Concise International Chemical Assessment Document 72

IODINE AND INORGANIC IODIDES: HUMAN HEALTH ASPECTS

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.[1]

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

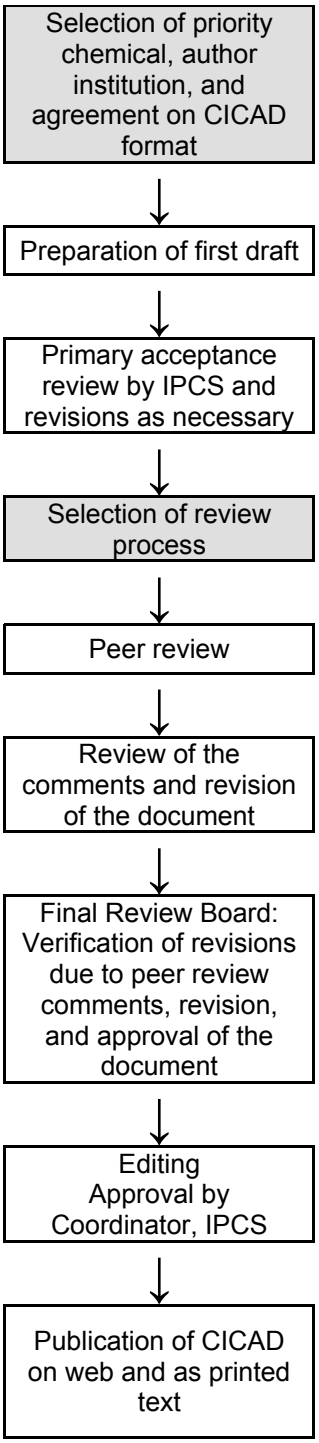
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a de novo CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional, or international review. When no appropriate source document is available, a CICAD may be produced de novo. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170) (also available at http://www.who.int/pcs/).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced de novo, provided it is not controversial. If no source document is available, IPCS may produce a de novo risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points;
- above + specialized experts;
- above + consultative group.

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared de novo, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

The source document upon which this CICAD[1] is based is the *Toxicological profile for iodine* published by the Agency for Toxic Substances and Disease Registry of the United States Department of Health and Human Services (ATSDR, 2004). Data identified as of January 2005 were considered in the source document. Information on the availability and peer review of the source document is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Nagpur, India, on 31 October – 3 November 2005. Participants at the Final Review Board meeting are presented in Appendix 4. The International Chemical Safety Cards for iodine (ICSC 0167), hydrogen iodide (ICSC 1326), and iodine cyanide (ICSC 0662), produced by IPCS in a separate, peer-reviewed process, have also been reproduced in this document (IPCS, 2005a,b,c). The radioactive iodine isotopes (e.g. ^{123}I, ^{125}I, and ^{131}I) are outside the scope of this document. The reader should refer to the WHO ionizing radiation web site (http://www.who.int/ionizing_radiation/en/) or ATSDR (1999, 2004) for information on radioactive iodine isotopes.

Iodine is a naturally occurring element. It occurs in various forms, ranging from colourless to a variety of colours, including blue, brown, yellow, red, and white, depending on the iodine concentrations in the solution and the solvents used. It is soluble in both water and organic solvents. Oceans are the primary source of naturally occurring iodine. Iodides in the sea accumulate in seafish, shellfish, and seaweed. From the seas, iodine enters the environment in the form of sea spray or gases. Once airborne, iodine can be deposited on land and on nearby agricultural crops. Once in the soil, iodine readily binds with organic material, resulting in a long soil residence time. Iodine also enters the air from burning fossil fuels as a fuel source, but this source contributes far less to the environment than the oceans do. In foods, iodine is present as iodide and non-elemental forms.

In industrial settings, iodine is used in the manufacture of inks, dyes, colouring agents, photographic chemicals, batteries, fuels, and lubricants. It is also used as a catalyst in the production of various chemicals, principally acetic acid, X-ray contrast media, surfactants, iodophors (surfactants that act as iodine carriers), and biocides, as a stabilizer in tall oil, and in iodized oil. In the health industry, iodine is also used as a disinfectant/biocide, in the production of certain soaps, bandages, and medicines, and in water purification. Since the 1950s, iodine has been added (as iodide or iodate) to salt in some countries to ensure appropriate dietary intake to prevent sequelae of iodine deficiency. It has also been added to some animal feed supplements.

Exposure to iodine includes the ingestion of iodized salts, sea salt, ocean fish and shellfish, kelp, baked products that use iodine as a conditioner in their processing, medicines, and dairy products (as a result of using iodine as a disinfectant for solid steel containers used to collect and transport milk). Ambient air contributes little to routine exposure to iodine.

Molecular iodine and inorganic compounds of iodine are readily and extensively absorbed by both the inhalation and oral routes. Dermal absorption has been experimentally shown to be 1% or less of the applied dose and is thus not considered to be a significant route of exposure. Iodide is eliminated from the body in the urine, sweat, faeces, and breast milk.

Iodine is essential in small amounts for normal physiological function. It is a critical component of thyroid hormones, which are necessary for controlling metabolic rate, growth, and development of body structures, as well as neuronal function and development. The WHO recommended intake (population requirement) of iodine is 150 µg/day for adults and adolescents 13 years of age and older, 200 µg/day for women during pregnancy and lactation, 120 µg/day for children 6–12 years of age, and 90 µg/day for children 0–59 months of age (WHO, 2004a).

Iodine deficiency disorders represent a group of diseases associated with a lack of dietary intake. Iodine deficiency is the most prevalent, yet easily preventable, cause of brain damage in the world today (WHO, 2004b). Iodine deficiency is believed to affect over 740 million people worldwide, or approximately 13% of the world's population. Serious iodine deficiency during pregnancy may result in stillbirths, miscarriages, and congenital abnormalities, such as cretinism, an irreversible form of growth and mental retardation affecting people living in iodine-deficient areas (particularly in lesser developed areas of the world, such as Africa and Asia). A less visible, yet serious, impact of iodine deficiency is a lower level of impairment that compromises intellectual prowess in home, school, and work environments. In adults, inadequate iodine intake can cause goitre (an enlargement of the thyroid gland), metabolic insufficiency, and impaired cognitive function.

The primary effects of long-term oral exposure to elevated amounts of inorganic iodide are, paradoxically, hyperthyroidism and/or hypothyroidism. This is due to the complex physiological processes involved in regulating thyroid activity to maintain iodine homeostasis.

[1] For a list of acronyms and abbreviations used in this report, please refer to Appendix 1.

Several studies have indicated that when iodine is added to the diet, the incidence of hyperthyroidism in the population increases, even when the average iodine intake does not exceed the recommended daily dosages.

Excess intake of iodide can inhibit thyroid hormone synthesis and release, which may result in hypothyroidism and goitre. Depression of thyroid function has been observed in euthyroid adults (i.e. adults with normal thyroid function) at a daily dose of ≥1700 μg of iodine per day.

Many case reports indicated that oral doses in the order of 300 mg of iodine and above have induced febrile reactions in patients with existing diseases. Oral doses of iodine have also caused dermal sensitivity reactions called iododerma. Dermal contact sensitization has been ascribed to organic iodine compounds, but not to iodine or inorganic iodides.

The results of some epidemiological studies suggest that residence in endemic goitre areas (low dietary iodide intake) may be a risk factor for thyroid cancer, whereas other studies have reported that increased dietary intake of iodide may also be a risk factor for thyroid cancer, specifically of papillary cancer, particularly in populations residing in areas with iodide-deficient soil.

Lifetime exposure to approximately 50 mg of potassium iodide per kilogram body weight per day induced a statistically borderline increase of salivary gland tumours in rats; in two two-stage studies, iodide had a promoting effect on thyroid tumours after initiation by a nitrosamine. There is no convincing evidence that iodine or iodide compounds have any mutagenic potential.

Large doses of iodide administered in the latter part of gestation induced neonatal mortality in rats and rabbits, but not in hamsters or swine. There are no studies on the embryotoxic or teratogenic effects of iodine or iodides. Human cases of neonatal hypothyroidism have been reported after in utero exposure to pharmacological doses of iodine administered to the mother.

Inhalation exposure to low iodine vapour concentrations have been shown to result in increases in airway resistance and a decrease in breathing rate in guinea-pigs.

In a large cross-sectional study on thyroid hormone status and iodine intake in children, an estimated average daily iodine intake of 0.03 mg/kg body weight was associated with elevated TSH concentrations in the blood, in comparison with an iodine uptake of 0.01 mg/kg body weight per day. Two experimental short-term studies in small groups of adults and two cross-sectional studies in elderly people supported 0.01 mg/kg body weight per day as a no-adverse-effect level. As this NOAEL is based on two potentially sensitive population groups, the elderly and children, it is considered to be a TDI.

The extent of variability in the need for dietary iodine between different individuals and populations contributes to the uncertainty of the TDI. This variation may increase or decrease the extent of iodine supplementation needed in iodine-deficient geographical areas.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Iodine is a non-metallic element belonging to the halogen family in Group VIIA of the periodic table. It exists in nature as a monovalent anion in brines and in molecular compounds (e.g. iodate, or IO_3^-). Iodine can exist in several oxidation states: −1, 0, +1, +3, +5, and +7. Stable, naturally occurring iodine is the isotope ^{127}I.

The chemical and physical properties of iodine vary with the elemental or molecular form of the element. These properties are shown in Table 1. Additional physical/chemical properties of iodine (ICSC 0167), hydrogen iodide (ICSC 1323), and iodine cyanide (ICSC 0662) are provided in the International Chemical Safety Cards reproduced in this document.

3. ANALYTICAL METHODS

A variety of analytical methods and equipment types are used for analysing iodine and its compounds. MS hyphenated techniques (adding a front-end HPLC, ICP, or other unit to an MS unit) achieve high sensitivity and accuracy. They and other methods are used by the International Resource Laboratories for Iodine, which is the first global network of iodine resource laboratories in support of national public health and industry monitoring. It functions to strengthen the capacity of laboratories to accurately measure iodine in urine and salt. The network is an integral monitoring component that contributes to sustaining progress towards optimal iodine nutrition and universal salt iodization. It is co-sponsored by WHO, CDC, the International Council for the Control of Iodine Deficiency Disorders, the Micronutrient Initiative, and UNICEF. A component is the CDC Global Micronutrient Reference Laboratory, which established an international laboratory intercomparison programme known as Ensuring the Quality of Iodine

Table 1. Chemical and physical properties of iodine and inorganic iodides.

Chemical property[a]	Iodine	Hydrogen iodide	Sodium iodide	Potassium iodide	Caesium iodide	Potassium iodate	Sodium periodate	Iodic acid	Calcium iodide	Copper(I) iodide
Chemical formula	I_2	HI	NaI	KI	CsI	KIO_3	$NaIO_4$	HIO_3	CaI_2	CuI
Synonyms	Actomar; diiodine; eranol; iodine-127; molecular iodine	Hydroiodic acid	Sodium monoiodide; sodium iodine	Hydroiodic acid, potassium salt; PIMA; SSK; iodide of potash	No data	Iodic acid, potassium salt; potassium iodate	Sodium metaperiodate	None	Calcium diiodide; calcium iodide hydrate	Copper monoiodide; natural marshite; cuprous iodide
CAS No.	7553-56-2	10034-85-2	7681-82-5	7681-11-0	7789-17-5	7758-05-6	7790-28-5	7782-68-5	10102-68-8	7681-65-4
Molecular mass (g/mol)	253.809	127.91	149.89	166.02	259.81	214.02	213.892	175.91	293.89	190.45
Colour	Bluish-black	Colourless	White	Colourless or white	Colourless	White	White	White	Yellow	Red-brown
Physical state	Solid; scales or plates	Gas	Solid; crystals or granules	Solid; crystals, granules, or powder	Solid; crystals or powder	Solid; crystals	Solid; crystals	Solid; crystals	Solid; lumps or powder	Solid; powder or crystals
Melting point	113.60 °C	−50.8 °C	651 °C	680 °C	621 °C	560 °C	Decomposes ~300 °C	No data	740 °C	588–606 °C
Boiling point	185.24 °C	−35.1 °C	1304 °C	1323 °C	~1280 °C	Decomposes	No data	Decomposes	1100 °C	~1290 °C
Odour	Characteristic	No data	Odourless	No data	No data	No data	No data	No data	No data	No data
Solubility in water (25 °C)	330 mg/l	2340 g/l (10 °C)	2000 g/l	1429 g/l	9.16 g/100 g	Soluble	308 g/100 g	Very soluble, value not found	80 mg/l (18 °C)	Miscible
Log K_{ow}	2.49	No data	No data	No data	No data	No data	No data	No data	No data	No data
Vapour pressure	40.7 Pa at 25 °C	101.3 kPa at −75.9 °C; 791.9 kPa at 25 °C	0.133 kPa at 767 °C	0.10 kPa at 731 °C	1.07 Pa at 523 °C	No data	No data	No data	1.07 Pa at 296 °C	1.0 kPa at 636 °C

[a] No data are available for odour threshold (in water or air) or log K_{oc}.

Procedures, or EQUIP (Caldwell et al., 2005a). EQUIP provides laboratories with an independent assessment of their analytical performance to eliminate bias and precision problems and to confirm the level of quality achieved by 52 laboratories in 34 countries (as of October 2005).

3.1 Environmental samples

A number of analytical methods can be used to determine iodine levels in air, water, soils, sediments, pharmaceuticals, and foods. INAA with gamma ray detector, IDMS, ion chromatography, colorimetry, ICP-AES, HPLC with UV, arsenic–cerium catalytic spectrometry, ICP-MS, and NIOSH Method No. 6005 have all been shown to be effective in determining the amount of iodine in a variety of environmental samples (ATSDR, 2004).

Ambient air: In this method, a known volume of air is passed through a multistage filter assembly to separately collect particulate iodine, hydrogen iodide (HI), molecular iodine (I_2) vapour, hypoiodous acid (HOI), and organoiodine. Different methods are used to extract the various species from the filter media for IDMS analysis. For the particulate iodine fraction, the filters are then extracted in a heated sodium hydroxide/sodium sulfite solution containing ^{129}I as an internal standard. Following filtration and acidification, silver nitrate is added to precipitate the iodine as silver iodide (AgI), which is then dissolved in aqueous ammonia and analysed using IDMS. The sample detection limit is 0.02–0.024 ng/m^3 (for average air volume 70 m^3), with a 97–99% recovery (Gäbler & Heumann, 1993).[1]

Air (occupational): OSHA Interim Method No. ID-212 requires measuring relative humidity. For <50% relative humidity, at least 2.5 litres of air are sampled slowly (0.5 l/min) using an impregnated activated beaded charcoal tube, desorbed with 1.5 mmol/l each of sodium carbonate and sodium bicarbonate, and analysed using ion chromatography and a pulsed electrochemical detector to achieve a detection limit of 0.01 mg/m^3; for >50% relative humidity, the impinger alternate method is used (OSHA, 1994). NIOSH Method No. 6005 recommends sampling 15–225 litres of air at 0.5–1 l/min through an alkali-treated charcoal tube, desorbing and eluting with sodium carbonate on anion separator and guard exchange columns, and analysing by ion chromatography, based on a 1981 method by Kim et al. (1981), to measure concentrations of 0.5–50 mg/m^3 (NIOSH, 1994).

Water, brines, and wastewater: EPA Methods 320.1 (for iodide and bromide) and 345.1 (for iodide only) involve removing interferences with calcium oxide or lime, conversion of iodide to iodate in a 100-ml sample using acetate and formate, addition of potassium iodide (KI), and titration with phenylarsenine oxide or sodium thiosulfate to measure iodine in the range of 2–20 mg/l.

Water: In this method, the sample is first acidified with hydrochloric acid and then oxidized with hydrogen peroxide or potassium permanganate to remove excess oxidant, before titration with potassium iodate (KIO_3) and submission for spectrophotometry. The sample detection limit of this method is 25 µg/l to 6.35 mg/l, with ~100% recovery (at 0.13–6.35 mg/l) (Pesavento & Profumo, 1985).

Drinking-water: In this method, using HPLC with UV detection, the sample is separated on a Dionex AS12 analytical HPLC column. The eluted iodate is reacted with acidified bromide in a post-column reaction to form tribromide, which is detected at 267 nm. The sample detection limit is 0.05 µg/l, with 100–111% recovery at 0.5–2.0 µg/l (Weinberg & Yamada, 1997).

Drinking-water (total iodine): After addition to potassium carbonate, the sample is centrifuged to remove precipitated alkaline earth metals. Iodine is measured by the addition of nitric acid, sodium chloride, ammonium ferric sulfate, and potassium sulfur cyanide before submitting for spectrophotometry. The sample detection limit is 0.2 µg/l, with 90–108% recovery (Moxon, 1984).

Seawater (iodine): Iodine in the sample is precipitated with silver nitrate, after which the precipitate is dissolved in acetic acid saturated with bromine. Following filtration, the filtrate is reduced in volume and then reacted with starch solution and cadmium iodide (CdI_2) for spectrophotometric analysis. The sample detection limit is 0.025 µg/l, with 99% recovery (at 10 µg of iodine per litre) (Tsunogai, 1971).

Soil: After the sample is dried, it is sieved (7-mm diameter), ground, resieved (2-mm diameter), and extracted with 2 N sodium hydroxide. Arsenious acid is then added before submission for automated analysis using arsenic–cerium catalytic spectrophotometry. The sample detection limit is 0.5 µg/g (Whitehead, 1979). The per cent recovery was not reported.

Soil, sediments, rock: After the sample is dried and pulverized, it is mixed with vanadium pentoxide and

[1] In keeping with WHO policy, which is to provide measurements in SI units, all concentrations of gaseous chemicals in air will be given in SI units in the CICAD series. Where the original study or source document has provided concentrations in SI units, these will be cited here. Where the original study or source document has provided concentrations in volumetric units, conversions will be done using the conversion factors given here, assuming a temperature of 20 °C and a pressure of 101.3 kPa. Conversions are to no more than two significant digits.

pyrohydrolysed. Evolved iodine is dissolved in sodium hydroxide solution and then digested with acid before submitting for arsenic–cerium catalytic spectrophotometry. The sample detection limit is 0.05 µg/g (for a 0.5-g sample size), with 75–90% recovery (Rae & Malik, 1996).

Vegetation: The sample is prepared by microwave digestion using nitric acid/hydrogen peroxide, treated with sodium thiosulfate or ascorbic acid solution to convert the iodate to iodide, and then submitted for ICP-MS. The sample detection limit is 100 pg/g, with 96–105% recovery (Kerl et al., 1996).

Environmental salt: A colorimetric method developed by the Salt Research Institute of the China National Salt Industry Corporation uses the WYD Iodine Checker. The WYD Iodine Checker is a single-wavelength spectrophotometer that measures the iodine level (mg/kg) in salt based on the absorption of the iodine–starch blue compound at 585 nm. The manufacturer specifies that the instrument's range of measurement is 10–90 mg/kg and that it has an analytical error of less than 2 mg/kg. Its weight (500 g) and dimensions (175 × 135 × 60 mm) make it easily transportable; the manufacturer states that it can withstand a damp and corrosive environment. It functions on 220 V AC or 9 V DC voltage, which requires six AA batteries.

3.2 Biological samples

Urine: A 500-µl sample of urine is diluted 1:10 with a diluent containing 1% tetramethylammonium hydroxide, 0.02% Triton-X100, 25 µg/l tellurium, 5 µg/l bismuth, 5% (v/v) ethanol, 1000 µg/l gold, and 0.5 g/l EDTA. Urinary iodine concentration is determined by quadrupole ICP-DRC-MS. Diluted urine samples are aerosolized within the spray chamber using a nebulizer. The ions and the argon carrier gas enter the MS through an interface that separates the ICP generator, which is operating at atmospheric pressure (approximately 101.3 kPa), from the MS, which is operating at approximately 1.33×10^{-3} Pa. DRC technology using collisional focusing provides additional control of ICP-MS sensitivity, which significantly extends the useful concentration measurement range. In this method, iodine (isotope mass 127), tellurium (isotope mass 130), and bismuth (isotope mass 209) are measured in urine by ICP-DRC-MS using 100% argon as the DRC gas utilizing collisional focusing. Urine samples are diluted 1 + 1 + 8 (sample + water + diluent) with water and diluent containing tellurium and bismuth for internal standardization. The limit of detection in urine is 1.75 µg/l, with an analytical range of 1.75–3000 µg/l (Caldwell et al., 2003, 2005b).

