EVALUATION OF THE HEALTH ASPECTS OF POTASSIUM IODIDE, POTASSIUM IODATE, AND CALCIUM IODATE AS FOOD INGREDIENTS

1975

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 72-85
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
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NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) or prior sanctioned food substances being made by the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using certain iodine salts as food ingredients. The evaluation has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1970.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of more than thirty scientific and statistical reference sources and compendia that are generally recognized as available, use of new, relevant books and reviews and the literature citations contained in them, consideration of current literature citations obtained through the online retrieval systems of the National Library of Medicine, searches for relevant data in the files of the FDA, and by the combined knowledge and experience of the members of the Select Committee and the LSRO staff.

In addition, announcement was made in the Federal Register on September 23, 1974 (39 FR 34218) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using potassium iodide, potassium iodate, and calcium iodate as food ingredients. The Select Committee held a hearing on these iodine salts on December 16, 1974. The data, information, and views presented at that hearing have been considered by the Select Committee in reaching its final conclusions.

Certain iodine salts are food substances that have been generally recognized as safe (GRAS) under the provisions of the Code of Federal Regulations (21 CFR 121.101), revised April 1, 1974. As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet.

*The document is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

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and safety factors appropriate for the utilization of animal experimentation data. The FDA recognizes further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accord with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health, and realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be re-conducted, using newly evolved technologies. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on potassium iodide, potassium iodate, and calcium iodate and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Iodine occurs naturally in soil, water, various plants, and especially in marine life (1,2). The iodine in food is reduced to iodide during digestion and absorption. The thyroid gland rapidly removes iodide from the blood and uses it in the synthesis of the iodine-containing hormones triiodothyronine and tetraiodothyronine (thyroxine). Iodine is essential in the nutrition of man and animals for normal thyroxine production (1,3).

Requirements for iodine are met primarily by food and possibly by drinking water in some areas. Historically, in some regions of the world including some parts of the United States, not enough iodine has been available in food and water to meet nutritional needs. Accordingly, iodine compounds are added to food and animal feed to supplement iodine intake.

The development of micro-techniques sufficiently sensitive to study metabolism of iodine in humans has revealed that only microgram quantities of the element are necessary (4). The Food and Nutrition Board of the National Research Council recommends the following daily dietary allowances
in micrograms of iodine: infants, 35 to 45; children, 60 to 110; male adults, 110 to 150; female adults, 80 to 115; pregnant women, 125; and lactating women, 150, respectively (5).

The following iodine compounds are Generally Recognized as Safe (GRAS) (6):

(a) Cuprous iodide and potassium iodide in table salt as sources of dietary iodine (not to exceed 0.01 percent); and,

(b) Calcium iodate, calcium iodobehenate, cuprous iodide, 3,5-diiodosalicylic acid, ethylenediamine dihydroiodide, potassium iodate, potassium iodide, sodium iodate, sodium iodide, and thymol iodide, as trace minerals added to animal feeds as dietary supplements.

It should be noted that certain iodine salts are also regulated, with stated tolerances, as Food Additives Permitted in Food for Human Consumption, including:

(a) Potassium iodide in special dietary foods labeled to indicate that maximum daily intake should not exceed 0.15 mg iodine (7); and,

(b) Calcium iodate and potassium iodate as dough conditioners in bread manufacture with the stipulation that the total quantity may not be more than 0.0075 parts per 100 parts by weight of flour used (8).

Biological and other relevant information on potassium iodide, potassium iodate, sodium iodide, and sodium iodate is available. In addition, some information on cuprous iodide is contained in the monograph supplied by FDA (1); however, the Select Committee prefers to assess the health aspects of cuprous iodide in its evaluation of other copper salts listed as GRAS. The Select Committee is aware that sodium iodide is not listed as GRAS in foods for human consumption. The Committee has no information on calcium iodate per se, but has included this iodate salt because iodates are known to be converted to iodides during baking of bread (9), and because calcium iodate is permitted as a dough conditioner in bread manufacture (8).

