing the various interactions of the different oxyhalides with cysteine and their relationships to the cytotoxic effects induced, the authors came to the following conclusion: Iodate proved to be cytotoxic, especially toward strains deficient in Sod or Cat-Sod, thus rendering likely the involvement of reactive oxygen species. Addition of cysteine diminished the oxidative cytotoxic damage that iodate inflicted on the bacteria. Bromate, on the other hand, did not produce cytotoxic oxidative damage unless co-incubated with cysteine. Also, the *in vitro* mutagenic activity of bromate was contingent on the presence of cysteine or other reducing agents, which obviously are acting as mediators of oxidative damage. A further hint at a possible involvement of reactive oxygen species in the effects of iodate on living cells may be derived from findings which have demonstrated a radiosensitizing effect of iodate (47,48).

Very recent investigations have demonstrated that iodate, in the absence as well as in the presence of glutathione, did not produce oxidative damage to calf thymus DNA as measured by the appearance of 8-hydroxy-deoxyguanosine, while bromate did (49,50). Similar to bromate, however, iodate, was able to induce DNA strand breakage in the rat epithelial kidney cell Comet assay. For iodate this effect was apparent at the first time point measured, i.e., 15 minutes after the start of the *in vitro* treatment. DNA strand breakage then had decreased at 4 hours and remained at that level at 24 hours (Parsons JL, personal communication), while the DNA breakage induced by bromate showed a second activity peak at 24 hours (50). This observation points again to a qualitative difference between the actions of these two compounds, possibly to an induction of lipid peroxidation by bromate, but not by iodate. Finally, for both compounds, the

depletion (oxidation) of glutathione proceeded in the same way and to the same extent. The lack of information on the effects of iodate in a conventional genotoxicity assay package precludes proper assessment of the relevance of the observed DNA strand breakage and of the difference between iodate and bromate in the time course of this effect.

### Carcinogenicity

Iodate has never been tested for carcinogenicity, in contrast to bromate, which is a recognized renal carcinogen. The International Agency for Research on Cancer has concluded in the monograph for potassium bromate (51) that "potassium bromate is possibly carcinogenic to humans (Group 2 B)," based on "inadequate evidence" for carcinogenicity in humans, but "sufficient evidence" in experimental animals. In view of the structural analogy and the physicochemical similarity between bromate and iodate, we must seriously consider whether iodate, could also present a certain carcinogenic hazard. The lack of data on the carcinogenicity of iodate and the incompleteness of data on its genotoxicity allow only for a tentative plausibility assessment (see below).

### Discussion of Toxicity and Assessment of Hazard

#### *Acute, chronic, and reproductive toxicity*

We found no recent systematic toxicology program carried out according to actual standards allowing a valid assessment of the risk by small oral doses of iodate, such as those envisaged by fortified salt. In particular, subchronic and chronic NOEL were not established because many aspects of potential toxicity were only covered by observation and relatively crude clinical and postmortem assessments. In addition, none of the acute, subacute, and chronic toxicity studies performed in the 1950s and 1960s paid attention to toxicokinetics (25,33,36-39). Exposures by the oral route in some of these studies may be questioned, because dosing occurred via drinking water. In the absence of analytical data on iodate concentration and stability in this medium, it is not possible to determine whether the actually ingested iodate dose was not lower than the investigators assumed.

Despite these reservations, we may conclude that the maximal exposure to 34 µg/kg per day of iodate through the use of iodized salt should present no risk for functional or structural lesions. This dose is lower than the peroral NOEL of iodine itself (2 to 3 mg/kg per day in reproductive toxicology, see Beckmann and Brent [52]) by a factor of roughly 100, the usual safety factor for establishing acceptable daily intakes (ADI). Ocular toxicity, in particular, is most unlikely to occur because repeated oral exposures to 100 mg/kg in dogs have failed to induce retinal damage (25). Contrary to Pahuja et al. (14), however, we do not recommend that persons exposed to fallout after a nuclear disaster receive iodate. The dose recommended for radioprotection is 100 mg of iodine daily over several days, which amounts to 138 mg (or 2.3 mg/kg) of iodate per day. This dose appears close to retinotoxic doses reported from human accidental intoxications (29).

