Health Implications Of Non-NTA Detergent Builders: Report to the Great Lakes Science Advisory Board of the International Joint Commission

Task Force on the Health Effects of Non-NTA Detergent Builders

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INTERNATIONAL JOINT COMMISSION

HEALTH IMPLICATIONS OF NON-NTA DETERGENT BUILDERS
REPORT TO THE

GREAT LAKES SCIENCE ADVISORY BOARD

OF THE
INTERNATIONAL JOINT COMMISSION

ON THE
HEALTH IMPLICATIONS
OF NON-NTA DETERGENT BUILDERS

FROM THE
TASK FORCE ON
THE HEALTH EFFECTS
OF NON-NTA DETERGENT BUILDERS

OCTOBER 1980
WINDSOR, ONTARIO

REVISED, MARCH 1981
NOTICE

Statements and views presented in this report are those of the Task Force members and do not necessarily reflect the views and policies of the International Joint Commission or the Great Lakes Science Advisory Board.
Great Lakes Science Advisory Board
International Joint Commission
Canada and the United States

Members of the Board:

The Task Force on the Health Effects of Non-NTA Detergent Builders as a requirement of its Terms of Reference, submits the following report on its findings prepared by the members.

Respectfully submitted,

J.H. Day (Chairman)

L. Fishbein

A.S. Kraus

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S.I. Shibko (Adjunct Member)

The Task Force wishes to acknowledge the invaluable contributions of resource persons Drs. Raymond Shapiro and Robert Tardiff to discussions relating to the human safety of Type A Zeolite.
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The International Joint Commission Great Lakes Science Advisory Board's Task Force on the Health Effects of Non-NTA Detergent Builders presents its final report. The following builders were studied and Chapters contributed by individual members of the Task Force, viz:

- Carbonates;
- Carboxymethyloxsuccinate (CMOS);
- Carboxymethyltartronate (Builder "M");
- Citrates;
- Phosphates;
- Soluble Silicates; and
- Aluminosilicates (Type A Sodium Zeolite).
ACKNOWLEDGEMENTS

The Task Force is indebted to those co-operating Soap and Detergent Association Member Industries of Canada and the United States for their invaluable assistance in providing reference material on the detergent builders studied. We appreciate also the contribution made by Miss April Welsh, Special Assistant to Dr. Day, Kingston General Hospital, for her review of the draft Task Force report and of the bibliography cited.

Special thanks are due to Dr. Irving J. Selikoff and his staff at the Mount Sinai School of Medicine, New York City, for having generously hosted two meetings for the Task Force on fibrous minerals.

Finally, we express our appreciation to the staff of the Great Lakes Regional Office, Windsor, of the International Joint Commission for their assistance in preparing this report.
SUMMARY

Introduction

Under the 1972 Great Lakes Water Quality Agreement between Canada and the United States, measures were taken to reduce the input of phosphorus to the lakes from municipal sewage; phosphate containing household detergents having been determined as major contributors. The consequent restrictions in the use of phosphate in detergents have led to an increase in the use of alternative detergent builders.

Three task forces were established by the Science Advisory Board (formerly the Research Advisory Board) to review the health effects of these materials resulting from man's exposure to the aquatic environment and to review the ecological safety of alternative builders in current or projected use, viz:

- Task Force on the Health Implications of NTA (nitrilotriacetic acid), final report published, May, 1977;
- Task Force on the Ecological Effects of Non-Phosphate Detergent Builders, a report on NTA, December, 1978, studies of other builders are still underway; and

Builders Studied

The latter task force studied the following builders:

1. Carbonates
2. Carboxymethyloxysuccinate (CMOS - Lever Brothers)
3. Carboxymethyltartronate (formerly Builder "M" - Monsanto Co.)
4. Citrates
5. Phosphates
6. Soluble Silicates
7. Type A Zeolite (a synthetic aluminosilicate)
The task force was aided in its quest by information provided under the auspices of the Canadian and U.S. Soap and Detergent Associations, respectively. Conclusions were based on present knowledge using current state-of-the-art techniques in toxicological assessment.

Results and Conclusions

A summary is provided below of the findings of the Task Force on the Health Effects of Non-NTA Detergent Builders as listed above.

1. **Carbonates.** The range of available toxicity studies in experimental animals is limited. No mutagenic or teratogenic effects have been reported. Carbonates occur naturally in water. They have a long history of use as food additives and as such are classified as Generally Recognized as Safe (GRAS). Carbonates have also been used at high levels for the treatment of peptic ulcers. It is concluded that the use of carbonates as detergent builders poses no human health hazard through their contribution of carbonate to drinking water.

2. **Carboxymethyloxysuccinate — CMOS (Lever Brothers).** The toxicological studies reported by Lever Brothers indicate that CMOS is essentially non-toxic and produces no demonstrable effects of carcinogenicity, mutagenicity or teratogenicity. It was concluded that, based on the Lever Brothers report, CMOS poses no health hazard to man from chronic ingestion from drinking water.

3. **Carboxymethyltartronate CMT — Formerly Builder "M" (Monsanto Co.).** This material is not presently commercially available but may still be a candidate builder. Toxicological studies have been reported by the Monsanto Company.

The task force concluded that, from its chemical structure and properties and the reported results of acute and subchronic toxicity tests, CMT would not be expected to pose an undue health hazard to man. The types of tests
performed on CMT have been appropriate for safety evaluation but the lack of primary data in most areas, including chronic toxicity data and reproductive studies in addition to the unknown genetic risk to man, precludes full assessment of the potential health affects of this substance following prolonged exposure by man to the chemical in drinking water.

4. Citrates. Citric acid and its potassium, sodium and calcium salts are GRAS substances, occurring both naturally and as additives in many foods and are also normal human metabolites of carbohydrates. Acute, subchronic and chronic toxicity tests of citrates show no oral or dermal effects or eye irritation. No mutagenic or teratogenic effects have been reported nor is potential carcinogenicity suspected of citrates.

In acknowledgment of the findings of these studies and of the World Health Organization's endorsement of an "unlimited" acceptable daily intake of citrates, the task force concludes that there is no evidence that ingestion of citrates in drinking water would pose a health hazard to humans.

5. Phosphates. Phosphates are ubiquitous in nature and widely used in industry. They are GRAS substances with allowable daily intakes of 800mg of phosphorus per day. Estimates of phosphorus intakes in food range from 300 to 1500mg per day. Worst-case estimates of phosphorus intakes in drinking water, assuming extensive use of phosphate in detergents, suggests intakes of less than 0.01 mg of phosphorus per day. In view of this trivial intake, and because animal studies show that very large quantities by various routes of application show no toxicity, mutagenicity, teratogenicity or carcinogenicity, it is concluded that phosphates used as detergent builders should produce no adverse health effects through their contribution to phosphorus in drinking water.

6. Soluble Silicates. Soluble silicates find a wide diversity of uses, including the food and medicinal industries. Sodium silicate is used as a
detergent builder. In the body, sodium silicate is metabolized to and excreted as silicic acid, which is relatively abundant in nature and a normal constituent of human urine.

Acute, subchronic and chronic toxicity tests indicate that sodium silicate is essentially non-toxic. No mutagenic effects were observed and no data are available on either teratogenic or carcinogenic effects.

The Select Committee of the Federation of American Societies for Experimental Biology (FASEB) concluded in a 1979 study that sodium silicates and certain other silicates used as food ingredients do not present a public health hazard under current usage. This conclusion supported the results of an earlier (1974) FAO/WHO toxicological evaluation of silica and certain silicates used as food additives, which established no limit for the acceptable daily intake of the silicates studied except for magnesium silicate and talc. The task force concurs with these conclusions in regard to the human health safety of soluble silicates used as detergent builders and their potential contribution of silicon to drinking water.

7. **Type A Zeolite (a synthetic aluminosilicate).** Aluminosilicates are widely utilized in the food industry and in treating drinking water, not posing a human health hazard under current conditions of use. Cubic Type A Zeolite, with a Na:Si:Al ratio of 1:1:1 is thermodynamically less stable than food grade aluminosilicate, with its corresponding ratio of 1:1:13, rapidly forming soluble aluminates and silicates in aqueous suspensions at a pH <8; hence rarely being found in the environment.

Type A Zeolite is essentially non-toxic in chronic toxicity tests on animals, the behaviour being representative of the silicates formed on hydrolysis rather than that of the aluminates. No carcinogenic or teratogenic effects result from Type A Zeolite exposure and it is unlikely to produce mutagenic behaviour.
Considering the normal exposure of man to natural silicon compounds without evident health hazards and the miniscule increase in silicon levels in drinking water resulting from the proposed use of Type A Zeolite in detergents, the task force concludes that use of this zeolite in detergents is not anticipated to lead to adverse human health effects.
1. INTRODUCTION

During the last two decades it has become clear that phosphorus is one of the principal nutrients contributing to the process of eutrophication observed in many inland waters, including The Great Lakes. While phosphorus loadings to the lakes have many origins, the contribution through domestic wastewater was identified as one of the principal sources. In recognition of this, the 1972 Great Lakes Water Quality Agreement between Canada and the United States called for the development and implementation of waste treatment programs and other measures to reduce inputs of phosphorus to the lakes from municipal sewage. Phosphate-containing detergents were identified as one of the main sources of controllable wastewater phosphorus. It was thought that restrictions on this detergent use of phosphate would immediately reduce phosphorus loadings to the lakes in the absence of the wastewater treatment technology and treatment plants with the capability to reduce the phosphorus from all sources in municipal wastewater to an acceptable effluent level. The restrictions which were therefore imposed on the use of phosphate in detergents have resulted in the increased use of alternative detergent builder materials and their consequent release to the aqueous environment.

The International Joint Commission Science Advisory Board created three task forces to investigate the state of knowledge of the health and ecological effects of the builder materials being used or that were anticipated to be used as a result of the restriction on the use of the phosphate materials.

A Task Force on the HEALTH IMPLICATIONS OF NTA AS A DETERGENT BUILDER has completed its study and reported its findings to the IJC in July 1977. (Reference: "A Report to The Great Lakes Research Advisory Board of the International Joint Commission on the Health Implications of NTA May 1977".) In response to this report, the Science Advisory Board concluded, "the Board's conclusion that on the basis of health hazard there is no reasonable cause for restricting the use of NTA as a replacement for phosphate in detergents in The Great Lakes Basin". (Reference: Annual Report of the Research Advisory Board, IJC, July 1977).
A second Task Force on the ECOLOGICAL EFFECTS OF NON-PHOSPHATE DETERGENT BUILDERS has completed its study of NTA and recommended, "that NTA should not be prohibited from use as a detergent builder." (Reference: Ecological Effects of Non-Phosphate Detergent Builders: Final Report on NTA, IJC December 1978.) This second task force has continued its study of materials other than NTA.

This third Task Force on the HEALTH EFFECTS OF NON-NTA DETERGENT BUILDERS was established to consider the health effects of detergent builder materials other than NTA that are currently in use or are likely to come into use. This third task force consisted of scientists selected from areas that address the health effects of such materials. In addition, to facilitate awareness of unpublished data and ongoing research being conducted by industry and governments, liaison members were solicited from the Soap and Detergent Associations of Canada and the United States and appropriate federal agencies from the two countries. Adjunct members with specific areas of expertise were added to assist the task force in its review. Appendix B lists the task force and liaison members and Appendix A lists the terms of reference of the task force.

Seven materials were identified for examination by the task force: the organic polycarboxylate builders other than NTA — citrate, carboxymethyloxy-succinate (CMOS), and carboxymethyltartronate (Builder M), and the inorganic builders - carbonate, silicate, aluminosilicate (Type A Zeolite) and phosphate.

One procedure followed by the task force was to arrange industry and/or company presentations on the current, known, information available on the health effects of these materials. These were arranged either as meetings with written summaries or as summaries provided only in written form. Task force and adjunct members reviewed this information and discussed and queried pertinent aspects. Another procedure was to undertake research of available information through computer assisted reviews of the published literature and through specially arranged conferences.

