Iodine, inorganic and soluble salts

Evaluation of health hazards and proposal of a health-based quality criterion for drinking water

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Preface

This report has been prepared by Elsa Nielsen, Krestine Greve, John Christian Larsen, Otto Meyer, Kirstine Krogholm and Max Hansen, Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been elaborated according to the general practice laid down in the Danish EPA guidance document for the setting of health-based quality criteria for chemical substances in relation to soil, ambient air and drinking water.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of the following representatives from Danish authorities:

- The Danish Nature Agency: Anne Christine Duer
- The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences): Niels Henrik Spliid
- The Danish Veterinary and Food Administration: Gudrun Hilbert
- The National Board of Health, Denmark, medical officer of health: Lene Garsdal
- Danish Regions: Arne Rokkjær,
- The Danish Environmental Protection Agency: Katrine Smith, Poul Bo Larsen, Finn Pedersen, Jette Rud Heltved.
1 General description

Iodine is a non-metallic element belonging to the halogen family in Group VIIA of the periodic table. Iodine can exist in several oxidation states: –1, 0, +1, +3, +5 and +7. Under normal environmental conditions, the -1, 0, and +5 oxidation states are the most important. Iodine is found in nature as molecular iodine (I₂), iodide (I⁻), or iodate (IO₃⁻). There are 36 isotopes of iodine and 14 of these yield significant radiation. The only naturally occurring isotopes of iodine are the stable isotope ¹²⁷I and the radioactive isotope ¹²⁹I. In this evaluation only non-radioactive iodine is considered.

Molecular iodine and water-soluble iodine salts release the iodide ion in contact with water. Thus, iodine occurs in water in the form of iodide (I⁻), which is largely oxidised to molecular iodine during water treatment. Molecular iodine as well as water-soluble iodine salts are rapidly converted into iodide in the gut following ingestion and this is efficiently absorbed throughout the gastrointestinal tract. Therefore, toxicological effects can be considered together for molecular iodine and water-soluble iodine salts to the extent that these effects are directly mediated by the iodide ion. This evaluation is limited to consider the toxicity of inorganic salts of the stable iodine (isotope ¹²⁷I) from which the iodide ion can be liberated, as this form is the relevant one in relation to estimation of a health-based quality criterion in drinking water.

This document is mainly based on evaluations prepared by ATSDR (2004), WHO (2003) and EFSA (2006).

In this evaluation, the term “molecular iodine” is used to refer to I₂ and the term “iodide” is used to refer to the anion I⁻. The term “iodine” is used in a generic sense and refers to the element in any form. For the purpose of comparison, concentrations and dose levels of the various iodide salts are expressed in terms of iodine equivalents (I) whenever possible.

1.1 Identity

The identity and physico-chemical properties of molecular iodine and selected soluble inorganic iodine salts are presented in Table 1.

1.2 Production and use

Approximately 54% of the iodine consumed in the world is obtained from Chile as a co-product from surface mineral deposits used to produce nitrate fertilizers and about 43% from brines processed in Japan, the United States and the former Soviet Union (ATSDR 2004).

Iodine is used as an antiseptic for skin wounds, as a disinfecting agent in hospitals and laboratories, and for the emergency disinfection of drinking-water in the field. Iodide is used in pharmaceuticals and in photographic developing materials. (WHO 2003).
Table 1. Identity and chemical properties of molecular iodine and selected water soluble 
inorganic iodine salts (ATSDR 2004).

<table>
<thead>
<tr>
<th></th>
<th>Iodine</th>
<th>Potassium iodide</th>
<th>Sodium iodide</th>
<th>Copper (I) iodide</th>
<th>Calcium iodide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>I₂</td>
<td>KI</td>
<td>NaI</td>
<td>CuI</td>
<td>CaI₂</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>253.8</td>
<td>166.0</td>
<td>149.9</td>
<td>190.5</td>
<td>293.9</td>
</tr>
<tr>
<td>CAS-number</td>
<td>7553-56-2</td>
<td>7681-11-0</td>
<td>7681-82-5</td>
<td>7681-65-4</td>
<td>10102-68-8</td>
</tr>
<tr>
<td>Description</td>
<td>Bluish-black scales or plates</td>
<td>Colourless or white crystals or granules</td>
<td>White crystals or granules</td>
<td>Red-brown powder or crystals</td>
<td>Yellow lumps or powder</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>113.6</td>
<td>680</td>
<td>651</td>
<td>588-606</td>
<td>740</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>185.2</td>
<td>1323</td>
<td>1304</td>
<td>~1290</td>
<td>1100</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>4.93</td>
<td>3.12</td>
<td>3.67</td>
<td>5.63</td>
<td>-</td>
</tr>
<tr>
<td>Water solubility (g/l)</td>
<td>0.3 at 25°C</td>
<td>1430 at 25°C</td>
<td>2000 at 25°C</td>
<td>0.08 at 18°C</td>
<td>Very soluble</td>
</tr>
</tbody>
</table>

1.3 Environmental occurrence and fate

Iodine is a naturally occurring constituent of the earth’s crust and is the least abundant of the halogen elements. The stable iodine isotope (¹²⁷I) is ubiquitous throughout the earth’s surface in igneous rocks and soils, most commonly as impurities in saltpetre and natural brines. The concentration of ¹²⁷I in the earth’s crust is approximately 0.5 mg/kg. (ATSDR 2004).

Releases of iodine into the environment occur from both natural sources and human activity. The natural sources include volatilisation of iodine from the oceans, weathering of rocks, and volcanic activity. Sources of iodine from human activities include release of iodine from waste stream effluent from municipal plants, and combustion of waste and fossil fuels. (ATSDR 2004).

1.3.1 Air

Iodine enters the atmosphere mainly through volatilisation of methyl iodide and, to a lesser extent, molecular iodine from the ocean surface. In the atmosphere, iodine undergoes extensive photochemical changes and can exist as gaseous inorganic, gaseous organic, or particulate forms. These forms have an average residency time in the atmosphere of 10, 18, and 14 days, respectively. (ATSDR 2004).

The gaseous inorganic and particulate forms of iodine are precipitated from the atmosphere through wet (rain, sleet, and snow) and dry (gravitational settling and wind turbulence) deposition processes. If precipitation occurs over land, iodine will be deposited onto plant surfaces or soil surfaces, or into surface waters. (ATSDR 2004).

Atmospheric iodine is present at levels of 3-50 ng/m³, the average global value being 10-20 ng/m³ (EFSA 2006, ATSDR 2004).

1.3.2 Water

Iodine occurs naturally in water in the form of iodide, which is largely oxidised to iodine during water treatment (WHO 2003).
Introduction of iodine into surface waters and groundwater occurs predominately through rainwater for non-coastal land regions and the combination of rainwater and ocean spray in coastal regions. The iodine in rainwater is derived from the volatilisation of iodine from the oceans to the atmosphere. Other natural releases of iodine into surface waters and groundwater include the leaching of iodine from the weathering of rocks and volcanic activity. In many areas of the world, the surface soil becomes progressively poorer in iodide through these leaching processes. (ATSDR 2004).

Iodine concentrations in tap water obtained from 55 different locations in Denmark varied from <1.0 to 139 µg/l. It is not stated in the paper when the samples were collected; however, the manuscript was received by the journal the 29th of October 1998 so the samples were probably collected in the second half of the 1990’ies. In general, the iodine content was low in Jutland (median: 4.1 µg/l, 95% confidence of median: 3.1-6.3 µg/l) with higher values on Zealand (median: 23 µg/l, 95% confidence of median: 10.4-26.6 µg/l) and other islands. The median of all samples was 7.5 µg/l (95% confidence of median: 4.7-14.0 µg/l). The iodine values found at different sites were very similar when measured in two samples collected at two-month intervals. The day-to-day variation measured at two sites on 10 consecutive days only showed little variation. (Pedersen et al. 1999).

In another study, iodine concentrations in tap water samples collected (in January and in June 1997) from 41 evenly distributed localities in Denmark varied from 2.1 to 30.2 µg/l. The iodine content in samples collected in January did not differ from the iodine content in samples collected in June. The iodine content was in general highest in the eastern part of Denmark (Zealand: mean 18.7 µg/l, range 5.7-30.2 µg/l, n = 20) and lowest in the western part of Denmark (Jutland: mean 5.7 µg/l, range 2.1-24.8 µg/l, n = 18) with the central part of Denmark being in between (Funen: mean 9.5 µg/l, range 7.8-12.3 µg/l, n = 2). (Rasmussen et al. 2000).

The average iodine content in Danish tap water (taken at households) from 48 localities as reported in the Danish Food Composition Databank is presented in Table 2. The concentrations varied from 0.9 µg/l (Grindsted) to 139 µg/l (Skagen). (Møller et al. 2005). It should be noted that the data in Table 2 are based on the publication Rasmussen et al. (2000).

The iodine in Danish drinking water was bound in relatively large organic compounds characterised as humic substances (Skagen 99%, Ringsted 98%, Nykøbing S 90%, Copenhagen 90%, Samsø 75%, Nakskov 40%), which have probably leached form marine sediments in the aquifers. A study investigating the bioavailability of iodine bound to humic substances showed that about 85% of the iodine in the drinking water from Skagen was bioavailable. (Andersen et al. 2002, 2008, Laurberg et al. 2003).

1.3.3 Soil

The contribution of iodine to soils is derived from natural sources, such as the weathering of rock, decay of vegetation, iodine received from rainfall, and from human activities. The concentration of the stable iodine isotope $^{127}$I in the earth’s crust is approximately 0.5 mg/kg. The concentration of iodine in bedrock varies between 0.5 and 380 mg/kg, depending on whether the rock is igneous or sedimentary. Most soils worldwide contain on average approximately 5 mg/kg of iodine. (ATSDR 2004).
Table 2. The average iodine content of Danish tap water from 48 localities as reported in the Danish Food Composition Databank (Møller et al. 2005). It should be noted that the data are based on the publication Rasmussen et al. (2000).

<table>
<thead>
<tr>
<th>Locality</th>
<th>Content µg/l</th>
<th>Variations µg/l</th>
<th>No. of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen municipality</td>
<td>16.0</td>
<td>8.6-26.8</td>
<td>14</td>
</tr>
<tr>
<td>Frederiksberg municipality</td>
<td>18.0</td>
<td>13.2-20.0</td>
<td>4</td>
</tr>
<tr>
<td>Frederikssund municipality</td>
<td>5.6</td>
<td>5.7-6.0</td>
<td>4</td>
</tr>
<tr>
<td>Kege municipality</td>
<td>25.0</td>
<td>25.2-27.4</td>
<td>4</td>
</tr>
<tr>
<td>Hillerød municipality</td>
<td>23.0</td>
<td>22.6-22.9</td>
<td>4</td>
</tr>
<tr>
<td>Slagelse municipality</td>
<td>30.6</td>
<td>26.6-34.5</td>
<td>2</td>
</tr>
<tr>
<td>Nykøbing Falster municipality</td>
<td>20.0</td>
<td>13.2-23.3</td>
<td>4</td>
</tr>
<tr>
<td>Odense municipality</td>
<td>10.0</td>
<td>9.5-12.3</td>
<td>4</td>
</tr>
<tr>
<td>Aabenraa municipality</td>
<td>7.0</td>
<td>6.2-8.0</td>
<td>4</td>
</tr>
<tr>
<td>Ribe municipality</td>
<td>6.1</td>
<td>6.0-6.1</td>
<td>2</td>
</tr>
<tr>
<td>Fredericia municipality</td>
<td>6.7</td>
<td>6.2-7.2</td>
<td>2</td>
</tr>
<tr>
<td>Thisted municipality</td>
<td>2.9</td>
<td>2.8-3.0</td>
<td>4</td>
</tr>
<tr>
<td>Aalborg municipality</td>
<td>5.0</td>
<td>2.5-8.5</td>
<td>2</td>
</tr>
<tr>
<td>Frederikshavn municipality</td>
<td>18.0</td>
<td>13.4-24.8</td>
<td>4</td>
</tr>
<tr>
<td>Varde municipality</td>
<td>3.6</td>
<td>3.5-3.7</td>
<td>2</td>
</tr>
<tr>
<td>Herning municipality</td>
<td>3.4</td>
<td>3.2-3.5</td>
<td>2</td>
</tr>
<tr>
<td>Ballerup municipality</td>
<td>23.7</td>
<td>23.6-23.8</td>
<td>2</td>
</tr>
<tr>
<td>Gladsaxe municipality</td>
<td>16.9</td>
<td>16.2-17.6</td>
<td>2</td>
</tr>
<tr>
<td>Skagen municipality</td>
<td>139</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Brønderslev municipality</td>
<td>4.6</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sæby municipality</td>
<td>6.5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Farsø municipality</td>
<td>1.9</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hobro municipality</td>
<td>8.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lyngby Taarbæk municipality</td>
<td>17.6</td>
<td>15.5-19.6</td>
<td>2</td>
</tr>
<tr>
<td>Gentofte municipality</td>
<td>10.5</td>
<td>10.0-11.0</td>
<td>2</td>
</tr>
<tr>
<td>Lemvig municipality</td>
<td>2.4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Holstebro municipality</td>
<td>6.3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Videbæk municipality</td>
<td>01.3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Grindsted municipality</td>
<td>0.9</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Kolding municipality</td>
<td>7.5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Tender municipality</td>
<td>3.3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Senderborg municipality</td>
<td>15.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Ærøskøbing municipality</td>
<td>16.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Faaborg municipality</td>
<td>14.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Middelfart municipality</td>
<td>8.8</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Nyborg municipality</td>
<td>25.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Korso municipality</td>
<td>25.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Skælskør municipality</td>
<td>15.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Kalundborg municipality</td>
<td>27.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Samsø municipality</td>
<td>48.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Roskilde municipality</td>
<td>5.8</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Vordingborg municipality</td>
<td>37.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Nykøbing Rørvig municipality (Nykøbing Sjælland)</td>
<td>57.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nakskov municipality</td>
<td>48.0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Læsø municipality</td>
<td>4.6</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Brande municipality</td>
<td>2.6</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Silkeborg municipality</td>
<td>3.8</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Marsø municipality</td>
<td>4.2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Jutland, unspecified</td>
<td>5.7</td>
<td>2.1-24.8</td>
<td>18</td>
</tr>
<tr>
<td>Funen, unspecified</td>
<td>9.5</td>
<td>7.8-12.3</td>
<td>2</td>
</tr>
<tr>
<td>Zealand, unspecified</td>
<td>18.7</td>
<td>5.7-30.2</td>
<td>20</td>
</tr>
</tbody>
</table>
Retention of iodine in the soil is influenced by a number of factors, including soil pH, soil moistness, porosity of soil, and composition of organic and inorganic (e.g., aluminum and iron oxides) components. Approximately 1% of iodine received through atmosphere-to-soil deposition is returned through volatilisation of molecular iodine and methyl iodide; the remaining iodine is eventually returned to the oceans through surface water and groundwater. In many areas of the world the surface soil becomes progressively poorer in iodide through these leaching processes. The average residency time of iodine in the soil at 0.3- and 1-meter depths has been suggested to be 80 and 800 years, with only 1-3% of deposited iodine migrating to the 1-meter depth. (ATSDR 2004, EFSA 2006).