Formal studies of reproductive toxicity of iodates are also lacking. In view of the toxic effects of excessive doses of iodine on the fetus and the unlikely exposure of the fetal sys-

tem to iodate for metabolic (toxicokinetic) reasons outlined above, there appears to be no need for additional studies.

#### Genotoxicity and carcinogenicity

There are no data on the carcinogenicity of iodate, but its carcinogenic risk may be estimated by extrapolation of the biological properties of bromate, a chemical congener and a known carcinogen. By doing so, we must take into account a number of aspects, including the available genotoxicity data, the potential mutagenic mechanism of action, the redox potentials, and the relative reactivity towards cellular components.

A meeting abstract (49) reported a lack of mutagenic activity for iodate toward Salmonella, but bromate also was reported negative, in contrast to other publications asserting its mutagenicity in the presence of an exogenous metabolic activation system (53,54). Therefore, this negative result for iodate may not carry much weight. On the other hand, mechanistic hypotheses presented and discussed in other papers, seem to point to a lower (or absent) mutagenicity of iodate in comparison to bromate. Several publications have shown that bromate, as a result of the oxidative stress it induces, increases the level of 8-hydroxy-deoxyguanosine (references in IARC [51] and Breckmann and Brent [52]). Bromate mutagenicity *in vitro* depends on the presence in the activation system of readily oxidizable substances, like glutathione, cysteine or reduced nicotinamide-adenine dinucleotide (NADH). This points to an indirect action, probably mediated by oxidizing species other than the bromate ion itself, rather than to a direct oxidative effect of bromate, as we have already discussed with the article by Ueno et al. (46). In agreement with this, an earlier article reported that the induction of oxidative DNA damage (i.e., increased formation of 8-hydroxy-deoxyguanosine) by potassium bromate *in vitro* required the concomitant presence of reduced glutathione (49,50,55). The experiments with a variety of quenchers and scavengers of reactive oxygen species suggest that the mutagenicity of bromate, as assessed by the formation of 8-hydroxy-deoxyguanosine in DNA, was probably mediated by a bromine (or hypobromite/bromite) radical, rather than by the creation of reactive oxygen species. The results of Ueno et al. (46) could then be interpreted to mean that a similar reaction of iodate with these substrates (i.e., cysteine, glutathione or NADH) would not lead to analogous reactive molecular species, i.e., iodine-derived radicals. Cytotoxicity of iodate would therefore involve a different mechanism, namely direct oxidative damage, e.g., to cell membranes, by reactive oxygen species. Indeed, under the same experimental conditions as those used with bromate, iodate was unable to induce the formation of 8-hydroxy-deoxyguanosine (49,50). Nevertheless, it does also cause DNA strand breaks, but the breaks are temporary and they are repaired (50). Therefore, compared to bromate, iodate might indeed turn out to be of lesser genotoxicity and/or carcinogenicity, or perhaps even be devoid of it. Taking into account data on the systemic exposure to iodate and on the extent of its presystemic conversion to iodide further decreases the likelihood of risk to humans.

In summary, only proper investigations on the mutagenic and carcinogenic activity of iodate (in combination with toxicokinetic studies) will confirm the above assessment, which is based on hypothetical extrapolations.

#### Suggested further research

For definite assessment, we need new data on genotoxicity utilizing a standard battery of *in vitro* and *in vivo* assays. The potential of iodates to form 8-hydroxy-deoxyguanosine *in vivo* should also be studied. Combined experiments, i.e., toxicokinetic studies together with measurement of 8-hydroxy-deoxyguanosine in intestinal mucosa, liver, bone marrow, and/or urine appear reasonable and cost effective, and these could be rapidly performed. In addition data on the reduction of iodate to iodide in food, on the intestinal handling, the bioavailability and the toxicokinetics of iodate, will allow a further refinement in the risk assessment. Depending on the outcome of the research we have suggested above, the conduct of a short-term carcinogenicity study with the transgenic p53<sup>+/-</sup> mouse might be appropriate.

