EVALUATION OF THE HEALTH ASPECTS OF CERTAIN AMMONIUM SALTS AS FOOD INGREDIENTS

October, 1974

Prepared for

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

Contract No. FDA 72-85
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

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

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

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

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

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

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using certain ammonium salts as food ingredients. The evaluation has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1970. * To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally recognized as available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, announcement was made in the Federal Register of September 23, 1974 (39 FR 34218) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using certain ammonium salts as food ingredients. The Select Committee received no requests for such a hearing on certain ammonium salts.

Certain ammonium salts are food substances that have been generally recognized as safe (GRAS) under the provisions of the Code of Federal Regulations (21 CFR 121.101, revised April 1, 1974). As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the prem­ marketing clearance that is required for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA recognizes further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

* The document is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health, and realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconducted, using new technologies. These conclusions will need to be reviewed as new or better information becomes available.

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

II. BACKGROUND INFORMATION

In the context of this report, "ammonia" refers to the ammonium ion in aqueous solution where it can exist in combination with a variety of anions as ammonium salts. Ammonia and several ammonium salts are ubiquitous among living organisms. Ammonia is an essential link in nature's nitrogen cycle. The ammonium ion plays a major role in essential physiological processes of man including involvement in acid-base balance and in intermediary metabolic cycles. Of the total urinary nitrogen, 2.5 to 4.5 percent is in the form of ammonium salts.

One of the mechanisms through which the kidney conserves sodium and bicarbonate ions, so important in electrolyte and acid-base balance, involves the substitution of the ammonium ion for the sodium ion in the urine, thus sparing the buffer reserve. Ammonium chloride is used as an acidifying diuretic in doses of 8 to 12 g daily, and in smaller doses of 1 to 2 g daily to correct alkalosis.

Sources of ammonia within the body include the deamination of amino acids and the deamidation of amides. The ammonia in the portal venous blood comes from the absorption of ammonia from the gastrointestinal tract from foods and after its generation by enteric bacterial action on nitrogenous compounds in food. Renal venous blood contains ammonia liberated from glutamine and some amino acids in the kidney. Ammonia is also normally produced in the brain and muscles.
Ammonia is converted to urea in the mammalian liver. Normally, about 20 percent of the urea produced is secreted into the intestine and broken down by the intestinal flora into ammonia and carbon dioxide. The ammonia is reabsorbed and resynthesized into urea and amino acids in the liver (2).

Ammonium compounds that are generally recognized as safe in the Code of Federal Regulations (3), classified by the function they are intended to perform, are:

**Stabilizers**
- Ammonium alginate

**Miscellaneous and/or general purpose food additives**
- Aluminum ammonium sulfate (ammonium alum)
- Ammonium bicarbonate
- Ammonium carbonate
- Mono-ammonium glutamate
- Ammonium hydroxide
- Ammonium phosphate, monobasic
- Ammonium phosphate, dibasic
- Ammonium sulfate

**Substances migrating to foods from paper or paperboard products used in food packaging**
- Ammonium chloride
- Ammonium hydroxide
- Alum (double sulfate of aluminum, ammonium, potassium or sodium)

Of those listed above, the following are not considered in this report: ammonium alginate which was considered in a report on the alginates (4); alum, ammonium alum, and mono-ammonium glutamate which will be considered in reports on the aluminum salts and the glutamates.

The Code of Federal Regulations (CFR) in its definitions and standards for food, also lists ammonium bicarbonate, ammonium carbonate, and ammonium hydroxide as optional ingredients in the preparation of cacao products (5) and ammonium phosphates, ammonium sulfate, and ammonium chloride as optional ingredients in bakery products at specified levels (6). The FDA recently proposed to amend 21 CFR 121.209 to permit use of 16 percent anhydrous ammonia as a component of a premix intended for addition to corn silage for cattle feed (7).

