REVIEW OF THE RECENT LITERATURE ON THE HEALTH ASPECTS OF NIACIN AND NIACINAMIDE AS FOOD INGREDIENTS

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BUREAU OF FOODS
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by

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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) provides scientific assessments of topics in the biomedical sciences. Reports 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 LSRO Select Committee on GRAS Substances (SCOGS) as a part of their review of the health aspects of using these food ingredients as stipulated in the Food, Drug, and Cosmetic Act for Generally Recognized as Safe substances. Dr. Michael J. Wade prepared the report based on a comprehensive search and evaluative assessment of the current literature in accordance with the provisions of contract no. FDA 223-75-2004. Acknowledgment is made of the assistance of the LSRO staff who provided much of the background information.

Kenneth D. Fisher, Ph. D.
Director
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INTRODUCTION

This report concerns the health aspects of using niacin and niacinamide as food additives. It reviews the world's scientific literature from 1972 through 1976.

To assure completeness and currency as of the date of this report, information has been obtained by searches 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; and by the combined knowledge and experience of members of the LSRO staff. This report supplements and updates information contained in a scientific literature review (monograph) prepared for FDA by Informatics, Inc.\(^1\) which summarizes the world's scientific literature up to 1974.

Niacin (21 CFR 182.5530) and niacinamide (21 CFR 182.5535) (Figure 1) are listed as GRAS substances in the Federal Regulations\(^2\) for use as nutrients and/or dietary supplements. In the scientific literature niacin is sometimes referred to as nicotinic acid and niacinamide as nicotinamide.

\[
\begin{align*}
\text{Niacin (Nicotinic Acid)} &
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \text{ - OH}
\end{array} \\
\text{Niacinamide (Nicotinamide)} &
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \text{ - NH}_2
\end{array}
\end{align*}
\]

Figure 1. Structures of niacin and niacinamide

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\(^1\)The document is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

I. ABSORPTION AND METABOLISM

Niacin and niacinamide are present throughout the body and are efficiently absorbed after oral or parenteral administration. A recent review by Matthews (1974) cites several investigations which indicate that neither of these compounds is absorbed by active transport. After absorption, niacin and niacinamide are converted to the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotidephosphate (NADP) in erythrocytes and other tissues. The first step in these conversions is the formation of nicotinic mononucleotide or nicotinamide mononucleotide from phosphoribosylpyrophosphate and niacin or niacinamide. Evidently there is no enzyme capable of direct synthesis of niacinamide from niacin. In the case of the synthesis of NAD or NADP from niacin, the amide function is added at a later step in the synthesis. NAD and NADP are catabolized to niacinamide which is then methylated to form N-methyl nicotinamide as the major excretory product (White et al., 1973). Only small amounts of niacin or niacinamide are excreted unchanged unless extremely high doses are given (Marks, 1975; Greengard, 1975).

Some nicotinic mononucleotide is synthesized by the body from tryptophan although only a fraction of the body's tryptophan supply is so used and this is not sufficient to meet daily niacin needs (Marks, 1975).

II. ACUTE TOXICITY

Bederka et al. (1975) determined the LD$_{50}$ of niacin and niacinamide to be 3.09 g per kg and 1.94 g per kg respectively when injected intraperitoneally in young adult, female mice. The ratio of the LD$_{50}$ to the LD$_{50}$ was 1.85 for niacin and 1.14 for niacinamide, indicating a steep curve for the dose lethality relationship. These values were obtained over a seven day observation period to determine death or survival. Most mice died between 10 and 72 hours after injection. In the 30-minute period following administration to mice of an LD$_{50}$ dose of niacin or niacinamide, their motor activity declined 89 and 95 percent respectively compared to control mice receiving only the vehicle. Control mice injected with 50 mg per kg hexobarbital had a mean sleeping time of 33 minutes compared to 203 minutes and 71 minutes respectively for mice receiving an LD$_{50}$ dose of niacin or niacinamide.
III. SHORT AND LONG-TERM TOXICITY STUDIES

No short-term or long-term studies of niacin or niacinamide toxicity were found for the time period encompassed by this review.