1.3.4 Foodstuffs

The iodide content of foods depends on geochemical, soil, and cultural conditions. The major natural food sources are marine fish, shellfish, marine algae, seaweed and sea salt. In industrialised countries, the most important sources of iodide are dairy products, e.g. whole cow’s milk, eggs, and grain and cereal products. Other food sources are freshwater fish, poultry and meat, fruits, legumes and vegetables. (EFSA 2006).

It should be noted, that Danish sea salt has not been identified as a major natural source of iodide (Rasmussen 2010), see also Table 3.

The content of iodine in various foods has been reported in the Danish Food Composition Databank (2009), see Table 3.

Iodine in boiled water, coffee and tea was generally similar to that in non-boiled showing that iodine in water is not lost during boiling (Pedersen et al. 1999, Rasmussen et al. 2000).

The mean concentration of iodine in organic and non-organic milk was 167 µg/kg (range: 125-189 µg/kg) and 268 µg/kg (range: 229-371 µg/kg), respectively (Rasmussen et al. 2000).

<table>
<thead>
<tr>
<th>Food</th>
<th>Content (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seaweed</td>
<td>360000</td>
</tr>
<tr>
<td>Fish (marine)</td>
<td>1-7000</td>
</tr>
<tr>
<td>Fish (fresh water)</td>
<td>53-190</td>
</tr>
<tr>
<td>Shellfish</td>
<td>300-2400</td>
</tr>
<tr>
<td>Meat</td>
<td>7-30</td>
</tr>
<tr>
<td>Plucks</td>
<td>11-44</td>
</tr>
<tr>
<td>Game and poultry</td>
<td>4-80</td>
</tr>
<tr>
<td>Eggs</td>
<td>210</td>
</tr>
<tr>
<td>Milk and dairy products</td>
<td>90-243</td>
</tr>
<tr>
<td>Bread</td>
<td>19-250</td>
</tr>
<tr>
<td>Grain and cereal products</td>
<td>5-50</td>
</tr>
<tr>
<td>Fruits</td>
<td>1-25</td>
</tr>
<tr>
<td>Vegetables</td>
<td>1.5-34</td>
</tr>
<tr>
<td>Salt, table</td>
<td>18300</td>
</tr>
<tr>
<td>Salt, sea (no iodine fortification)</td>
<td>420</td>
</tr>
</tbody>
</table>
The iodine content in Danish bread was measured after mandatory iodine fortification was introduced. In six different kinds of rye bread (125 samples) and 14 different kinds of wheat bread (187 samples), the mean concentration of iodine was 220 µg/kg (range: 14-380 µg/kg) and 210 µg/kg (range: 0-460 µg/kg), respectively. Approximately 98% of the rye breads and 90% of the wheat breads were iodized. (Rasmussen et al. 2007).

Human milk was reported in the 1980s to contain 12 µg/l in Eastern Germany, 27 µg/l in Italy, 95 µg/l in France, and 178 µg/l (median) in the U.S. (Gushurst et al. 1984 – quoted from EFSA 2006).


1.3.5 Bioaccumulation

Iodine content of aquatic plants varies, depending on whether they are in fresh or salt water. Freshwater algae contain $10^{-3}$ % by weight of iodine, whereas marine algae contain $10^{-3}$ % by weight. In freshwater fish, iodine concentrations in tissues range from 0.003 to 0.81 mg/kg, which gives concentration ratios (fish/water) of 0.9-810. In marine fish, the iodine concentrations range between 0.023 and 0.11 ppm, yielding concentration ratios of 10-20. (ATSDR 2004).

In terrestrial plants, iodine can be taken up through the roots, mainly as iodide and to a lesser extent, as iodate or iodine. The average iodine concentration in terrestrial plants is 0.42 µg/g. The uptake is dependent on soil conditions and the use of fertilizers. Distribution of iodine and iodide varies throughout the plant. The uptake of iodine into terrestrial plants in combination with deposition of iodine onto the surfaces of plants plays an important role in the transfer of iodine through the soil-plant-cow-milk pathway. (ATSDR 2004).

Although aquatic plants and fish concentrate iodine in their tissues, there is little evidence for bioaccumulation of iodine in the food chain (ATSDR 2004).


1.4 Human exposure

Human exposure to iodide can result from inhalation of air, consumption of food and drinking water, incidental ingestion of soil, and use of iodine containing supplements (mineral or seaweed-based dietary supplements), medications and antiseptics. Food is generally the predominant source of exposure to iodide; however, use of iodine containing dietary supplements or medications would be a major source as well.

Using the average global ambient air concentration of 10-20 ng/m$^3$, and assuming the inhalation rate at 0.5 m$^3$/kg bw/day (for children 1-5 years old), the inhalation exposure to iodine would be 5-10 ng/kg bw/day. For an adult, assuming an average inhalation rate at 13 m$^3$/day or a high inhalation rate at 20 m$^3$/day, the daily inhalation exposure to iodine from ambient air would be about 130-260 ng (average, about 1.9-3.7 ng/kg bw/day assuming an adult body weight of 70 kg) or 200-400 ng (high, about 2.9-5.7 ng/kg bw/day).
The importance of the content of iodine in drinking water for the known regional differences in iodine intake in Denmark has been evaluated by Pedersen et al. (1999). Iodine in tap water obtained from 55 different locations in Denmark varied from below 1.0 to 139 μg/l, see section 1.3.2. For 41 of these locations, values of urinary iodine excretion were available (collected around 1967 from young males). A statistically significant correlation (P<0.001, r = 0.68) was found between the tap water iodine content (1999) and the urinary iodine excretion measured in the young males in 1967. The calculated regression corresponded to a basic urinary iodine excretion in Denmark of 43 μg/24 hours if the water contained no iodine. Values above this level corresponded to an average daily intake of 1.7 litre of water.

Using the average (Zealand) and highest (Skagen) reported concentrations of iodine in Danish tap water of 18.7 and 139 μg/l, respectively, from the Danish Food Composition Databank (Møller et al. 2005), and 0.03 and 0.08 l/kg bw/day as the median and 95th percentile consumption rates, respectively, (for children 1-10 years old), the intake from drinking water would be 0.6 and 11 μg I/kg bw/day, respectively. For an adult, assuming an average consumption rate of 1.4 l/day or a 90th percentile of 2.3 l/day, the daily exposure to iodine from drinking water would be 26 μg (average, about 0.4 μg/kg bw/day assuming an adult body weight of 70 kg) or 320 μg (90th percentile, about 4.6 μg/kg bw/day).

Using the reported average concentration of 5 mg/kg of iodine for most soils worldwide, and an intake of 0.0001 kg soil/day (median value for children 1-3 years old), the intake from soil would be 0.04 μg/kg bw/day (body weight of 13 kg).

In 2000, the iodisation of household salt and for salt used in commercial bread production became mandatory in Denmark. The iodine intake before and after mandatory iodization in Denmark has been assessed in two cross-sectional studies (Rasmussen et al. 2008). The first study (4946 participants) was performed in 1997-1998, i.e., before fortification of salt was introduced and the second study (3570 participants) was performed in 2004-2005, 4-5 years after mandatory iodization of salt. The studies took place in two cities (Copenhagen and Aalborg) representing areas with mild and moderate iodine deficiency, respectively, before fortification and comprised women aged 18-22, 25-30, 40-45 and 60-65 years and men aged 60-65 years. Iodine intake was assessed by a Food Frequency Questionnaire (FFQ) without taking the fortified products into account (i.e., without including iodine added to bread and household salt). Furthermore, the iodine concentration was measured in casual urine samples and the 24-hour iodine excretion was estimated.

The iodine excretion indicated an intake below the recommended level (150 μg/day) in all age groups before the fortification (median: 94 μg/day, 25th and 75th percentiles: 60 and 159). The iodine excretion increased significantly in all age groups after fortification (median: 145 μg/day, 25th and 75th percentiles: 100 and 226), but was still below the recommended level in the two youngest age groups in both cities and in women 40-45 years of age in Aalborg. The iodine excretion was higher in participants from Copenhagen than in participants from Aalborg. The iodine excretion was significantly lower in participants who did not take dietary supplements with iodine than in participants who took iodine supplements. The iodine intake from non-iodized food (based on FFQ) did not change (median: 109/110 μg/day, 25th and 75th percentiles: 79/82 and 149/146 before/after fortification, respectively).

In Denmark, a nation-wide dietary survey information on intake of iodine from food and beverages (including drinking water) was collected in the period 2003-
2008 from a representative sample of 3354 individuals aged 4-75 years (Pedersen et al. 2010), see Table 4 and Figure 1.

Table 4. Intake of iodine (μg/day) in Denmark 2003-2008 (Pedersen et al. 2010).

<table>
<thead>
<tr>
<th>Group</th>
<th>Group size</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>size</td>
<td></td>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Boys 4-9 year</td>
<td>253</td>
<td>191</td>
<td>62</td>
<td>185</td>
</tr>
<tr>
<td>Boys 10-17 years</td>
<td>265</td>
<td>206</td>
<td>77</td>
<td>198</td>
</tr>
<tr>
<td>Men 18-75 years</td>
<td>1569</td>
<td>210</td>
<td>79</td>
<td>199</td>
</tr>
<tr>
<td>Girls 4-9 year</td>
<td>229</td>
<td>168</td>
<td>50</td>
<td>158</td>
</tr>
<tr>
<td>Girls 10-17 years</td>
<td>330</td>
<td>164</td>
<td>63</td>
<td>153</td>
</tr>
<tr>
<td>Women 18-75 years</td>
<td>1785</td>
<td>176</td>
<td>67</td>
<td>167</td>
</tr>
<tr>
<td>Children 4-9 year</td>
<td>482</td>
<td>180</td>
<td>58</td>
<td>172</td>
</tr>
<tr>
<td>Children 10-17 years</td>
<td>595</td>
<td>183</td>
<td>73</td>
<td>174</td>
</tr>
<tr>
<td>Adults 18-75 years</td>
<td>3354</td>
<td>192</td>
<td>75</td>
<td>181</td>
</tr>
</tbody>
</table>

Figure 1. Content of iodine per 10 MJ in the diet (μg), frequency distribution and recommended nutrient density (▼) for planning diets for groups of individuals of both sexes aged 6-60 years (Pedersen et al. 2010).

Iodine containing dietary supplements could also be a major source of the daily human exposure to iodine. Recent dietary surveys indicate that about half (45%) of the adult Danish population and about two-thirds (64%) of the children regularly take vitamin and mineral supplements. About 28% of children and 26% of adults in Denmark daily consume a vitamin tablet all year around and another 28% and 12%, respectively, take vitamin tablets daily in the winter season. The frequency of regular intake has only decreased about 10% from 1995 to 2002 indicating that a fairly large and stable fraction of the population use multi-vitamin supplements. (Dietary habits of Danes 1995, 2000-2002).
Rasmussen et al. (2006) have estimated the upper 95th percentile intake of vitamins and minerals from food in various Danish age and gender groups and suggested that a daily multivitamin-mineral tablet is included in the calculation of total dietary intake levels of all vitamins and minerals.

The most common supplement used in Denmark is a combined multi-vitamin-mineral tablet usually containing 100% of the reference value for the recommended daily intake of vitamins and minerals. Two sets of reference values are used in the Danish legislation on dietary supplements; one valid for children aged 1-10 years and one for older children and adults. For iodine the reference values are 70 and 150 μg/day, respectively. (Rasmussen et al. 2006).

Table 5 summarises the estimated exposure from the various media.

Table 5. Estimated exposures from various media

<table>
<thead>
<tr>
<th>Medium</th>
<th>Adults (70 kg)</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>High exposure</td>
</tr>
<tr>
<td>Ambient air a)</td>
<td>1.9-3.7 ng/kg bw/day</td>
<td>2.9-5.7 ng/kg bw/day</td>
</tr>
<tr>
<td>Drinking water b)</td>
<td>0.4 μg/kg bw/day</td>
<td>-</td>
</tr>
<tr>
<td>Drinking water c)</td>
<td></td>
<td>4.6 μg/kg bw/day</td>
</tr>
<tr>
<td>Soil</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diet d)</td>
<td>2.7 μg/kg bw/day</td>
<td>4.0 μg/kg bw/day</td>
</tr>
<tr>
<td>Dietary supplement h)</td>
<td>2.1 μg/kg bw/day</td>
<td>3.5 μg/kg bw/day</td>
</tr>
</tbody>
</table>

a) Estimations based on an average global ambient air concentration of 10-20 ng/m³. For adults, average and high exposures are for average (13 m³/day) and high (20 m³/day) inhalation rates, respectively.

b) Estimations based on the average (Sjælland) reported concentration of iodine in Danish tap water of 18.7 μg/l.

c) Estimations based on the highest (Skagen) reported concentrations of iodine in Danish tap water of 139 μg/l.

d) Mean dietary intake of iodine from food and beverages of 192 μg/day.

e) 90 percentile intake of iodine from food and beverages of 282 μg/day.

f) Mean dietary intake of iodine from food and beverages, 180 μg/day for children (4-9 years), assumed body weight of 20 kg for children 4 years old.

g) 90 percentile intake of iodine from food and beverages, 256 μg/day for children (4-9 years), assumed body weight of 20 kg for children 4 years old.

h) Reference value for older children and adults of 150 μg/day.

i) Reference value for children 1-10 years old of 70 μg/day, assumed body weight of 20 kg for children 4 years old.

j) It should be noted that the estimated exposures from the diet also include iodide from drinking water.
2 Toxicokinetics

2.1 Absorption

2.1.1 Oral intake

Ingested molecular iodine is reduced to iodide in the gut and almost completely absorbed in this form by the small intestine (EFSA 2006, WHO 2003).