Food Chemicals Codex specifications for the food grade ammonium salts considered in this report are given in Table I (8).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Composition</th>
<th>Limits of impurities</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arsenic (ppm)</td>
<td>Heavy metals (as lead) (ppm)</td>
<td>Sulfur compounds (ppm)</td>
<td>Chloride (ppm)</td>
<td>Fluoride (ppm)</td>
</tr>
<tr>
<td>Ammonium bicarbonate</td>
<td>99.0 percent NH₄HCO₃</td>
<td>≥3</td>
<td>≥10</td>
<td>≥70</td>
<td>≥30</td>
<td>-</td>
</tr>
<tr>
<td>Ammonium carbonate³</td>
<td>≥90.0 percent and ≥34.0 percent NH₃</td>
<td>≥3</td>
<td>≥10</td>
<td>≥50</td>
<td>≥30</td>
<td>-</td>
</tr>
<tr>
<td>Ammonium chloride</td>
<td>≥99.0 percent NH₄Cl</td>
<td>≥3</td>
<td>≥10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ammonium hydroxide</td>
<td>≥96.0 percent and ≥102 percent by weight NH₃</td>
<td>≥3</td>
<td>≥5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ammonium phosphate, monobasic</td>
<td>≥96.0 percent NH₄H₂PO₄</td>
<td>≥3</td>
<td>≥10</td>
<td>-</td>
<td>-</td>
<td>≥10</td>
</tr>
<tr>
<td>Ammonium phosphate, dibasic</td>
<td>≥96.0 percent (NH₄)₂HPO₄</td>
<td>≥3</td>
<td>≥10</td>
<td>-</td>
<td>-</td>
<td>≥10</td>
</tr>
<tr>
<td>Ammonium sulfate⁴</td>
<td>≥99.0 percent (NH₄)₂SO₄</td>
<td>≥3</td>
<td>≥10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

¹ ≥ = not less than
² + = not more than
³ Consists of ammonium bicarbonate and ammonium carbamate in varying proportions.
⁴ Should contain not more than 30 ppm of selenium
The year of first use in food in the United States, and the total poundages of each ammonium compound used in all food products in 1970 are given in Table II (9). Table II also provides data on the annual poundages used in 1960 and 1970 in those food products for which comparative figures are available. These data are provided to present an estimation of the trends in use in foods of the several ammonium salts over the 10 year period.

The several ammonium compounds are used in the foods and at the levels indicated in Table III (9). Despite the trends evident in the use in food of the ammonium compounds for which data are available (Table II), the Select Committee has no information to indicate whether the ammonium compound content of the food categories shown in Table III changed significantly during that period.

### TABLE II

<table>
<thead>
<tr>
<th>Ammonium compound</th>
<th>Year of first use</th>
<th>Quantity used in those foods for which comparable figures available</th>
<th>Total quantity used</th>
<th>pounds</th>
<th>pounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1960*</td>
<td>1970*</td>
<td>1970*</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>1902</td>
<td>1,744,700</td>
<td>3,443,195</td>
<td>4,269,995</td>
<td></td>
</tr>
<tr>
<td>Carbonate</td>
<td>1965</td>
<td>40,550</td>
<td>32,220</td>
<td>32,240</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
<td>No data available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxide</td>
<td>1962</td>
<td>299,333</td>
<td>740,673</td>
<td>740,673</td>
<td></td>
</tr>
<tr>
<td>Phosphate, monobasic</td>
<td>1969</td>
<td>0</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Phosphate, dibasic</td>
<td>1902</td>
<td>348,833</td>
<td>529,595</td>
<td>584,595</td>
<td></td>
</tr>
<tr>
<td>Sulfate</td>
<td>1957</td>
<td>1,082,167</td>
<td>1,829,796</td>
<td>1,982,386</td>
<td></td>
</tr>
</tbody>
</table>

*These figures are estimated by the NRC subcommittee to represent about 60 percent of the amounts actually used (9).
<table>
<thead>
<tr>
<th>Food category</th>
<th>Ammonium compound, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bicarbonate</td>
</tr>
<tr>
<td></td>
<td>Usual</td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.346</td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td>0.060</td>
</tr>
<tr>
<td>Cheese</td>
<td></td>
</tr>
<tr>
<td>Processed fruit, juices, and drinks</td>
<td>0.002</td>
</tr>
<tr>
<td>Condiments, relishes, salt substitute</td>
<td>0.846</td>
</tr>
<tr>
<td>Soft candy</td>
<td>0.072</td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>1.500</td>
</tr>
<tr>
<td>Snack foods</td>
<td>0.100</td>
</tr>
<tr>
<td>Beverages</td>
<td></td>
</tr>
<tr>
<td>Type I (non-alcoholic)</td>
<td></td>
</tr>
<tr>
<td>Beverages</td>
<td></td>
</tr>
<tr>
<td>Type II (alcoholic)</td>
<td></td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td>0.044</td>
</tr>
<tr>
<td>Baby foods, baked goods</td>
<td>0.370</td>
</tr>
</tbody>
</table>
III. CONSUMER EXPOSURE DATA

The National Research Council subcommittee has supplied the following information on the possible daily human intakes of several of the ammonium compounds by individuals in various age groups (9) (Table IV). The Select Committee has converted these figures to possible intakes per kilogram of body weight.