IV. SPECIAL STUDIES

A. BIOCHEMICAL STUDIES

Magide and Myant (1974) observed the effects of single and multiple injections of niacin on the serum lipid content of immature rhesus monkeys. When the animals were injected subcutaneously with a single dose of 250 mg per kg of niacin, serum niacin levels rose to 150 mg per liter after 30 minutes and fell to a negligible level within 24 hours. The serum triglyceride level dropped to 50 percent of the basal level six hours after the injection, and returned to the normal level during the following 18 hours. Serum-free fatty acids dropped to 50 percent of normal values 30 minutes after injection and had returned to basal level by 24 hours after injection.

Six hours after niacin injection there were small, consistent decreases in serum phospholipid and cholesterol concentrations which returned towards normal values in the following 18 hours. The monkeys were also injected daily for seven days with 150 mg per kg niacin. Serum niacin concentrations were the same each day when measured 30 minutes after dosing. Over the course of the injections, serum cholesterol levels decreased in a stepwise manner to about 75 percent of the basal level by the end of the seventh day. Serum triglyceride levels fell off after each injection but returned to basal level within 24 hours. Experiments were also performed at a higher niacin dosage — 250 mg per kg given twice daily for 15 to 28 days. At this dosage serum cholesterol levels dropped to about two-thirds of the normal value and did not return to the pretreatment value until three or four weeks after cessation of niacin dosing. As measured 30 minutes prior to niacin injection, serum triglyceride levels were about 64 percent of the basal level. When measured 30 minutes after niacin injection, the serum niacin level did not change over the course of the injections. During the three to four-week regimen of twice daily 250 mg per kg injections of niacin, the monkeys showed no signs of the side effects such as flushing, headache, itching or palpitations which humans may experience after a single high dose of niacin. Liver biopsies of the monkeys after three weeks on the twice daily injections showed no abnormalities under light microscopy. Biopsy slices of liver were taken from the monkeys before and after 20 to 30 days of twice daily 250 mg per kg injections of niacin. Samples taken after niacin treatment had significantly lower rates of cholesterol synthesis.
Somewhat conflicting results were reported by Orbetsova et al. (1976a, b) who found that after daily subcutaneous injection for 21 days with 200 mg per kg niacin, liver homogenates from male rats showed up to severalfold increases in incorporation of labeled $2^{-14}$C mevalonate into cholesterol fractions as compared to saline injected controls.

Magide and Myant (1975) also studied the effect of daily 250 mg per kg subcutaneous injections of niacin on the cholesterol content of skin and muscle in the monkey. After a five-week course of injections there was a decrease in cholesterol content of about 37 percent in serum, 49 percent in muscle and 43 percent in skin. In the muscle most of the cholesterol loss occurred in the free, as opposed to esterified cholesterol fraction, and in the cytoplasmic, as opposed to the mitochondrial fraction. There was a net loss of cholesterol from the muscle tissues since protein, water and DNA levels were not altered. No reduction in muscle strength or physical activity was noted in the animals during the course of the experiment.

In addition to its effects on lipid levels, niacin has been shown by several investigators to affect levels of cyclic AMP. Andersson et al. (1973) found that the increases in lipolysis and cyclic AMP concentrations following incubation of perirenal fat tissue from male rats with norepinephrine or theophylline could be blocked by addition of niacin to the tissues. Similar results were found by Fain (1975) who reported that a one-hour incubation of rat white-fat cells with 1.2 $\mu$g per ml niacin blocked the increase in cyclic AMP concentration caused by norepinephrine addition. In addition, lipolysis by the cells was inhibited by 60 percent to 80 percent in the presence of 1.2 $\mu$g per ml niacin.

