EVALUATION OF THE HEALTH ASPECTS OF NIACIN
AND NIACINAMIDE AS FOOD INGREDIENTS

1979

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

Contract No. FDA 223-75-2004
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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 concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior-sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 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 to the public 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.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Background information</td>
<td>3</td>
</tr>
<tr>
<td>III. Consumer exposure data</td>
<td>7</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>11</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>23</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>25</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>34</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using niacin and niacinamide as food ingredients. It 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 1974.* In addition, the Select Committee was provided with a review prepared by LSRO (2).* 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 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 May 25, 1979 (44 FR 30446) 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 niacin and niacinamide as food ingredients. None requested opportunity to be heard.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (3) [21 CFR 170.3 and 170.30] 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. These sections of the Code also indicate 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 (3) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluation of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds

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*These documents (PB-241 952/1) and (PB-275 752/4WJ) are available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
to suspect, a significant risk to the public health. While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its 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 niacin and niacinamide 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

Pellagra had been endemic in corn-eating areas of the world for more than 200 years before it was recognized as a dietary deficiency disease (4). The early symptoms are weakness, lassitude, anorexia, and indigestion, followed by the classic "three D's" characteristic of the disease: dermatitis, diarrhea, and dementia. In industrialized countries, pellagra is often the result of the vitamin- and protein-deficient diets of chronic alcoholics. It is also encountered in patients with cirrhosis of the liver, chronic diarrheal diseases, diabetes mellitus, neoplasias, or prolonged infectious diseases (5). Before its structure had been elucidated, the active principle was variously termed the pellagra-preventive factor, vitamin G, and vitamin PP. This principle was ultimately identified as nicotinic acid (pyridine-3-carboxylic acid), which is readily converted in the body to the physiologically active nicotinamide (pyridine-3-carboxylic acid amide) (4). These terms, nicotinic acid and nicotinamide, are recommended by the International Union of Nutrition Sciences and by the American Institute of Nutrition, and will be used in this report. The term niacin is used only as a generic descriptor for nicotinic acid and derivatives exhibiting qualitatively the biological activity of nicotinamide (6). Thus, phrases such as "niacin activity" and "niacin deficiency" are commonly used, and will be applied in this report. In the older literature, and in the Code of Federal Regulations (3), "niacin" and "nicotinic acid" are synonymous.

Because niacin deficiency can be corrected by ingestion of any substance having niacin activity, the term "nicotinamide equivalent" is used to apply to the summation of contributions to the dietary intake of precursors and of all active forms of niacin, including tryptophan, a precursor of nicotinamide (6). Evidence from a number of studies of human subjects has been widely interpreted to indicate that 60 mg of tryptophan is equivalent to 1 mg of nicotinamide (7). However, this ratio may not apply in the absence of dietary intake of niacin, with limited intake of tryptophan, or under other special conditions (8). Thus, women in the third trimester of pregnancy can convert tryptophan three times more efficiently than nonpregnant women (4). There is also evidence that the amino acid leucine may increase requirements for niacin or tryptophan. A high intake of leucine in a presumably adequate diet in dogs has been reported to cause black tongue, the canine counterpart of pellagra. In rat and man, dietary supplementation with leucine enhanced the excretion of quinolinic acid, a tryptophan metabolite (9). In addition, bound forms of niacin present especially in cereals may be of limited bioavailability (9). Rich sources of preformed niacin are liver, yeast, lean meat, poultry, peanuts, and legumes (5). Nicotinamide equivalents provided by various foods are indicated in Table I.
TABLE I

Nicotinamide Equivalents of Representative Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Niacin mg per 1000 calories</th>
<th>Tryptophan mg per 1000 calories</th>
<th>Nicotinamide equivalents per 1000 calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow milk</td>
<td>1.21</td>
<td>673</td>
<td>12.4</td>
</tr>
<tr>
<td>Human milk</td>
<td>2.46</td>
<td>443</td>
<td>9.84</td>
</tr>
<tr>
<td>Beef, round</td>
<td>24.7</td>
<td>1280</td>
<td>46.0</td>
</tr>
<tr>
<td>Whole eggs</td>
<td>0.60</td>
<td>1150</td>
<td>19.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Salt pork</td>
<td>1.15</td>
<td>61</td>
<td>2.17</td>
</tr>
<tr>
<td>Wheat flour</td>
<td>2.48</td>
<td>297</td>
<td>7.43</td>
</tr>
<tr>
<td>Corn grits</td>
<td>1.83</td>
<td>70</td>
<td>3.00</td>
</tr>
<tr>
<td>Corn</td>
<td>4.97</td>
<td>106</td>
<td>6.74</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adapted from reference 4.

<sup>b</sup>Erroneously listed as 10.8 in reference 4.
Niacin deficiency has been reported in human adults receiving as much as 4.9 mg per 1000 kcal or 8.8 mg daily of nicotinamide equivalents (7). However, Horwitt et al. (10) observed no signs of pellagra among 15 subjects receiving 4.4 mg nicotinamide equivalents per 1000 kcal or 9.2 to 12.3 mg daily for 38 to 87 weeks.