It is to be noted that two other ammonium compounds are added to foods in small amounts, primarily for flavoring purposes, representing a relatively inconsequential addition to the ammonium ion intakes shown in Table IV. Ammonium sulfide is added to certain baked goods, meat products, condiments and relishes, and gravies in amounts that would raise the daily consumption by an adult about 3 to 7 mg; ammonium isovalerate is added to certain baked goods, cheese, frozen dairy products, meat products, hard and soft candy, gelatins and puddings, and non-alcoholic beverages, raising the usual daily consumption of an adult by an additional 6 to 10 mg (9, 10).

Estimates of the possible average daily intake of each of the ammonium compounds can also be made from the total quantity used in food as given in Table II. Assuming that the figures in Table II represent 60 percent of actual usage, as is indicated in the footnote to Table II, recalculating these figures to 100 percent, and assuming a population of 210 million, enough of the bicarbonate, carbonate, hydroxide, monobasic phosphate, dibasic phosphate, and sulfate were added to foods in 1970 to provide an average daily per capita intake of 42, 0.3, 7, <0.1, 6, and 20 mg, respectively, rather than the corresponding possible average adult daily intakes of 497, 742, 535, 8, 120, and 61 mg given in Table IV.

On the basis of these considerations, the Select Committee agrees with the NRC subcommittee that the intake estimates derived from its survey data are overstated, often by considerable margins*.

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations", of the NRC subcommittee's report (9). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
TABLE IV

Possible Daily Intake of Certain Ammonium Salts

<table>
<thead>
<tr>
<th>Ammonium compound</th>
<th>Possible daily intake by age groups, mg</th>
<th>Per kilogram of body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>0-5 mos.</td>
</tr>
<tr>
<td></td>
<td>Av</td>
<td>Max</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>12</td>
<td>59</td>
</tr>
<tr>
<td>Carbonate</td>
<td>41</td>
<td>56</td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxide</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>Phosphate, mono-b</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Phosphate, dibasic</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Sulfate</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*Calculations based on the average weight of 60 kg for an adult (11) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (12).
The Select Committee regards the figures in Table IV as levels that are highly unlikely to be achieved by any of the age groups.

The Joint FAO/WHO Expert Committee on Food Additives has concluded that "there appear to be no toxicological grounds to limit" the use of ammonium bicarbonate, ammonium carbonate, and ammonium hydroxide when used in accordance with good manufacturing practice (13).

Japanese standards for food additives (14) place no maximum limits on the use in foods and beverages of the following ammonium compounds: bicarbonate, carbonate, mono- and dibasic phosphates, and sulfate. In the case of ammonium chloride, its use in miso is limited to 500 ppm; its use in sake is limited to 100 ppm.

IV. BIOLOGICAL STUDIES

The Select Committee has found few reports of experiments expressly conducted to determine the oral toxicity of ammonium compounds, and none concerning their long-term chronic effects. In the absence of direct data from feeding tests, extrapolation of results of studies conducted for other purposes yields some relevant information. In these studies the concentration of the ammonium salt was usually adjusted to produce the specific biochemical behavior of interest. Most of the experiments were performed with ammonium chloride. Further, in these studies, the ammonium salts were usually administered in pure form or in drinking water, rather than mixed with foods, as would normally be the case when they are used as food ingredients.

The oral lethal dose of ammonium sulfate for the rat is reported to be between 3 and 4 g per kg (15). The oral lethal dose of ammonium hydroxide for cats is reported to be 250 mg (as NH₃) per kg (16). In other studies, 41 cats given a single dose of 1 g of ammonium chloride per kg body weight by stomach tube, showed no untoward effects (17). Cats fed 1 to 2 g of ammonium chloride in their food daily for 5 months, followed by the same amount daily of ammonium chloride plus 1 g cholesterol for up to 10 months, did not exhibit atherosclerotic deposits in their blood vessels (18).

Development of atheromatous lesions in the aorta of the rabbit was unaffected by the administration of 30 to 50 ml of 2 percent
ammonium chloride (0.6 to 1.0 g) daily by stomach tube and 3 to 4 g cholesterol per week for 4 weeks. No untoward results were noted from the same dosage of ammonium chloride alone given daily to rabbits by stomach tube for 4 weeks (18).