Urine: Following purification of the sample on a Dowex 1 × 8 resin column, the dried resin is fused with sodium hydroxide/potassium nitrate and dissolved in water. A dry 0.5-ml aliquot is then placed on a polyethylene sheet, irradiated, and dissolved in water with an iodine carrier. The iodine is extracted with trioctylamine/xylene, then back-extracted with 1 N ammonia, giving a silver iodide precipitate. The precipitate is then subjected to INAA with gamma ray spectrometry. This method has a detection limit of 0.01 µg/l and 94% recovery (Ohno, 1971).

Urine: Following sample digestion in chloric acid, arsenious acid is added and then submitted for automated analysis by arsenic–cerium catalytic spectrophotometry. The detection limit of this method is between 0.01 and 0.06 µg per sample (0.02–0.50 ml sample volume). Reported recovery is 96–97% (Benotti & Benotti, 1963; Benotti et al., 1965).

Thyroid tissue: Powdered or fresh tissue is digested with sulfuric acid. The sample is then converted to aluminium hexaiodide (Al_2I_6) and neutron irradiated. The iodine is precipitated with palladium, and the sample is submitted to neutron activation plus MS. The detection limit is 0.11–2.17 µg/g (range of measured values) (Boulos et al., 1973; Ballad et al., 1976; Oliver et al., 1982). No per cent recovery data are available.

Non-thyroid tissue: Tissue samples are lyophilized, sealed in polyethylene film, and irradiated with epithermal neutrons using a boron nitride shield, then submitted to INAA (gamma ray spectrometry). The sample detection limit for this method is 9.2–2880 ng/g (range of measured values) (Hou et al., 1997). No per cent recovery data are available.

Adipose tissue: The sample is placed into polyethylene vials and neutron irradiated. The sample then undergoes INAA (gamma ray spectrometry). The sample detection limit is 1.4–8.4 µg/g (EPA, 1986). No per cent recovery data are available.

Tissues: Preparation consists of the addition of aqueous sodium hydroxide and sodium pyrosulfite to the tissue homogenate. Following ashing, the residue is dissolved in water and injected into an HPLC for the separation of components on a two-column system, followed by UV quantification of iodine. The sample detection limit is 0.07–1060 µg/g (range of measured values), with 87–97% recovery (Andersson & Forsman, 1997).

Faeces: The sample is dried, pulverized, digested in nitric acid/hydrofluoric acid, treated with sodium chloride/nitric acid, and subjected to ICP-AES analysis. The sample detection limit of this method is 0.1 µg/mg, with 88–90% recovery (Que Hee & Boyle, 1988).

Faeces: The sample is dried, pulverized, and digested in chloric acid. Arsenious acid is then added and the sample submitted for automated analysis using arsenic–cerium catalytic spectrophotometry. The sample detection limit is between 0.01 and 0.06 µg per sample (20–30 mg sample size), with 77–101% recovery (Benotti & Benotti, 1963; Benotti et al., 1965).

Milk: The sample is mixed with acetonitrile (1:2) and centrifuged, and the supernatant is dried before dissolving in acetonitrile/water and a 1-ml aliquot derivatized with 2-iodosobenzoate in phosphate buffer containing 2,6-dimethylphenol. Analysis is via HPLC with UV detection. The sample detection limit is 0.5 µg/l, with 97.6–102.4% recovery (Verma et al., 1992).

Tissues (general): Tissue is homogenized, sodium hydroxide and sodium pyrosulfite are added, the solution is ashed and redissolved in water, and an aliquot is injected into an HPLC, followed by column separation and analysis by UV spectroscopy. This method has a detection limit of 0.07 µg/g or greater, based on tissue type, and 87–97% recovery (Andersson & Forsman, 1997). Alternatively, an electrochemical detector can be used.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Iodine is a naturally occurring constituent of the earth's crust and the least abundant of the halogen elements (Straub et al., 1966). The average concentration of iodine in the earth's crust is approximately 0.5 mg/kg (ranging up to 380 mg/kg in sedimentary rock). In the oceans, the concentration is 45–60 µg/l, and in the atmosphere, the concentration ranges from 10 to 20 ng/m^3 (depending on the proximity to the seacoast and the soil type).

Iodine is introduced into the air by both naturally occurring and anthropogenic activities. The primary source of iodine on land surfaces is volatilization of iodine from the ocean surface, which may include organic iodine vapour emitted by marine algae (Laturnus, 2001; Mäkelä et al., 2002). Total atmospheric iodine accounts for about 4×10^7 kg, with an average concentration of 10–20 ng/m^3 (Whitehead, 1984). Other mechanisms by which iodine can enter the air from the oceans include the photochemical or ozone-induced oxidation of iodide to elemental iodine (NCRP, 1983; Whitehead, 1984). Another mechanism suggested for atmospheric iodine deposition involves the formation of methyl iodide and other alkyl iodides from the biological metabolism of iodine/iodide. Once in the atmosphere, iodide could undergo photolytic dissociation into methyl and iodine radicals, with the resultant formation of elemental iodine and other forms of inorganic iodine, including HI, HOI, INO_2, $IONO_2$, and OIO (Chameides & Davis, 1980; Cox et al., 1999; Vogt et al., 1999). It has been suggested that this method may play a major role in the annual transfer of approximately $1.3–2.0 \times 10^9$ kg of iodine from the ocean to the atmosphere (USNRC, 1981; Rasmussen et al., 1982; Whitehead, 1984).

Combustion of fossil fuels also results in the transfer of iodine to the atmosphere. The average iodine content of coal has been reported to be ~4 mg/kg, and petroleum contains an average iodine concentration of 1 mg/kg (Chameides & Davis, 1980). At the current rate of global coal and petroleum consumption, the introduction of iodine into the atmosphere from these sources would be expected to account for 5×10^5 kg of iodine per year for the first few years of the 21st century.

The weathering of rock, volcanic activity, decay of vegetation, iodine deposited in rainfall, and human activities all contribute to the deposition of iodine in soil. The average iodine concentration in soils worldwide is 5 mg/kg (Whitehead, 1984). While many consider rock weathering to contribute little to soil iodine (Goldschmidt, 1958; Whitehead, 1984; Fuge, 1987), others believe the relative contribution to vary with the rock. In areas in which the bedrock is composed primarily of igneous rock, the contribution of weathering to total soil iodine might be expected to be much less than in regions in which the bedrock is composed of sedimentary rock with a higher iodine content (NAS, 1974; Whitehead, 1984; Cohen, 1985).

The concentration of iodine in soil shows a very broad variation, from <0.1 to 150 mg/kg. The iodine content is generally higher in soils than in the rocks from which they derive: the majority of the iodine in soils is derived from the atmosphere and ultimately from the marine environment. The concentrations of iodine in soil are thus low at long distances from the sea; this concentration gradient coincides with the prevalence of iodine deficiency disorders (Fuge, 2005).

Iodine released through flue gases in the combustion of coal and petroleum can ultimately contribute to soil iodine, adding 4×10^5 kg iodine to soils globally on an annual basis.

Agricultural activities add to the soil iodine content primarily through animal excrement and the use of iodine-containing fertilizers and pesticides. Faeces from farm animals can contain as much as 10 mg of iodine per kilogram, and urine can contain up to 4 mg of iodine per litre. Fertilizers containing Chilean nitrate can contain as much as 80 µg of iodine per gram (0.08 mg/kg), and superphosphate and compound fertilizers derived from

rock phosphate can contain up to 26 µg of iodine per gram (0.026 mg/kg) (Whitehead, 1979). Iodine-containing herbicides, such as ioxynil octanoate, and fungicides, such as benodanil, can also provide iodine to soils, but their contribution is considerably less (Whitehead, 1979, 1984).

Worldwide production of iodine was estimated to be 20 900 tonnes in 2003; iodine was used in X-ray contrast media (23%), in the catalytic production of acetic acid and the manufacture of other chemicals (17%), iodophors (surfactants that act as iodine carriers) and biocides (17%), organic chemicals (12%), pharmaceuticals (8%), nylon (6%), animal feed supplements (5%), and herbicides (4%), and in human nutrition (8%). Other small uses include batteries, high-purity metal, inks and colorants, laboratory reagents, lubricants, photographic chemicals, as a stabilizer in tall oil, in iodized oil, and motor fuels (Lyday, 2004). In the health industry, iodine is used as a disinfectant/biocide, in the production of certain soaps, bandages, and medicines, and in water purification. The addition of iodine to table salt as a result of the Universal Salt Iodization project results in 70% of all households in the world having access to iodized salt (CDC, 2003).

Iodine is also being used to disinfect drinking-water (Parfitt, 1999). Municipal wastewater treatment plants are also a source of iodine in surface waters.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

The environmental transport, distribution, and transformation of iodine are driven by a complex series of physical, chemical, and biological processes that are collectively referred to as the global iodine cycle. The cycle (Figure 1) can be represented as three groups of compartments with essentially steady-state iodine content interconnected in a manner to show transfer rates among the ocean (atmosphere, water at two depths, and sediment), land (atmosphere and soil at three depths), and terrestrial biosphere. The overall effect is to move iodine from soil and ocean sediment to water and the atmosphere and then cycle it back down in a manner that makes it available to the entire aquatic and terrestrial biosphere.

The rate constants in Figure 1 show that the driver for the entire cycle is the interchange of iodines between the ocean water and its atmosphere (USNRC, 1979; Kocher, 1981). Some aquatic biological aspects involve the reduction of iodate to iodide and then its conversion to organic iodine compounds (Vogt et al., 1999) by algae and plankton in ocean surface water. The relative volatility of these compounds combined with direct evaporative losses results in a range of iodine compounds being transferred to the ocean atmosphere. The major component is alkyl iodides (mostly methyl iodide) and, to a lesser extent, molecular iodine.

In air, some of these iodine compounds photochemically decompose to iodine and its radicals (I· and IO·), which react with atmospheric gases to produce a range of additional reactive iodine species. Some environmental results are the conversion of atmospheric nitrous oxide, nitrogen dioxide, and ozone, the latter of which produces oxygen in a manner that uses I· as a catalyst. The iodine species can also react with aerosols or water droplets to form iodine anions and add to the range of species available.

The introduction of iodine into surface waters and groundwater occurs principally through rainwater for non-coastal land regions and the combination of rainwater and ocean spray in coastal areas. This iodide can oxidize in water to form hypoiodous acid (HOI), which in turn can react with organics to adversely affect the taste and odour of drinking-water (Bichsel & von Gunten, 1999). Andersen et al. (2002) found that iodine in some drinking-waters mainly eluted with a humic substance derived from a marine source.

The global iodine cycle is crucial to terrestrial life, since the majority of iodine in the earth's surface is inaccessible, with only small amounts being liberated at the surface by weathering and dissolution. The transfer to land and the terrestrial biosphere (1.0×10^{11} g of iodine per year) decreases with distance from the ocean and occurs by direct uptake of gases and by dry and wet deposition onto plant and soil surfaces. The deposition of iodine to the soil from rainfall and snowfall is believed to account for about 16 g/ha per year, with dry deposition adding about 9.6 g/ha per year (Whitehead, 1984). This provides input for the soil–plant–cow–milk pathway, which has seasonal, temperature, and pasture-land nutritional quality components (Tracy et al., 1989; Pennington, 1990a). Iodine can react with the organic components of soil, such as humic substances, to undergo iodination reactions with polyphenols and tyrosine residues (Whitehead, 1984). Decreases in pH can reduce the proportion of iodide to iodate in both soil and water by protonating iodide to form volatile hydrogen iodide.

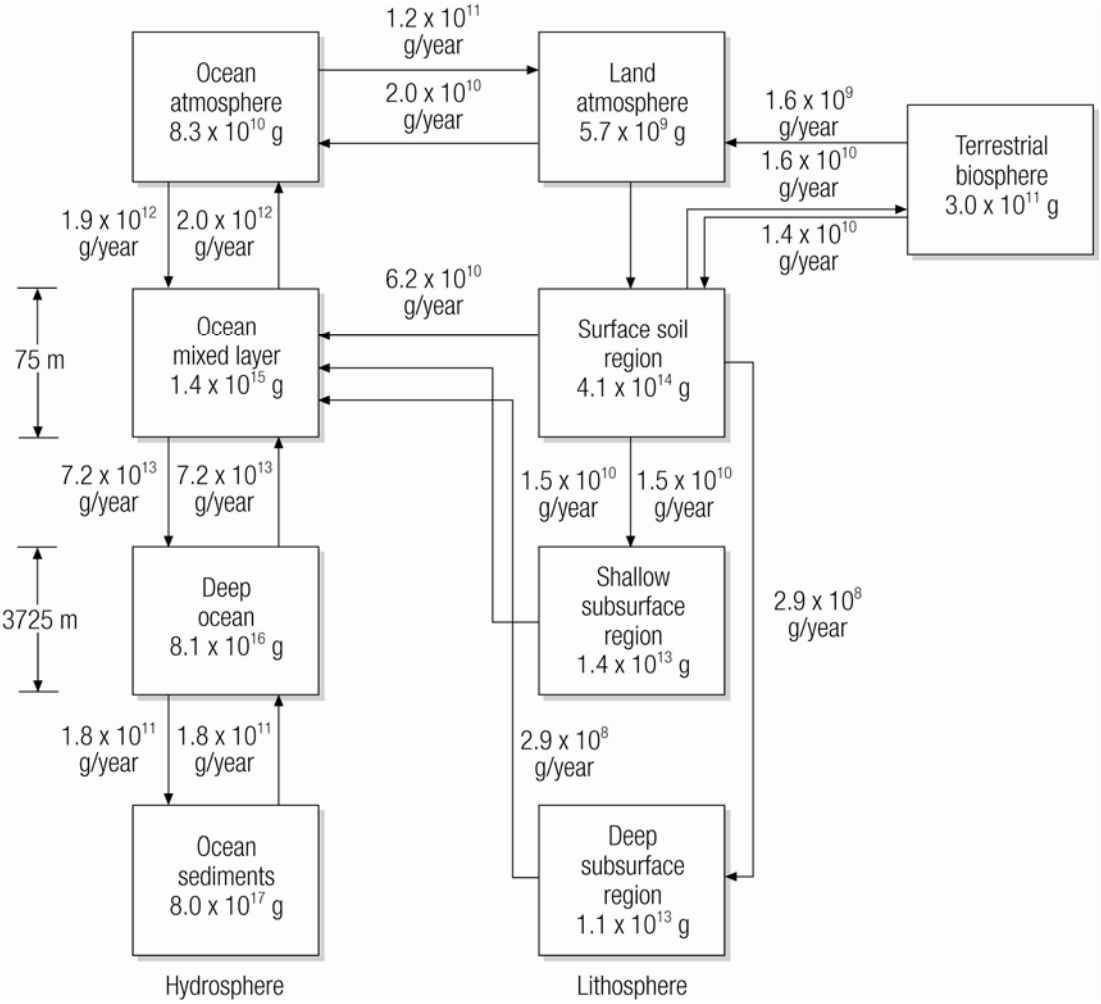


Figure 1. Global iodine cycle (Kocher, 1981).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Essentiality in human nutrition

Iodine is essential in small amounts for normal physiological function. It is a critical component of thyroid hormones, which are necessary for controlling metabolic rate, growth, and development of body structures, as well as neuronal function and development. The WHO recommended intake (population requirement) of iodine is 150 µg/day for adults and adolescents 13 years of age and older, 200 µg/day for women during pregnancy and lactation, 120 µg/day for children 6–12 years of age, and 90 µg/day for children 0–59 months of age (WHO, 2004a).

6.2 Environmental levels

Iodine is a naturally occurring element, having a concentration of 0.5 mg/kg in the earth's crust. It is ubiquitous in the environment, with concentrations typically ranging from 2 to 14 ng/m^3 in air over land, from 17 to 52 ng/m^3 in air over the oceans, from 45 to 60 µg/l in seawater, from 1 to 15 µg/l in rainwater over oceans, from 0.1 to 15 µg/l in rainwater over land, from 0.1 to 18 µg/l in river water, and from 1.0 to 16 µg/l in municipal wastewater. Concentrations range from 0.2 to 5.8 mg/kg in igneous and sedimentary rock and are 5–10 times higher in soils, coals, and shales rich in organic matter (NAS, 1974; USNRC, 1979; ATSDR, 2004). The atmospheric concentration range of 10–20 ng/m^3 is believed to be primarily the result of the vaporization of seawater (WHO, 1988; Berthelsew & Thorup, 2002).

6.3 Human exposure

The levels of iodine in various typical sources of human exposure are provided in Table 2. While no specific data regarding occupational exposures could be located, the various uses of iodine in industrial settings, as noted in section 4 of this CICAD, most certainly result in some occupational exposures.

Table 2. Estimated average concentrations of iodine in typical human exposure media.

Medium	Total iodine	Source
Atmosphere	10–20 ng/m^3	Whitehead (1984)
Drinking-water	0–8 µg/l	FDA (1974)
Freshwater fish	0.003–0.81 mg/kg	Poston (1986)
Ocean fish	0.023–0.11 mg/kg	Poston (1986)
Dairy products	17–55 mg/kg	Pennington (1990a)
Dietary meats	260 ± 70 µg/kg	FDA (1974)
Dietary plants	320 ± 100 µg/kg	FDA (1974)
Iodized salt	76 mg/kg	FDA (1989)

Inhalation exposure to iodine in a coastal area has been estimated to be 5 µg/day. This was based on a scenario that assumed part-time outdoor exposure to coastal air at a concentration of 0.7 µg/m^3, with the remaining exposure at the associated indoor iodine air concentration ranging from 0 to 0.74 µg/m^3. The time spent outdoors and indoors was not specified (FDA, 1974).

Iodine vapour has been shown to penetrate the skin (Gorodinskiy et al., 1979). However, the amount of radiolabelled ^{131}I absorbed dermally is only 1–2% of that absorbed through the lungs from the same air concentration. Consequently, dermal absorption is not considered to be a major contributor to total daily iodine exposure from air.

Dietary intake is the primary source of iodine intake for the general population. Marine seafoods typically contain the highest amount of iodine (range 160–3200 µg/kg; mean 660 µg/kg), with shellfish having a mean iodine concentration of 0.798–1.6 mg/kg. Kelp and other seaweeds (1–2 mg/kg) and sea salt (up to 1.4 mg/kg) provide other abundant sources of iodine. In industrialized countries, the most important sources of iodides are dairy products, such as whole cow's milk (mean 27–47 µg/kg), eggs (mean 93 µg/kg), and grain and cereal products (mean 47 µg/kg, depending on the soil); other food sources are freshwater fish (mean 30 µg/kg); poultry and meat (mean 50 µg/kg); fruits (mean 18 µg/kg), legumes (mean 30 µg/kg), and non-legume vegetables (mean 29 µg/kg) (WHO, 1996; MAFF, 2000; Souci et al., 2000; EGVM, 2002).

Since the 1950s, in some countries, iodine is routinely added to table salt (NaCl) to ensure adequate iodine intake from the diet to prevent sequelae of iodine deficiency. Some reported iodide levels in iodized salt utilized in various countries include 15–25 mg of iodine per kilogram (as potassium iodate) in Germany; 20 mg of iodine per kilogram (as potassium iodide) in Austria; and 25 mg of iodine per kilogram (as potassium iodide) in Switzerland. Cooking reduces the iodine content of foods: frying by 20%, grilling by 23%, and boiling by 58% (WHO, 1996).

Iodine concentrations in foods of plant origin vary considerably, depending on the species of plant, proximity to bodies of salt water, and the use of iodine-containing fertilizers. Since surface waters rarely have an iodine concentration above 5 µg/l, drinking-water is not typically a significant contributor to iodine intake. Food additives containing iodine can also contribute to human dietary intake of this mineral. Copper(II) iodide (CuI) and potassium iodide (in table salt), alginic acid, and alginate salts used as emulsifiers, stabilizers, and thickeners can contain as much as 9 mg of iodine per kilogram, but their contribution to total dietary iodine intake is believed to be small (average intake of 1 µg/day) (FDA, 1974). The estimated average dietary intake of iodine from different food categories has been reported to range from 3 µg/day by both sexes for beverages (excluding milk) to 84.5 µg/day by males and 49.9 µg/day by females for meat and meat products (FDA, 1974).