The Recommended Dietary Allowance (11) for adults is 6.6 mg niacin per 1000 kcal, with not less than 13 mg daily. This allowance is expressed in preformed niacin rather than in nicotinamide equivalents, because the contribution from tryptophan is considered variable and unpredictable. An additional 2 mg daily is recommended during pregnancy and 4 mg during lactation to meet the increased energy intakes. The niacin allowance recommended for infants up to 6 months is 8 mg per 1000 kcal, and for children over 6 months and for adolescents, 6.6 mg per 1000 kcal with a total of not less than 8 mg daily. Average diets in the United States supply 500 to 1000 mg or more of tryptophan daily and 8 to 17 mg preformed niacin, thus providing 16 to 33 mg of nicotinamide equivalents (9).

The Code of Federal Regulations (3) classifies niacin (nicotinic acid) [21 CFR 182.5530] and niacinamide (nicotinamide) [21 CFR 182.5535] as nutrients and/or dietary supplements with GRAS status. Nicotinic acid is a nonhygroscopic, stable, white, crystalline solid which sublimes without decomposition at about 230°C. It is soluble in water (1 g in 60 ml) and in alcohol (1 g in 80 ml) at room temperature and freely soluble in boiling water or alcohol. It is insoluble in ether. Nicotinamide is a white, crystalline powder, much more soluble than nicotinic acid in water (1 g per ml) and alcohol (1 g in 1.5 ml) at room temperature. It is also soluble in ether and glycerol (4,12).

The Food Chemicals Codex (12) specifies that preparations of nicotinic acid used in foods, must contain from 99.5 to 101.0 percent of the vitamin calculated on the dried basis. It must lose not more than 1 percent on drying at 105°C for 1 hour and have a residue of not more than 0.1 percent after ignition. Its melting range should be between 234° and 238°C and its heavy metal content expressed as lead must be no more than 20 ppm. Food grade nicotinamide must contain not less than 98.5 nor more than the equivalent of 101.0 percent of the compound after drying over silica gel for 4 hours. Its melting range should be between 128° and 131°C. Its loss on drying should be not more than 0.5 percent and the residue after ignition not more than 0.1 percent. It should contain no more than 30 ppm of heavy metals expressed as lead.

Nicotinic acid or nicotinamide is used to enrich various foods such as bakery, cereal, and pasta products. Limits are specified and vary from 10 to 15 mg per lb (4.5 to 6.8 mg per kg) for enriched bread, rolls, etc. to 27 to 34 mg per lb (12.3 to 15.5 mg per kg) for enriched macaroni and noodle products (3).
Nicotinic acid or nicotinamide is incorporated in tablets, capsules, and liquids, singly or in combination with other dietary supplements, for over-the-counter sale. The Physicians' Desk Reference (13) lists more than 100 preparations containing these compounds sold in the United States. However, only the health aspects of nicotinic acid and nicotinamide used as food ingredients are evaluated in this report.
III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) (14) surveyed manufacturers in 1970 concerning the level of addition of GRAS substances to foods and estimated the possible average daily intake of these substances by persons in various age groups. Based on information supplied by those manufacturers who reported adding the substances to at least one food product in the category, a weighted mean was calculated for the usual and maximal percentage addition of the substance to foods in that category. Such weighted means for the usual levels of addition of nicotinic acid and nicotinamide are presented in Table II. Because many foods in these categories probably do not contain nicotinic acid or nicotinamide and because few, if any, of the foods contain both substances, the estimated levels of addition presented in Table II are likely to be high.

The NRC subcommittee (14) estimated possible average daily intakes of nicotinic acid and nicotinamide based on Market Research Corporation of America data on mean frequency of eating foods by food category, Department of Agriculture data on mean portion size of foods in these categories, and the assumption that all food products within a category contain the substance at the level indicated in Table II. Such an assumption is likely to lead to overestimation of intake, and the NRC subcommittee has recognized that in most cases its calculations of possible intakes are overstated.* Possible average daily intake calculated in this manner was 27 mg for nicotinic acid and 11 mg for nicotinamide.

An alternative calculation of per capita daily "intakes" of nicotinic acid and nicotinamide added to foods may be made from data provided in the NRC report (49) concerning the total quantities of the substances added annually to processed foods. Based on these data, the daily per capita "intakes" in 1975 from nicotinic acid and nicotinamide added to foods were 7.5 and 2.2 mg, respectively (Table III). Such disappearance data are likely to be somewhat in excess of per capita consumption because of wastage and other factors. Nevertheless, the data in Table III suggest considerably lower per capita intakes than those calculated by the NRC subcommittee on the basis of data in Table II, and the Select Committee considers the data in Table III to provide more reasonable estimates of average intakes.