Adult rats given 1.5 percent ammonium chloride for 330 days weighed significantly less than the controls. Bone formation was not affected, although bone resorption increased (19). In another study, rats given 2 g per kg of ammonium chloride in their diet showed a lower increase in glucuronic acid excretion in the urine than when such compounds as lactic acid and acetic acid were fed (20).

In dogs, 200 mg of ammonium chloride per kg per day in 3 divided oral doses produced a mild systemic acidosis. The normal pH of the urine (6.6) decreased to an average of 5.5 (21).

Several investigators have reported kidney enlargement after feeding large doses of ammonium chloride. Lotspeich (22) reported that consumption of ammonium chloride in drinking water by rats for 7 days (ad libitum consumption of a 0.28 molar solution, estimated from data presented to be of the order of 700 mg per kg per day) resulted in new cell formation and enlargement of existing cells in the kidney. Later work in the same laboratory confirmed the hyperplastic response of the kidney in rats fed ammonium chloride at a level of approximately 700 mg per kg per day (23). Janicki (24) gave rats ammonium chloride by gastric intubation (approximately 1 g per kg per day) and found renal enlargement but concluded it was not due to hyperplasia. Thomson and Halliburton (25) supplemented rat diets with 3 percent ammonium chloride for 6 days (dose level not stated) and found kidney enlargement. Since ammonium citrate or sodium chloride at equivalent levels did not cause hypertrophy, it was concluded that the effectiveness of ammonium chloride in this respect was due to its acidotic effect. Seegal (26) found rabbit kidneys on histologic examination to be moderately swollen with some degeneration of the epithelium of the convoluted tubules after daily intragastric doses of ammonium chloride (approximately 750 mg per kg) for 11 days. Similar effects were also reported in rabbits (27) and dogs (26). These data indicate that ammonium chloride fed at very high levels can cause kidney damage, probably due to its acidotic effects. Because no reports have been found where kidney effects have been studied at ammonium chloride ingestion
levels comparable to those likely to be present in the daily diet, the practical significance of these effects, as related to their evaluation, is difficult to assess.

Fazekas (28) found that rabbits develop enlarged parathyroids and adrenals after feeding ammonium acetate, ammonium chloride, ammonium lactate, ammonium phosphate, or ammonium sulfate (dose level approximately 0.5 g per kg per day), for several months. Consumption of ammonium chloride (about 750 to 1,000 mg per kg per day) led to osteoporosis in dogs (29).

Adult, colostomized hens absorbed 97.8 percent of the nitrogen of diammonium phosphate and 99.0 percent of that of diammonium citrate in their diets (30). The addition of 1.5 percent diammonium phosphate to the minimal amino acid diet of chicks produced a significant increase in live weight at 4 weeks. However, levels of 3.0 or 4.4 percent depressed the weight significantly (31). The albumen quality in the newly laid eggs was significantly improved by the addition of 2 percent ammonium chloride in the diet of the hens. However, an increase in the number of grade AA eggs was accompanied by a decrease in shell thickness (32). The relevance of these studies to mammals is not clear since it is recognized that the avian and mammalian mechanisms for metabolism and excretion of nitrogen differ.

Patients ingesting ammonium chloride (100 to 150 mg per kg per day) for several days showed an increased urinary excretion of calcium and magnesium; excretion of other cations and anions was also affected (33, 34, 35, 36). Since the smallest dose of ammonium compounds used in these studies was considerably higher than that likely to be consumed in man's daily diet, the significance of these effects to current food practices is not interpretable.

Metabolic studies with patients, including pregnant women, have provided significant data. For example, in one study, 1 g of ammonium chloride was given to middle aged and older patients at 2-hour intervals during the day for 7 doses and once during the night for a total dose of 8 g. Four patients were receiving maintenance antimalarial doses of 0.2 or 0.3 g of quinacrine hydrochloride, 5 daily doses of 0.2 or 0.4 g of chloroquine, and one dose of 400 mg of santoquine. The ammonium chloride increased the renal excretion of all three compounds (37). No toxic effects were recorded from these doses of ammonium chloride.