Iodine in water and other beverages can also provide significant amounts of iodine in the diet, and tap water iodine is important for iodine intake in many countries (Hales et al., 1969; Pedersen et al., 1999; Rasmussen et al., 2000; Andersen et al., 2002). Pedersen et al. (1991) found that iodine concentrations in tap water obtained from 55 locations in Denmark ranged from <1.0 to 139 µg/l, which resulted in regional differences in iodine intake. In general, the iodine content was low in Jutland (median 4.1 µg/l), with higher values in Sealand (23 µg/l) and other islands. In Denmark, iodine in groundwater is bound to humic substances that have probably leached from marine sediments in the aquifers (Laurberg et al., 2003). In Greenland, tap water is mainly surface water from glacial or snowmelt reservoirs (Andersen et al., 2002).

Levels of iodine were determined in selected foods and dietary supplements and in samples of the British "total diet" (Lee et al., 1994). British milk collected in 13 areas on four occasions during 1990 and 1992 contained iodine at 150 µg/kg (range 140–310 µg/kg) compared with 230 µg/kg in 1977–1979. Iodine levels in

fish and fish products were between 110 and 3280 µg/kg. The intake of iodine as estimated from that total diet study was 173 µg/day in 1985 and 166 µg/day in 1991.

A recent survey of sources of dietary iodine in 20 brands of bread, 18 brands of cows' milk, and 8 infant formulas within the Boston, Massachusetts, USA, area between 2001 and 2002 was reported by Pearce et al. (2004). Three bread varieties contained more than 300 µg of iodine per slice, and the iodine content in other brands was far lower (mean ± SD: 10.1 ± 13.2 µg of iodine per slice). All cows' milk had at least 88 µg of iodine per 250 ml, ranging from 88 to 168 µg (116 ± 221 µg per 250 ml). Infant formula values ranged from 16.2 to 56.8 µg of iodine per 150 ml (23 ± 13.78 µg per 150 ml). There is a wide amount of variation in the iodine content of some common foods, and the iodine content of foods is often not well reflected by package labelling (Pearce et al., 2004). Some of the iodide in cereal products is derived from iodate-containing dough conditioners (European Commission, 2002).

The use of iodine/iodophors as disinfectants or sanitizers in the dairy industry has contributed to milk being a significant dietary source of iodine. Consequently, cheeses and ice cream also contain biologically relevant amounts of iodine. Pennington (1988) reported milk iodine concentrations ranging from 0.10 to 0.70 mg/l, and cheeses containing iodine levels as high as 425 µg/kg have been reported (FDA, 1974). Feed supplementation and teat dips and udder washings containing iodophors also contribute to the iodine content of milk (FDA, 1974). Such teat dips contain up to 1% available iodine and have been shown to significantly increase milk iodine residues by absorption through the skin and incorporation into milk (Conrad & Hemken, 1978). Povidone-iodine (consisting of molecular iodine and polyvinyl pyrrolidone as a solubilizing agent) disinfecting solutions used to clean tanker trucks, vats, and milking equipment may contain 12.5–25 mg of iodine per litre (Pearce et al., 2004). Chlorine has begun replacing iodine for dairy applications in some countries. This action, along with efforts to reduce the iodine content of bread conditioners and salt intake for medical reasons, has contributed to an observed reduction of dietary iodine (Caldwell et al., 2005a).

Certain medications and vitamin/mineral supplements also contribute to daily iodine exposure. Tincture of iodine is believed to have first been used as an antiseptic by a French surgeon in 1839, and it has been used as such since (Hardman et al., 2001). Aqueous iodine solutions (e.g. Lugol's solution) have also been used because of their bactericidal, sporicidal, fungicidal, and other antiseptic properties. Iodophors (combinations of iodine with a surfactant carrier, which serves as a sustained-release reservoir of iodine, e.g. sodium iodide, NaI) currently have widespread medical use, primarily in the prophylaxis of post-operative infections.

Dietary supplements often contain iodine, typically as potassium iodide, sometimes with a manufacturer recommendation of consumption of 300 µg daily.

The normal concentration of stable iodine in human milk was reported by ICRP (1975) to range from 20 to 150 µg/l (mean 70 µg/l) and by the United States Institute of Medicine (IOM, 2000) to be 110 ± 40 µg/l. Guswurst et al. (1984) reported international values in the 1980s as 12 µg/l in the former German Democratic Republic; 27 µg/l in Italy; 95 µg/l in France; and 178 µg/l (median) in the United States, with values as high as 700 µg/l occasionally being reported. More recent studies have reported iodine levels in breast milk in Germany in the 1990s as follows: 36 µg/l in 1992, 86 µg/l in 1994, and 95 µg/l in 1995–1996 (Meng & Schindler, 1998; European Commission, 2002). Measurements in Spain in the early 1990s indicated a mean of 100 µg/l (Ares et al., 1994).

In general, breast-feeding women produce 500–800 ml (average 780 ml) of breast milk (SCF, 1993) daily, which provides a multiplier for assessing infant exposure based on iodine concentration.

Excretion of iodine in breast milk is addressed below in section 7.4.

Dietary intake of iodine in the United States population has been closely followed by CDC in its National Health and Nutrition Examination Survey, or NHANES. Iodine intake was shown to have a significant downward trend from an initial evaluation in 1971–1974 (320 ± 6 µg/l) to the third evaluation in 1988–1994 (145 ± 3 µg/l). That trend has now stabilized, based on a 2001–2002 evaluation (167.8 ± 10 µg/l) (Caldwell et al., 2005a). Dietary iodine supplementation is also a significant source of iodine in many individuals. According to NHANES III (Hollowell et al., 1998), the United States median intake of iodine from dietary supplements was 140 µg per male or female adult; in 1986, approximately 12–15% of the United States population was taking dietary iodine supplements (IOM, 2001). FDA surveys suggest that the daily median adult iodine intake in the United States was 240–300 µg for males and 190–210 µg for females and that the highest intake of any life stage and sex for the 95th percentile excluding supplements was 1.15 mg/day (IOM, 2001).

Dietary iodine intake varies geographically. Urinary iodine concentrations were used to assess the iodine status of European countries (ICCIDD, 2003). Among 13 nations or kingdoms investigated, the iodine sufficiency status was found to range from as low as 38 µg/l to as high as 160 µg/l. Even within some countries, a

wide range in iodine status was found to exist. For example, the range of urinary iodine levels was from 10 to 38 µg/l in Denmark, from 50 to 100 µg/l in Spain, and from 84 to 160 µg/l in Greece. The Netherlands (155 µg/l), Switzerland (115 µg/l), and the United Kingdom (141 µg/l) had optimal iodine status, as did parts of Greece. Belgium (80 µg/l), Germany (83–99 µg/l), France (83 µg/l), and Hungary (<100 µg/l) were evaluated as having marginally insufficient iodine status, and Austria (98–120 µg/l), Poland (>100 µg/l), and Sweden (>100 µg/l) were found to have adequate iodine status.

WHO, UNICEF, and ICCIDD recommend that the optimal daily intake of iodine should be 90 µg for preschool children (0–59 months), 120 µg for school-children (6–12 years), 150 µg for adults (above 12 years), and 200 µg for pregnant and lactating women (WHO/UNICEF/ICCIDD, 2001; WHO, 2004a).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The physiological regulation of the thyroid gland by iodine is complex, involving feedback mechanisms at several biochemical and physiological steps that depend on the amount of iodine and the rate of administration.

7.1 Absorption

Molecular iodine has been reported to be readily absorbed through the lungs and gastrointestinal tract. In a study in which radioiodine (as I_2 vapour) was inhaled by human volunteers, essentially all of the inhaled iodine was cleared from the respiratory tract with a half-time of approximately 10 min (Black & Hounam, 1968; Morgan et al., 1968). Mucociliary clearance resulted in much of the inhaled iodine being transferred to the gastro-intestinal tract. Relatively rapid absorption of inhaled iodine is supported by studies in mice, rats, dogs, and sheep (Willard & Bair, 1961; Bair et al., 1963).

Inorganic compounds of iodine are also rapidly absorbed when inhaled in vapour or aerosol form. Monkeys that inhaled particulate aerosols containing sodium iodide retained the inhaled iodide with a half-life of about 10 min (Thieblemont et al., 1965; Perrault et al., 1967). Relatively rapid absorption of iodine through the lungs has also been demonstrated in mice and sheep that inhaled radioiodine as either sodium iodide or silver iodide particulate aerosols (Willard & Bair, 1961; Bair et al., 1963), as well as in rats and dogs exposed to caesium chloride aerosols containing ^{131}I (McClellan & Rupprecht, 1968; Thomas et al., 1970).

Ingestion of iodine in the form of water-soluble salts typically results in 100% absorption from the gastro-intestinal tract. Ingested inorganic iodine and iodate are reduced to iodide in the gut and almost completely absorbed by the small intestine. In seven euthyroid adults who ingested a single tracer dose of ^{131}I, <1% of the administered radiolabel was found in the faeces, suggesting nearly complete absorption of the ingested radioiodine (Fisher et al., 1965). Similarly, 20 other euthyroid adults receiving daily oral doses of potassium iodide for 13 weeks had daily iodine urinary excretion levels of approximately 80–90% of the estimated daily intake, also suggesting near-complete absorption (Fisher et al., 1965). In yet another acute ingestion study of nine healthy adults, urinary and thyroid radioiodine accounted for 97% of a single ingested traced dose of radioiodine; and two individuals ingesting stable iodide (compound not specified) in the same study had similar results (Ramsden et al., 1967). More recently, a faecal excretion range of 1–2% was reported (Larsen et al., 1998; Hays, 2001).

Gastrointestinal absorption of iodine appears to be similar in children, adolescents, and adults, based on 24-h thyroid radioiodine uptake levels following oral administration (Oliner et al., 1957; Van Dilla & Fulwyler, 1963; Cuddihy, 1966). However, uptake from oral administration to newborns has been shown to be lower than that for older infants and adults, with uptakes estimated to range from 2% to 20% for other than the most soluble forms (Ogborn et al., 1960; Morrison et al., 1963; ICRP, 1996).

Iodine in foods appears to be almost completely absorbed. A dietary balance study in which 12 healthy adult women were given daily intakes of 170–180 µg for two 7-day periods revealed that 96–98% of the daily intake was excreted in the urine, indicating near-total absorption of the administered dose (Jahreis et al., 2001). The near-complete absorption of iodine in cows' milk has also been demonstrated (Comar et al., 1963; Cuddihy, 1966). The bioavailability of iodine from normal diets rich in dairy products was described in a two-period dietary balance study in 12 healthy adult German women. The mean iodine intake amounted to 175 ± 10 µg/day in the form of solid food and 27 ± 15 µg/day in fluid form. Milk and dairy products represented the main source of iodine (37%). Iodine was predominantly excreted in the urine (89%) (171 ± 45 µg/day) and the faeces (11%) (20 ± 11 µg/day). The resulting iodine balance was approximately +5%.

Dermal absorption of iodine was studied in human subjects receiving topical applications of ^{131}I as potassium iodide or molecular iodine (Harrison, 1963). In one part of this study, topical applications of tracer concentrations of a $K^{131}I$ aqueous solution were administered to a 12.5-cm^2 area of one forearm on each individual.

Using 3-day cumulative urine radioactivity as a measure, absorption was estimated to be approximately 0.1%. In another part of the study, two women received similar topical applications of aqueous tracer $^{131}I_2$ along with 0.1 mg of $^{127}I_2$ carrier. The absorption was estimated to be 0.06–0.09% of the applied dose. In the same study, when a 12.5-cm^2 area of the skin was exposed to iodine vapour for 30 min or 2 h, absorption was found to vary depending on the amount of $^{127}I_2$ carrier in the vapour. At the lowest carrier amount (~0.8 mg applied to the skin), the absorption of ^{131}I was 1.2% of the activity that was on the skin at the end of the 2-h exposure. This conclusion is supported in a study by Gorodinskiy et al. (1979), in which the whole-body skin of seven human male volunteers was exposed for 4 h to a low concentration (~4 Bq/l) of ^{131}I gas with protection against inhalation. Accumulation of ^{131}I in the thyroid was used as the measure of dermal uptake. The results were compared with those from a previous inhalation study, and it was determined that, for comparable air concentrations, dermal absorption was 1–2% of the inhalation uptake.

7.2 Distribution

The distribution of absorbed iodine is similar, regardless of the particular route of exposure to inorganic iodine. In a study in which human subjects were exposed via ingestion to tracer levels of radiolabelled iodine as sodium iodide, approximately 20–30% of the iodine was distributed to the thyroid, and 30–60% was excreted in the urine in about 10 h. Essentially the same results were seen following ingestion of a tracer dose of $Na^{132}I$ (Morgan et al., 1967a,b). Similar results were obtained when human volunteers inhaled tracer levels of radioiodine as I_2 (Black & Hounam, 1968). Similar results were seen in monkeys that inhaled particulate aerosols of sodium iodide and in monkeys ingesting iodide (Thieblemont et al., 1965; Perrault et al., 1967).

Dietary iodine absorption and incorporation are reduced by smoking, thiocyanates, isothiocyanates, nitrates, fluorides, calcium, magnesium, and iron in food and water (Ubom, 1991). Large amounts of absorbed iodine — e.g. from radiological contrast media, from iodide liberated from erythrosine, from the antiarrhythmic drug amiodarone, from water purification tablets, from skin and dental disinfectants — also reduce iodine uptake, resulting in the production of iodine deficiency symptoms (European Commission, 2002).

The human body contains approximately 10–15 mg of iodine, of which about 70–90% is in the thyroid gland, where it is involved in the synthesis of the thyroid hormones triiodothyronine, or T_3, and tetraiodothyronine, or T_4, also known as thyroxine (Stather & Greenhalgh, 1983; Cavalieri, 1997; Hays, 2001). The normal serum iodine level ranges from 50 to 100 µg/l, with approximately 5% of the iodine in inorganic form and 95% in organic form, primarily as T_3 and T_4 (Wagner et al., 1961; Fisher et al., 1965; Nagataki et al., 1967; Sternthal et al., 1980).

Iodide is primarily confined to the extracellular fluid, with the exception of tissues that possess specialized transport mechanisms for the accumulation of iodide, including the thyroid, salivary glands, gastric mucosa, choroid plexi of the ventricles of the brain, mammary glands, placenta, and sweat glands (Brown-Grant, 1961).

Serum iodide concentrations typically range from 5 to 15 µg/l, with total extracellular iodide content being about 85–170 µg, assuming an extracellular fluid volume of approximately 17 litres (Cavalierei, 1997; Saller et al., 1998). Iodide concentrations in the thyroid are usually 20–50 times those of serum, but concentrations in excess of 100 times those in the blood occur when the thyroid gland is stimulated by TSH released by the anterior pituitary. Thyroid iodide concentrations more than 400 times those in blood have been reported (Wolff, 1964). The iodide actively transported into the thyroid follicle is oxidized to molecular iodine and is bound to the amino acid tyrosine in thyroglobulin in the colloid to produce the thyroid hormones T_3 and T_4 and their various synthesis intermediates and degradation products. The uptake of iodide into the thyroid is dependent upon the intake of iodide into the body, with the percentage of thyroid intake increasing with decreasing levels of iodide intake (Delange & Ermans, 1996).

The thyroid hormones are lipophilic and can cross the placental barrier. Thus, maternal exposure to iodine typically results in exposure of the fetus to thyroid hormones (ICRP, 2001). Accumulation of iodide in the fetal thyroid commences in humans at about 70–80 days of gestation and precedes the development of thyroid follicles (Evans et al., 1967; Book & Goldman, 1975). Fetal iodide uptake increases with the development of the fetal thyroid and reaches its peak at approximately 6 months of gestation (Aboul-Khair et al., 1966; Evans et al., 1967).

Uptake of iodide by the thyroid gland is 3–4 times greater during the first 10 days of postnatal life than in adults, but declines to adult levels after about 10–14 days of age (Van Middlesworth, 1954; Ogborn et al., 1960; Fisher et al., 1962; Kearns & Philipsborn, 1962; Morrison et al., 1963).

7.3 Metabolism

The metabolism of absorbed iodine is similar, regardless of the route of exposure to inorganic iodine. Ingested sodium iodide and inhaled methyl iodide (CH_3I) and molecular iodine all appear to undergo rapid

conversion to iodide (Morgan & Morgan, 1967; Morgan et al., 1967a,b, 1968; Black & Hounam, 1968). However, it has been suggested that by-products of metabolic reactions in the gastrointestinal tract may differ for iodine and iodide, and these may be responsible for reported differences in some reported effects (Sherer et al., 1991).

The metabolic process involved in the synthesis of thyroid hormones is as follows. The iodide ion is actively transported from the blood to the cytosol of thyroid follicular cells. At the same time, the follicular cells are synthesizing thyroglobulin, a high molecular weight glycoprotein that contains about 5000 amino acids, over 100 of which are tyrosines that can serve as the site of iodination. The completed thyroglobulin is then transferred to the colloid by the process of exocytosis. Since negatively charged I^- cannot bind to tyrosine, the iodine ions are converted to I_2 by the action of peroxidase before being released into the colloid to bind with the tyrosine residues on thyroglobulin. As iodine attaches to a tyrosine on the thyroglobulin molecule in the colloid, monoiodotyrosine (T_1) is formed; a second iodination yields diiodotyrosine (T_2). The next step is the coupling of two T_2 molecules to form T_4 or one T_1 and one T_2 to form T_3. Droplets of colloid eventually re-enter the follicular cells by pinocytosis and merge with lysosomes, which break down the thyroglobulin, cleaving off molecules of T_3 and T_4. T_1 and T_2 are also released, but they undergo deiodination, with the released iodine being reused to synthesize more T_3 and T_4. The lipid-soluble T_3 and T_4 diffuse through the plasma membrane to enter the blood, where more than 99% of both combine with blood transport proteins, primarily thyroxine-binding globulin. This process in under the control of TSH from the anterior pituitary, which is released in response to thyrotropin releasing hormone from the hypothalamus as a result of low blood thyroid hormone level or lowered metabolic rate or body temperature (Guyton & Hall, 1996).

The primary metabolic pathways for iodine outside the thyroid gland involve the catabolism of T_3 and T_4 and include deiodination reactions, ether bond cleavage of thyronine, oxidative deamination and decarboxylation of the side-chain of thyronine, and conjugation of the phenolic hydroxyl group on thyronine with glucuronic acid and sulfate. Monodeiodination of T_4 to T_3 is the major source of production of peripheral T_3, which has a greater hormonal potency than T_4, and, together with the production of 3,3′,5-triiodo-L-thyronine, account for about 80% of total T_4 turnover in humans (Engler & Burger, 1984; Visser, 1990). Iodothyronine deiodinases also catalyse the inactivation of T_4 and T_3 (Darras et al., 1999; Peeters et al., 2001). Deiodination is catalysed by selenium-dependent deiodinase enzymes.

Oxidative deamination and decarboxylation of the alanine side-chain of the iodothyronines represent approximately 2% and 14% of total T_3 and T_4 turnover, respectively (Braverman et al., 1970; Gavin et al., 1980; Pittman et al., 1980; Visser, 1990). The enzymes that catalyse these reactions have not been well characterized.

Sulfate conjugation of the phenolic group of iodothyronines occurs in the liver and probably in other tissues. In humans, this reaction in the liver is catalysed by phenolic arylsulfotransferase (Young, 1990). Iodothyronines having one iodine moiety on the phenolic ring are preferentially sulfated (Sekura et al., 1981; Visser, 1994), with the sulfated products then undergoing deiodination.

Glucuronide conjugation of the phenolic hydroxyl group of the iodothyronines also occurs in the liver, and probably in other tissues as well. While the identity of the glucuronyltransferase enzymes that participate in the conjugation of iodothyronines in humans has not yet been determined, such activity has been shown to occur in rats for microsomal bilirubin, *p*-nitrophenol, and androsterone uridine diphosphate–glucuronyltransferases (Visser et al., 1993).

A minor pathway of metabolism of iodotyrosines under normal conditions is ether bond cleavage. This mechanism does explain, however, the observation of diiodotyrosine in serum of some patients who received high dosages of T_4 or who had severe bacterial infections (Meinhold et al., 1981, 1987, 1991).

7.4 Elimination and excretion

The principal route of excretion of iodine from the human body is the urine, primarily as iodide (Bricker & Hlad, 1955; Walser & Rahill, 1965). Urinary excretion accounts for >97% of the elimination of absorbed iodine, with faeces accounting for another 1–2% (Larsen et al., 1998; Hays, 2001). However, not all iodide filtered by the kidney remains in the urine. Under steady-state conditions of radioiodine concentration, the renal plasma clearance of radioiodine was about 30% of the glomerular filtration rate, suggesting tubular reabsorption of the element (Vadstrup, 1993). Studies of the renal clearance of radioiodide in dogs provide further evidence for tubular reabsorption of iodide (Walser & Rahill, 1965; Beyer et al., 1981). The precise mechanism of this reabsorption has not been clearly established.

