IODINE IN FOODS:
CHEMICAL METHODOLOGY AND
SOURCES OF IODINE IN THE HUMAN DIET

MAY 1974

Prepared for

DIVISION OF NUTRITION
BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

Under

Contract Number FDA 71-294
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by

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C. Jelleff Carr, Ph.D.

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FOREWORD

The Federation of American Societies for Experimental Biology (FASEB) recognizes that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to provide scientific assessments of topics in the biomedical sciences. The Life Sciences Research Office (LSRO), established by FASEB in 1962, provides scientific assessments of topics in the biomedical sciences. Reports of these studies are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was prepared for the Division of Nutrition, Bureau of Foods, Food and Drug Administration, by the staff of the LSRO, FASEB, in accordance with the provisions of Contract No. 71-294.

The LSRO acknowledges the contributions of the numerous investigators and consultants who have assisted with this study. The report reflects the opinions expressed by participants in two ad hoc study groups that met at Beaumont House, FASEB, on April 5, 1973 and November 5, 1973 and other consultants. A judicious attempt has been made to incorporate the different viewpoints and opinions.

This report has been reviewed by these consultants; however, the authors accept responsibility for the contents of the report. The listing of the consultants' names in Section XI does not imply that they endorse the conclusions of this study. The report has been 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 report has been approved and transmitted to FDA by the Executive Director, 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
SUMMARY

This report includes a review of analytical methodology used in estimating the iodine in foods and includes qualitative and quantitative data on iodine in foods. It documents sources of iodine in animal feeds and human foods and assesses the current status of human iodine nutrition.

Accurate determination of the total iodine in various biological materials has been possible for many years. However, estimation of iodine in foodstuffs is difficult. Analysis of the low concentrations of iodine in plant and animal tissues and processed foods requires extremely sensitive methods and careful attention to avoid contamination during sample preparation, storage, and analysis. Current methodology is based on modifications of procedures that utilize the catalytic effect of iodine on reduction of ceric salts by arsenious acid. Satisfactory iodide selective electrodes have been developed for use with fluid samples. Neutron activation analysis is a promising analytical technique that may be useful in the determination of iodine in food, or as a reference technique in evaluating other methods of analysis.

The total iodine intake of domesticated animals is increasing as a result of the iodine added in mineral supplements to feeds, supplied in iodized salt blocks, or as veterinary medications. These sources of iodine are more significant than those naturally occurring in forage and feed grains. In addition to iodine naturally present in foods of plant origin and in water, an increasing amount of iodine is entering the human diet from meat, eggs, and dairy products obtained from animals receiving iodine supplemented rations or veterinary medications. Iodine from iodized salt, sanitizing agents, food additives, coloring substances, and medicinals adds to the total iodine intake of the North American population. In addition, there is evidence that processed and prepared foods as well as atmospheric iodine may be significant sources of iodine in urban North America.

Data reviewed in this study support the conclusion that the average iodine intake in North America has increased in recent years. Measurements of actual dietary iodine intake and estimates based on food consumption suggest that intake levels are generally in excess of amounts recognized as necessary for adequate nutrition. In addition, the elevation of observed and calculated estimates of intake is consistent with indirect measurements of iodine intake including iodine excretion studies and clinical tests of radioactive iodine uptake by the thyroid gland.
While there is an increase in intake and excretion of iodine, there are no current reports that document a corresponding increase in the incidence of iodine toxicity or hypersensitivity. Similarly, the frequency of reports of metabolic diseases induced by excess iodine is relatively stable according to experts in the field of thyroid diseases. According to some surveys, thyroidal enlargement is evident in a small, but significant number of the North American population. The possible antecedents to this type of goiter and the public health implications are, at present, only speculative.
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I. INTRODUCTION

Iodine* is recognized as an essential nutrient for animals and man. It is an important constituent of the thyroid hormones and is present in most tissues. Iodine deficiency results in enlargement of the thyroid because of hypertrophy and hyperplasia of the thyroid cells. This enlargement, or goiter, is generally considered a classic manifestation of lack of adequate iodine intake. Changing food habits, agronomic practices, techniques of food processing and marketing practices suggest that greater amounts of iodine are now consumed in the United States from food colorings, increased levels of iodine in dairy products, baked goods, and other sources. In addition, recent reports of decreased $^{131}$I thyroid uptake by euthyroid subjects suggest that iodine intake has increased in the United States in the past 15-20 years.

The 1968-1970 Ten-State Nutrition Survey (U.S. Department of Health, Education, and Welfare, 1972) has provided some information on iodine excretion and the prevalence of goiter throughout the United States. Data suggested that goiter was still present in the United States; however, normal to high iodine excretion levels in goitrous and nongoitrous subjects were observed and there was a lack of correlation between excretion levels and incidence of goiter. In view of these and other data, it is difficult for regulatory bodies to determine if there is a nutritional need to alter the amount of iodine in foods through promulgation of food composition or labeling regulations. For example, is there a need to iodize all table salt?

Moreover, there are claims of idiosyncratic or allergic reactions to iodine in drugs or foods including salt, and it is difficult to ascertain if these claims are valid and clinically significant. To assist the consumer in identifying iodized and uniodized table salt marketed for home consumption, the Food and Drug Administration (FDA) proposed and enacted regulations that stipulate label statements that must appear on the packaging of the two forms of table salt (Edwards, 1971).

*In this report "iodine" is used in a generic sense. The element may be present as iodide or bound to protein complexes in foods, body fluids, and tissues. The oxidation-reduction state may not be known in many instances and is designated only when specifically noted by the authors of reports.
A. BACKGROUND

The Division of Nutrition, Bureau of Foods, Food and Drug Administration (FDA) has a continuing interest in the iodine content of the American diet because the agency is responsible for evaluating the safety of foods and establishing food labeling regulations. There are three major areas of concern with respect to iodine. The first is whether or not endemic goiter in the United States is due entirely to iodine deficiency. The second involves possible "hidden" sources of iodine of significance in the diet, e.g., from pesticide, fertilizer or cleansing agent residues. The third is whether or not claims of idiosyncratic and allergic reactions to iodine in foods (including salt) made by many consumers and some physicians are genuine and/or clinically significant. Appropriate regulatory approaches to this subject depend in part on a thorough understanding of the validity and nature of idiosyncratic and allergic reactions to iodine.

B. SCOPE

The Life Sciences Research Office has been requested by the Division of Nutrition, Bureau of Foods, FDA to review current scientific information on idiosyncratic, allergic and other untoward reactions related to adventitious or added inorganic and organic iodine in foods. The ultimate goals of this study are to document the extent of confirmed allergic reactions to iodine in foods, to separate fact from hearsay, and to assess the magnitude of the medical problem of food iodine hypersensitivity.

At preliminary planning meetings, authorities in the field of iodine metabolism assisted in outlining the scope of this study. During these deliberations, the validity of the reports documenting the iodine content of foods was questioned and the experts stated that the true status of the iodine level in the United States diet was unknown. In addition, it became evident that there were also questions as to the utility or accuracy of the analytical methods for assessing the iodine content of foods.

These issues appeared to be of paramount importance to this study. Therefore, this report focuses upon analytical methodology and the evidence for the actual iodine content of foods as a basis for a subsequent review of idiosyncratic, allergic and other untoward reactions to dietary iodine by this office.
II. RESUME OF IODINE METABOLISM

Ingested free and bound iodine and iodosides are absorbed through the gastrointestinal tract as iodide and rapidly distributed throughout the body. The blood of normal fasting individuals contains less than 0.5 μg iodide per 100 ml as inorganic iodide, or the free and protein bound thyroid hormones, triiodothyronine (T₃) or thyroxine (T₄). Unless removed by the thyroid gland, the inorganic iodide of the plasma is rapidly excreted by the kidney (Figure 1).

While nearly every cell in the body contains iodide, the thyroid gland is the depot for iodine reserves in the body. Iodide is converted in the thyroid cells to an oxidized state by the enzyme iodide peroxidase. This active form of iodide reacts with the tyrosine of thyroglobulin to form mono- and di-iodotyrosine and eventually the active hormones. The thyroid hormones are known to have a role in calorigenesis and thermoregulation, intermediary metabolism, reproduction, growth and development, hematopoiesis and circulation, and neuromuscular functioning.

The iodine content of thyroglobulin in the euthyroid individual varies widely depending on age, sex and in part on the iodide available in the body. The National Research Council, Food and Nutrition Board, (1974) has recommended daily dietary allowances for iodine that vary from 35-150 μg depending on age and sex. If the diet becomes iodine deficient, the body iodine diminishes. The renal excretion of iodine continues, and the thyroid gland responds to its obligatory task of thyroxine synthesis with insufficient iodide by excessive proliferation of the thyroid epithelium. On the other hand, if iodide intake is increased, renal excretion increases and, at some point, thyroidal storage of iodide also increases. In the euthyroid individual, iodine equilibrium is continually reestablished, depending on the level of iodine intake.

A number of clinical metabolic conditions in man and animals are related to alterations in the patterns of synthesis, storage, secretion, delivery, or utilization of the thyroid hormones. The normal utilization of iodine is modified in metabolic diseases and the resultant hypothyroid or hyperthyroid state is often associated with changes in specific enzymic activities. Physiologically, the net effect is often an inadequate synthesis or delivery of the thyroid hormones to the target organs of the body (Stanbury et al., 1972).
Schematic diagram of iodine metabolism in euthyroid individuals. TriAc and TetrAc are the acetic acid analogues of tri- and tetraiodothyronine, respectively. TBG, thyroxine-binding globulin; TBPA, thyroxine-binding prealbumin. From Stanbury et al., 1972 with permission of the copyright holder.
III. ANALYTICAL METHODS FOR DETERMINATION OF FOOD IODINE

It is generally recognized that the concentration of iodide in most biological tissues is low. Accurate determination of iodine in food requires very sensitive methods of analysis with freedom from reagent contamination. The estimation of iodine in a complex food-stuff is difficult because the large sample required must be digested and concentrated. The Chilean Iodine Educational Bureau in their 1952 report on the iodine content of various foods noted that standardized analytical methods were not available and individual laboratory differences were often substantial. In 1958, the Bureau reviewed the methods of iodine determination in various biological materials; however, significant advancement in methodology has occurred in the intervening years.

A. CHEMICAL METHODS

The official method of the Association of Official Analytical Chemists (AOAC) for the determination of iodine in foods is a modified Elmslie-Caldwell dry ash procedure (AOAC, 1970). This method requires initial heating of processed samples at 100°C followed by ashing at 500°C for at least 15 minutes. Iodine is determined by titration with sodium thiosulfate in the presence of starch. This method, while adequate for samples with relatively high iodine content, is tedious, and may give erroneous results because of partial sample losses during dry ashing.

Barker (1948) developed a procedure for determining protein-bound iodine in various tissues including blood plasma that has been modified subsequently. The technique involves precipitation, washing and oxidation of the protein, distillation of the iodine, and colorimetric iodine determination. The colorimetric determination is based on the earlier method of Sandell and Kolthoff (1937), that makes use of the catalytic effect of iodine on reduction of ceric sulfate by arsenious acid. Barker (1948) noted that the technique could be used satisfactorily on samples as small as 2 ml.

Binnerts (1954) used the Barker method to determine iodine in milk. He found that distillation and extraction with organic solvents was not necessary in analyzing milk. This technique is frequently employed for iodine determinations in fluid milk or related products.
Menschenfreund (1956) developed a quantitative method for determining low amounts of iodine (0.01-0.1 μg) in small samples of food and drugs. The method consists of oxidation of microquantities of iodide in the sample to iodine, xylene extraction of the iodine, and subsequent spectrophotometric determination. This is considered an excellent modification of the Sandell-Kolthoff method (iodine catalysis of ceric sulfate reduction in the presence of arsenious acid). He measured the rate of ceric ion disappearance spectrophotometrically and determined the quantity of iodine from a standard curve. As little as 0.01 μg of iodine may be determined by Menschenfreund's method with a relative error of approximately ±2 % (Olson, 1961). However, minute traces of mercury, silver, fluoride, cyanide, bromide, and osmium may interfere in the cerium-arsenic reaction (Zak et al., 1952). This could be an important consideration when this system is used in determining the iodine content of foods.

Zak et al. (1952) developed a technique of "wet ashing" the sample with chloric acid to determine iodine in blood serum. The method is based on the catalytic effect of iodine on ceric sulfate reduction by arsenious acid. In 1963, Benotti and Benotti modified the Zak method for use in determining protein-bound iodine by automating the colorimetric determinations and data recording. Automation increased the accuracy of this time-sensitive method and permitted numerous rapid determinations with adequate controls to overcome manipulation variables. This method was employed by these workers in support of the investigations of Vought and London, 1964a, 1964b). The Benotti-modified-Zak method is used widely in clinical and commercial laboratories.

Malmstadt and Hadjiioannou (1963) studied the reaction mechanisms and conditions for the rapid automated determination of microamounts of iodine using the Sandell-Kolthoff reaction. Total quantities of iodide in aqueous solutions (0.015-0.45 μg) were determined with relative errors of about 1-2 % and measurement times of 10-100 seconds. They used their technique to estimate protein-bound iodine in serum, but noted that it could be adapted to iodine determinations in milk, drinking water, plant material or salt.

Cuthbert and Ward (1964) determined the iodide content of air-dried plant material by the cerium-arsenic reaction after oxidation of the dry sample in a Schöniger combustion flask and subsequent collection of the iodide in 1N NaOH. According to these authors, 1 mg/kg iodide in a 0.1 g sample of vegetation could be measured successfully. The speed of sample oxidation and the small sample are the chief advantages claimed for the method. A number of modifications of this method have been developed for use with dried plant materials.
Benotti et al. (1965) reviewed the various methods employed for the determination of total iodine in samples of urine, stool, tissues, and other biological materials. They stressed the importance of homogenization of food samples in the wet state and lyophilization to insure uniform sampling. The lyophilized sample (approximately 30 mg) is digested with chloric acid and the sample size is adjusted to make the total iodine content between 0.01-0.06 μg per sample. After complete digestion the analysis is continued in a manner similar to that used for blood serum using a modification of the Zak method.

Keller et al. (1973) studied the optimal conditions for the automated determination of low iodine concentrations by the Sandell-Kolthoff reaction. They used an Auto Analyzer System to determine μg/liter amounts of iodine in natural and potable waters. This automated technique may be useful in the analysis of foods or natural products.

B. ELECTROCHEMICAL METHODS

Although potentiometric determination of hydrogen ion concentration is a standard laboratory practice, the widespread use of ion-selective electrodes for determination of other ions is a relatively recent development. These electrodes are unique in that they sense ionic activity which may be more meaningful physiologically, but they can also be made to read both free and total ion concentration (Durst, 1971). Both solid-state crystal and heterogeneous membrane type electrodes that detect iodide ions are commercially available (Durst, 1971; Mesaric and Dahmen, 1973).

Rechnitz (1974) has pointed out that the availability of ion- and gas-sensing membrane electrodes represent a major advance in analytical methodology that will probably lead to development of methods replacing many techniques using optical detectors. He noted that ion-selective electrodes possess numerous advantages, including 1) indifference to suspended materials and thus do not require dialysis of biological fluids, 2) elimination of the need for color development reactions, 3) minimization of the need for analytical separation and other chemical manipulations because of inherent selectivity, and 4) initial cost reduction and ease of automation that further reduces time and costs. Bailey and Pungor (1973) have shown that silver-silver iodide type ion-selective electrodes can be calibrated accurately over a relatively broad range of concentrations.

Barkley and Thompson (1960) used a platinum electrode technique of Potter and White (1957) to determine the iodine content of seawater. They
observed that the technique, which is not used widely, compared favorably with the catalytic Sandell-Kolthoff reaction method.

Hoover et al. (1971) used ion-selective electrode analysis to estimate microgram quantities of iodide in animal feeds and plant material. They found the technique did not require ashing of samples prior to iodide determination when using a solid state iodide electrode (Orion Research Model 94-53). In addition, the large number of inorganic ions found in animal feeds did not interfere with the determination. The simplicity and rapidity of the method was stressed by these investigators. The method provided acceptable recoveries of iodide and compared favorably with the AOAC official method.

Curtis and his associates in the Michigan Department of Agriculture, and Lawyer of Wyeth Laboratories, Inc., Mason, Michigan have employed a simplified electrochemical method for determination of the iodide content of raw milk (Curtis, 1973). The method is based on the use of a solid state-ion-selective electrode (Orion Research Model 94-53) to measure iodide directly because iodine in cow's milk is primarily in the iodide form.

This method requires certain technical assumptions regarding the complexing of iodides by the milk phospholipids and proteins, the electrical activity of the ion, and the liquid junction potential of the electrode. While the method does not provide absolute values for total iodine in milk, it does give relative estimates of the iodide content of different milk samples and can be employed for the routine measurement of raw milk from various sources.