The findings of the Task Force on the Health Effects of Non-NTA Detergent Builders are presented in the following chapters.
Introduction

The available information on the biological effects of "carbonates" has been summarized in the GRAS Monograph and in the SCOGS (Select Committee on GRAS Substances) Report. These reports were prepared for the U.S. FDA, as part of its ongoing survey of the safety of GRAS (Generally Recognized as Safe) food chemicals. The documents are available from the National Technical Information Service, U.S. Department of Commerce, VA 22151. The following information has been abstracted from this document. It is considered to be the most relevant for evaluating the possible health effects of carbonates to man.

Environmental Levels

The major source of exposure of man to carbonates and bicarbonates is through the diet (food and water). The average dietary intake of carbonates and bicarbonates by adults through their use in food may exceed 1g/day. This may be a gross overestimate, since this is based on (a) total usage based on the amount used in foods and (b) total consumption in 1970 and a U.S. population of 210 million. The actual level depends on the nature of the diet and frequency with which certain foods are eaten, as well as the characteristics of the food preparation process since carbonates and bicarbonates, which are often used as leavening agents, are no longer present in the processed food (1). The normal level of carbonate and bicarbonate in raw drinking water ranges from 0-1 mg/L, at 15-322 mg/L, respectively (2) Table 1).

Estimates of the contribution of detergent carbonates to environmental levels of carbonates, based on an average level of 20% on all granular laundry detergent, show that the contribution to raw sewage would be 9.3 mg/L, and to surface water, 0.0093 mg/L (Table 2, (3)).

*Contributed by S.I. Shibko
<table>
<thead>
<tr>
<th>Location</th>
<th>Great Lakes CO\textsubscript{3}^- (mg/L)</th>
<th>Great Lakes HCO\textsubscript{3}^- (mg/L)</th>
<th>Eastern Coast CO\textsubscript{3}^- (mg/L)</th>
<th>Eastern Coast HCO\textsubscript{3}^- (mg/L)</th>
<th>Mid-West CO\textsubscript{3}^- (mg/L)</th>
<th>Mid-West HCO\textsubscript{3}^- (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milwaukee, Wisc.</td>
<td>0</td>
<td>134</td>
<td>Newark, N.J. 0</td>
<td>23</td>
<td>Topeka, Kan. 0</td>
<td>322</td>
</tr>
<tr>
<td>Chicago, Ill.</td>
<td>1</td>
<td>132</td>
<td>Richmond, VA. 0</td>
<td>41</td>
<td>Des Moines, Iowa 0</td>
<td>340</td>
</tr>
<tr>
<td>Detroit, Mich.</td>
<td>1</td>
<td>95</td>
<td>Charlotte, N.C. 0</td>
<td>20</td>
<td>Kansas City, Mo. 0</td>
<td>198</td>
</tr>
<tr>
<td>Buffalo, N.Y.</td>
<td>0</td>
<td>111</td>
<td>Atlanta, Ga. 0</td>
<td>15</td>
<td>Omaha, Neb. 0</td>
<td>238</td>
</tr>
<tr>
<td>Avg.</td>
<td>118</td>
<td>25</td>
<td></td>
<td></td>
<td>Avg. 275</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2

RAW SEWAGE AND SURFACE WATER LEVELS RESULTING FROM THE USE OF SODIUM CARBONATE IN LAUNDRY DETERGENTS

I. Bases

U.S. Laundry Detergent Market Volume\(^1\): \(3 \times 10^9\) lb./yr. (1974)

Product Composition: 20% \(\text{Na}_2\text{CO}_3\)

U.S. Population\(^2\): 211, 381, 000 (July 1, 1974)

U.S. Sewage Flow\(^3\): 100 gal/capita/day

U.S. Sewage Effluent Dilution (Avg.) = 1:100

II. Calculation - Raw Sewage

\[
\frac{3 \times 10^9 \text{ lb detergent}}{\text{year}} \times 0.20 \frac{\text{Na}_2\text{CO}_3}{\text{detergent}} \times 454 \text{ g/lb} \times 10^3 \text{ mg/g} \\
211 \times 10^6 \text{ capita} \times 100 \text{ gal/cap/day} \times 365 \text{ days/year} \times 3.79 \text{ litres/gal} \\
= 9.3 \text{ mg/L}
\]

III. Calculation - Surface Waters

\[
9.3 \text{ mg/L} \times \frac{1}{100} = 0.093 \text{ mg/L}
\]
Acute Toxicity

<table>
<thead>
<tr>
<th>Substance</th>
<th>Animal</th>
<th>No.</th>
<th>Route</th>
<th>LD₅₀ (Dosage mg/kg body weight)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium carbonate</td>
<td>rats</td>
<td>unk.</td>
<td>oral</td>
<td>1870</td>
<td>(4)</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>rats</td>
<td>unk.</td>
<td>oral</td>
<td>4300 (a)</td>
<td>(5)</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>rats</td>
<td>unk.</td>
<td>oral</td>
<td>6000 (b)</td>
<td>(5)</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>rats</td>
<td>unk.</td>
<td>oral</td>
<td>5500 (c)</td>
<td>(5)</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>rats</td>
<td>unk.</td>
<td>oral</td>
<td>4850 (d)</td>
<td>(5)</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>rats</td>
<td>unk.</td>
<td>oral</td>
<td>5900 (e)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

a in a 20% slurry
b in a 50% slurry
c dose volume 20 mL/kg
d dose volume 50 mL/kg
e dose volume 20 mL/kg + 30 mL water

Subchronic Toxicity and Metabolism

The available data in mammalian species is extremely limited. Calcium carbonate fed to rats at a dietary level of 3% for 4 months resulted in suppression of growth. The decrease in growth may have been due to an imbalance in the Ca/PO₄ ratio, since no additional phosphate was added to the experimental diets (6). C from C¹⁴ carbonates, is readily incorporated into the metabolic pool. It is mainly excreted by respiration, but some is incorporated into liver glycogen, fats and proteins (7).

Reproduction Studies

Swiss white mice were fed diets containing 0, 0.5, 1 and 1.9% calcium carbonate. There was a significant decrease in the total weight of the young at weaning in the 1.9% group. The same effect was observed in subsequent litters. Autopsy of the offspring at 21 days of age, in the 1.9% group, showed pale speckled livers, enlarged heart and small thymus glands (8).
Chronic Toxicity and Carcinogenicity

No data available.

Mutagenicity

The genetic activity of sodium bicarbonate and potassium carbonate was assessed in microbial assays, with and without the addition of mammalian metabolic enzymes. The indicator organisms used for the tests were *Saccharomyces cerviseae*, strain D4, and *Salmonella typhimurium*, strains TA-1535, TA-1537 and TA-1538. Sodium bicarbonate and potassium carbonate were not mutagenic either directly or in the presence of organ homogenates in any of the *in vitro* systems tested (9).

Teratogenicity

The following studies have been carried out to evaluate the possible teratogenic effects of sodium carbonate and sodium bicarbonate:

**Sodium bicarbonate**

Albino mice (CD-1 outbred mice) were dosed on day 6-15 of gestation by oral intubation at dose levels of 5.80, 27.0, 125.0, or 580.0 mg/kg.

Albino rats (Wistar derived stock) were dosed on day 6-15 of gestation by oral intubation at dose levels of 3.40, 15.8, 73.3, or 340.0 mg/kg.

**Sodium carbonate**

Albino mice (CD-1 outbred mice) were dosed on day 6-15 of gestation by oral intubation with dose levels of 3.40, 15.8, 73.4, or 340.0 mg/kg.

Albino rats (Wistar derived stock) were dosed on day 6-15 gestation by oral intubation at dose levels of 2.45, 11.4, 52.9, or 240.0 mg/kg.
Sodium bicarbonate

Dutch-belted rabbits were dosed on day 6-18 of gestation by oral intubation at dose levels of 3.30, 15.3, 71.2, or 330.0 mg/kg.

Parameters evaluated included fetal mortality, internal, external or skeletal alterations. No fetacidal or teratogenic effects were reported (10).

Studies with Man

The available information is primarily derived from the effect of an extremely high dosage carbonate treatment on peptic ulcer patients. 2,300 mg/kg NaHCO₃ administered daily for 3 weeks to 33 patients resulted in marked alkalosis but no other adverse effects. Although the glomerular filtration rate increased on dosing, no renal damage was detected (11).

In another study, one individual received 32,000 g of sodium bicarbonate over a period of 20 months without any effect on acid-base balance, urea clearance, or red and white blood cell counts of hemoglobin (12).

Normal humans absorbed 8-18% of a single oral dose of 16.6-200 mg/kg CaCO₃ (13). Patients with mild alkalosis absorbed 12-37% of the dose (14). At plasma levels below 24 μM/L in man, essentially all bicarbonate from sodium bicarbonates entering the renal tubule is absorbed. Above this level, the excess bicarbonate is excreted. Ingestion of high levels of sodium bicarbonate has caused potassium retention and decreased excretion of calcium in the urine.

Summary

The range of available studies in mammalian species including man is quite limited, and does not meet the usual requirements for safety evaluation. However, the use of carbonates and bicarbonates at extremely high levels for the treatment of individuals with peptic ulceration indicates no adverse effects other than transient changes in acid-base ratio. In normal
individuals, bicarbonate is readily metabolized and excreted through the lungs as CO₂ or through the kidneys. Abnormal effects reported in experimental animals fed calcium carbonate appear to be related to the excess calcium, causing a mineral imbalance, rather than to carbonate or bicarbonate per se.

Conclusions

The available biological data indicate that the present-day human exposure to carbonates and bicarbonates from food and other sources does not pose a health hazard. No hazard is anticipated from the use of carbonates and bicarbonates as detergent builders, through their contribution to the loads of carbonates and bicarbonates in drinking water.

References


10. Food and Drug Research Laboratories, Inc. Teratologic evaluation of FDA 71-84 (sodium carbonate) and FDA 71-79 (sodium bicarbonate) in mice and rats. Four final reports prepared under DHEW contract no. FDA 71-260. Waverly, N.Y. (54 pp.).


3. CARBOXYMETHYLOXYSUCCINATE (CMOS)*

Introduction

A potential detergent builder developed recently, it is empirically isomeric with citric acid. The structure is shown in Figure 1. It should be noted that the abbreviation "CMOS" stands for the tricarboxylic anion.

\[
\begin{align*}
\text{CH}_2\text{-COONa} & \quad \text{CH}_2\text{-COONa} \\
\text{CH-CONa} & \quad \text{OH-C-CONa} \\
\text{O} & \quad \text{CH}_2\text{-COONa} \\
\text{CH}_2\text{-COONa} &
\end{align*}
\]

Sodium CMOS** Sodium Citrate

FIGURE 1

Lever Brothers have carried out the development work on CMOS and it is their view that this material may be used as a phosphate replacement.

Data in this review have been taken from a summary report by Lever Brothers presented in the United States Department of Health, Education and Welfare Committee to Coordinate Toxicology and Related Programs, January 25, 1977, as well as primary data supplied by the Company. Although the Company has presented the toxicology information in some detail, the material has not been published for peer review.

Environmental Levels

Although the trisodium salt of CMOS is used in detergent products, the sodium calcium salt (NaCaCMOS) will be the chemical species found in the wash

* Contributed by G.C. Becking
** Trisodium 2-oxa-2,3,4-Butanetricarboxylate
water and the environment. The polarity and metabolic fate in the environment precludes bioaccumulation or biomagnification in mammals. Environmental levels will range from 0.015 to 0.18 mg CMOS/L in receiving streams depending on whether secondary or primary sewage treatment is utilized. Based on the metabolic fate of CMOS, levels in drinking water are unlikely to exceed 0.05 mg/L.

Acute Toxicity

Lever Brothers have studied in some detail the acute toxicity of CMOS salts in several animal species. The results of these tests are summarized in Table 1. It is apparent that CMOS salts are not acutely toxic to mammals.