Glucuronide and sulfate conjugates of T_3, T_4, and their metabolites are secreted into the bile. Total biliary secretion of T_4 and metabolites was approximately 10–15% of the daily metabolic clearance of T_4 (Myant, 1956; Langer et al., 1988). In rats, about 30% of T_4 clearance has been reported to be accounted for by the

biliary secretion of the glucuronide conjugate and 5% as the sulfate conjugate. Once secreted, the conjugates undergo extensive hydrolysis, with reabsorption of the iodothyronine in the small intestine (Visser, 1990).

Absorbed iodine can also be excreted in breast milk, saliva, sweat, tears, and exhaled air (Cavalieri, 1997). In an adult patient who received an oral tracer dose of radioiodine (^{123}I), approximately 0.01% of the dose was recovered in the tears over a 4-h period, with peak activity 1 h after dosing (Bakheet et al., 1998). The radioactivity was still present in tears 24 h post-exposure. The secretion of iodine in human saliva has also been observed (Brown-Grant, 1961; Wolff, 1983; Mandel & Mandel, 2003), although the relative contribution of this route to overall excretion of iodine is probably minimal. Appreciable amounts of iodide can also be excreted in the sweat under conditions of strenuous physical activity (Mao et al., 2001).

The elimination of iodide in the breast milk of humans has been substantially documented and is discussed in section 6.2 of this CICAD (Hedrick et al., 1986; Spencer et al., 1986; Dydek & Blue, 1988; Lawes, 1992; Robinson et al., 1994; Rubow et al., 1994; Morita et al., 1998). A transfer coefficient of 0.12 day per litre of milk (with group values of 0.043 and 0.37 day per litre for low- and normal-excretion groups) has been estimated for ^{131}I from intake to breast milk (ratio of steady-state ^{131}I concentration in breast milk to ^{131}I intake rate) (Simon et al., 2002). The fraction of absorbed iodide excreted in breast milk is a function of both thyroid status and iodine intake, with a larger fraction of the absorbed dose excreted in breast milk in the hypothyroid state. Morita et al. (1998) reported the case of a hyperthyroid woman who received an oral tracer dose of Na^{123}I during lactation and excreted approximately 2.5% of the dose over a 5.5-day period. Similarly, about 2.6% of an oral dose was excreted in breast milk in another hyperthyroid patient (Hedrick et al., 1986). In contrast, a hypothyroid patient administered Na^{123}I orally excreted 25% of the radioiodine in her breast milk in 41 h (Robinson et al., 1994).

Human exposure from breast milk is addressed above in section 6.4.

The whole-body elimination half-time of absorbed iodine has been estimated to be approximately 31 days in healthy adult males, although considerable inter-individual variability exists (Van Dilla & Fulwyler, 1963; Hays, 2001).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Short-term exposure

In a three-part experiment, the effects of various iodine salts were studied in female Sprague-Dawley rats (Cantin, 1967). In the first experiment, 10 rats per dose group were administered gavage doses of 0.81 or 0.99 mg of sodium iodide, potassium iodide, ammonium iodide (NH_4I), or magnesium iodide ($MgI_2 \cdot 8H_2O$) per kilogram body weight (plus a control group) twice daily for 9 days. In the second experiment, 10 animals were put on food restriction to render their body weight equal to that of another group of 20 rats that were dosed with sodium iodide at a concentration equivalent to 0.99 mg of iodine per kilogram body weight per day for 9 days. A control group of 10 rats was used in experiment 2. In the third experiment, a group of 10 control animals was compared with a group of 10 thyroparathyroidectomized rats and a group of 10 parathyroidectomized animals. Beginning 5 days after surgery, all animals in experiment 3 received daily doses of 0.81 mg of iodine per kilogram body weight for 15 days. The animals treated with iodides developed generalized erythema, which was completely abolished by thyroparathyroidectomy and markedly diminished by parathyroidectomy. Muscular cramps of approximately equal intensity were induced in all treated groups, being evident by day 2 and steadily increasing in severity with time. All animals had severe muscular rigidity, and 50% mortality was observed in sodium iodide–treated animals in experiment 1. Of those that died, all showed laboured breathing prior to death. Mortality was highest in magnesium iodide–treated rats. Pronounced lesions were located on the intercostals muscles, the quadriceps, and the triceps brachii. Less severe lesions were found in the muscles of the forelimbs and hindlimbs, the glutei, and the intrinsic muscles of the larynx (Cantin, 1967).

8.2 Medium-term exposure

Weanling rats (BB/Wor strain) with an inbred susceptibility to autoimmune thyroiditis showed an increased incidence of thyroid autoimmunity when administered 0.05% iodide in their drinking-water for 8 weeks (daily dose ~85 mg/kg body weight). This autoimmunity was characterized by a lymphocytic infiltration of the thyroid in 27 of 35 (77%) iodide-exposed 1-month-old animals. Thyroid weights and levels of antithyroglobulin antibodies were significantly increased in the iodide-treated group (Allen et al., 1986). In Buffalo strain rats (a Sprague-Dawley strain) thymectomized to increase the incidence of lymphocytic thyroiditis, the administration of 0.05% iodide to drinking-water for 12 weeks (average dosage ~70 mg/kg body weight per day) resulted in a significant increase in the

incidence of lymphocytic thyroiditis, accompanied by increased serum titres of antibodies to thyroglobulin and increased serum TSH concentrations (Allen & Braverman, 1990).

Cornell C strain (CS) chickens fed a regular diet and given drinking-water containing 0, 2, or 20 mg of iodine per decilitre for 10 weeks were examined for lymphocytic infiltration of the thyroid. Autoantibodies for thyroglobulin, T_3, and T_4 were also measured. Thyroglobulin, T_3, and T_4 antibodies increased in groups that received iodine, and the degree of lymphocytic infiltration of the thyroid glands increased in a dose-dependent manner. Iodine did not cause hypothyroidism at the doses used following 4 weeks of exposure (Bagchi et al., 1985).

A study using male Wistar rats (36 per group) compared the results of dietary administration of iodide (0.0635 mg of sodium iodide per kilogram body weight per day) in water for 21 days with control rats receiving tap water. The effects on normal rats and thyroparathyroidectomized rats were compared. In iodine-treated rats, mean body weights were significantly lower in the thyroparathyroidectomized group than in controls (Krari et al., 1992).

Female Wistar rats were fed diets containing iodine at concentrations equivalent to 0.015, 0.077, 0.15, or 0.23 mg/kg body weight per day for 10 weeks. The thyroids of animals in the two highest dose groups were significantly larger than those in the lowest dose group. The size of the thyroid was increased in a dose-dependent fashion, and the production of thyroglobulin antibodies was also increased in a dose-dependent fashion (Fischer et al., 1989).

Twenty-five thyroiditis-prone BB/W rats were prenatally and postnatally exposed to iodine in drinking-water at dosages equivalent to 0, 0.059, or 59 mg/kg body weight per day for about 12 weeks (Li & Boyages, 1994). These rats were exposed prenatally through maternal drinking-water and then postnatally for 12 weeks. An increase in the number of lysosomes and lipid droplets was observed in the treated animals, especially in the higher exposure group. There was also evidence of dilated rough endoplasmic reticulum and swollen mitochondria with disrupted cristae in the thyrocytes of iodine-treated animals. All changes were more frequently seen in the high-iodine dose group (Li & Boyages, 1994).

In a study by Newton & Clawson (1974), 62 pigs (7–8 per dosage group) were fed various concentrations of iodine as calcium iodate [$Ca(IO_3)_2$] in the diet for 97–111 days at average daily dosages of 0, 3.41, 6.8, 13.6, 54.6, 109, or 218 mg of iodine per kilogram body weight. Animals in the two highest dosage groups had body weights (72.2 kg and 55.5 kg, respectively) significantly lower than controls (91.5 kg). This corresponded to significantly reduced food intakes in the respective treated versus control groups. Thyroid weights increased across all dosage groups from 82.0 mg/kg body weight in the control group to 237.0 mg/kg body weight in the high-dose group. Whether decreased food consumption in treated animals was a direct effect of absorbed iodine or was due to taste avoidance was not determined (Newton & Clawson, 1974).

Female calves (seven per treatment group) were fed diets containing the equivalent of 0, 0.011, 0.2, 1.0, 1.98, or 3.96 mg of iodine per kilogram feed twice daily for 5 weeks beginning at 4 days of age. A significant decrease in weight gain was found in the high-dose group (34.3%) compared with controls (38.9%). Food intake was correspondingly decreased between the control (0.86 kg/day) and high-dose (0.75 kg/day) groups. Blood packed cell volume also decreased between the control and high-dose groups, and clinical signs, including nasal discharge and lacrimation, were seen in both the 1.98 mg/kg feed dose group (5/7 calves) and the 3.96 mg/kg feed group (7/7 calves) (Jenkins & Hidiroglou, 1990).

The spontaneous incidence of lymphocytic thyroiditis in the Buffalo strain rat (a Sprague-Dawley strain) was increased after neonatal thymectomy (Noble et al., 1976). In thymectomized Buffalo rats, 12 weeks of exposure to 0.05% iodide in drinking-water (approximately 70 mg/kg body weight per day) resulted in a significant increase in the incidence of lymphocytic thyroiditis (73%) compared with a control group that received tap water (31%) (Allen & Braverman 1990). The treatment group also had significantly higher serum TSH concentrations and significantly higher serum titres of antithyroglobulin antibody. Dietary iodine intake was approximately 0.05 mg/kg body weight per day.

In a study in which cattle were administered doses equivalent to 0.2, 1, or 5 mg of iodine per kilogram body weight per day in water for 6 months, 2 of 10 calves in the high-dose group died by 10 weeks and had severe bronchopneumonia, keratitis, and dermatitis. Lung lesions were observed in 5 of 10 high-dose animals, and 3 of 10 animals in the low-dose group had slight gross lesions in the apical lobes, comprising 5–10% of lung tissue. Squamous metaplasia of tracheal epithelium occurred in calves in the high-dose group. Squamous metaplasia was evident in the salivary glands of 2 of 3 high-dose calves and 1 of 10 mid-dose calves. High-dose calves had significantly heavier thyroids and significantly lower body weights (Mangkoewidjojo, 1979).

Rats exposed to concentrations of 0, 1, 3, 10, or 100 mg of iodine or iodide (as sodium iodide) per litre of drinking-water for 100 days showed compound-specific changes in thyroid weights, which were dependent on

both dose and sex of the exposed animals. Increases in thyroid weights of males were seen at all doses of iodide, but not iodine. A decrease in thyroid weight was seen in females at the highest dose only, and only with iodide (Sherer et al., 1991).

Groups of BB/W rats were exposed to either 0.043 or 42.6 mg of iodine per kilogram body weight per day in drinking-water. A separate control group of BB/W rats was fed sterilized tap water (0.002 mg/kg body weight per day), and an additional control group of Wistar Furth rats was given sterilized tap water. Treatment commenced at breeding and continued through pregnancy and lactation. Normal histology was observed in all rats from birth until 6 weeks. Offspring were maintained on the same iodine load as the parents. The development of lymphocytic thyroiditis and follicular disruption was accelerated by the amount of iodine dose at 12 and 15 weeks. The grade of lymphocytic infiltration correlated with the iodine load at the same age. The number of cells expressing Ia antigen and Il-2 receptor in the interfollicular areas increased significantly with both dose and duration of exposure. The number of helper T cells in the lymphocytic aggregates decreased significantly with increased iodine load (Li et al., 1993).

Gao et al. (2002) studied the dose–response relationship between the iodine dose administered and the morphology of the thyroid gland in mice. Seven groups of mice were fed with distilled water containing potassium iodate at doses of 50, 250, 500, 1000, 1500, 2000, or 3000 µg/l for 100 days. Stereological parameters of the thyroid follicles and follicular cavities were measured, and the thyroid gland was weighed. Thyroid weights, both absolute and relative, were found to be proportional to the iodine dose, and the effects on thyroid follicle and follicular cavities showed similar dose-dependent tendencies. A dose–response relationship was observed between the morphological stereology of the thyroid follicle and follicular cavities at doses of 250 µg/l and above. The 50 µg/l dose was the NOAEL of potassium iodate in this study.

8.3 Long-term exposure and carcinogenicity

Female Holstein cows were administered iodine at dosages equivalent to >68–600 mg/kg body weight per day for up to 7 years. Clinical signs in the high-iodine-diet cows included coughing, nasal discharge, and decreased milk production, which were found to be reversible within 4 weeks of reducing the iodine in the diet to a normal level (Olson et al., 1984).

In another study, Fischer 344 rats were given 0, 10, 100, or 1000 mg of potassium iodide per kilogram in the drinking-water for 2 years (0, 0.55, 5.31, and 53.0 mg/kg body weight per day in males and 0, 0.66, 6.73, and 66.6 mg/kg body weight per day in females). Increased colloid in the follicular lumen and flattened epithelia, but no tumours, were detected in the thyroid gland. In the high-dose group, 7 of 80 rats (4 males, 3 females) had squamous cell carcinomas in the submandibular salivary gland. The difference was not statistically significant for the sexes separately, but was significant for both sexes combined ($P = 0.014$). In addition, 65 of 80 rats (31 male, 34 female) in the high-dose group exhibited lobular atrophy and ductular proliferation, and 55 of 80 rats (25 male, 30 female) exhibited squamous metaplasia in the submandibular gland (Takegawa et al., 1998, 2000). Survival was decreased in the high-dose group in both males and females, but no treatment-related effects were observed in tissues other than thyroid and the salivary gland.

In a two-stage carcinogenicity study, Fischer 344 rats were given potassium iodide (1000 mg/l in drinking-water for 82 weeks) after an initiating dose of *N*-bis(2-hydroxypropyl)nitrosamine, or DHPN (2800 mg/kg body weight). Thyroid follicular cell carcinoma was found in 18 of 25 of the treated animals, while this effect was seen in just 2 of 19 of the controls given DHPN only (Takegawa et al., 2000).

In another two-stage carcinogenicity study (Kanno et al., 1992), the thyroid tumour–promoting effects of iodine deficiency and iodine excess were investigated to estimate an optimal iodine intake range that would not promote the development of thyroid neoplasias. In this study, iodine was administered in drinking-water to groups of 20 6-week-old male F344 rats following an intramuscular initiation dose of 2800 mg of DHPN per kilogram body weight. The dosage was supplemented with various amounts of potassium iodide up to 260 mg/l in drinking-water to generate conditions ranging from severe iodine deficiency to severe iodine excess. In rats not pretreated with DHPN, iodine deficiency produced diffuse thyroid hyperplasia, together with a decrease in T_4 and an increase in TSH. Iodine excess produced colloid goitre, normal serum T_4, and slightly decreased TSH. In DHPN-treated rats, high tumour incidences (up to 85%) were observed in animals given less than 0.80 µg of iodine per day; lowest tumour rates (<5%) were observed in animals receiving 2.6–760 µg of iodine per day. In two groups receiving 2300 and 3000 µg of iodine per day, the thyroid tumour rates were 20% and 10% (Kanno et al., 1992).

8.4 Irritation and sensitization

The ability of iodine vapour to cause respiratory irritation has been demonstrated in guinea-pigs (Amdur, 1978). One-hour exposures to average airborne iodine vapour concentrations of 8.9 mg/m^3 and above resulted in statistically significant increases in airway resistance,

and concentrations of 32 mg/m^3 and greater caused a decrease in breathing rate (Amdur, 1978).

8.5 Genotoxicity and related end-points

A number of studies have shown that iodine does not cause mutagenic effects. Solutions of potassium iodide, molecular iodine, or povidone-iodine at concentrations of 0.1–10 mg/ml did not cause mutagenic effects in L5178Y mouse lymphoma cells or transforming activity in Balb/c3T3 cells grown in culture (Merkle & Zeller, 1979; Kessler et al., 1980). No lethal mutations were produced in *Drosophila melanogaster* when eggs were incubated in molecular iodine at 0.38 mg/ml or potassium iodide at 0.75 mg/ml (Law, 1938). Molecular iodine did not cause mutagenic activity in the His+ revertant assay in *Saccharomyces cerevisiae* (Mehta & von Borstel, 1982).

Sodium iodate ($NaIO_3$) was found not to be mutagenic in the bacterial Ames assay, the mouse bone marrow micronucleus test, or the recessive lethal test in *Drosophila melanogaster* (Eckhardt et al., 1982).

Iodide is a free radical scavenger and has been shown to decrease hydrogen peroxide–induced reversion in the TA104 strain of *Salmonella typhimurium* (Han, 1992).

8.6 Reproductive and developmental toxicity

In a series of studies, Arrington et al. (1965) investigated the survival of pups, duration of parturition, and presence/absence of signs of lactation in laboratory animals given iodine, as sodium or potassium iodide, in the diet.

Long-Evans rats administered iodine at 2500 mg/kg in the diet for 12 days in the latter part of gestation had an increased incidence of death in the neonates, with <10% of the young surviving for 3 days. There was also an increase in parturition time, with about 25% of the rats having times of 24 h or more. No signs of the beginning of lactation were observed (Arrington et al., 1965).

In pups of Syrian hamsters fed diets containing iodine at 2500 mg/kg during the latter part of gestation for 12 days, feed intake was reduced approximately 10% compared with controls, and the weaning weights of the surviving young were significantly less at 21 days postpartum. Pup survival, gestation and parturition time, and lactation were not affected by treatment (Arrington et al., 1965).

Dutch and New Zealand rabbits were fed diets containing iodine at 250, 500, or 1000 mg/kg (whether potassium or sodium iodide not clearly specified) for 2–5 days before parturition. At the dose levels of 250 or 500 mg/kg fed for 2 days prior to parturition, the survival of the pups was decreased by two thirds. At longer durations of dosage or at higher doses, the survival was <5%. The young were normal in size and development, but generally died within the first few hours after birth (Arrington et al., 1965).

Pregnant pigs receiving diets containing 1500 or 2500 mg of iodine (as potassium iodide) per kilogram for the last 30 days of gestation and allowed to litter normally were not affected by dietary levels of iodine shown to be toxic to rabbits and rats. Lactation and body weights of pigs after 2 weeks of nursing were not affected (Arrington et al., 1965).

9. EFFECTS ON HUMANS

Iodine is an essential component of the thyroid hormones T_3 and T_4, which are essential for growth, neuronal development, and regulation of metabolic rate. Without adequate dietary iodine intake, the thyroid gland cannot function optimally, and signs of thyroid insufficiency will ultimately affect necessary physiological processes. While both insufficiencies and excessive intake can result in adverse health outcomes, inadequate iodine intake is a major problem in the world today, affecting approximately one sixth of the world's population (Maberly, 1994; MAF, 2000).

Iodine deficiency disorders have been acknowledged to be a significant health problem in 130 countries, variously estimated to affect 740 million to 2.2 billion individuals (Vitti et al., 2001; WHO/UNICEF/ICCIDD, 2001; Delange et al., 2002; Hetzel, 2002; Delange & Hetzel, 2003; WHO, 2004b). Iodine deficiency disorders are related to the degree of iodine deficiency. In a number of European countries characterized by mild to moderate iodine deficiency, neurological deficits or minor neuropsychological impairments have been described. Urinary iodine excretion ranged from 30 to 170 µg/l, millions of people were at risk of iodine deficiency disorders, 97 million were affected by goitre, and 0.9 million had impaired mental development (Vitti et al., 2001).

Iodine deficiency disorders may occur from fetal development through adulthood. Spontaneous abortion (miscarriage), stillbirths, congenital anomalies, dwarfism, increased perinatal mortality, and psychomotor defects can occur during the fetal stage. The primary effects of inadequate thyroid function in neonates and small children include cretinism, neonatal goitre, retarded growth, and brain dysfunction. In older children

and adults, goitre is the most common manifestation of thyroid insufficiency, often accompanied by some degree of impaired mental function. Compared with iodine deficiency, the excessive iodine intake can also result in adverse health sequelae, some of which are paradoxically similar to the signs of iodine insufficiency.

NOTE TO THE READER: The entry of the chemical element iodine through the oral route is typically in the monovalent anionic iodide form (I^-). Once absorbed into the thyroid, two iodide ions are enzymatically converted to an iodine molecule before incorporation into the thyroid hormones. This iodine can be eliminated from the body either as iodine or as iodide, depending on the specific mechanism of elimination. It should be noted that the literature often uses iodine and iodide interchangeably without regard to speciation, as is the case with other metals. The terms we use in this CICAD are the same as those used in the primary article cited.