The measurements are made under standardized conditions and compared with a reference iodide standard solution that reflects the chemical composition of the milk sample as closely as possible. The millivolt readings permit the calculation of the amount of iodide in parts per million in the sample. The recovery of added iodide is reported to range from 97-109% in concentrations of 0.1-5 mg/liter. Lower amounts (20 μg/liter) could be estimated but the electrode response time was long. Essentially similar data on milk samples were obtained by this method in a collaborative study in the two laboratories where the iodide concentrations ranged from 0.12-2.80 mg/liter.
C. NEUTRON ACTIVATION AND ELECTRON CAPTURE TECHNIQUES

Neutron activation analysis is based upon production of radioactive nuclides from stable elements within the sample under investigation by means of neutron bombardment and subsequent determination of the radioactivity of the induced derivative (Schulze, 1969). While the use of this method requires substantial initial investment, it is extremely accurate and subject to minimal interference by other substances that may be present.

Rivieré et al. (1965) studied the distribution of iodine among several body compartments in normal and hyperthyroid human subjects using neutron activation techniques. They measured specific radioactivity of iodine ($^{131}$I) in plasma, urine, feces, and the thyroid gland itself. Cottino et al. (1967) also studied iodine balance in man using neutron activation analysis. They cited the difficulties associated with analytical chemical methods and suggested that the neutron activation technique was preferred because of the higher sensitivity, specificity, and precision in analyses of water, foods, and biological tissues with very low (1-2 nanogram/liter) iodine content.

Methods based on neutron activation analyses have been proposed for determination of iodine in vegetable matter and biological fluids by Ohno (1971) and by Heurtebise (1971). Both techniques require purification of samples by ion-exchange chromatography or solvent extraction prior to gamma-spectroscopy. Ohno (1971) used NaOH fusion 450°C prior to neutron activation and was able to determine 0.01 μg iodine with an accuracy of ± 6% in plant material and urine.

The initial equipment costs required for neutron-activation analysis may preclude its routine use on a wide scale for iodine analysis alone. However, a recent World Health Organization report (1972) on the significance of trace elements and cardiovascular diseases noted that neutron activation analysis had been the principal analytical technique used in that extensive study. While neutron activation analysis is not necessarily the most suitable technique for each specific trace anion or cation, it is sufficiently precise and reproducible to provide useful information on reliability of various chemical and other analytical techniques of trace element analysis.

Hasty (1971) has proposed a gas-chromatographic method for the determination of iodine. This technique involves conversion of iodine by reaction with acetone to a form which can be separated by gas chromatography and detected by electron capture. The utility of this method for analysis of iodine in foods has not been evaluated.
IV. SOURCES OF IODINE IN ANIMAL NUTRITION

Total iodine intake of animals and man is derived from several sources. The element is present in soil, air, and water and also becomes a constituent of plants and animals used for food as a result of intentional fortification, adulteration or accidental contamination. Iodine from air and water contributes to the total iodine intake of both animals and man. Similarly, iodine-containing disinfectants and drugs are sources of iodine that may become incorporated into food, may be absorbed dermally, or ingested in water and beverages (Boehne, 1970).

Because the normal human diet contains a significant quantity of nutrients derived from animals and animal products, the sources of iodine within the animal diet have been reviewed in detail. However, in this review, emphasis has been placed on all aspects of iodine intake by man. Where available, quantitative data are presented; however, such data are limited. In most cases, sources of iodine in animal and human diets can only be estimated from indirect qualitative observations.

A. FORAGE AND FEEDS

The most frequently quoted data on naturally occurring iodine in forage plants and animal feeds are those of the Chilean Iodine Educational Bureau (Table 1). These workers recognized that the iodine content of plants and plant products is markedly influenced by the amount and availability of nitrogen and iodine in the soil, the type of plant, soil pH, and other factors. For example, fertilization practices may alter iodine content of pasture grasses. Alderman and Jones (1967) observed a reduction in mean iodine content of pasture grasses from 410-270 μg/kg (dry weight basis) following fertilization with ammonium sulfate. The range of mean iodine values reported by Alderman and Jones (1967) for seven species of pasture grasses (140-450 μg/kg) is consistent with data noted in Table 1. However, Horn et al. (1974) have reported no effect of nitrogen and microelement fertilization on iodine content of orchard grass.

A 1971 compilation of information on composition of animal feeds contains little data on actual iodine content of forage plants and animal feeds used in North America (National Research Council, United States, Committee on Animal Nutrition and Department of Agriculture, Canada, Committee on Feed Composition, 1971). Related information on nutrient requirements of specific domesticated animals lists some iodine composition data for plants and plant products used in animal feeds (Table 2). Differences in values of alfalfa products suggest these data...
### TABLE 1
IODINE CONTENT OF SOME ANIMAL FEEDS

<table>
<thead>
<tr>
<th>Type of Feed</th>
<th>Average Iodine Content $\mu g/kg$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fresh Wt. Basis</td>
</tr>
<tr>
<td>Green Forage</td>
<td></td>
</tr>
<tr>
<td>Alfalfa</td>
<td>28</td>
</tr>
<tr>
<td>Mixed Pasture</td>
<td>60</td>
</tr>
<tr>
<td>Hay</td>
<td></td>
</tr>
<tr>
<td>Alfalfa</td>
<td>188</td>
</tr>
<tr>
<td>Meadow</td>
<td>194</td>
</tr>
<tr>
<td>Oat</td>
<td>219</td>
</tr>
<tr>
<td>Soybean</td>
<td>225</td>
</tr>
<tr>
<td>Sweet Clover</td>
<td>-</td>
</tr>
<tr>
<td>Timothy</td>
<td>80</td>
</tr>
<tr>
<td>Oil Seed Meals</td>
<td></td>
</tr>
<tr>
<td>Cottonseed</td>
<td>-</td>
</tr>
<tr>
<td>Groundnut</td>
<td>-</td>
</tr>
<tr>
<td>Linseed</td>
<td>-</td>
</tr>
<tr>
<td>Soybean</td>
<td>-</td>
</tr>
<tr>
<td>Straw</td>
<td></td>
</tr>
<tr>
<td>Barley</td>
<td>-</td>
</tr>
<tr>
<td>Oat</td>
<td>-</td>
</tr>
<tr>
<td>Rye</td>
<td>-</td>
</tr>
<tr>
<td>Wheat</td>
<td>-</td>
</tr>
</tbody>
</table>

*From data published by the Chilean Iodine Educational Bureau (1952).
TABLE 2
NATURALLY OCCURRING IODINE IN PLANTS AND PLANT PRODUCTS USED IN COMMERCIAL ANIMAL FEEDS

<table>
<thead>
<tr>
<th>Plant or Plant Part</th>
<th>Reference No.*</th>
<th>Iodine Content Dry Wt. Basis µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfalfa (Medicago sativa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aerial parts, dehydrated, ground, minimum 15% protein</td>
<td>1</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>120</td>
</tr>
<tr>
<td>aerial parts, dehydrated, ground, minimum 17% protein</td>
<td>1</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>2, 3</td>
<td>150</td>
</tr>
<tr>
<td>aerial parts, dehydrated, ground, minimum 20% protein</td>
<td>2, 3</td>
<td>140</td>
</tr>
<tr>
<td>aerial parts, dehydrated, ground, minimum 22% protein</td>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td>Bermuda grass (Cynodon dactylon) suncured hay</td>
<td>1</td>
<td>115</td>
</tr>
</tbody>
</table>

represent cumulative mean values. It should be noted that these values in Table 2 are on a "moisture free - as fed basis" rather than the "dry weight as collected" basis for the figures in Table 1; therefore, direct comparison of figures in Tables 1 and 2 is not possible.

Using hay and grain from Ohio and Indiana, Swanson (1972) reported iodine content of several animal feeds in a study of the effects of dietary iodine on thyroxine secretion of lactating cows. Average iodine content of the three feeds: alfalfa-grass hay, corn silage, and feed concentrate (containing corn, 53%; oats, 20%; soybean meal, 25%; uniodized salt, 1%; and dicalcium phosphate, 1%, were 102, 50, and 62 μg/kg of feed, respectively. These average values are considerably lower (10 fold) than those reported by Hemken et al. (1972) for feed samples from Maryland.

Hemken et al. (1972), in a study of milk iodine and dairy cattle performance, collected feed samples from 8 Maryland and 13 Northern Illinois farms. Moisture-free samples of hay from Maryland farms contained 1.31-2.54 mg/kg iodine (mean, 1.87 mg/kg) while those from Illinois contained 0.62-1.02 mg/kg iodine (mean, 0.82 mg/kg). Corn silage from Maryland had 1.00-1.87 mg/kg iodine (mean, 1.64 mg/kg), and that from Illinois, 0.34-0.70 mg/kg iodine (mean 0.52 mg/kg). Differences due to location were large for both types of forage and the values reported from Northern Illinois are more consistent with those indicated in Table 1.

The higher mean figures for hay and corn silage from Maryland may be indicative of a greater variation in iodine content of plants than that assumed by most investigators. As noted previously, most workers related such observations to the influence of soil factors and growing conditions, but few data are available that actually support this hypothesis (See page 33 for further pertinent discussion).

Baker and Lindsey (1968) have reported goiter in thoroughbred horses resulting from excess dietary iodide intake. Dietary intake of inorganic iodide by mares bearing goitrous foals ranged from 48-432 mg/day compared with values of 7 mg/day or less observed in horses on farms where no goiter was observed. Baker and Lindsey (1968) determined that dried seaweed (kelp) was the principal source of iodide in the goitrogenic diets of these horses. After elimination of the sources of excess iodine from the diet, goiters regressed in size and new cases of goiter were not observed. Baker and Lindsey (1968) concluded that this iodine goiter in horses was similar to an analogous disease in man, iodine-induced goiter.
B. FEED SUPPLEMENTS

Numerous studies and clinical experience have shown that human iodine deficiency can be avoided or corrected by supplementing the diet with small quantities of iodine. For similar reasons, iodine has been added to animal feeds or made available in salt blocks to provide sufficient quantities to meet nutritional requirements. Because of the uncertainties associated with the actual iodine content of forage grasses and feed grains and because of the widespread occurrence of goitrogens in forage plants and animal feeds, iodine fortification of animal feed has become an accepted practice throughout the world.

The National Research Council (NRC), Committee on Animal Nutrition (1968, 1970, 1971a, 1971b) has prepared guidelines on nutritional requirements of domesticated animals. These recommendations suggest that iodine should be incorporated into the vitamin and mineral supplement added to the diet, made available in salt blocks, or mineral mixtures offered in free choice rations. Symptoms of iodine deficiency in most animals can be prevented by feeding salt containing 0.0007 % "stable" iodine. This level of iodine intake is likely to be exceeded under normal conditions because feeding iodine-fortified salt at the rate of 0.25 % of the dry diet would provide 0.19 mg/kg iodine in the diet (NRC, Committee on Animal Nutrition, 1970). This level of salt intake would be approximately double the 800 μg/day suggested allowance for a mature animal. Such considerations suggest that feed supplements can be a significant source of iodine in animal diets.

Information supplied by the American Feed Manufacturers, Inc. (Arlington, Virginia) indicates that most fortified feeds reach NRC recommended levels as a standard practice. In a subsequent survey conducted by the authors of this review, State Agriculture Departments in nine major dairy states reported that analyses of feeds or dairy products for iodine content is not a routine practice. Most respondents indicated that they do analyze for iodine upon request or in cases where iodine derivatives are added to animal feeds as medications. These data were not made available to the Life Sciences Research Office.

However, studies by Iwarsson et al. (1972) and Hemken et al. (1972) suggest that iodine supplementation of feeds markedly affects the iodine available to dairy cows. In a survey of iodine content of forage, grain, and the milk produced from 13 Illinois farms, Hemken et al. (1972) found that some form of iodine supplementation was available to animals above and beyond that which had been added to the feed grain ration on 7 of the 13 farms. They concluded that while the range in milk iodine was large,
it reflected the iodine content of the mineral supplements more than the iodine in the forage and grain. For example, in one case where iodized salt (0.0076 % iodine) and a high iodine mineral mixture (0.055 % iodine) were fed, milk samples contained 1610 μg iodine per liter.

There has been considerable research on methods of supplying iodine to animals in a form that will be readily and continuously available. Early workers observed that sodium or potassium iodide satisfactorily prevented thyroid enlargement in several animal species fed goitrogenic diets (Ammerman and Miller, 1972). Iodine is often supplied to foraging animals by providing iodine fortified salt blocks. Because the salt blocks are subjected to atmospheric conditions, it is necessary to use a stable form of iodine. Currently, calcium and potassium iodate, pentacalcium orthoperiodate, cuprous iodide, and diiododithymol are used as nutritional sources of iodine because of their ease of conversion to absorbable iodide and their physical properties which provide relative stability over time (Ammerman and Miller, 1972; Miller et al., 1965, 1968; Moss and Miller, 1970). Diiodosalicylic acid has been used as an iodine source, but cattle have less ability to use iodine from this source than other species, such as the rat (Aschbacher and Feil, 1971; Aschbacher et al., 1963).

It is generally agreed that the orally ingested iodates used as sources of iodine are readily converted to iodides in most animals. A detailed review of the qualitative aspects of iodine fortification of animal feeds has been prepared (Ammerman and Miller, 1972).

An additional source of iodine may be veterinary medications added to feeds. For example, ethylenediamine dihydroiodide is widely used at relatively high dietary levels to prevent or treat foot rot and soft tissue lumpy jaw in cattle (Miller and Tillapaugh, 1966). Herrick (1972) has suggested that ethylenediamine dihydroiodide may breakdown differently than iodine compounds in the ruminant digestive tract; however, Miller and Swanson (1973) have demonstrated its conversion to and absorption as iodide. Radiolabeled ethylenediamine dihydroiodide is absorbed to an equal or better extent than sodium iodide and is retained in cartilage and soft tissues longer (Miller and Swanson, 1973).

At the recommended preventive level of 50 mg ethylenediamine dihydroiodide/cow/day, Miller and Swanson (1973) found serum iodide levels and milk iodine levels significantly elevated over control animals. On the other hand, Long et al. (1956) reported no effect on serum iodide in cows fed approximately 22 mg/cow/day. At the therapeutic dosage level (200 mg/cow daily) whole serum iodide values were 10 times those of control animals and milk iodine levels as high as 1559 ± 771 μg/liter.
were found. Cows receiving 1000 mg ethylenediamine dihydroiodide/day were ingesting 50 mg/kg/day iodine in the diet. Serum iodine and milk iodine values were correspondingly high (1971 ±295 μg/liter for serum and 2393 ±379 μg/liter in milk). Urine and fecal iodine excretion increased as the level of ethylenediamine dihydroiodide fed was increased. These experimental levels would not be reached in normal feeding practices. Miller and Swanson (1973) noted no signs of iodine toxicity at the highest intake levels in these experiments with lactating animals (50 mg/kg/day iodine). However, Newton et al. (1972) have reported iodine toxicity in young calves (100–250 kg body weight) fed iodine as calcium iodate in the basal diet. They concluded that 50 mg/kg basal diet was the minimum toxic level although some animals exhibited slower growth rates and larger adrenal glands at lower dosages. Feeding of 100 and 200 mg iodine/kg diet produced coughing, nasal discharge, heavier adrenal and thyroid glands and elevated serum iodine levels. They suggested that iodine in feeds at levels of 25 mg/kg ration were undesirable. Newton et al. (1973) did not assay skeletal muscle for iodine content at slaughter.

In summary, the total iodine intake of domesticated animals appears to be markedly increased by the iodine added to feed in the mineral supplement, supplied in iodized salt blocks, or administered as medications. There is sufficient evidence to suggest that these sources of iodine are normally more important than iodine naturally occurring in forage and feed grains. Meat and dairy products from these animals might contain relatively high levels of iodine; for example, Miller et al. (1973) found iodide in all tissues of dairy cows after administration of 300-600 μCi 125I or 131I as sodium iodide. There is a need for further study of actual iodine content of animal tissues used as human food.

C. ADVENTITIOUS SOURCES

1. Water

Seawater contains approximately 50 μg/kg iodine as iodide and iodate salts although the concentration varies widely in the oceans (Altman and Dittmer, 1966). Iodine content of fresh water is lower than that of seawater. Early studies suggested that prevalence of goiter was inversely proportional to iodine content of drinking water. Olin (1924) found drinking water supplies in Michigan contained from 0-8.7 μg/liter iodine. Matovinovic (1970) reported the iodine content of drinking water from the Tecumseh, Michigan area ranged from 0.7-2.4 μg/liter. Koutras et al. (1970) reported that drinking water from a generally goiter-free area in Greece had a mean iodine value of 4.7 μg/liter, while water from an area where goiter was endemic averaged 2.4 μg/liter. Connolly et al. (1970) observed that drinking water in Tasmania contained 0.6-4.1 μg/liter iodine with lower values from areas where goiter was more prevalent.
Vought et al. (1970) found that the Potomac River above Washington, D.C. averaged 4.0 μg/liter iodine, while downstream at Alexandria, Virginia the iodine concentration was 8.0 μg/liter. Higher concentrations were found in sewage, and the increased value for downstream river water was associated with discharge of sewage effluent.