Several different chemical forms of iodine are used for salt iodization throughout the world. Because sodium and potassium iodides are hydroscopic, the more stable sodium and potassium iodates are widely used in Europe, South America, and tropic countries. In these goiter prevention programs, potassium iodate is used at 0.005 to 0.0001 percent, a level of
iodine which is less than the current level of use for potassium iodide (0.01 percent) in the United states (10).

Accordingly, this report reviews the health aspects of potassium iodide, potassium iodate, and calcium iodate because these are the only iodine salts (except cuprous iodide which is being considered separately) that either are listed as GRAS as a source of iodine in the human diet or are precursors of iodides occurring in the diet of the population of the United States. The scientific information necessary to evaluate the human health aspects of the several other iodine salts added to animal feeds as dietary supplements in this country has not been made available to the Select Committee.

The Food Chemicals Codex (11) provides that potassium iodide should assay not less than 99.0 percent and not more than the equivalent of 101.5 percent KI after drying, and should contain not more than 3 ppm arsenic, 10 ppm heavy metals (as lead), and 4 ppm iodate. Calcium iodate should assay not less than 99.0 percent and not more than the equivalent of 101.0 percent Ca(IO₃)₂·H₂O and should contain not more than 3 ppm arsenic or 10 ppm heavy metals (as lead). Potassium iodate should assay not less than 99.0 percent and not more than the equivalent of 101.0 percent KIO₃ after drying, and should contain not more than 3 ppm arsenic, 10 ppm heavy metals (as lead), 20 ppm iodide, and 0.01 percent chlorate.

According to a comprehensive survey conducted by a National Research Council subcommittee, potassium iodide is currently used in various food categories in the amounts shown in Table I (12). No usage data are available for other iodine compounds.

TABLE I

Addition of Potassium Iodide to Foods by Food Category (12).¹

<table>
<thead>
<tr>
<th>Food category</th>
<th>Usual use percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonings and flavorings</td>
<td>0.00866</td>
</tr>
<tr>
<td>Imitation dairy products</td>
<td>0.00043</td>
</tr>
<tr>
<td>Baby formulas</td>
<td>0.00013</td>
</tr>
<tr>
<td>Processed fruit</td>
<td>0.00010</td>
</tr>
<tr>
<td>Milk products</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

¹Level of addition is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in the category.
Potassium iodide was first added to foods in the United States in 1927. The total poundage of potassium iodide used by the U.S. food industry in 1960 was about 86,400 lb; usage declined to about 61,700 lb in 1970 (12). However, there is no information available to the Select Committee that permits it to determine the extent to which there has been significant change over the past decade in the potassium iodide content of the food categories listed in Table I.

III. CONSUMER EXPOSURE DATA

The National Research Council subcommittee has provided information on the possible daily intake of potassium iodide in various age groups (Table II) (12). The Select Committee has converted these figures to possible intake per kilogram of body weight.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Intake</th>
<th>Intake mg/kg**</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 mo</td>
<td>0.44</td>
<td>0.09</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>0.16</td>
<td>0.02</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>0.14</td>
<td>0.01</td>
</tr>
<tr>
<td>2-65+ yr</td>
<td>0.13</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*One mg of KI would provide 0.764 mg of iodine.
**Possible daily intake of added potassium iodide by age group was estimated from weighted means of the levels of addition as indicated in Table I. Calculated intake, mg/kg body weight, was based on an average weight of 60 kg for an adult (13) and the following estimated weights of infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; and 12-23 mo, 11 kg (14).

It is recognized that the figures calculated for the daily intake of potassium iodide per kg of body weight in the age group 2-65+ years could be low for some, since most individuals from age 2 to maturity will obviously weigh less than 60 kg. However, such deviations from the figures in Table II should also be considered in respect to the total use of potassium iodide in foods in the U.S., which the NRC subcommittee found to be 37,050 pounds (16,841 kg) in 1970; the NRC subcommittee estimated that
this amount constituted approximately 60 to 70 percent of the quantity actually used (12). On the basis of 60 percent adjusted to 100 percent (28,068 kg) and a U.S. population of 210 million, the per capita daily average intake of potassium iodide would be 0.37 mg rather than the 0.13 mg shown in Table II.