9.1 Acute toxicity

A review of medical records from the New York City Medical Examiners Office (USA) revealed that, in a period of 6 years, there were 18 suicides in which adults ingested iodine tinctures (Finkelstein & Jacobi, 1937). Doses of iodine from ingestion of the tinctures ranged from 1200 to 9500 mg (17–120 mg/kg body weight), and deaths usually occurred within 48 h of ingestion. In one suicide attempt, an adult male survived the ingestion of 15 g of iodine as a potassium iodide solution; 18 h after the dose, his serum iodide concentration was 2.95 mg/ml (Tresch et al., 1974). Symptoms of toxicity that have been observed in lethal or near-lethal poisonings have included abdominal cramps, bloody diarrhoea and gastrointestinal ulceration, oedema of the face and neck, pneumonitis, haemolytic anaemia, metabolic acidosis, fatty degeneration of the liver, and renal failure (Finkelstein & Jacobi, 1937; Tresch et al., 1974; Dyck et al., 1979; Clark, 1981).

9.2 Irritation and sensitization

Van Ketel and van den Berg (1990) described eight patients who had skin reactions from topical administration of povidone-iodine (5% or 10% in petrolatum or Betadine solution, ointment, or scrub) and patch-tested positively to these applications. In five of eight patients also tested with potassium iodide in concentrations ranging from 5% to 20% in petrolatum, the reactions were negative. Open tests with iodine tincture performed in three patients were completely negative, which suggests that allergy to povidone-iodine appears not to be based on sensitization to iodine (van Ketel & van den Berg, 1990). Administration of iodine-containing radiocontrast media has induced adverse reactions, such as urticaria, angio-oedema, bronchospasm, laryngospasm, and shock. However, these reactions are likely to be caused by the high osmolality of the products, rather than by an immunoglobulin E–dependent reaction towards iodine-containing organic molecules (Sicherer, 2004).

Oral exposure to markedly excess iodide can produce skin lesions, referred to as ioderma, which are thought be a form of cell-mediated hypersensitivity and unrelated to thyroid gland function (Rosenberg et al., 1972; Stone, 1985). Characteristic symptoms include acneiform pustules, which can coalesce to form vegetative (proliferating) nodular lesions on the face, extremities, trunk, and mucous membranes. The lesions regress and heal when the excess iodide intake is discontinued. The clinical literature includes cases of ioderma that occurred subsequent to oral doses of iodide at 300–1000 mg/day (5–14 mg/kg body weight per day) (Shelly, 1967; Rosenberg et al., 1972; Khan et al., 1973; Baumgartner, 1976; Kint & Van Herpe, 1977; Kincaid et al., 1981; Soria et al., 1990; PeZa-Penabad et al., 1993). However, in many of these cases, pre-existing disease and related drug therapy may have contributed to the reaction to the iodine; thus, the dose–response relationship for ioderma in healthy people remains highly uncertain.

9.3 Endocrine and other systemic effects

The principal direct effects of excessive iodine ingestion on the endocrine system are on the thyroid gland and regulation of thyroid hormone production and secretion. Adverse effects on the pituitary and adrenal glands derive secondarily from disorders of the thyroid gland. Effects on the thyroid gland include both hypothyroidism and hyperthyroidism, both of which may involve inflammatory features (i.e. thyroiditis).

Iodine is a component of the thyroid hormones T_3 and T_4 and thus is required for the normal function of the thyroid. Insufficient intake of iodine leads to hypothyroidism and compensatory hypertrophy of the thyroid gland; in many areas, low iodine intake has led to endemic hypothyreosis and goitre.

A modest increase in the iodine intake promotes temporary increases in the uptake of iodine by the thyroid gland and the formation of organic iodine, without inhibiting the capacity to release iodine in response to physiological demand. A larger excess iodine intake inhibits iodine release from the thyrotoxic thyroid or from thyroids in which iodine release has been accelerated by TSH. Still higher iodide intakes transiently decrease the production of thyroid hormones, an effect known as the acute Wolff-Chaikoff effect (Wolff et al., 1949; WHO, 1996). In normal people, this is followed by a return to normal levels of hormone synthesis, referred to as escape from the acute Wolff-

Chaikoff effect, without a significant change in circulating hormone levels. An acute or chronic excess of iodide can also decrease circulating T_4 and T_3 levels and induce a hypothyroid state in some people who have underlying thyroid disorders. These effects are the result of a failure to escape from the acute Wolff-Chaikoff effect. Most people who experience iodine-induced hypothyroidism recover when the excess iodine intake is discontinued.

Oral exposures to markedly excess iodide can induce fevers that are thought to have an immunological basis (Horn & Kabins, 1972; Kurtz & Aber, 1982). Reported clinical cases have almost always involved a pre-existing disease, usually pneumonia or obstructive lung disease, in which potassium iodide was administered for treatment purposes, along with other drugs, including antibiotics, barbiturates, and methylxanthines. In one case, recurrent fevers occurred in an adult male who was receiving oral iodine (as potassium iodide) doses of approximately 1080 mg/day for approximately 15 years (Kurtz & Aber, 1982). The fevers stopped within 2 weeks after the potassium iodide was discontinued. In another case, an adult male developed a fever 8 days after the start of a daily regimen of approximately 1440 mg of iodine (as potassium iodide) per day for treatment of a respiratory illness; the fever stopped within 3 days after the potassium iodide was discontinued (Horn & Kabins, 1972). In another case, an adult female developed a fever after a dosage of approximately 1620 mg of iodine per day along with ampicillin to treat pneumonia (Horn & Kabins, 1972). The fever stopped within 36 h after the potassium iodide administration was discontinued. The fever returned when a challenge dose of potassium iodide was administered.

9.3.1 Hypothyroidism

Boyages et al. (1989) compared the thyroid status in groups of children, aged 7–15 years, who resided in two areas of north-central China where drinking-water iodine (as iodide) concentrations were either 462.5 µg/l (n = 120) or 54 µg/l (n = 51) (Li et al., 1987; Boyages et al., 1989). Urinary iodine concentrations were 1236 µg/g creatinine in the high-iodine group and 428 µg/g creatinine in the low-iodine group. To transform the measured urinary iodide levels into estimates of iodine intakes, steady-state baseline dietary intakes of iodide were assumed to be equivalent to the reported 24-h urinary iodine excretion rates (Konno et al., 1993; Kahaly et al., 1998). Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the urinary iodine/creatinine ratios reported by Boyages et al. (1989) can be converted to approximate equivalent iodine intake rates of 1150 µg/day (0.029 mg/kg body weight per day) and 400 µg/day (0.01 mg/kg body weight per day) for the high- and low-iodine groups, respectively. Although the subjects were all euthyroid, with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher ($P < 0.05$ using chi-squared analysis with a continuity correction factor) in the high-iodine group. The high-iodine group had a 65% prevalence of goitre and a 15% prevalence of Grade 2 goitre compared with 15% for goitre and 0% for Grade 2 goitre in the low-iodine group.

Healthy euthyroid adults (study population of 9 males and 23 females) who had no history of thyroid disease or detectable antithyroid antibodies received various daily oral doses of iodine (as sodium iodide) (Paul et al., 1988). Doses of 125, 250, or 750 µg iodine were administered twice daily (corresponding to daily doses of 250, 500, or 1500 µg, respectively) to nine females per dose group for 14 days (Paul et al., 1988). Nine males received only the 750 µg treatment (total 1500 µg/day). A control group of five age-matched males served as untreated controls. (Some females were studied at two dose levels, separated by an interval of at least 1 year.) Based on 24-h urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be approximately 200 µg/day; thus, the total iodide intake was approximately 450, 700, or 1700 µg/day (approximately 0.0064, 0.01, or 0.024 mg/kg body weight per day, assuming a 70-kg body weight).

In the same study by Paul et al. (1988), subjects who received 1700 µg/day (0.024 mg/kg body weight per day) had a statistically significant depression (5–10%) of serum concentrations of total T_4, free T_4, and total T_3 compared with pretreatment levels, and serum TSH concentrations were significantly elevated (47%) compared with pretreatment values. Hormone levels were within the normal range during treatment. In this same study, nine females received daily supplemental doses of 250 or 500 µg iodine (as sodium iodide) per day for 14 days (total intake was approximately 450 or 700 µg/day; 0.0064 or 0.010 mg/kg body weight per day), and there were no significant changes in serum hormone concentration or thyroid function.

In a similar study (Gardner et al., 1988), 30 healthy, euthyroid, adult males were randomly assigned to receive daily oral doses of 500, 1500, or 4500 µg iodine (as sodium iodide) per day for 14 days. Based on 24-h urinary excretion of iodide of 256–319 µg/day prior to the iodide supplement, the total estimated iodine intakes were 800, 1800, or 4800 µg/day, or approximately 0.011, 0.026, or 0.069 mg/kg body weight per day. In this study, there were no effects on serum thyroid hormone or TSH concentrations at the 800 µg/day intake (0.011 mg/kg body weight per day); however, intakes of 1800 or 4800 µg iodine per day (0.026 or 0.069 mg/kg body weight per day) produced small (10%), but significant, transient decreases in serum total T_4 and free T_4

concentrations and an increase (48%) in serum TSH concentration, relative to the pretreatment values.

In a study by Chow et al. (1991), 30 healthy elderly adult females without evidence of thyroid peroxidase antibodies received daily doses of 500 µg iodine (as potassium iodide) per day for 14 or 28 days. Serum concentrations of free T_4 were significantly decreased and serum TSH concentrations were significantly elevated in the women who received the iodide supplements, relative to a placebo control group. On average, the magnitude of the changes did not produce clinically significant depression in thyroid hormone levels; however, five subjects had serum TSH concentrations that exceeded 5 mU/l. The pre-existing dietary iodine intake was approximately 72–100 µg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 µg/day (0.0087 mg/kg body weight per day, based on a 69-kg body weight for women).

In another study, thyroid status was compared in 423 residents (ages 66–70 years) of Jutland, Denmark, who had iodine intakes of 40–60 µg/day (0.57–0.86 µg/kg body weight per day) and 100 residents of Iceland who had intakes of 300–350 µg/day (4.3–5.0 µg/kg body weight per day) (Laurberg et al., 1998). Subjects from the high-iodine-intake region had a significantly higher prevalence (18%) of serum TSH levels above the high end of the normal range (>4 mU/l) compared with subjects from the low-iodine-intake region (3.8%). The prevalence of serum TSH concentrations above 10 mU/l was 4.0% in the high-iodine region and 0.9% in the low-iodine region. Females in both regions had a significantly higher prevalence of elevated TSH concentrations than males. Serum concentrations of T_4 were not depressed, even in subjects with TSH concentrations that exceeded 10 mU/l. Thus, although the subjects appeared to be euthyroid, the higher iodine intakes were associated with a subclinical suppression of the thyroid gland, as indicated by a high prevalence of elevated serum TSH concentrations. All subjects with serum TSH levels above 10 mU/l had autoantibodies in serum, but antibodies were, in general, more common in East Jutland, Denmark, than in Iceland. Abnormalities in populations with low iodine intake and those in populations with high iodine intake develop in opposite directions: goitre and thyroid hyperfunction when iodine intake is relatively low, and impaired thyroid function when iodine intake is relatively high. The authors suggested that probably mild iodine deficiency partly protects against autoimmune thyroid disease, and thyroid autoantibodies may be markers of an autoimmune process in the thyroid or secondary to the development of goitre.

Szabolcs et al. (1997) conducted a comparative nursing home screening for thyroid disorders among elderly subjects (n = 119; median age 81) in three areas of Europe. The study regions were northern Hungary, a region known to be iodine deficient; Slovakia, an area of obligatory iodine fortification since the 1950s; and eastern Hungary, considered to be an abundant iodine intake area. The authors found that the prevalence of hypothyroidism increased with increasing iodine intake. Urinary iodine concentrations were 72, 100, or 513 µg iodine per gram creatinine in the nursing home residents in northern Hungary, Slovakia, and eastern Hungary, respectively. Corresponding iodine intakes were approximately 117, 163, or 834 µg/day (0.0017, 0.0023, or 0.012 mg/kg body weight per day for low [n = 119], moderate [n = 135], or high intake [n = 92], respectively). The prevalence of elevated serum TSH concentrations together with serum free T_4 concentrations below the normal range was 0.8%, 1.5%, and 7.6% in the low-, moderate-, and high-iodine groups, respectively.

Many other studies have confirmed the ability of orally administered iodide to induce hypothyroidism. Some of them are described briefly below; for further details, see the source document (ATSDR, 2004).

Seven healthy adults who had no history of thyroid disease were given a flavoured drink into which tetraglycine hydroperiodide (which releases iodide when dissolved in water) had been dissolved; the dosage was 32 mg of iodine per day for 7 consecutive days. A statistically significant decrease in serum concentration of T_4 and T_3 and a significant increase in TSH concentration occurred during the treatment (Georgitis et al., 1993). The effects of ingesting four tetraglycine hydroperiodide tablets daily (liberating 8 mg free iodine per tablet) for 3 months on thyroid size, function, and radioactive iodine uptake were studied prospectively in eight healthy volunteers at the Madigan Army Medical Center in Takoma, Washington, USA (LeMar et al., 1995). Neither hyperthyroidism nor hypothyroidism was observed. In normal subjects, a reversible TSH-dependent thyroid enlargement occurred in response to the iodine load from daily use of tetraglycine hydroperiodide water purification tablets.

In a more extensive study of similar design, eight healthy euthyroid adults ingested approximately 32 mg iodine per day as tetraglycine hydroperiodide dissolved in juice or water, for 90 days (LeMar et al., 1995). Thyroid gland volumes increased significantly during the treatment and reverted to pretreatment volumes after the iodine dosing was discontinued. Serum TSH concentrations increased significantly during treatment. None of the subjects developed clinical hypothyroidism.

Daily doses of 27 mg of iodine (as licorice lecithin-bound iodide) per day, given for 28 days to 10 healthy, euthyroid adult males, induced a statistically significant increase in thyroid gland volume (Namba et al., 1993). Serum concentrations of free T_4 and T_3 were decreased, and serum TSH and thyroglobulin concentrations were significantly elevated, although the values were all within the normal ranges. All values returned to normal within 28 days after the last iodide supplement.

When 33 healthy, euthyroid, adult males who had no history of thyroid-related illness ingested approximate daily oral doses of 0.3 or 1 mg iodine (as either I_2 or I^-) per kilogram body weight per day for 14 days (Robison et al., 1998), some changes in the status of thyroid hormone were observed. Serum TSH levels were slightly, but significantly, increased by the high dose of both I_2 and I^-, compared with a sodium chloride control group. Serum total T_4 and total T_3 were not significantly different. Irritant effects were observed as a sensation of "burned throat" in the I_2-exposed group, but not in those subjects exposed to I^-. Clinical observations, however, revealed no signs of damage to the throat. The authors noted that this effect might be expected from consumption of molecular iodine, since high concentrations are known to damage mucous membranes (Gosselin et al., 1976).

When 11 healthy euthyroid adults received 25 mg of iodine per day for 14 days in seaweed, the mean serum TSH concentrations were significantly increased, but did not exceed the normal range.

In a longer-duration experimental study, four healthy adults received a daily oral dose of approximately 1000 mg iodine per day for 11 weeks (Jubiz et al., 1977). A small, but statistically significant, decrease in the mean serum concentration of T_4 and an increase in TSH concentration were observed. The above changes were no longer evident within 1 week after the treatment was discontinued.

Zhao et al. (2000) compared the prevalence of thyroid enlargement among children 5–15 years of age with drinking-water and urinary iodine levels in residents of 65 townships in Jiangsu Province, China. The prevalences of goitre and abnormal thyroid volume increased with increasing urinary iodine concentration. The prevalences of goitre increased from 15% (802 µg iodine per litre urine) to 38% (1961 µg iodine per litre urine). The prevalences of abnormal thyroid volume increased from 5% to 17% over this same range of urinary iodine concentrations. Similarly, a high incidence of goitre was observed in two coastal Chinese villages where the average urinary iodine excretion was 1423 and 2097 mg/kg creatinine (Zhu et al., 1984). Excess iodine in household water was the likely cause of endemic goitre and elevated urinary iodine levels in the study area.

A cross-sectional survey of United States Peace Corps volunteers in Nigeria revealed a high rate of thyroid dysfunction and goitre attributable to excess iodine from water filters (Khan et al., 1998). Forty-six of 96 volunteers had enlarged thyroid glands, 29/96 had elevated serum TSH concentrations, and 4/96 had depressed serum TSH concentrations. The mean iodide concentration in filtered drinking-water was 10 mg/l, which corresponded to a daily intake of iodide from drinking-water of 50–90 mg/day. When the excess iodine was removed from the drinking-water, all measures of thyroid function returned to normal (Pearce et al., 2002).

Examples of much higher intakes (equivalent to 0.4–0.7 mg/kg body weight per day) have been reported in hypothyroid patients who consume seaweed (Tajiri et al., 1986). In this study, 22 patients with spontaneously occurring primary hypothyroidism were studied to evaluate the spontaneous reversibility of the hypothyroid state. Following restriction of iodine intake for 3 weeks, 12 became euthyroid. When seven patients in this "reversible" group were given daily doses of 25 mg iodine, all became hypothyroid again. In the remaining 10 patients in the study cohort of 22, thyroid function did not improve with restriction of iodine alone. Of the 12 determined to have reversible-type hypothyroidism, 2 patients had a history of habitual ingestion of seaweed (25.4 and 43.1 mg iodine per day, respectively); the other 10 patients ingested ordinary amounts of iodine (1–5 mg) daily. Histologically, the patients with the reversible type of hypothyroidism had focal lymphocytic thyroiditis changes in the thyroid biopsy specimen, but those with the irreversible type of hypothyroidism had more severe destruction of the thyroid gland. These results clearly demonstrate the existence of a reversible type of hypothyroidism, sensitive to iodine restriction and characterized by relatively minor histological changes in lymphocytic thyroiditis (Tajiri et al., 1986).

The prevalence of thyroid dysfunction in relation to iodine intake was studied in 1061 adults in five coastal areas of Japan that produce iodine-rich seaweed (kelp) (Konno et al., 1994). The prevalences of elevated serum TSH concentrations and urinary iodide concentrations in this population were both significantly higher in the coastal regions than in the inland regions. Serum TSH concentrations were positively correlated with the urinary iodide concentrations, and the prevalence of elevated serum TSH concentrations in the seven areas correlated positively with the prevalence of high urinary iodide concentrations (Konno et al., 1994).

Casey et al. (2005) found that T_4 deficiency in euthyroid mothers contributes to preterm birth, which in

turn could contribute to neurodevelopmental abnormalities in newborn infants born to affected mothers.

9.3.1.1 Neonatal hypothyroidism

Several case reports demonstrate that maternal exposures to excess iodine during pregnancy may induce goitre and hypothyroidism in neonates. In general, clinical cases have involved maternal exposures to several hundred milligrams of iodine per day, with the lowest reported dose being 130 mg/day (Martin & Rento, 1962; Hassan et al., 1968; Iancu et al., 1974; Penfold et al., 1978; Coakley et al., 1989; Bostanci et al., 2001). In one case, a woman ingested approximately 260–390 mg of iodine per day (3.7–5.6 mg/kg body weight per day) during pregnancy, and her infant developed goitre in utero, which was successfully treated in utero with levothyroxine; the thyroid gland and hormone status of the infant were normal at birth (Vicens-Calvet et al., 1998).

In two cases, infants died with complications related to a goitrous thyroid gland compression of the trachea; the mothers had ingested potassium iodide during their pregnancies at total doses of approximately 234 g and 324 g (Galina et al., 1962).

In a study of iodide supplementation during pregnancy in an iodine-deficient area of Denmark, 28 women received daily doses of 200 µg iodine per day from the 17th to 18th week of pregnancy through the first 12 months after delivery, and 26 women received no supplementation (Pedersen et al., 1993). Pretreatment urinary iodide levels were 51 and 55 µg/l, respectively, in the two groups, suggesting a pre-existing dietary iodine intake of approximately 75 µg/day (assuming that the urinary iodide concentration reflected the 24-h average and that urine volume was approximately 1.4 litres per day) and a total iodine intake of 275 µg/day (4 µg/kg body weight per day). There were no statistically significant differences in serum total T_4, free T_4, T_3, or TSH concentrations in the infants in the two groups at birth, and there were no abnormal values for the hormones in any of the infants.