Vought et al. (1970) observed relatively high concentrations of iodine in other adventitious locations such as dry sewage sludge (7 mg/kg), sewage treatment effluent (1910 μg/liter), and urban vegetation upwind (727 μg/kg) and downwind (1288 μg/kg) to a heavily traveled roadway. Soils from these two locations contained an average of 4.523 mg/kg and 3.006 mg/kg, respectively. The significance of these data in relation to water, soil, and vegetation in the rural environment is unknown; however, these levels of iodine may be more closely related to the urban site rather than the amount of iodine present in the soil, atmosphere, and vegetation.

In summary, the iodine content of natural water is variable, but relatively low. Fresh water from mountainous areas appears to be lower in iodine content than fresh water from coastal rivers and lakes. Seawater contains higher levels of iodine than fresh water but this is only available in animal feeds and human food containing seaweed, fish, or fishmeals. There is little evidence to suggest that drinking water is a source of relatively large amounts of iodine, unless the water is contaminated with industrial wastes or sewage.

2. Air

The iodine in the atmosphere and that subsequently deposited on land by rain is derived from the iodine in seawater (Miyake and Tsunogai, 1963). While no documented information has been uncovered, it seems logical to suggest that animals would be exposed to and might absorb significant quantities of atmospheric iodine. Similarly, dairy cows confined in pens or buildings where iodine-containing cleansing agents are used, could be exposed to higher levels of atmospheric iodine. There appears to be a need to collect additional data on the contribution of atmospheric iodine to the total intake of iodine by animals and man.

D. GOITROGENIC FACTORS

A number of plants and plant products used in animal feeds or for forage are known to contain substances which can induce goiter in animals. In addition, agronomic practices, such as fertilization, may alter plant composition and when the forage is consumed, goitrogenic effects may become evident. Goitrogens in plants are less important in the human diet because the enzymes which activate progoitrogens to goitrogens are destroyed by cooking.
Over 300 natural or synthetic chemicals possess goitrogenic activity and the majority of these appear to be thioamide or aniline derivatives (Greer et al., 1964). Among the naturally occurring goitrogens, the best characterized are the several glucosinolate (thioglucoside) derivatives isolated from Brassica sp. and other Cruciferae (Hino et al., 1961; VanEtten and Wolff, 1973; Wills, 1966). Recent studies of the oilseed crops, rape and crambe, suggest that the by-product meal may be used as animal feed if the toxic glucosinolates are removed (VanEtten and Wolff, 1973). Because glucosinolates are converted to goitrogenic isothiocyanates, the genetic or chemical alteration of glucosinolate content of such plants could be a desirable characteristic.

The occurrence of a potent goitrogen in soybean flour and meal is well documented (Halverson et al., 1949; Hemken et al., 1971; Sharpless et al., 1939; Wilgus et al., 1941). Ingestion of this substance produces thyroid enlargement and decreased iodine content of the entire gland in experimental animals. Heating the soybean flour during processing reduced the goitrogenic activity of the soybean flour (Halverson et al., 1949). Konijn et al. (1973) have recently characterized the goitrogenic principle in soybean as an oligopeptide or a glycopeptide composed of one molecule of sugar and one or two amino acids. The active oligopeptide or glycopeptide could be present in many premixed animal feeds containing soybean products. Soybean products are used in animal feeds and the presence of the soybean goitrogen is one of the reasons usually given for addition of iodine to mineral supplements (Hemken et al., 1972). As noted by Wills (1966), increased iodine intake will not overcome completely goitrogen activity.

Goitrogenic activity has been attributed to many other substances normally found in plants including calcium, cobalt, the halogens, and cyanoglycosides (Wills, 1966). Ergothionine, certain polysulfides and the plant hormone, indolylacetonitrile, possess goitrogenic activity; however, many naturally occurring goitrogens have not been identified chemically.

Goitrogens in rutabaga, turnip, cabbage, and mustard are most likely to be found in the human diet. There is circumstantial evidence that these plants may contribute directly or indirectly to a small fraction of human goiter in the world (VanEtten and Wolff, 1973). Gaitan (1973) has recently implicated water supplies in endemic goiter areas as a possible source of goitrogens. He pointed out bacterial contamination of ground water as a possible source of sulfur containing organic compounds possessing goitrogenic activity in animals and potentially man, within specific endemic goiter regions. The possible involvement of bacteria in producing water-borne goitrogens was previously noted by Vought et al. (1967).
The consumption of goitrogen-containing feed or forage by dairy cows may also be of significance to human nutrition. Milk from cows fed forage containing either cruciferous weed or other plants containing goitrogens, could interfere with normal thyroid function of individuals consuming this milk or products made from the milk (Peltola, 1960; White and Moghissi, 1971; Wills, 1966). While the transfer of goitrogens or metabolites with goitrogenic properties from animals to man via milk has been shown by several investigators (Clements, 1958; Clements and Wishart, 1956; Greene et al., 1958; Peltola, 1960; Wills, 1966), other investigators have found little or no goitrogenic activity in milk (Broadhead et al., 1965a, 1965b; Virtanen, 1961). Most studies suggest that goitrogen transfer does occur, but the quantities of goitrogen appearing in the milk are well below the amounts known to induce thyroid enlargement. For further discussion of this issue, see p 58. The recent review of VanEtten and Wolff (1973) should be consulted for further information on goitrogens and their effects.
V. SOURCES OF IODINE IN HUMAN NUTRITION

There are no extensive data that have been collected in recent years on the iodine content of foods. The most complete data available were compiled by the Chilean Iodine Educational Bureau in 1952 (Table 3). It should be noted that this report includes information collated over several years, and reports values determined by different investigators using several methods of analyses. The majority of the data refers to raw food and may not correspond to actual iodine available from processed, frozen or cooked food.

Vought and London (1964a) have observed that direct measurements of dietary iodine were rare even in spite of long standing public health concern over prevalence and severity of endemic goiter. With few exceptions, this observation is still accurate in 1974. These investigators assayed both whole meals and food categories for iodine content in a study of controlled dietary intake at the National Institutes of Health (Vought and London, 1964b). Iodine determinations were made by the modified Zak method (See Section III, p 14). In general, the mean values for iodine in each food category were greater than those reported by the Chilean Iodine Educational Bureau (Tables 3 and 4). No other recent studies of the iodine content of the U.S. diet have been found.

However, Koutras et al. (1970) used a modified Zak method to determine the iodine content of several dietary items in two areas of Greece (Table 5). They reported mean values somewhat lower than Vought and London (1964b) for similar foods; however, they found that most dietary iodine was derived from foods of animal origin. This is consistent with previous studies (Table 4). Koutras et al. (1970) attributed the wide range of values and variation in their data to the use of iodinated substances on farms and in bakeries. They concluded that the iodine content of natural foods does not adequately meet adult nutritional needs in Greece and recommended universal iodization of salt as a prophylactic measure.

A. IODINE IN PLANTS AND PLANT PRODUCTS

An intensive search for published reports has not uncovered any recent analyses of iodine content of vegetable, fruit, cereal, and other plants found in the human diet. Most authors refer to the data compiled by the Chilean Iodine Educational Bureau (1952) or the study of Vought and London (1964a).
**TABLE 3**

**AVERAGE IODINE CONTENT OF FOODS AND COMMODITIES USED IN PREPARED FOODS**

<table>
<thead>
<tr>
<th>Food or Product</th>
<th>Iodine Content μg/kg</th>
<th>Food or Product</th>
<th>Iodine Content μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fresh Basis</td>
<td>Dry Basis</td>
<td>Fresh Basis</td>
</tr>
<tr>
<td>Cereal Grains</td>
<td></td>
<td>Legumes</td>
<td></td>
</tr>
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<td>22</td>
<td>Peas</td>
<td>23</td>
</tr>
<tr>
<td>Maize</td>
<td>27</td>
<td>Beans</td>
<td>36</td>
</tr>
<tr>
<td>Wheat</td>
<td>37</td>
<td>Mean</td>
<td>30</td>
</tr>
<tr>
<td>Flour</td>
<td>42</td>
<td></td>
<td>234</td>
</tr>
<tr>
<td>Bread</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barley</td>
<td>58</td>
<td>Meat</td>
<td></td>
</tr>
<tr>
<td>Oats</td>
<td>60</td>
<td>Mutton</td>
<td>27</td>
</tr>
<tr>
<td>Rye</td>
<td>72</td>
<td>Beef</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>Veal</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pork</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacon</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggs</td>
<td>93</td>
<td>Lard</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Fish</td>
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<td>Milk</td>
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<td>Cow’s Milk</td>
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<td>Cheese</td>
<td>51</td>
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<tr>
<td>Salmon</td>
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<td>Butter</td>
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<tr>
<td>Mean</td>
<td>340</td>
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<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Carp</td>
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<td>Meat</td>
<td>47</td>
</tr>
<tr>
<td>River Bass</td>
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</tr>
<tr>
<td>Lake Trout</td>
<td>31</td>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marine</td>
<td></td>
<td>Shell Fish</td>
<td></td>
</tr>
<tr>
<td>Sole</td>
<td>163</td>
<td>Crab and Crabmeat</td>
<td>308</td>
</tr>
<tr>
<td>Sea Bass</td>
<td>250</td>
<td>Oysters</td>
<td>577</td>
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<tr>
<td>Sardines</td>
<td>284</td>
<td>Clams</td>
<td>783</td>
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<td>Mackerel</td>
<td>371</td>
<td>Lobster</td>
<td>1020</td>
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<tr>
<td>Halibut</td>
<td>520</td>
<td>Shrimps</td>
<td>1300</td>
</tr>
<tr>
<td>Herring</td>
<td>520</td>
<td>Mean</td>
<td>798</td>
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<tr>
<td>Sea Perch</td>
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<td>3866</td>
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<tr>
<td>Cod</td>
<td>1463</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haddock</td>
<td>3150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>322</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
<td>Vegetables</td>
<td></td>
</tr>
<tr>
<td>Pears</td>
<td>10</td>
<td>Gourds, Pumpkins,</td>
<td></td>
</tr>
<tr>
<td>Tomatoes</td>
<td>17</td>
<td>and Marrow</td>
<td>12</td>
</tr>
<tr>
<td>Apples</td>
<td>16</td>
<td>Cauliflower</td>
<td>12</td>
</tr>
<tr>
<td>Cranberries</td>
<td>29</td>
<td>Beets</td>
<td>21</td>
</tr>
<tr>
<td>Mean</td>
<td>18</td>
<td>Onions</td>
<td>22</td>
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<tr>
<td></td>
<td></td>
<td>Cucumber</td>
<td>25</td>
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<td></td>
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<td>Lettuce</td>
<td>26</td>
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<td></td>
<td></td>
<td>Carrots</td>
<td>38</td>
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<tr>
<td></td>
<td></td>
<td>Turnips</td>
<td>40</td>
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<td></td>
<td></td>
<td>Asparagus</td>
<td>42</td>
</tr>
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<td></td>
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<td>Potatoes</td>
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<td></td>
<td></td>
<td>Cabbage</td>
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<td></td>
<td></td>
<td>Spinach</td>
<td>201</td>
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<td></td>
<td></td>
<td>Mean</td>
<td>29</td>
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Data compiled up to 1951; presentation of data modified from Chilean Iodine Educational Bureau, 1952.
<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>190× 10</td>
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<td>280</td>
<td>540</td>
</tr>
<tr>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
<td>Median</td>
<td>Iodine (μg/wet Kg)</td>
<td>Food Category</td>
</tr>
<tr>
<td>Samples</td>
<td>18</td>
<td>18</td>
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<td>No. of</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**TABLE 4**
<table>
<thead>
<tr>
<th>Food Category</th>
<th>Athens (goiter-free area)</th>
<th>Thessalia (endemic area)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Samples</td>
<td>Iodine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drinking Water</td>
<td>12</td>
<td>4.7 ± 0.3</td>
</tr>
<tr>
<td>Milk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cow</td>
<td>12</td>
<td>41.5 ± 3.6</td>
</tr>
<tr>
<td>Goat</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sheep</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Soft Cheese</td>
<td>15</td>
<td>151.2 ± 18.5</td>
</tr>
<tr>
<td>Chicken Dishes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>16</td>
<td>30.1 ± 10.2</td>
</tr>
<tr>
<td>Meat Dishes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>10</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Fish Dishes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>9</td>
<td>14.2 ± 6.6</td>
</tr>
<tr>
<td>Legume Dishes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>14</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Bread</td>
<td>12</td>
<td>15.6 ± 12.0</td>
</tr>
</tbody>
</table>

<sup>1</sup>Data recalculated from Koutras et al. (1970).

<sup>2</sup>Mean and standard error of mean.

<sup>3</sup>Estimated mean values based on average portion size.
The presence of high concentrations of iodine in bread and bakery products has been reported (London et al., 1965). Calcium or potassium iodates, used as dough conditioners, appear to be the source of this iodine rather than naturally occurring iodine in the dough ingredients (See p 37).

The iodine content of certain seaweeds used as food can be as high as 0.8-4.5 g/kg of dried material (McClenon, 1933). While this estimate may include iodine deposited upon the surface as well as that within the kelp, the mean values exceed those for land plants, including those receiving iodine in fertilizer (Table 2). The higher mean values for kelps are usually associated with the relatively high concentration of iodine in seawater (50 μg/kg).

Reports of iodine in plants generally suggest that the iodine is absorbed by the root system from the soil. However, it should be noted that iodine is not considered an element essential for growth of vascular plants. While most reports suggest absorption or adsorption from soil by the root system, there is some evidence that suggests iodine uptake by the root system is not an important source of the iodine found in plants. Hungate et al. (1963) showed that $^{131}$Iodine can be absorbed through the leaves from the atmosphere but it is not translocated to other plant parts. These investigators were unable to show root uptake of $^{131}$Iodine. These data suggest that the atmosphere rather than the soil or ground water may be the source of the iodine found in higher green plants.

Vought et al. (1970) indicated that polluted natural water may contain high concentrations of iodine. If such water were used for irrigation of crop plants, foliar iodine absorption, either in solution or released into the atmosphere, could be a source of iodine in the human diet. There is an urgent need to establish more definitively, the pathways by which iodine enters plants and plant products that are in the human diet.

B. IODINE FROM ANIMAL SOURCES

Milk and milk products, eggs, meat, and fish apparently contain larger amounts of iodine than the vegetable foods in the human diet (Tables 3 and 4). Vought and London (1964b) concluded that the major sources of iodine in their metabolic balance studies were milk and eggs. This observation is analogous to the probable source of iodine in the "average diet" of most adults. While fish and fish products contain relatively more iodine, seafoods are not a major dietary item in the United States (U.S. Department of Agriculture, Agriculture Research Service, 1972).
Because eggs accumulate systemic iodides, they may contain high concentrations as a result of iodine compounds in feed supplements or drinking water. For example, Vought and London (1964a) reported 260±30 μg of iodine/wet kg of eggs purchased locally for a metabolic study. Marcilrese et al. (1968) fed high concentrations of iodine (100 mg/day) in a study of iodine metabolism in laying hens. The iodine content of the egg increased linearly for 10 days, and reached a plateau of 3 mg/egg (±5mg/100g). Concentrations of iodine in eggs from chickens fed 500 mg/day increased rapidly to an average of 7 mg/egg (±12mg/100g) in 8 days. However, these levels of iodine would not be encountered in commercial poultry production because limitations (maximum 12.5 mg/kg or liter) on iodine in feed and drinking water have been established (Korp, 1972).

Milk and related dairy products appear to be an important source of iodine in the human diet. The iodine content of milk can be affected by the use of supplemented animal feeds, iodized salt blocks for maintenance of adequate iodine intake by dairy cows, and the use of iodine containing disinfectants, sanitizers, and veterinary medications.

The mammary glands concentrate iodine and it is readily secreted by lactating animals (Anonymous, 1962; Miller and Swanson, 1963). Secretion of iodine into milk is influenced by iodine intake, season, level of production, and fullness of the mammary gland. Reineke (1961) suggested that iodide secretion into milk in high-yielding cows would be greater because of the higher volume of milk production and a greater concentration gradient between blood and milk. However, Miller and Swanson (1963) showed that iodide diffuses between the blood and mammary gland of the cow quite readily and that iodide can enter the milk independently of milk secretion. Thus, milk from dairy cows selected for high milk production is more likely to have more iodine because of the larger volume of milk produced. It follows that high milk producing animals fed iodine supplemented feeds or exposed to other sources of iodine could produce milk with significant quantities of iodine. For example, Hemken et al. (1972) observed that daily supplementation of concentrate feed of lactating holstein cows with 0, 6.8 mg and 68.0 mg potassium iodide resulted in mean milk iodine values of 8, 81, and 694 μg/liter iodine, respectively.