Several additional points should be emphasized in this regard. First, no consumption of annual poundage data are available from which to estimate intakes of other iodides and iodates used in foods. Specifically, the Select Committee has no data on the extent to which the iodates are used as dough conditioners in the manufacture of bread and related bakery products. Because iodates are readily converted to iodides either in the baking process or during absorption in the gastrointestinal tract, these compounds would add to the total iodide intakes indicated for potassium iodide alone in Table II. In addition, the unknown amounts of iodized salt added to foods during home preparation and consumption would increase individual iodine consumption estimates. Finally, there are several reports that note an increase in iodine in foods, presumably from the use of organic iodine compounds as sanitizing agents and in food processing (15-19). It has also been shown that erythrosine (FD & C Red #3; 2, 4, 5, 7-tetraiodofluorescein), when used as a food coloring contributes metabolizable iodide to the diet. Vought et al. (20) have estimated that a usual serving of an erythrosine-colored breakfast cereal could increase the daily intake of iodine by approximately 400 µg.

These possible sources of dietary iodine, in addition to that known to be due to potassium iodide added to the foods indicated in Table I, will need to be considered if the biological impact of total dietary iodine should become a matter of concern. The Select Committee is aware of a recent report of the Life Sciences Research Office, FASEB, which concludes that the average iodine intake in the North American population from dietary and other sources has increased in the past several years (21).

IV. BIOLOGICAL STUDIES

Acute toxicity

Acute toxicity data for potassium and sodium iodides and iodates in mice are summarized in Table III. These studies were prompted by a proposal that potassium iodate or sodium iodate be used in table salt in place of potassium iodide as a prophylactic agent for endemic goiter.
Table III

Acute Toxicity of Certain Iodides and Iodates in Mice (20)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>LD$_{50}$ mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>KI</td>
<td>I. P.</td>
<td>1117 ± 30</td>
</tr>
<tr>
<td>KI</td>
<td>oral</td>
<td>2068 ± 140</td>
</tr>
<tr>
<td>KI</td>
<td>oral</td>
<td>1982 ± 90 (fasted)</td>
</tr>
<tr>
<td>KI</td>
<td>oral</td>
<td>1862 ± 100 (fasted)</td>
</tr>
<tr>
<td>KIO$_3$</td>
<td>I. P.</td>
<td>136 ± 5</td>
</tr>
<tr>
<td>KIO$_3$</td>
<td>oral</td>
<td>1177 ± 61</td>
</tr>
<tr>
<td>KIO$_3$</td>
<td>oral</td>
<td>815 ± 29 (fasted)</td>
</tr>
<tr>
<td>KIO$_3$</td>
<td>oral</td>
<td>531 ± 21 (fasted)</td>
</tr>
<tr>
<td>NaI</td>
<td>I. P.</td>
<td>1690 ± 85</td>
</tr>
<tr>
<td>NaI</td>
<td>I. V.</td>
<td>&gt; 1500</td>
</tr>
<tr>
<td>NaI</td>
<td>oral</td>
<td>1650 ± 90</td>
</tr>
<tr>
<td>NaIO$_3$</td>
<td>I. P.</td>
<td>119 ± 5</td>
</tr>
<tr>
<td>NaIO$_3$</td>
<td>I. V.</td>
<td>108 ± 4</td>
</tr>
</tbody>
</table>

Webster et al. (22, 23) found the oral acute LD$_{50}$ of potassium iodate for the fasted guinea pig to be less than 400 mg per kg, and the oral minimum lethal dose of the same salt for the dog to be between 200 and 250 mg per kg.