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report. 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 of the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
**TABLE II**

**Level of Addition of Nicotinic Acid and Nicotinamide to Foods by Food Category (14)**

<table>
<thead>
<tr>
<th>Food category</th>
<th>Nicotinic acid</th>
<th>Nicotinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted mean</td>
<td>Weighted mean</td>
</tr>
<tr>
<td></td>
<td>mg/kg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>102</td>
<td>143</td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>Milk products</td>
<td>92</td>
<td>13</td>
</tr>
<tr>
<td>Meat products</td>
<td>160</td>
<td>47</td>
</tr>
<tr>
<td>Poultry products</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td>19</td>
<td>68</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Reconstituted vegetable protein</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Dairy product analogs</td>
<td></td>
<td>150</td>
</tr>
<tr>
<td>Baby food, baked goods</td>
<td>130</td>
<td>51</td>
</tr>
<tr>
<td>Baby food, cereals</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Baby food, formulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baby food, combination dinners</td>
<td></td>
<td>90</td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of nicotinic acid and nicotinamide is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in a food category. For discussion of weighted mean, see Section X and Exhibit 50 of reference 14.
TABLE III

Quantity of Nicotinic Acid and Nicotinamide Added Annually to Foods and Calculated Per Capita Daily "Intake" (49)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used(^a) 1975/1970</th>
<th>Total used (1975) kg</th>
<th>Per capita daily intake (^b) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic acid</td>
<td>2.9</td>
<td>590,000</td>
<td>7.5</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>2.9</td>
<td>180,000</td>
<td>2.2</td>
</tr>
</tbody>
</table>

\(^a\)Based only on the reports from respondents to the National Research Council survey who submitted information for both 1970 and 1975 (49).

\(^b\)Based on a U.S. population of 215 million in 1975.
Table III also provides estimates of the relative amounts of each compound used in 1970 and 1975. For the period 1970 to 1975, the data indicate an approximate tripling of the usage of both nicotinic acid and nicotinamide.

A nutritional survey (15) completed in 1974 of about 21,000 members of the U.S. population included measurements of the daily per capita consumption of "preformed niacin." This measurement included nicotinic acid and nicotinamide, both naturally occurring and added by manufacturers. Males between the ages of 25 and 34 had a mean intake of about 25 mg per day (0.31 mg per kg body weight) of "preformed niacin." The corresponding figure for females between the ages of 25 and 34 was about 15 mg (0.23 mg per kg body weight). The average for both sexes was about 20 mg daily (0.28 mg per kg body weight). Similar intakes were reported for all age groups between 15 and 64 years: male, 19.6 to 24.6 mg (0.25 to 0.34 mg per kg); female, 12.8 to 15.1 mg (0.20 to 0.24 mg per kg).

If one assumes the per capita daily intake values in Table III to be correct, the niacin added to food represents less than half of the estimated daily intake from all dietary sources.
IV. BIOLOGICAL STUDIES

Absorption, distribution, and metabolism

Both nicotinic acid and nicotinamide are readily absorbed from all portions of the gastrointestinal tract (16). In vitro studies using everted sacs of the small intestine of rat and hamster strongly suggest that absorption of nicotinic acid and nicotinamide is by passive diffusion (17-19). No data on their absorption by man were available to the Select Committee. Deamidation of nicotinamide to nicotinic acid is not a prerequisite for absorption from the digestive tract (20).

In the mouse, some nicotinic acid is converted to nicotinamide in the liver, and to a lesser extent in the intestine (20). After absorption, nicotinic acid and nicotinamide react with 5-phosphoribosyl-1-phosphate to form the corresponding mononucleotides, which are subsequently converted to nicotinamide adenine dinucleotide (NAD) (21). NAD in turn is converted into nicotinamide adenine dinucleotide phosphate (NADP) by the enzymatic transfer of a phosphate group from adenosine triphosphate. NAD and NADP are coenzymes functioning as prosthetic groups for a large number of metabolic enzymes involved in a variety of essential biological oxidation-reduction reactions.

The metabolic pathway of nicotinamide and of the pyridine nucleotide coenzymes has been the subject of numerous investigations (22-33). The principal route in man is the methylation of nicotinamide to form N^1-methyl nicotinamide (22). This is further metabolized to N^1-methyl-2-pyridone-5-carboxamide (2-pyridone) (23,24) and N^1-methyl-4-pyridone-3-carboxamide (4-pyridone) (25-28). Nicotinuric acid, the glycine peptide of nicotinic acid (29,30), and the 6-hydroxy derivatives of nicotinic acid and nicotinamide (31) have also been identified as metabolites.

An hepatic aldehyde oxidase from rabbits catalyzes the formation of the 2-pyridone (32) and a soluble enzyme from rat liver that of the 4-pyridone (28) from N^1-methyl nicotinamide. In the rat, the formation of these two pyridones appear to be catalyzed by separate enzymes (28), but this has not been demonstrated in other species.

Perlzweig et al. (24) fed two normal human adults 500 mg (8.3 mg per kg) of nicotinamide daily for 5 days. During the last 3 days of dosing, the subjects excreted daily between 190 and 280 mg of N^1-methyl nicotinamide, 230 to 280 mg of 2-pyridone, and about 4.5 to 7.5 mg of "niacin." On the day before dosing, the same subjects fed a normal diet excreted 6 to 9 mg of N^1-methyl nicotinamide, 10 to 12 mg of 2-pyridone, and about 1 mg of "niacin." It was estimated that on an average diet about 80 percent of the ingested vitamin is excreted in these forms. Similar
results were obtained with dog, rat, and pig but not with rabbit, guinea pig, calf, goat, and sheep. The investigators suggested that carnivora and omnivora dispose of excess "niacin" by methylating mechanisms, but that herbivora utilize other pathways.