Yeh (1976) observed that intraperitoneal administration of 250 mg per kg of niacin to fasted rats reduced the elevated concentrations of ketone bodies, free fatty acids and glycerol caused by fasting. The fasted rats had cyclic AMP levels in liver and adipose tissue which were about 50 percent to 100 percent higher than fed controls. Intraperitoneal administration of 250 mg per kg niacin to the fed rats one hour before sacrifice reduced the liver and adipose levels of cyclic AMP to levels slightly below those of the fed controls.

Balasse and Neef (1973) studied the effect of niacin administration on the turnover and oxidation of $^{14}$C glucose infused into normal and obese volunteers. A total of ten subjects, all female, had normal glucose tolerance. Six of the subjects were ambulatory and were studied after an overnight fast; three of these subjects were normal and three were obese. The other four subjects, obese hospitalized patients, were studied after 10-11 days of fasting when they consumed only vitamins, minerals and
noncaloric liquids. Two sets of glucose-turnover and oxidation-rate determinations were made. The experimental set was made during the administration of a series of 11 intravenous boluses of 100 or 150 mg of niacin given every 20 minutes for the duration of the experiment — 210 minutes (18.3-27.3 mg per kg total dose). A control set of measurements, made after saline injections, were obtained several days prior to the niacin set. Compared to control values there were average increases of about 2 percent in plasma glucose level, 26 percent in glucose turnover rate and 32 percent in glucose oxidation as measured by $^{14}$C CO$_2$ production when the subjects were administered niacin. Total CO$_2$ production increased 13 percent. These workers also found decreases of 60 percent in the plasma level of free fatty acids, 30 percent in immune-reactive insulin, 62 percent in blood glycerol and 73 percent in blood ketone level for the set of measurements made during niacin administration. All the above values represent averages from the 10 subjects. Two of the starved, obese hospitalized subjects did not respond to niacin administration by increased lipolysis, nor did they exhibit increased glucose turnover. No side effects were noted from niacin administration except cutaneous flush during niacin infusion and some instances of nausea several hours after the end of the experiment.

Similarly, Davidson and Bernstein (1973) found that oral administration of 1 g of niacin (16.7 mg per kg) to five fasted, normal male volunteers caused a significant increase in the plasma glucose uptake following intravenous administration of 25 g of glucose when compared to the uptake of glucose in subjects not ingesting niacin. The glucose tolerance tests were begun one hour after niacin administration. Basal plasma glucose and insulin levels were unchanged one hour after niacin injection, but there was a 33 percent decrease in the basal plasma free fatty acid levels as compared to values obtained before niacin ingestion.

Administration of a single 50 g oral dose of niacin to four healthy, mature, nonlactating cows caused significant decreases in serum free fatty acids and ketones up to ten hours after administration (Nurmio et al., 1974). By contrast, there was a marked rise (more than twofold) in serum ketone levels when four mature lactating cows were given six doses of 50 or 100 g each of niacin at 12-hour intervals. Peak ketone levels were reached on the third day of dosing and there was a large drop to below basal levels on the day after the last dose was administered. Serum free fatty acid levels also were elevated, rising to almost double basal levels on the second day of dosing and remaining elevated even on the day after the dosing was discontinued. Five cows succumbing to ketosis were given three doses of 50 g each of niacin administered at 12-hour intervals. Serum ketone levels decreased about 36 percent during the first two days of treatment; however, there was a sharp rise of more than twofold over the basal level on the third day.
The rate of radiolabeled CO$_2$ production by slices of guinea pig brain cortex was reduced by 11 percent in slices incubated with $^{14}$C glucose in the presence of 30 µg of niacin as compared to control slices incubated without added niacin (Joanny et al., 1973).