Gastrointestinal absorption of iodine is generally considered to be approximately 100% after ingestion of water-soluble iodine salts, such as potassium or sodium iodide. This conclusion is based on several types of observations made in human subjects who received oral doses of radioiodine (radioactive iodine). (ATSDR 2004):

Faecal excretion of $^{131}$I was <1% of the dose in seven euthyroid (the state of having normal thyroid gland function, as opposed to hyperthyroid (overactive thyroid) and hypothyroid (underactive thyroid)) adult subjects who ingested a single tracer dose of $^{131}$I, suggesting near complete absorption of the ingested radioiodine (Fisher et al. 1965 – quoted from ATSDR 2004). In the same study, 20 euthyroid adults received daily oral doses of potassium iodide for 13 weeks (0.25 or 1.0 mg I/day). Daily urinary iodine excretion was approximately 80-90% of the estimated daily intake, also suggesting near complete absorption.

Similarly, in an acute ingestion study of nine healthy subjects, urinary and thyroid radioiodine accounted for 97% of a single ingested tracer dose of radioiodine ($^{131}$I or $^{132}$I), suggesting near complete absorption of the tracer dose (Ramsden et al. 1967 – quoted from ATSDR 2004). In this same study, two subjects ingested the tracer dose together with a dose of 5 or 15 mg stable iodide (the chemical form of the stable iodide was not specified, but presumably, it was either potassium or sodium iodide) and the recoveries of radioiodine in the thyroid and urine were 96 and 98%, respectively. In one subject who ingested the tracer dose either after a fast (duration not specified) or with a “full stomach”, the recoveries of radioiodine in thyroid and urine were 97 and 98%, respectively.

Measurement of radioiodine uptake in the thyroid gland is also an indicator of absorption. Studies of iodine kinetics in subjects who received intravenous injections of tracer doses of radioiodine have shown that the fraction of an injected dose that accumulates in the thyroid is affected by many variables; however, it does not vary greatly among individuals who have the same iodine intake and whose thyroid glands are “normal”. This fraction has been shown to be similar (20-35%) when radioiodine is administered to adults by the intravenous or oral routes, suggesting extensive, if not complete, absorption of ingested radioiodine. (ATSDR 2004).

Gastrointestinal absorption of iodine appears to be similar in children, adolescents and adults, as assessed from measurements of 24-hour thyroid uptakes of radioiodine administered orally. Absorption in infants, however, may be lower than in children and adults, as assessed from studies in which thyroid uptake of radioiodine was measured in newborns who received tracer doses of radioiodine orally. (ATSDR 2004).
Iodide incorporated into food appears to be nearly completely absorbed. In a dietary balance study in which dietary iodide intakes (170-180 μg/day) and excretion were measured in 12 healthy adult women over two 7-day periods, urinary iodide excretion was 96-98% of the daily intake (Jahreis et al. 2001 – quoted from ATSDR 2004).

Iodine is extensively absorbed in rats when it is ingested as either molecular iodine or sodium iodide (ATSDR 2004):

When fasted rats were administered oral gavage tracer doses of $^{131}$I as either molecular iodine or sodium iodide, 8-9% of the dose was excreted in faeces in 72 hours and 34-35% of the dose was excreted in the urine (Thrall and Bull 1990 – quoted from ATSDR 2004). In the same study, similar results were obtained in rats that were allowed free access to food before the oral radioiodine dose; 6-7% of the dose was excreted in faeces in 78 hours and 22-29% was excreted in urine (22% of the molecular iodine dose and 29% of the sodium iodide dose).

### 2.1.2 Dermal contact

Systemic iodine toxicity has occurred following dermal exposures to iodine compounds, suggesting that these compounds of iodine are absorbed across the skin of humans (ATSDR 2004).

Dermal absorption rates for solutions of potassium iodide were measured in humans after topical applications of $^{131}$I (as potassium iodide) from the cumulative urinary excretion of radioactivity and the 24-hour radioactivity in the thyroid. Three subjects received a topical application of tracer concentrations of potassium iodide on a 12.5 cm² area of the forearm and the site was left uncovered. After 2 hours, all of the applied radioactivity could be detected on the skin and approximately 90% of the radioactivity could be recovered from the skin by washing with soap and water. Absorption was estimated to be approximately 0.1% of the applied dose (range 0.09-0.13) based on 3-day cumulative urine radioactivity. Thyroid radioactivity 24 hours after the topical dose was below the limits of detection. (Harrison 1963 – quoted from ATSDR 2004).

### 2.2 Distribution and elimination

The human body contains approximately 10-15 mg of iodine, of which approximately 70-90% is in the thyroid gland (ATSDR 2004, WHO 2003).

The concentration of iodine in serum is approximately 50-100 μg/l under normal circumstances. Approximately 5% in serum is in the inorganic form as iodide; the remaining 95% consists of various organic forms of iodine, principally protein complexes of the thyroid hormones $T_4$ and $T_3$. (ATSDR 2004).

Other tissues that can accumulate iodide to a concentration greater than that of blood or serum include the salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta and sweat glands (Brown-Grant 1961 – quoted from ATSDR 2004).

Muscle and eyes also contain high iodide concentrations (WHO 2003).

Absorbed iodine is excreted primarily in the urine and faeces, but is also excreted in breast milk, exhaled air, sweat and tears. Urinary excretion normally accounts for >97% of the elimination of absorbed iodine, while faecal excretion accounts for
approximately 1-2%. The whole-body elimination half time of absorbed iodine was estimated to be approximately 31 days in healthy adult males; however, there appears to be considerable inter-individual variability. (ATSDR 2004).

Maternal exposure to iodine results in exposure to the foetus. In humans, the accumulation of iodine in the foetal thyroid starts at approximately 70-80 days of gestation, and precedes the development of thyroid follicles and follicle colloid, which are generally detectable at approximately 100-120 days of gestation. Foetal iodide uptake activity increases with the development of the foetal thyroid and reaches its peak at approximately 6 months of gestation at which point, the highest concentrations in thyroid are achieved, approximately 5% of the maternal dose/g foetal thyroid (approximately 1% of the maternal dose). Following long-term exposure, the foetal/maternal ratio for thyroid radioiodine concentration has been estimated to be approximately 2-3. (ATSDR 2004).

Iodide is excreted in human milk. It has been shown that the fraction of an absorbed iodide dose excreted in the human milk varies with functional status of the thyroid gland and with iodine intake. A larger fraction of the absorbed dose is excreted in human milk in the hypothyroid state compared to the hyperthyroid state. In the hypothyroid state, uptake of absorbed iodide into the thyroid and incorporation into thyroid hormones is depressed, resulting in greater availability of the absorbed iodide for distribution to the mammary gland and human milk. (ATSDR 2004).

Measured concentrations of iodine in human milk are presented in section 1.3.4.

2.3 Physiological role

Iodine is an essential element in the synthesis of the thyroid hormones thyroxine (T4, 3,5,3',5'-tetraiodothyronine) and triiodothyronine (T3, 3,5,3'-triiodothyronine).

The recommended mean population intake for iodine is 100-150 μg/day and is considered adequate to maintain normal thyroid function, growth and development. In the presence of goitrogens (substances that interferes with thyroid function) in the diet, the iodine intake should be 200-300 μg/day. Pregnant and breastfeeding women need a higher iodine intake. (WHO 1996 – quoted from EFSA 2006).

The daily iodine intake recommendations by the WHO, UNICEF and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) are summarised in Table 6 (WHO 2004).

Table 6. Daily iodine intake recommendations by the WHO, UNICEF and ICCIDD (WHO 2004).

<table>
<thead>
<tr>
<th>Iodine intake</th>
<th>μg/day</th>
<th>μg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and children, 0-59 months</td>
<td>90</td>
<td>6-30</td>
</tr>
<tr>
<td>Children, 6-12 years</td>
<td>120</td>
<td>4</td>
</tr>
<tr>
<td>Adolescents and adults, from 13 years</td>
<td>150</td>
<td>2</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>200</td>
<td>3.5</td>
</tr>
<tr>
<td>Lactating women</td>
<td>200</td>
<td>3.5</td>
</tr>
</tbody>
</table>
The Nordic Nutrition Recommendations (NNR 2004) gives recommended daily intakes of certain vitamins and minerals in different age and sex groups. The recommended daily intake of iodine is summarised in Table 7.

Table 7. Recommended daily intake of iodine in the Nordic countries including Denmark (NNR 2004).

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended daily intake μg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>-</td>
</tr>
<tr>
<td>6-11 months</td>
<td>50</td>
</tr>
<tr>
<td>12-23 months</td>
<td>70</td>
</tr>
<tr>
<td>2-5 years</td>
<td>90</td>
</tr>
<tr>
<td>6-9 years</td>
<td>120</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>10-13 years</td>
<td>150</td>
</tr>
<tr>
<td>14-17 years</td>
<td>150</td>
</tr>
<tr>
<td>18-30 years</td>
<td>150</td>
</tr>
<tr>
<td>31-60 years</td>
<td>150</td>
</tr>
<tr>
<td>61-74 years</td>
<td>150</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>150</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>10-13 years</td>
<td>150</td>
</tr>
<tr>
<td>14-17 years</td>
<td>150</td>
</tr>
<tr>
<td>18-30 years</td>
<td>150</td>
</tr>
<tr>
<td>31-60 years</td>
<td>150</td>
</tr>
<tr>
<td>61-74 years</td>
<td>150</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>150</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>175</td>
</tr>
<tr>
<td>Lactating women</td>
<td>200</td>
</tr>
</tbody>
</table>

2.4 Mode of action

All biological actions of iodide in humans are attributed to the thyroid hormones. The major thyroid hormone secreted by the thyroid gland is T4. T4 in circulation is taken up by the cells and is de-iodinated to T3, the active form of thyroid hormone. While a physiological amount of iodine is required for insuring a normal thyroid function, a large excess of iodine can be harmful to the thyroid by inhibiting the process of synthesis and release of thyroid hormones, the Wolff-Chaikoff effect. (WHO 2004).

The Wolff-Chaikoff effect is temporary, and with repeated exposure to high doses of iodide, the thyroid gland return to normal levels of hormone synthesis, referred to as escape from the Wolff-Chaikoff effect. The mechanism for the Wolff-Chaikoff effect appears to involve inhibition of both iodide transport and iodination reactions. Escape is thought to be the result of down regulation of NIS (the iodide carrier in the thyroid gland) resulting in a decrease in the intra-thyroidal iodine and the resumption of normal hormone synthesis. Escape occurs when transport of iodide into the thyroid gland and the thyroid iodide concentration are sufficiently depressed to cancel the inhibition of the production of the thyroid hormones. (ATSDR 2004).

Humans seem to be less sensitive than rodents concerning thyroid disturbances even though the basic hypothalamic-pituitary-thyroid axis functions in a similar way in animals and humans. The greater sensitivity in rodents is partly due to considerable species differences with respect to binding of hormones to transport
proteins in the plasma. In humans and monkeys, circulating T4 is bound primarily to TBG (thyroxine binding globulin) (50-80% T4 binding in plasma), which has a binding affinity for T4 approximately one thousand times higher than TTR (transthyretin). This high affinity binding protein is only present in smaller amounts in dogs, and not (or only to a negligible extent) present in rodents, birds, amphibians or fish. In these species, T4 is primarily bound to TTR. In humans only 10-40% are transported by TTR. As a result of this weaker binding to TTR, the total plasma T4 concentration is lower, the unbound or free fraction of circulation T4 is higher, and hormone turnover is more rapid in these species compared with man (t½ is 12-24 hours in rats and 5-9 days in humans). The result of the shorter plasma half-life is that a rat without a functional thyroid gland requires about ten times more T4 for full substitution than an adult human. The differences are also reflected in the circulating TSH (thyroid stimulating hormone) levels, which are about twenty times higher in rodents than in man. T3 is transported bound to TBG and albumin in humans, monkeys and dogs, but only to albumin in rodents and chickens. (TemaNord 2002).
3 Human toxicity

All biological actions of iodine in humans are attributed to the thyroid hormones (T4 and T3) and the synthesis of normal quantities of thyroid hormones requires an adequate intake of iodide (ATSDR 2004, EFSA 2006).

The principal direct effects of excessive intake of stable iodine are on the thyroid gland and regulation of thyroid hormone production and secretion. Effects on the thyroid gland can be classified into three types: hypothyroidism and hyperthyroidism, the outcome depending on the initial and current iodine status and current thyroid dysfunction, as well as thyroiditis. (ATSDR 2004, EFSA 2006). Hypothyroidism refers to the diminished production of thyroid hormones leading to clinical manifestations of thyroid insufficiency and can occur with or without goitre, a functional hypertrophy (enlargement) of the thyroid gland in response to suppressed thyroid hormone production and elevated serum thyroid stimulating hormone (TSH, the pituitary hormone also known as thyrotropin) concentrations. Typical biomarkers of hypothyroidism are a depression in the circulating levels of T4 and/or T3 below their normal ranges, which is always accompanied by an elevation of TSH above the normal range (Wolff-Chaikoff iodide effect), often referred to as 'clinical hypothyroidism'. An observed increase in serum TSH level and normal T4 and T3 levels is referred to as 'subclinical hypothyroidism'. The effects may be transient and in many individuals, the thyroid can escape the Wolff-Chaikoff effect.