<table>
<thead>
<tr>
<th>Test</th>
<th>Species (M&amp;F)</th>
<th>Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral LD$_{50}$</td>
<td>Rat</td>
<td>2.4-3.5 g/kg</td>
<td>LD$_{50}$ NaCa CMOS (species in the environment) = 29.5 g/kg</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Rabbit</td>
<td>Nonirritant</td>
<td>Intact and abraded skin utilized</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>Rabbit</td>
<td>Nonirritant</td>
<td>Cornea, Iris and Conjunctiva studied</td>
</tr>
<tr>
<td>Acute Dermal</td>
<td>Rabbit</td>
<td>LD$_{50}$ &gt;5.9 g/kg</td>
<td>No lethality at 5.9 g/kg</td>
</tr>
<tr>
<td>Acute Inhalation</td>
<td>Rat</td>
<td>6-hr LC$<em>{50}$ &gt;8.25 g/m$</em>{3}$</td>
<td>No lethality at 8.25 g/m$_{3}$</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Guinea Pig</td>
<td>Nonsensitizing</td>
<td>Intradermal injection</td>
</tr>
</tbody>
</table>

Detergent formulations containing sodium CMOS were tested for consumer safety. Powdered formulations, similar to those available commercially, but containing CMOS, were essentially non-toxic with an oral LC$_{50}$ >5 g/kg in rats. They were noncorrosive in an esophageal corrosivity test, were only mild-to-moderate irritants in an occluded rabbit skin test and were only
slightly irritating to rabbit eyes. Human patch tests further confirmed the safety of CMOS-containing detergents. Detergent formulations containing sodium CMOS were both nonirritating and nonsensitizing.

**Subchronic Toxicity and Metabolism**

Subchronic studies in rats at doses of sodium CMOS up to 1.0 g/kg for 30 days and 4.5 g/kg for 10 days indicated minimal toxicity for this material. In the ten day rat studies, marked diarrhea, decreased growth rate and increased spleen weight were noted only at doses approaching the LD₅₀ (2.6-4.5 g/kg). No changes in histopathology, hematology or urinalysis were reported, but an increase in blood urea nitrogen and a decrease in serum globulin was observed in male rats fed 1.0 g/kg/day for 30 days. The conclusion that CMOS exerts its minimal toxicity via a non-specific disturbance of pH, mineral and water balance related to its chelating properties seems reasonable, although data substantiating this hypothesis are lacking.

The biological fate of sodium CMOS was investigated in the rat, monkey and man. Tissue levels were determined only in the rat.

No alterations in tissue levels or metabolism of CMOS were seen in rats fed CMOS for six months compared to controls. This indicates that CMOS does not induce enzyme systems involved in metabolizing this chemical.

Results of the absorption/excretion studies are presented in Table 2.

After 72 hours, only traces of CMOS were found in the rat skeleton and vital organs; it is therefore apparent that, even if absorbed, CMOS is rapidly and completely cleared from the mammalian body. Approximately 55% of the CMOS absorbed by the rats was metabolized, primarily to oxalates and oxaloacetates, whereas in primates, including man, little is absorbed and that which is absorbed is excreted as unchanged CMOS.
MAMMALIAN ABSORPTION AND EXCRETION OF CMOS

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of Subjects</th>
<th>Dose</th>
<th>Percent of Dose Excreted</th>
<th>G.I. Tract</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percent of Dose Excreted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urine 24 hr</td>
<td>24-72 hr</td>
<td>Feces 24 hr</td>
</tr>
<tr>
<td>Rat</td>
<td>3</td>
<td>25 mg; 12 uCi</td>
<td>71.2</td>
<td>2.3</td>
<td>26.9</td>
</tr>
<tr>
<td>Monkey</td>
<td>3</td>
<td>487 mg; 232 uCi</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Man</td>
<td>3</td>
<td>500 mg</td>
<td>2</td>
<td>1</td>
<td>not assayed</td>
</tr>
</tbody>
</table>

*average recovery from the GI tracts of monkeys at necropsy 72 hr post dosing (range 24-45%)

Chronic Studies

Although three separate chronic studies were carried out in rats, the appropriateness of the maximum dose utilized (300 mg/kg) and the material tested should be examined. It is true that no pathological lesions were noted in 6, 12 and 24 months, but is unusual to carry out a chronic toxicity study where no overt signs of toxicity were noted in the high dose animals. The lack of observed toxicity may simply be an indication of the relative non-toxicity of CMOS, but such an hypothesis requires experimental verification. The use of NaCaCMOS in chronic toxicity studies would seem appropriate. From the physical chemical properties of CMOS it can be calculated that man will be exposed to the CaCMOS ion, not to the CMOS species.

No toxicity was noted in male or female rats fed diets containing 63, 250, 1000 or 4000 mg CMOS/kg diet for six months. In a 16 month study NaCaCMOS (the probable environmental species) was fed at 1000 and 5000 mg/kg diet to male and female rats prior to and after mating, as well as to the progeny for 16 months. No treatment-related toxic response was noted. In the final chronic toxicity test, male and female rats were fed diets containing 22, 216 and 3600 mg CMOS/kg for one year and diets containing 25, 246 and 4100 mg NaCaCMOS for another year. A small decrease in ovary weight was noted, but no morphological changes were noted in the tissue sections.
When evaluated on the basis of growth rate, food consumption, survival, gross observations, hematology and gross and microscopic observations of tissue, it was concluded that levels of CMOS as high as 3600/4100 mg Na3CMOS/NaCaCMOS/kg of diet caused no significant chronic adverse effects in rats.

The effect of CMOS salts on reproduction in rats was studied in a three generation study. No alterations in fertility, gestation, viability or lactation indices were reported when Na3CMOS and NaCaCMOS were fed at dietary levels of 63, 250, 1000 and 4000 mg/kg. In a second study, these results were corroborated. Also in the latter study, no teratogenic effects were reported in the F1 generation after feeding diets containing 3600 mg Na3CMOS/kg of diet. The Company concludes that CMOS salts do not adversely affect the reproductive ability, nor the embryonic and fetal development in rats. Such a conclusion seems reasonable, in view of the results of specific teratogenic experiments to be reported later in this review.

Carcinogenicity

The Company has reported no significant differences in tumour incidence between control and animals consuming diets containing levels of Na3CMOS and NaCaCMOS as high as 3600 and 4100 mg/kg. The lack of tumour pathology in the 16 month, two-generation chronic toxicity study can be taken as further evidence of the non-carcinogenicity of CMOS salts. Before one can fully accept such negative data, it is imperative to ascertain whether these doses approached the maximum tolerated level. That is, a dose where some minimal target organ toxicity, or other manifestation of minimal general toxicity was noted.

Mutagenicity

The mutagenicity of Na3CMOS and NaCaCMOS was studied in Salmonella typhimurium strains TA200, 1538, 1535, 98, and 1537 at levels up to 4000 µg/plate with and without activation by mammalian microsomes.
compounds were nonmutagenic. In the host-mediated assay utilizing *S. typhimurium* TA 1530 and G-46, as well as *Saccharomyces cerevisiae* D-3, no mutagenicity was noted after dosing mice with 4, 40 or 400 mg/kg body weight/day.

No chromosome aberrations were noted in male rats fed diets containing levels of NaCMOS as high as 500 mg/kg for 3 generations.

After six months exposure of male rats to dietary levels of Na$_3$CMOS or NaCaCMOS of 4000 mg/kg, no mutagenic activity was noted in a dominant lethal test.

It was concluded that CMOS did not pose a mutagenic hazard to man. The negative mutagenicity data also support the negative carcinogenicity data discussed previously.

**Teratology**

Extensive teratology experimentation, using several protocols, was reported by Lever Brothers. The teratological potential of Na$_3$CMOS, sodium citrate, distilled water and Vitamin A were compared in rats. While Vitamin A caused a significant number of teratogenic changes, no such adverse effects were seen in the water control, CMOS or citrate dosed animals. Doses of NaCMOS up to 300 mg/kg were given between days 6-15 of gestation, and doses of NaCMOS as high as 1000 mg/kg were administered to rats between days 1-7, 7-14, 14-21 and 1-21 of gestation (period of organogenesis). No mobilization of heavy metals by CMOS was reported, nor was any potentiation of cadmium toxicity noted in the hamster.

**Summary**

Lever Brothers have concluded, on the basis of their toxicological examination, that CMOS poses no hazard to man from chronic ingestion from drinking water. Acute toxicity was similar to other builders now in use. Based on their summary report, and the primary data available this conclusion is probably valid.
4. CARBOXYMETHYLTARTRONATE (Builder 'M')*

Introduction

Monsanto has developed a new polycarboxylic acid detergent builder, called carboxymethyltartronatic acid (CMT). This builder has often been referred to as Builder "M", and the structures of the major components are shown in Figure 1.

\[
\begin{align*}
\text{COONa} & \quad \text{COONa} \\
\text{HC} & \quad - \quad \text{O} & \quad \text{CH}_2 \\
\text{COONa} & \quad \text{COONa} & \quad \text{COONa} \\
\text{HC} & \quad - \quad \text{O} & \quad \text{CH} \\
\text{COONa} & \quad \text{COONa} & \quad \text{COONa} \\
\text{HC} & \quad - \quad \text{O} & \quad \text{CH}_2 \\
\end{align*}
\]

Sodium Carboxymethyltartronate (NaCMT - 76%) Sodium Ditartronate (7%) Sodium Diglycolate (3%)

Figure 1

The builder is composed of all three chemicals shown in Figure 1. The term CMT used in this report refers to the mixture used in detergents.

At present, this material is not commercially available, but given the proper economic situation, the chemical properties of CMT as a builder might place it in a competitive position with other chemicals. For this reason, a discussion of the human health aspects of this builder seems in order.

Monsanto Company has informed the Task Force that research is still proceeding on CMT, but with a very low priority. The only report available on CMT was prepared by Monsanto (Builder "M", Environmental and Human Safety, March 1978). No primary toxicological data have been reviewed, nor have any of the test results been published for peer review.

Environmental Levels

It has been estimated that drinking water could contain less than 0.02 mg CMT/L under use conditions where all detergents contained 25% w/w CMT. Based

* Contributed by G.C. Becking
on chemical properties and economic factors, CMT would never be used at this level.

Acute Toxicity

The oral LD$_{50}$ for CMT in rats has been reported as 2-3 g/kg while the dermal MLD in rabbits was found to be greater than 8 g/kg. CMT was reported as non-irritating to rabbit eyes and skin. No evidence of primary irritation, fatiguing or sensitization was found in 200 human subjects.

Subchronic Toxicity and Metabolism

Monsanto has carried out 90-day feeding studies in dogs and rats. The rat appeared to be more sensitive to CMT than dogs. No adverse effects were reported in dogs fed diets containing 10,000 mg CMT/kg for 90 days, whereas a no-effect level in rats of 3000 mg/kg diet was reported. The only adverse effect in rats fed CMT at 10,000 mg/kg diet was an increased urinary excretion of calcium. In a 30-day study, rats were fed diets containing 3000 mg CMT/kg diet and no enhancement of methyl mercury toxicity by CMT was noted. In all subchronic studies, the indicators of toxicity were mortality, gross and histopathology, hematology and urinalysis.

Metabolism data on CMT are minimal, based only on single doses of $^{14}$C-labelled CMT administered to rats. In such experiments, 90 percent of the dose was excreted in 48 hours; 58 percent in the feces and 32 percent in the urine. It is still not certain whether the excreted material is unchanged CMT or various metabolites.