In another study, 38 pregnant women from a potentially iodine-deficient region of Germany received daily doses of 230 µg iodine (as potassium iodide) per day during pregnancy and lactation, and 70 women received no supplementation. Pretreatment urinary iodide levels were 53 µg/g creatinine (median), suggesting a pre-existing iodide intake of approximately 90 µg/day (Liesenkötter et al., 1996) and a total iodine intake of 320 µg/day (5 µg/kg body weight per day). Thyroid gland volumes were significantly decreased in infants from the supplemented group compared with the control group (median control, 1.5 ml; median treated, 0.7 ml). One infant (1/38, 2.6%) from the supplemented group was classified as having an enlarged gland (>1.5 ml), compared with 14 (14/70, 20%) from the control group. The report indicates that "no hypothyroidism or hyperthyroidism was observed in the mothers or newborns", although the end-points evaluated, other than serum TSH, were not indicated.

9.3.2 Hyperthyroidism

Oral exposure to excess iodide can, under certain circumstances, induce hyperthyroidism. The epidemiological and clinical literature suggests that hyperthyroidism occurs most often in people who have a previous history of iodine deficiency, goitre, or thyroid diseases, including nodular goitre or Graves disease (Fradkin & Wolff, 1983; Leger et al., 1984; Paschke et al., 1994; Braverman & Roti, 1996). Cases of iodine-induced hyperthyroidism in people who were euthyroid and without apparent thyroid disease have been reported (Savoie et al., 1975; Rajatanavin et al., 1984; Shilo & Hirsch, 1986); however, only a few have provided dose information. In one case, a 72-year-old female without apparent pre-existing thyroid disease developed clinical hyperthyroidism after ingesting approximately 2.8–4.2 mg iodine per day (average of 0.05 mg/kg body weight per day) in the form of sea-kelp tablets; her thyroid status reverted to normal within 6 months after she stopped taking the tablets (Shilo & Hirsch, 1986). In another case, a 15-year-old male developed hyperthyroidism after receiving 1440 mg iodine (as potassium iodide) per day for 4 months (Ahmed et al., 1974). The thyroid status reverted to normal within 6 months after the potassium iodide was discontinued.

In a case-study, eight healthy adult euthyroid females who had non-toxic goitre received oral doses of 180 mg iodine (as a saturated potassium iodide solution) per day (2.6 mg/kg body weight per day) for 10–18 weeks (Vagenakis et al., 1972). Four of the eight patients developed clinical hyperthyroidism, which was aggravated after the iodine supplementation was stopped.

In an epidemiological study conducted in Austria, the annual incidence of hyperthyroidism was evaluated in patients examined at nuclear medicine centres (where all thyroid examinations are conducted in Austria) before and after an upward adjustment was made in the use of iodized table salt in 1991 (Mostbeck et al., 1998). The mean urinary iodide concentration was 42–78 µg/g creatinine before the adjustment and 120–140 µg/g creatinine after the adjustment; these are approximately equivalent to 77–146 µg/day (1.1–2.1 µg/kg body weight per day) and 225–263 µg/day (3.2–3.8 µg/kg body weight per day), respectively. The analysis included 392 820 patients examined between 1987 and 1995 in 19 nuclear medicine centres. A significant relative risk

of hyperthyroidism, for both Graves disease and intrinsic thyroid autonomy, was found when the annual incidences of each in the post-adjustment period (1991–1995) were compared with those in the pre-adjustment period (1987–1989). The highest relative risks were for Graves disease: 2.19 (95% confidence interval 2.01–2.38) for overt clinical disease and 2.47 (95% confidence interval 2.04–3.00) for subclinical disease. Regression analysis of the pre- and post-adjustment incidence found a significant increasing temporal trend for hyperthyroidism of both types in the post-adjustment period and no trend in the pre-adjustment period. When the post-adjustment incidence data were stratified by time periods 1990–1992 or 1993–1995 and by sex and age, higher relative risks were evident for intrinsic thyroid autonomy among males compared with females and in subjects older than 50 years compared with subjects younger than 50 years. The incidence of hyperthyroidism (all forms of overt or subclinical) was 70.1 per 100 000 in the pre-adjustment period and reached a peak of 108.4 per 100 000 in 1992, after the adjustment. During the period 1963 through 1990, salt in Austria was iodized (7.5 mg iodide per kilogram salt) to prevent goitre.

Data collected on the incidence of hyperthyroidism in Tasmania also show that a 2- to 4-fold increase in hyperthyroidism cases occurred within a few months after diets were supplemented with iodide for preventing endemic goitre from iodide deficiency (Connolly et al., 1970). The approximate supplemental dose was 80–200 µg/day from the addition of potassium iodide to bread. Mean 24-h urinary iodide excretion rates suggested a total post-supplementation iodide intake of approximately 230 µg/day (3.3 µg/kg body weight per day; range 94–398 µg/day, or 1.3–5.7 µg/kg body weight per day), some of which may have come from sources other than supplemented bread (Connolly, 1971a,b). The highest incidence of hyperthyroidism after the iodine supplementation began occurred in people over 50 years of age (Stewart, 1975; Stewart & Vidor, 1976).

A large multinational epidemiological study was conducted in Africa to evaluate the effectiveness and possible adverse consequences of the introduction of iodized salt into diets of populations residing in iodine-deficient and endemic goitre regions of Africa (Delange et al., 1999). In each study area, urine and table salt were collected from a group of 100–400 randomly selected children aged 6–14 years. Health-care facilities were surveyed for information on thyroid disease in each area. In Zimbabwe, the incidence of hyperthyroidism increased by a factor of 2.6 within 18 months after the widespread introduction of iodized salt into the diet (from 2.8 in 100 000 to 7.4 in 100 000). Females accounted for 90% of the cases, with the highest incidence in the age group 60–69 years. The most common disorders were toxic nodular goitre (58%) and Graves disease (27%) (Todd et al., 1995). Urinary iodide concentrations in children increased by a factor of 5–10 over this period. Urine samples were reported as "casual samples"; thus, there is a large uncertainty in translating the concentrations into intakes. Median urinary iodide concentrations ranged from 290 to 560 µg/l. Reported estimates of iodide intake from salt and seafood were 500 µg/day (7.1 µg/kg body weight per day) and 15–100 µg/day (0.2–1.4 µg/kg body weight per day), respectively. Increased numbers of cases of thyrotoxicosis along with an increase in urinary iodide levels (from 16 to 240 µg/l) occurred after iodized salt was introduced into the diet of an iodine-deficient population in the Kivu region of Zaire (Bourdoux et al., 1996). In contrast, orally administered iodized oil did not induce hyperthyroidism in treated adults from seven villages in Senegal. The response to 480 mg of oral iodized oil assessed at 6 and 12 months was characterized by a 35.8% increase in mean free T_4, a 25% decrease in free T_3, and a 50% decrease in TSH at 12 months associated with a significant decrease in goitre size measured in 70 treated persons compared with 65 untreated controls not receiving iodine (Lazarus et al., 1992). Iodine deficiency was treated effectively for about a year in 75 subjects aged 22 and 23 years in Zaire given a single oral dose of 47 or 118 mg iodized oil (Tonglet et al., 1992).

An epidemiological study in Switzerland examined the incidence of hyperthyroidism before and after the iodine content of salt was increased from 7.5 to 15 mg/kg (Baltisberger et al., 1995; Bürgi et al., 1998). The study population included 109 000 people. The mean urinary iodide concentration was 90 µg/g creatinine before the supplementation and 150 µg/g creatinine after the supplementation. This is equivalent to an increase in intake from approximately 170 to 280 µg iodine per day (from 2.4 to 4 µg/kg body weight per day, assuming a body weight of 70 kg). During the first year after supplementation began, the combined annual incidence of hyperthyroidism diagnosed as either Graves disease or toxic nodular goitre increased by 27% (from 62.3 per 100 000 to approximately 80 per 100 000).

9.3.3 Thyroiditis

Otherwise healthy adults living in an endemic goitre area in Germany, who had goitre but no evidence of clinical hypothyroidism or hyperthyroidism or anti-thyroid antibodies, received either a placebo or 200 µg iodine per day for 12 months (Kahaly et al., 1997). A significant decrease in thyroid volume occurred in the treated group relative to the control group. Three of 31 subjects in the treatment group (9.7%) developed elevated levels of thyroglobulin and thyroid microsomal antibodies compared with none in the control group. Two of these subjects developed hypothyroidism, and one subject developed hyperthyroidism; all three

subjects reverted to normal thyroid hormone status when the iodide supplementation was discontinued.

In a similar study, 31 adult euthyroid patients from an endemic goitre region who had goitre received 500 µg potassium iodide per day (382 µg iodine per day) for 6 months, and 31 patients received 0.125 µg T_4 per day (Kahaly et al., 1998). Six of the patients who received iodide (19%) developed high titres of thyroglobulin and thyroid microsomal antibodies, compared with none in the T_4 group. Four of the high-antibody patients became hypothyroid, and two patients became hyperthyroid. The thyroid hormone status reverted to normal and antibody titres decreased during a 6-month period following the treatment.

Koutras (1996) reported that 30% of a group of goitre patients developed thyroid autoimmunity several weeks after receiving 150 or 300 µg iodine per day.

Other studies have not found increases in autoimmunity associated with iodine supplementation (Li et al., 1987; Boyages et al., 1989).

9.4 Cancer

Benign thyroid tumours are common in humans, but carcinomas are rare, with incidence rates in the order of $1–4 \times 10^{-5}$ in men and $2–10 \times 10^{-5}$ in women (IARC, 2003). Differentiated tumours form up to 90% of all thyroid carcinomas and are usually divided into papillary and follicular carcinomas. The diagnostic criteria for these two entities have evolved during the years, making comparisons of incidence rates difficult. Furthermore, diagnostic procedures have changed markedly, and thus the proportion of microcarcinomas and silent carcinomas has increased — this is also reflected in a decreasing mortality from thyroid cancer — while increases in the reported incidence of papillary carcinomas have occurred (Franceschi & La Vecchia, 1994; Pukkala, 1995; Franceschi, 1998; Franceschi et al., 1998; Capen et al., 1999; Franceschi & Dal Maso, 1999; Verkooijen et al., 2003).

The incidence of papillary thyroid cancer was reported to be higher in geographic areas with high dietary iodine content, whereas that of follicular cancer was high in areas of endemic goitre (Williams et al., 1977; Hakulinen et al., 1986; Bakiri et al., 1998; Franceschi et al., 1998). In Austria, iodized salt was introduced into the diet in 1963 and then increased further in 1991. The mean urinary iodide concentration was 42–78 µg/g creatinine before the adjustment and 120–140 µg/g creatinine after the adjustment; these are approximately equivalent to 77–146 µg/day (1.1–2.1 µg/kg body weight per day) and 225–263 µg/day (3.2–3.84 µg/kg body weight per day), respectively (Bacher-Stier et al., 1997; Mostbeck et al., 1998). A retrospective analysis of medical records in the Tyrol region of Austria (1 063 395 inhabitants) concluded that the incidence of thyroid cancer increased from 3.1 per 100 000 for the period 1960–1970 to 7.8 per 100 000 for the period 1990–1994 (Bacher-Stier et al., 1997). The prevalence of papillary tumours appeared to increase relative to that of follicular tumours after supplementation; the ratio of papillary:follicular tumours was 0.6:1 before supplementation and 1.5:1 after supplementation. Improved diagnosis (shift towards differentiated forms of thyroid cancer that are diagnosed at earlier stages) may have contributed to the increased incidence. In support of this, a trend was observed towards increased prevalence of less advanced tumour stages in 439 patients for whom complete medical records were available. An increase in the incidence of papillary thyroid tumours, a decrease in the incidence of follicular thyroid tumours, and a decrease in mortality from thyroid tumours with time were also observed in Switzerland in 1974–1987 (Levi et al., 1991).

Two case–control studies on thyroid cancer have been conducted on populations whose iodine intakes are sufficient. A case–control study of women residents of the San Francisco Bay area of the United States examined dietary habits, including iodine intake and other variables, in 608 cases of thyroid cancer (91% papillary cancer) diagnosed during the period 1995–1998 and 558 age- and ethnicity-matched controls from random digit dialling (Horn-Ross et al., 2001). Dietary iodine intakes were estimated based on a food frequency questionnaire and published compilations of the iodine content of various foods and from the analysis of iodine in toenails. Compared with the lowest quintile (<273 µg of iodine per day), the odds ratio for the highest quintile of estimated dietary iodine intake (>537 µg/day) was 0.49 (95% confidence interval 0.29–0.84). No association was observed between thyroid cancer and toenail iodine concentration. The authors concluded that iodine exposure appears to have, at most, a weak effect on the risk of papillary thyroid cancer.

Another case–control study of residents of Hawaii, USA, examined dietary habits, including iodine intake and other variables, in 191 histologically confirmed cases (64% female) of thyroid cancer, diagnosed during the period 1980–1987, and 441 age- and sex-matched controls from five ethnic groups (Kolonel et al., 1990). Dietary iodine intakes were estimated based on the results of a dietary habits questionnaire and published compilations of the iodine content of various foods. Female cases had significantly higher dietary iodine intakes (seafood, especially shellfish, and harm ha, a fermented fish sauce) than controls, although the group mean differences were not substantial: cases, 394 µg/day (6.1 µg/kg body weight per day), and controls, 326 µg/day (5.0 µg/kg body weight per day), both based on a 65-kg body weight for women. When cases and

controls were classified according to dietary iodine intake (quartile), the odds ratios for thyroid cancer in females increased with increasing iodine intake; however, odds ratios were not statistically significant, and there were no significant trends in the odds ratio with increasing iodine intake.

Several epidemiological studies have investigated possible associations between thyroid cancer and iodine intake in populations residing in iodine-deficient regions. A cohort study compared thyroid cancer rates in iodine-sufficient and iodine-deficient regions of Sweden during the period 1958–1981. In Sweden, dietary iodine intake increased over the study period as a result of dietary supplementation, which began in 1936 and was subsequently increased in 1966 and 1971 (Pettersson et al., 1996). A multivariate model that included sex, age, dates of diagnosis, and region (i.e. iodine deficient or sufficient) as variables was applied to a sample of 5838 thyroid cancer cases to estimate the adjusted rate ratio for thyroid cancer, or ratio of the adjusted cancer incidence rate for iodine-deficient regions to that for iodine-sufficient regions. The rate ratio for papillary thyroid cancer was 0.8 (95% confidence interval 0.73–0.88), suggesting a lower rate in iodine-deficient areas. The rate ratio for follicular thyroid cancer was 1.98 (95% confidence interval 1.60–2.4) in males and 1.17 (95% confidence interval 1.04–1.32) in females. Analysis of the incidence of thyroid cancer as a function of dates of diagnosis revealed a significant trend for increasing follicular cancers in the iodine-deficient areas, but not in the iodine-sufficient areas. A significant trend for increasing papillary cancers was evident in both the iodine-sufficient and iodine-deficient regions.

A similar trend for an association of thyroid cancer incidence with the duration of residence in goitre areas was observed among thyroid cancer cases diagnosed in Sweden in 1980–1992 (Galanti et al., 1995). The trend was clearest for follicular cancer.

Another cohort study examined the prevalence of thyroid cancer during the period 1979–1985 in populations living in iodine-deficient and iodine-sufficient areas of Sicily (Belfiore et al., 1987). The mean urinary iodine excretion rate was approximately 19–43 μg/day in the iodine-deficient regions and approximately 114 μg/day in the iodine-sufficient regions. The prevalence of cold nodules among randomly selected subjects in the iodine-deficient region was significantly greater (72/1683, 4.3%) than in the iodine-sufficient group (21/1253, 1.7%). In the second phase of this study, all patients who had cold nodules in the two study areas, 911 patients from the iodine-deficient region and 2537 patients from the iodine-sufficient region (a control area), were biopsied. The prevalence of thyroid cancer among patients who had one or more cold nodules was higher in the iodine-sufficient region (139/2537; 5.48%) than in the iodine-deficient region (27/911; 2.96%). The prevalence of papillary tumours, relative to that of follicular tumours, was higher in the iodine-sufficient region (3.8) than in the iodine-deficient region (1.0). When the thyroid cancer prevalence among patients with cold nodules was adjusted for the estimated prevalence of cold nodules in the two regions, the estimated prevalence of thyroid cancer in the iodine-deficient region was significantly higher (127 in 100 000) than in the iodine-sufficient region (93 in 100 000).

In another case–referent study in northern Italy (Franceschi et al., 1989; D'Avanzo et al., 1995; Fioretti et al., 1999), an increased risk of thyroid cancer was associated with residence in endemic goitre areas (odds ratio 2.29, 95% confidence interval 1.23–4.29) for residence of 20 years or more. Franceschi et al. (1989) attributed about 60% of thyroid cases in northern Italy to be attributable to residence in an endemic goitre area and a poor diet. A significant protection against this cancer was associated with frequent use of dietary items considered to be rich in iodine (fish, green vegetables, fruit).

9.5 Susceptible populations

Individuals susceptible to iodine-induced hypothyroidism include fetuses and newborn infants, the elderly, persons who have underlying thyroid disease, and patients who have received treatment with antithyroid medications. A complete list of susceptible groups is presented in Table 3. Recovery occurs when the excess iodine is discontinued.

10. EFFECTS EVALUATION

10.1 Hazard identification and dose–response assessment

Iodine is an element essential to the normal physiological function of the human body. It is therefore essential that iodine be incorporated as part of the human diet. WHO (1996) has determined that there is a need for an average of 150 μg of iodine to be consumed daily as part of the diet, with another 50 μg/day added during pregnancy and lactation.

A number of health effects can be attributed to both deficiency and excess of iodine in the diet. While inadequate intake of iodine leads to hypothyroidism and compensatory increase in the size of the thyroid gland (goitre), excessive intake of iodine can be associated with both hyperthyroidism and hypothyroidism.

Table 3. Risk groups for iodine-induced hypothyroidism.[a]

Risk group / subgroup
• **No underlying thyroid disease**
Fetus and neonate, mostly preterm
Secondary to transplacental passage of iodine or exposure of neonate to topical or parenteral iodine-rich substances
Infant
Occasionally reported in infants drinking iodine-rich water (China)
Adult
In Japanese subjects with high iodine intake where Hashimoto thyroiditis has been excluded
Elderly
Reported in elderly subjects with and without possible defective organification and autoimmune thyroiditis
Chronic non-thyroidal illness
Cystic fibrosis
Chronic lung disease (including Hashimoto thyroiditis/chronic autoimmune thyroiditis)
Chronic dialysis treatment
Thalassaemia major
Anorexia nervosa
• **Underlying thyroid disease**
Hashimoto thyroiditis
Euthyroid patients previously treated for Graves disease with ^{131}I, thyroidectomy, or antithyroid drugs
Subclinical hypothyroidism, especially in the elderly
After transient postpartum thyroiditis
After subacute painful thyroiditis
After hemithyroidectomy for benign nodules
• **Euthyroid patients with a previous episode of amiodarone-induced destructive thyrotoxicosis**
• **Euthyroid patients with a previous episode of interferon-alpha-induced thyroid disorders**
• **Patients receiving lithium therapy**

[a] From NRC (2004).

Inflammatory reaction of the thyroid, or thyroiditis, has been described after excessive iodine intake. No definitive conclusions of the causality of the associations may be drawn at present. The limited studies available on the genotoxicity of iodides are consistently negative. Data regarding the reproductive/developmental effects of iodine/iodides on animals are limited, but human case reports show that highly excessive intake of iodine (lowest reported dose 130 mg/day) during pregnancy may result in neonatal goitre/hypertrophy. Febrile and dermal (ioderma) reactions have been reported following high-level oral intakes. No reports are available indicating respiratory sensitization by iodine or iodine compounds; people who are sensitive to povidone-iodine do not react to potassium iodide.

Increased incidence of thyroid cancer has been observed both in association with endemic hypothyroidism and with increased dietary iodine intake in endemic goitre areas. Follicular cell tumours appear to dominate in areas of poor iodine intake, whereas an apparent shift in the histopathology towards a higher prevalence of papillary cancers occurred following iodine supplementation in otherwise iodine-deficient populations (Belfiore et al., 1987; Kolonel et al., 1990; Pettersson et al., 1991, 1996; Bakiri et al., 1998; Feldt-Rasmussen, 2001). Studies of populations in which iodine intakes are sufficient have not found significant associations between iodine intake and thyroid cancer (Kolonel et al., 1990; Horn-Ross et al., 2001).