Hyperthyroidism is an excessive production and/or secretion of thyroid hormones. Typical biomarkers of hyperthyroidism are an elevation in the circulating levels of T4 and/or T3 above their normal ranges, which is always accompanied by a depression of TSH below the normal range. The clinical manifestation of abnormally elevated circulating levels of T4 and/or T3 is often referred to as thyrotoxicosis or Graves disease or Basedows disease. The term 'subclinical hyperthyroidism' refers to a condition in which the circulating levels of T4 or T3 are normal and the serum TSH concentration is suppressed.

Thyroiditis refers to an inflammation of the thyroid gland, which is often secondary to thyroid gland autoimmunity and can result in hypothyroidism or hyperthyroidism. Thyroid autoimmunity can be detected as a presence of IgG antibodies to thyroglobulin and thyroid peroxidase in serum.

The above three types of effects can occur in children and adults, in foetuses exposed in utero, or in infants during lactation (ATSDR 2004, EFSA 2006). Some subpopulations such as those suffering from autoimmune thyroiditis, from iodine deficiency disorders (IDD) or nodular goitre with autonomous functioning nodules are sensitive to external iodine supply. They tend to respond adversely to levels of iodide, which are without adverse effects in the general population. (EFSA 2006).

Adverse effects on a wide variety of other organ systems can derive secondarily from iodine-induced disorders of the thyroid gland, including disturbances of the skin, cardiovascular system, pulmonary system, kidneys, gastrointestinal tract, liver, blood, neuromuscular system, central nervous system, skeleton, male and female reproductive systems, and numerous endocrine organs, including the pituitary and adrenal glands. (ATSDR 2004, EFSA 2006).
Chronic iodide exposure results in iodism; the symptoms resemble those of a sinus cold but may also include salivary gland swelling, gastrointestinal irritation, acneform skin, metallic or brassy taste, gingivitis, increased salivation, conjunctival irritation, and oedema of eyelids (WHO 2003).

3.1 Single dose toxicity

Oral doses of 2000-3000 mg iodine (30-40 mg I/kg bw) are probably lethal to humans, but survival has been reported after ingestion of 10-15 g (WHO 2003, EFSA 2006).

Iodide has been used in the past as an expectorant in the treatment of asthma and related conditions at a typical dose of 3.3 mg/kg mostly without adverse reactions (EFSA 2006, WHO 2003).

Acute oral toxicity is primarily due to irritation of the gastrointestinal tract, marked fluid loss and shock occurring in severe cases (WHO 2003).

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 (ATSDR 2004).

3.2 Irritation

Irritation of the gastrointestinal tract has been observed following oral ingestion of high doses (WHO 2003).

3.3 Sensitisation

In rare instances, a hypersensitisation reaction may occur immediately after or within several hours of oral or dermal exposure to iodide. The most striking symptoms are angio-oedema (acute, transitory swelling of the face, hands, feet, or viscera) and swelling of the larynx, which may cause suffocation. (WHO 2003).

Iodide can give rise to reactions such as urticaria, angio-oedema, polymyalgia, conjunctivitis, coryza (inflammation of the mucous membranes lining the nasal cavity), iodide fever, headache, salivary gland enlargement, cerebral symptoms and hypotension. Iododerma, eosinophilia, pruritic rashes, vesicular eruptions and fungoid eruptions may also occur. (EFSA 2006).

3.4 Repeated dose toxicity

A large number of studies have examined the effects of excess iodine on thyroid hormone status or the occurrence of thyroid diseases. Below, the information on repeated dose toxicity of iodine and water-soluble inorganic iodides of relevance for the estimation of a health-based quality criterion in drinking water for iodides is summarised.

Experimental studies, where the effects of an increased iodine intake have been investigated in subjects given iodide supplementation, are presented in section 3.4.1. Epidemiological studies are presented in section 3.4.2.
3.4.1 Experimental studies

Healthy euthyroid (9 men, mean age 34 years; 23 women, mean age 32 years) as well as 5 age-matched euthyroid controls received daily oral doses of 250, 500 or 1500 μg I/day (as sodium iodide) for 14 days. The parameters examined were PBI (protein-bound iodine), total serum iodine, T4, T3, TSH, integrated 1-hour serum TSH response to an intravenous dose of 500 μg thyrotropin-releasing hormone (TRH), and 24-hour urinary iodine excretion. Based on the 24-hour urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be approximately 200 μg I/day; thus, the total iodide intake was approximately 450, 700 or 1700 μg I/day (approximately 6.4, 10, 24 μg I/kg bw/day, respectively, for a 70-kg adult). (Paul et al. 1988 – quoted from EFSA 2006 and ATSDR 2004).

Subjects who received 1700 μg I/day had increased total serum iodine without affecting the PBI, significantly decreased (5-10%) serum T4 (total and free) and T3 (total) compared to pre-treatment levels, significantly increased (47%) serum TSH compared to pre-treatment levels, and increased TSH response to TRH (in women more than in men). The TSH response to TRH was also increased (not significantly) in subjects receiving 700 μg I/day. No biochemical effects were detected in subjects receiving 450 μg I/day.

According to ATSDR all hormone levels were within the normal range during treatment and, therefore, the subjects were not hypothyroid. However, a limitation of the study was that it included a relatively small number of subjects, although the exposures to these subjects were controlled and quantified with high certainty. According to EFSA, the study used only small groups, extended over only 2 weeks and the dietary iodine intake was not determined analytically but was estimated.

In a similar type of study, groups of 10 healthy, euthyroid males (mean age 27 years) received daily oral doses of 500, 1500 or 4500 μg I/day (as sodium iodide) for 2 weeks. Serum levels of T3, T4, TSH, PBI, and total iodide, the TSH response to intravenous TRH, and 24-hour urinary excretion of iodide were measured before treatment and again on day 15. Based on 24-hour urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be 250-320 μg/day; thus, the total estimated iodide intake was approximately 300, 800, 1800 or 4800 μg I/day (approximately 4, 11, 26, or 69 μg I/kg bw/day, respectively, for a 70-kg adult). (Gardner et al. 1988 – quoted from EFSA 2006 and ATSDR 2004).

Serum T4 (total and free) decreased significantly (10%), relative to pre-treatment levels, after intakes of 1800 and 4800 μg I/day, but not after 800 μg I/day. Serum T3 did not change at any dose level. Serum TSH was significantly increased (48%), relative to pre-treatment levels, in subjects receiving 1800 and 4800 μg I/day, but remained unchanged in those receiving 800 μg I/day. The TSH response to TRH was significantly enhanced with all iodide doses administered.

According to EFSA, no adverse effects were reported and no significant symptoms of thyroid dysfunction were noted. However, only small groups of subjects were studied, only males were examined, exposure was rather short and the actual dietary intake of iodine was not determined analytically but estimated.

According to ATSDR, the magnitude of the changes at the higher iodide dosages yielded hormone concentrations that were within the normal range and, thus, would not represent a significant thyroid suppression. This suggests that an oral intake of 500 μg I/day above a pre-existing dietary intake, or approximately 800 μg I/day total (11 μg I/kg/day), is tolerated without thyroid gland suppression in healthy adult males, and intakes as high as 4800 μg I/day (69 μg I/kg/day) may be tolerated in some people without clinically adverse effects. ATSDR also noted that the study
included a relatively small number of subjects, whose exposures were controlled and quantified with high certainty.

No clinical abnormalities in thyroid hormone status occurred when healthy, euthyroid, adult males (n = 6 or 7), who had no history of thyroid-related illness, ingested daily oral doses of 300 or 1000 μg I/kg bw/day (21 or 70 mg I/day for a 70-kg adult) as either molecular iodine or sodium iodide for 14 days. Based on measurements of urinary iodide excretion rates, the pre-treatment iodide intakes were approximately 100 μg I/day. The high dosage produced a small but statistically significant increase in serum TSH compared to a sodium chloride control group; the serum TSH did not exceed the normal range and reverted to control levels within 10 days after the iodine supplementation was ended. Serum T4 and T3 were not significantly different in the treatment groups, compared to the control group. (Robison et al. 1998 – quoted from ATSDR 2004).

According to ATSDR, studies of this size have low statistical power, which complicates the interpretation of findings of no significant effect.

In a study, 30 healthy elderly adult females, without evidence of thyroid peroxidase antibodies (TPA), received daily oral doses of 500 μg I/day (as potassium iodide) for 14 or 28 days. Based on urinary iodide measurements prior to the iodide supplement, the background iodine intake was estimated to be 72-100 μg/day; thus, the total estimated iodide intake was approximately 600 μg I/day (approximately 9 μg I/kg bw/day, for a 70-kg adult). (Chow et al. 1991 – quoted from ATSDR 2004).

Serum T4 (free) was significantly decreased and serum TSH was significantly increased in the treated group, relative to a placebo control group. According to ATSDR, on average, the magnitude of the changes did not produce clinically significant depression in thyroid hormone levels; however, five subjects had serum TSH that exceeded the normal range.

The effect of supplementation of normal dietary intakes (about 250 μg I/day) with 500 μg I/day, giving a total iodide intake of approximately 750 μg I/day, or a placebo for a period of 28 days, on the serum levels of free T4 and TSH was carried out in women selected from a general practice in Cardiff. The groups studied were aged 25-54 years and thyroid antibody positive (sub-clinical Hashimoto’s thyroiditis) (n = 20) or antibody negative (n = 30), or aged 60-75 years and from an area with adequate dietary iodine supply (n = 29) or from an area that was previously iodine deficient (n = 35). According to EFSA, the study was described as a randomised placebo-controlled trial, but it is not clear whether the study was of crossover or parallel group design. (Chow et al. 1991 – quoted from EFSA 2006).

Small decreases in T4 (free) levels and small increases in TSH levels, indicating mild biochemical hypothyroidism, occurred in all iodide-supplemented subjects of all groups. None of the groups on supplemental iodide showed any incidence of hyperthyroidism. Following iodide supplementation, TSH levels increased above the normal level in 3 of the 60-75 year old subjects, while the raised TSH levels increased even further in 2 antibody-positive subjects.

Euthyroid patients (37 females, 3 males) from an iodine-deficient region, who were diagnosed with Hashimoto’s thyroiditis and who were positive for anti-thyroid (thyroid peroxidase) antibodies, received an oral dose of 250 μg potassium iodide (190 μg I/day) for 4 months. A similar group of thyroiditis patients (41 females, 2 males) served as controls. Based on urinary iodide measurements of 72 μg I/g creatinine before the iodide supplementation, the pre-existing iodide intake was approximately 125 μg I/day and thus, the total iodide dosage was 315 μg I/day (4.5.
μg I/kg bw/day) in the treatment group. (Reinhardt et al. 1998 – quoted from ATSDR 2004).

Seven patients in the treatment group developed elevated serum TSH concentrations (> 4 mIU/l) and one patient developed overt clinical hypothyroidism with a TSH concentration of 43.3 mIU/l and a serum T4 (free) concentration of 7 pmol/l. One patient in the treatment group became clinically hyperthyroid with a serum T4 (free) concentration of 30 pmol/l and a TSH concentration below 1 mIU/l. One patient in the control group developed mild sub-clinical hypothyroidism. After the iodine supplementation was discontinued, three of the seven hypothyroid patients in the treatment group reverted to normal thyroid status. An additional patient in the treatment group became hypothyroid, requiring T4 supplements. The patient who became hyperthyroid while in the treatment group reverted to normal thyroid status after the iodide supplement was discontinued.

No adverse health effects were reported in men who drank water providing iodide at doses of 0.17-0.27 mg/kg bw/day for 26 weeks (Morgan and Karpen 1953 – quoted from WHO 2003).

In a 5-year study where iodinated drinking water (1 mg/l, for disinfection purposes) was supplied to 750 male and female prison inmates, no cases of hyper- or hypothyroidism, no sensitisation reactions, and no iodism were noted. The average dose was approximately 30 μg/kg bw. There was a small but statistically significant decrease in 131I uptake by the thyroid and an increase in protein-bound iodine (PBI). Four hyperthyroid women became more hyperthyroid. (Stockton and Thomas 1978 – quoted from EFSA 2006; Thomas et al. 1969 – quoted from WHO 2003). According to EFSA, the difficulties with this study were the imprecise estimates of intakes from the diet and fluid consumption of the participating individuals as well as the variable exposure time but the group size and duration of exposure were adequate.

### 3.4.2 Epidemiological studies

A number of epidemiological studies have addressed the effect of varying amounts of iodine intake on the prevalence rate of various thyroid abnormalities. Some of these studies, considered of relevance for the estimation of a health-based quality criterion in drinking water for iodides, are addressed below and summarised in Table 8.

Random samples of elderly subjects were selected from Randers (Jutland, Denmark) (n = 423, age 68 years) with low iodine intake (40-60 μg I/day) and from Iceland (n = 100, age 66-70 years) with longstanding relatively high iodine intake (300-350 μg I/day) (Laurberg et al. 1998).

The median iodine concentration in morning spot urine was 38 μg/l (range: 6-770 μg/l) and 150 μg/l (range: 33-703 μg/l) in the subjects from Jutland and Iceland, respectively. Females from Jutland had a high prevalence of goitre or previous goitre surgery (12.2%), compared with males from Jutland (3.2%) and females (1.9%) and males (2.2%) from Iceland. Abnormal thyroid function was very common in both areas, with serum TSH outside the reference range in 13.5% of subjects from Jutland and 19% of those from Iceland. In Jutland, it was mainly thyroid hyperfunction (9.7% had low, 3.8% had high serum TSH), whereas in Iceland, it was impaired thyroid function (1% had low, 18% had high serum TSH). All subjects with serum TSH above 10 mIU/l had auto-antibodies in serum; antibodies were, in general, more common in Jutland than in Iceland. According to the authors, a major source of iodine intake in Iceland may be iodine in dairy products caused by feeding of cattle with fish meal as the iodine
concentrations in two dairy milk samples from Reykjavik were 270 and 229 μg/l, whereas tap water contained less than 1 μg/l.