Nicotinuric acid appeared in the urine when nicotinic acid, but not nicotinamide, was fed (29). Nicotinuric acid was the major metabolite excreted by four men in the 3 hours following their ingestion of a dose of 100 mg (1.7 mg per kg) of nicotinic acid. When the subjects were dosed after breakfast, free nicotinic acid did not appear in the urine except in one subject, who also reacted with a strong flushing of the skin. If nicotinic acid was given before breakfast, about 10 percent of the dose was excreted unchanged and the subjects exhibited intense flushing. No nicotinuric acid was excreted by either man or rat when nicotinamide was administered (32).

Petrack et al. (33) noted that when large doses (about 500 mg per kg body weight) of nicotinic acid or nicotinamide were given by intraperitoneal injection to female Sprague-Dawley rats, the compounds were excreted largely unchanged in the urine. However, at low doses (5 mg per kg), N1-methylnicotinamide was the major excretory product of nicotinamide. Small amounts of nicotinamide and pyridone derivatives were also excreted. In the case of injected nicotinic acid, about equal amounts of N1-methylnicotinamide and nicotinuric acid were excreted along with small quantities of nicotinic acid, nicotinamide, nicotinamide N-oxide, and the pyridone derivatives.

Leifer et al. (30) injected mice, hamsters, and rats intraperitoneally with 20 mg per kg nicotinic acid labeled with 14C on the carboxyl carbon; about 3, 4, and 7 percent, respectively, of the injected dose was exhaled as 14CO2 in the 24 hours following injections. These workers also injected a female dog intravenously with 20 mg per kg labeled nicotinic acid or nicotinamide. Less than 1 percent of either compound was exhaled as 14CO2 in the 24 hours following dosing.

In more recent studies, Lee et al. (31) found small amounts (0.6 to 1.2 percent) of 6-hydroxynicotinic acid and 6-hydroxynicotinamide after intraperitoneal injection of carbon-14 labeled nicotinic acid or nicotinamide into rats. Small amounts of nicotinamide N-oxide have also been found as a minor metabolite of nicotinic acid and nicotinamide in the rat (33).

Based on observations after intravenous administration of 200 mg (about 3.0 mg per kg) of sodium nicotinate to adult male volunteers, Harthon and Svedmyr (34) estimated that the plasma half-life during the distribution phase was 3.2 minutes. The infusion of sodium nicotinate at the rate of 0.07 mg per kg per minute for 30 minutes suggested that, for a two compartment system, the plasma half-life for the distribution phase was 4.1 minutes and
the half-life of the disposition-excretion phase was 12.4 minutes. Petrack et al. (33) had noted that with doses of 500 mg per kg of nicotinic acid and nicotinamide injected intraperitoneally, the half-life in the blood of rats was 1.1 hour and 5.3 hours, respectively.

**Acute toxicity**

**Animal studies.** Only Unna (35) appears to have studied acute toxicity in experimental animals using the oral route of administration. However, he reported little difference in results with oral and subcutaneous administration. In mice and rats (strains not identified), with 5 to 10 animals per dose level, toxic manifestations were not detected after oral or subcutaneous administration of 1 g of sodium nicotinate or nicotinamide per kg of body weight. After subcutaneous administration of 3.0 g per kg of sodium nicotinate or 1.8 g per kg nicotinamide, some deaths occurred. Deaths occurred within 12 to 36 hours and were preceded by ataxia, respiratory depression, and cyanosis.

Acute toxicity data reported by Unna and other investigators for several species and by various routes of administration are summarized in Table IV. The data by Lipkan (37) suggests that intraperitoneal injection may be more toxic than subcutaneous or intravenous administration.

The most satisfactory acute toxicity data, because of the number of animals employed, are those by Bederka et al. (39). Young adult female Swiss albino and Charles River mice weighing 20 to 32 g were studied. The LD_{25} after intraperitoneal administration of nicotinic acid to approximately 160 mice was 3.1 g per kg (ratio LD_{75} to LD_{25}: 1.85). The LD_{25} after intraperitoneal administration of nicotinamide to the same number of animals was 1.9 g per kg (ratio LD_{75} to LD_{25}: 1.14). Death generally occurred between 10 and 72 hours after administration of the dose. Surviving animals demonstrated increased hexobarbital sleep time. Toxicity by oral administration was not determined.

Nicotinamide acts also in conjunction with reserpine and chlorpromazine to decrease spontaneous activity and increase the duration of anesthesia in mice (40).