In the same study, Hemken et al. (1972) reported milk iodine values from 13 Illinois farms averaged 425 μg/liter, and samples from 8 Maryland farms averaged 457 μg/liter. The range in iodine content of milk was wide, and reflected the level of iodine supplementation more than the iodine content of the hay, silage or grain itself. Other investigators (Braodhead et al., 1965a; Iwarsson et al., 1972; Swanson, 1972) have reported higher milk iodine values where iodine supplementation was practiced.
Finally, White and Moghissi (1972) have shown that iodine, iodide, or iodate (\(^{131}\)I) readily transferred from milk to cheese during curd formation. By analogy, milk containing high concentrations of iodine, e.g. 425 µg/liter, used in manufacture of cheese, could result in cheese containing substantial iodine. Connolly (1971a) has reported iodine values in excess of 436 µg/kg for milk chocolate, cheese, and ice cream; however, iodine content of the milk used to produce these foods was not stated. Additional data on iodine carryover from milk to dairy products are required to evaluate adequately the iodine content of such foods.

The widespread use of sanitizing agents such as iodophors in the dairy industry has been suggested as an indirect source of iodine in the human diet. These substances are regulated and a limit of 25 ppm titratable iodine is specified for usages involving equipment and utensils which contact food or food products (Office of the Federal Register, 1973a). If improperly used, iodophors might be present in milk or dairy products. Similarly, domesticated animals confined in pens or buildings where iodophors are employed as cleansing agents might be exposed to higher levels of atmospheric iodine.

The iodophors sharply reduce iodine vapor pressure and depending upon their formulation, liberate volatile iodine slowly. Because iodine in aqueous solution is broadly biocidal, iodine-containing products such as the iodophors are widely used in the dairy industry as teat dips and udder washes before and after the application of milking machines. In addition, iodophor solutions are also used as sanitizing solutions for cleansing equipment used in handling, storing and transporting fluid milk (Trueman, 1971; Twomey, 1968, 1969). In the widespread use of iodophors as teat dips for mastitis control, these products are used undiluted as topical "sanitizers" in concentrations from 0.5-1.0%. However, iodophor solutions used for sanitizing equipment are normally diluted to give available iodine concentrations from 0.001-0.0025%. The teat dip and udder wash products vary widely in iodine volatility and perhaps degree of dermal absorption, depending on their formulation and there is little standardization of these preparations.

Iwarsson and Ekman (1974) have shown that during periods of teat dipping, the iodine content of bulk herd milk increased 174 µg/liter (range 55-353 µg/liter) in comparison to control periods when no iodine disinfectants were used. There is a need for additional study on iodine carryover in milk from topical application and equipment sanitation with iodophors.

In Tasmania, Connolly (1971a) found that milk from five localities where iodophors were used as sanitizing agents contained 113-346 µg/liter
iodine. Milk from dairies in the same localities not using iodophors contained only 13-23 μg/liter iodine. Similar increases in iodine content of milk related to use of iodophors either topically or in equipment cleansing have been reported by Iwarsson and Ekman, 1973, 1974; Joerin and Bowering, 1972; Stockl and Weiser, 1968; Twomey and Joerin, 1973; Zackerl et al., 1969).

However, Joerin and Bowering (1972) noted that 6 of the 24 herds exposed to iodophors for both topical and equipment sanitation also received salt and feed supplements. The cows on farms where no iodophors were used for either purpose received no salt nor supplementary feed. Furthermore, Curtis (1973) has reported that raw milk from Michigan producers using iodophors averaged 370 μg/liter iodine, while samples from producers not using iodophors contained 310 μg/liter. He concluded that the difference in mean values was most likely a result of feeding practices and not the result of iodophor use. It should be noted that Curtis (1973) as well as Iwarsson and Ekman (1973, 1974), Joerin and Bowering (1972) and Stockl and Weiser (1968) sampled raw milk. The other investigators (Connolly, 1971a; Twomey and Joerin, 1973) sampled milk and dairy products after processing.

While it is evident that the iodine content of milk can be elevated by certain uses of iodophors, there are no reports of adverse effects from such uses on lactating cows. Similarly there are no reports of adverse health effects in persons consuming milk containing elevated amounts of iodine that can be attributed to the iodine alone. Further studies on iodine carryover from equipment or foods such as milk should be conducted to validate the adequacy of label directions for use of iodophors in the dairy and food processing industries.

Finally, it should be recognized that the values for iodine in certain foods of animal origin may not reflect the actual amount of iodine ingested. For example, Harrison et al. (1965) found not only a marked variation in iodine content of fish, but also a marked reduction in iodine content after cooking and preparation. It is probable that the iodine content of many cooked foods may differ significantly from that reported for raw plant or animal products.

C. IODINE IN PREPARED AND PROCESSED FOODS

Food consumption patterns in the United States exhibit an increasing trend toward use of industrially processed and prepared food. Intentional addition of iodine compounds to foods is limited to salt, dietary supplements, infant formulas, and meat substitutes (Boehne, 1970). For the most part, the use of iodized salt in processed and prepared food is reported to be minimal (Kuhajek and Fiedelman, 1973; Reed, 1970). However, recent reports suggest that processed and prepared foods may also contain high amounts of iodine from unidentified sources.
The iodine content of 12 types of frozen fried-chicken dinners has been shown to range from 9.9-429.9 μg iodine per package (Anonymous, 1973). The iodine content was estimated by a modified Elmslie-Caldwell method (AOAC, 1970). The report (Anonymous, 1973) stated that iodized salt was the source of the iodine, but no supportive data were given. On the basis of the stated quantities of salt in the frozen fried-chicken dinners, iodized salt could not be the major source of the iodine. No other reports of iodine analysis in such processed ready-to-eat foods have been found.

In another recent study, the Wisconsin Alumni Research Foundation, Inc. (WARF, 1973) analyzed the nutritive quality of the products of MacDonald's Corporation (Oak Brook, Illinois 60521). Analysis by the Binnerts method provided the following data on iodine content:

<table>
<thead>
<tr>
<th>Product</th>
<th>Iodine content μg/100 g product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg McMuffin</td>
<td>22</td>
</tr>
<tr>
<td>Hamburger</td>
<td>49</td>
</tr>
<tr>
<td>Cheeseburger</td>
<td>43</td>
</tr>
<tr>
<td>0.25 lb. Hamburger</td>
<td>42</td>
</tr>
<tr>
<td>0.25 lb. Cheeseburger</td>
<td>45</td>
</tr>
<tr>
<td>Big Mac</td>
<td>42</td>
</tr>
<tr>
<td>Filet of Fish</td>
<td>84</td>
</tr>
<tr>
<td>French Fries</td>
<td>20</td>
</tr>
<tr>
<td>Chocolate Shake</td>
<td>47</td>
</tr>
<tr>
<td>Vanilla Shake</td>
<td>47</td>
</tr>
<tr>
<td>Strawberry Shake</td>
<td>49</td>
</tr>
</tbody>
</table>

The consumption of one meat-containing product, one serving of french fries, and a chocolate shake would provide between 124.6 and 155.9 % of the recommended daily allowance (150 μg/day) for a male 14-18 years old. The source of iodine was not specified, although it seems logical to suggest that dairy products, meat, and bread would contribute a significant quantity (WARF, 1973).

Potassium iodate and to a limited extent, calcium iodate, are used in the production of some bread and related baked foods. Conn et al. (1950) showed that iodate salts decomposed primarily to iodides during baking; thus, either form is readily bioavailable.

According to the American Institute of Baking (Chicago, Illinois 60611) potassium iodate or calcium iodate may be used in the continuous mix process along with potassium bromate, calcium bromate or calcium peroxide to increase dough stability. When used, iodate
is commonly added at levels of 12.5-20.0 μg iodine/g flour. If no loss of iodine occurred during baking, this would ultimately result in about 5 μg iodide/g of bread. Smaller amounts of iodine may be incorporated into conventional sponge-dough bread if the baker uses a yeast food containing an iodate salt. Such products contain about 0.1 % potassium iodate and are used at the rate of 3.0-6.0 μg/g flour. This would result in about 1-2 μg iodide/g of bread, again assuming no loss during mixing and baking.

The Standards of Identity for bread and rolls (Office of the Federal Register, 1973b) limit the combined use of bromate and iodate to 75 μg/g flour. Because the technological requirements for bromate are higher than that of iodate in practice, the quantity of iodate would contribute less than half of this amount.

The use of iodates as dough conditioners has been reported to be decreasing (National Research Council, Committee on Food Protection, 1970). An informal survey of major baking companies in the United States was conducted by the American Institute of Baking in May, 1974 in response to a request for information concerning use of iodates in continuous and conventional mix bread production. The six organizations responding indicated that iodate usage over the past several years has either decreased or shown little discernible change. Of the six major baking companies, two do not use iodates at all; one uses iodate dough conditioner in all plants throughout the country uniformly. The remaining three organizations estimated that one-third to one-half of continuous mix plants and about one-fourth of the conventional mix plants were using dough conditioners containing iodates.

Studies at the American Institute of Baking, Laboratories, School of Baking (1967) suggest that azodicarbonamide in combination with bromates can substitute for iodates as a satisfactory dough conditioner. Respondents to the May 1974 survey suggested that increased use of azodicarbonamide and more recently, use of encapsulated ascorbic acid may account for the lack of increased use of iodates. It is probable that iodate use has remained unchanged or has diminished in the past decade but it is not possible to determine if iodate use in the production of bread and related bakery products is actually changing without further investigation of quantities produced and consumed by the baking industry throughout the country. It is possible that iodine values for bread reflect other adventitious sources of iodate, iodide, and iodine. There is a need to collect definitive data on the sources and quantities of iodine in bread and bakery products throughout the United States.

Iodation of bread in Tasmania proved to be more effective in goiter prevention than distribution of iodated salt tablets. Based on
average bread consumption figures for several age groups, Clements et al. (1970) calculated that iodine intake from bread (prepared with up to 2 mg/kg potassium iodate as a dough conditioner) was 80-270 µg/person/day. It should be noted that Connolly et al. (1970) have reported an increased prevalence of thyrotoxicosis in adult females with preexisting goiter in Tasmania following universal iodine fortification of bread (for further discussion of iodine toxicity see p 68).

No other data on iodine content of commercially processed or prepared foods have been found. The values reported in the two studies cited indicate that baked goods may well be a significant source of iodine in the contemporary North American diet. Additional information on a broad range of processed and prepared foods is required.
OTHER SOURCES OF IODINE

Iodine may be ingested or absorbed directly from a number of sources that are not usually considered as items in dietary intake. These include drinking water, beverages, medications, salt, and other seasonings, food additives, the atmosphere, and substances inadvertently introduced in food and water. The actual iodine intake from all such sources is poorly documented; however, iodine is usually in a form, or can be converted to a form, that is readily absorbed.

1. Water and Beverages

As noted in the section on Sources of Iodine in Animal Nutrition (p 25), the iodine concentration in natural water rarely exceeds 5.0 µg/liter. The use of iodine for purification of municipal water supplies has not been generally approved; however, its use has been approved, in specified dosages, for water treatment under military field and other emergency situations. With such exceptions water is not considered a major source of iodine for man (Connolly et al., 1970; Koutras et al., 1971; Matovinovic, 1970; Vought et al., 1970). Koutras et al. (1971) indicated the iodine content of beer and wine was 43-46 µg/kg and 8-32 µg/kg, respectively.

2. Medications

A survey was made of therapeutic drugs and their salts containing iodine in some form. Examples of such preparations are listed in Table 6. The categories overlap but the large number of iodine-containing dosage forms is impressive. These preparations, used in general medical practice or in specialized diagnostic procedures, constitute a major source of iodine intake for a large number of people. In addition, iodine and iodine salts are present in many over the counter remedies that are taken without physicians' prescriptions. For example, 10 ml of the vitamin supplement, Cod Liver Oil NF, could supply as much as 163 µg iodine (Kline and Boehne, 1970).

Iodine containing substances such as erythrosine (FD & C Red #3; 2, 4, 5, 7-tetraiodofluorescein) are used widely in foods, drugs and cosmetics to provide red coloration (Anonymous, 1968; Office of the Federal Register, 1973c). Medicinal preparations such as vitamin and mineral tablets coated and colored with erythrosine may provide an amount of available iodine in excess of the labeled quantity of iodine usually supplied by potassium iodide. For example, several multi-vitamin capsules colored with erythrosine have been shown to contain
Determined from a computerized listing of OTC Drug Products

<table>
<thead>
<tr>
<th>Number of Products</th>
<th>Example</th>
<th>Type of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Potassium Iodide</td>
<td>Expectorants</td>
</tr>
<tr>
<td>2</td>
<td>Sodium Iodopropionate</td>
<td>Kidney Function Tests</td>
</tr>
<tr>
<td>4</td>
<td>Sodium 131 Iodide</td>
<td>Antineoplastic Agents</td>
</tr>
<tr>
<td>14</td>
<td>Potassium Iodide</td>
<td>Inorganic Iodine Salts</td>
</tr>
<tr>
<td>21</td>
<td>Dihydroxypropylthion</td>
<td>Anti-Infective Agents</td>
</tr>
<tr>
<td>23</td>
<td>131 Iodine</td>
<td>Radioactive Iodine</td>
</tr>
<tr>
<td>33</td>
<td>Acetic Acid</td>
<td>Radioactive Substance for Radiotherapy</td>
</tr>
<tr>
<td>30</td>
<td>Thyroglobulin</td>
<td>Thyroid Preparations</td>
</tr>
</tbody>
</table>

In Various Forms Therapeutic Drug Preparations Containing Iodine

Table 6
from 4-625 μg/g of iodine per capsule. An antacid preparation in tablet form contains 233 μg/g iodine presumably from the same dye used for pink coloration (Vought et al., 1972). Erythrosine is also used to identify plaque during dental examination and cleaning.

The medicinal agents containing potassium iodide or organic iodine compounds often prescribed for therapy of asthmatic conditions, emphysema, cystic fibrosis and the treatment of hyperthyroidism have been reviewed by Davis (1966). Relatively massive doses of iodine may be ingested by these patients over long periods of time. Lugol's solution (a 5% solution of iodine made soluble by the presence of 10% potassium iodide) in doses of 0.3-0.6 ml (15-30 mg iodine) may be administered in the routine treatment of thyrotoxicosis prior to surgery. There does not appear to be any undue medical concern about the possible hazards of excess iodine intake that may result from use of these medications. This subject is discussed further in Section V, p 40).

It is recognized that iodine compounds are also administered for diagnostic purposes. For example, iodine in oil is used for bronchograms, lymphangiograms, and myelograms. The compound is excreted slowly and in predisposed individuals may induce abnormalities in iodine metabolism. Similarly, intravenous urography with x-ray opaque iodine-rich organic compounds (e.g., sodium diatrizoate; sodium 3,5-diacetamido-2,4,6-triiodobenzoate) is a widely employed diagnostic procedure. Relatively large doses, as much as 30 ml of a 50% solution are injected. The cholecystographic agents (e.g., iopanoic acid, β-[3 amino-2,4,5-triiodophenyl]-α-ethylpropionic acid) are administered orally in doses of 3-4 grams as radiopaque media for visualization of the gall bladder. Because sensitivity reactions are fairly common, patients usually receive intradermal test injections to detect any particular sensitivity to these iodine compounds.

3. **Salt, Food Additives and Food Colors**

Based upon a 1968 survey by the Salt Institute, Wood (1970) reported that the quantity of iodized salt sold in the United States had increased from 52.1% in 1958 to 54.8% in 1968; slight geographic differences were noted. However, the survey data indicated that nationwide, per capita consumption of all salt decreased from 4.42 g/day in 1959 to 3.42 g/day in 1968. Based on per capita use of iodized salt calculated from production figures, Wood (1970) estimated that the average intake of iodine from iodized salt would be 260 μg/person/day.
Based on data from a 1971 survey of food manufacturers and food processors, the Select Committee on Generally Recognized as Safe Substances (1974) calculated that the per capita per day average intake of iodine from potassium iodide would be 280 μg if all potassium iodide were used to iodize salt. Because potassium iodide is known to be used as an animal feed additive as well, this estimate of human intake is probably high.

The following iodine compounds are Generally Recognized as Safe (GRAS): (Office of the Federal Register, 1973e)

a) cuprous iodide and potassium iodide as nutrients and/or dietary supplements in table salt (limited to 0.01 %) as a source of dietary iodine; and

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

Certain iodine salts are also used as Food Additives Permitted in Food for Human Consumption. Potassium iodide may be in special dietary foods labeled to indicate that maximum daily intake per person should not exceed 0.15 mg iodine; and calcium iodate and potassium iodate are permitted as dough conditioners in bread manufacture with the stipulation that the total quantity may not exceed 0.0075 parts per 100 parts by weight of flour used (Office of the Federal Register, 1973b).