Chronic Toxicity and Carcinogenicity

The chronic toxicity and carcinogenicity tests have not been reported in final form. A 2-year rat study and an 18-month mouse study at NaCMT dietary levels between 1 and 10 g/kg were to be completed in 1979. A 2-year study in rats, where drinking water contained 1.7g/L of NaCaCMT, was also due to be completed in 1979. The only information received to date indicates that no compound-related, in-life toxic signs were noted in these chronic studies.
Mutagenicity

The sodium and calcium salts of CMT have been tested for potential mutagenicity in five strains of Salmonella typhimurium and Saccharomyces cerevisiae D-3 with and without metabolic activation. Even when 5 percent solutions of NaCMT were studied, results were negative.

Dominant lethal tests in mice fed diets containing 5 g NaCMT/kg or presented drinking water containing 1.7 mg CaCMT/L were negative. Also, after 8 weeks of dosing, no chromosome aberrations were found in bone marrow cells.

At a level of 1.7 g NaCaCMT/L in drinking water, two reciprocal translocations were noted in 400 F1 male mice. Negative results were obtained at 0.17 g NaCaCMT/L. The significance of these results is as yet unknown.

Teratogenicity

The teratogenic potential of CMT was studied in rats and rabbits, using fetal mortality, internal, external or skeletal alterations as indicators of teratogenicity. Doses of 100-1000 mg NaCMT/kg were given orally to rats between days 6-18 of gestation. No fetacidal or teratogenic effects were noted. Similarly, no fetacidal or teratogenic effects were reported in rabbits given oral doses of 100-300 mg/kg between days 6-18 of gestation.

In the rat, an oral dose of 100 mg/kg of NaCMT did not alter the classical toxicity and teratogenic effects of methyl mercury.

Monsanto Company has reported that multigeneration reproductive studies are in progress. No experimental results are available.

Summary

From its chemical structure and properties, and the results of acute and subchronic toxicity tests, one would not expect CMT to pose an undue health hazard to man. The types of tests carried out on CMT have been appropriate
for safety evaluation but, given the lack of primary data in most areas, the lack of chronic toxicity data and reproductive studies, as well as the unknown genetic risk to man one cannot assess fully the potential health effects of CMT after continual exposure to this chemical in drinking water.
5. CITRATES*

Introduction

This report concerns the health aspects of using citric acid and its salts as builders in household detergents. The most extensive uses for citrates are in the food and pharmaceutical industries. Citrates effectively chelate most divalent and trivalent ions (1), thus making effective detergent builders. Other industrial uses include metal cleaning, electrolytic polishing and plating, dyeing, water treatment and other miscellaneous industrial processes.

Citrates (particularly sodium and potassium) are ubiquitous in nature, appearing in small amounts in most organisms. Citrate is a normal metabolite in most lifeforms during the metabolism of carbohydrate.

Environmental Levels

In general, ambient citrate levels in the aquatic environment range between 0.025 - 0.145 mg/L, while values as high as 8.7 mg/L have been reported (2). The median citrate concentration in sewage effluent has been found to be 0.2 mg/L. Citrate levels as high as 10 mg/L are rapidly degraded to normal ambient levels (2).

Long-term human exposure to citrate resulting from detergent use would be primarily oral, through ingestion of drinking water. On the average, drinking water contains 0.002 - 0.005 mg citrate/L and this would increase to 0.0085 mg/L if all detergents were built with 25% citrate (2). If this occurred without degradation, man would consume 0.02 mg citrate/day from his drinking water, compared to 4.5 g from food sources (3).

* Contributed by G.C. Becking
Acute Toxicity

A succinct summary of the acute toxicity of citrates is presented in a report to the Food and Drug Administration (3). The oral LD$_{50}$ of sodium citrate in mice was 7.1 g/kg. All mice receiving 4.8 g citrate/kg survived. Another study indicated the oral LD$_{50}$ for citric acid in mice was 5 g/kg and in rats as 12 g/kg. The signs of acute toxicity from citric acid in mice and rats are those of organic acidosis and calcium deficiency.

Acute oral toxicity studies of citric acid in man have not been reported, but daily doses of potassium citrate as high as 10 g have been used to render urine less acid and as a mild diuretic (4).

Subchronic Toxicity

Rats administered citric acid in the diet (0.6 g/kg body weight) for 90 days exhibited no significant changes in body weight gain, blood parameters, histopathology or reproduction (5). No behavioural, biochemical or histopathological abnormalities were produced in dogs fed citric acid, 1.38 g/kg, for 112-120 days (4).

It has been reported that citric acid fed to rats at a level of 4.67 g/kg body weight for 6 weeks produced a slight thymus atrophy and microscopic splenic follicles (3).

Chronic Toxicity

Horn, et al., (6) fed citric acid to rats at levels of 1.2 and 2.0 g/kg body weight for 2 years. Survival rates were not affected, but treated animals grew more slowly than controls. After 2 years, organ weights were not affected and no histopathological changes were seen in thyroid, lung, heart, liver, spleen, kidney, adrenal, stomach, small and large intestine, pancreas, bone marrow or testicular tissue.
Rats fed diets containing 1.2% citric acid (daily intake 0.8 g/kg) showed no harmful effects with respect to growth in 2 successive generations over a 90 week period. No reproductive effects were noted, nor were significant changes noted in hematology or histopathology (4).

**Carcinogenicity**

No carcinogenicity bioassay has been carried out on citric acid or its salts. If citrate was carcinogenic to rats, one would have expected significant histopathological changes in the chronic studies since such high doses were utilized (4,6).

**Mutagenicity**

Citric acid, potassium and sodium citrate have been studied in a variety of systems, both microbial and mammalian, with and without metabolic activation. Microbial tests in *Salmonella typhimurium* (strains TA-1535, 1537 and 1538) and *Saccharomyces cerevisiae*, D₄ were negative for sodium and potassium citrate.

Citric acid was found to be non-mutagenic in a host-mediated assay using *S. typhimurium* TA-1530 and G-46, and *S. cerevisiae* D₄. Doses up to 3.5 g/kg body weight were utilized. Citric acid given orally to rats at 3 g/kg/day for 5 days did not produce significant chromosome aberrations. Similarly, at 0.6 mg/mL of media, citric acid did not produce significant chromosome aberrations in human embryo lung cells (WI-38). Citric acid was also found to be negative in the dominant lethal assay in rats at doses of 3 g/kg/day for 5 days (3).

**Teratogenicity**

The teratogenic potential of citric acid has been studied in mice, rats, hamsters, and rabbits by administration of doses between 241 - 425 mg/kg during the period of organogenesis. No adverse effects on oval implantation, maternal or fetal survival were noted. The number of abnormalities seen in either soft or skeletal tissues did not differ in control of treated animals (3).
Summary

No evidence exists to indicate man's present daily intake of approximately 4.5 g of citrate poses a health hazard. Even if citrates were used at the level of 25% in all detergents (highly unlikely), man's daily intake would increase by less than 0.001% (0.4 mg/day). The World Health Organization (4) indicated that an acceptable daily intake for citrates was "not limited". The use of citrates in detergents poses no hazard to man.

References


6. PHOSPHATES*

Introduction

Phosphorus is an element essential to all forms of life, both animal and plant. Phosphorus is present in water as orthophosphate, and in soils as soluble orthophosphate and the insoluble apatite form. Enough CO₂ is present in soil water, in equilibrium with the CO₂ in the air, to create slightly acidic conditions, and thus permit continuing solubilization of the apatite to the orthophosphate form that can be utilized by organisms (1). Many other chemical forms of phosphorus anion exist; the relevant ones are discussed below.

Phosphate-transfer reactions are vital to energy transfer and to the metabolism of lipid, protein and carbohydrate. Phosphate is also an essential part of the nucleic acid structure. Phosphorus is a major component of the body, predominantly in the bones and teeth. The blood serum levels of phosphorus in adults are usually in the 2.5-4.5mg/100mL range (1, 2, 3).

Phosphates have many important uses in industry and agriculture. Salts of various forms of phosphate have been used extensively in detergents and cleaning agents for many years. In detergents the condensed and polymeric phosphate salts function as detergency builders while the salts of orthophosphate provide alkalinity and emulsifying action (4). Approximately 95% of the phosphate used as detergent builder is sodium tripolyphosphate, Na₅P₃O₁₀, and most of the rest is tetrapotassium pyrophosphate, K₄P₂O₇, and tetraysodium pyrophosphate, Na₄P₂O₇ (5). Trisodium orthophosphate, Na₃PO₄, has been used in heavy duty cleaning compounds or, in the dodecahydrate form, is sold as such for that purpose (4).

There have been three general reviews relating to the safety of phosphates to humans. A 1978 review (5) by the FMC Corporation, Monsanto, Olin and

* Contributed by R.D. O'Brien
Procter & Gamble deals specifically with detergent phosphates, their chemistry, industrial production methods and amounts and levels achieved in water and sewage. The Food and Drug Administration reviewed in 1975 (3) the health effects of phosphates in foods. The National Academy of Sciences surveyed (6) in 1972 the extent of use of phosphate and other food chemicals "generally recognized as safe."

Levels

Since no known organisms can synthesize the phosphate anion, it has to be absorbed through the food supply. Animal and cereal products are quite high in phosphorus. For example, in approximate figures, cheddar cheese has 524 mg/100g, oatmeal 395mg/100g, eggs 224mg/100g, lean beef 240mg/100g. Plant products have considerably less--lettuce 28mg/100g, potatoes 56mg/100g, oranges 21mg/100g (2).

It has been estimated that the total food supplies in the United Kingdom provide about 1500mg of phosphorus per person per day (7). The 1972 NAS study (6) estimated the average U.S. intake of phosphorus was 300mg per day, with one third as calcium phosphates. The Food and Nutrition Board of the National Research Council (USA) recommends a dietary allowance of 800mg of phosphorus per day.

We now consider phosphorus intake from water. The total phosphorus content in waters can be divided into that which is available and that which is unavailable for biological assimilation. Part of the phosphorus associated with any soil particle may be chemically or physically bound to the particle and therefore unavailable. Based on river mouth data, the total phosphorus load in the Great Lakes (presumably in the absence of detergent contribution) consists of a soluble fraction and a particulate fraction. The soluble fraction is essentially all readily available, but only a portion of the particulate fraction is available.

The average contribution of household cleaners to the total phosphorus load in domestic sewage was about 53% in 1969 and had been reduced to 38% by
Other major contributors of phosphorus to receiving waters in addition to households are the non-point sources which include agricultural, forest and urban runoff and atmospheric sources. The phosphorus contribution from detergents flowing into the Great Lakes is 10% of the total phosphorus load to the Lakes.

Another calculation, by the detergent manufacturers (5), was based on a "worst-case scenario" in which there was no phosphorus removal at municipal sewage treatment plants, and only a hundred-fold dilution of the phosphorus prior to discharge into receiving waters; the calculation also assumed that phosphates made up 20% of detergents, which is no longer the case. This calculation showed 0.023mg of detergent phosphorus per litre as the averaged value of phosphorus contribution to surface waters; local concentration could of course vary substantially.

If the above calculations are correct, an individual drinking two litres of water a day would take in 0.046mg of available phosphorus from detergent, and about half as much from other sources. Another more specific calculation from the same source computed in the case of Lake Erie is an intake of 0.008mg per day derived from detergent. Either amount is small compared with the 300mg of phosphorus estimated above as the intake in the U.S.A. from food sources.

**Acute Toxicity**

The detergent phosphates are categorized as having slight to moderate acute toxicity (8). Massive ingestion of phosphoric acid and its salts results in acidosis and hypocalcemia. Oral doses to produce death are very large, e.g. the LD₅₀ (the dose lethal to 50% of the animals) of monobasic sodium phosphate for the guinea pig is over 449mg of phosphorus per kg of body weight (3). The acute oral LD₅₀ of pentasodium tripolyphosphate in mice is 811mg of phosphorus per kg of body weight (2). The acute oral LD₅₀ for rats of sodium tripolyphosphate is 6.50g/kg; of tetrasodium pyrophosphate, 4.00g/kg; of trisodium orthophosphate dodecahydrate, 7.40g/kg (9). Comparable published acute toxicity data on potassium phosphates are not available, but
they are expected to be more toxic than the corresponding sodium salts due to the inherently greater toxicity of potassium (8). The types of detergents that contain phosphate builders, i.e. laundry detergents, automatic dishwasher detergents, and hard surface cleaners and cleansers, are of low toxicity having acute oral LD₅₀'s for rats of 3 to 13g/kg (10).