10.2 Criteria for setting tolerable intakes and tolerable concentrations for iodine

Boyages et al. (1989) compared thyroid status in groups of children 7–15 years of age who resided in two areas of China where drinking-water iodide concentrations were either 462.5 µg/l (n = 120) or 54 µg/l (n = 51). Urinary iodine concentrations were 1236 µg/g creatinine in the high-iodine group and 428 µg/g creatinine in the low-iodine group. Although the subjects were all euthyroid, with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher ($P < 0.05$) in the high-iodine group. The high-iodine group had a 65% prevalence of goitre and a 15% prevalence of Grade 2 goitre compared with 15% for goitre and 0% for Grade 2 goitre in the low-iodine group. To transform the measured urinary iodine levels into estimates of iodine intakes, steady-state baseline dietary intakes of iodide were assumed to be equivalent to the reported 24-h urinary iodine excretion rates (Konno et al., 1993; Kahaly et al., 1998). Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the urinary iodine/creatinine ratios reported by Boyages et al. (1989) can be converted to approximate equivalent intake rates of 1150 µg/day (0.029 mg/kg body weight per day) and 400 µg/day (0.01 mg/kg body weight per day) for the high- and low-iodine groups, respectively. Thus, the NOAEL for this study is considered to be 0.01 mg/kg body weight per day.

Supporting studies indicate that the NOAEL from the Boyages et al. (1989) study would be applicable for both acute and chronic-duration exposure of elderly adults, who may represent another sensitive subpopulation (Chow et al., 1991; Szabolcs et al., 1997). In the Chow et al. (1991) study, 30 healthy 60- to 75-year-old females from Cardiff, Wales, received daily doses of 500 µg iodine per day for 14 or 28 days. Serum concentrations of free T_4 were significantly decreased, and serum TSH concentrations were significantly elevated. On average, the magnitude of the changes did not produce clinically significant depression in thyroid

hormone levels; however, five subjects had serum TSH concentrations that exceeded 5 mU/l. The pre-existing dietary iodine intake was approximately 72–100 μg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 μg/day (0.0087 mg/kg body weight per day, based on a mean weight of 69 kg for women 19–64 years of age in the British National Diet and Nutrition Survey; British Nutrition Foundation, 2004). Szabolcs et al. (1997) studied elderly nursing home residents who had received long-term exposure to iodine in one of three regions where the intakes were estimated to be approximately 117, 163, or 834 μg/day (0.0017, 0.0023, or 0.012 mg/kg body weight per day for low, moderate, or high intake, respectively). The prevalence of clinical hypothyroidism was 0.8%, 1.5%, and 7.6% in the low-, moderate-, and high-iodine groups, respectively. Serum TSH concentrations were elevated as free T_4 levels were reduced ($P = 0.006$).

In a study by Paul et al. (1988), healthy euthyroid adults (nine males, nine females) who had no history of thyroid disease or detectable antithyroid antibodies received daily oral doses of 250, 500, or 1500 μg iodine (as sodium iodide) per day for 14 days. Based on 24-h urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be approximately 200 μg/day; thus, the total iodide intake was approximately 450, 700, or 1700 μg/day (approximately 0.0064, 0.01, or 0.024 mg/kg body weight per day, assuming a 70-kg body weight). Subjects who received 1700 μg/day (0.024 mg/kg body weight per day) had significantly depressed (5–10%) serum concentrations of total T_4, free T_4, and total T_3 compared with pretreatment levels, and serum TSH concentrations were significantly elevated (47%) compared with pretreatment values. Hormone levels were within the normal range during treatment. In this same study, nine females received daily doses of 250 or 500 μg iodine per day for 14 days (total intake was approximately 450 or 700 μg/day; 0.0064 or 0.010 mg/kg body weight per day), and there were no significant changes in serum hormone concentrations.

In a comparable quality study by Gardner et al. (1988), 10 healthy adult euthyroid males received daily oral doses of 500, 1500, or 4500 μg iodine (as sodium iodide) per day for 14 days. Based on 24-h urinary excretion of iodide of 256–319 μg/day prior to the iodide supplement, the total estimated intakes were 800, 1800, or 4800 μg/day, or approximately 0.011, 0.026, or 0.069 mg/kg body weight per day. In this study, there were no effects on serum thyroid hormone or TSH concentrations at the 800 μg/day intake (0.011 mg/kg body weight per day); however, intakes of 1800 or 4800 μg iodine per day (0.026 or 0.069 mg/kg body weight per day) produced small (10%), but significant, transient decreases in serum total T_4 and free T_4 concentrations and an increase (48%) in serum TSH concentration, relative to the pretreatment values.

Other data suggest an effect level of 1 mg/kg body weight per day and a no-effect level of 0.3 mg/kg body weight per day (Robison et al. 1998). This is substantially higher than comparable levels reported by Paul et al. (1988) and Gardner et al. (1988), suggesting that some people tolerate high doses of iodine without producing thyroid gland suppression.

From the Boyages et al. (1989) study, supported by the studies of Gardner et al. (1988), Paul et al. (1988), and others, a TDI of 0.01 mg/kg body weight, based upon reversible subclinical hypothyroidism, can be established by dividing the NOAEL of 0.01 mg/kg body weight per day by an uncertainty factor of 1.

An uncertainty factor of 1 was considered appropriate because the dose was a NOAEL, this was a human study, and the study cohort was considered to represent the most sensitive population. Supporting studies indicate that the NOAEL would be applicable to elderly adults, who may represent another sensitive population.

10.3 Sample risk characterization

For the general population in the United States, exposure to iodine through ambient air (average concentration, 0.7 $\mu g/m^3$) and drinking-water (<5 μg/l) led to an intake in the order of 2 orders of magnitude less than the TDI. Of the dietary items, iodinated salt and iodine food additives are by far the most important iodine sources, providing more than 50% of all dietary iodine; the average dietary intake of iodine for adult males and females in the United States is approximately 60% of the TDI. This may be contrasted with the dietary reference intake, formerly known as the recommended daily allowance, of 150 μg/day for individuals over 12 years of age (WHO/UNICEF/ICCIDD, 2001; WHO, 2004a). The dietary reference intake is the average amount of an essential nutrient that will ensure optimal physiological function for 97.5% of the population. This is not an absolute amount to be taken in on a daily basis, but rather is an amount to be consumed on average over a period of approximately 7 days (FAO/WHO, 2002).

10.4 Uncertainties in the evaluation of health risks

Iodine is a substance for which there are an extensive number of credible human data from both clinical and epidemiological studies collectively covering a broad diversity of populations and all age groups. It is also essential to normal physiological function and is necessary for human growth, development, metabolism, and nerve function. Thus, care must be taken in calculating a TDI to ensure that any such

health-based tolerable intake is not so conservative that it is below levels determined to be essential to the maintenance of human health. An uncertainty factor of 1 is commensurate with the intent of the TDI and the protection of human health. The 0.01 mg/kg body weight TDI satisfies the requirements of both protecting human health from excessive iodine exposure and ensuring that iodine exposure does not conflict with essential dietary intake levels.

The extent of the variability in the need for dietary iodine between different individuals and populations is not known, and this contributes to the uncertainty of the TDI. This variation may increase or decrease the extent of iodine supplementation needed in iodine-deficient geographic areas. This may be due to genetic variability within the global population, differences in the bio-availability of iodine in various diets, and the development of tolerance (or lack thereof) to increased iodine intake. A number of other factors potentially influencing the biological demand for iodine and the physiological regulation of iodine-containing thyroid hormones are also relevant. In addition, an increased awareness among health-care personnel and among the general population following the introduction of dietary iodine fortification may also have an influence on interpretation of findings of hyperthyroidism at levels below the TDI.

11. PREVIOUS EVALUATIONS BY IOMC BODIES

The WHO-recommended intake (population requirement) of iodine is 150 µg/day for adults, 200 µg/day during pregnancy and lactation, and 50, 90, and 120 µg/day for children 1–12 months, 1–6 years, and 7–12 years of age, respectively (WHO/UNICEF/ICCIDD, 2001; WHO, 2004a).

WHO did not set a guideline for iodine in drinking-water (WHO, 2004c), as there are few relevant data; as iodine is not used for long-term water disinfection, lifetime exposure is unlikely through this medium.

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APPENDIX 1 — ACRONYMS AND ABBREVIATIONS

AES	atomic emission spectrometry
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention (USA)
CICAD	Concise International Chemical Assessment Document
DHPN	*N*-bis(2-hydroxypropyl)nitrosamine
DRC	Dynamic Reaction Cell
EDTA	ethylenediaminetetraacetic acid
EPA	Environmental Protection Agency (USA)
EQUIP	Ensuring the Quality of Iodine Procedures
FDA	Food and Drug Administration (USA)
HPLC	high-performance liquid chromatography
ICCIDD	International Council for the Control of Iodine Deficiency Disorder
ICP	inductively coupled plasma
ICSC	International Chemical Safety Card
IDMS	isotope dilution mass spectrometry
INAA	instrumental neutron activation analysis
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety (World Health Organization)
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
MS	mass spectrometry
NHANES	National Health and Nutrition Examination Survey (USA)
NIOSH	National Institute of Occupational Safety and Health (USA)
NOAEL	no-observed-adverse-effect level
OSHA	Occupational Safety and Health Administration (USA)
SD	standard deviation
SI	International System of Units (Système international d'unités)
T_1	monoiodothyronine
T_2	diiodithyronine
T_3	triiodothyronine
T_4	tetraiodothyronine; thyroxine
TDI	tolerable daily intake
TSH	thyroid stimulating hormone
U	enzyme unit
UNICEF	United Nations Children's Fund
USA	United States of America
UV	ultraviolet
v/v	by volume
WHO	World Health Organization

APPENDIX 2 — SOURCE DOCUMENT

ATSDR (2004)

The *Toxicological profile for iodine* was prepared by ATSDR through a contract with the Syracuse Research Corporation. The profile was published in final form in April 2004. Copies of the profile can be obtained from:

Division of Toxicology
Agency for Toxic Substances and Disease Registry
Public Health Service
United States Department of Health and Human Services
1600 Clifton Road NE, Mailstop E-32
Atlanta, Georgia, USA 30333

The document is also available on the web at http://www.atsdr.cdc.gov/toxprofiles/tp158.html.

Dr John Risher, ATSDR, Division of Toxicology, and Drs Gary Diamond, Steven Swarts, and Richard Amata, Syracuse Research Corporation, contributed to the development of the toxicological profile as chemical manager and authors. The profile has undergone three ATSDR internal reviews, including a Health Effects Review, a Minimal Risk Level Review, and a Data Needs Review. An external peer review panel was assembled for the update profile for iodine. The panel consisted of the following members: Dr Lewis Braverman, Boston Medical Center; Dr Richard Leggett, Oak Ridge National Laboratory; Dr Ray Lloyd, University of Utah School of Medicine; Dr Marvin Rallison, University of Utah School of Medicine; Dr Elaine Ron, National Cancer Institute; Dr Kiyohiko Mabichi, National Cancer Institute; Dr Noel Rose, Johns Hopkins University; and Dr Roy Shore, New York University School of Medicine. These experts collectively have knowledge of iodine's physical and chemical properties, toxicokinetics, key health end-points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the United States Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from ATSDR reviewed the peer reviewers' comments and determined which comments were to be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content.

APPENDIX 3 — CICAD PEER REVIEW

The draft CICAD on human health aspects of iodine and inorganic iodides was sent for review to institutions and organizations identified by IPCS after contact with IPCS National Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

M. Baril, Institut de recherche Robert Sauvé en santé et en sécurité du travail, Montreal, Canada

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K. Ziegler-Skylakakis, European Union, Luxembourg

APPENDIX 4 — CICAD FINAL REVIEW BOARD

Nagpur, India
31 October – 3 November 2005

Members

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IODINE

ICSC: 0167
April 2004

CAS #	7553-56-2	Jod
RTECS #	NN1575000	Iode
EC Annex 1 Index #	053-001-00-3	Iodio
EC/EINECS #	231-442-4	Yodo
		I_2
		Molecular mass: 253.8

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Not combustible but enhances combustion of other substances. Many reactions may cause fire or explosion. Gives off irritating or toxic fumes (or gases) in a fire.	NO contact with flammable substances.	In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		STRICT HYGIENE!	
Inhalation	Cough. Wheezing. Laboured breathing. Symptoms may be delayed (see Notes).	Ventilation (not if powder), local exhaust, or breathing protection.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves. Protective clothing.	First rinse with plenty of water, then remove contaminated clothes and rinse again.
Eyes	Causes watering of the eyes. Redness. Pain.	Face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Diarrhoea. Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into sealable containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Do NOT absorb in saw-dust or other combustible absorbents. Do NOT let this chemical enter the environment. Personal protection: filter respirator for inorganic gases, vapours and halogens.	EU Classification Symbol: Xn, N R: 20/21-50 S: (2-)23-25-61
EMERGENCY RESPONSE	STORAGE
	Separated from incompatible materials. See Chemical Dangers. Well closed. Ventilation along the floor.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

IODINE

ICSC: 0167

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
BLUISH BLACK OR DARK PURPLE CRYSTALS , WITH PUNGENT ODOUR.

PHYSICAL DANGERS
Iodine readily sublimes.

CHEMICAL DANGERS
Upon heating, toxic fumes are formed. The substance is a strong oxidant and reacts with combustible and reducing materials. Reacts violently with metal powders, antimony, ammonia, acetaldehyde, acetylene causing fire and explosion hazard.

OCCUPATIONAL EXPOSURE LIMITS
TLV: (inhalable fraction & vapour) 0.01 ppm as TWA; TLV: (vapour) 0.1 ppm as STEL; A4 (not classifiable as a human carcinogen); (ACGIH 2008).
MAK: IIb (not established but data is available) (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
Lachrymation. The substance is severely irritating to the eyes and the respiratory tract, and is irritating to the skin. Inhalation of the vapour may cause asthma-like reactions (RADS). Inhalation of the vapour may cause lung oedema (see Notes). The effects may be delayed. Medical observation is indicated.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization in rare cases. Repeated or prolonged inhalation exposure may cause asthma-like syndrome (RADS). The substance may have effects on the thyroid.

PHYSICAL PROPERTIES

Boiling point: 184°C
Melting point: 114°C
Relative density (water = 1): 4.9
Solubility in water, g/100 ml at 20°C: 0.03
Vapour pressure, kPa at 25°C: 0.04
Relative vapour density (air = 1): 8.8

Relative density of the vapour/air-mixture at 20°C (air = 1): 1
Octanol/water partition coefficient as log Pow: 2.49

ENVIRONMENTAL DATA

This substance may be hazardous in the environment; special attention should be given to fish.

NOTES

The occupational exposure limit value should not be exceeded during any part of the working exposure. Rinse contaminated clothes (fire hazard) with plenty of water. The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation is therefore essential. Immediate administration of an appropriate inhalation therapy by a doctor or a person authorized by him/her, should be considered. The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Card has been partially updated in October 2005: see Emergency Response. Card has been partially updated in August 2008: see Ingestion First Aid. Card has been partially updated in July 2009: see Occupational Exposure Limits.

ADDITIONAL INFORMATION

HYDROGEN IODIDE

ICSC: 1326
October 1999

CAS # 10034-85-2
RTECS # MW3760000
UN # 2197
EC Annex 1 Index # 053-002-00-9
EC/EINECS # 233-109-9

Anhydrous hydriodic acid
HI
Molecular mass: 127.9

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION			
EXPOSURE		AVOID ALL CONTACT!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Burning sensation. Cough. Laboured breathing. Shortness of breath. Sore throat. Symptoms may be delayed (see Notes).	Closed system and ventilation.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Skin burns. Pain. Blisters. (See Inhalation). ON CONTACT WITH LIQUID: FROSTBITE.	Cold-insulating gloves. Protective clothing.	ON FROSTBITE: rinse with plenty of water, do NOT remove clothes. Refer for medical attention.
Eyes	Redness. Pain. Severe deep burns.	Face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Ventilation. Personal protection: chemical protection suit including self-contained breathing apparatus.	EU Classification Symbol: C R: 35 S: (1/2-)9-26-36/37/39-45 UN Classification UN Hazard Class: 2.3 UN Subsidiary Risks: 8
EMERGENCY RESPONSE	**STORAGE**
Transport Emergency Card: TEC (R)-20G2TC NFPA Code: H3; F0; R0;	Fireproof if in building.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

HYDROGEN IODIDE

ICSC: 1326

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS GAS , WITH PUNGENT ODOUR.

PHYSICAL DANGERS
The gas is heavier than air.

CHEMICAL DANGERS
Reacts with strong oxidants, magnesium, causing fire hazard. The solution in water is a strong acid, it reacts violently with bases and is corrosive.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation.

INHALATION RISK
A harmful concentration of this gas in the air will be reached very quickly on loss of containment.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is corrosive to the eyes, the skin and the respiratory tract. Inhalation of this gas may cause lung oedema (see Notes). The effects may be delayed. Medical observation is indicated. See Notes.

PHYSICAL PROPERTIES

Boiling point: -35.5°C
Melting point: -51°C
Solubility in water, g/100 ml at 20°C: 57
Vapour pressure, kPa at °C: 756
Relative vapour density (air = 1): 4.4

ENVIRONMENTAL DATA

NOTES

Copper-nickel alloys and copper-tin alloys, as well as, stainless steel and nickel-chromium alloys, offer the best resistance to corrosion. The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation is therefore essential. Immediate administration of an appropriate inhalation therapy by a doctor or a person authorized by him/her, should be considered. Turn leaking cylinder with the leak up to prevent escape of gas in liquid state.
Card has been partly updated in April 2005. See sections EU classification, Emergency Response.

ADDITIONAL INFORMATION

IODINE CYANIDE

ICSC: 0662
April 2005

CAS #	506-78-5	Cyanogen iodide
RTECS #	NN1750000	CNI
UN #	1588	Molecular mass: 152.9
EC Annex 1 Index #	006-007-00-5	
EC/EINECS #	208-053-3	

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			In case of fire: cool drums, etc., by spraying with water but avoid contact of the substance with water.
EXPOSURE		PREVENT DISPERSION OF DUST! STRICT HYGIENE!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Sore throat. Headache. Confusion. Weakness. Shortness of breath. Convulsions. Unconsciousness. See Notes.	Local exhaust or breathing protection.	Fresh air, rest. Artificial respiration may be needed. No mouth-to-mouth artificial respiration. Administer oxygen by trained personnel. Refer for medical attention.
Skin	MAY BE ABSORBED! Redness. Pain. (See Inhalation).	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain.	Safety goggles, face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation. Nausea. Vomiting. Diarrhoea. (See Inhalation).	Do not eat, drink, or smoke during work. Wash hands before eating.	Induce vomiting (ONLY IN CONSCIOUS PERSONS!). Wear protective gloves when inducing vomiting. Give a slurry of activated charcoal in water to drink. No mouth-to-mouth artificial respiration. Administer oxygen by trained personnel. Refer for medical attention. See Notes.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Evacuate danger area! Consult an expert! Personal protection: complete protective clothing including self-contained breathing apparatus. Ventilation. Sweep spilled substance into sealable containers. Carefully collect remainder, then remove to safe place. Do NOT let this chemical enter the environment.	Airtight. Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs. Marine pollutant. EU Classification Symbol: T+, N R: 26/27/28-32-50/53 S: (1/2-)7-28-29-45-60-61 Note: A UN Classification UN Hazard Class: 6.1 UN Pack Group: I
EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-61GT5-I or 61GT5-I-Cy	Separated from incompatible materials, food and feedstuffs. Dry. Well closed. Keep in a well-ventilated room. Store in an area without drain or sewer access.

IPCS
International Programme on Chemical Safety

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SEE IMPORTANT INFORMATION ON BACK

IODINE CYANIDE

ICSC: 0662

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE CRYSTALS , WITH PUNGENT ODOUR.

CHEMICAL DANGERS
The substance decomposes on contact with acids, bases, ammonia alcohols, and on heating producing toxic gases including hydrogen cyanide. Reacts with carbon dioxide or slowly with water to produce hydrogen cyanide.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. Decomposition in moist air results in hydrogen cyanide exposure: TLV: (for Hydrogen cyanide and some cyanide salts, as CN) 4.7 ppm as STEL; (Ceiling value); (skin) (ACGIH 2008).
MAK: (as CN) (Inhalable fraction) 2 mg/m³;
Peak limitation category: II (1); skin absorption (H); Pregnancy risk group: C; (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

INHALATION RISK
A harmful concentration of airborne particles can be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is severely irritating to the eyes the skin and the respiratory tract. The substance may cause effects on the cellular respiration , resulting in convulsions and unconsciousness. Exposure may result in death. Medical observation is indicated. See Notes.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The substance may have effects on the thyroid.

PHYSICAL PROPERTIES

Melting point: 146-147°C
Density: 2.84 g/cm³

Solubility in water: slow reaction
Vapour pressure, Pa at 25.2°C: 130
Relative vapour density (air = 1): 1.54

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms.

NOTES

Specific treatment is necessary in case of poisoning with this substance; the appropriate means with instructions must be available. Do NOT take working clothes home.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Le document de base à partir duquel le présent CICAD[1] a été établi repose sur le *Profil toxicologique de l'iode* publié par l'Agence pour les produits toxiques et le Registre des maladies du Département de la Santé et des services humains des Etats-Unis (Agency for Toxic Substances and Disease Registry of the United States Department of Health and Human Services) (ATSDR, 2004). Les données prises en compte dans le document vont jusqu'à janvier 2005. Des renseignements sur la disponibilité du document de base et son examen par des pairs sont donnés à l'appendice 2. L'appendice 3 donne des indications sur l'examen par des pairs du présent CICAD. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Nagpur (Inde) du 31 octobre au 3 novembre 2005. La liste des participants à cette réunion figure à l'appendice 4. Les Fiches internationales sur la sécurité chimique de l'iode (ICSC 0167), de l'iodure d'hydrogène (ICSC 1326) et du cyanure d'iode – également appelé iodure de cyanogène – (ICSC 0662), établies selon un processus distinct et sous le contrôles de pairs par le Programme international sur la sécurité chimique, sont également reproduites dans le présent document (IPCS, 2005a,b,c). Les isotopes radioactifs de l'iode (par ex.^{123}I, ^{125}I et ^{131}I) n'entrent pas dans le cadre du présent document. Le lecteur désireux d'obtenir des informations au sujet de des radioisotopes de l'iode est invité à consulter le site Internet de l'OMS consacré aux rayonnements ionisants (http://www.who.int/ionizing_radiation/en/) ou l'ATSDR (1999, 2004).

L'iode est un élément naturellement présent dans l'environnement. En solution, il existe sous diverses formes qui peuvent être incolores ou prendre des couleurs variées telles que le bleu, le brun, le jaune, le rouge ou le blanc, en fonction de la concentration de l'iode dans la solution et de la nature des solvants utilisés. L'iode est soluble dans l'eau et les solvants organiques. Les océans sont la source principale d'iode d'origine naturelle. Les iodures présents dans l'eau de mer s'accumulent dans les poissons, les algues et les invertébrés marins. A partir de la mer, l'iode pénètre dans l'environnement sous la forme d'embruns ou de vapeurs. Une fois présent dans l'atmosphère, l'iode peut se déposer sur le sol ou les cultures voisines. Dans le sol, l'iode se fixe facilement aux matières organiques, d'où sa longue durée de résidence dans ce milieu. L'iode pénètre également dans l'atmosphère lorsqu'on fait brûler des combustibles fossiles comme source d'énergie, mais la contribution de cette source à la teneur de l'environnement en iode est beaucoup moindre que celle des océans. Dans les aliments, l'iode est présent sous forme d'iodures et autres formes non élémentaires.

Dans l'industrie, l'iode est utilisé pour fabriquer des encres, des colorants – notamment des colorants alimentaires – des produits pour la photographie, des piles électriques, des combustibles et des lubrifiants. On l'emploie également comme catalyseur dans la préparation de divers produits chimiques, principalement de l'acide acétique, des produits de contraste radiologique, des agents tensio-actifs, des iodophores (agents tensio-actifs qui assurent le transport de l'iode) et des produits biocides , comme stabilisant dans le tall-oil ou encore dans l'huile iodée. Dans les industries de la santé, on l'utilise aussi comme désinfectant et biocide, pour la fabrication de certains savons, bandages et médicaments ou pour purifier l'eau. Depuis les années 1950, on ajoute dans certains pays de l'iode au sel de table sous forme d'iodure ou d'iodate afin d'éviter les séquelles de la carence en iode par un apport alimentaire suffisant de cet élément.

L'exposition à l'iode est due à l'ingestion de sel iodé, de sel de mer, de poissons ou d'invertébrés marins, de varech, de produits de boulangerie qui utilisent de l'iode comme additif pour leur préparation ou encore de produits laitiers (en raison de l'utilisation d'iode pour désinfecter les récipients en acier qui servent à recueillir et à transporter le lait). L'air ambiant ne contribue guère à l'exposition habituelle à l'iode.

L'iode moléculaire et les dérivés minéraux de l'iode sont facilement et largement absorbés tant par la voie respiratoire que par la voie orale. On a montré expérimentalement que la résorption dermique de l'iode ne dépassait pas 1% de la dose appliquée; elle n'est donc pas considérée comme une voie d'exposition importante. L'iode est éliminé de l'organisme dans les urines, la sueur, les matières fécales et le lait maternel.

De petites quantités d'iode sont essentielles pour assurer les fonctions physiologiques normales. Il est un constituant essentiel des hormones thyroïdiennes, qui sont nécessaires au contrôle du métabolisme, de la croissance et du développement des structures de l'organisme, ainsi qu'au fonctionnement et au développement des neurones. L'apport d'iode recommandé par l'OMS (au niveau de la population) est de 150 µg par jour pour les adultes et les adolescents à partir de 13 ans, de 200 µg par jour pour les femmes enceintes et allaitantes, de 120 µg par jour pour les enfants de 6 à 12 ans et de 90 µg par jour pour les enfants de 0 à 59 mois (WHO, 2004a).

Les troubles liés à une carence en iode constituent un ensemble de maladies imputables à un apport alimentaire insuffisant. La carence en iode est aujourd'hui la cause la plus fréquente, mais pourtant

[1] La liste des acronymes et abréviations utilisés dans le présent rapport figure à l'appendice 1.

facilement évitable, de lésions cérébrales dans le monde (WHO, 2004b). On estime que la carence en iode touche plus de 740 millions de personnes dans le monde, soit environ 13 % de la population mondiale. Une grave carence en iode pendant la grossesse peut entraîner des mortinaissances, des fausses couches et des anomalies congénitales telles que le crétinisme, qui constitue une forme irréversible d'arriération mentale et développementale dont sont victimes les personnes vivant dans des régions où l'iode fait défaut (en particulier dans les zones les moins développées de la planète telles que l'Afrique et l'Asie). La carence en iode peut également avoir des effets moins visibles mais non moins graves qui se traduisent par une moindre aptitude intellectuelle aux tâches domestiques et scolaires et au travail en général. Chez l'adulte, un apport d'iode insuffisant peut provoquer l'apparition d'un goitre (hypertrophie de la thyroïde), des troubles du métabolisme et un déficit cognitif.

Les principaux effets d'une exposition prolongée par voie orale à des quantités importantes d'iodures minéraux ont paradoxalement pour conséquence une hyper- ou une hypothyroïdie. Cet état de choses résulte des processus physiologiques complexes qui interviennent dans la régulation de l'activité thyroïdienne nécessaire au maintien de l'homéostase de l'iode. Plusieurs études ont montré que lorsqu'on ajoute de l'iode aux aliments, l'incidence de l'hyperthyroïdie augmente dans la population et cela même lorsque l'apport moyen d'iode ne dépasse pas la dose journalière recommandée.

Une absorption excessive d'iode peut inhiber la synthèse et la libération des hormones thyroïdiennes, d'où un risque d'hypothyroïdie et de goitre. Une dépression de la fonction thyroïdienne peut également s'observer chez des sujet euthyroïdiens (c'est-à-dire des adultes dont la fonction thyroïdienne est normale) lorsque la dose journalière est supérieure ou égale à 1700 µg.

Selon de nombreux rapports médicaux, une dose de l'ordre de 300 mg d'iode prise par voie orale peut provoquer une réaction fébrile chez des patients déjà malades. De l'iode pris par voie orale peut également entraîner une réactions de sensibilisation cutanée appelée iododermite. Contrairement à l'iode élémentaire ou à ses dérivés minéraux, les dérivés organiques de l'iode peuvent provoquer une sensibilisation par contact avec la peau.

Selon certaines études épidémiologiques, on est amené à penser que le fait d'habiter dans une zone d'endémie goitreuse (faible apport d'iode par la voie alimentaire) pourrait constituer un risque de cancer de la thyroïde, mais d'autres travaux indiquent que l'augmentation de l'apport alimentaire d'iode pourrait également constituer un facteur de risque de cancer thyroïdien, notamment de cancer papillaire, en particulier dans les régions où le sol est pauvre en iode.

Chez des rats ayant reçu pendant toute leur vie une dose quotidienne de 50 mg d'iodure de potassium par kg de poids corporel, on a observé une augmentation, à la limite de la significativité statistique, des tumeurs des glandes salivaires. Lors d'études en deux temps, on a constaté que l'administration d'iodure avait un effet promoteur sur les tumeurs de la thyroïde après initiation par une nitrosamine. Il n'existe aucune preuve convaincante que l'iode ou les iodures soient dotés d'activité mutagène.

L'administration de doses importantes d'iodure pendant la dernière partie de la gestation a induit une mortalité néonatale supplémentaire chez le rat et le lapin, mais pas chez le hamster ou le porc. Il n'existe pas d'études consacrées aux effets embryotoxiques ou tératogènes de l'iode ou des iodures. On a fait état de cas humains d'hypothyroïdie néonatale consécutifs à une exposition in utero à des doses pharmacologiques d'iode administrées à la mère.

On a montré que l'exposition par la voie respiratoire à de faibles concentrations de vapeurs d'iode provoquait une augmentation de la résistance des voies aériennes et à une diminution de la fréquence respiratoire chez le cobaye.

Une vaste étude transversale portant sur le bilan hormonal thyroïdien et l'apport d'iode chez l'enfant a montré qu'un apport estimatif journalier de 0,03 mg d'iode par kg de poids corporel entraînait une élévation du taux sanguin de TSH, comparativement à un groupe recevant seulement 0,01 mg d'iode par kg de poids corporel. Deux études expérimentales de brève durée portant sur de petits groupes d'adultes ainsi que deux études transversales sur des personnes âgées ont confirmé que la dose sans effet indésirable observé (NOAEL) était égale à 0,01 mg d'iode par kg de poids corporel et par jour. Comme la détermination de cette NOAEL repose sur l'étude de deux groupes de population potentiellement sensibles, les personnes âgées et les enfants, on considère qu'elle représente la dose journalière tolérable (TDI).

L'ampleur des variations qui existent entre les différents individus ou populations en ce qui concerne les besoins en iode d'origine alimentaire contribue à l'incertitude qui entache la valeur de la dose journalière tolérable. Compte tenu de ces variations, il pourrait être nécessaire d'augmenter ou d'accroître la supplémentation en iode dans les régions où cet élément fait défaut.

RESUMEN DE ORIENTACIÓN

El documento original en el que se basa este CICAD[1] es el "*Toxicological profile for iodine*" (Perfil toxicológico del yodo), publicado por la Agencia para el Registro de Sustancias Tóxicas y Enfermedades, del Departamento de Salud y Servicios Sociales de los Estados Unidos (ATSDR, 2004). En el documento original se examinaron los datos identificados hasta enero de 2005. La información sobre la disponibilidad del documento original y su examen colegiado se presenta en apéndice 2. La información sobre el examen colegiado de este CICAD figura en el apéndice 3. Su aprobación como evaluación internacional se realizó en una reunión de la Junta de Evaluación Final, celebrada en Nagpur (India) del 31 de octubre al 3 de noviembre de 2005. La lista de participantes en esta reunión figura en el apéndice 4. También se reproducen en este documento las Fichas internacionales de seguridad química para el yodo (ICSC 0167), el yoduro de hidrógeno (ICSC 1326) y el cianuro de yodo (ICSC 0662), preparadas por el Programa Internacional de Seguridad de las Sustancias Químicas en un proceso de revisión colegiada separado (IPCS, 2005 a,b,c). Los isótopos radiactivos del yodo (por ejemplo, ^{123}I, ^{125}I y ^{131}I) quedan fuera del ámbito de este documento. Para obtener información sobre los isótopos radiactivos del yodo, el lector debe consultar la página web de radiaciones ionizantes de la OMS (http://www.who.int/ionizing_radiation/en/) o ATSDR (1999, 2004).

El yodo es un elemento que está presente en la naturaleza. Se encuentra en diversas formas, que van desde una variedad incolora a una serie de colores, entre ellos el azul, el marrón, el amarillo, el rojo y el blanco, en función de las concentraciones de yodo en la solución y los disolventes utilizados. Es soluble tanto en agua como en disolventes orgánicos. Los océanos son la fuente principal del yodo que se encuentra en la naturaleza. En el mar, los yoduros se acumulan en el pescado, los mariscos y las algas. A partir de los mares, el yodo pasa al medio ambiente en forma de espuma de agua marina o gases. Una vez suspendido en el aire se puede depositar en el suelo o en las cercanías de cultivos agrícolas. Cuando llega al suelo, se une con facilidad a la materia orgánica, lo que determina un periodo de permanencia prolongado. El yodo también pasa al aire a partir de la quema de combustibles fósiles como fuente de combustible, pero su contribución al medio ambiente es muy inferior a la de los océanos. En los alimentos está presente como yoduro y como formas no elementales.

En entornos industriales, el yodo se utiliza en la fabricación de tintes, colorantes, agentes colorantes, sustancias químicas de uso fotográfico, pilas, combustibles y lubricantes. También se emplea como catalizador en la producción de varias sustancias químicas, en particular ácido acético, medios de contraste para rayos X, sustancias tensioactivas, iodóforos (sustancias tensioactivas que actúan como portadoras de yodo) y biocidas, como estabilizador de "*tall oil*" (resina de lejías celulósicas) y en el aceite yodado. En la industria sanitaria, el yodo se utiliza también como desinfectante/biocida, en la producción de ciertos jabones, vendajes y medicamentos y en la purificación del agua. A partir del decenio de 1950, se ha añadido yodo (en forma de yoduro o yodato) a la sal en algunos países para garantizar la ingesta apropiada con la alimentación, a fin de prevenir las secuelas de la deficiencia de yodo. También se ha incorporado a algunos complementos de los piensos.

La exposición al yodo incluye la ingestión de sales yodadas, sal marina, pescado, mariscos y algas de origen marino, productos de panadería en cuya elaboración se utiliza yodo, medicamentos y productos lácteos (debido a la utilización de yodo como desinfectante de los recipientes de acero empleados para recoger y transportar la leche). El aire ambiente contribuye poco a la exposición cotidiana al yodo.

El yodo molecular y los compuestos inorgánicos de yodo se absorben con rapidez y amplitud, tanto por inhalación como por vía oral. Se ha demostrado experimentalmente que la absorción cutánea es del 1% o menos de la dosis aplicada, por lo que no se la considera una vía importante de exposición. El yodo se elimina del organismo en la orina, el sudor, las heces y la leche materna.

El yodo es esencial en pequeñas cantidades para la función fisiológica normal. Es un componente fundamental de las hormonas tiroideas, necesarias para controlar el metabolismo, el crecimiento y la formación de estructuras corporales, así como la función y el desarrollo neuronal. La ingesta de yodo recomendada por la OMS (necesidad de la población) es de 150 µg/día para los adultos y los adolescentes a partir de los 13 años, 200 µg/día para las mujeres durante el embarazo y la lactación, 120 µg/día para los niños de 6 a 12 años de edad y 90 µg/día para los niños de 0 a 59 meses de edad (WHO, 2004a).

Los trastornos por deficiencia de yodo representan un grupo de enfermedades asociadas con la falta de su ingesta en la alimentación. La deficiencia de yodo es la causa más frecuente de daños cerebrales en todo el mundo en la actualidad, aunque es fácil de evitar (WHO, 2004b). Se considera que afecta a más de 740 millones de personas en todo el mundo, alrededor del 13% de la población mundial. Una deficiencia de yodo importante durante el embarazo puede producir casos de

[1] En el apéndice 1figura una lista de las siglas y abreviaturas utilizadas en este informe.

mortinatalidad, abortos y anomalías congénitas como el cretinismo, una forma irreversible de retraso del crecimiento y mental que afecta a las personas que viven en zonas con deficiencia de yodo (sobre todo en las zonas menos desarrolladas del mundo, como África y Asia). Un efecto menos visible, pero grave, de la deficiencia de yodo es un nivel inferior de trastorno que compromete la capacidad intelectual en el hogar, la escuela y el trabajo. En los adultos, una ingesta insuficiente de yodo puede provocar bocio (aumento de la glándula tiroidea), insuficiencia metabólica y alteración de la función cognitiva.

Los efectos principales de la exposición prolongada por vía oral a cantidades elevadas de yodo inorgánico son, paradójicamente, hipertiroidismo y/o hipotiroidismo. Esto se debe a los complejos procesos fisiológicos que intervienen en la regulación de la actividad tiroidea para mantener la homeóstasis del yodo. En varios estudios se ha indicado que cuando se incorpora yodo a la alimentación hay un aumento de la incidencia de hipertiroidismo en la población, aun cuando la ingesta media de yodo no sea superior a la dosis diaria recomendada.

Una ingesta excesiva de yoduro puede inhibir la síntesis y liberación de hormonas tiroideas, que a su vez puede causar hipotiroidismo y bocio. Se ha observado depresión de la función tiroidea en adultos eutiroideos (es decir, adultos con una función tiroidea normal) con una dosis diaria ≥ 1700 μg de yodo al día.

Los informes de muchos casos indican que dosis orales del orden de 300 mg de yodo y superiores han inducido reacciones febriles en pacientes que sufrían enfermedades. Con dosis orales de yodo se han producido también reacciones de sensibilidad cutánea, denominadas yododerma. La sensibilización cutánea por contacto se atribuye a compuestos orgánicos de yodo, pero no al yodo o los yoduros inorgánicos.

Los resultados de algunos estudios epidemiológicos parecen indicar que la residencia en zonas de bocio endémico (ingesta baja de yoduro con los alimentos) puede ser un factor de riesgo para el cáncer de tiroides, mientras que en otros estudios se ha notificado que un aumento de la ingesta de yodo con los alimentos también puede ser un factor de riesgo para dicho tipo de cáncer, específicamente el cáncer papilar, sobre todo en poblaciones que residen en zonas con suelos pobres en yoduros.

La exposición a lo largo de toda la vida a unos 50 mg de yoduro de potasio por kg de peso corporal al día indujo un aumento en el límite de la significación estadística de tumores en las glándulas salivales de ratas; en dos estudios de dos etapas, el yoduro tuvo un efecto estimulante sobre los tumores tiroideos tras la iniciación mediante una nitrosamina. No hay pruebas convincentes de que los compuestos de yodo o de yoduro tengan algún potencial mutagénico.

La administración de grandes dosis de yoduro hacia el final de la gestación produjo mortalidad neonatal en la rata y el conejo, pero no en el hámster ni el cerdo. No hay estudios sobre los efectos embriotóxicos o teratogénicos del yodo o los yoduros. Se ha informado de casos humanos de hipotiroidismo neonatal tras la exposición del útero a dosis farmacológicas de yodo administradas a la madre.

Se ha demostrado que la exposición por inhalación a concentraciones bajas de vapor de yodo da lugar a un aumento de la resistencia de las vías respiratorias y a una disminución del ritmo respiratorio en cobayas.

En un estudio transversal amplio sobre la situación de las hormonas tiroideas y la ingesta de yodo en los niños se asoció una ingesta estimada diaria media de yodo de 0,03 mg/kg de peso corporal con concentraciones elevadas de hormona estimulante del tiroides (TSH) en la sangre, en comparación con una ingesta de yodo de 0,01 mg/kg de peso corporal al día. Dos estudios experimentales de corta duración en pequeños grupos de adultos y dos estudios transversales en personas ancianas respaldaron la concentración de 0,01 mg/kg de peso corporal al día como un nivel sin efectos adversos. Habida cuenta de que esta NOAEL se basa en dos grupos de población potencialmente sensibles, los ancianos y los niños, se la considera una ingesta diaria tolerable (IDT).

El grado de variabilidad en las necesidades de yodo alimentario entre distintas personas y poblaciones contribuye a la incertidumbre de la IDT. Esta variación puede hacer que aumente o disminuya la cantidad de yodo complementario que se necesita en las zonas geográficas con deficiencia de yodo.

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