Elderly patients (nursing home residents) were screened for thyroid disorders from A) an iodine-deficient area in Northern Hungary (n = 119, median age 81 years, median iodine excretion 72 μg I/g creatinine); B) an area of obligatory iodinated salt prophylaxis since the 1950s in Slovakia (n = 135, median age 81 years, median iodine excretion 100 μg I/g creatinine); and C) an abundant iodine intake area in Eastern Hungary (n = 92, median age 78 years, median iodine excretion 513 μg I/g creatinine). According to ATSDR the iodine intakes were approximately 117, 163, or 834 μg I/day (1.7, 2.3, or 12 μg I/kg bw/day) for the three regions, respectively. The prevalence of hypothyroidism (clinical: elevated serum TSH together with serum FT4 (free T4) below the normal range; subclinical: elevated serum TSH together with normal serum FT4) was highest in the iodine-rich regions (B and C) with all clinical cases except one being antibody positive and with 3/5, 5/14 and 3/22 subclinical cases from region A, B and C, respectively, being antibody positive. The overall prevalence of antibody positivity was similar in the three regions (A: 19.3%; B: 24.4%; C: 22.8%). In contrast, the occurrence of hyperthyroidism (clinical plus sub-clinical) and goitre was highest in the iodine-deficient region A. (Szabolcs et al. 1997).

Thyroid status was examined in children (7-15 years) from two villages in central China where the iodine concentrations in drinking water were 463 μg/l (120 children) or 54 μg/l (51 children). Clinical thyroid status was assessed and goitre size was graded with modified WHO criteria (grade 0: no goitre, grade 1: palpable goitre, grade 2: visible goitre, grade 3: very large goitre). (Li et al. 1987). Urinary iodine was 1236 μg I/g creatinine in the high iodine group and 428 μg I/g creatinine in the low iodine group. According to ATSDR (2004), the above urinary iodine/creatinine ratios are approximately equivalent to iodine excretion rates or steady state ingestion rates of 1150 μg I/day (29 μg I/kg bw/day) and 400 μg I/day (10 μg I/kg bw/day) in the high and low iodide groups, respectively (assuming a body weight of 40 kg and lean body mass of 85% of body weight).

All subjects from both villages were clinically euthyroid with normal values for serum thyroid hormones and serum TSH. The mean serum T4 was similar in the two groups, the mean serum FT4 (free T4) was slightly higher in the high iodine group, the mean T3 was significantly lower in the high iodine group, and the mean serum TSH was significantly higher in the high iodine group. Goitre was present in 65% of children in the high iodine group (20% grade 2) compared to 15% in the low iodine group (none grade 2). Thyroid ultrasound assessment accorded with the clinical goitre grading. The mean thyroid gland volume, measured with ultrasonography, was greater in the high iodine group (13.3 ml) than in the low iodine group (5.9 ml).

The relation of iodine content of household water to thyroid size and urinary iodine excretion was assessed among children in an area with high iodine concentration in the water in the Jiangsu Province, China (Zhao et al. 2000). The goitre prevalence in schoolchildren in the 1980s was 25%, suggesting iodine deficiency, whereas urinary iodine concentrations in adults indicated iodine excess. The iodine concentration in drinking water was measured in 1151 wells from 65 townships; concentrations ranged from 0.4 to 2804 μg I/l (median: 552 μg I/l), 76% of the samples had a median greater than 300 μg I/l. The 65 townships were divided into 5 groups based on the median water iodine concentrations (<300, 300-499, 500-699, 700-899, ≥ 900 μg I/l). In 12 townships, 2-3 selected from each of the 5 groups, palpation of the thyroid was performed in a total of 2471 children (6-15 years); the prevalence of goitre ranged from 12-38%. Ultrasonography was performed in 1069 children from 5 townships; the prevalence
of abnormal thyroid volume (not defined in the publication) ranged from 5-17%. The median urinary iodine concentration from 607 adults (47-53 individuals from each of the 12 townships) ranged from 520-1961 μg/l; 85% of the urine samples had concentrations greater than 500 μg/l, and 53% had concentrations greater than 1000 μg/l. There was a positive correlation between water iodine levels and urinary iodine as well as indicators of thyroid size (goitre and volume), see also Table 8. According to ATSDR (2004), the observed range of urinary iodine concentrations in adults (520-1961 μg/l) corresponded to approximate intakes of 730-2750 μg I/day (12-46 μg I/kg bw/day) (assuming an adult urine volume of 1.4 l/day and an adult body weight of 60 kg).

In China, with the introduction of iodized salt in 1996, the median urinary iodine increased from 165 μg I/l in 1995 to 330 μg I/l in 1997 and stabilized at a similar level of 306 μg I/l in 1999. (Chen et al. 2001 – quoted from Teng 2006, 2008).

A cohort study (1999-2004) including 3761 subjects (> 13 years of age) from three regions in China with different iodine intake levels examined the effect of iodine intake on thyroid diseases in China. Of the 3761 subjects who were enrolled at baseline (1999), 3018 (80.2%) participated in the follow-up study. Levels of thyroid hormones and thyroid auto-antibodies in serum, and iodine in urine were measured, and ultrasonography of the thyroid was performed, at baseline and follow-up (2004). (Teng et al. 2006).

The cohorts from the three regions were characterised based on median urinary iodine excretion as having a 'mildly deficient' iodine intake (excretion 84/88 μg I/l), a 'more than adequate' intake (excretion 243/214 μg I/l), and an 'excessive' intake (excretion 651/634 μg I/l) in 1999/2004, respectively. The median iodine content in drinking water was 8.2/10, 4.6/7.8, and 202/202 (1999/2004, respectively) in the 'mildly deficient', 'more than adequate', and 'excessive' intake regions, respectively. Iodine in salt was <3.4/<3.4, 54.5/45.6, and 23.3/25.9 mg/kg (1999/2004, respectively) in the three regions, respectively. The prevalence of thyroid diseases was calculated at baseline (1999), and the incidence is the cumulative incidence between 1999 and 2004. For autoimmune thyroiditis, the prevalence was 0.5, 1.7 and 2.8%, and the cumulative incidence 0.2, 1.0 and 1.3%, in the three regions respectively; and for Graves’ disease (an autoimmune disease of the thyroid gland that results in the overproduction of thyroid hormone): 1.4, 1.3 and 1.1% (prevalence), 0.8, 0.6, 0.6% (incidence), respectively. The prevalence and cumulative incidence for overt and sub-clinical hypothyroidism and hyperthyroidism are presented in Table 8. The authors concluded that ‘more than adequate’ or ‘excessive’ iodine intake may lead to hypothyroidism and autoimmune thyroiditis.

In a more recent study (from 2005) of 778 women, the optimal range of iodine intake was investigated by comparing the prevalence of thyroid disease in three areas in China with slightly different iodine intake levels (Teng et al. 2008). The same parameters as in the Teng et al. (2006) study were analysed, see above.

The groups from the three areas were characterised based on median urinary iodine excretion as having 'mild iodine deficiency' (excretion 78 μg I/l), 'iodine adequacy' (excretion 114 μg I/l), and 'iodine more than adequacy' (excretion 223 μg I/l). The prevalence of hypothyroidism (clinical and sub-clinical) was 0, 1.13 and 2.84%, in the three areas, respectively; that of hyperthyroidism (clinical and sub-clinical) was 6.6, 3.1 and 3.3%, respectively; and that of thyroid goitre was 25, 5.7 and 11%, respectively. According to the authors, median urinary iodine excretion of 100-200 μg I/l, may reflect a safe range of iodine intake levels.
Table 8. Summary of effects on the thyroid, epidemiological studies.

<table>
<thead>
<tr>
<th>Urinary iodine (μg/litre)</th>
<th>Iodine intake (μg/day)</th>
<th>Iodine drinking water (μg/litre)</th>
<th>Prevalence subclinical hypothyroidism b) (%)</th>
<th>Prevalence clinical hypothyroidism (%)</th>
<th>Prevalence subclinical hyperthyroidism (%)</th>
<th>Prevalence clinical hyperthyroidism (%)</th>
<th>Prevalence thyroid goitre (%)</th>
<th>Prevalence abnormal thyroid volume (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 (6-770)</td>
<td>40-60</td>
<td>See text</td>
<td>See text</td>
<td>See text</td>
<td>See text</td>
<td>$\delta$: 3.2; $\varphi$: 12.2</td>
<td>Laurberg et al. (1998)</td>
<td></td>
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<tr>
<td>150 (33-703)</td>
<td>300-350</td>
<td>&lt; 1</td>
<td>See text</td>
<td>See text</td>
<td>See text</td>
<td>$\delta$: 2.2; $\varphi$: 1.9</td>
<td>Laurberg et al. (1998)</td>
<td></td>
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<tr>
<td>72 $^a$</td>
<td>117 $^a$</td>
<td>4.2</td>
<td>0.8</td>
<td>3.4</td>
<td>39.4</td>
<td>Szabolcs et al. (1997)</td>
<td></td>
<td></td>
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<tr>
<td>100 $^a$</td>
<td>163 $^a$</td>
<td>10.4</td>
<td>1.5</td>
<td>3.0</td>
<td>16.4</td>
<td>Szabolcs et al. (1997)</td>
<td></td>
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<tr>
<td>513 $^a$</td>
<td>834 $^a$</td>
<td>23.9</td>
<td>7.6</td>
<td>0</td>
<td>12.2</td>
<td>Szabolcs et al. (1997)</td>
<td></td>
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<tr>
<td>428 $^a$</td>
<td>400 $^a$</td>
<td>54</td>
<td>15</td>
<td></td>
<td></td>
<td>Li et al. (1987)</td>
<td></td>
<td></td>
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<tr>
<td>1236 $^a$</td>
<td>1150 $^a$</td>
<td>463</td>
<td>65</td>
<td></td>
<td></td>
<td>Li et al. (1987)</td>
<td></td>
<td></td>
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<tr>
<td>520</td>
<td>730 $^a$</td>
<td>187</td>
<td></td>
<td>12</td>
<td>-</td>
<td>Zhao et al. (2000)</td>
<td></td>
<td></td>
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<tr>
<td>619</td>
<td>204</td>
<td></td>
<td>15</td>
<td>-</td>
<td>Zhao et al. (2000)</td>
<td></td>
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<tr>
<td>802</td>
<td>290</td>
<td></td>
<td>15</td>
<td>5</td>
<td>Zhao et al. (2000)</td>
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<td></td>
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<tr>
<td>759</td>
<td>311</td>
<td></td>
<td>22</td>
<td>-</td>
<td>Zhao et al. (2000)</td>
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<tr>
<td>871</td>
<td>315</td>
<td></td>
<td>21</td>
<td>9</td>
<td>Zhao et al. (2000)</td>
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<td>1194</td>
<td>537</td>
<td></td>
<td>22</td>
<td>-</td>
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<td>1256</td>
<td>543</td>
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<td>23</td>
<td>10</td>
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<tr>
<td>1260</td>
<td>550</td>
<td></td>
<td>28</td>
<td>-</td>
<td>Zhao et al. (2000)</td>
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<tr>
<td>1352</td>
<td>745</td>
<td></td>
<td>30</td>
<td>-</td>
<td>Zhao et al. (2000)</td>
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<tr>
<td>1483</td>
<td>754</td>
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<td>35</td>
<td>13</td>
<td>Zhao et al. (2000)</td>
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<td>1282</td>
<td>952</td>
<td></td>
<td>36</td>
<td>-</td>
<td>Zhao et al. (2000)</td>
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<td></td>
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<tr>
<td>1961</td>
<td>2750 $^a$</td>
<td>1145</td>
<td>38</td>
<td>17</td>
<td>Zhao et al. (2000)</td>
<td></td>
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<tr>
<td>84 / 88 $^a$</td>
<td>8.2 / 10 $^b$</td>
<td>0.9 / 0.2 $^b$</td>
<td>0.3 / 0.2 $^b$</td>
<td>3.7 / 1.4 $^b$</td>
<td>1.6 / 1.4 $^b$</td>
<td>Teng et al. (2006)</td>
<td></td>
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<tr>
<td>243 / 214 $^a$</td>
<td>4.6 / 7.8 $^a$</td>
<td>2.9 / 2.6 $^a$</td>
<td>0.9 / 0.5 $^a$</td>
<td>3.9 / 2.0 $^a$</td>
<td>2.0 / 0.9 $^a$</td>
<td>Teng et al. (2006)</td>
<td></td>
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<tr>
<td>651 / 634 $^a$</td>
<td>202 / 202 $^a$</td>
<td>6.1 / 2.9 $^a$</td>
<td>2.0 / 0.3 $^a$</td>
<td>1.1 / 1.0 $^a$</td>
<td>1.2 / 0.8 $^a$</td>
<td>Teng et al. (2006)</td>
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<tr>
<td>78.1</td>
<td>0</td>
<td>0</td>
<td>4.69</td>
<td>1.88</td>
<td>24.88</td>
<td>Teng et al. (2006)</td>
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<tr>
<td>113.8</td>
<td>1.13</td>
<td>0</td>
<td>2.26</td>
<td>0.85</td>
<td>5.65</td>
<td>Teng et al. (2006)</td>
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<tr>
<td>223.3</td>
<td>1.9</td>
<td>0.95</td>
<td>2.64</td>
<td>0.45</td>
<td>11.37</td>
<td>Teng et al. (2006)</td>
<td></td>
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</tbody>
</table>

a) Median value
b) TSH↑, fT4 normal
c) TSH↑, fT4

1) Unit: μg/I/g creatinine
2) Intake calculated from μg/I/g creatinine (ATSDR 2004)
3) Assuming a body weight of 40 kg and lean body mass of 85% of body weight
4) Intake calculated from urinary iodine (μg/litre) assuming an adult urine volume of 1.4 l/day and an adult body weight of 60 kg
5) Values are for 1999 / 2004, respectively
Laurberg et al. (2001) have suggested iodine intake intervals associated with an increase in the risk of thyroid disease based on epidemiological data. The intake level was defined from the median 24-hour urinary iodine excretion of the adult population or subpopulation, see Table 9. The optimal iodine intake was defined as a relatively narrow interval of 120-220 μg iodine excreted in the urine per 24 hours. This included the officially recommended intake of 150 μg/day, as the urinary iodine excretion was approximately 90% of intake (WHO-FAO-IAEA 1996 – quoted in Laurberg et al. 2001).