Dietmann and Stork (1976) found that a temporary bilirubinemia developed in male volunteers administered oral doses of niacin. Following a single dose of 420 mg of niacin (7 mg per kg) there were transient increases in total serum bilirubin and serum niacin in the subjects. The serum niacin increased from a preadministration level of almost 0 to a peak value of over 180 µg per 100 ml about one hour after administration, and declined to almost nothing in the following 24 hours. Serum bilirubin concentration rose sharply after niacin administration increasing to more than threefold the basal levels after 4 hours. The bilirubin levels returned to normal values within about 24 hours after niacin administration. This transient rise in bilirubin concentration did not occur after subjects were given niacin daily for one week.

B. PHARMACOLOGICAL STUDIES

Gershon and Fox (1974) studied the effects of niacin on human purine metabolism with respect to the hyperuricemia sometimes seen in patients treated with large doses of the compound. A total of seven men and three women was studied; five of these patients were diagnosed as having gout and five were control subjects. The subjects were placed on a purine-free diet three days prior to oral dosing with 1 g of niacin or niacinamide (16.7 mg per kg). All ten patients experienced flushing and a burning sensation within 30 minutes of administration of 1 g of niacin; these effects lasted up to two hours. The renal clearance of uric acid was reduced by a mean value of 62 percent in the patients during the first three to four hours after niacin administration. Niacinamide had only a small effect on the uric acid clearance. There was an 80 percent decrease in the erythrocyte level of phosphoribosylpyrophosphate one hour after niacin administration. The level then returned towards normal values in the next six hours. There was a gradual decrease to 33 percent below the normal erythrocyte level of phosphoribosylpyrophosphate in the first four hours following niacin administration. Since purine synthesis may be regulated by phosphoribosylpyrophosphate levels, Gershon and Fox (1974) speculated that niacin may affect both purine synthesis and excretion of purine catabolites.

Male rats given 250 mg per kg of niacin intragastrically daily for ten days, had 38 percent and 24 percent increases in blood and liver niacin concentrations respectively as compared to undosed control animals (Baker et al., 1973). Alcohol dehydrogenase activity of liver extracts from the niacin-dosed animals was 30 percent lower than found in extracts from control
animals and reductions in total fat and nonesterified fat were also seen in the livers of the niacin-treated animals.

Niacin at a concentration of 20 or 100 mg per liter in the perfusate had no effect on resting and action potentials of isolated preparations of calf ventricular trabeculae (Beresewicz and Wojtczak, 1976). In contrast, Paranjpe et al. (1975) reported that injection through a cannula into the sinus venosus of 1 mg of niacin resulted in a significant increase in heart rate and force of myocardial contraction in isolated frog heart preparations. In some instances there was an initial transient inhibition in heart rate and contraction force. The authors postulated that the observed effect was due to release of endogenous norepinephrine since guanethidine and propranolol abolished the niacin response. These authors also reported that doses of 100 μg to 4 mg per heart produced a dose-dependent inhibitory effect on isolated rabbit heart which was not abolished by atropine treatment. No explicit details of the inhibitory effect were given by Paranjpe et al. (1975) who also reported that niacin relaxed isolated rabbit ileum preparations.

Åberg (1973) proposed that the cutaneous flush observed in man and animals after nicotinic acid administration is due to release of a vasoactive compound, possibly a prostaglandin. He used the temperature of the guinea pig ear as an index of flush. The ear temperature was measured with a very sensitive infrared detector. Following their pre-treatment with sodium carboxymethylcellulose, control animals were given an oral dose of 10 mg per kg niacin. The experimental groups received the same dose of niacin but were pretreated with either indomethacin, acetylsalicylic acid or diphenylhydramine. The first two compounds, known inhibitors of prostaglandin synthetase, decreased the magnitude of the flushing response, while the third compound diphenylhydramine, an antihistamine, did not influence the response.