The data reported by Webster et al. (22) consist of extensive comparative evaluations of acute single doses to female white Swiss mice (NIH strain) fasted for 17 to 20 hours and housed on screen bottom cages or on sawdust. The dose (70-3500 mg per kg) was based on the fasted body weight. Various experimental conditions modified the LD$_{50}$ values. However, the relatively greater acute toxicity of the iodate salts as compared to the iodide salts at the doses given was clearly evident.

Fatty changes in the cells of several viscera were observed within 24 hours after administration of either iodide or iodate salts (22). The iodates produced hemoglobinuria, and on histological examination, casts and hemosiderin deposits were found in kidney sections. After oral doses of 140 to 500 mg per kg in mice, the gastric contents had a higher pH and extensive but rapidly reparable degenerative changes in the parietal cells of the stomach (22).

Webster et al. (23) determined the subacute toxic dose of potassium and sodium iodates in mice and guinea pigs and found no gross lesions or abnormalities, but microscopic examination showed hemosiderin deposits in the renal convoluted tubules in nearly all mice receiving 0.5 percent potassium
iodate in their drinking water for 16 weeks. Significantly lower hematocrit and hemoglobin levels were found in mice receiving 0.75 percent potassium iodate in their drinking water. Fed mice had a better tolerance than fasted mice for small doses (277-540 mg per kg per day), administered for several months and only minimal toxic effects were observed after a single dose (1120 mg per kg) of potassium iodate, a dose approaching the LD₅₀. On a regimen of 0.5-0.25 percent in drinking water over a 4-week period (an intake that exceeded the estimated single dose LD₅₀ for this species), guinea pigs exhibited no postmortem gross abnormalities or significant histological changes. During a 5-day period, maximal intake of 485 mg per kg per day was attained by animals drinking water containing 0.5 percent potassium iodate.

Webster et al. (24) determined the minimum lethal dose, the maximum allowable dose, and the acute and subacute toxic effects of potassium iodate in dogs. Three groups of fasted mongrel dogs were given potassium iodate in gelatin capsules in single doses. None of four died at 100 mg per kg, one of three dogs died at 200 mg per kg, and all three of three died at 250 mg per kg so that the minimum lethal dose was estimated to be between 200 and 250 mg per kg. Fatty changes in viscera, and necrotic lesions in the liver, kidney and mucosa of the gastrointestinal tract were sometimes present. The only non-reversible effect was retinal changes, noted in one dog given 200 mg per kg but not established as an iodine effect. In the subacute studies, four dogs (3 females and 1 male), weighing 8 to 16 kg were given iodate, usually added to milk or given by capsule at levels of 6 to 100 mg per kg for 68 to 92 days. When appetite or body weight declined, treatment was suspended until recovery occurred. Occasional emesis, slight anorexia, and listlessness were observed, but normal appetite and weight returned upon suspension of the treatment during the experiment. The maximum tolerable dosage level for dogs over periods of 3-7 weeks was less than 60 mg per kg per day. Periodic checks of the urine were made for iodate, iodine, and hemoglobin. Numerous blood examinations were performed, and at the end of the experiment, biochemical determinations on the urine as well as gross and microscopic studies of many organs and tissues were made. Pathological changes at the 50-100 mg per kg level were confined largely to deposits of hemosiderin in the spleen, liver, and kidneys and mild to moderate inflammation of the mucosa of the gastrointestinal tract.

Based on these several studies, these investigators concluded that the toxicity of potassium iodate for man would be reduced or that repeated small doses would be better tolerated when the iodate salt was mixed with food at dosages several orders of magnitude below those used in their investigations (22-24).

Excess dietary iodine has been shown to produce adverse effects in some animals. Female rats fed 500 to 2500 ppm (estimated to be 300 to
1500 mg per kg per day) of potassium iodide in their diet from zero to approximately 35 days prepartum failed to lactate sufficiently to feed their offspring (25, 26). No other abnormalities of reproduction were observed but increasing mortality of young after birth occurred with increasing levels and approached 100 percent at 2500 ppm of iodide in the diet. High mortality of newborn rabbits has been reported from females fed 250 to 1000 ppm (estimated to be 75 to 300 mg per kg per day) of potassium or sodium iodide for 2 to 5 days, but hamsters and swine were essentially unaffected (26). These effects of high iodine intake are presumed to be hormonally related (25).