According to the authors, the upper limit of mild iodine deficiency of 120 μg per 24 hours was based on studies from Copenhagen demonstrating that nodular thyroid disease with hyperthyroidism is prevalent even when the median urinary iodine excretion approaches 100 μg per 24 hour. The upper limit of optimal iodine intake of 220 μg per 24 hours was set relatively low, as the incidence of hypothyroidism apparently starts to increase slowly with increasing iodine intake already below the optimal iodine intake level and this becomes worse with higher iodine intake.

Table 9. Deficient and excessive population iodine intake (Laurberg et al. 2001).

<table>
<thead>
<tr>
<th>Median 24-hour urinary iodine excretion of population or subpopulation</th>
<th>Risk associated with iodine intake level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe iodine deficiency</td>
<td>&lt; 25 μg</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Moderate iodine deficiency</td>
<td>25-60 μg</td>
</tr>
<tr>
<td>Mild iodine deficiency</td>
<td>60-120 μg</td>
</tr>
<tr>
<td>Optimal iodine intake</td>
<td>120-220 μg</td>
</tr>
<tr>
<td>Mild iodine excess</td>
<td>220-400 μg</td>
</tr>
<tr>
<td></td>
<td>400-800 μg</td>
</tr>
<tr>
<td>Severe iodine excess</td>
<td>&gt; 800 μg</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) If the 24-hour urine volume is around 1.5 litre, optimal iodine intake gives a median non-fastiging spot urine concentration of ~80-150 μg/l. Values are for populations of adults. Intake should be ~50 μg per 24 hours higher in pregnant and lactating women (Laurberg et al. 2001).

Oral exposure to excess iodide can, under certain circumstances, induce hyperthyroidism. The epidemiological and clinical literatures suggest that iodide-induced hyperthyroidism occurs most often in people who have a previous history of iodine deficiency and goitre. Epidemiological designs have been applied to several populations, in which dietary iodide was supplemented as a prophylaxis for iodine deficiency and goitre. These studies confirm that iodide supplementation of iodide-deficient diets, to achieve intakes in the range of 3-7 μg I/kg bw/day (210-470 μg I/day – 70 kg person), results in a detectable increase in the incidence of hyperthyroidism. Cases of iodine-induced hyperthyroidism in people who were euthyroid and without apparent thyroid disease have also been reported; however, only a few have provided dose information, suggesting effects after oral doses of 3-1440 mg/day (0.04-21 mg/kg bw/day – 70 kg person) for 6 months. (ATSDR 2004).
Several studies have been conducted in people who reside in endemic goitre areas and who received iodide supplementation. These studies suggest that iodine intakes of 230-420 μg I/day (3.3-6.0 μg I/kg bw/day for a 70 kg person) for 12 months can induce thyroid autoimmunity. (ATSDR 2004).

Whether iodine excess may trigger the development of autoimmune thyroid disease such as lymphocytic Hashimotos thyroiditis (LT) was examined by comparing the presence of thyroid autoantibodies in goitrous children (29, age: 7-15 years), from an iodine excess area, with healthy children (26, age: 7-15 years), from an iodine sufficient area, of north central China (Boyages et al. 1989). The children were from the same area as those examined in the epidemiological study by Li et al. (1987), see previous section.

Urinary iodine was 1236 μg I/g creatinine in the high iodine group and 428 μg I/g creatinine in the low iodine group. According to ATSDR (2004), the above urinary iodine/creatinine ratios are approximately equivalent to iodine excretion rates or steady state ingestion rates of 1150 μg I/day (29 μg I/kg bw/day) and 400 μg I/day (10 μg I/kg bw/day) in the high and low iodide groups, respectively (assuming a body weight of 40 kg and lean body mass of 85% of body weight).

In the high iodine group 11 of 29 (38%) individuals had elevated TSH levels, but only one case showed serum TSH greater than 10 mIU/l. In all cases except the latter, serum T4 levels were in the normal range. No increased prevalence of LT was found in patients with endemic iodine goitre as the levels of various antibodies did not differ significantly between the two groups of children.

### 3.5 Toxicity to reproduction

Repeated oral exposure to excess iodine may produce hypothyroidism or hyperthyroidism (see section 3.4) and may cause disruption of reproductive function and may give rise to developmental defects secondary to thyroid gland dysfunction. (ATSDR 2004).

Hypothyroidism can produce changes in the menstrual cycle in humans, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation). Abortions, stillbirths, and premature births have also been associated with hypothyroidism. Hypothyroidism may be associated with impairment in neurological development of the foetus or growth retardation. Reproductive impairments associated with hyperthyroidism include amenorrhea (absence or cessation of menstruation), alterations in gonadotropin release and sex hormone-binding globulin, and changes in the levels and metabolism of steroid hormones in both females and males.

In the 5-year study where iodinated drinking water (1 mg/l, for disinfection purposes) was supplied to 750 male and female prison inmates (see section 3.4.1), 177 women inmates delivered 181 infants showing no thyroid-related adverse effects. According to EFSA, the difficulties with this study were the imprecise estimates of intakes from the diet and fluid consumption of the participating individuals as well as the variable exposure time but the group size and duration of exposure were adequate. (Stockton and Thomas 1978 – quoted from EFSA 2006).

Clinical cases demonstrate that doses of iodide exceeding 200 mg/day (2.8 mg/kg bw/day) during pregnancy can result in congenital goitre and hypothyroidism in the newborn infant (ATSDR 2004).

Cases of goitre and severe transient hypothyroidism, without neurological sequelae in infants born to mothers who ingested potassium iodide during pregnancy have
been reported; the approximate dosages were 920 and 1530 mg I/day (13 and 22 mg/kg bw/day) (Martin and Rento 1962 – quoted from ATSDR 2004).

In a study of iodide supplementation during pregnancy in an iodide-deficient area of Denmark, 28 women received daily doses of 200 μg I/day from the 17th-18th week of pregnancy through the first 12 months after delivery and 26 women received no supplementation. Pre-treatment urinary iodide levels were 51 and 55 μg/l, respectively, in the two groups, suggesting, according to ATSDR, a pre-existing dietary iodine intake of approximately 75 μg/day (assuming that the urine iodide concentration reflected the 24-hour average and that urine volume was approximately 1.4 l/day) and a total iodide intake of 275 μg/day (4 μg/kg bw/day). There were no statistically significant differences in serum T4, T3, 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. (Pedersen et al. 1993 – quoted from ATSDR 2004).

In a similar type of study, 38 pregnant women from a potentially iodine-deficient region of Germany received daily doses of 230 μg I/day as potassium iodide during pregnancy and lactation and 70 women received no supplementation. Pre-treatment urinary iodide levels were 53 μg I/g creatinine (median), suggesting a pre-existing iodide intake of approximately 90 μg/day and a total intake of 320 μg/day (5 μg/kg bw/day). Thyroid gland volumes were significantly decreased in infants from the supplemented group, compared to the control group (control: 1.5 ml (median); treated: 0.7 ml (median)). One infant (1/38, 2.6%) from the supplemented group was classified as having an enlarged gland (>1.5 ml) compared to 14 (14/70, 20%) from the control group. According to the authors, no hypothyroidism or hyperthyroidism was observed in the mothers or newborns; however, according to ATSDR, end points evaluated, other than serum TSH, were not indicated. (Liesenköter et al. 1996 – quoted from ATSDR 2004).

3.6 Mutagenic and genotoxic effects

No data have been located.

3.7 Carcinogenic effects

The relationship between iodide intake and thyroid cancer has been examined in several epidemiology studies. The results of these studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, particularly in populations in iodine-deficient, endemic goitre regions. Studies of populations in which iodine intakes are sufficient have not found significant associations between iodine intake and thyroid cancer; however, an apparent shift in the histopathology towards a higher prevalence of papillary cancers, relative to follicular cancers, after increased iodine intake (e.g., dietary supplementation) in otherwise iodine-deficient populations has been observed. (ATSDR 2004).
4 Animal toxicity

As in humans, excess iodine intake leads to acute inhibition of iodine uptake followed by thyroid disturbances in experimental animals. However, humans seem to be less sensitive than rodents concerning thyroid disturbances even though the basic hypothalamic-pituitary-thyroid axis functions in a similar way in animals and humans. The greater sensitivity in rodents is partly due to considerable species differences with respect to binding of hormones to transport proteins in the plasma, see section 2.4.

Therefore, animal toxicity data are only very briefly addressed and only information considered of relevance for the estimation of a health-based quality criterion in drinking water for iodides is summarised.

4.1 Single dose toxicity

According to EFSA (2006), an oral LD_{50} of 3320 mg I/kg bw has been reported in rats for sodium iodide, and for potassium iodide an oral LD_{100} of 1425 mg I/kg bw has been reported for mice (Stokinger, in Clayton and Clayton 1981 – quoted from EFSA 2006).

According to WHO (2003), the acute oral LD_{50} value for potassium iodide in rats was 3320 mg I/kg bw, and the lowest oral lethal dose in mice was 1425 mg I/kg bw (Stokinger, in Clayton and Clayton 1981 – quoted from WHO 2003).

4.2 Irritation

-

4.3 Sensitisation

-

4.4 Repeated dose toxicity

Studies in rats indicate that doses of 70-95 mg I/kg/day (in drinking water) for 8-12 weeks may increase the incidence of autoimmune thyroiditis in inbred strains of rats that develop spontaneous thyroid autoimmunity (ATSDR 2004).

4.5 Toxicity to reproduction

Groups of female rats were exposed to potassium iodide at levels of 0, 500, 1000, 1500 and 2000 mg/kg diet (as KI according to EFSA, as I according to WHO) throughout gestation, lactation and weaning. Pup survival was dose-related and ranged from 93% in controls to 16% in high-dose rats (2000 mg/kg). Milk secretion was absent or greatly diminished in high-dose females; according to WHO, the high mortality in pups at this dose level was attributed to the dams.
lactational failure. There were no adverse effects on ovulation rate, implantation rate and foetal development. (Ammermann et al. 1964 – quoted from EFSA 2006, WHO 2003).

Pregnant rats were exposed to 11 mg KI/day in their drinking water (37 mg/kg bw/day). Serum T4 levels in pups were unchanged compared to controls. (Morales de Villalobos et al. 1986 – quoted from EFSA 2006 and WHO 2003).

4.6 Mutagenic and genotoxic effects

The data on mutagenicity for iodine are generally negative (EGVM 2000 – quoted from EFSA 2006).

4.6.1 In vitro studies

Potassium iodide (0.1-10 mg/ml) did not show mutagenic effects in L5178Y mouse lymphoma cells or transforming activity in Balb/c 3T3 cells grown in culture (Kessler et al. 1980, Merkle and Zeller 1979 – quoted from ATSDR 2004).

4.6.2 In vivo studies

Potassium iodide did not produce lethal mutations in Drosophila melanogaster when eggs were incubated in 0.75 mg/ml potassium iodide (Law 1938 – quoted from ATSDR 2004).

4.7 Carcinogenic effects

Groups of 20 rats were fed diets containing 0 or 1000 mg/kg diet as potassium iodide (39 mg I/kg bw/day) for 19 weeks. No tumours of the thyroid were found either in controls or in treated animals. (Hiasa et al. 1987 – quoted from EFSA 2006 and WHO 2003).

According to EFSA and WHO, the exposure period in this inadequate study was too short for any carcinogenic effect to be detected.

Metaplasia of the thyroid was reported in rats given potassium iodide in their drinking water for two years. This was thought to occur through a non-genotoxic proliferation dependent mechanism. (EGVM 2002 – quoted from EFSA 2006).
5 Regulations

5.1 Ambient air

-  

5.2 Drinking water

Denmark: -  

WHO: Available data suggest that derivation of a guideline value for iodine on the basis of information on the effects of iodide is inappropriate, and there are few relevant data on the effects of iodine. Because iodine is not recommended for long-term disinfection, lifetime exposure to iodine concentrations such as might occur from water disinfection is unlikely. For these reasons, a guideline value for iodine has not been established at this time. (WHO 2003).

Iodine is included in the plan of work of the rolling revision of the WHO Guidelines for Drinking-water Quality.

5.3 Soil

-  

5.4 Occupational Exposure Limits

-  

5.5 Classification

-  

5.6 IARC

-  

5.7 WHO/FAO: JECFA

An iodine intake of 1 mg per day or less is probably safe for the majority of the population, but may cause adverse effects for some individuals, e.g., people with thyroid disorders or people who are particularly sensitive to iodine. For purposes of
safety, a provisional maximum tolerable daily intake of 1 mg iodine/day (0.017 mg/kg bw/day) from all sources is set. (JECFA 1989).

5.8 EFSA

The European Food Safety Authority (EFSA 2006) has derived a Tolerable Upper Intake Level (UL) 600 μg/day (10 μg/kg bw/day for a 60 kg adult person). The UL was based on the noted biochemical changes in TSH levels and the TSH response to TRH administration, which were considered marginal and unassociated with any clinical adverse effects at estimated intakes of 1700 and 1800 μg/day in the experimental studies by Paul et al. (1988) and Gardner et al. (1988), see section 3.4.1. EFSA noted that although the studies were only of short duration, involved only a small number of individuals, and lacked precision of the actual total dietary intakes, their results were supported by the study covering a 5-year exposure at approximately similar iodide intake levels of 30 μg/kg bw/day (equivalent to approximately 1800 μg/day) in which no clinical thyroid pathology occurred (Stockton and Thomas 1978). An uncertainty factor of 3 was thus considered adequate and provides an UL for adults of 600 μg/day. The UL of 600 μg/day was also considered adequate for pregnant and lactating women based on evidence of lack of adverse effects at exposures significantly in excess of this level. ULs for children (see Table 10) were derived by adjustment of the adult UL on the basis of body surface area (body weight 0.73) since there is no evidence of increased susceptibility in children.

Table 10. Tolerable Upper Intake Levels (UL) for iodine (EFSA 2006).

