EVALUATION OF THE HEALTH ASPECTS OF PROPYLENE GLYCOL AND PROPYLENE GLYCOL MONOSTEARATE AS FOOD INGREDIENTS

DECEMBER, 1973

Prepared for

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

THIS DOCUMENT HAS NOT BEEN APPROVED FOR PUBLIC RELEASE

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

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

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of 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. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

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

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using propylene glycol and propylene glycol monostearate as food ingredients, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents, including current literature citations obtained through Toxline* and Medline*, available as of December, 1973. Propylene glycol and propylene glycol monostearate are food substances that have been generally recognized as safe (GRAS) under the provisions of Sections 121.101, 121.1099, and 121.1113 of the Code of Federal Regulations (21 CFR, revised April 1, 1973).

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the requirement of premarketing clearance for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. It is recognized further (21 CFR 121.3) 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 evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accord with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health, and realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee's conclusions, based as they are on the information now available, cannot anticipate and be guided by experiments.

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*Nationwide online bibliographic retrieval systems initiated by the National Library of Medicine, Bethesda, Maryland.
not yet done or by the results of tests that may be reconducted, using new technologies that are continually being evolved. These conclusions will need to be reviewed as new or better information becomes available.

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

II. BACKGROUND INFORMATION

Propylene glycol, or 1,2-propanediol (CH₃CH(OH)CH₂OH), is prepared commercially from propylene or glycerol. It is a colorless, viscous, and hygroscopic liquid which is miscible with water and many organic solvents (1,2). The Food Chemicals Codex specifies that the food grade products must contain not less than 97.5 percent propylene glycol, and must not contain more than 3 ppm of arsenic, 10 ppm of heavy metals (as lead), 0.07 percent ash, and 0.2 percent moisture (3).

Propylene glycol monostearate, also used in food, is not a single chemical entity but is a mixture of propylene glycol mono- and di-esters of stearic and palmitic acids, produced commercially by catalytic transesterification between propylene glycol and a hydrogenated vegetable oil such as soybean oil (1,3). The food grade product consists of white beads or flakes that are water insoluble, but are soluble in organic solvents and conform to the following specifications: total mono-ester content, not less than the minimum percent claimed by the vendor; hydroxyl, iodine, and saponification values, not greater than the values stated or within the range claimed by the vendor; free propylene glycol, soap (as potassium stearate), arsenic, and heavy metals (as lead), not more than 1.5, 7, 0.0003, and 0.001 percent, respectively (3).

Propylene glycol is listed as Generally Recognized as Safe (GRAS) in the Code of Federal Regulations [21 CFR 121.101(d)(3), 121.101(d)(8), and 121.101(h)]. Propylene glycol monostearate is not included as GRAS but 21 CFR 121.1113 indicates that "propylene glycol mono- and di-esters of fats and fatty acids may be safely used in food, subject to the following prescribed conditions: (a) they are produced from edible fats and/or fatty acids in compliance with 21 CFR 121.1070 and/or oleic acid derived from tall oil fatty acids in compliance with 21 CFR 121.1237; (b) they are used in food in amounts not in excess of that reasonably required to produce their intended effect" (4).
Use of propylene glycol, in amounts sufficient for the purpose, is permitted by the U.S. Department of Agriculture to serve as a cooling and retort water treatment agent in the preparation of meat products. Propylene glycol mono- and di-esters of fats and fatty acids are permitted to be used, in amounts sufficient for the purpose, as emulsifying agents in rendered animal fat or in combinations of such fat with vegetable fat (5).

Because of its solubility in aqueous and nonaqueous media and its hygroscopicity, propylene glycol is used in food as an emulsifying and plasticizing agent, surfactant, humectant, and solvent for flavoring compounds (2). Because of its surfactant properties, propylene glycol monostearate is used to improve texture, softness, and keeping quality in several foods (2, 4). Percentage use of the two compounds, by food categories, is shown in Table I.

Propylene glycol was first used in food in the United States in 1920 and propylene glycol monostearate was first used in 1958. The total amount of propylene glycol used in foods annually has remained relatively constant in recent years, whereas the total annual use of the monostearate increased about threefold between 1960 and 1970 (6). The Select Committee has no information to indicate whether the content of either compound in the food categories indicated in Table I has changed in recent years.