These levels for acute toxicity can be compared with the above data on human intakes, recalculated on a body weight basis and assuming a body weight of 70kg. The phosphorus intake from food (using the U.S. value of 300mg per day) would be 4mg/kg, or about one-hundredth of the guinea pig oral LD₅₀. The intake from water, assuming a quantity of 0.075mg daily (which includes potential detergent), would be 0.001mg/kg, which is less than the guinea pig oral LD₅₀ by a factor of 450,000.

Weaver and Griffith (11) have shown that sodium tripolyphosphate, granular detergents that contain 50-60% of this builder, and potassium pyrophosphate are potent, prompt acting emetics when given orally to beagles. As induction of vomiting is widely used as a first aid measure in product ingestion, these authors suggested that the emetic action of the phosphate builders provides a safety factor in preventing the retention of detergent in the stomach. Gosselin, et al., (8) confirm that nausea and vomiting, and diarrhea as well, are probable after ingestion of tripolyphosphate or pyrophosphates. These phosphates are thought to be hydrolyzed to orthophosphate before absorption. If appreciable amounts of complex phosphate are absorbed, there may be binding of ionized serum calcium with a danger of hypocalcemic tetany. One such episode apparently occurred in a case involving a water softener.

Trisodium orthophosphate or TSP, which has been sold in the dodecahydrate form as a cleaning agent, forms strongly alkaline solutions in water and is reported to have produced injuries on ingestion similar to those caused by lye (8).

As for other routes of entry, there is an example of acute orthophosphate toxicity in which a 2 1/2 year old girl developed marked hyperphosphatemia, hypernatremia, hypocalcemia and acidosis after two pediatric sodium dihydrogen
phosphate enemas of 67.5mL each which contained 3.7g of phosphorus (12). Symptoms started to appear after 90 minutes and were relieved with the administration of calcium gluconate.

On the other hand, several thousand cases of accidental ingestion of detergents by children occur annually in the United States (13). Many of the products involved contain phosphates, and follow-up studies confirm that complications (other than nausea, vomiting, or diarrhea) rarely occur (14).

Topical exposure of skin and eyes to phosphate builders usually occurs in the context of handling or using the detergent products that contain them. Thus most reports of testing involve formulated products. However, Nixon, et al., (15) reported that 50% aqueous sodium tripolyphosphate caused negligible irritation to intact skin of rabbits, guinea pigs, or humans in four-hour patch test exposures. Under the same test conditions, guinea pig and rabbit skin showed slight and moderate irritation, respectively, from a detergent product that contained 50% sodium tripolyphosphate, which suggests that the ingredients other than the phosphate were more likely the source of irritation. Human skin showed negligible irritation from the detergent.

A battery of skin and eye irritancy tests on animals or human subjects was used on two detergents that contained 50% "condensed phosphate" (sodium tripolyphosphate) to assess effects on skin and eyes (16). Another study (17) involved similar products that also contained proteolytic enzymes. Both studies showed mild irritant effects from the products. Predictive, repeated application patch tests for skin sensitization involved 2055 human subjects in the first series and 1478 in the second. There was no evidence of skin sensitization, thus sodium tripolyphosphate appears to have no allergenic propensities.

Subchronic Studies

Many studies have been done to investigate the short-term effects of phosphates added to the diets of experimental animals. One of the signs indicating a phosphate overdose is the occurrence of metastatic calcium in the kidney, stomach and aorta. Resorption of bone is also characteristic.
Male rats fed diets containing either 8% metaphosphate or 8% sodium orthophosphate for seven months or until death showed increased urinary excretion of inorganic phosphorus, enlarged parathyroids (2 to 8 times that of controls), and calcium deposits in the tubules of the outer medulla of the kidney (18). Calcification occurs in the area of the Loop of Henle and the terminal part of the proximal tubule.

Hodge carried out short-term feeding studies with rats and dogs of sodium tripolyphosphate, sodium trimetaphosphate, sodium tetrametaphosphate, and sodium hexametaphosphate (19). The studies were designed to detect and assess renal damage in view of reported harmful effects of large amounts of orthophosphate on the kidney. Weanling rats were fed diets for one month that contained 0.2, 2.0, or 10% of the test phosphate. Control rats received basal diet alone, or supplemented with 10% sodium chloride or 5% sodium orthophosphate. Growth retardation was seen with the sodium chloride and sodium phosphate control rats and with the rats receiving 10% of condensed phosphate. The latter rats also had tubular degeneration and necrosis of the kidneys. The "no-effect" level of the condensed phosphates was 2% in all cases. Dogs fed 0.1g/kg/day of the condensed phosphates showed no effects. Exposure up to 5 months to from 1 to 4g/kg/day produced renal lesions similar to those seen in rats at 10% of the diet.

Ten female adult mongrel dogs fed diets supplemented with potassium phosphate at 2.8g phosphorus/day for four months and then 3.1g/day for six months showed multiple microscopic areas of calcification in the kidney medulla, decreased urinary calcium excretion, increased urinary phosphate excretion, increased bone resorption. Eight out of the ten dogs developed calcium deposits in their eye lenses. In five of these eight, the calcium deposits were associated with changes compatible with cataracts (20).

If the levels fed to dogs in the above experiments had comparable effects in humans, and if we assume the dogs weighed 7kg and the humans 70kg, then the daily amounts that showed undesirable effects were equivalent to 30,000mg of phosphorus per human, which is 100 times the U.S. intake in food and 400,000 times the intake in water.
Chronic Studies

There are two relevant long-term feeding studies of condensed phosphates used in detergents. Hodge fed groups of 50 weanling male and female rats for 24 months with laboratory chow diets containing zero, 0.05, 0.5, or 5% sodium tripolyphosphate (19). The added phosphorus equivalents were 0.012, 0.125, and 1.25%; FASEB estimated that the highest level was equivalent to 630mg of phosphorus added per kg of body weight (3). On the basis of growth, food consumption, hematology, urine analysis, mortality, organ weights, and histopathology, 0.05 and 0.5% sodium tripolyphosphate were no effect levels. The high level produced greatly increased kidney weight and size in males, accompanied by dilated convoluted tubules, interstitial and glomerular fibrosis and intertubular calcification.

In the second study, two detergents containing 50% condensed phosphate (sodium tripolyphosphate) were added to laboratory chow diets of separate groups of 40 male and 40 female rats each for two years at levels of phosphorus equivalent to 0.063% (21). There were no toxic effects to test animals compared with control animals that received the basal diet.

If the highest no-effect level in these two studies, 63mg of phosphorus added per kg of body weight, is compared with the "worst-case" human intake of detergent-derived phosphorus in drinking water of 0.046mg phosphorus (in 2 litres of water per day) for a 50kg adult, there is a safety factor of more than 68,000.

Carcinogenicity and Mutagenicity

In feeding studies of sodium tripolyphosphate by Hodge (19) and Snyder, et al., (21), rats fed diets containing up to 5% in the first case and at 0.25% in the second showed no qualitative or quantitative change from the normal incidence of tumors found in control animals.

No evidence of mutagenic effects for sodium acid pyrophosphate was obtained in a study that included: (a) host-mediated assay in mice using
Salmonella typhimurium TA1530 and mitotic recombination frequency in Saccharomyces cerevisiae D3; (b) in vitro mutagenic assay with S. typhimurium strains TA1535, TA1536, TA1537, and TA1538 in the presence and absence of metabolic activation; (c) dominant lethal test in rats; and (d) translocation test in mice (3).

Teratogenicity and Reproductive Effects

Sodium tripolyphosphate was embryotoxic but not teratogenic in avian embryos at levels up to 32mg of phosphorus per kg of egg. Sodium tripolyphosphate was given on day 6 through day 15 of gestation to pregnant mice (up to 60mg/kg as phosphorus), pregnant rats (up to 43mg/kg as phosphorus), pregnant hamsters from day 6 to day 10 (up to 36mg/kg as phosphorus), and pregnant rabbits from day 6 through day 18 (up to 63 mg/kg as phosphorus). No effects on oval implantation or maternal or fetal survival were seen. There was no significant increase in the number of abnormalities in soft or skeletal tissue (3).

Sodium tripolyphosphate, sodium trimetaphosphate, or sodium hexametaphosphate had no effect on fertility or litter size nor on growth or survival of offspring in reproduction studies with three generations of rats maintained on diets containing 0.5% of condensed phosphate (19).

Conclusions

The amount of phosphorus contributed by detergents to human intake is in the range of 0.01 to 0.1mg per person per day, and is therefore exceptionally small compared with the estimated U.S. food intake of 300mg per person per day.

Two lines of evidence suggest that detergent phosphorus derived through drinking water poses no health hazard. One is that, in comparison with the above human intakes, enormously larger amounts, by factors of several hundred thousand, are needed to produce detectable toxic effects (acute, subchronic or chronic) in laboratory animals and even these very large quantities are not carcinogenic, mutagenic, or teratogenic.
A second line of evidence is that a 1975 review (3) for the Food and Drug Administration of health aspects of phosphates in foods showed that there was no hazard from the 300mg of phosphorus taken in daily by humans in food; indeed such large amounts are essential for health. These food intakes of phosphorus are 6,000 times greater than water intakes, even under a "worst-case" scenario. Phosphorus occurs in numerous forms; all the 23 forms which have any significant representation in food and these include the forms found in detergents and natural water, were specifically exonerated from any hazards when used at current levels. In December 1979 the Food and Drug Administration proposed to affirm that such phosphates should be generally regarded as safe for addition to food. They exempted calcium hexametaphosphate and potassium polymetaphosphate from this status because they were not normally used as food additives (22).

It is concluded that phosphates used as detergent builders do not pose a health hazard through their contribution of phosphorus to drinking water.

References


7. SOLUBLE SILICATES*

Introduction

Soluble silicates possess utility in a spectrum of applications including food packaging, medical products, the treatment of drinking water and in high phosphate, reduced phosphate and non-phosphate detergents.

The Select Committee of the Federation of American Societies for Experimental Biology (FASEB, 1979) in a final evaluation for the U.S. Food and Drug Administration of the health aspects of certain silicates as food ingredients, concluded that sodium silicate, sodium aluminosilicate, calcium aluminosilicate, calcium silicate, magnesium silicate, potassium silicate, tricalcium silicate, silica aerogel and talc do not present a hazard to the public under current use.

It should be recognized that this conclusion was in basic agreement with an earlier FAO/WHO (1974) toxicological evaluation which established no limit for the acceptable daily intake of the above silicates with the exception of magnesium silicate and talc.

The principal objective of this report is to review the available literature on the toxicity of the soluble silicates with a primary focus on sodium silicate. It is, however, useful to initially review the germane aspects of the chemistry, use patterns and environmental aspects of the soluble silicates.

Chemistry, Use Patterns and Environmental Aspects

The soluble silicates cover a range of compositions. On the high alkaline side, species are stoichiometric and crystalline, e.g., sodium metasilicate

* Contributed by L. Fishbein
(Na$_2$SiO$_3$). On the high silica side, commercial materials are non-stoichiometric. These are available as viscous solutions or as amorphous solids. They are specified in terms of their weight ratios of SiO$_2$/Na$_2$O. Sodium silicate, ranging from 2.0 to 2.5 SiO$_2$/Na$_2$O, is most frequently used in laundry detergents (Sturm, et al., 1978). The colloquial term "waterglass" is now obsolete. It had been applied to viscous sodium silicate solutions of about 3.3 SiO$_2$/Na$_2$O as used for egg preserving (Wills, 1969).