The inhibition of the free fatty acid mobilization by niacin in female dogs was studied in vivo in the general circulation and in isolated perfused adipose tissue (Fredholm, 1973). Groin adipose tissue was isolated from surrounding tissue and the artery and vein supplying the tissue were cannulated. Blood was directed into the adipose tissue via a plastic loop from the ipsilateral femoral artery. Venous blood flow from the isolated tissue was shunted back to the circulation via the ipsilateral femoral vein. The nerve supplying the tissue was cut and placed on a bipolar silver electrode. Intravenous infusion of 4 mg per kg niacin into dogs caused no change in mean arterial blood pressure; however, there was a decrease of 5-10 mm Hg in blood pressure when 40 mg per kg niacin was administered via the brachial vein.
Niacin administration did not cause significant changes in adipose tissue blood flow or the vasoconstrictor response to nerve stimulation. In the 10-50 minute period following niacin infusion at a dose of 4 mg per kg there was a 32 percent decrease in the arterial free fatty acid level and a 26 percent increase in arterial lactate concentration, while glycerol and glucose levels were essentially unchanged. In the period 60-110 minutes following the 4 mg per kg niacin infusion glycerol levels increased 127 percent over baseline values, while no significant change from pre-infusion levels was found in arterial levels of free fatty acids, glucose or lactate. The adipose tissue uptake or release of these substances was also determined. After 4 mg per kg niacin infusion the only significant changes were an increase in lactate release in the 10-50 minute period, and glycerol release in the 60-110 minute period following niacin infusion. When a tenfold higher niacin dose (40 mg per kg) was infused, there was a significant increase of 26 percent in the arterial level of lactate and significant decreases of 40 percent and 33 percent respectively in glycerol and free fatty acid levels in the 10-50 minute period following infusion. In the 60-110 minute period following 40 mg per kg niacin dosing there were no significant changes from baseline arterial levels in any of the five compounds. Adipose tissue release of lactate was significantly increased and glucose uptake significantly decreased at both time intervals, and the pre-infusion release by adipose tissue of free fatty acids was significantly reversed to a net uptake of free fatty acids in the 10-50 minute period following 40 mg per kg niacin infusion. Both dosage levels of niacin caused significant inhibition of the evolved release of free fatty acids and glycerol following nerve stimulation of the isolated adipose tissue.

C. CLINICAL STUDIES

Liver toxicity was reported in a 35-year-old man taking niacinamide orally for a psychiatric disorder (Winter and Boyer, 1973). The man had been taking 3 g of niacinamide (50 mg per kg) and 5 mg of fluphenazine enanthate and thiothixene hydrochloride daily for a psychiatric disorder for 18 months prior to his admission. He had been hospitalized for nausea and vomiting four times in the six months preceding his last admission. His prior admissions had shown elevated levels of serum-glutamate-pyruvate transaminase, serum glutamate-oxaloacetate transaminase and bilirubin. Liver biopsy revealed an increase in portal fibrosis and swollen centrilobular parenchymal cells with vacuolated cytoplasm. The patient admitted that he had increased his niacinamide dose to 9 g per day (150 mg per kg) for several days prior to each episode of nausea and vomiting. Challenge of the patient with increasing doses of niacinamide to 9 g daily caused a recurrence of the nausea and vomiting and an increase of serum
bilirubin, serum glutamate-pyruvate transaminase, serum glutamate-oxaloacetate transaminase and prolonged prothrombin times. After discontinuation of the niacinamide the patient's symptoms disappeared, and his liver function tests returned to normal.

Sugerman and Clark (1974) described the case of a 69-year-old man who developed cholestatic jaundice following treatment with 750 mg of niacin daily (12.5 mg per kg) for organic brain syndrome. The patient had received niacin for about three months when he developed jaundice; his total serum bilirubin was 8.3 mg per 100 ml. The normal value is less than 1.2 mg per 100 ml (Raphael et al., 1976). Niacin treatment was discontinued but his bilirubin level rose over the next ten days to 19.6 mg per 100 ml. Liver biopsy showed cholestatic hepatitis with minimal lymphocytic infiltration. The patient's serum bilirubin level declined over the next ten days to 9.2 mg per 100 ml; the jaundice then gradually disappeared over a period of several months.