<table>
<thead>
<tr>
<th>Age</th>
<th>UL (μg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>200</td>
</tr>
<tr>
<td>4-6</td>
<td>250</td>
</tr>
<tr>
<td>7-10</td>
<td>300</td>
</tr>
<tr>
<td>11-14</td>
<td>450</td>
</tr>
<tr>
<td>15-17</td>
<td>500</td>
</tr>
</tbody>
</table>

5.9 US-EPA

-

5.10 ATSDR

A Minimal Risk Level (MRL, an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure) of 0.01 mg/kg bw/day has been derived for acute-duration oral exposure (1-14 days) to iodine. The acute MRL is based on a NOAEL of 0.01 mg/kg bw/day in healthy adult humans (Gardner et al. 1988, Paul et al. 1988). Although the NOAEL is derived from acute studies of healthy adults, supporting studies indicate that the NOAEL would also be applicable to children and elderly adults (Boyages et al. 1989, Chow et al. 1991). On this basis, an uncertainty factor is not needed to adjust the NOAEL to account for human variability in sensitivity. (ATSDR 2004).
An MRL of 0.01 mg/kg bw/day has been derived for chronic-duration (>365 days) oral exposure to iodine. The chronic MRL is based on a NOAEL of 0.01 mg/kg bw/day and a LOAEL of 0.029 mg/kg bw/day for sub-clinical hypothyroidism in healthy human children (Boyages et al. 1989, Li et al. 1987). An uncertainty factor is not needed to adjust the NOAEL to account for human variability in sensitivity because the NOAEL is based on a sensitive endpoint in children, a sensitive subpopulation. Supporting studies indicate that the NOAEL would be applicable to elderly adults who may represent another sensitive subpopulation (Chow et al. 1991, Szabolcs et al. 1997). (ATSDR 2004)
6 Summary and evaluation

6.1 Description

Iodine is a non-metallic element. It can exist in several oxidation states: −1, 0, +1, +3, +5 and +7. Under normal environmental conditions, the -1, 0, and +5 oxidation states are the most important. Iodine is found in nature as molecular iodine (I2), iodide (I−), or iodate (IO3\(^-\)). The only naturally occurring isotopes of iodine are the stable isotope \(^{127}\text{I}\) and the radioactive isotope \(^{129}\text{I}\).

This evaluation is limited to consider the toxicity of inorganic salts of the stable iodine isotope \(^{127}\text{I}\) from which the iodide ion can be liberated, as this form is the relevant one in relation to estimation of a health-based quality criterion in drinking water.

6.2 Environment

Iodine is a naturally occurring constituent of the earth’s crust with a concentration of the stable \(^{127}\text{I}\) of approximately 0.5 mg/kg. Iodine occurs ubiquitously in igneous rocks and soils, most commonly as impurities in saltpetre and natural brines.

Releases of iodine into the environment occur from both natural sources and human activity.

Introduction of iodine into surface waters and groundwater occurs predominately through rainwater for non-coastal land regions and the combination of rainwater and ocean spray in coastal regions. The iodine in rainwater is derived from the volatilisation of iodine from the oceans to the atmosphere. Other natural releases of iodine into surface waters and groundwater include the leaching of iodine from the weathering of rock and volcanic activity.

Iodine in tap water obtained from different locations in Denmark varied from <1.0 to 139 µg/l, see Table 2. In general, the iodine content was low in Jutland (average 5.7 µg/l) with higher levels on Zealand (average 18.7 µg/l) and other islands.

The contribution of iodine to soils is derived from natural sources, such as the weathering of rock, decay of vegetation, iodine received from rainfall, and from human activities. Most soils worldwide contain on average approximately 5 mg/kg of iodine.

The iodide content of foods and total diets differs depending on geochemical, soil, and cultural conditions. The major natural food sources are marine fish, shellfish, marine algae, seaweed, and sea salt. In industrialised countries, the most important sources of iodides are dairy products, eggs, and grain and cereal products. Other food sources are freshwater fish, poultry and meat, fruits, legumes and vegetables.
6.3 Human exposure

Human exposure to iodide can result from inhalation of air, consumption of food and drinking water, incidental ingestion of soil, and use of iodine containing supplements, (mineral or seaweed-based dietary supplements), medications and antiseptics. Food is generally the predominant source of exposure to iodide; however, use of iodine containing dietary supplements or medications would be a major source as well.

Using the average global ambient air concentration of 10-20 ng/m³, the inhalation exposure to iodine would be 5-10 ng/kg bw/day for children and about 2-4 ng/kg bw/day for adults, see also Table 5.

Using the average reported concentrations of iodine in Danish tap water (Zealand) of 18.7 μg/l (Danish Food Composition Databank), the intake from drinking water would be 0.6 μg I/kg bw/day for children and about 0.4 μg/kg bw/day for adults, see also Table 5.

Using the reported average concentration of 5 mg/kg of iodine for most soils worldwide, the intake from soil would be 0.04 μg/kg bw/day for children, see also Table 5.

In Denmark (2003-2008), the mean dietary intake of iodine from food and beverages (including drinking water) was 180 μg I/day for children (4-9 years), 183 μg I/day for adolescents (10-17 years), and 192 μg I/day for adults (18-75 years), see also Table 4.

The intake of iodine (3553 participants, 2004-2005) has been reported at 145 μg/day (median, 25th and 75th percentiles: 100 and 226) based on the excretion of iodine in urine. The iodine excretion was higher in participants from Copenhagen than in participants from Aalborg, and lower in participants who did not take dietary supplements with iodine than in participants who took iodine supplements.

Iodine containing dietary supplements could also be a major source of the daily human exposure to iodine. About half (45%) of the adult Danish population and about two-thirds (64%) of the children regularly take vitamin and mineral supplements. The most common supplement used in Denmark is a combined multi-vitamin-mineral tablet usually containing 100% of the reference value for the recommended daily intake of vitamins and minerals. For iodine the reference values are 70 and 150 μg/day for children aged 1-10 years and for older children and adults, respectively.

6.4 Toxicokinetics

Ingested molecular iodine is reduced to iodide in the gut and almost completely absorbed in this form by the small intestine.

In humans, the gastrointestinal absorption of iodine is generally considered to be approximately 100% after ingestion of water-soluble iodine salts, such as potassium or sodium iodide, and appears to be similar in children, adolescents and adults, but may be lower in infants. Iodide incorporated into food appears also to be nearly completely absorbed with a urinary iodide excretion of the daily intake of 96-98%.
Iodine is extensively absorbed in rats when it is ingested as either molecular iodine or sodium iodide.

The human body contains approximately 10-15 mg of iodine, of which approximately 70-90% is in the thyroid gland. Other tissues that can accumulate iodide to a concentration greater than that of blood or serum include the salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta and sweat glands.

Absorbed iodine is excreted primarily in the urine (>97%) with only small amounts being excreted in the faeces (1-2%). Iodine is also excreted in breast milk, exhaled air, sweat and tears. The whole-body elimination half time of absorbed iodine has been estimated to be approximately 31 days in healthy adult males; however, there appears to be considerable inter-individual variability.

6.5 Physiological role

Iodine is an essential element in the synthesis of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). According to the Nordic Nutrition Recommendations (NNR 2004), the recommended daily intake of iodine is 50-120 μg/day for children (6 months to 9 years), 150 μg/day for adolescents and adults, 175 μg/day for pregnant women and 200 μg/day for lactating women, see Table 7.

6.6 Human toxicity

All biological actions of iodine in humans are attributed to the thyroid hormones (T4 and T3) and the synthesis of normal quantities of thyroid hormones requires an adequate intake of iodide.

The principal direct effects of excessive intake of stable iodine are on the thyroid gland and regulation of thyroid hormone production and secretion. Effects on the thyroid gland can be classified into three types: Hypothyroidism, which refers to the diminished production of thyroid hormones leading to clinical manifestations of thyroid insufficiency and can occur with or without goitre. Typical biomarkers are a depression in the circulating levels of T4 and/or T3 below their normal ranges, which is always accompanied by an elevation of TSH above the normal range (Wolff-Chaikoff iodide effect). Hyperthyroidism, which refers to an excessive production and/or secretion of thyroid hormones. Typical biomarkers are an elevation in the circulating levels of T4 and/or T3 above their normal ranges, which is always accompanied by a depression of TSH below the normal range. Thyroiditis, which refers to an inflammation of the thyroid gland, often secondary to thyroid gland autoimmunity. The above-mentioned three types of effects can occur in children and adults, in foetuses exposed in utero, or in infants during lactation. Some subpopulations are particularly sensitive to external iodine supply and tend to respond adversely to levels of iodine, which are without adverse effects in the general population.

Adverse effects on a wide variety of other organ systems can derive secondarily from iodine-induced disorders of the thyroid gland, including disturbances of the skin, cardiovascular system, pulmonary system, kidneys, gastrointestinal tract, liver, blood, neuromuscular system, central nervous system, skeleton, male and
female reproductive systems, and numerous endocrine organs, including the pituitary and adrenal glands.

Chronic iodide exposure results in iodism; the symptoms resemble those of a sinus cold but may also include salivary gland swelling, gastrointestinal irritation, acneform skin, metallic or brassy taste, gingivitis, increased salivation, conjunctival irritation, and oedema of eyelids.

### 6.6.1 Single dose toxicity

Oral doses of 2000-3000 mg iodine (30-40 mg I/kg bw) are probably lethal to humans, but survival has been reported after ingestion of 10-15 g.

Iodide has been used in the past as an expectorant in the treatment of asthma and related conditions at a typical dose of 3.3 mg/kg mostly without adverse reactions.

Acute oral toxicity is primarily due to irritation of the gastrointestinal tract, marked fluid loss and shock occurring in severe cases. 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.

### 6.6.2 Irritation

Irritation of the gastrointestinal tract has been observed following oral ingestion of high doses.

### 6.6.3 Sensitisation

In rare instances, a hypersensitisation reaction may occur immediately after or within several hours of oral or dermal exposure to iodide. Iodide can also give rise to reactions such as urticaria, angio-oedema, polymyalgia, conjunctivitis, coryza, pruritic rashes, vesicular eruptions and fungoid eruptions.

### 6.6.4 Repeated dose toxicity

Several experimental studies have investigated the thyroid response to supplementary intake of iodine.

In one study, a daily supplementary oral dose of 1500 μg I/day (total dose: 1700 μg I/day) to healthy, young euthyroid men and women for 14 days resulted in increased total serum iodine without affecting the protein-bound iodine, decreased (5-10%) serum T4 and T3, increased serum TSH (47%), and increased TSH response to TRH. An increased TSH response to TRH was also observed at a daily supplementary dose of 500 μg I/day (total dose: 700 μg I/day). No biochemical effects were detected at a daily supplementary dose of 250 μg I/day (total dose: 450 μg I/day).

In a similar study, serum T4 was decreased (10%) and serum TSH increased (48%) after daily supplementary oral doses of 1500 and 4500 μg I/day (total dose: 1800 and 4800 μg I/day) to healthy, young euthyroid men for 2 weeks, but did not change after a daily supplementary dose of 500 μg I/day (total dose: 800 μg I/day).
The TSH response to TRH was enhanced at all dose levels. Serum T3 levels did not change at any dose level.

In another similar study, serum T4 was decreased and serum TSH increased, relative to a placebo control group, in healthy elderly adult females, who received daily oral supplementary doses of 500 μg I/day (total dose: 600 μg I/day) for 14 or 28 days.

In a study of healthy, adult males receiving very high daily oral doses of up to 70 mg I/day for 14 days, the only finding at this dose level was a small increase in serum TSH, serum T4 and T3 were not significantly altered.

Small decreases in serum T4 and small increases in serum TSH was observed in women (24-54 years and either thyroid antibody positive or negative; or 60-75 years and either from an area with adequate dietary iodine supply or an area that was previously iodine deficient) following a supplementary dose of 500 μg I/day (total dose: 750 μg I/day) for 28 days. TSH levels increased above the normal level in 3/64 of the 60-75 year old subjects, while the raised TSH levels increased even further in 2/20 antibody-positive subjects.

Overt clinical hypothyroidism (1/40 patients), clinical hyperthyroidism (1/40 patients), and elevated serum TSH (above the normal range in 7/40 patients) was observed among patients with Hashimoto’s thyroiditis and who were positive for anti-thyroid (thyroid peroxidase) antibodies following a supplementary dose of 190 μg I/day (total dose: 315 μg I/day) for 4 months.

No adverse health effects were reported in men consuming drinking water providing iodide at doses of 0.17-0.27 mg/kg bw/day for 26 weeks.

In a 5-year study of prison inmates consuming drinking water containing iodine (approximately 30 μg/kg bw/day), no cases of hyper- or hypothyroidism, sensitisation reactions, or iodism were seen. A small but statistically significant decrease in radioactive iodine uptake by the thyroid and an increase in protein-bound iodine concentrations were reported.

A number of epidemiological studies have addressed the effect of varying amounts of iodine intake on the prevalence rate of various thyroid abnormalities among children, adults and elderly adults, see Table 8.

Among elderly subjects with either a low iodine intake (40-60 μg I/day, Denmark) or with a longstanding relatively high iodine intake (300-350 μg I/day, Iceland), females from Denmark had a high prevalence of goitre or previous goitre surgery compared with males from Denmark and the subjects from Iceland. Abnormal thyroid function was very common in both areas, mainly thyroid hyperfunction in Denmark and mainly impaired thyroid function in Iceland.

Among elderly patients from A) an iodine-deficient area (Northern Hungary), B) an area of obligatory iodinated salt prophylaxis since the 1950s (Slovakia), and C) an abundant iodine intake area (Eastern Hungary), the prevalence of hypothyroidism was highest in the iodine-rich regions (B and C) with all clinical cases except one being antibody positive and with a number of subclinical cases from all three regions also being antibody positive; the overall prevalence of antibody positivity was similar in the three regions. In contrast, the occurrence of hyperthyroidism (clinical plus sub-clinical) and goitre was highest in the iodine-deficient region A.