According to a survey conducted by a National Research Council subcommittee [Subcommittee on Review of the GRAS List (Phase II), 1972], potassium iodide is used in various food categories in the amounts shown in Table 7. There is no available information to indicate any recent significant changes in these values.

Connolly (1971b) suggested that one group of food additives, the alginates, may be an additional source of iodine in processed foods. He reported concentrations of up to 9 mg/kg iodine in several alginate samples. Alginic acid and several alginate salts are used in a wide variety of processed foods as emulsifiers, stabilizers, and thickeners. The use of alginates in foods has been reviewed recently (Select Committee on GRAS Substances, 1974). Based upon data supplied by a subcommittee of the National Research Council on commercial production of alginates [Subcommittee on Review of the GRAS List (Phase II), 1972] and an iodine content of 9 mg/kg, the
### TABLE 7

**USE OF POTASSIUM IODIDE IN FOODS**

<table>
<thead>
<tr>
<th>Food Categories</th>
<th>Usual Use (%)</th>
<th>Maximal Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonings and Flavorings</td>
<td>0.00866</td>
<td>0.00926</td>
</tr>
<tr>
<td>Imitation Dairy Products</td>
<td>0.00043</td>
<td>0.0043</td>
</tr>
<tr>
<td>Baby Formulas</td>
<td>0.00013</td>
<td>0.00015</td>
</tr>
<tr>
<td>Processed Fruit</td>
<td>0.00010</td>
<td>0.00010</td>
</tr>
<tr>
<td>Milk Products</td>
<td>0.00002</td>
<td>0.00007</td>
</tr>
</tbody>
</table>

Figures from the Subcommittee on Review of the GRAS List (Phase II), 1972.
estimated average intake of iodine from alginates in the United States would be less than 1.0 μg/person/day.

However, brown algae, or kelp, are recognized as a source of iodine in foods for special dietary use (Office of the Federal Register, 1973d). The Code of Federal Regulations specifies that such use is safe provided that the total amount of iodine in the food product does not supply more than 150 μg iodine/day. Estimates of iodine in algae have ranged from 0.8 to as high as 4.5 g/dry kg (McClendon, 1933). There appears to be a need for additional data on iodine content of foods containing additives such as alginates, agar-agar, carrageenan, and other substances derived from algae. The National Research Council subcommittee survey does not contain consumption data for any of the other iodine compounds known to be used in foods or animal feeds [Subcommittee on Review of the GRAS List (Phase II), 1972]. Additional data on consumption of iodine-containing food additives have not been found.

Food coloring substances, such as erythrosine (see p 40), may add iodine to the diet. Vought et al. (1972) found concentrations of iodine up to 175 μg/g in dry cereals, fruit cocktails, maraschino cherries and cake mixes, presumably from this red dye.

Erythrosine is partially degraded in the digestive tract, thus releasing iodide which is readily absorbed and metabolized (Vought et al., 1972). In the rat, ingestion of the dye results in elevated serum protein-bound-iodine levels and decreases 131I uptake by the thyroid gland (Andersen et al., 1964; Bora et al., 1969; Vought et al., 1972). The latter investigators pointed out that if erythrosine was deiodinated by man in a manner similar to that observed in the rat, a single service of erythrosine-colored dry cereal would increase the daily iodine intake by approximately 400 μg. They concluded that, in view of the widespread use of erythrosine, foods and drugs containing this coloring agent could contribute substantially to the dietary iodine intake (Vought et al., 1972).

4. Atmospheric and Other Sources

It is generally agreed that the ocean is the major source of iodine. It enters the atmosphere continuously and is deposited on land and vegetation by rainfall and snow (Vought et al., 1970; Miyake and Tsunogai, 1963). According to Vought et al. (1970), most circumstantial evidence suggests that atmospheric iodine is in the form of free iodine, inorganic salts, organic compounds, or bound to particulate matter. These investigators pointed out that respiratory absorption of such compounds from the atmosphere could contribute to human nutritional needs for iodine.
Salter (1940) reported that seacoast atmosphere may contain up to 400 \( \mu g \) iodine/m\(^3\) and that an individual might inhale 4 \( \mu g \) iodine/day from such air. Vought \textit{et al.} (1964) found that ambient air contained 0-7.4 \( \mu g \) iodine/m\(^3\). In a subsequent study of iodine in the environment, Vought \textit{et al.} (1970) noted that iodine deposition on plants along a roadway appeared to be related to combustion of gasoline and oil and prevailing wind direction. They concluded that a realistic estimate of normal human respiratory exposure to atmospheric iodine would be 5 \( \mu g \)/day from an atmospheric level averaging 0.7 \( \mu g \)/m\(^3\). From the above studies, they calculated that an atmospheric iodine level of 5 \( \mu g \)/m\(^3\) would result in an approximate exposure of the human respiratory tract to 100 \( \mu g \) of iodine/day if it was totally absorbed.

In another study, atmospheric iodine in subjects' hospital rooms reached levels of 280-11,000 \( \mu g \)/m\(^3\) (probably as iodide) as compared with a mean value of 4 \( \mu g \)/m\(^3\) for outside air (Vought \textit{et al.}, 1963). Atmospheric iodine levels in hospital rooms declined during the following six months and this decline was attributed to the cessation of use of an iodophor detergent and a gradual dilution and washing away of the iodine-containing residue from the floors and walls. In a subsequent investigation of a laundry using an iodophor containing detergent, Vought \textit{et al.} (1964) concluded that laundry workers were exposed periodically to higher than normal atmospheric levels of iodine.

In addition to normal atmospheric iodine \textit{per se}, there are a number of adventitious sources of iodine that may enter ecological food chains or the human diet. For example, weather modification may add to total atmospheric iodide in localized regions where artificial nucleating agents, primarily silver iodide, are used for hail suppression and rain or snow augmentation.

Iodophors as sanitizing agents in the dairy industry have been discussed previously (see p 35). Iodophors are also employed in the food processing industry as cleansing agents, sanitizers, and general disinfectants (Anonymous, 1974; Cantor, 1968; Office of the Federal Register, 1973a; Trueman, 1971; Schmidt and Winicov, 1967). The high iodine content of cheese, ice cream, milk chocolate and other processed milk products may result from use of iodophors during milk production (Connolly, 1971b) or from use of alginates containing iodine in ice cream production (Connolly, 1971a). However, beyond the data reviewed by Vought (1972), and the cited studies of iodophor content of milk (see p 35), there are few definitive studies of iodophors as adventitious sources of iodine in foods other than milk and dairy products.

While only fragmentary data have been uncovered, it seems logical to suggest that man may be exposed to and might absorb
significant quantities of atmospheric iodine from combustion products, or in buildings and confined locations where volatile iodine may be present in cleansing and detergent solutions. Because iodophors are a class of complexed iodine products in which the reduction in the vapor pressure of the iodine varies with the product formulation (Schmidt and Winicov, 1967), there appears to be a need to collect additional data on the contribution of iodophors to atmospheric iodine. More importantly, there is an urgent need to collect additional data on the absorption of iodine from the air by the respiratory tract and the amount of iodine this may contribute to total human intake.

E. TOTAL IODINE INTAKE FROM DIETARY SOURCES

Because of the multiplicity of sources of iodine, iodides, and iodates it is difficult to determine the total iodine intake of a large population. The iodine intake by individuals can be measured by careful analysis of the food and water consumed, by estimation from urinary excretion of iodine, or retrospectively, by measuring radioactive iodine uptake by the thyroid.

Determination of iodine intake requires rigorous experimental protocols and only a limited number of investigators have measured total dietary intake. In addition, ingested iodine is not an accurate measure of actual metabolism of iodine because the thyroid gland by secretion of stored hormones compensates for changes in the amount of iodine consumed and available for absorption. However, several studies provide data that suggest total iodine intake is increasing (Table 8).

Vought and London (1964a) reported the range in individual daily iodine content of 18 metabolic diets was 15-219 μg/day (mean 89 μg/day) based on assay of food items in the diet. Analysis of 36 individual meals indicated a daily range of iodine intake of 65-529 μg based on consumption of 3 meals/day. The above figures do not include salt added for seasoning (an additional 122 μg/person/day).

In a subsequent study, Vought and London (1964b) measured the dietary iodine intake, excretion, and iodine balance of 13 healthy nonhospitalized subjects. Total iodine intakes ranged from a low of 18 μg/day by one adult female to a high of 1540 μg/day by an adolescent male. The range of mean daily iodine intake values was from 58±7 to 830±252 μg/person. Median intake from food, salt and water for four adult females was calculated to be 519 μg/person/day and 237 μg daily for each of the nine children in the study.
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Subject Characteristics</th>
<th>Iodine Intake $\mu$g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vought and London (1964a)</td>
<td>Metabolic diets, euthyroid, hospitalized</td>
<td>89$\mu$, 15-219$\mu$</td>
</tr>
<tr>
<td></td>
<td>Cafeteria meals, euthyroid, hospitalized</td>
<td>175, 65-529</td>
</tr>
<tr>
<td>Vought and London (1964b)</td>
<td>Euthyroid, nonhospitalized</td>
<td>395, 18-154</td>
</tr>
<tr>
<td>London et al. (1965)</td>
<td>Eastern Kentucky, goiter present</td>
<td>64, 17-408</td>
</tr>
<tr>
<td></td>
<td>Eastern Kentucky, goiter absent</td>
<td>96, 30-817</td>
</tr>
<tr>
<td>Vought et al. (1967)</td>
<td>Northern Virginia, goiter present</td>
<td>379, 17-1579</td>
</tr>
<tr>
<td></td>
<td>Northern Virginia, goiter absent</td>
<td>230, 4-877</td>
</tr>
<tr>
<td>Pittman et al. (1969)</td>
<td>Hospitalized, euthyroid</td>
<td>533, 274-482</td>
</tr>
<tr>
<td></td>
<td>Hospitalized, euthyroid, iodized salt</td>
<td>677, 595-713</td>
</tr>
</tbody>
</table>
In further studies London et al. (1965) and Vought et al. (1967) investigated the total dietary iodine intake of individuals in eastern Kentucky and northern Virginia. They compared iodine intake values of persons with goiter with those of subjects free of goiter (Table 8). While mean iodine intake levels of subjects in rural eastern Kentucky are lower than those of subjects in other studies, the range of individual values includes individuals with iodine intakes exceeding 150 µg/person daily.

Pittman et al. (1969) determined the iodine content of representative meals at two southeastern hospitals and reported average daily intake values of 533±82 µg (range 274-842 µg) and 677±19 µg (range 595-713 µg). These investigators suggested that the use of iodized salt in the latter hospital was the reason for the higher iodine mean and range values.

The mean daily iodine intake values calculated from dietary intake by these investigators (London et al., 1965; Pittman et al., 1969; Vought and London, 1964a, 1964b; Vought et al., 1967) are generally in excess of recommended daily allowances for children and adults (National Research Council, Food and Nutrition Board, 1974) except for the data collected in eastern Kentucky. With this exception, all the data reported from these studies in which dietary intake was measured by chemical analyses of ingested food are relatively close to estimates of iodine intake calculated from data on food consumption and iodine content of foods (Table 9).

The data in Table 9 are estimates of average daily iodine intakes for adults on a 2400 kcal diet. These figures were calculated from survey data on mean daily food consumption of several food categories (U.S. Department of Agriculture, Agricultural Research Service, 1972) and from the iodine content of foods (Vought and London, 1964a; Vought et al., 1970). The values for salt intake and iodine from food additives are calculated values. The approximations in Table 9 include neither any additional iodine from adventitious sources nor reflect the changing patterns of food consumption since 1965. Iodine from these sources would tend to increase the total iodine intake. While it may be coincidental, these calculated estimates agree, in general, with dietary iodine intakes determined from urinary excretion data and thyroid radiiodine uptake measurements made in the last five years.

To obtain additional information on the iodine content of foods, the FDA has included iodine in its 1974 Market Basket Survey.

In summary, measurements of actual dietary iodine intake and estimates based on food consumption suggest that iodine intake
<table>
<thead>
<tr>
<th>Food Category</th>
<th>Average Daily Consumption g/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Average Daily Iodine Intake μg/day&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Milk and Milk Products</td>
<td>397</td>
<td>269</td>
</tr>
<tr>
<td>Eggs</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>Meat and Meat Products</td>
<td>325</td>
<td>192</td>
</tr>
<tr>
<td>Seafood</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Legumes</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>Grain and Cereal Products</td>
<td>122</td>
<td>81</td>
</tr>
<tr>
<td>Yellow and Green Vegetables</td>
<td>104</td>
<td>88</td>
</tr>
<tr>
<td>Other Vegetables and Fruits</td>
<td>96</td>
<td>56</td>
</tr>
<tr>
<td>Sugar and Sweets</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>Beverages (excluding milk)</td>
<td>749</td>
<td>739</td>
</tr>
<tr>
<td>Estimated Salt Intake&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.42</td>
<td>3.42</td>
</tr>
<tr>
<td>Iodine in Food as Additives&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>454.0</td>
<td>382.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data from Household Food Consumption Survey 1965-1966 (U.S. Department of Agriculture, Agricultural Research Service, 1972 on 20-34 year olds.

<sup>b</sup> Calculated from figures on iodine content of foods, from Vought and London (1964a) and Vought et al. 1970.

<sup>c</sup> No figures available for iodine content.

<sup>d</sup> From Wood (1970). Mean U.S. daily salt intake of 3.42 g/day @ 0.0076 % 1=260 μg/day but 1968 figure of 54.8 % of all salt iodized, therefore 260 μg/day x 54.8 % =142 μg/day.

<sup>e</sup> Based on the estimated mean daily potassium iodide intake for adults; 131 μg KI/day=100.1 μg iodine/day; does not include iodine from other food additives for which estimates are unavailable Select Committee on GRAS Substances, 1974).
levels in North America generally exceed amounts recognized as necessary for adequate nutrition. Both observed and calculated estimates of iodine intake appear to be in excess of nutritional requirements, and are consistent with similar observations derived from indirect measurements of total iodine intake, calculated from iodine excretion studies and evaluation of radioactive iodine uptake by the thyroid gland.
VI. ASSESSMENT OF THE CURRENT STATUS OF HUMAN IODINE NUTRITION

A. INDIRECT MEASURES OF TOTAL IODINE INTAKE

1. Iodine Excretion

In the euthyroid individual in iodine balance (with normal thyroidal iodine concentration) dietary iodine intake in excess of normal thyroid requirements is excreted. The major pathway of excretion is renal, with minor amounts lost through feces, sweat, expired air and in pregnant women through the placenta to the fetus, as well as in the milk of lactating women (Stanbury et al., 1972; Wayne et al., 1964). Urinary iodide is directly related to plasma inorganic iodide concentration, while fecal excretion is principally organic iodide from unabsorbed thyroxine and its derivatives after being excreted in the bile (Wayne et al., 1964). Iodine is excreted as iodide in sweat and milk; the existence of iodine or iodide loss by expired air has been questioned (Riggs, 1952). Sweat loss in sedentary or hospitalized subjects is generally considered negligible, although Consolazio et al. (1966) have reported iodine sweat losses of 146.50±31.08 μg/day in 12 moderately active euthyroid adult males.

While total iodine excretion is a more complete and accurate measure of iodine losses, urinary excretion is generally recognized to be an adequate indicator. Outside a hospital setting, urine analyses are more feasible than food analyses. Determination of urinary excretion in terms of grams of creatinine excreted or total urinary excretion per 24 hours provides a convenient basis for calculation of intake (Dworkin et al., 1966; Follis 1964a, 1964b; Vought and London, 1965a, 1965b, 1967; Vought et al., 1963). For epidemiological surveys, the single urine sample collection has proven valuable and expedient; however, there is general agreement that the 24-hour collection, although more difficult is also more accurate (Frey et al., 1973; Vought and London, 1965b; Vought et al., 1963).

Follis (1964b) reported a mean urinary iodine excretion of 189 μg iodine/g of creatinine in a study of 133 adolescent females. Vought and London (1965b) determined iodine excretion in five women over a 5-day period in 1 week and then 1 day in each of the following 5 weeks. Mean urinary excretion values from 24-hour collections and random samples were 264.4±31 μg and 242.1±23.3 μg iodine/day, respectively. More recent data from the Ten-State Nutrition
Survey (Table 10) included higher mean urinary excretion values from several subsets of the general population. The data from these several studies suggest that mean urinary iodine excretion values are high and may have increased during the 5-year period from 1964-1965 to 1968-1970. Trowbridge et al. (1973) alluded to high urinary excretion values in children examined in four states in the Ten-State Nutrition Survey (Georgia, Kentucky, Michigan, and Texas) [U.S. Department of Health, Education, and Welfare (U.S. DHEW), 1972].

It is generally agreed that urinary excretion of iodine over a 24-hour period is a valuable index of possible deficient or excess iodine intake; however, plasma inorganic iodide is a more exact indicator, but it is more difficult to measure (Wayne et al., 1964).

2. Thyroidal Radioiodine Uptake and Clearance

Because the thyroid gland does not distinguish among the several iodine isotopes, determination of the uptake or clearance of radioiodine by the thyroid is a convenient measure of thyroid function. Furthermore, measurement of thyroidal uptake or clearance is an indirect indication of iodine entering the total body iodine space. The typical clinical procedure involves oral administration of \(^{131}\)I and subsequent determination of thyroidal clearance and uptake at 1-2 hours and over 24-48 hour periods, respectively (Riggs, 1952; Stanbury et al., 1972; Wayne et al., 1964).

Using thyroidal radioiodine uptake data, Oddie et al. (1968a, 1968b) noted geographic variations in uptake by euthyroid individuals in the United States. In a reassessment of the status of iodine intake in the United States, Oddie et al. (1970) computed average daily iodine intake values of 240-738 μg from thyroidal radioiodine uptake data on 30,000 euthyroid individuals. Obvious geographical differences in mean intake estimates were noted; estimates for mean daily iodine intake were lowest (238-307 μg) in the northeastern, northwestern and the Rocky Mountain regions. Highest daily intake estimates were found in the southwestern United States (500-738 μg).

Oddie et al. (1970) concluded that iodized salt contributed a significant proportion of the daily iodine intake throughout the country. However, they noted that the general increase in mean iodine intake levels was modifying the accepted normal values for radioiodine uptake. Because radioiodine uptake rates are used as diagnostic criteria in evaluating thyroid function, Oddie et al. (1970) suggested normal standards for thyroidal radioiodine uptake should be established locally.
Mean, median, and grand mean and grand median weighted by number of individuals.

<table>
<thead>
<tr>
<th>State Class</th>
<th>Ethnic Group</th>
<th>Sex</th>
<th>Income Category</th>
<th>Number of Individuals</th>
<th>Mean Iodine Values (ug/L creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Male</td>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>American</td>
<td></td>
<td>Male</td>
<td>200</td>
<td>196</td>
</tr>
<tr>
<td>Female</td>
<td>American</td>
<td></td>
<td>Female</td>
<td>200</td>
<td>196</td>
</tr>
<tr>
<td>Low</td>
<td>Male</td>
<td></td>
<td>Low</td>
<td>200</td>
<td>196</td>
</tr>
<tr>
<td>Female</td>
<td>American</td>
<td></td>
<td>Female</td>
<td>200</td>
<td>196</td>
</tr>
<tr>
<td>High</td>
<td>Male</td>
<td></td>
<td>High</td>
<td>200</td>
<td>196</td>
</tr>
<tr>
<td>Female</td>
<td>American</td>
<td></td>
<td>Female</td>
<td>200</td>
<td>196</td>
</tr>
</tbody>
</table>

From the Ten-State Nutrition Survey

IODINE EXCRETION DATA FOR ADULTS

TABLE 10
The percent radioiodine uptake reported by Oddie et al. (1970) is lower than that reported by Grayson (1960). Similarly, Pittman et al. (1969) suggested an increase in dietary intake of iodine from foods and other sources. They based this conclusion on the reduction in mean 24-hour thyroidal radioiodine uptake rates in over 50 euthyroid subjects (28.6±6.5 % in 1959 to 15.4±8.8 % in 1967-1968). Recently Bernard et al. (1970) have also reported lower values for thyroid uptake rate of euthyroid patients.

More recently, Caplan and Kujak (1971) reported elevated urinary iodine excretion, increased plasma inorganic iodide concentrations, and decreased thyroidal clearance of iodide in 44 euthyroid adults in La Crosse, Wisconsin. The mean 24-hour thyroid radioiodine uptake was 12.1±6.1 %. In a second series of euthyroid, hypothyroid and hyperthyroid patients, they reported uptake values of 14.3±7.7, 3.9±3.0, and 48.7±19.0 %, respectively. They concluded that increasing but variable dietary iodine intake required computation of normal values for thyroidal iodine uptake within localized geographic areas.

Gahremani et al. (1971), Harvey et al. (1972) and Alazraki et al. (1972) reached similar conclusions in studies of euthyroid adults in other parts of the United States. However, Keeling and Williams (1972), in a study of 4-hour and 24-hour $^{131}$I uptakes in two series of British patients, concluded that increased popularity of iodized medications rather than increased dietary iodine might be the cause of the reduced uptake values observed in these British adults. Similarly, Blum and Chandra (1971) reported reduced radioiodine uptake and implicated items other than dietary iodine as sources of increased iodine.

3. Other Indirect Methods

Other indirect measurements that provide a basis for calculating dietary iodine intakes include plasma inorganic iodide, salivary iodine concentration, and salivary iodine secretion. Because each of these parameters is proportional to intake and total excretion, they are indices of iodine balance (Vought and London, 1965a, 1967). However, none has been used extensively with a large number of euthyroid subjects.

Finally, Wartofsky (1973) has noted a reduction in the rate of remission of thyrotoxicosis following thioamide antithyroid therapy. He suggested that there is an inverse relationship between increasing average dietary iodine intake and remission rate after for Graves' disease. Regression analyses of remission rates reported for patients studied from 1962-1973 indicated that declining efficacy of
antithyroid therapy could be associated with the apparent rise in iodine intake as measured in dietary analysis and decreased normal values for thyroid radiiodine uptake. While this observation by Wartofsky (1973) involves a selected sample of the general population, it is additional indirect evidence of increased dietary iodine intake in North America.

B. IODINE BALANCE IN THE EUTHYROID INDIVIDUAL

Iodine balance studies in man are difficult; control of dietary intake, risks of contamination, complete collection of excreted iodine, and relative accuracy and reliability of analytical methodology are major problems. Furthermore, iodine balance studies of several days duration may not reflect entirely intra-individual variation which is known to occur over time. In the critical balance studies on euthyroid individuals reported to date, there was an apparent negative balance (Dworkin et al., 1966; Vought and London, 1964a, 1964b, 1967).

However, as pointed out by Dworkin et al. (1966), prolonged negative balance would lead to progressive increases in the prevalence and severity of iodine deficiency goiter in the general population. Such is not the case in the United States where dietary intake, iodine excretion, and thyroidal radiiodine uptake and clearance suggest that total body iodine may be increasing without an increase in the prevalence of iodine deficiency goiter. In fact, most evidence suggests iodine deficiency goiter in the United States is decreasing (See p 58).

Accurate assessment of the iodine requirements for man is also quite difficult. Most authorities agree that a minimum iodine requirement would be that which prevents the occurrence of iodine deficiency goiter. The National Research Council, Committee on Food Protection (1970) accepted as safe, a daily intake of iodine of 50 μg to 1000 μg based on studies of balance and excretion per 24 hours. Wolff (1969) has indicated that 2000 μg/day may be an acute level of intake which should be considered toxic. The daily intake generally accepted as desirable for adolescents and adults is approximately 100-300 μg/day (National Research Council, Food and Nutrition Board, 1974). However, it should be noted that biological variation is an important component in accurate assessment of adequacy or need for a nutritional factor in the diet.

Background level of iodide in food and water, geographic location, age, sex, occurrence of debilitating diseases and the extent to which iodine is supplied by adventitious sources may result in several fold differences in the quantity of iodine necessary for normal metabolism within the members of a specific population.
The National Research Council, Food and Nutrition Board (1974) has revised its Recommended Daily Allowances (RDA) for various age groups as follows: infants (0-6 months), 35 μg; children (1-10 years), 60-110 μg depending on age; males over age 11 years, 110-150 μg. The highest allowance for males is 150 μg/day in the period of 15 through 18 years of age. The RDA for females age 11 through 18 years is 115 μg, and 100 μg for females 19-50 years old. The RDA is 80 μg for females over 51 years old, 125 μg during pregnancy and 150 μg for lactating mothers. All of these figures based primarily upon balance studies in adults, indicate that the daily requirement for iodine is approximately 1 μg/kg body weight or 50 to 75 μg iodine/day. The daily allowances for iodine recommended by the National Research Council, Food and Nutrition Board can be met by the consumption of iodized salt, assuming that figures calculated for average salt consumption reflect approximately the range of iodized salt consumption for all age groups and that all iodide in iodized salt was absorbed.

Wayne et al. (1964) concluded from evidence collected in England that 160 μg iodine/day was an acceptable minimum daily allowance which must be available in the individual diet in order to avoid development of iodine-deficiency goiter. They indicated further that it might be advisable to raise the intake level to 200 μg iodine in children and pregnant women.

C. PREVALENCE AND SEVERITY OF IODINE DEFICIENCY GOITER

In the earlier decades of the twentieth century, goiter in the United States was endemic throughout the Appalachian range, the Rocky Mountain area and the northern tier of states from the Great Lakes to the Pacific northwest. It is clear from numerous clinical studies and population surveys that this was iodine deficiency goiter. In 1924, iodization of salt was introduced in Michigan. Since that time, iodized salt has been available throughout the United States.

In addition, education and communication have led to a better understanding of human nutritional needs. Food transport, distribution, and marketing methods have improved the availability of food commodities from areas where no iodine deficiency exists and have lessened the dependence upon locally grown foodstuffs in areas where goiter was endemic. As a result, the prevalence and severity of iodine deficiency goiter in the United States in 1974 are relatively low. The Ten-State Nutrition Survey (U.S. DHEW, 1972) using levels of iodine excretion as a criterion of iodine nutriture concluded that most
populations studied had urinary iodine excretion values far above levels that would suggest any risk of iodine deficiency goiter (Table 11). The geographic areas where clinical evidence of goiter were observed did not generally correspond to geographic areas previously considered within the "goiter belt." Moreover, goiter prevalence did not appear to be related to below average urinary iodine excretion values. The survey concluded that some population subgroups could be iodine deficient but that the goiters found were generally related to factors other than lack of adequate iodine intake. The survey suggested that goitrogens or other abnormalities of the thyroid may be responsible for the 0.4-7.2 % of the population with thyroid enlargement.

The report also concluded that many individuals with enlarged thyroid glands may have had "normal iodine supply and normal thyroid function, with no health consequence related to the thyroid enlargement (U.S. DHEW, 1972). No further explanation of the high urinary excretion levels found throughout the surveyed population was given although most authorities agree that high urinary excretion levels are a result of intake exceeding nutritional requirements (Follis, 1964b).

In Canada, all salt sold for table or general household use must contain 0.01 % potassium iodide. This regulation has been in force for over 20 years. In a recent survey of the nutritional status of the Canadian population, urinary iodine excretion data indicated adequate to high iodine intakes throughout the several provinces. Moderate enlargement of the thyroid was observed in a portion of the population studied and the report concluded that it was unlikely that the goiter observed was due to iodine deficiency. Possible reasons for the thyroid enlargement were not given; however, a more definitive report on iodine nutrition in Canada is in preparation [Nutrition Canada (National Survey), 1973].

In summary, recent epidemiological data suggest iodine deficiency goiter in North America is not an endemic problem except in a few socioeconomic or geographically isolated populations. Urinary iodine excretion values are generally in excess of levels needed for adequate nutrition; this suggests that iodine intake levels are more than adequate. Thyroidal enlargement is evident in a small, but significant number of the North American population. The possible antecedents to this type of goiter, and the public health implications are, at present, only speculative.

D. PREVALENCE AND SEVERITY OF IODINE TOXICITY

Ingbar (1972), Nagataki (1974), Yamada et al. (1973) and Wolff (1969) have outlined the effects of excess iodine on thyroid metabolism.
### TABLE 11

RANGE OF URINARY IODINE EXCRETION IN ADULTS

IN THE UNITED STATES

<table>
<thead>
<tr>
<th>Iodine Values μg/g Creatinine</th>
<th>Number of Individuals</th>
<th>Low Income States</th>
<th>High Income States</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>&lt;25</td>
<td></td>
<td>2</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>25-49</td>
<td></td>
<td>16</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>50-99</td>
<td></td>
<td>54</td>
<td>142</td>
<td>232</td>
</tr>
<tr>
<td>100-199</td>
<td></td>
<td>158</td>
<td>438</td>
<td>410</td>
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<tr>
<td>200-299</td>
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<td>300-399</td>
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<td>400-499</td>
<td></td>
<td>69</td>
<td>150</td>
<td>43</td>
</tr>
<tr>
<td>500-599</td>
<td></td>
<td>48</td>
<td>120</td>
<td>34</td>
</tr>
<tr>
<td>600-699</td>
<td></td>
<td>36</td>
<td>74</td>
<td>16</td>
</tr>
<tr>
<td>700-799</td>
<td></td>
<td>19</td>
<td>41</td>
<td>13</td>
</tr>
<tr>
<td>&gt;799</td>
<td></td>
<td>66</td>
<td>206</td>
<td>43</td>
</tr>
</tbody>
</table>

| Subtotals:                  |                       |      |        |      |        |       |
| White                       |                       | 260  | 463    | 882  | 1478   | 3083  |
| Black                       |                       | 269  | 803    | 156  | 544    | 1772  |
| Spanish/                    |                       | 196  | 489    | 110  | 251    | 1046  |
| American                    |                       |      |        |      |        |       |
| Grand Totals                |                       | 725  | 1755   | 1148 | 2273   | 5901  |

Cumulative number of individuals in iodine value classes, pooled by race and income, age 17-59 years (U.S. DHEW, 1972).
They have delineated the known biochemical and physiological aspects of the role of iodine in clinical control of hyperthyroidism, development of iodine goiter and the effects of iodine on other thyroid diseases. Cardinal points to be considered in a review of possible harmful effects of ingestion of excessive amounts of iodine are discussed in the following sections.

As noted previously, the increased urinary excretion rates and the recognized decrease in the degree of $^{131}$I uptake in subjects examined for possible thyroid disease suggests an increase in the amount of dietary iodine in recent years. However, the thyroid gland may indeed take up iodide, originating as exogenous iodide, from the blood plasma but not "organify" it. The capacity of the thyroid to accomplish this is remarkable; but, when the daily intake exceeds 2 mg or more the process of organification decreases (Nagataki, 1974; Nagataki et al., 1967). These facts may, in part, explain the rarity of iodine-caused hypothyroidism and iodine goiter despite extensive exposure to excess iodine. Investigators have recognized for years that some experimental animals such as the rat do not develop hypothyroidism or goiter after high doses of iodine administered over a long time (Wolff, 1969).

It is important to note that thyroidal organification (prior to formation of hormones) increases gradually as the daily exogenous amounts of iodine increase, without stimulating a concomittant change in thyroid hormone secretion. The reutilization of internal iodide is significant and may not reflect the extent of exogenous iodide influencing plasma iodide. The process that regulates the balance between these two changing reservoirs is incompletely understood (Ingbar, 1972). The normal thyroid gland produces the amount of thyroid hormone required for homeostasis despite a variable intake of iodine. Thus, iodide goiter, hypothyroidism, or hyperthyroidism as a result of excess iodine, are considered rarities by clinicians concerned with these metabolic conditions (Nagataki, 1974). Approximately 50 cases of iodine-induced goiter and/or myxedema have been reported (Wolff, 1964).

Wolff (1969) has defined four degrees of excess iodine intake based on quantity of intake and distinguishes among "small to moderate" intakes, intermediate quantities with physiological consequences and "excessive" amounts of 2 mg or more daily. The first degree of excess results in temporary increases in absolute iodine uptake by the thyroid and may involve reduction of thyroid iodine clearance. The second degree of excess may inhibit iodine release from thyrotoxic thyroid glands or from the thyroid when iodine release has been stimulated by thyroid-stimulating hormone. Thirdly, progressively larger doses produce decreased formation of organic iodide, or the classical
Wolff-Chaikoff effect. Finally, excess iodine chronically administered or consumed results in complete saturation of the iodide-transport mechanism. It is generally agreed that large doses (40 mg or more) produce complete inhibition of thyroid hormone synthesis; however, if such doses are temporary, the effects are transitory in euthyroid individuals.

There are extensive references on the inverse relationship between $^{131}\text{I}$ uptake and the amount of dietary iodine (Nagataki, 1974; Wartofsky, 1973). However, the majority of these studies in euthyroid subjects do not document the presumption of long-continued, high-iodine intake that appears to be characteristic of the United States population in recent years. These investigators focus primarily on the need to establish a normal baseline of thyroidal uptake for the clinical evaluation of patients who present themselves for diagnosis and therapy of thyroid diseases.

A dual need exists for clinical baseline studies and epidemiologic surveys to determine the true incidence of thyroid abnormalities, sensitivity reactions, and the general state of health of a representative cross-section of the United States population, as related to individual total iodine intakes. There remains the need to study the special issue of the unusual, rare patient who is a candidate for hypothyroidism or hyperthyroidism and who will develop the disease state presumably due in part to the increased intake of iodine.

Hyperthyroidism as a result of excessive iodine intake by some individuals with "hot" overactive nodules in a nontoxic nodular, iodine-deficient goiter was observed 150 years ago. Kocher in 1910 named this condition Jod-Basedow, i.e. hyperthyroidism (Basedow's disease). It has only been in the past 15 years that clinical reports have appeared noting the development of iodine induced goiter following the administration of iodides (Nagataki, 1974; Wolff, 1964). The mechanism through which goiter is produced remains unknown and why excess iodine produces this effect only in certain persons has not been explained.

The minimal dosage required to suppress the uptake of $^{131}\text{I}$ by the normal thyroid was reported to be 3-4 mg/day for adults and 1-2 mg/day for children 1 to 11 years of age (Saxena et al., 1962). This unusual property of the thyroid gland to accumulate enough iodide ion to inhibit the further metabolism of iodine has been reviewed by Wolff (1964). Most experts in the field of thyroid metabolism agree that this property of the gland very likely accounts for the fact that the incidence of iodine-induced goiter is quite low.
1. **Acute Toxicity**

The health aspects of potassium iodide as a food ingredient and the animal toxicity studies on several iodine salts have been reviewed (Select Committee on Gras Substances, 1974). Several years ago, the proposed use of potassium or sodium iodate in table salt prompted toxicity studies on these salts and comparisons of these with the iodides.

High doses of potassium and sodium iodide and iodate can be lethal by several routes of administration (Webster *et al*., 1957). Oral LD$_{50}$ values were in excess of 500 mg/kg for mice and 400 mg/kg with guinea pigs (Webster *et al*., 1959). In toxicity studies with mice, fatty infiltration of the viscera was observed within 24 hours after administration of either iodides or iodate salts. The iodates produced hemoglobinuria, and on histological examination, casts and hemosiderin deposits were found in kidney sections. After oral doses of 140-500 mg/kg in some animals, the gastric contents had a higher pH and extensive but rapidly reparable degenerative changes in the parietal cells (Webster *et al*., 1957).

Webster *et al*. (1959) determined the subacute toxicity 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 % potassium iodate in their drinking water for 16 weeks. Significantly lower hematocrit and hemoglobin levels were found in mice receiving 0.75 % potassium iodate in their drinking water. Mice fed potassium iodate had a better tolerance than fasted mice for small doses (277-540 mg/kg/day) administered for several months; only minimal toxic effects were observed after a single dose (1120 mg/kg), approximating the LD$_{50}$ of potassium iodate. On a regimen of 0.5-0.25 % potassium iodate in drinking water over a 4-week period, guinea pigs exhibited no postmortem gross abnormalities or significant histological changes at intake levels that exceeded the estimated single dose LD$_{50}$ for this species. During a 5-day period, maximal intake of 485 mg/kg/day was attained by animals drinking water containing 0.5 % potassium iodate.

Webster *et al*. (1966) determined the minimum lethal dose, the maximum allowable dose and the acute and subacute toxic effects of potassium iodate for dogs. Three groups of fasted mongrel dogs were given potassium iodate in gelatin capsules in single doses. None died at 100 mg/kg, one of three dogs died at 200 mg/kg and all three died at 250 mg/kg so that the minimum lethal dose was estimated to be between 200 and 250 mg/kg. Fatty changes in viscera, and necrotic lesions in the liver, kidney and mucosa of the gastrointestinal tract were sometimes present. The only nonreversible effects were retinal changes, noted in one dog given 200 mg potassium iodate/kg.
but this was not conclusively established as an iodine effect. In the sub-
acute studies, 3 female dogs and 1 male dog (8-16 kg each) were given
iodate, added to milk or given by capsule at levels of 6-100 mg/kg for
68-92 days. When appetite or body weight declined, treatment was
suspended until recovery occurred.

Periodic checks of the urine and blood were made
for iodate, iodine and hemoglobin. Following sacrifice of the animals,
gross and microscopic studies of the viscera were made. Pathological
changes at the 50-100 mg/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. 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 potassium iodate/kg.

Excess dietary iodine has been shown to produce adverse
effects in some experimental animal studies. Ammerman et al. (1964)
fed female rats 500-2500 ppm potassium iodide (estimated to be 300-
1500 mg/kg/day) in their diet from 0-35 days postpartum. They observed
that the rats failed to lactate sufficiently to feed their offspring. No other
abnormalities of reproduction were observed but increasing mortality of
young after birth occurred with increasing levels and approached 100 %
at 2500 ppm of iodide in the diet. High mortality of newborn rabbits
from females fed 250-1000 ppm (estimated to be 75-300 mg/kg/day of
potassium or sodium iodide) for 2-5 days has been reported, but
hamsters and swine were essentially unaffected (Arrington et al., 1965).
These effects of high iodine intake are presumed to be hormonally related
(Arrington et al., 1965).

Single daily doses of 100 mg or 500 mg of $^{131}$I-labeled
sodium iodide fed to white leghorn hens on a basal diet containing negli-
gible iodine, caused an increase in the iodine content of eggs from
"extremely low" to as much as 7 mg/egg after the 500 mg/kg dose was
fed for 8 days (Marcilese et al., 1968). By this time 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 dose.

Perdomo et al. (1966) fed mature leghorn hens
(weight of hens and feed consumption not indicated) potassium iodide
in their diet at dosage levels of 312-5000 mg/kg feed. No influence on egg
fertility was observed but early embryonic death and delayed or reduced
hatching occurred. Arrington et al. (1967) 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.

Mittler and Benham (1954) demonstrated that insoluble cuprous iodide was absorbed by rats, but single oral doses of 0.5 g/kg produced no ill effects and doses of 2 g/kg caused only diarrhea.

In a study of iodine transfer and concentrations of iodine in the postpartum cow, fetus and neonatal calf, Miller et al. (1970) observed that the iodine concentration in the circulation of the fetus was over five times that found in the plasma of the dam. Amnionic fluid contained more iodine that fetal plasma but chorionic fluid iodine concentration was midway between maternal and fetal plasma levels. The authors concluded that the fetus was unable to excrete iodine via the urinary pathway and that this mechanism was a major contributing factor in the high fetal iodine levels observed at birth. They indicated that the high iodine concentration in the newborn calf represents an excessive accumulation which was eliminated after birth by normal urinary and fecal excretion.

In each of the above investigations, the dietary iodine levels were far in excess of the possible burden that might be reasonably expected even with high intake levels in humans. Acute toxicity consisted primarily of embryo toxic effects in poultry and increased urinary excretion in other animals. Very limited tests for mutagenicity, teratogenicity and carcinogenicity by potassium and sodium iodide and iodate have produced no significant positive results in animals (Select Committee on Gras Substances, 1974).

Bock and Wright (1964) explored the significance of genetic factors on acute iodide toxicity in mice. They found large differences in the LD₅₀ when sodium iodide was injected intraperitoneally as a 10 % solution into 14 strains of mice. The LD₅₀ dose ranged from 0.43 g/kg for the most sensitive F₁ hybrids to 2.03 g/kg for the most resistant DBA/1 strain. These authors concluded that genetic factors are capable of causing the variability in response to iodine administration exhibited by experimental animals and humans. Similar concepts have been stressed for many years by clinical investigators but unfortunately the necessary genetic and epidemiologic human studies with man are costly and laborious (Stanbury et al., 1972).

2. Chronic Toxicity

Wolff (1969) discussed selected published data on 154 cases of "iodine goiter" resulting from, or associated with, the
administration of iodine-containing therapeutic products. Goiter was associated with euthyroidism in about 39% of these cases whereas hypothyroidism was present in 17% without clear evidence of thyroid enlargement. In the remainder, goiter and hypothyroidism coexisted. Apparently iodide goiter may occur at any age and is more frequently found in females; however, the undesirable changes in iodine metabolism and goiter usually disappear within 2-6 weeks after iodine withdrawal. It may be concluded that the condition is neither long lasting nor serious if recognized and treated.

Why certain individuals respond in this untoward manner to high doses of iodide either in inorganic or organic form, is uncertain (Nagataki, 1974). Wolff (1969) reviewed the etiologic factors thought to contribute to the induction of iodide goiter including familial predisposition, relation to hyperthyroidism, or damaged thyroid parenchyma. The evidence is not convincing for the first two possible causes; however, tissue injury resulting from several causes may be significant. Subclinical thyroiditis as reflected in autoantibody titers, or the effects of goitrogens in conjunction with iodide may produce an inhibition of organification in the gland. Individuals not taking goitrogenic drugs such as sulfonamides who develop iodide goiter may possibly be affected by co-goitrogens in food.

Dietary-induced iodine goiter has been documented most convincingly by the Japanese workers who reported goiter in populations eating iodine-rich seaweeds (Suzuki et al., 1965; Nagataki, 1974; Wolff, 1969). These subjects, who are considered euthyroid, excreted large amounts of iodide in their urine, their \(^{131}I\) uptake was very low, plasma inorganic iodine and thyroidal iodine were increased markedly, and thiocyanate administration caused a significant \(^{131}I\) clearance from the thyroid. After removal of seaweed from the diet, the symptoms subsided and in some patients there was a marked decrease in the size of the goiter. Other than the cosmetic effects of goiter, there has not been any concern about this form of endemic goiter in Japan. This population experience is perhaps the most convincing evidence of the lack of serious toxic effects resulting from the ingestion of an iodine-rich diet.

On the other hand, Stanbury (1970) called attention to the fact that 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 the large consumption of either fish or seaweed. However, Stanbury (1970), in noting this association, concluded that whether or not this was a cause and effect relationship was highly speculative. Subsequent reviews on prevalence of papillary thyroid carcinoma in the United
States have related radiation exposure to this disease rather than excessive iodine intake (DeGroot and Paloyan, 1973; McClintock, 1974; McDougall, 1974) although this is not universally accepted (Jackson, 1974).

These regional dietary idiosyncrasies can be contrasted with large doses of iodides administered for relatively short periods. Danowski and Greenman (1949) 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 daily) produced no significant changes in serum iodine. Doses of 3-7 g of potassium iodide given daily for from 1-4 months greatly increased the total iodine serum levels. No evidence of hyperthyroidism or toxic reaction was observed despite the massive doses of potassium iodide.

Subjects receiving oral doses of iodides for extended periods of time often have conditions other than goiter. A number of reports cite the untoward effects of ingestion of iodides in the treatment of asthma including vegetating iododerma (Aquilina and Bissell, 1955; Cape, 1954; Rosenberg et al., 1972; Weber, 1923), thyroid abnormalities (Burrows et al., 1960), parotitis (Carter, 1961), vascular lesions of periarteritis nodosa (Wahlberg and Wikström, 1963) and iodine-induced hypothyroidism (Chapman and Main, 1967). Bernecker (1969) reported relatively minor side effects in about 11% of 2404 patients with chronic obstructive disease of the airways who received long-term therapy with oral doses of potassium iodide. The effects were dose dependent and approximately 40% of the patients complained of stomach distress at the higher dosages (as much as 36 g/day). Swelling of the salivary glands, a reliable indication of excessive dosage of potassium iodide, was also reported by this investigator.

Many cases of long-term continuous consumption of the iodine medications should be noted. For example, Begg and Hall (1963) observed that thyroid disorders usually become evident after 3 and up to 8 years of medication. Some patients had assiduously consumed their asthmatic powder daily for 20 years and only a specific search revealed evidence of iodide goiter. In most instances, these patients do not seek medical advice and one might conclude that any symptoms as the result of iodine ingestion were not distressing.

In considering prolonged use of iodide by asthmatics, Hall et al. (1966) observed that goiter and iodine induced hypothyroidism are more likely to develop in those patients with a latent thyroid autoimmunity. Thyroid antibodies were found more frequently in the sera of 27 patients with iodine goiter than in healthy control subjects. These observations support the evidence marshalled by Wolff (1969) in his review of etiologic factors of iodine goiter.
Harrison et al. (1963) reviewed the long-term use of iodine preparations in patients with bronchial asthma and suggested that the basic metabolic abnormality in such patients may be an inability of the thyroid to cease iodine uptake when large amounts of iodine are available. They proposed that this inability results from autonomous pituitary or thyroid activity. Harrison et al. (1963) indicated that this failure of the normal homeostatic control of the thyroid may not be the only mechanism leading to this untoward effect.

The prolonged ingestion of bread fortified with KIO₃ (estimated equivalent to between 80-270 μg/iodide/person/day) apparently caused an increase in the incidence of thyrotoxicosis in Tasmania (Connolly, 1971b; Connolly et al., 1970). These workers stated that dietary supplementation of iodine above 100 μg/day may produce thyrotoxicosis in chronically iodine deficient individuals. Stewart et al. (1971) confirmed the increased incidence of thyrotoxicosis in Tasmania following iodation of bread and suggested that in iodine deficient people the rapid availability of iodine via bread may have simplified the detection of new cases of hyperthyroidism. The population over 50 years of age are more susceptible to this form of thyrotoxicosis because they may have experienced marginal iodine deficiency for several decades (Stewart et al., 1971), and have developed mechanisms over the years that result in increased thyroid hormone synthesis in response to elevated dietary iodine (Vidor et al., 1973). While this hypothesis is as yet unproved, it does explain the higher incidence of thyrotoxicosis in that segment of the Tasmanian population which occurred after iodation of bread. However, Connolly (1973) has observed a similar rise in prevalence of thyrotoxicosis in younger (age 0-39 years) Tasmanians. The increased incidence in this age group has been maintained and is rising gradually while incidence of thyrotoxicosis in persons over 40 years of age appears to be declining.

The chronic ingestion of large doses of iodides during pregnancy may pose a special hazard for the fetus or the neonate. Recent reports emphasize the importance of restricting iodine-containing preparations during pregnancy (Ayromlooi, 1972; Carswell et al., 1970; Galina et al., 1962; Senior and Chernoff, 1971). These studies noted that most of the mothers consumed several grams of iodide daily for asthma and bronchitis. At birth, children with enlarged thyroid glands had respiratory difficulties because of the pressure of the enlarged glands on the trachea. Some of these infants have shown evidence of hypothyroidism with retarded bone development, mental impairment, and cretinism. In one instance, a hyperthyroid mother who was treated with potassium iodide throughout pregnancy, gave birth to a baby with a large goiter although the infant was hypothyroid (Senior and Chernoff, 1971). These examples stress the vulnerability of the fetus to iodine in these excessive doses. No reports have been found that suggest high dietary iodine alone could produce this type of fetal injury.
In the past 15 years clinical reports have appeared noting the development of hypothyroidism following the administration of large doses of iodides (Nagataki, 1974). Braverman et al. (1969) reviewed the literature on this subject and noted that an "escape" or "adaptation" phenomenon takes place in the thyroid gland of the vast majority of subjects who ingest large quantities of iodides for a long time. This mechanism probably results from the decreased thyroid iodide transport, which prevents accumulation in the thyroid gland of iodide concentrations sufficient to inhibit hormone synthesis (Braverman and Ingbar, 1963).

However, in a small number of peculiarly susceptible people goiter and iodine myxedema develop when iodide is administered for prolonged periods. Braverman et al. (1969) reported that 10 patients with diffuse toxic goiter, who had been treated with radio-iodine and were euthyroid, became hypothyroid after the administration of 5 drops daily of a saturated solution of potassium iodide (180 mg) for from 1-6 weeks. They speculated that there was "something inherent in the thyroid gland of these patients with diffuse toxic goiter that renders them inordinately susceptible to the induction of myxedema by iodide." Generally, iodide myxedema does not appear until iodides have been taken for many months and sometimes years.

Braverman et al. (1971) conducted a prospective study in 7 patients with chronic lymphocytic thyroiditis (Hashimoto's disease) by administering orally 180 mg of potassium iodide daily for 4-6 weeks to determine their susceptibility to iodide myxedema. In 4 of the 7 patients previously euthyroid, hypothyroidism developed as demonstrated by clinical findings of subnormal values for serum thyroxine and elevated values for serum thyroid stimulating hormone concentrations. These values quickly returned to normal when iodide administration was discontinued. In the other three patients no evidence of hypothyroidism was detected, even though the iodide administration was continued for as long as 17-30 weeks. The authors suggest that the susceptibility of patients with Hashimoto's disease to iodine-induced hypothyroidism may be connected in some obscure way with the relationship between Hashimoto's disease and Graves' disease. Thus the mechanism related to the excess iodide effect in certain persons is unknown.

It is interesting that Masi et al. (1964) in their scholarly critical review of the epidemiologic aspects of Hashimoto's disease did not suggest excessive or prolonged iodine ingestion as a causative factor. For example, excess iodide produces goiter in less than 4% of patients treated for pulmonary disease (Braverman et al., 1971). Workers in this field do not suggest undesirable or harmful effects per se from the ingestion of large doses
of iodine except for the few individuals who for unknown reasons have some abnormality in the iodide-binding mechanism in the thyroid gland.

Furszyfer et al. (1970) reviewed 70 cases of subacute (granulomatous) thyroiditis diagnosed in Olmstead County, Minnesota from 1960-1967. They suggested that the increased rise in incidence during the 8-year period was due to improved diagnosis and recognition rather than more frequent occurrence of the disease.