Jaundice developed in a 22-year-old woman who had been treated for a psychological disturbance for two and one-half years with daily doses of 3 g niacin (50 mg per kg), 3 g vitamin C, 100 mg pyridoxine, 2400 I. U. vitamin E and a multivitamin tablet (Einstein et al., 1975). The patient developed malaiaise, pruritus, dark urine and light stools. Liver function tests were abnormal including elevated bilirubin, alkaline phosphatase, serum glutamate-pyruvate transaminase, and serum glutamate-oxaloacetate transaminase. Liver biopsy showed acute hepatitis with submassive necrosis, cholestasis and bile duct proliferation. Niacin medication was discontinued and cholestyramine therapy was instituted. The patient's liver function improved; she was released and became asymptomatic.

Gass (1973) reported on three middle age male patients who suffered loss of central vision while taking from 1.5 to 5 g of niacin daily (25.0-83.3 mg per kg) for hypercholesterolemia. The visual loss, due to the development of cystoid macular edema, disappeared or improved markedly in each case following cessation of niacin therapy.

Parsons (1975) has noted that niacin therapy may also result in reduction in skin oiliness with localized thickening and tanning of the skin.

The clinical use of niacin to lower serum cholesterol and triglyceride levels has been extensively studied (Coronary Drug Project, 1975; Eder, 1975) and the use of both niacin and niacinamide has been investigated for the treatment of schizophrenia (Anonymous, 1973). Levy et al. (1974) reviewed treatments for hyperlipidemia and suggested that niacin is primarily indicated in the treatment of hyperlipidemias characterized by high levels of very low density lipoproteins (VLDL). Doses begin at 100 mg taken
three times daily (5 mg per kg per day), and build up to doses as high as 3 g to 9 g per day (50-150 mg per kg per day). Initial side effects include cutaneous flushing and pruritus. About 85 percent of the patients experience tachyphlaxis to these effects in one or two weeks. Long-term side effects include abnormal liver function tests, abnormal glucose tolerance tests and hyperuricemia. These effects disappear upon discontinuance of niacin therapy. Additional, usually transient, side effects include nausea, vomiting and diarrhea.

Parsons (1975) reported on the decrease in mean serum cholesterol and triglyceride levels in a group of hyperlipemic patients who received 3 g of niacin daily for four months. At the end of this period patients exhibiting types II, IIIB or IV hyperlipidemia showed prompt and sustained reductions in serum triglycerides and cholesterol.

A five-year study involving 500 men, 30-64 years old, taking 3 g of niacin a day showed that the mean cholesterol level of these men was about 225 mg per 100 ml and the mean triglyceride level was 4.5 mEq per liter compared to values of about 250 mg per 100 ml cholesterol and 6 mEq per liter triglycerides in approximately 1500 men of the same age range taking placebo lactose tablets (Coronary Drug Project, 1975). All the men in the study had a previous history of at least one myocardial infarction prior to beginning the regimen. The placebo and niacin groups had nearly identical mortality rates over the course of the experiments. However, there was a higher incidence of gouty arthritis and a lower rate of definite non-fatal myocardial infarctions in the niacin group. The niacin group also showed increased levels of serum glutamic-oxaloacetate transaminase, creatinine phosphokinase, alkaline phosphatase, plasma glucose; lower levels of serum total bilirubin, plasma urea, plasma nitrogen; and reduced white blood cell and neutrophil count. There also appeared to be a higher incidence of men developing atrial fibrillation among the niacin group as well as increased incidence of dermal disorders.

Niacin and niacinamide have been advocated by some researchers for the treatment of schizophrenia, but a recent review concluded that these compounds showed no efficacy in the treatment of this disorder (Anonymous, 1973). For example, in a 90-day study involving 14 male schizophrenic men receiving increasing doses of niacin up to 3 g per day and 13 controls not receiving the substance, niacin was not efficacious; no toxic side effects were noted during treatment (Sehdev and Olson, 1974).
V. REFERENCES CITED