#### Conclusions

Taking into consideration that iodate:

- has been conferred GRAS ("generally recognized as safe") status by the FDA;
- has been used for decades as an additive to salt and bread without notable toxic effects (except iodine-induced hyperthyroidism); is added to salt in low amounts; is probably reduced to iodide in food or at the latest in the intestinal mucosa, thus decreasing systemic exposure; and
- has shown no toxic effect levels with regard to organ toxicity that are at least 100 times higher than the exposure to be expected from the intake of iodized salt, it seems that at the present time there is no urgent need to change existing programs from iodate to iodide. However, the additional toxicological safety data suggested in this text should expediently be acquired.

#### References

1. Arroyave G, Pineda O, Scrimshaw NS 1956 The stability of potassium iodate in crude table salt. Bull WHO 14:183-185.
2. Joint WHO/FAO Expert Committee on Food Additives 1991 Matters of interest arising from the forty-third World Health Assembly. In: Evaluation of Certain Food Additives and Contaminants. World Health Organization (WHO technical report series No. 806, Annex 5), Geneva.
3. WHO/ UNICEF/ ICCIDD Joint Consultation 1996 Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness World Health Organization (WHO/NUT 96/13), Geneva, p 4
4. Boudène C, Jaffiol C 1999 Rapport sur un projet modifiant l'arrêté du 28 mai 1997 relatif au sel alimentaire et aux substances d'apport nutritionnel pouvant être utilisées pour sa supplémentation. Bull Acad Natl Med 38:1779-1782.
5. Stanbury JB 1991 The safety of iodate as a salt additive. IDD Newsletter 7:23.
6. Schulte-Hermann R 1997 Stellungnahme zur gesundheitlichen Unbedenklichkeit der Verwendung von Kaliumjodat zur Jodierung des Speisesalzes. Unpublished report commissioned by the Austrian Ministry of Health and Consumer Protection. Vienna.
7. The Merck Index, 1996 12th edition, Merck Research Laboratories, Whitehouse Station, NJ, No. 7808 Potassium Iodate, p. 1315, No. 8776 Sodium Iodate, p 1478.