III. CONSUMER EXPOSURE DATA

A National Research Council subcommittee (6) has supplied the following information on the possible daily human intake of propylene glycol and propylene glycol monostearate in the total diet, by individuals in various age groups. The Select Committee has converted these figures to possible intakes per kilogram of body weight.
<table>
<thead>
<tr>
<th>Food category</th>
<th>Propylene glycol</th>
<th>Propylene glycol monostearate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual Use</td>
<td>Maximum use</td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td>percent</td>
<td>percent</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>5.073</td>
<td>5.086</td>
</tr>
<tr>
<td>Processed vegetables, juice</td>
<td>---</td>
<td>0.500</td>
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<tr>
<td>Sweet sauce, toppings, syrups</td>
<td>0.310</td>
<td>0.421</td>
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<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.138</td>
<td>0.213</td>
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<tr>
<td>Soft candy</td>
<td>0.089</td>
<td>0.144</td>
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<tr>
<td>Baked goods, baking mixes</td>
<td>0.079</td>
<td>0.244</td>
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<tr>
<td>Hard candy</td>
<td>0.072</td>
<td>0.135</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>0.068</td>
<td>0.300</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>0.066</td>
<td>0.588</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.049</td>
<td>0.098</td>
</tr>
<tr>
<td>Processed fruit, juices, drinks</td>
<td>0.049</td>
<td>0.082</td>
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<tr>
<td>Non-alcoholic beverages</td>
<td>0.038</td>
<td>0.124</td>
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<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.036</td>
<td>0.068</td>
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<td>Meat products</td>
<td>0.023</td>
<td>0.053</td>
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<tr>
<td>Milk, milk products</td>
<td>0.023</td>
<td>0.038</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>0.014</td>
<td>0.032</td>
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<tr>
<td>Cheese</td>
<td>0.007</td>
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<td>Reconstituted vegetable proteins</td>
<td>0.006</td>
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<td>Snack foods</td>
<td>0.002</td>
<td>0.092</td>
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<td>Poultry products</td>
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<td>0.010</td>
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<tr>
<td>Other grain products</td>
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<td>0.001</td>
</tr>
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<td>Eggs, egg products</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dairy product analogs</td>
<td>---</td>
<td>---</td>
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</table>

- 4 -
<table>
<thead>
<tr>
<th>Age group</th>
<th>Total</th>
<th>Per kg of body weight&lt;sup&gt;1&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Glycol Ester</td>
<td>Glycol Ester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>11</td>
<td>81</td>
<td>30</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>102</td>
<td>511</td>
<td>333</td>
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<tr>
<td>12-23 mos.</td>
<td>183</td>
<td>1029</td>
<td>594</td>
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<tr>
<td>2-65+ yrs.</td>
<td>349</td>
<td>2596</td>
<td>1380</td>
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</tbody>
</table>

<sup>1</sup>Calculations based on an average weight of 60 kg for an adult (7) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; 12-23 mos., 11 kg (8).

The possible average daily intake of propylene glycol per kg of body weight, calculated as the sum of propylene glycol itself and that which could be produced on hydrolysis of the monostearate, can be estimated for the four age groups from the figures in Table II as about 5, 24, 33, and 13 mg, respectively. The maximum intake, estimated similarly, could be about 9, 70, 84, and 36 mg, respectively.

It is recognized that in the age group 2-65+ years, the figures for daily intake per kilogram of body weight would be low for some, since children from age two to maturity will obviously weigh less than 60 kg.

However, such deviations from the figures in Table II must also be considered in respect to the total production and use of propylene glycol and its fatty acid esters. The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins*<sup>1</sup>. That intakes of propylene glycol and its monostearate are overstated is supported by the following calculations:

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (6). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
The NRC subcommittee has provided data (6) which show that the use of propylene glycol for food purposes in the United States was 5,703,895 pounds (2,592,680 kg) in 1970. This figure is reported to comprise between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (4,321,133 kg) and a U.S. population of 210 million, the per capita per day average intake would be 56 mg instead of the 349 mg indicated in Table II. Contrasting with these figures, data from other sources (9,10) indicate that only 428,181 pounds (194,628 kg) of propylene glycol were produced in the United States and only 1,031,111 pounds (468,687 kg) of propylene glycol and butylene glycol combined were imported in 1970.

Data from the NRC subcommittee (6) also indicate that the use of propylene glycol monostearate for food purposes in the United States was 7,056,922 pounds (3,207,692 kg) in 1970. This figure is reported to comprise between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (5,346,153 kg) and a U.S. population of 210 million, the per capita per day average intake would be 70 mg instead of the 2596 mg indicated in Table II.

Another source (9) indicates that 3,788,000 pounds (1,721,818 kg) of 1,2 propanediol monostearate were produced in the U.S. in 1970. The Bureau of the Census (10) indicates that the total imports of fatty acid ethers and esters from polyhydric alcohols were 1,034,558 pounds (470,254 kg) in 1970. If one assumes that all of the reported domestically produced and imported esters were propylene glycol monostearate and that all (2,192,072 kg) were used in food, the per capita per day average intake would be 29 mg instead of the 2596 mg indicated in Table II.