In a subsequent study, Furszyfer et al. (1972) evaluated the changing prevalence of Hashimoto's disease and Graves' disease in Rochester, Minnesota over a 33-year period (1935-1967). They observed that the average annual incidence rates per 100,000 females increased from 6.5 (1935-1944) to 69.0 (1965-1967). They noted that Hashimoto's disease was more frequently seen in younger female patients, a fact that is consistent with other published studies. In evaluating these incidence rates and the apparent increase over the 33-year period, the investigators commented that both the overall rate and the increased incidence most likely reflect the thorough medical coverage and the extensive medical indexing applied to the study population, as well as the availability of a patient record-retrieval system for that group of individuals. There was no evidence of any consistent or significant change in Grave's disease over the 33-year period.

Furszyfer et al. (1972) did not discuss any potential relationship between levels of dietary iodine and the incidence of Hashimoto's disease. However, other workers, in referring to the increase in incidence, have postulated that chronic, high intake of iodine from food with excessively high iodine content could promote goiter development in individuals with Hashimoto's thyroiditis and in individuals with an oversensitivity of the thyroid to the thyroid inhibitory effect of large quantities of iodine. To date, there are no results from clinical or experimental studies that support or refute this hypothesis.

3. Iodine Hypersensitivity

Weber (1923) reviewed the published literature related to various drug eruptions and other dermatoses attributed to iodide administration. The effects appear to be dose-related; however, cases of idiosyncrasy to relatively small doses of iodine compounds have been noted. Twenty years later, Jacobs and Colmes (1940) cited cases of hypersensitivity to iodine including apparent cutaneous hypersensitivity to tincture of iodine. They concluded that this type of dermatitis is infrequent.
Peacock and Davison (1957) conducted a retrospective survey of the records of 502 asthmatic patients treated with intensive iodide medication over a two-year period. Unfortunately, the therapy prescribed contained potassium arsenite solution (Fowler's solution) in addition to the 4.8-6.4 g of KI administered daily. The authors did not believe the arsenical contributed to the untoward reactions which were reported in detail. They found 16% of the patients had sufficient reactions to iodides to warrant discontinuance or sharp reduction of their medication. Rash, nausea, bad taste, salivary gland edema, face and eye edema, and gastrointestinal symptoms were the most common reactions. "True hypersensitivity" was not noted in any patient.

Freund et al. (1966) observed the effects of exposure to iodinated water supplies on 730 individuals in a prison population for a period of 9 months. Iodine, as free iodine, was added to the prison water supply at 1 mg/liter for 7 months and increased to 5 mg/liter for two months as a method of water purification. Prior to the 9 month experimental period, subjects were examined twice in a 2 month period. The investigators reported a reduction in radioactive iodine uptake and increased urinary iodine excretion during the experimental period. However, no enlargement of the thyroid or change in serum thyroxine levels were noted in any subject. Freund et al. (1966) also stated that no evidence of iodine-induced allergic phenomena or hypersensitivity to iodine was reported by the subjects or observed by the investigators throughout the study.

A search of the files of the Division of Epidemiology and Drug Experience, Office of Scientific Coordination, Bureau of Drugs, Food and Drug Administration, revealed that over one-half of the adverse reactions to inorganic iodides reported were listed as "rash." A total of 62 patients exhibited adverse reactions to inorganic iodides in the period October, 1969 to March, 1974.

Other aspects of iodine hypersensitivity were discussed in the previous section of this report (see p 59). A review of idiosyncratic, allergic and other untoward reactions related to naturally occurring, adventitious or added inorganic and organic iodine in foods is being conducted by the Life Sciences Research Office. A separate report will be prepared on this subject.

4. **Fluorine Interaction**

On several occasions in the past few decades, it has been proposed that the thyroid may have an affinity for elements of the seventh periodic group in general rather than a specific affinity for iodine (World Health Organization, 1970). While a slight affinity for
chlorine and bromine is known, no selectivity for fluorine has been observed (Wolff, 1964). The widespread use of fluorides for dental caries prevention would make fluorine antagonism of iodine an important consideration if iodine intakes were excessively low or high.

In a recent review of iodine-fluorine antagonism, the World Health Organization (1970) concluded that there is no evidence to indicate fluorine has a specific toxicity toward the thyroid gland. The following evidence from numerous studies is cited; a) fluorine does not accumulate in the thyroid; b) fluorine does not alter the rate of thyroidal iodine uptake; c) water fluoridation does not precipitate demonstrable pathological changes in thyroid tissues; d) administration of fluorine does not interfere with iodine prophylaxis of iodine-deficiency goiter; and, e) the beneficial effects of iodine at threshold dosages to experimental animals is not inhibited by administration of high dosages of fluorine.
VII. CONCLUSIONS

The accurate determination of the total iodine in various biological materials has been possible for many years; however, estimation of iodine in foodstuffs continues to be difficult. Analysis of the low concentrations of iodine in plant and animal tissues and processed foods requires extremely sensitive methods and careful attention to avoid contamination during sample preparation, storage, and analysis. There is no unanimity of scientific opinion concerning the most efficient and acceptable method of iodine analysis. Additional study and development of methods of determining iodine in foods is required.

The evidence reviewed in this study supports the conclusion that the actual quantity of iodine consumed by individuals throughout North America has increased in recent years. Dietary iodine intake levels calculated from food analyses also substantiate the conclusion that the amount of iodine ingested or absorbed from all sources appears to have increased to levels above that amount considered necessary to meet nutritional needs.

The total iodine intake of domesticated animals is increasing as a result of the iodine supplied in mineral feed supplements, iodized salt blocks, and veterinary medications. These sources of iodine are more significant than those naturally occurring in forage and feed grains. Because animal products constitute a major portion of the North American diet, animal iodine intake ultimately affects the levels of human iodine consumption. In addition to iodine naturally present in plants and water, increasing amounts of iodine enter the human diet in meat, eggs, and dairy products derived from animals receiving iodine supplemented rations or veterinary medicinals. Intentional and accidental sources of iodine such as iodized salt, food additives, food coloring substances, medicinals, and sanitizing agents add to total human iodine intake. Preliminary evidence suggests that some processed and prepared foods contain significant amounts of iodine. In addition, atmospheric iodine may be an unrecognized source of iodine in urban North America.

Urinary iodine excretion values, a convenient measure of iodine intake, also suggest that consumption is in excess of levels needed for adequate nutrition. The rate of thyroid radioidine uptake and clearance that is characteristic of normal euthyroid individuals has been reported to be decreasing throughout the country. These observations support the conclusion that levels of daily iodine intake and excretion have increased over the past several years.
It is noteworthy that no recent reports document endemic dietary iodine deficiency in North America. Iodine deficiency goiter continues to be reported, but appears to be restricted to a few socioeconomic or geographically isolated populations.

Despite the evidence for increasing amounts of dietary iodine consumption, there are no current reports that document an increase in the incidence of iodine toxicity or hypersensitivity. Similarly, the frequency of reports of metabolic disorders induced by excess iodine is relatively stable according to experts in the field of thyroid diseases. According to some surveys, thyroidal enlargement is evident in a small but significant number of the North American population. The possible antecedents to and public health implications of this type of goiter remain to be determined.
VIII. SUGGESTIONS FOR FUTURE CONSIDERATION

A number of research needs and opportunities have been identified in this study. It is not possible to assign priorities to specific topics because the suggestions encompass several diverse fields. However, the suggestions for future consideration by research administrators and investigators are summarized in this section with reference to the appropriate part of the report that discusses the topic.

Current methodology is based on modifications of procedures that utilize the catalytic effect of iodine on reduction of ceric salts by arsenious acid. Satisfactory iodide selective electrodes have been developed for use with fluid samples. Neutron activation analysis is a promising analytical technique that may be useful in the determination of iodine in food, or as a reference technique in evaluating other methods of analysis. There is a need for additional study and further development of efficient and uniformly acceptable techniques for determining iodine in feed, foods, and food products (See Section III, p 13).

The total iodine intake of domesticated animals in the United States appears to be markedly increased by the iodine added to feed in the mineral supplement, supplied in iodized salt blocks, or administered as medications. These sources of iodine are grossly more important quantitatively than iodine naturally occurring in forage and feed grains. For these reasons meat and dairy products from these animals appear to be rich in iodine. Studies should be undertaken to measure the quantity of iodine in these foods (See Section IV, B, p 23).

From the information available, it seems logical to suggest that animals and man would be exposed to and might absorb significant quantities of atmospheric iodine under the proper conditions. Similarly, domesticated animals confined in pens or buildings where iodophors are used as cleansing agents could be exposed to high levels of atmospheric iodine. There is a need to collect additional data on the contribution of atmospheric iodine to the total intake of iodine by animals and man (See Section IV, C, p 25 and Section V, D, p 40).

The significance of goitrogens in animal nutrition requires further investigation as these compounds find their way into feed and water supplies. The consumption of goitrogen-containing feed, forage, or water by dairy cows may be of significance to human nutrition. Milk from cows fed forage containing either cruciferous weed or other plants containing goitrogens, could interfere with normal thyroid function of individuals consuming this milk or products made from this milk. Investigators are not in agreement
regarding the possible hazards to man from goitrogens from these sources. The subject should be considered in future research plans involving the etiology of goiter in the United States (See Section IV, D, p 26).

The various factors that influence the uptake and storage of iodine by edible plants needs to be studied in greater detail. Natural and polluted water may contain high concentrations of iodine. If used for plant irrigation purposes foliar absorption of the iodine, either in solution or released into the atmosphere, could be a significant source of iodine in the diet. This possible source of dietary iodine should be investigated (See Section V, A, p 29).

It is known from radioactive fallout studies that $^{131}$I will be secreted in the milk of dairy cows and this iodine is transferred from milk to milk products. The amount of iodine lost or introduced during processing of cheese, ice cream, and similar dairy products is uncertain. With the mounting evidence of increasing quantities of iodine in milk, additional data are required on iodine carryover to such foods (See Section V, B, p 34).

Data from a few studies suggest that cooking and preparation may markedly alter the iodine content of raw foodstuffs. It is probable that the iodine content of many cooked foods is considerably less than that of the raw plant or animal product. The effects of cooking and preparation on iodine content of specific food items should be investigated (See Section V, B, p 36).

There is a requirement to assess the iodine content of all types of processed and prepared foods; bread, and bakery products should receive special attention. There are few data on the identity of the source and the nature of iodine in commercially available bread and bakery products. It is possible that the use of iodate as a dough conditioner has diminished, and iodine values for bread reflect other adventitious sources of iodate, iodide, or iodine. There is a need to collect definitive data on the source and quantity of iodine in bread and bakery products throughout the United States (See Section V, C, p 37).

There are few data on iodine content of prepared and processed infant and special dietary food items. Similarly, food products with additives known to contain iodine, such as the alginates, agar-agar and carrageenan are being used to an increasing extent in foods. There is need for additional data on the iodine content of these substances and their extent of use in the diet in the United States (See Section V, D, p 42).
Many therapeutic drugs taken for long periods of time contain iodine in some form. This source of iodine is not usually considered in nutritional surveys. It is suggested that future nutrition surveys include data on the consumption of these substances. Attention is specifically directed to the "hidden" sources of iodine in these products such as dyes containing iodine (See Section V, D, p 40).

There is evidence that iodine excretion values and estimates of radioiodine uptake by the thyroid vary geographically within the United States. The iodine content of the diet within these geographic regions should be investigated to determine how environmental levels, dietary intake, excretion rates, thyroid uptake, and prevalence of enlarged thyroid gland are interrelated (See Section V, E, p 47, VI, A, p 53 and p 54).

Epidemiologic overviews should be undertaken to develop clinical norms or baselines for thyroid\textsuperscript{131}I uptake, the prevalence of abnormal thyroid states or metabolic conditions, and untoward reactions to iodine in representative samples of the U.S. populations as related to their total iodine intake. It is recognized that such studies are difficult and require suitable analytical methods to measure dietary iodine (See Section VI, A, p 54).

While the metabolic role of iodine in thyroid metabolism is well understood, there are few long term studies of iodine balance in man. It is recognized that such investigations are difficult experimentally; however, clarification of several aspects of iodine balance over prolonged time periods appears necessary in the light of changing intake and excretion patterns. Annual models are available for such studies (See Section VI, B, p 57).

The question of why certain individuals respond in an untoward manner to high doses of iodide remains unanswered. Genetic factors have been suggested as a logical basis for the variability in response in experimental animals and man. Similar concepts have been stressed in the writings of clinical investigators for years, but unfortunately the necessary genetic and epidemiologic studies with man are costly and laborious. It may be possible to include food iodine analyses in future nutrition surveys along with adequate genetic data to establish relationships indicative of association or causality (See Section VI, D, p 59).
IX. BIBLIOGRAPHY


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X. GLOSSARY

Basedow's disease . . . . . . See Graves' disease and hyper-thyroidism.

Chronic lymphocytic thyroiditis . . Inflammation of the thyroid gland characterized by marked lymphocytic infiltration, numerous lymphoid follicles within the gland substance, striking eosinophilic change in the epithelium of the acini, reduction in the number of acini, and extensive connective tissue formation. Also known as Hashimoto's disease.

Endemic goiter . . . . . . See iodine-deficiency goiter.

Euthyroid . . . . . . . . . . With a normally functioning thyroid gland.

Goiter . . . . . . . . . Chronic enlargement of the thyroid gland. Usually described further, e.g., iodine-deficiency goiter, iodine-excess goiter, simple goiter, endemic goiter, or toxic goiter.

Goitrogens . . . . . . . Naturally occurring plant constituents that induce goiter.

Graves' disease . . . . . Disorder marked by an enlarged pulsating thyroid gland, acceleration of the pulse rate, exophthalmos, a tendency to sweat profusely, nervous symptoms (including fine muscular tremors, and psychic disturbance), emaciation, and increased basal metabolism. Also called Basedow's disease, exophthalmic goiter, hyper-thyroidism, or thyrotoxicosis.

Hashimoto's disease . . . . . See chronic lymphocytic thyroiditis.
Hyperthyroidism . . . . . . . . Constellation of signs and symptoms arising from an excessive concentration of thyroid hormones in the blood usually because of diffuse hyperplasia and hypertrophy of the thyroid (Basedow's disease, Graves' disease, toxic goiter) or because of excessive functional activity of autonomous nodules of the thyroid gland (thyrotoxicosis). Hyperthyroidism is frequently characterized by exophthalmos, increased basal metabolism and disturbed neuromuscular system activities.

Hypothyroidism . . . . . . . . Deficiency of thyroid activity or the condition resulting from the deficiency. Often associated with an enlargement of the thyroid gland neither inflammatory nor malignant and not characterized by toxic features; historically synonymous with endemic goiter or simple goiter.

Iodine deficiency goiter . . . . Hypothyroidism caused by lack of iodine; also called endemic goiter or simple goiter.

Iodine goiter in newborn . . . . Occurs in infants born of mothers taking excess iodine.

Iodine goiter . . . . . . . . . . Caused by ingestion of excessive amounts of iodine; also called iodine excess goiter.

Iodism . . . . . . . . . . . . . . State of hypersensitivity to iodine or iodine compounds, marked by headache, coryza, weakness, a metallic taste in the mouth, and acneform skin lesions; may occur in sensitized persons after small doses of iodides.

Iododerma . . . . . . . . . . Skin eruptions due to consumption of iodine or iodide compounds.
Iodophor . . . . . . . . . . Combination of iodine with a carrier, usually polyvinylpyrrolidone. Used in sanitizers and disinfectants. The microbial activity is associated with the iodine that is slowly released from the carrier.

Jodbasedow . . . . . . . . Iodine-induced hyperthyroidism.

Myxedema . . . . . . . . . Condition characterized by edema of tissues, subnormal temperature, loss of hair, muscle weakness, and dry skin. Associated with advanced deficiency of thyroid hormone.

Simple goiter . . . . . . . . See goiter and hypothyroidism.

Subacute granulomatous thyroiditis . . . . . . . . Form of thyroiditis usually characterized by round cell lymphocytic infiltration, obstruction of thyroid cells, and giant cell proliferation with evidence of regeneration.

Thyroiditis . . . . . . . . . Inflammation of the thyroid gland.

Thyrotoxicosis . . . . . . . . Morbid form of hyperthyroidism resulting from overactivity of the thyroid gland. May involve iodine-induced hyperthyroidism; in this condition the thyroid gland traps excessive amounts of iodine and secretes excess thyroid hormone.

Toxic goiter . . . . . . . . . See hyperthyroidism.

Wolff-Chaikoff effect . . . . . Observation that the quantity of organic iodine formed in the thyroid as a function of iodide concentration supplied increases to a maximum and then declines with further increase of plasma iodide concentration.
XI. SCIENTIFIC CONSULTANTS

ON

IODINE IN FOODS: CHEMICAL METHODOLOGY AND
SOURCES OF IODINE IN THE HUMAN DIET

A. ATTENDEES, AD HOC STUDY GROUP MEETING,
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