**Human studies.** Several outbreaks of apparent food poisoning have been reported from consumption of meat to which nicotinic acid or sodium nicotinate was added to preserve the red color. Lyman et al. (41) reported that 88 of 145 individuals in 38 families developed symptoms including cutaneous flushing, sensation of warmth, itching, and nausea after consumption of meat purchased from the same butcher shop over a 13-day period. The meat was found to contain approximately 0.5 to 3.7 g of nicotinic acid per kg. Press and Yeager (42) reported that 44 of 121 persons dining
<table>
<thead>
<tr>
<th>Animal</th>
<th>Route</th>
<th>Measurement</th>
<th>Dosage (mg/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>iv</td>
<td>LD&lt;sub&gt;0&lt;/sub&gt;</td>
<td>4000</td>
<td>36</td>
</tr>
<tr>
<td>Mouse</td>
<td>iv</td>
<td>LD&lt;sub&gt;100&lt;/sub&gt;</td>
<td>4500</td>
<td>36</td>
</tr>
<tr>
<td>Mouse</td>
<td>or</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>5000-7000</td>
<td>35</td>
</tr>
<tr>
<td>Mouse</td>
<td>sc</td>
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**Nicotinamide:**

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in a sorority house developed itching of the skin and redness and flushing of the face, neck, extremities, and trunk 10 to 60 minutes (the majority within 20 to 40 minutes) after consuming Swedish meatballs. The symptoms lasted about 40 minutes with a range of 15 minutes to 4 hours. Sodium nicotinate had been sprinkled on the meat. There was apparently an uneven distribution of the substance; one sample contained 2.25 g of sodium nicotinate per kg of meatball while another sample showed none. Several other outbreaks of similar signs and symptoms presumably resulting from consumption of nicotinic acid in meat are cited by Press and Yeager (42) but the majority are personal communications and impossible to evaluate.

Short-term studies

Animal studies. Handler and Dann (43) reported depression of growth rate in male Vanderbilt strain rats fed diets containing 10 percent casein and large amounts of nicotinic acid or nicotinamide. The rats weighed 48 to 54 g at the onset of the study and received diets containing 1 or 2 percent (1.0 or 2.0 g per kg body weight) of the vitamin for 30 days in some experiments and 40 days in other experiments. Each feeding group consisted of six rats and most experiments were repeated three times. Growth depression was considerably greater with nicotinamide than with nicotinic acid. A slight growth depression was noted at the 2 percent level with nicotinic acid feeding, but not at 1 percent. Fatty liver formation was noted at both nicotinic acid feeding levels. Almost complete growth inhibition occurred in animals fed 1 percent nicotinamide (43). However, large amounts of nicotinamide in the diets of rabbits and guinea pigs were innocuous (44).

Weanling rabbits weighing approximately 1.25 kg were fed diets containing 1 or 2 percent nicotinamide (300 to 600 mg per kg body weight per day) for 20 days with no impairment of growth. Guinea pigs, 7 days of age and 124 g in weight at the onset of the experiment, demonstrated no growth depression when fed diets containing 0.5, 1.0, or 2.0 percent (200, 400, or 800 mg per kg body weight per day) nicotinamide (44).

Male albino rabbits (age not indicated) received in their diets 600 mg (180 mg per kg body weight) of cholesterol and 500 mg (150 mg per kg) of nicotinic acid daily for 3 months. Hypercholesterolemia and the degree of atheromatosis were less in this group than in rabbits receiving cholesterol without nicotinic acid. Nicotinic acid did not influence the concentration of serum cholesterol nor the cholesterol-induced accumulation of lipids in the parenchyma of the liver. No untoward effects were noted in animals fed nicotinic acid but no cholesterol (45).

Rikans et al. (46) studied weanling male albino rats in each of four feeding groups: high fat with or without added nicotinamide (0.1 percent of the diet, 100 mg per kg body weight per day); low fat with or without added nicotinamide. There were ten
animals per group. Increased concentrations of fat in the liver 3 and 6 weeks after instituting the diet were found only when the high fat diet was combined with an excessive intake of nicotinamide. A further study suggested that the fatty livers resulted from an induced choline deficiency brought about by the methylation of nicotinamide to the excretory product N^1-methylnicotinamide (47). Handler (44) had earlier hypothesized that nicotinamide induced a choline deficiency in rats, but not in rabbits and guinea pigs.

Unna (35) fed ten 6-week-old rats 1 g per kg of sodium nicotinate daily for a period of 40 days. The animals showed normal growth with no toxic signs. Gross and microscopic examination of the heart, lungs, liver, spleen, kidney, intestinal tract, bone marrow, and genital organs revealed no pathological changes. A group of five chickens received 100 mg per kg of sodium nicotinate daily for 21 days; gains in weight were normal and no toxic reactions were observed. Three young dogs were given daily doses of 1 g per kg for 63 days with three litter mates serving as controls. Growth was normal. Two adult dogs tolerated 2 g per kg daily for 35 days without untoward signs.

Groups of 12 male rats (110 to 135 g) were fed nicotinamide in their diet for a period of 8 to 12 weeks (48). At 0.1 percent of the diet (100 mg per kg body weight per day), nicotinamide caused no significant change in the growth rate; at 0.2 percent, growth was enhanced; but at 0.4 percent, a marked inhibition of growth resulted.

Two adult dogs (13.8 and 15 kg) were given daily doses of 2 g of nicotinic acid by mouth (36). The smaller dog began excreting bloody feces on the eleventh, convulsed on the twelfth, and died on the nineteenth day with a total loss of 4.2 kg of body weight. There was fatty metamorphosis of the liver. The larger dog, after receiving 40 g of nicotinic acid in 20 days, lost 3.6 kg in weight and suffered convulsions. The animal had six erosions of the stomach, petechiae in the mucosa of the colon, and fatty metamorphosis of the liver. In both dogs, a few ganglion cells of the cortex, hippocampus, and basal ganglia were shrunken and deeply stained.