On the basis of these considerations, the Select Committee recognizes that there are obvious major discrepancies among the sources available to the Committee with respect to the amounts of these substances that are available for use in food in the United States. However, since the available import and domestic production figures indicate a substantially lower supply annually than that estimated in the NRC subcommittee report, the Select Committee regards the figures in Table II as levels that are highly unlikely to be achieved by any of the age groups, but more likely are considerably overstated estimates of the propylene glycol and propylene glycol monostearate content of the daily diet.

The Joint FAO/WHO Expert Committee on Food Additives indicates the acceptable daily intake for man of propylene glycol, as such or in the form of its fatty acid esters, as up to 125 mg per kg body weight
calculated as propylene glycol (11). This figure exceeds the liberal estimates for daily intake of propylene glycol indicated in Table II and elsewhere in this section of this report.

IV. BIOLOGICAL STUDIES

Propylene glycol has been reported to be readily absorbed from the gastrointestinal tract (12, 13). Propylene glycol esters are readily hydrolyzed and the fatty acid moities enter well recognized metabolic pathways. Independent studies have indicated that absorption of propylene glycol was rapid and complete and that formation of glycogen was promoted (14, 15). After administration of radioactive propylene glycol, substantial amounts were excreted as $^{14}$CO₂ during the first 24 hours. These findings indicated that in vivo propylene glycol enters the carbohydrate cycle as is also suggested by examining its in vitro metabolism in rat liver slices. Most authorities agree that propylene glycol can be utilized as an energy source (16).

After absorption, propylene glycol disappeared rapidly from the blood of fasted animals (17, 18). Because propylene glycol enters normal carbohydrate metabolic pathways and promotes glycogen formation, its rapid disappearance from the blood in fasted animals is not surprising. However, it is unclear as to how rapidly propylene glycol would disappear from the blood of well-fed animals in which there is only limited glycogen formation.

Although most orally-administered propylene glycol is metabolized, an appreciable fraction is excreted unchanged in the urine. In one human study, 20 to 25 percent of a 70 g dose (approximately 1 g per kg) was excreted within 10 hours; in experiments with dogs, 20 percent of a 150 g dose was excreted within 24 hours (19).

The available information indicates that propylene glycol and its fatty acid esters have a very low order of acute toxicity in a variety of animals. In all animal species tested, the acute LD₅₀ of propylene glycol amounts to several grams per kg of body weight (20, 21, 22). In mice, estimates ranged from 8.0 g per kg intravenously to 31.8 g per kg orally. Intraperitoneal administration generally yielded values equivalent to those obtained intravenously. In other species, the LD₅₀ values were essentially within the same limits, the lowest intravenous LD₅₀ values reported being 6.5 g per kg for rabbits and 6.8 g per kg for rats.
In short-term chick feeding studies, a diet containing up to 10 percent propylene glycol was generally well tolerated (23). Mortality was apparently not affected by even the highest doses of propylene glycol in the food. However, diets of 5 percent or more appeared to have some adverse effects on chicks; some investigators reported growth retardation (23), while others reported hock and toe deformities, diarrhea, or changes in the ratio of protein and fat in the carcass (24). In rats, the levels of propylene glycol needed to elicit undesirable responses in feeding studies appeared to be about 30 percent (25). Dogs tolerated the equivalent of 8 percent in the diet, or 10 percent in drinking water, without any noteworthy evidence of toxicity (26,27).

A long-term study on rats, extending over two years, showed that up to 50,000 ppm (2500 mg per kg per day) of propylene glycol in the diet failed to produce an increased or accelerated lethality (28). Propylene glycol, when administered to rats in high doses (up to 7.5 percent of the diet) for 20 weeks, did not produce tissue damage. However, rats fed 20 percent or more exhibited hepatic and renal pathology (25).

In reproduction studies, 30 percent propylene glycol was found to decrease reproduction in the third generation and the mothers were unable to feed the young satisfactorily. However, when rats were fed 7.5 percent propylene glycol, no deleterious effect on reproduction was observed through three generations (25). In chicks fed diets containing 5 percent or more propylene glycol, a deformity of the toe (outward curling of the toes at each joint) was reported and the incidence of the defect seemed to be dose-dependent (29,30). These investigators observed that similar deformities occur in chicks fed diets high in lactose, and suggested that some common metabolite of lactose and propylene glycol may be responsible for this condition.