As a detergent builder sodium silicate plays several roles, depending on the function and composition of the detergent. For example, in phosphate-built detergents, sodium silicate maintains soil particles in suspension and is not a water softener. In contrast, in the carbonate/silicate builder combination, the silicate buffers the solution at an alkaline pH where calcium carbonate and magnesium hydroxide precipitate most effectively. The silicate may sequester magnesium in carbonate and zeolite-built detergents. Additionally, sodium silicate also deflocculates particulate soil, emulsifies and saponifies greasy oil, absorbs liquid detergent ingredients, provides crisp, free-flowing granules when spray dried and may also inhibit the corrosion of metal in the washing machine (Sturm, et al., 1978).

The levels of sodium silicate (Na$_2$O·2SiO$_2$) in detergent based on various use patterns are as follows (Sturm, et al., 1978): (1) based on historical use: 5%; (2) based on current use in reduced phosphate detergent: 10%; (3) based on possible use in non-phosphate detergent: 20%. At concentrations below 120 ppm, the only stable species in aqueous solution is monomeric and is indistinguishable from naturally dissolved silica (Sturm, et al., 1978; Stumm, 1970).

Sodium silicate (at a concentration of 8 mg/L SiO$_2$) is added to municipal and domestic water supplies to inhibit the corrosion of pipes, pumps and tanks (Sturm, et al., 1978).

It is important to note that silica, silicic acid and the calcium, magnesium and aluminum salts are ubiquitous in the environment and hence it can be considered unlikely that man can avoid silicon exposure. At least 25%
of the earth's crust is composed of silicon in the form of silicon dioxide (sand and quartz) and the salts of silicic acid (FASEB, 1979).

Silicon is found in all natural waters (Krauskopf, 1967). Ground waters contain the highest concentrations of natural silica. Streams and rivers contain more dissolved silica than do the lakes and oceans. For example, the worldwide concentration of silica is 13.1 mg/L while that of the Great Lakes, is about 4 mg/L (Sturm, et al., 1978). Silica levels found in surface waters as a result of detergent use (at the 20% level) are of the order of 0.064 mg/L (6.4 mg/L raw sewage, assuming a sewage effluent dilution of 1:100) (Sturm, et al., 1978).

A survey of the mineral content of finished water in public water supplies of 100 largest U.S. cities in 1962 indicated that the median, high and low concentrations of silica were 7.1, 7.2 and 0.07 mg/L respectively (Durfor and Becker, 1964).

Silicon is found in almost all terrestrial and aquatic organisms (Allison, 1968). In humans, the lungs and peribronchial lymph nodes have the highest silica content, 14-2000 mg/100g and 27-5000 mg/100g respectively (King and Belt, 1938). The silica content of these tissues increases with age and this has been suggested to be due primarily to the continual inhalation of house and street dust. In contrast there is a constant low concentration in other organs and muscle that does not appear to vary with time (e.g., psoas muscle and kidney concentrations are of the order of 23/100 mg/100g and 11-27 mg/100g respectively) (King and Belt, 1938).

It should be additionally noted that foods contain naturally occurring silicates. For example, levels of silicon (in the form of silicon dioxide) in raw potatoes are about 10.1 mg/kg, in milk 2.1 mg/L and in beer 131 mg/L (FASEB, 1979). Silica compounds used in food packaging include silicon dioxides, sodium silicate and talc. The estimated possible intake of sodium aluminosilicate, the principal silicate food additive, is about 0.8 mg/kg/day (FASEB, 1979). An additional human intake of silicon can arise from its
medicinal applications. For example, magnesium trisilicate is used as an antacid in the treatment of hyperchlorhydria as found in peptic ulcers and gastritis.

Although the function of silica in the body is not definitively known, studies with chicks (Carlisle, 1972), rats (Levier, 1975; Schwarz and Milne, 1972) and monkeys (Levier, 1975) suggest that silica may play a role in the calcification process in bones.

Toxicity

Since sodium silicate occurs naturally and has been used in home laundry products in the United States and United Kingdom for approximately 120 and 150 years, respectively, few formal toxicity studies exist relating to sodium silicate per se or in any soap and/or detergent formulation.

a. Acute Toxicity

The signs observed during eye, skin, esophageal and oral toxicity tests included conjunctivitis, erythema, small blisters on skin, burns in oral and alimentary canal, nausea and vomiting (International Tech. Inform. Inst.). The acute oral LD₅₀ for sodium silicate (Na₂O·nSiO₂ x H₂O, n = 3.25, "water glass") is 1100 mg/kg. The oral LD₅₀ for sodium silicate (silicic acid disodium salt) is 1280 mg/kg in the rate (NIOSH, 1975; Philadelphia Quartz Co., 1961). The oral LD₅₀ for sodium silicate (3.0 SiO₂/Na₂O) in the rat is 1600 mg/kg. (NIOSH, 1975; Soap and Detergent Association, 1972).

In man, the estimated oral lethal doses are: >15g/kg for silica (silicon dioxide) and magnesium trisilicate and between 0.5 and 5g/kg for sodium silicate and in the latter case, may well be due to the compound's alkalinity (Anon, 1964; FAO/WHO, 1974).

The intraperitoneal LDLₙ for sodium silicate (designated water glass) in the guinea pig is 200 mg/kg (NIOSH, 1975). The minimal lethal i.v. dose of sodium metasilicate (Na₂SiO₃·9H₂O) for rabbits is 175 mg/kg. Doses between 110 and 172.5 mg/kg caused anemia. Sodium silicate at levels of 20.28-55.9% was eliminated in the urine within 11-48 hours (Gajatto, 1951).
In a comprehensive recent study of the rate and extent of urinary excretion in rats after oral administration of magnesium trisilicate, food-grade sodium aluminosilicate and Zeolite Type A administered in doses of 0, 40, 200 or 1000 mg/kg, and sodium silicate in doses of 40 and 1000 mg/kg, it was found that urinary silicon excretion increased rapidly after dosing and peak excretion rates occurred within 24 hours in all test groups (Benke and Osborne, 1979). Zeolite A had the most rapid urinary excretion rate (half-life, 6-8 hr). The half-lives of magnesium trisilicate, sodium silicate and food grade sodium aluminosilicate were 16-20 hr, 24 hr and 38 hr, respectively. When expressed as a percentage of dose, the total urinary silicon excreted was roughly equal for magnesium trisilicate, sodium silicate and Zeolite A but considerably less for food grade sodium aluminosilicate*. For all four test materials urinary silicon excretion increased with dose level. However, it should be noted that the magnitude of this increase (two to eightfold) was not as great as the increase in the amount dosed (25-fold). The observation that the percentage of silicon excreted decreased as the dose was increased suggested that some process in the absorption or excretion was becoming saturated. Similar findings were reported by King, et al., (1933) who administered silicic acid to dogs and found that increasing the dose caused a smaller fraction of the silicon to be excreted in urine. Comparable data in humans is limited and appears to be available only for magnesium trisilicate (Page, et al., 1941). When administered to volunteers at a dose level of 35 mg/kg/day for 4 days and the urine is collected for 48 hrs after the last dose, the total excess silicon recovered in urine averaged 5.2%. It was noted by Benke and Osborn (1979) that although the data of Page, et al., (1941) were not directly comparable to the single-dose data reported above in the rat, it would appear that man absorbs less silicon from magnesium trisilicate than does the rat. The hazards of ingested silicates are believed to be generally limited to effects on the kidney and bladder (Emerick, et al., 1963; Tracor-Jitco, 1973).

In man, except for non-specific irritation or corrosion of skin, cornea and mucous membranes, no apparently toxic actions of sodium metasilicate are recognized (Gleason, et al., 1968; Sax, 1968; Wills, 1969).

*Unlike Zeolite A, food grade sodium aluminosilicate is amorphous and differs in its Al/Si ratio.
b. Subchronic Toxicity

There may be species related susceptibility to renal damage from ingestion of sodium silicate. When 15 rats of both sexes of the Charles River CD strain were fed sodium silicate (no specified composition) at levels of 2.4 gm/kg/day in a semi-synthetic diet for 4 weeks, the only clinical symptoms observed were polydipsia, polyurea, and soft stools observed in a few animals. No compound-related lesions were found and all clinical chemical tests were within normal limits (Newberne and Wilson, 1970).

Pure-bred beagles of both sexes about 6 months of age were fed 2.4g/kg/day of sodium silicate in a semi-synthetic diet for 4 weeks (equivalent to 0.8g/kg/day of silicon dioxide as the end product). Gross cortical lesions of the kidney were observed in 8/8 male dogs and in 7/8 female dogs. The lesions appeared to be focal, subcapsular hemorrhages and on the cut surface the lesions suggested cortical infarcts (Newberne and Wilson, 1970). Although the nature of the lesion was the same in all cases, the severity varied from one animal to another, and from one area to another within the kidney. Hypertrophy of tubular epithelium, with or without degenerative changes, inflammatory cell infiltration into the interstitium, and dilatation of some and collapse of other tubular epithelium were all observed to varying degrees within localized areas of the kidney. The general impression was one of irritation of tubular epithelium followed by degenerative and regenerative changes. These alterations were accompanied by inflammatory cell infiltration into the interstitium. Although there was presence of extensive renal damage, impairment of renal function was not detected by any of the clinical tests conducted on serum or urine. It should be noted that magnesium trisilicate administered to dogs at 1.8g/kg/day (also equivalent to 0.8g/kg/day of silicon dioxide) for 4 weeks produced the same lesions. It was speculated that both sodium silicate and magnesium trisilicate were apparently absorbed from the gut and damaged the kidney as they or their metabolic products were excreted in the urine (Newberne and Wilson, 1970).

Settle and Sauer (1960) earlier reported that siliceous deposits formed in the kidneys of guinea pigs given large dose of soluble silica orally or intraperitoneally.
c. Chronic Toxicity and Carcinogenicity

There are no apparent reports in the literature of chronic testing or carcinogenicity of sodium silicate in any form.

d. Mutagenicity

Sodium silicate was not mutagenic when tested with E. coli (Demerec, et al., 1951).

e. Teratogenicity

There are no existing teratogenicity data on sodium silicates.

f. Epidemiology

There have been no epidemiological studies related to sodium silicate per se. Endemic Balkan nephropathy (BN) including marked kidney fibrosis has been associated with a long period of human consumption of drinking water believed by some to be contaminated by silicates (Markovic, 1972a,b; Markovic and Arambasic, 1971). However, it should be noted that other suggested etiologic agents have included plant and fungal toxins, viruses, lead and uranium (Austwick, 1975; Barnes, et al., 1977; Georgescu, 1976; Krogh and Elling, 1976; Sattler, et al., 1977). It was suggested (Markovic, 1972a,b; Marovic and Arambasic, 1971) that these silicates decomposed in the body after ingestion, releasing silicic acid which was excreted in concentrated form by the kidneys and appeared to be the cause of the fibrosis. It was believed that malignant tumors of the urinary tract found in approximately one-third of those autopsied in Yugoslavia was related to heavy and radioactive metals present with the silicates and released during their decomposition in the body (Markovic, 1972a,b).

A study of Benninger, et al., (1974) failed to produce renal changes in the guinea pig by chronic administration of silicic acid. The authors suggested that since silicic acid was not nephrotoxic, silicates in the
drinking water are not of primary significance in the pathogenesis of endemic Balkan nephropathy as has been previously proposed (Markovic, 1972a,b; Markovic and Arambasic, 1971).

All sodium silicate species, whether of natural or synthetic origin, lead to the same monomeric silica in solution. Above the solubility limit for monomeric silica, which is pH-dependent, oligomeric and finally polymeric silica form. These processes are the same internally as elsewhere in nature (Stumm, 1970; FASEB, 1979).

g. Metabolism

After ingestion, silicates have been reported to be decomposed in humans to silicic acid which is excreted in concentrated form by the kidneys (Markovic, 1972a,b). It has been postulated that when a silicate (e.g., magnesium trisilicate) is ingested or administered, part of the silica so formed is precipitated as a gel and part remains in solution.