Four other dogs given smaller doses (0.06, 0.1, 0.2, or 0.5 g) by mouth five times a week for eight weeks appeared in good health and gained weight (36).

Human studies. An extensive literature is available concerning the effects of large doses (1 to 10 g daily) of nicotinic acid or nicotinamide to human subjects administered for periods of a few days to several years. Nicotinic acid is known to decrease serum concentrations of lipids in some patients with hyperlipoproteinemia (50-52). Both nicotinic acid and nicotinamide have been
used in treatment of schizophrenia. However, reports of success by Hoffer (53-55) and by Denson (56) in treating patients with schizophrenia have generally not been confirmed by other investigators (57-62).

As pointed out by Mosher (63), it is not clear why adverse effects have been reported so much more frequently when nicotinic acid is employed in treatment of hypercholesterolemia than when nicotinic acid or nicotinamide is employed in treatment of schizophrenia. The difference in reporting of adverse effects is particularly impressive because the LD$_{50}$ in animal studies is less for nicotinamide than for nicotinic acid. Although it is possible that the difference may be explained by the younger age and better general physical health of the schizophrenic patients than of the patients treated for hypercholesterolemia, it seems likely that evidence of adverse effects has been sought more systematically in patients with hypercholesterolemia.

When nicotinic acid is administered, the initial side effects of cutaneous flushing and pruritus, nausea, vomiting, and diarrhea generally decrease in a few weeks. More troublesome side effects are production of abnormal liver function tests, abnormal glucose tolerance, and hyperuricemia (50,52,64).

Charman et al. (64) reported long-term observations of 160 hypercholesterolemic patients given 3 g daily of nicotinic acid; 51 patients were followed for more than 5 years, 16 patients for more than 10 years. The observations covered 868 patient years. Flushing of the skin and pruritus were sufficiently troublesome to result in discontinuation of treatment in only 10 patients. Approximately 26 percent of the patients experienced "dyspepsia" or nausea and vomiting and 45 percent of this group discontinued the medication. Clinical evidence of active peptic ulcer developed in nine patients (three with previous history of duodenal ulcer disease). Liver function studies were not routinely carried out. However, hepatomegaly, jaundice, increased serum glutamic oxalacetic transaminase, and alkaline phosphatase developed in three patients and ascites in one of these. Liver biopsy in one instance demonstrated "patchy fibrosis with mononuclear infiltration and some areas of necrosis" and in another "intrahepatic cholestasis with periportal hepatitis." No biopsy was taken from the third patient. All liver function studies returned to normal after cessation of nicotinic acid therapy. Three patients were known to have gout before onset of treatment and only one had an acute attack after onset of treatment. Eight patients had diabetes mellitus when drug therapy was initiated. A moderate increase in glycosuria was noted in three of these and one patient without previously recognized diabetes manifested hyperglycemia on nicotinic acid therapy. No patient discontinued therapy because of carbohydrate intolerance.
In a five-year review of clinical findings not present at entry, data were compared from patients receiving 3 g nicotinic acid daily and from patients receiving placebo (52). "Any abnormality of gastrointestinal system" was reported for 25.7 percent of 1017 patients receiving nicotinic acid and for 20.1 percent of 2548 patients receiving placebo. Diarrhea, nausea, vomiting, and stomach pain were reported more commonly among the patients receiving nicotinic acid. As was to be anticipated, flushing, itching of the skin, urticaria, and excessive sweating were more common among patients receiving nicotinic acid. These patients were also more prone to "other types of rash." Most of the significant clinical findings concerned the dermal system. Patients receiving nicotinic acid had an increased incidence of acanthosis nigricans, ichthyosis, and hyperpigmentation.

During the five-year observation period, insulin therapy was begun in 1.3 percent of 1073 patients receiving nicotinic acid and in 0.9 percent of 2694 patients receiving placebo (52). Oral hypoglycemic agents were prescribed for 4.3 percent of 1014 patients receiving nicotinic acid and 4.6 percent of 2548 patients receiving placebo. Medication for gout was prescribed for 11.4 percent of 1040 patients receiving nicotinic acid and for 6.1 percent of 2620 patients receiving placebo.

Increases in serum levels of the following constituents were significantly greater for patients receiving nicotinic acid for five years than for those receiving placebo: total bilirubin, serum glutamic oxalacetic transaminase, alkaline phosphatase, creatine phosphokinase, glucose (both fasting and one hour post-challenge), and uric acid (52).

**Effect on carbohydrate and lipid metabolism**

Nicotinic acid in daily doses of 1 to 3 g (15 to 50 mg per kg body weight) significantly diminished carbohydrate tolerance in most nondiabetic patients (65-68). The hyperglycemia commonly observed during nicotinic acid therapy subsided promptly after discontinuance of the vitamin and is considered by some investigators to be of no clinical significance (68).

Administration of large doses (1 to 4 g daily) of nicotinic acid was shown by Altschul et al. (69) to lower serum concentrations of cholesterol in man. Subsequent studies have confirmed this observation (50-52, 70-74).