Thirteen women and two men between the ages of 22 and 60 years, given 1 g ammonium chloride every other day for 20 days, followed by a
pause of 10 days, developed headaches and neurasthenia. Disturbance of menses occurred in 10 of the women. An initial loss of appetite disappeared after the sixth day, followed by an increased desire to eat, which lasted long after the treatment period. A significant weight gain, consisting primarily of body fat, occurred in all subjects (38).

Acidosis was reported in another study involving 5 men each of whom ingested 10 to 20 g of ammonium chloride over each 24 hour period for 11 to 18 days (39). In a similar study, 6 to 8 g of ammonium chloride per day for 6 to 9 days produced a mild metabolic acidosis in 11 healthy subjects 21 to 28 years of age (40).

Five female patients with rheumatoid arthritis were given 6 to 8 g of ammonium chloride daily for varying lengths of time. There was a significant loss in body weight, which was ascribed mainly to the water loss from the body. At the same time there was a decrease in joint swelling. A progressive increase in mobility of the joints occurred in three patients. There had been no initial improvement in joint mobility in the fourth and fifth patients, who had severe joint destruction with some ankylosis. All patients experienced relief of joint pains during the treatment (41).

Six subjects with normal pregnancy, eight with toxemia of pregnancy, and three with essential hypertension associated with pregnancy were given an average dose of 15 g ammonium chloride dissolved in orange juice daily for 3 days. All of the patients tolerated the dosage fairly well. Three experienced nausea, but vomiting occurred in only two instances. There were no changes in blood pressure or pulse rate. The pattern of acid-base regulation following the ingestion of ammonium chloride in pregnant subjects did not differ from that of nonpregnant individuals (42).

In patients with substantial impairment of liver function who become comatose, an elevation of plasma ammonia level is frequently, although not invariably, observed (43). The degree of neurological abnormality is not always correlated with the degree of ammonia increase in the blood. This phenomenon is thought to be attributable to the failure of adequate urea formation by the liver, thus permitting the accumulation of absorbed ammonium ion in the blood. Under similar conditions, repeated ammonia infusions produce a state of confusion and coma in monkeys resembling that seen in man (44). In addition, there are rare individuals who have genetically determined metabolic disorders that may limit their ability
to tolerate large amounts of ammonia or ammonium salts in the diet (45). However, it is doubtful that these effects could be significant in the oral administration of ammonium salts except in individuals already seriously ill with liver disease.

A few experiments on animals relating to carcinogenicity have been reported. Oral administration of ammonium chloride and ammonium acetate was claimed to exert an inhibiting effect on Twort-carcinoma in mice (46). Twenty rats were given 1 g per kg of ammonium chloride daily in the feed for 6 months, following which they were inoculated with 26 million cancer cells per animal. They survived 2 to 3 weeks longer than the controls, with only rare cases of metastases. Similar results were found in another rat study in which 1 to 1.5 g per kg ammonium chloride was added to the feed (47). Precancerous changes were observed in the stomachs of rats fed daily for 1 to 2 years with about 1 g ammonium chloride per kg body weight (48). The survival time of mice with chloroleukemia 1394 was not significantly prolonged with a combination dosage of sodium bicarbonate and ammonium chloride (49). No evidence of tumor formation was found after feeding female rabbits ammonium carbonate, chloride, hydroxide, or sulfate in doses up to 700 mg per kg body weight for 5 to 16 months (50).

To the Select Committee's knowledge, no studies of the mutagenic or teratogenic potential of ammonium salts have been reported.

The Select Committee recognizes that a considerable literature exists which indicates that parenterally administered ammonium salts can elicit toxic reactions (ammonia toxicity) that fail to occur when equivalent doses are administered orally (1). These data are considered irrelevant to this report because the normal liver so readily detoxifies ammonium ion from alimentary sources that blood concentrations of ammonium salts do not rise to the levels necessary to evoke toxic response. For the same reason studies on the toxic effects of inhaled ammonia are not considered in this report.

V. OPINION

Ammonia and the ammonium ion are integral components of normal metabolic processes and play an essential role in the physiology of man.
Although there have been no significant feeding studies specifically designed to ascertain the safety threshold of ammonium compounds as food ingredients, numerous metabolic studies have been reported in the scientific literature. Extrapolation of these findings to the concentrations of ammonium compounds normally present in foods does not suggest that there would be untoward effects at such levels.

In the light of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on ammonium bicarbonate, ammonium carbonate, ammonium chloride, ammonium hydroxide, mono- and dibasic ammonium phosphate, and ammonium sulfate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in future.
VI. REFERENCES CITED


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