Silicic acid has been reported to be a normal constituent of human urine. The amount excreted is in the range of 10-30 mg/day depending on the diet. Ingested silicic acid rapidly penetrates the intestine and is distributed throughout the extracellular fluid. Silicic acid has also been found in blood at levels below 1 μg SiO₂/cm³. It has not been found to bind to protein or to other large macromolecules (FAO/WHO, 1974).

Previous Evaluations and Summary

The FAO/WHO (1974) toxicological evaluation of silicon dioxide and certain silicates in relation to food additives concluded that with the exception of the reported damage to dog kidney by sodium silicate and magnesium trisilicate, any silicate absorbed is excreted by the kidneys without evidence of toxic cumulation in the body. The available data on orally administered silica and silicates appeared to substantiate the biological inertness of these compounds.
As noted previously in this report, FASEB (1979) in a review and evaluation of the health aspects of certain silicates as food ingredients for the U.S. Food and Drug Administration concluded that sodium silicate (as well as aluminum calcium silicate, calcium silicate, magnesium silicate, potassium silicate, sodium aluminosilicate, tricalcium silicate, silica aerogel and talc) do not present a hazard to the public under current use. The "unpublished GRAS status" of sodium silicate for direct use in food should also be noted (SCOGS-61 report, FASEB, 1979).

The U.S. Public Health Service has also stated that "the use of small amounts of sodium silicate added to drinking water would, as far as is known, produce no ill-effects upon the users of the water" (Vail, 1952).

Conclusion

It is concluded that the use of sodium silicate in detergents poses no hazard to man.
Bibliography


16. International Technical Information Institute, "Toxic and Hazardous Industrial Chemicals".


Introduction

Aluminosilicates have a variety of uses, including the food industry. Food grade aluminosilicate is approved for use in certain foods up to levels of 2 percent. Aluminosilicates, aluminum compounds and silicates are widely used in the treatment of drinking water.

Recently, the Federation of American Societies for Experimental Biology completed a review and evaluation of the health aspects of certain silicates as food ingredients for the United States Food and Drug Administration. (1) The conclusion of the committee was that aluminum calcium silicate, calcium silicate, magnesium silicate, potassium silicate, sodium silicate, sodium aluminosilicate, tricalcium silicate and silica aerogel, do not present a hazard to the public under current use. This conclusion was in agreement with earlier decisions by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), which established no limit for the acceptable daily intake of these same silicates, with the exception of magnesium silicate.

This report concerns the health aspects of synthetic Type A Zeolite (sodium aluminosilicate) utilized in household detergents. A review of the chemical and toxicological data on this aluminosilicate (2,3,4) will be made to ascertain whether the potential health risk is markedly different from other widely used silicon compounds (e.g. sodium silicate, sodium aluminosilicate, etc.).

Chemistry and Environmental Levels

A knowledge of the chemistry of Type A Zeolite is essential for proper evaluation of the results from toxicological experiments.

* Contributed by G.C. Becking
It is a synthetic, crystalline, inorganic sodium aluminosilicate, having a Na:Al:Si ratio of 1:1:1, and is cubic in structure. Type A Zeolite is more thermodynamically unstable than food grade aluminosilicate, which has a Na:Al:Si ratio of 1:1:13. In aqueous suspensions, it will transform to amorphous aluminates (clay-like materials) and sodium silicates. The presence of protons or chelators in the environment will enhance the removal of silicates from the cuboidal structure, destroying the rigid cubic structure. At pH <5 the transformation takes place in a few seconds, and at pH values between 5 and 8, the rate is fast, but may take a few minutes to complete. At a pH above 8 the same transformation occurs but at a slower rate.

Given this instability, cuboidal Type A Zeolite will rarely be found in the environment. It will rapidly transform to amorphous aluminates and soluble silicates under the acid conditions of the stomach and the neutral conditions of other tissues and the general environment. Both transformation products have an extensive history of safe usage.

In the United States, the median levels of soluble silicate (measured as SiO₂) and soluble aluminate (measured as Al) are 7.1 mg/L and 0.054 mg/L respectively. Assuming an exaggerated use pattern, that is, where all detergents were built with 20 percent Type A Zeolite, environmental studies showed that transformation products would result in 0.00003 mg/L Al/L and 0.00007 mg/L SiO₂ in potable water. These findings have been confirmed in both laboratory and pilot scale studies of drinking water treatment processes and conditions. No particles resembling the cuboidal structure of Type A Zeolite have been found in these studies.

**Acute Toxicity**

Extensive acute toxicity studies on Type A Zeolite indicate that this material is an acutely nontoxic chemical (5). It is non-toxic when ingested in a single dose and is relatively non-irritating to the eye and skin. Type A Zeolite does not produce sensitization and is non-irritating to the respiratory system after a single inhalation exposure. The studies on which the above conclusions were made are summarized in Table 1.
TABLE 1
ACUTE ORAL, DERMAL, OCULAR, AND INHALATION STUDIES

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral LD&lt;sub&gt;50&lt;/sub&gt; (Rat)</td>
<td>&gt;27.0 g/kg; no lethality at 27 g/kg</td>
</tr>
<tr>
<td>Oral toxicity (Dog)</td>
<td>1 g/kg produced slight hyperemia of stomach</td>
</tr>
<tr>
<td>Eye irritation (Rabbit)</td>
<td>Non-irritating</td>
</tr>
<tr>
<td>3 mg unrinsed</td>
<td>Slight irritation which subsided within 48 hours</td>
</tr>
<tr>
<td>3 mg rinsed</td>
<td></td>
</tr>
<tr>
<td>0.1 mL of 10% aqueous</td>
<td></td>
</tr>
<tr>
<td>Eye irritation (Monkey)</td>
<td>Mild irritation consisting of mild erythema</td>
</tr>
<tr>
<td>35 mg unrinsed</td>
<td></td>
</tr>
<tr>
<td>Skin irritation (Rabbit)</td>
<td>Non-irritating</td>
</tr>
<tr>
<td>Abraded and Non-Abraded</td>
<td>No deaths; mild erythema at treatment site</td>
</tr>
<tr>
<td>Slightly moistened; 20% aqueous slurry Zeolite A 24-hour, closed patch</td>
<td></td>
</tr>
<tr>
<td>Skin irritation (Human)</td>
<td>Non-sensitization</td>
</tr>
<tr>
<td>Single patch, 50% aqueous slurry</td>
<td></td>
</tr>
<tr>
<td>Acute Percutaneous Toxicity (Rabbit)</td>
<td>No sensitization</td>
</tr>
<tr>
<td>Abraded and Non-abraded</td>
<td></td>
</tr>
<tr>
<td>2 g/kg; 24-hour closed patch</td>
<td></td>
</tr>
<tr>
<td>Sensitization (Guinea Pig)</td>
<td>No sensitization</td>
</tr>
<tr>
<td>50% aqueous slurry</td>
<td></td>
</tr>
<tr>
<td>(3 weekly applications and challenge)</td>
<td></td>
</tr>
<tr>
<td>Sensitization (Humans)</td>
<td>No sensitization</td>
</tr>
<tr>
<td>5% aqueous slurry</td>
<td></td>
</tr>
<tr>
<td>(9 weekly applications and challenge)</td>
<td></td>
</tr>
<tr>
<td>Acute inhalation (Rats)</td>
<td>No observable toxic effects</td>
</tr>
<tr>
<td>Single 1-hr exposure: 2.4 and 18.3 mg/L</td>
<td></td>
</tr>
<tr>
<td>Single 4-hr exposure: 0.08 and 0.14 mg/L</td>
<td></td>
</tr>
<tr>
<td>Acute intratracheal instillation (Rats)</td>
<td>Irritation potential of Type A Zeolite is similar to calcium carbonate and less than silica flour</td>
</tr>
<tr>
<td>In vitro (Rabbits) and in vivo (Rats and Hamsters) alveolar macrophage</td>
<td>Toxicity rating: Type A Zeolite&lt;Clay&lt;Quartz</td>
</tr>
</tbody>
</table>
Metabolism and Subchronic Toxicity Studies

Both acute and sub-chronic metabolic studies have been conducted on Type A Zeolite in rat, monkey and man to determine its absorption, distribution and excretion pattern. Additionally, reactions to Type A Zeolite in a model human stomach were studied, as was the relationship between the concentration of soluble and particulate silicon species in human urine and the level of silicon in potable water. A summary of the various metabolic tests was presented to the IJC Task Force by the Procter and Gamble Company (2,3) and is reproduced with minor changes in Table 2.

**TABLE 2**

**Metabolism Studies**

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach Model - Human</td>
<td>Type A Zeolite is hydrolyzed to aluminates and silicates</td>
</tr>
<tr>
<td>Acute (single dose) rat and monkey: 0, 40, 200 or 1000 mg Type A Zeolite/kg</td>
<td>Urinary silicon markedly increased, urinary aluminum unchanged</td>
</tr>
<tr>
<td>man: 0 or 40 mg Type A Zeolite/kg</td>
<td>85-110% of dosed aluminum found in rat feces</td>
</tr>
<tr>
<td></td>
<td>In man, blood Al &lt;1 μg/mL after single 40 mg/kg dose</td>
</tr>
<tr>
<td></td>
<td>Similar urinary silicon excretion (% of dose) in all 3 species</td>
</tr>
<tr>
<td>Sub-chronic in rats 0 and 2% in diet - 8 weeks</td>
<td>Increase in urinary silicon; urinary aluminum unchanged</td>
</tr>
<tr>
<td></td>
<td>No significant tissue storage of aluminum</td>
</tr>
<tr>
<td></td>
<td>No kinetic evidence for multiple tissue binding sites for silicon</td>
</tr>
<tr>
<td>Excretion of urinary particulate Silicon (rats); 0, 0.125, 0.25, 0.5, 1 and 2% in diet 3 - 16 weeks</td>
<td>A marked increase in excretion of particulate silicon noted at 0.125 - 0.25% Type A Zeolite</td>
</tr>
<tr>
<td>Human Urinary Silicon - Excretion in relation to drinking water silicon levels</td>
<td>Drinking water silicon (median level 7 mg/L) does not affect urinary particulate silicon excretion</td>
</tr>
<tr>
<td></td>
<td>&lt;1 μg/L silicon contributed to drinking water through use of Type A Zeolite would increase urinary excretion of soluble silica &lt;0.02%.</td>
</tr>
</tbody>
</table>
Acute and sub-chronic metabolic studies have been conducted with Type A Zeolite and other silicon containing compounds, such as sodium silicate, magnesium trisilicate and food grade sodium aluminosilicate, which have been approved as safe for food use by the U.S. Food and Drug Administration (FDA), the WHO and other international agencies. The above studies indicate that Type A Zeolite is hydrolyzed in the stomach to silicates and aluminates and only the silicon moiety of Type A Zeolite is partially absorbed.

The acute studies show that, as the dose of Type A Zeolite is increased, urinary silicon excretion is increased. Aluminum is recovered in the feces. This fecal aluminum represents unabsorbed aluminum, since analysis of bile from animals dosed with Type A Zeolite show that bile is not a route of excretion for Type A Zeolite.

Urinary excretion of silicon, expressed as percent of silicon dosed, was similar for rat, monkey and man when dosed with a single large dose of Type A Zeolite. To this extent the rat is an appropriate model for chronic toxicity studies on Type A Zeolite.

The sub-chronic metabolic studies conducted in rats provide additional support for the conclusion that Type A Zeolite is hydrolyzed in the stomach to silicates and aluminates and that only the silicon moiety of Type A Zeolite is absorbed. These studies show that as the dose of Type A Zeolite in the rat diet is increased, the amount of silicon excreted in the urine is markedly increased while urinary aluminum and tissue aluminum remain unchanged. Urinary silicon excretion is such that at dietary concentrations greater than 0.125% Type A Zeolite, the urinary silicon burden becomes so great that the urine becomes saturated with soluble silicate and silicate precipitation occurs in the urine (referred to herein as "particulate" silicon).