Among children, from two villages in central China where the iodine concentrations in drinking water were 463 μg/l or 54 μg/l, the mean serum T4 was similar in the two groups, the mean serum fT4 was slightly higher in the high iodine group, the mean T3 was significantly lower in the high iodine group, and the
mean serum TSH was significantly higher in the high iodine group. Goitre was present in 65% of children in the high iodine group (20% grade 2) compared to 15% in the low iodine group (none grade 2).

Among children, in an area in China with high iodine concentration in the water, the goitre prevalence in schoolchildren in the 1980s was 25%, suggesting iodine deficiency, whereas urinary iodine concentrations in adults indicated iodine excess. The prevalence of abnormal thyroid volume (not defined in the publication) ranged from 5-17% among children from 5 selected townships and there was a positive correlation between water iodine levels and urinary iodine as well as indicators of thyroid size (goitre and volume).

In a cohort study (1999-2004) including subjects (> 13 years of age) from three regions in China with different iodine intake levels, the authors concluded that ‘more than adequate’ or ‘excessive’ iodine intake may lead to hypothyroidism and autoimmune thyroiditis. In a more recent study (from 2005) of women, the optimal range of iodine intake was investigated by comparing the prevalence of thyroid disease in three areas in China with slightly different iodine intake levels; the authors concluded that median urinary iodine excretion of 100-200 μg I/l, may reflect a safe range of iodine intake levels.

Iodine intake intervals associated with an increase in the risk of thyroid disease have been suggested based on epidemiological data (see Table 9). The optimal iodine intake was defined as an interval of 120-220 μg iodine excreted in the urine per 24 hours.

Oral exposure to excess iodide can, under certain circumstances, induce hyperthyroidism. The epidemiological and clinical literature suggests that iodide-induced hyperthyroidism occurs most often in people who have a previous history of iodine deficiency and goitre. Cases of iodine-induced hyperthyroidism in euthyroid people and without apparent thyroid disease have also been reported suggesting effects after oral doses of 3-1440 mg/day (0.04-21 mg/kg bw/day – 70 kg person) for 6 months.

Several studies have been conducted in people who reside in endemic goitre areas and who received iodide supplementation. These studies suggest that iodine intakes of 230-420 μg I/day (3.3-6.0 μg I/kg bw/day for a 70 kg person) for 12 months can induce thyroid autoimmunity.

### 6.6.5 Toxicity to reproduction

In a 5-year study of prison inmates consuming drinking water containing iodine (1 mg/l, approximately 0.03 mg/kg bw/day), 177 women inmates delivered 181 infants showing no thyroid-related adverse effects.

Clinical cases demonstrate that doses of iodide exceeding 200 mg/day (2.8 mg/kg bw/day) during pregnancy can result in congenital goitre and hypothyroidism in the newborn infant.

In 28 women from an iodide-deficient area of Denmark, receiving daily doses of 200 μg I/day (total intake of 275 μg I/day) from the 17th–18th week of pregnancy through the first 12 months after delivery, no statistically significant differences in serum T4, T3, or TSH concentrations in the infants were observed at birth (compared to controls), and there were no abnormal values for the hormones in any of the infants. However, in a similar German study of 38 pregnant women from a potentially iodine-deficient region receiving daily doses of 230 μg I/day (total...
intake of 320 µg I/day), thyroid gland volumes were significantly decreased in infants (compared to the controls); no hypothyroidism or hyperthyroidism was observed in the mothers or newborns.

### 6.6.6 Mutagenic and genotoxic effects

No data have been located.

### 6.6.7 Carcinogenic effects

The relationship between iodide intake and thyroid cancer has been examined in several epidemiology studies. The results of these studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, particularly in populations in iodine-deficient, endemic goitre regions. Studies of populations in which iodine intakes are sufficient have not found significant associations between iodine intake and thyroid cancer.

### 6.7 Animal toxicity

As in humans, excess iodine intake leads to acute inhibition of iodine uptake followed by thyroid disturbances in experimental animals. However, humans seem to be less sensitive than rodents concerning thyroid disturbances even though the basic hypothalamic-pituitary-thyroid axis functions in a similar way in animals and humans. Animal data are therefore of limited value in relation to human toxicity.

The data on mutagenicity for iodine are generally negative.

### 6.8 Evaluation

Molecular iodine and water soluble iodine salts release the iodide ion in contact with water. Thus, iodine occurs in water in the form of the iodide ion (I⁻). Molecular iodine as well as water soluble iodine salts are rapidly converted into iodide in the gastrointestinal tract following ingestion and iodide is efficiently absorbed throughout the gastrointestinal tract. Therefore, toxicological effects can be considered together for molecular iodine and water soluble iodine compounds to the extent that these effects are directly mediated by the iodide ion.

This evaluation is limited to consider the toxicity of inorganic salts of the stable iodine isotope (¹²⁷I) from which the iodide ion can be liberated, as this form is the relevant one in relation to estimation of a health-based quality criterion in drinking water.

All biological actions of iodine in mammals are attributed to the thyroid hormones (T₄ and T₃) and the synthesis of normal quantities of thyroid hormones requires an adequate intake of iodide. According to the Nordic Nutrition Recommendations (NNR 2004), the recommended daily intake of iodine is 150 µg/day for older children (from 10 years) and adults, see also Table 7.

Being an essential element, the relationship between iodine intake and thyroid disturbances is U-shaped with an increased risk from both low and high iodine intakes. This evaluation is limited to consider the effects that might be exerted following an excessive intake of iodine as this situation is the relevant one in relation to the estimation of a health-based quality criterion in drinking water.
Humans seem to be less sensitive than rodents concerning thyroid disturbances and thus, animal data are of limited value in relation to an evaluation of the toxicity of iodine to humans. Therefore, only human data are considered in this evaluation.

The gastrointestinal absorption of iodine is generally considered to be complete after ingestion of water-soluble iodine salts, such as potassium or sodium iodide, and appears to be similar in children, adolescents and adults, but may be lower in infants. Iodide incorporated into food appears also to be nearly completely absorbed. Absorbed iodine is excreted primarily in the urine (>97%) with only small amounts being excreted in the faeces (1-2%). Therefore, 24-hour urinary iodine can be used as an estimate for the daily intake of iodine.

Oral doses of 2000-3000 mg iodine (30-40 mg I/kg bw for an adult person, assumed body weight of 70 kg) are probably lethal to humans, but survival has been reported after ingestion of 10-15 g. Acute oral toxicity is not considered as being critical in relation to the estimation of a health-based quality criterion for iodine in drinking water as acute toxicity has only been reported following intake of high doses in comparison to the much lower oral doses giving rise to toxic effects following repeated exposure.

In rare instances, a hypersensitisation reaction may occur immediately after or within several hours of oral or dermal exposure to iodine. No details have been located regarding the dose levels resulting in such reactions. Therefore, hypersensitisation, being only rarely observed, is not considered as being a critical effect for the general population in Denmark following exposure to iodine from drinking water.

The thyroid gland is the critical target organ in humans following excessive repeated oral intake of stable iodine and the effects on the thyroid gland can be classified into three types: 1) Hypothyroidism (diminished production of thyroid hormones leading to thyroid insufficiency), 2) hyperthyroidism (excessive production and/or secretion of thyroid hormones), and 3) thyroiditis (an inflammation of the thyroid gland often secondary to thyroid gland autoimmunity). The thyroid response is dependent on dose, age, and iodine status and thyroid status of the subjects before the supplementary (excessive) exposure to iodine. Some subpopulations, e.g., patients suffering from various thyroid disorders, are particularly sensitive to external iodine supply and tend to respond adversely to levels of iodide, which are without adverse effects in the general population. Adverse effects on other organ systems can derive secondarily from iodine-induced disorders of the thyroid gland.

In the experimental studies with healthy subjects given supplementary doses of iodine (from 250 μg I/day to 70 mg I/day) for a short time period (14-28 days), the observed effects were all of biochemical nature (primarily a small iodine-induced decrease in serum T4 and occasionally also in serum T3, accompanied by a rise in serum TSH) and the changes were in general within the normal range for the reference values for the parameters examined. The biochemical effects were not associated with any clinical adverse effects in these healthy subjects. Adverse effects (overt clinical hypothyroidism, clinical hyperthyroidism) have only been reported in one experimental study of patients (with Hashimoto’s thyroiditis and who were positive to thyroid peroxidase antibodies) following a supplementary dose of 190 μg I/day for 4 months.

No adverse health effects were reported among men consuming drinking water providing iodide at dose levels of 170-270 μg/kg bw/day for 26 weeks, or in prison
inmates consuming drinking water providing iodide at a dose level of about 30 μg/kg bw/day for 5 years.

A number of epidemiological studies have addressed the effect of varying amounts of iodine intake on the prevalence rate of various thyroid abnormalities among children, adults and elderly adults, see Table 8. In general, subjects from high iodine regions had a higher prevalence of hypothyroidism compared to subjects from low-level regions. On the contrary subjects from low iodine regions had in general a higher prevalence of hyperthyroidism compared to subjects from high-level regions. The lowest prevalence of thyroid goitre (about 5 / 2%) was observed in regions with an adequate intake of iodine (urinary iodine of 114 / 150 μg I/l, respectively, corresponding to an intake of approximately 110 / 150 μg I/day, respectively). The observed prevalence of goitre was 11-38% in regions with a higher than adequate iodine intake (urinary iodine ranging from 223-1961 μg I/l) and 12-25% in regions with a lower than adequate iodine intake (urinary iodine 38-78 μg I/l). However, as the thyroid response, in addition to the intake of iodine, also is dependent on the iodine status and the thyroid status of the subjects, it is not possible to assess the dose-response relationship and thus, to establish a NOAEL for iodine induced thyroid effects based on the epidemiological studies.

Based on the experimental studies in healthy subjects, a NOAEL of 4500 μg I/day (supplementary dose, total ingested dose: 4800 μg I/day, Gardner et al. 1988) is considered for the general healthy population as only biochemical thyroid parameters were altered at this supplementary dose given for 14 days and no adverse thyroid effects were observed. A NOEL of 250 μg I/day (supplementary dose, total ingested dose: 450 μg I/day, Paul et al. 1988) is considered for the general healthy population as none of the examined biochemical thyroid parameters were altered at this supplementary dose given for 14 days. The NOAEL and NOEL of 4500 and 250 μg I/day, respectively, corresponds to 64 μg and 3.5 I/kg bw/day, respectively, assuming an adult body weight of 70 kg.

Repeated oral exposure to excess iodine may produce hypothyroidism and may cause disruption of reproductive function and may give rise to developmental effects secondary to the thyroid gland dysfunction. As being effects secondary to the iodine thyroid gland dysfunction, reproductive and developmental effects are not considered to be manifest at dose levels not giving rise to thyroid effects. Thus, protection of subjects against iodine thyroid disorders will implicitly protect against iodine induced reproductive and developmental effects.

No human data on mutagenic and genotoxic effects have been located. The limited data from in vitro tests indicate that iodine is not a genotoxic compound.

Results of epidemiology studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, particularly in populations in iodine-deficient, endemic goitre regions. However, studies of populations in which iodine intakes are sufficient have not found significant associations between iodine intake and thyroid cancer. Therefore, thyroid cancer is not considered as being a critical effect for the general population in Denmark as iodine intake is sufficient in the Danish population.

### 6.8.1 Critical effect and NOAEL

The thyroid gland is the critical target organ in humans following excessive repeated oral intake of stable iodine.
Adverse effects on other organ systems can derive secondarily from iodine disorders of the thyroid gland. As being effects secondary to the iodine thyroid gland dysfunction, these effects are not considered to be manifest at dose levels not giving rise to thyroid disturbances. Thus, protection of subjects against iodine thyroid disturbances will implicitly protect against iodine induced effects on other organ systems.

The thyroid response to excessive iodine is dependent on dose, age, and iodine status and thyroid status of the subjects before treatment. A number of epidemiological studies have addressed the effect of iodine intake on the prevalence rate of various thyroid disturbances among children, adults and elderly adults from both low as well as high iodine regions. However, it is not possible to assess the dose-response relationship between iodine intake and thyroid disturbances and thus, to establish a NOAEL for iodine induced thyroid effects based on the epidemiological studies. Two drinking water studies are available reporting no adverse health effects; however, both studies are inadequate for a dose-response assessment as well as for establishing a NOAEL for iodine induced thyroid effects. Therefore, the experimental studies, although being only of short duration, will form the basis for the establishment of a NOAEL for iodine induced thyroid effects.

Based on the experimental studies in healthy subjects, a NOAEL of 4500 μg I/day (supplementary dose, total ingested dose: 4800 μg I/day, Gardner et al. 1988) is considered for the general healthy adult population as only biochemical thyroid parameters (thyroid hormone and TSH serum levels) were altered at this supplementary dose given for 14 days and no adverse thyroid effects were observed. This short-term NOAEL is supported by the results from the 5-year drinking water study also reporting no adverse health effects in a general healthy adult population following exposure to iodine at a similar intake level (approximately 30 μg/kg bw/day) and thus, supporting that this short-term NOAEL is probably also valid for a longer duration of repeated exposure. It should be noted that although altered thyroid hormone and TSH serum levels are not clinically adverse, at least as indicated by the available experimental studies, such alterations could be regarded as indicators of a risk of induced hypothyroidism.

A health-based quality criterion for iodine in drinking water will not be estimated because the mandatory iodisation of household salt and for salt used in commercial bread production has been decided based on a health rationale and because the most recent study (Rasmussen et al. 2008) indicate that the intake of iodine in the general population is within the recommended intake values (see Table 7).
7 TDI and quality criterion

A health-based quality criterion for iodine in drinking water will not be estimated because the mandatory iodisation of household salt and for salt used in commercial bread production has been decided based on a health rationale and because the most recent study (Rasmussen et al. 2008) indicate that the intake of iodine in the general population is within the recommended intake values (see Table 7).
8 References


Rasmussen LB (2010). Personal communication.


Iodine, inorganic and soluble salts
The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to the inorganic and soluble salts of iodine. This resulted in 2013 in the present report which includes estimation of a quality criterion in drinking water for the mentioned substances.