Reports of studies specifically designed to detect carcinogenesis or mutagenesis have not been found. However, in a two-year study on dogs maintained on diets containing up to 8 percent propylene glycol (about 2 g per kg per day), the investigators observed no evidence of induction of carcinoenic changes (26). Further, no carcinogenic potential was revealed in a two-year study in which rats were fed up to 2500 mg per kg per day (28).

A recently conducted evaluation has shown that propylene glycol is not teratogenic and has no adverse effect on maternal or fetal survival in mice, rats, hamsters, and rabbits at oral dosage levels of 1600, 1600, 1550, and 1230 mg per kg of body weight, respectively (31). In the chick embryo, 0.05 ml of propylene glycol was not teratogenic, but when 0.2 ml was introduced into the yolk on the fourth day of incubation, a
large liquid-containing cyst was observed on the dorsal side of many embryos (32).

There are reports that indicate propylene glycol, at extremely high doses, causes kidney damage. Degeneration of the tubular epithelium, interstitial hemorrhage, and glomerular nephritis were found in rats fed 20 percent or more of propylene glycol (25). Karel et al. (33) found that some of a series of several glycols tested by intraperitoneal injection of LD₅₀ doses in mice, produced glomerular and tubular kidney damage; however, propylene glycol was among the least harmful in this respect. In rabbits, evidence of some hemolytic action of propylene glycol administered at a dose of 5 ml intravenously, was visible in the kidneys in the form of hemoglobin-containing casts (34). In mice, rats, and guinea pigs administered lethal or near lethal doses of propylene glycol by stomach tube, nuclear pyknosis and vacuolar degeneration of the cytoplasm in kidney tubule epithelial cells, as well as protein debris and casts in the lumina of the tubules, have been observed (35). Hematuria was observed following intravenous administration of sublethal (6 g per kg intravenously) doses of propylene glycol to rats (22). There is a consensus among these investigators that propylene glycol at lethal or near lethal doses can cause some kidney damage. It is also clear that in this regard, propylene glycol is the least toxic of the glycols tested.

On the other hand, Morris et al. (36) and Seidenfeld and Hanzlik (37) found no evidence of chronic kidney damage resulting from feeding propylene glycol to rats at levels as high as 4.9 percent for one year or at 13.3 g per kg per day for 140 days. A functional study, done by Van Winkle and Newman in 1941 (27), showed that when kidney function was evaluated in dogs by measuring phenolsulfonphthalein excretion over a 2-hour period in dogs that had been given drinking water containing 5 to 10 percent propylene glycol for 5 to 9 months, no abnormal changes were observed. Gaunt et al. (28) and Weil et al. (26), in more recent studies, also failed to detect any indication of impaired kidney function in rats and dogs fed 2 to 20 g propylene glycol per kg per day for 2 years.

While propylene glycol, fed in extremely high amounts can produce kidney damage, the available evidence does not implicate it as a nephrotoxic agent even when it is fed at levels manyfold greater than those existing in man's daily diet. It is noteworthy in this regard that the reported studies indicating the very rapid absorption and metabolism of propylene glycol have been made in fasted animals, where absorption and metabolism are likely to be favored and blood concentration is likely to be low. No reports have been found that consider blood levels of propylene glycol under conditions where glycogenesis is not favored. Since the possibility exists that higher than the reported concentrations
of propylene glycol in the blood could occur in well-fed animals to which the substance is fed in large amounts, and since there is evidence that very large doses can cause some kidney damage, it may be advisable in due course, to reexamine the absorption, excretion, and metabolism of propylene glycol taking into account the nutritional state of the experimental animals.

V. OPINION

Propylene glycol is metabolized by animals and can be used as a carbohydrate source. Propylene glycol can be ingested over long periods of time and in substantial quantities (up to 5 percent of the total food intake) without causing frank toxic effects. Propylene glycol monostearate is readily hydrolysed in vivo and the propylene glycol and fatty acid moieties enter their respective metabolic pathways. At lethal or near lethal doses (6 g per kg or more), however, it has been reported to cause kidney damage in several species and toe deformities in chicks. These doses contrast with the few mg per kg per day estimated in Section III of this report to be the human daily dietary intake of propylene glycol.

The Select Committee has weighed the available information and concludes that:

There is no evidence in the available information on propylene glycol and propylene glycol monostearate that demonstrates, or suggests reason to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in future.
VI. REFERENCES CITED


32. Gebhardt, D.O.E. 1968. The teratogenic action of propylene glycol (propanediol-1,2) and propanediol-1,3 in the chick embryo. Teratology 1:153-162.


VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

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Report submitted by:

January 17, 1974
Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances