EVALUATION OF THE HEALTH ASPECTS
OF ETHOXYLATED SOYA FATTY ACID AMINES
AS FOOD PACKAGING INGREDIENTS

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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
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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 (SCOGS), 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
Life Sciences Research Office
FASEB
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**I. INTRODUCTION**

This report concerns the health aspects of using ethoxylated soya fatty acid amines as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (Dailey, 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 November 7, 1980 (45 FR 74059) 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 ethoxylated soya fatty acid amines as food packaging ingredients. The Select Committee received one request which was subsequently withdrawn.

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 ethoxylated soya fatty acid amines 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. This report is intended for the use of
FDA in determining the future status of these substances 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

Soya fatty acid amines substituted with ethylene oxide are considered GRAS as components of lubricants in forming metal cans used as food and beverage containers (Cassidy, 1961). The amines are prepared by hydrolyzing refined soybean oil to free fatty acids, distilling and converting the fatty acids to nitriles, and then distilling the nitriles and converting them to primary amines by catalytic hydrogenation (Sonntag, 1964; Markley, 1964; Link, 1979). Each mole of the primary amines is reacted with 2-30 moles of ethylene oxide to form tertiary amines having the structure:

\[(\text{OCH}_2\text{CH}_2)_n\text{-1OCH}_2\text{CH}_3\]

\[\text{R-N-}\]

\[(\text{OCH}_2\text{CH}_2)_m\text{-1OCH}_2\text{CH}_3\]

Assuming ethylene oxide to be distributed equally between the two available positions on the nitrogen atom, n and m may have values ranging from 1-15. R represents the carbon chains of the soya fatty acids, of which about 53% is linoleic, 25% oleic, 10% palmitic, 7% linolenic, 4% stearic, and the remainder C14, C20, and C22 fatty acids (SCOGS, 1976). Most of the unsaturation in the soya fatty acids is retained during the catalytic hydrogenation step; a distilled soya primary amine has an iodine value of 90 (Link, 1979), compared to 130 for soya oil (SCOGS, 1976).

Ethoxylated soya amines prepared by reaction with 2-5 moles of ethylene oxide/mole of primary amine are liquids; those prepared by reaction with 30 moles are solids (Link, 1979). Food Chemicals Codex (National Research Council, 1972) lists no specifications for food grade ethoxylated soya amines. The specifications of one manufacturer stipulate no less than 97.0% tertiary amine and no more than 0.1% moisture (Link, 1979).

Aqueous solutions of lubricant formulations (3-15% concentration) serve both as lubricants and coolants (Jacobs, 1979) in the manufacture of two-piece drawn and ironed beverage containers (Kaercher, 1972). The residual lubricant is removed by washing prior to applying a resin coating to the interior surface of the can (Kaercher, 1972). Steel cans undergo a three-stage washing operation: an alkaline wash at 160°F, a hot water rinse, and a final cold rinse with deionized water (Neal, 1979). Aluminum cans are subjected to a seven-stage washing operation: an acid-etching wash at pH 1.1-1.5, followed by six water washes. Failure to remove lubricant from the can results in poor adhesion of the resin coating which darkens during subsequent baking at about 425°F. Beverage manufacturers apply various tests, including taste panel evaluation, to ensure that no substance in the can coating affects the taste or other properties of the product.

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III. CONSUMER EXPOSURE DATA

A survey of five suppliers of can-forming lubricants disclosed that none used ethoxylated soya fatty acid amines as a component of their formulation (Senti, 1979). One supplier indicated that ethoxylated soya amine was being incorporated into one experimental formulation; however, no decision on marketing had been reached.

If ethoxylated soya fatty acid amines were to be used in can-forming lubricants, the amount migrating into food would probably be minute. Only negligible amounts would survive the seven-stage washing for aluminum cans, which comprise the bulk of the two-piece cans in industrial use. The migration of any remaining trace would be further limited by the follow-on resin coating. The removal of the lubricants necessitated by the manufacturing process ensures the effectiveness of the washing process. Cassidy (1961) estimated that the concentration of ethoxylated soya fatty acid amine in food resulting from migration of residual lubricant would be less than 0.05 ppm.
IV. BIOLOGICAL STUDIES

No chronic toxicity studies on ethoxylated soya fatty acid amines have come to the attention of the Select Committee. Such studies have been reported, however, for ethoxylated tallow fatty acid amines. The fatty acid composition of the tallow adducts should be similar to that of the soya adducts and would be expected to have similar biological properties. Acute toxicity studies have been conducted with both types of adducts; their LD$_{50}$ values are similar in magnitude.

Table 1. Acute Toxicities of Ethoxylated Fatty Acid Amines in Rats

<table>
<thead>
<tr>
<th>Fatty acid source</th>
<th>Moles ethylene oxide/mole fatty amine</th>
<th>LD$_{50}$ g/kg</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soya oil</td>
<td>2</td>
<td>1.5</td>
<td>Evans et al., 1950</td>
</tr>
<tr>
<td>Soya oil</td>
<td>5</td>
<td>1.0</td>
<td>&quot;</td>
</tr>
<tr>
<td>Tallow</td>
<td>2</td>
<td>1.1</td>
<td>Doyle &amp; Majors, 1973</td>
</tr>
<tr>
<td>Tallow</td>
<td>5</td>
<td>0.5-0.6</td>
<td>Evans et al., 1950</td>
</tr>
<tr>
<td>Tallow</td>
<td>50</td>
<td>&gt;2</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

In their acute toxicity studies, Evans et al. (1950) administered aqueous solutions or suspensions of the compounds to rats by stomach tube, using 10 rats at each of two dosage levels. Duration of the observation period was 5 d. Doyle and Majors (1973) administered aqueous suspensions of tallow adduct by stomach tube to groups of 5 rats (200-230 g body weight) at dosage levels of 0.10-2.15 g/kg body weight. Normal behavior and appearance were exhibited by all rats receiving the 0.100 and 0.215 g/kg dosages over the 14 d observation period. Gross necropsy findings in rats which died after receiving 1.0 or 2.15 g/kg generally included congested lungs, kidneys and adrenals, peritoneal wall inflammation, and diffuse inflamed areas of the gastrointestinal tract filled with fluid resembling the test compound.

An ethoxylated tallow fatty amine (2 moles ethylene oxide/mole fatty amine) was fed for 90 d to young adult, specific pathogen-free, Wistar rats (Goater et al., 1965a). Groups of 25 males and 25 females were fed dietary levels of 170, 500, or 1500 ppm; corresponding intake levels were 10, 30, or 80 mg/kg body weight. A group of 10 animals of each sex was fed 4500 ppm (about 120 mg/kg intake) in their diet. The palatability of the diet was apparently affected by the addition of the test compound, especially
at levels of 1500 and 4500 ppm, and average daily feed consumption was reduced from 19.5 g in the controls to 14.1 and 6.3 g, respectively, in the two groups treated at the highest levels. No weight gain occurred in animals receiving 120 mg/kg from their diet; gains were reduced 11 and 45% at intake levels of 30 and 80 mg/kg, respectively, compared with the control group. Apart from failure to gain weight normally, the general condition of the rats was unaffected at 80 mg/kg and lower intake levels. Gross pathological changes confined to the gastrointestinal tract were noted only at the 120 mg/kg level. The stomach and bowel content of all rats at this intake was yellow and the mucosa of the small intestine was thickened and yellow. Engorgement of the villi and lamina propria of the small intestine with swollen foamy macrophages and occasional macrophages in the regional mesenteric nodes were found at intake levels of 80 and 120 mg/kg, but not at levels of 30 mg/kg or less. The macrophages were sudanophilic and were presumed to contain deposits of the test compound.

Ethoxylated tallow fatty acid amine (2 moles ethylene oxide/mole fatty amine) also was fed for 90 d to beagles, eight animals/group, at intake levels of 0, 13, 40, or 120 mg/kg body weight (Goater et al., 1965b). No significant abnormal effects were observed at the 13 mg/kg level in the following parameters: food consumption, body weight gain, hematology, blood urea, serum alkaline phosphatase activity, liver function tests, urinalysis, and gross and microscopic pathology. Sporadic vomiting and anorexia occurred among animals given 40 mg/kg body weight of the test compound. Frequent vomiting and body weight loss led to dis-continuance of the experiment with the group fed 120 mg/kg after 5 to 6 weeks. Animals fed 40 mg/kg or more showed decreased weight gains, gastric inflammation, and increased numbers of foamy macrophages in the villi of their small intestines and regional lymph nodes.

No reports of mutagenicity, teratogenicity, reproduction, or long-term feeding studies with ethoxylated soya fatty acid amines were available to the Select Committee.
V. OPINION

Ethoxylated soya fatty acid amines were considered in 1961 to be GRAS for use as components of can-forming lubricants. Available information indicates that these compounds are not presently in use, although there are indications that they may be used in the future. If used commercially, the multiple washings and subsequent resin coating and baking required in the production process should remove all but minute traces of the compound from the food contact surface of the can. It has been estimated that a concentration less than 0.05 ppm in a food might result from migration of residual lubricant.

Should ethoxylated soya fatty acid amines be used commercially in the future, it is suggested that specifications for food grade material be established.

Although no chronic toxicity studies have been reported with ethoxylated soya fatty acid amines, such studies have been conducted with ethoxylated tallow fatty acid amines, whose biological properties would be expected to be similar to those of the soya adduct. Acute oral LD$_{50}$'s in rats for the soya and tallow fatty adducts were similar and ranged from 0.5 to over 2 g/kg, depending on the extent of ethoxylation. Ninety-day feeding tests with the tallow adduct showed no deleterious effects in rats fed a diet providing 10 mg/kg body weight, and in dogs consuming 13 mg/kg body weight. Should ethoxylated soya fatty acid amines be used as can-forming lubricants in the future, consideration should be given to completing analogous chronic exposure studies.

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

There is no evidence in the available information on ethoxylated soya fatty acid amines that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public should they be used as components of can-forming lubricants.
VI. REFERENCES CITED


Neal, R.A. 1979. The Ironsides Company, Columbus, OH. Memorandum, dated November 15, of telephone conversation, with F.R. Senti, Federation of American Societies for Experimental Biology, Bethesda, MD.


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April 29, 1981

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