8. CRC Handbook of Chemistry and Physics 1993 73rd edition, CRC Press, Boca Raton, Ann Arbor, London, Tokyo. pp 8–19
9. London T, Vought RL, Brown BS 1965 Bread: A dietary source of large quantities of iodine. *N Engl J Med* **273**:381.
10. Hollowell JG, Staehling NW, Hannon WH, Flanders WH, Gunter EW, Maberly GF, Braverman LE, Pino S, Miller DT, Garbe PL, DeLozier DM, Jackson RJ 1998 Iodine nutrition in the United States. Trends and public health implications: Iodine excretion data from national health and nutrition examination surveys I and III (1971–1974 and 1988–1994). *J Clin Endocrinol Metab* **83**:3401–3408.
11. Dunn JT 1998 What's happening to our iodine [editorial]? *J Clin Endocrinol Metab* **83**:3398–3400.
12. Hird FJR, Yates JR 1961 The oxidation of protein thiol groups by iodate, bromate and persulphate. *Biochem J* **80**:612–616.
13. Wiechen A, Hoffmann W 1994 Studies on the iodination of cheese during cheese making process. *Milchwissenschaft* **49**:74–78.
14. Pahuja DN, Rajan MGR, Borkar AV, Samuel AM 1993 Potassium iodate and its comparison to potassium iodide as a blocker of <sup>131</sup>I uptake by the thyroid in rats. *Health Physics* **65**:545–549.
15. Leblond CP, Süe P 1941 Iodine fixation in the thyroid as influenced by the hypophysis and other factors. *Am J Physiol* **134**:549–561.
16. Taurog A, Howells EM, Nachimson HI 1966 Conversion of iodate to iodide in vivo and in vitro. *J Biol Chem* **241**:4686–4693.
17. Olsen KJ, Ehlers N, Schonheyder F 1979 Studies on the handling of retinotoxic doses of iodate in rabbits. *Acta Pharmacol Toxicol* **44**:241–250.
18. Wyngaarden JB, Wright BM, Ways P 1952 The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland. *Endocrinology* **50**:537–549.
19. Anke M, Gleit M, Groppe B, Rother C, Gonzales D 1998 Mengen-, Spuren- und Ultraspurenelemente in der Nahrungskette. *Nova Acta Leopoldina NF* **79**:157–190.
20. Murray MM, Pochin EE 1951 Thyroid uptake of iodine from ingested iodate in man. *J Physiol* **114**:6–7.
21. Scrimshaw NS, Cabezas A, Castillo F, Méndez J 1953 Effect of potassium iodate on endemic goitre and protein-bound iodine levels in school-children. *Lancet* **ii**:166–168.
22. Wolff J, Maurey JR 1963 Thyroidal iodide transport. IV. The role of ion size. *Biochim Biophys Acta* **69**:58–67.
23. Anghileri LJ 1965 Reduction of iodate and periodate by rat tissues in vitro. *Die Naturwissenschaften* **52**:396.
24. Clarkson TW, Rothstein A, Cross A 1961 Transport of monovalent anions by isolated small intestine of the rat. *Am J Physiol* **200**:781–788.
25. Webster SH, Stohlman EF, Highman B 1966 The toxicology of potassium and sodium iodates. III. Acute and subacute oral toxicity of potassium iodate in dogs. *Toxicol Appl Pharmacol* **8**:185–192.
26. Bürgi H 1999 The Swiss legislation on iodized salt. *IDD Newsletter* **15**:57–58.
27. Singalavanija A, Dongosintra N, Dulayajinda D 1994 Potassium iodate retinopathy. *Acta Ophthalmol (Copenh)* **72**:513–519.
28. Singalavanija A, Ruangvaravate N, Dulayajinda D 2000 Potassium iodate toxic retinopathy: A report of five cases. *Retina* **20**:378–383.
29. Tong Y 1995 A case of blindness caused by acute iodine poisoning. *Chin Med J* **108**:555–556.
30. Potts AM 1996 Toxic responses of the eye. In: Klaassen CD (ed) Casarett and Doull's Toxicology, Mc Graw Hill, New York, pp 601–602
31. Webster SH, Rice B, Highman B Von Oettingen WF 1957 The toxicology of potassium iodate: acute toxicity in mice. *J Pharmacol Exp Ther* **120**:171–192.
32. Lewis RJ 1996 In: Sax NI (ed.) Dangerous Properties of Industrial Materials, 9th ed. Van Nostrand Reinhold, New York, p 2972
33. Gosselin RE, Hodge HC, Smith RP, Gleason MN 1976. Clinical Toxicology of Commercial Products, 4th ed. Williams and Wilkins, Baltimore, pp II–77
34. Webster SH, Rice ME, Highman B, Stohlman EE 1959 The toxicology of potassium and sodium iodates. II. Subacute toxicity of potassium iodate in mice and guinea pigs. *Toxicology* **1**:87–96.
35. Newton GL, Clawson AJ 1974 Iodine toxicity: Physiological effects of elevated dietary iodine on pigs. *J Anim Sci* **39**:879–884.
36. Newton GL, Barrick ER, Harvey RW, Wise MB 1974 Iodine toxicity: Physiological effects of elevated dietary iodine on calves. *J Anim Sci* **38**:449–455.
37. Murray MM, Pochin EE 1953 The effects of administration of sodium iodate to man and animals. *Bull WHO* **9**:211–216.
38. Grant WM 1974. Toxicology of the eye (2nd ed), Charles C. Thomas, Springfield, Illinois, pp 381–383.
39. Ogata N, Kanai K, Ohkuma H, Uyama M 1989 Pathologic response of the weakly damaged retinal pigment epithelium (RPE) affected by sodium iodate. *Acta Soc Ophthalmol Jpn* **93**:439–448.
40. Sugimoto S, Imawaka M, Kurata K, Kanamaru K, Ito T, Sasaki S, Ando T, Saijo T, Sato S 1996 A procedure for recording electroretinogram (ERG) and effect of sodium iodate on ERG in mice. *J Toxicol Sci* **21**:15–32.
41. Sorsby A, Harding R 1966 Oxidizing agents as potentiators of the retinotoxic action of sodium fluoride, sodium iodate and sodium iodoacetate. *Nature* **210**:997–998.
42. Heike M, Marmor MF 1990 L-cystein protects the pigment epithelium from acute sodium iodate toxicity. *Doc Ophthalmol* **75**:15–22.
43. Sorsby A, Reading HW 1964 Experimental degeneration of the retina. XI. The effect of sodium iodate on retinal-SH levels. *Vision Res* **4**:511–514.
44. Eckhardt K, Gocke E, King M-T Wild D 1982 Mutagenic activity of chlorate, bromate and iodate [Abstract]. *Mutation Res* **97**:185.
45. Francis AR, Shetty TK, Bhattacharya RK 1988 Modifying role of dietary factors on the mutagenicity of Aflatoxin B<sub>1</sub>: In vitro effect of trace elements. *Mutation Res* **199**:85–93.
46. Ueno H, Oishi K, Sayato Y, Nakamuro K 2000 Oxidative cell damage in Kat-Sod Assa of oxyhalides as inorganic disinfection by-products and their occurrence by ozonation. *Arch Environ Contam Toxicol* **38**:1–6
47. Myers DK, Chetty KG 1973 Effect of radiosensitizing agents on DNA strand breaks and their rapid repair during irradiation. *Radiat Res* **53**:307–314.
48. Kada T 1969 Radiosensitization by potassium iodate and related compounds. *Int J Rad Biol* **15**:271–274.
49. Parsons JL, Chipman JK 1999 Comparison of DNA damage induced by potassium chlorate, bromate and iodate and their interaction with glutathione [Abstract]. *Toxicol Lett* **109**(suppl 1):48.
50. Parsons JL, Chipman JK 2000 The role of glutathione in DNA damage by potassium bromate in vitro. *Mutagenesis* **15**:311–316.
51. IARC 1999 Potassium bromate. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 73, Some chemicals that cause tumours of the kidney or urinary

- bladder in rodents and some other substances. International Agency for Research on Cancer, Lyon pp 481–496
52. Beckmann DA, Brent RL 1984 Mechanisms of teratogenesis. *Ann Rev Pharmacol Toxicol* **23**:483–500.
  53. Kawachi T, Yahagi T, Kada T, Tazima Y, Ishidate M, Sasaki M, Sugimura T 1980 Cooperative programme on short-term assays for carcinogenicity in Japan. In: Montesano R, Bartsch H, Tomatis L (eds) *Molecular and Cellular Aspects of Carcinogen Screening Tests* (IARC Scientific Publications No. 27), IARC Lyon, pp 323–330.
  54. Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A 1984 Primary mutagenicity screening of food additives currently used in Japan. *Food Chem Toxicol* **22**:623–636.
  55. Ballmaier D, Epe B 1995 Oxidative DNA damage induced by potassium bromate under cell-free conditions and in mammalian cells. *Carcinogenesis* **16**:335–342.
  56. U.S. Government Printing Office 1997 Direct Food Substances Affirmed as Generally Recognized as Safe. Code of Federal Regulations, title 21, volume 3, part 184, p 508 (21CFR184.1635).
  57. MSDS Index 2000 Vermont safety information resources. Internet access: <http://hazard.com/msds/>.

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