Single doses of 100 mg, or 500 mg of $^{131}$I-labeled sodium iodide fed daily to white leghorn hens on a basal diet containing negligible iodine, caused an increase in the iodine content of eggs from "extremely low" to as much as 7 mg per egg after the 500 mg per day dose for 8 days (28). At this time (8 days) hens had ceased egg production; ova continued to develop although many ova were regressing. It was suggested that when a threshold amount of iodine reaches an ovum, development ceases and regression takes place. This threshold was not reached with the 100 mg per day dosage level.

Perdomo et al. (29) fed mature leghorn hens (weight of hens and feed consumption not indicated) potassium iodide in their diet at dosage levels of 312 to 5000 ppm. No influence on egg fertility was observed but early embryonic death and delayed or reduced hatching occurred. Arrington et al. (30) conducted a similar experiment with pullets. When the pullets ceased to lay it was noted that, although mature ova were present, ovulation did not occur.

Bianco et al. (31) observed that acute iodide intoxication in man is rare. The signs of angioneurotic edema, fever, arthralgia, lymphadenopathy, eosinophilia, and occasional multiple petechiae of the skin and mucous membranes are suggestive of subacute or chronic iodide poisoning but can be easily confused with clinical manifestations of other disorders. Chronic iodism may be characterized by gingivitis, increased salivation with a metallic taste, eye irritation, and puffy eyelids. The salivary glands may enlarge and the throat may become inflamed. Diarrhea, fever, and headache may accompany chronic iodism in persons taking multivitamin preparations with iodides, or patients taking iodides for asthma and emphysema. Myxedema and enlarged thyroid glands have been reported in susceptible patients who have had long histories of high iodine intake, but since these are relatively common results of untreated endemic goiter, the role of iodine in these disease states is not clear.

Potassium iodate has been used as a source of iodine to prevent goiter in a number of countries (10). In 1955, potassium iodate, at a level of about 2 ppm, was introduced into bread flour used in Tasmania (32). In a 60 kg
man consuming 200 g of bread per day, this would be equivalent to 0.007 mg per kg per day of potassium iodate. The addition of potassium iodate to the bread proved effective in overcoming goiter. However, evidence was found in the same area of a concurrent increase in the incidence of thyrotoxicosis, mostly in women 40 to 80 years of age who had preexisting goiter (33).

**Metabolism**

Silberberg et al. (34) reported that the intraperitoneal injection of 0.1 ml of a 2.5 percent aqueous solution equivalent to 2.5 mg of potassium iodide, stimulated skeletal tissue development in growing mice. The effects resembled, to a lesser degree, those caused by administration of anterior hypophyseal hormone or thyroxine.

In a study by Taylor and Barrett (35), a combination of thiouracil and potassium iodide depressed growth of young rats, but thiouracil alone or potassium iodide alone, the latter usually present in the diet at a level of 0.0498 percent, did not depress growth. Synergism was postulated as an explanation, although the mechanism was unclear. In studying the stimulating effect of potassium iodide on thyroid, parathyroid, and adrenal glands as measured by the mitotic activities of those tissues, Blumenthal (36) fed guinea pigs diets with or without iodine as potassium iodide, at different age levels from two weeks of age to four months. One group received potassium iodide in daily doses of 0.01 or 0.05 g for five to fifty days. At autopsy, the three glands were removed and cytological determinations of mitotic activity were made. Younger animals, up to six weeks of age, showed an increased mitotic activity in the thyroid and parathyroid; older animals showed no effect. There was evidence of a slight increase in mitotic activity in the adrenal cortex during a part of the potassium iodide treatment. These experiments were repeated by Gray and Loeb (37) and Margolin (38) with essentially the same results. Danowski and Greenman (39) studied the effects of moderate and massive doses of potassium iodide on the protein-bound iodine in the blood of hospital patients. Moderate doses of potassium iodide (0.2 ml of a saturated solution equivalent to about 255 mg daily), produced no significant changes in serum iodine. Doses of 3 to 9 g of potassium iodide given daily for from one to four months greatly increased the total serum iodine levels. No evidence of hyperthyroidism or toxic reaction were observed despite the massive doses of potassium iodide.

Over a ten-year period, 1207 patients with asthma were administered potassium iodide (3.6-4.8 g per day) for 4 days followed by a 3-day rest interval (40). The treatment periods were from 3 weeks to 6 months. Another 814 patients were observed over several years. Immediate side effects were swelling of salivary glands, coryza, and acne. Long term
effects were mainly stomach upsets and myxedema. The incidence of the latter varied from 0.2 percent in patients on a therapeutic dose of 5 to 7 g per day to 2.9 percent in patients on a dose of 18 to 36 g of potassium iodide per day.

Small to moderate doses of iodide result in an increase in the incorporation of iodine in the thyroid. Increasing dosage levels over time reach a critical point in relation to intrathyroidal inorganic iodide concentration and produce a decline in organic iodination until large doses (40 mg or more) produce inhibition of thyroid hormone synthesis. However, on chronic administration, hypothyroidism does not normally develop, suggesting an adaptation to excess iodine; furthermore, excess iodide produces goiter in less than 4 percent of patients treated for pulmonary disease (41).

A determination of the smallest dose of potassium iodide that completely inhibited thyroid uptake of iodine in humans was made by Koutras and Livadas (42). Doses of potassium iodide ranging from 5 to 80 mg with ten microcuries of iodine-131 were given orally to 60 volunteers. Ten additional persons served as controls and received only ten microcuries of iodine-131. The minimal dose affecting thyroidal iodine uptake was found to be 40 mg of potassium iodide. Strisower et al. (43) observed no consistent changes in serum lipoproteins or cholesterol concentrations in human patients given single daily doses of either 30 g of tyrosine or 30 mg of potassium iodide over a period of several months.

Absorption and excretion

Small et al. (44) proved that the small intestine is the principal site of iodine absorption in rats and humans. In rat studies, a solution of potassium iodide was gastrically or duodenally intubated in separate groups of animals. Comparisons were made of the degree of absorption from the stomach (15 percent) and the duodenum (49 percent). In human subjects, a saliva test was applied to patients given potassium iodide orally or by duodenal administration. A positive iodine saliva test appeared within six to ten minutes after oral ingestion, and only two to four minutes after duodenal intubation of potassium iodide.

In another investigation, Harrison et al. (45) studied fish, the chief dietary source of iodine in Great Britain. Fish were injected with $^{131}$I iodide and after 48 hours were fed to patients who completely absorbed the iodide from the fish. Boiling the fish reduced the available iodine by 50 to 80 percent, while grilling or frying reduced the available iodine by 10 to 40 percent. Working with patients having normal thyroid function and others with abnormalities, they found that a fixed dietary level of iodine led to a fecal iodine excretion that varied with thyroid activity, while urinary
excretion of iodine was essentially normal in thyrotoxic and hypothyroid patients but low in non-toxic goiter patients. Certain derivatives of thiourea and thiouracil, which are used in the treatment of hyperthyroidism, impair the utilization of iodine (46). The many factors which interfere with iodine uptake have been reviewed (47).

A number of studies have shown that iodates are readily converted to iodides during food processing or in the gastrointestinal tract after ingestion and are absorbed directly through the intestinal wall (1, 9, 17).

In investigating the effect of environmental conditions, particularly temperature, upon the excretion of iodine from the human body, Spector et al. (48) placed five young men, for eight hours a day, five days a week for eight weeks, in a room that was alternately comfortable for a week and "hot moist" for a week. The food consumed was measured, and the feces, urine, and sweat were collected and analyzed for iodine. Two mg of potassium iodide were administered orally daily for periods up to 14 days. About 75 percent of the total iodine loss from the body was by urinary excretion. Increased iodine intake increased urinary output of iodine. Fecal iodine excretion increased under "hot moist" conditions with increased intake but not under comfortable conditions.

**Special studies**

Chronic iodine deficiency in the hamster results in goiter formation and an increased frequency of thyroid cancer. Sichuk et al. (49), administered 80 ppm potassium iodide in drinking water to 118 male and 113 female Syrian golden hamsters for 32 months and found that potassium iodide supplementation prevented goitrogenesis but did not affect frequency of thyroid cancers. Adenoma and papillary cancer with metastases were observed in control animals and those receiving potassium iodide supplementation; however, these investigators concluded that potassium iodide supplementation had no significant effect on frequency of cancer or other tumors of the thyroid.

The incidence of papillary carcinoma of the thyroid is more prevalent in Japan and Iceland than in the United States. In both Japan and Iceland, high dietary iodine intakes occur because of large consumption of either fish or seaweed. However, Stanbury (50) in noting this association concluded that whether this is a cause and effect relationship is highly speculative. Subsequent reviews on the prevalence of papillary carcinoma in the United States have related radiation exposure to this disease rather than excessive iodine intake (21).

As part of a study of effects of metals on chick embryotoxicity and teratogenicity, Ridgeway et al. (51) injected an aqueous solution of potassium
iodide onto the chorioallantoic membrane or into the yolk sac of 4 and 8 day old White Leghorn embryos. While no mutagenetic activity was observed, there was some embryotoxicity at the LD$_{50}$ value of 8 mg potassium iodide per egg.

A number of studies with several animal species have shown that iodine and iodine-containing compounds are transferred across the placenta and may concentrate in either maternal or fetal plasma and thyroid tissues (52-56). There is circumstantial evidence that placental transfer occurs in man, however, whether it is bound to protein or passes as a free ion is not known (57-59).

It is recognized that iodine deficient mothers may give birth to infants with mild to severe hyperthyroidism (56). Green et al. (59) presented one case of fetal hypothyroidism resulting from iodine therapy of the mother for diffuse toxic goiter (Graves disease). They also referred to several case reports of hypothyroidism in infants borne to mothers receiving therapeutic iodine treatments. They concluded that iodine therapy, specifically administration of radiiodine during pregnancy, was clearly contraindicated.

The Select Committee is not aware of any published studies on the effects of dietary iodine per se on thyroid metabolism or iodine balance in normal pregnant females.

V. OPINION

Iodine occurs widely and is present in most human foods. While the quantity of iodine in specific foods is highly variable, the average diet usually contains sufficient iodine to supply man's requirement for this essential element. In addition to the iodine in foods, iodine-containing compounds are ingested in the form of dietary supplements, food processing adjuncts, food colors, sanitizing agents, and pharmaceuticals. While no comprehensive consumption data are available for any iodine compound except potassium iodide, there is evidence that the total quantity of iodine consumed daily by individuals has increased in the past several years.

Potassium iodide, potassium iodate, and calcium iodate are only three of the many iodine-containing compounds to which man is exposed. In addition, many iodine-containing substances including iodates are converted to iodides in food processing or often consumption. Therefore, the Select Committee has limited its evaluations in this report to potassium iodide, potassium iodate and calcium iodate. This is, in effect, evaluating the health aspects of adding iodide ion to certain foods.
Available biological information shows that ingested potassium iodide and other iodides are readily absorbed and utilized to the extent required for nutritional needs, the excess being excreted primarily in the urine. There is no evidence in the studies on experimental animals and man available to the Committee that indicates acute or chronic toxic effects, including mutagenic, teratogenic, and carcinogenic effects, resulting from the consumption of potassium iodide by euthyroid individuals in amounts that are several orders of magnitude greater than those now being consumed in the daily diet.

Based upon consideration of the available data, the Select Committee concludes that:

There is no evidence in the available information on potassium iodide, potassium iodate, or calcium iodate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced, or those which might reasonably be expected in the future under existing limitations.
VI. REFERENCES CITED


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