Although Miettinen (75) reported stimulation of cholesterol synthesis in human subjects receiving large doses of nicotinic acid, other investigators have reported inhibition of synthesis in human subjects (50,51) and in rhesus monkeys (76).
Paul et al. (77), using a constant infusion of $^{14}$C-glucose, studied the effects of sodium nicotinate on rates of turnover and oxidation of plasma glucose and free fatty acid levels in normal dogs. Infusion of 1.01 mg per kg per minute for 45 minutes was associated with a decrease in plasma concentration of free fatty acids and increased rates of turnover and oxidation of glucose.

Carlson and Orö (78) reported that intravenous administration of a total dose of 100 mg nicotinic acid per kg body weight in ten divided doses to dogs inhibited the mobilization of free fatty acids from adipose tissue by norepinephrine. In human subjects, 2 g nicotinic acid by mouth (about 30 mg per kg) produced a marked decrease in plasma free fatty acids within 15 to 30 minutes. After 60 to 90 minutes the levels rose above the basal levels. Davidson and Bernstein (79) cited a number of studies with human subjects demonstrating that nicotinic acid decreases the concentration of free fatty acids in the blood in the basal state, after starvation, exercise, cold exposure, and administration of various agents. The effects of a number of lipolytic agents are blocked by nicotinic acid, apparently by inhibiting the formation of cyclic adenosine monophosphate (AMP) (80-83).

Balasse and Neef (84) studied ten female subjects 17 to 34 years of age with body weights 95 to 190 percent of ideal weight. Three normal and three obese subjects fasted for 15 hours (overnight) and 4 obese subjects starved for 10 or 11 days. All had normal oral glucose tolerance before study. A total dose of 12.1 to 18.9 mg nicotinic acid per kg body weight was then delivered as intravenous pulses of 100 to 150 mg every 20 min. All the nonstarved and two of the starved subjects demonstrated a decrease in free fatty acid concentrations of the plasma and an increase in the rates of turnover and oxidation of glucose in plasma. These changes were not noted in the other two starved subjects.

**Effects on liver.** Although abnormalities in liver function are commonly observed in studies of patients receiving large doses of nicotinic acid (65,85), it has been suggested that these are based on the interference of nicotinic acid with various enzyme activities and represent temporary changes of little or no medical significance (74,86). Hoffer (87) reported only two cases of possible liver toxicity in a series of 1000 patients treated with large doses of nicotinic acid or nicotinamide for schizophrenia. One of these patients was believed to have infectious hepatitis and the other was receiving translycypromine sulfate (Parnate®) in addition to nicotinic acid. Clinical findings suggesting abnormality of the liver (enlargement, jaundice, etc.) were similar for patients receiving nicotinic acid to those for controls in the report of the Coronary Drug Project Research Group (52). Nevertheless, a number of reports suggest that in some instances liver disease is associated with administration of large doses of nicotinic acid.
In 1969, Kohn and Montes (88) reported the case of a man who had received 3 g of aluminum nicotinate daily for 4 years and had developed impaired carbohydrate metabolism and intrahepatic obstructive jaundice with hypoalbuminemia and edema. Evidence of toxicity subsided after cessation of therapy. The patient died of cardiac disease two years later and necropsy revealed evidence of hepatic fibrosis. The large amount of aluminum could have had some deleterious effect resulting from its interference with phosphate metabolism (89). Kohn and Montes (88) cited several other reports (85,90-92) suggesting significant liver disease during the course of treatment with high doses of nicotinic acid. Berge and coworkers (65,93) reported that 23 of 52 patients treated with 3 g or more of nicotinic acid daily for periods of approximately 1 to 4 years exhibited at least one abnormal result in tests of liver function. In three patients tests were persistently abnormal, and in two patients jaundice was present.

Baggenstoss et al. (94) reported fine structural changes observed by electron microscopy in the livers of patients receiving nicotinic acid therapy for hypercholesterolemia for periods of 22 months to 9 years. Dilatation of the endoplasmic reticulum resulted in the formation of numerous vesicles and sacs of various sizes and shapes.

Winter and Boyer (95) reported a case of a 35-year-old man treated for schizophrenia for 18 months with 3 g daily of nicotinamide together with other drug treatment. On several occasions the patient increased the dosage to 9 g daily and subsequently developed nausea, vomiting, and abnormal liver function tests. Liver biopsy suggested parenchymal cell injury, portal fibrosis, and cholestasis. Nausea, vomiting, and abnormal liver function tests were provoked in the hospital by challenge with 9 g daily of nicotinamide. All liver function tests returned to normal after discontinuance of nicotinic acid.

Jaundice developed and liver function tests became abnormal in a 69-year-old man treated for "organic brain syndrome" for less than 3 months with nicotinic acid (250 mg, three times daily), thiamin (500 mg, twice daily), and ascorbic acid (100 mg, three times daily) (96). Biopsy demonstrated "cholestatic hepatitis with minimal lymphocyte infiltrate." The most notable finding was increased bile stasis. Even after discontinuing all medications, the jaundice increased for several weeks before subsiding over an additional period of several weeks.

Einstein et al. (97) reported on a 22-year-old woman treated for a "psychological disturbance" for 2 years with 3 g nicotinic acid, 3 g ascorbic acid, 100 mg pyridoxine, 2400 IU vitamin E, and a multivitamin tablet daily. The woman was admitted to the hospital because of jaundice and pruritus. The liver was enlarged and tender. Liver function tests were abnormal and liver biopsy revealed active hepatitis, submassive necrosis,
marked cholestasis, and bile duct proliferation. When medications were discontinued the jaundice subsequently cleared and liver function tests returned to normal.

In diabetic subjects, administration of 1 to 3 g of nicotinic acid daily is associated with glycosuria, decreased plasma lipids, and increased plasma glucose, free fatty acids, and ketones. Increased requirements for insulin or oral hypoglycemic agents were reported by Molnar et al. (98). However, subsequent reports by other investigators fail to mention such increased requirements.

Effects on serum uric acid. Hyperuricemia has been reported in approximately 60 percent of patients receiving 3 to 6 g of nicotinic acid daily (65,85,91). Possible mechanisms for this effect are decreased renal excretion of uric acid and decreased intestinal uricolyis (99). Overt attacks of gout during treatment with large doses of nicotinic acid appear to be rare (52,65).

Long-term studies

No reports of lifetime or multigeneration studies of animals receiving large doses of nicotinic acid or nicotinamide have come to the attention of the Select Committee.

Mutagenicity

Brusick evaluated nicotinic acid (100) and nicotinamide (101) for mutagenic activity in microbial assays with and without the additions of mammalian metabolic activation preparations. The indicator microorganisms were Saccharomyces cerevisiae, strain D4 and Salmonella typhimurium strains TA-1535, -1537, -1538, -98 and -100. For activation assays, tissue homogenates from mouse, rat, and monkey were added to the bacterial and yeast cells. Neither nicotinic acid nor nicotinamide exhibited mutagenic activity in any of the assays employed in these studies.

Teratogenicity

Alterman (104) investigated the possible teratogenic effects of nicotinic acid on the developing chick embryo. She administered an aqueous solution of the compound into the air cell and into the egg yolk at 0 and 98 hours of incubation. There was no significant difference from controls in the number or type of observed abnormalities. The Select Committee is not aware of any studies on the possible teratogenicity of nicotinamide.
Carcinogenicity

Nicotinamide was administered in drinking water to mice of both sexes for 4 weeks (about 250 mg per kg body weight per day) (102). A single application on the skin of 9,10-dimethyl-12-benzanthracene was followed, after a 3-week interval, with weekly paintings of croton oil for 15 weeks. There was no significant difference in the production of papillomas between the control mice and those receiving nicotinamide.

Nicotinamide alone, given intraperitoneally in two injections of 350 mg, to 27 male Holtzman rats, caused no tumors during 550 days of observation (103). It did, however, promote markedly the appearance of the pancreatic islet cell tumors induced by streptozotocin.
V. OPINION

The term niacin as adopted by the American Institute of Nutrition, is a generic form including both nicotinic acid and its amide, nicotinamide (or niacinamide), to which it is readily converted in the body. However, niacin as employed by the Code of Federal Regulations refers only to nicotinic acid. Nicotinamide is a component of two essential coenzymes, nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate. The body is also able to form nicotinamide from tryptophan (60 mg of tryptophan provide 1 mg of niacin equivalent) and much of the total niacin equivalents of the diet are supplied in this manner.

Disappearance data suggest that per capita daily intakes of nicotinic acid and nicotinamide added to foods are less than 7.5 and 2.2 mg, respectively. Thus the amount added to foods (about 0.15 mg per kg body weight) is approximately one-half the total dietary intake of these substances from both added and natural sources. The LD50 for various laboratory animals given the substances parenterally has generally been found to be more than 1 g per kg per day. Limited data on oral ingestion by mice and rats suggest that the LD50 may be more than 4 g per kg per day. Young laboratory animals fed diets containing 1 or 2 percent nicotinic acid or nicotinamide (1 to 2 g per kg body weight per day) have demonstrated growth depression in some but not all studies. At levels of 0.1 percent in the diet, fatty livers may occur, reflecting an induced choline deficiency.

Because large doses of nicotinic acid are known to reduce serum concentration of cholesterol, administration of nicotinic acid has been employed in management of patients with hypercholesterolemia. Dosage commonly employed is 3 to 9 g daily (50 to 150 mg per kg). Initially experienced side effects, including cutaneous flushing, pruritus, and nausea, usually subside with continued therapy and the great majority of subjects then appear to experience no adverse effects. However, abnormal values in liver function tests have been detected rather frequently and at least a few subjects have developed jaundice. These manifestations generally subside promptly after discontinuation of treatment. Pathologic changes in the liver, possibly irreversible, have been associated with treatment with large daily doses in a few instances.

Although there have been no short- or long-term animal studies defining the greatest no-adverse-effect level of intake of nicotinic acid or nicotinamide, the adverse effects reported in animals and man have been associated with intakes at least a hundredfold greater than those likely to be achieved from fortification of foods.
In the light of these considerations, the Select Committee concludes that:

There is no evidence in the available information on niacin (nicotinic acid) or niacinamide (nicotinamide) 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 the future.
VI. REFERENCES CITED


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September 28, 1979
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Select Committee on GRAS Substances