EVALUATION OF THE HEALTH ASPECTS OF THE SODIUM SALT
OF AMINOTRIS(METHYLENEPHOSPHONIC) ACID AS IT MAY
MIGRATE TO FOOD FROM PACKAGING MATERIALS

1981

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

Contract No. FDA 223-78-2100
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
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NOTICE

This report, one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior-sanctioned food substances as food ingredients, is being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-78-2100 with the Food and Drug Administration (FDA), U.S. Department of Health and Human Services. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshaling 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 Dockets Management Branch, 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
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I. INTRODUCTION

This report concerns the health aspects of using the sodium salt of aminotris(methyleneephosphonic) acid as it may migrate to food from packaging materials. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (Rogers, 1978), which summarizes the world's scientific literature from 1920 through 1978. To ensure 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, an announcement was made in the Federal Register of April 21, 1981 (46 FR 22810-22814) 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 the sodium salt of aminotris(methyleneephosphonic) acid as it may migrate to food from packaging materials. The Select Committee received no request for a hearing.

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 (Office of the Federal Register, 1980) [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 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 reviewed and evaluated the available information on the sodium salt of aminotris(methyleneephosphonic) acid in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, relied primarily on the absence of substantive evidence of, or reasonable grounds
to suspect, a significant risk to the public health. While the Committee realized that a conclusion based on reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognized that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. This report is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act. The Committee anticipates that its conclusions will be reviewed as new information becomes available.
II. BACKGROUND INFORMATION

Salts of certain organic phosphonic acids are effective as corrosion or scale inhibitors in such industrial processes as oil well pumping, and as stabilizers of solutions of various peroxides used in bleaching cellulosic materials such as cotton, linen, jute, rayon, and paper. The sodium salt of aminotris(methylene-phosphonic) acid, also called penta-sodium aminotris(methylene phosphonate) or penta-sodium nitrilotris(methylene phosphonic) acid, is one compound used for these purposes (Slyker, 1969; Ralston, 1969, 1972; Irani, 1966).

![Sodium aminotris(methylene phosphonate)](image)

Sodium aminotris(methylene phosphonate)

In 1967, FDA approved the sodium salt of aminotris(methylene phosphonic) acid as a scale inhibitor in pulp digester systems used in manufacturing paper and paperboard intended for food-contact use (Orr, 1967). The compound effectively controls scales containing calcium, including those typically found in continuous digesters and pulp-washing systems. For example, it can be added at a feed rate of 0.7 lb/ton in pulp and papermill water systems to control deposits, including calcium and aluminum oxalates, silicates, and sulfates (Merck Chemical Division, undated). Use of aminotris(methylene phosphonate) at a rate of 25 ppm in a commercial continuous pulp digester prevented significant scale buildup after 4 wk of operation (Windhager, 1973).

The product, as used commercially, is apparently a 40% aqueous solution of penta-sodium aminotris(methylene phosphonate). In aqueous solution, the compound is stable to hydrolysis at all pH values and at temperatures as high as 150°C (Rogers, 1978).
Radioactively labeled penta-sodium aminotris(methylene-phosphonate) was added to the water system in a papermaking operation and handsheets were prepared. Even with a great excess of the compound (12-60 times the maximum recommended addition level in commercial papermaking practice), calculation of the concentration of the salt from presence of the radiolabel indicated that the handsheets contained a maximum of 33 ppm, indicating that the compound was not concentrated in the paper. The handsheets were extracted with water at 60°C for 72 h at which time equilibrium was achieved. From a sheet containing 33 ppm of the compound, which amounts to 0.00091 mg/in² (0.00014 mg/cm²), 30% or 0.0003 mg/in² was extracted*. Assuming that this amount would be extracted by food packaged in the paper, and that 100 in² of paper packages 1 kg of food, there would be 0.03 mg of penta-sodium aminotris(methylenephosphonate) per kg of food. If a person weighing 60 kg were to eat 1.5 kg of food/day, and if 10% of his diet were packaged in paper made with sodium aminotris(methylene-phosphonate), he might consume about 0.075 μg of the compound/kg body wt/d (Larsen, 1980a).

No information is available to the Select Committee concerning the quantity of food-contact paper that is made with sodium aminotris(methyleneephosphonate) as a processing aid.

* Considerably less would be expected to be extracted from papers made using the maximum recommended addition level in commercial papermaking practice.
IV. BIOLOGICAL STUDIES

Occurrence of amino phosphonic acids

The presence in nature of compounds having a carbon-phosphorus bond was first demonstrated by Horiguchi and Kandatsu (1959) when they isolated 2-aminoethylphosphonic acid

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CH}_2 & \quad \text{CH}_2 & \quad \text{P} \\
& \quad & \quad & \quad \text{OH} \\
\text{OH} & \quad & \quad & \quad & \quad \text{OH}
\end{align*}
\]

from the washed and dried, bacteria-free, ciliated protozoa of the sheep rumen. The same investigators (Kandatsu and Horiguchi, 1962) later surveyed other natural products and found little or none of that compound in yeast, fungi, or the animal and plant tissues they examined, but they observed large amounts, 13-15% of the total phosphorus, in the protozoan Tetrahymena pyriformis grown in culture. Kittredge et al. (1962) isolated free 2-aminoethylphosphonic acid, as well as the free glycerol ester of that acid, from the sea anemone, Anthopleura elegantissima. The presence of 2-aminoethylphosphonic acid in mammalian tissue was demonstrated by Shimizu et al. (1965) who isolated the compound from the neutral amino acid fraction of a trichloracetic acid extract of bovine brain.

The biochemistry of the aminophosphonates has been reviewed by Kittredge and Roberts (1969) and Geike (1971). The first of the aminophosphonates discovered was 2-aminoethylphosphonic acid. Although several aminoethylphosphonic acids [2-methylaminoethylphosphonic acid, 2-dimethylaminoethylphosphonic acid, 2-trimethylaminoethylphosphonic acid, and 2-amino-3-phosphonopropionic acid (phosphonoalanine)] have been found in nature, the corresponding methyl compounds have not been reported.

Little appears to be known concerning the catabolism of the phosphonates in mammals. However, Roberts et al. (1968) reported the transamination between phosphonoalanine and α-ketoglutarate in mouse liver homogenate.

Acute toxicity

The oral LD$_{50}$ for penta-sodium aminotris(methyleneephosphonate), administered as a 40% aqueous solution to male and female rats, was found to be 15.7-20.3 g/kg body wt (Younger Laboratories, 1962a). Survival time was several hours to 3 d with most deaths occurring in the first 24 h. Toxic manifestations included weakness, appetite loss, and severe diarrhea; necropsy showed renal, liver and pulmonary hyperemia. The salt in 40% aqueous solution was nontoxic when applied to the skin of female
rabbits in doses up to 15.8 g/kg; there was slight transitory
erthema but no indication of systemic toxicity. The salt caused
slight eye irritation in rabbits. Instillation of 0.1 ml of a 40% aqueous solution (40 mg) into the eye caused very slight transitory edema and a trace of corneal dullness. The oral LD$_{50}$ of the salt, administered as a 20% solution, was estimated by Wells Laboratories (1975) to be 6.8 g/kg in the rat.

Study of the acute toxicity of the free acid, aminotris-
(methyleneephosphonic) acid, also showed it to be relatively non-
oxic. The oral LD$_{50}$ of a 50% aqueous solution in rats was 6.8-8.4
g/kg; no sytemic toxicity was observed in rabbits after skin
application of 15.8 g/kg, and only mild local irritation was
produced by instillation of 0.1 ml of a 50% aqueous solution (50
mg) in the eyes of rabbits (Younger Laboratories, 1962b).

Other studies

The Select Committee knows of only two other reports of
studies of aminotris(methyleneephosphonic) acid or its sodium salt
These are based on a 90-d rat feeding study where no adverse
effects were observed, and 4-d toxicity studies in rainbow trout
and sunfish fingerlings in which the compound had a low order of
toxicity. These studies have yet to be validated (Larsen, 1980b,c),
and were not considered by the Select Committee in reaching the
conclusion of this report.

The Select Committee is not aware of studies of the car-
cinogenic, mutagenic, or teratogenic potential of sodium aminotris-
(methyleneephosphonate) or the corresponding free acid.
V. OPINION

The acute oral toxicities of sodium aminotris(methylene-phosphonate) and its free acid for rats are of very low order. Neither induces systemic toxicity after skin application at high doses. No data are available concerning the actual concentration of sodium aminotris(methyleneephosphonate) in commercially manufactured food packaging paper or the amount that would be extracted by the food contained in it under practical conditions.

However, experimental food packaging papers, made with a great excess of penta-sodium aminotris(methyleneephosphonate) as a scale inhibitor, did not concentrate the compound. The paper was subsequently extracted with water at 60°C to equilibrium. Even under these extreme conditions, the amount of the compound extracted was such that an adult consuming food wrapped in such paper would receive about 0.075 μg of sodium aminotris(methyleneephosphonate)/kg body wt/d.

Validated reports of feeding studies of sodium aminotris-(methyleneephosphonate) have not been found, nor have reports of studies of the compound's carcinogenic, mutagenic, or teratogenic potential.

In light of the foregoing, it is concluded that:

In view of the deficiency of relevant biological studies, the Select Committee has insufficient data upon which to base an evaluation of the sodium salt of aminotris(methyleneephosphonic) acid when it is used as a scale inhibitor in the manufacture of paper or paperboard intended for food contact.
VI. REFERENCES CITED


Younger Laboratories, Inc. 1962a. The oral LD50 of pentasodium aminotrimethyleneephosphonate for rats (Table 1); the minimum lethal dose of aminotrimethyleneephosphonate by skin absorption in rabbits (Table 2); skin irritation in rabbits after application of aminotrimethyleneephosphonate (Table 3); eye irritation in rabbits after application of aminotrimethyleneephosphonate (Table 4). Analysis Y-62-105. p.3-6. (Available with Rogers, 1978).
Younger Laboratories, Inc. 1962b. The oral LD<sub>50</sub> of aminotrimethylene phosphonic acid for rats (Table 1); the minimum lethal dose of aminotrimethylene phosphonic acid by skin absorption in rabbits (Table 2); skin irritation in rabbits after application of aminotrimethylene phosphonic acid (Table 3); eye irritation in rabbits after application of aminotrimethyl-phosphonic acid (Table 4). Analysis Y-62-104. p.3-6. (Available with Rogers, 1978).
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Report submitted by:

August 18, 1981

Date

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Select Committee on GRAS Substances