A human urinary silicon monitoring program investigating the relationship between natural levels of silicon in the drinking water (1-10 ppm SiO₂) and the excretion of soluble and "particulate" silicon (silicon precipitate >0.4μ) in the urine shows that drinking water containing up to 10 ppm SiO₂ has no effect on urinary "particulate" silicon excretion, thus indicating that the
parts per billion of silicon added to the drinking water through the large scale use of Type A Zeolite in the detergent industry is not likely to cause an increase in urinary "particulate" silicon.

The above extensive metabolic experiments in several species, including man, have provided ample proof that the oral toxicity of Type A Zeolite is that of soluble silicates. Also, the sub-chronic feeding studies, in which rats were fed diets containing 0.1 to 2% Type A Zeolite for periods of time between 90 and 200 days, indicate that Type A Zeolite is a relatively non-toxic chemical. Significant toxic manifestations were only noted at doses producing high levels of urinary particulate silicon.

In Cox or Long Evans rats, dietary levels of Zeolite A as high as 2% failed to cause dose related effects on organ weights, hematology, blood chemistry or kidney function after 168 or 200 days. Body weights of animals receiving 2% Type A Zeolite were lower than controls. Also, an increased urine volume and decreased specific gravity were noted in animals receiving 2% Zeolite in the diet. Siliceous particles were noted in the urine of all rats receiving >0.125% Type A Zeolite in the diet. The quantity of particles appearing in the urine was dose related. Additionally, at dietary levels greater than 0.125% Type A Zeolite, the siliceous particles aggregated to form bladder and kidney stones. Such stones did not appear until after 90 days on test and the incidence of stones increased with time and dietary levels above 0.125%. Below this "threshold" dietary level for particle formation, no compound related stones were observed. The particles and stones were amorphous, high in silicon content, with no detectable aluminum.

Compound related microscopic changes were observed in the kidneys and/or bladders of animals receiving greater than 0.125% Type A Zeolite in the diet for 168 or 200 days. The microscopic changes consisted of hyperplasia of the transitional cell epithelium of the mucosa of the urinary bladder and the kidney pelvic epithelium. When such changes were found particulate material or calculi were also found. Also, after microscopic examination of the kidney, ureters and urinary bladder of animals receiving 2% Type A Zeolite in the diet, alterations characterized by an increase in the incidence and
severity of interstitial nephritis and regenerative epithelium were noted. No histopathological lesions were found in animals fed diets containing 0.125% Zeolite A. The microscopic changes appeared to be related to the urinary silicate burden and siliceous material in the tissues. They were similar to those reported for other silicates, such as sodium silicate, magnesium trisilicate and silicic acid.

Twenty-eight-day and 91-day dermal toxicity studies conducted in rabbits showed that Type A Zeolite had no systemic or dermal effects. Application of 2 mL/kg bodyweight of a 10% aqueous slurry of Type A Zeolite to the backs of rabbits 6 hr/day, 5 days per week for 4 or 13 weeks was non-irritating to the skin and had no adverse effect on bodyweight, hematology, clinical chemistry or histology.

**Chronic Toxicity**

Based on sub-chronic metabolic studies and 200 day sub-chronic feeding studies, the highest dietary dose level used in chronic studies was 0.1%. This should be considered a maximum tolerated dose, since higher levels result in siliceous material causing physical tissue damage. The exact effect of such non-physiological action on chronic toxicity is unknown.

Administration of 0.001%, 0.01% and 0.1% Type A Zeolite in the diet of Wistar rats for 78 weeks had no compound related effects on physical appearance, hematology, blood chemistry or urinalysis.

Gross necropsy of animals revealed no abnormal findings. This study cannot be considered an adequate chronic toxicity study, but the carcinogenicity bioassay (using a similar dosing regimen) utilized an experimental design, making it a combined carcinogenicity and 104 week chronic toxicity study.

In the carcinogenicity bioassay, results of blood chemistry, hematology, urinalysis and body weight/food consumption studies, as well as the histopathological examination for non-cancerous lesions, support the results
of the 78 week chronic experiment. That is, the administration of 0.1% Type A Zeolite in the diet for 104 weeks does not produce chronic toxicity in rats.*

No evidence of fibrosis was observed in hamsters exposed to $\approx 20 \text{ mg/m}^3$ of Type A Zeolite, 3 days per week, 5 hours per day for 52 weeks. The only observation was the presence of the test material in the alveolar macrophage and lymph nodes.

Exposure of Cynomolgus monkeys to 1 and 6 mg/m³ of Type A Zeolite or Type A Zeolite detergent (detergent micronized to maximize inhalation) for 24-months and to 50 mg/m³ of Type A Zeolite or quartz for 12 months had no adverse effects on bodyweight gain, hematology, serum chemistry or urinalysis. The only alteration in pulmonary function was a decrease in the mean vital capacity of the monkeys exposed to quartz for 12 months. Histopathology of the various tissues indicated that exposure to $\approx 1$ and 6 mg/m³ of Type A Zeolite-containing detergents for 6 hours per day, 5 days per week for 104 weeks produced only an increase in alveolar and septal macrophages. Exposure to $\approx 1$ and 6 mg/m³ Type A Zeolite for 104 weeks and $\approx 50 \text{ mg/m}^3$ Type A Zeolite for 52 weeks produced an increase in alveolar and septal macrophages. In addition, at the 6 and 50 mg/m³ Type A Zeolite doses, sporadic inflammatory reactions were observed in the lungs of some of the treated animals. These inflammatory reactions were observed primarily in lobes of the lung previously compromised by mites and kaolin. Neither Type A Zeolite nor Type A Zeolite-containing detergents produced pulmonary fibrosis after 104 weeks of exposure.

Compound related effects were not observed in any other tissues. Quartz produced progressive pulmonary fibrosis in monkeys as early as 30 weeks after initial exposure. The observed increase in alveolar and septal macrophages with Type A Zeolite and Type A Zeolite detergents is a classical pulmonary clearance response to relatively innocuous, insoluble, materials deposited in the lungs. These results support the conclusion that Type A Zeolite and Type A Zeolite-containing detergents are relatively innocuous materials.

* Personal Communication from the Procter and Gamble Company, regarding information supplied to them by the Henkel Company.
Carcinogenicity

To determine the carcinogenic potential of Type A Zeolite, it was administered at 0.001, 0.01 and 0.1% in the diet of rats for 104 weeks. At the 0.1% dose there was an exacerbation of glomerulonephrosis, a spontaneous kidney disease which develops in aging rats. The 0.1% dose is considered a maximum tolerated dose because of the reported exacerbation of this spontaneous kidney disease in female rats and because it is the "breakpoint" at which there is an increase in particulate silicon in the urine which could lead to stone formation, compromising the carcinogenic assessment in bladder and kidneys.

Tumor incidence was reported to be essentially identical among groups and sexes whether broken down as total tumors, malignant tumors or benign tumors. No treatment associated carcinogenicity was identifiable.

Mesenteric-lymphangiomas and pituitary tumors were the most common tumors in males, whereas pituitary tumors were the most prevalent type of tumor in females. In both cases, no treatment associated or dose-response associated carcinogenic effect was reported.

In conclusion, an essentially lifetime feeding study which was designed and conducted in a fashion similar to those in the NCI's bioassay program has yielded data strongly supporting the conclusion that the chronic feeding of high doses of Type A Zeolite does not produce cancer or chronic organ toxicity in rodents.

No carcinogenic or fibrogenic effects were observed in rats exposed to \( \approx 20 \text{ mg/m}^3 \) of Type A Zeolite, for three days per week, 5 hours per day for 22 months. The only compound related effect observed was the presence of the test material in the alveolar macrophage and the lymph nodes, indicative of detoxification mechanisms for airborne foreign insoluble particulate matter.

No carcinogenic effects were observed in rats given a single 50 mg intraperitoneal injection of quartz or Type A Zeolite and then observed for
various time periods up to 24 months. Under the above dosing conditions, Type A Zeolite produced a fibrogenic response within the peritoneal cavity. The response was qualitatively and quantitatively different from the fibrogenic response produced by quartz. Specifically, the response observed with Type A Zeolite regressed with time, whereas the response after administration of quartz progressed with time. Unpublished, preliminary studies, utilizing this technique in mice, found that an intraperitoneal injection of 20 mg of fibrous natural zeolite resulted in the production of mesotheliomas in less than one year (Personal Communication - Dr. I. Selikoff). It is thus a valid model to indicate carcinogenic or toxic potential of relatively insoluble materials.

The effects of chronic inhalation of Zeolite A containing detergent formulations were studied in monkeys exposed to 1 and 6mg/m³ of these materials. Exposure was for 6 hrs/day, 5 days per week for 104 weeks. None of the test materials had adverse effects on body weight gain, hematology, serum chemistry or urinalysis. The only alteration in pulmonary function was noted in monkeys treated with quartz. Histopathological examination of the various tissues indicated that exposure to approximately 1 and 6 mg/m³ of Type A Zeolite, or detergent formulations with Zeolite A produced only an increase in alveolar and septal macrophages, and the expected response to inhaled insoluble particulate matter. These inhalation studies in monkeys support the conclusion that chronic exposure to Type A Zeolite dusts poses a negligible health hazard.

**Mutagenicity**

No mutagenicity tests on Type A Zeolite have been reported. Food grade sodium aluminosilicate has been found non-mutagenic in host mediated assays with *Salmonella typhimurium* and *Saccharomyces cerevisiae* as well as a dominant lethal assay in which male rats were intubated with 4.25, 42.5 or 425 mg/kg of sodium aluminosilicate daily for 5 days prior to mating.

Silicon dioxide and hydrated calcium silicate did not induce mutations in the host mediated assay with *Salmonella typhimurium* or *Saccharomyces cerevisiae*, nor did these two silicon materials produce significant
aberrations in the bone marrow metaphase chromosomes of rats; nor did they produce abnormal changes in anaphase chromosomes of human embryonic lung cells in tissue culture.

Based on the fact that other silicates are non-mutagenic, it is unlikely that Type A Zeolite would be positive in mutagenicity tests.

Teratology

In the rat teratology study, dams were given either 74 mg/kg or 1600 mg/kg Type A Zeolite by gavage on days 6-15 of gestation inclusive. In the rabbit teratology study, dams were given 74 mg/kg, 345 mg/kg or 1600 mg/kg of Type A Zeolite on days 6 through 18 of gestation. Like other silicates, Type A Zeolite has a teratogenic potential comparable to food grade sodium aluminosilicate.

Conclusions

The toxicological data base on Type A Zeolite is much more extensive than that available for other synthetic and natural silicates, even those used by the food industry. Type A Zeolite is essentially non-toxic via oral, dermal, ocular and respiratory routes of exposure and adverse effects are noted only after oral doses several million times that of calculated human exposures. These effects are similar to those noted after administration of massive oral doses of other widely used silicates (e.g. magnesium trisilicate, food grade sodium aluminosilicate and sodium silicate).

Laboratory and environmental studies have shown that man will not be exposed to cuboidal Type A Zeolite, only to soluble silicates and insoluble aluminates (clay-like material). Extensive metabolic studies have shown that only the silicate, but not the aluminate, moiety of Type A Zeolite is absorbed; supporting the conclusion that the oral toxicity of Type A Zeolite is that of soluble silicate.
The median level of SiO₂ in drinking water is 7 mg/L. Assuming an exaggerated use pattern for Type A Zeolite in detergents, this level of silicon will increase by less than 0.001%.

During animal studies, marked histopathological lesions were noted only in the kidney and bladder from animals fed diets containing Type A Zeolite at levels exceeding 0.125 percent. Such dose levels lead to increased particulate silicon and frank kidney and bladder stones after 90 days. Naturally occurring levels of silicon in drinking water (up to 10 mg/mL) have not been shown to lead to detectable levels of urinary particulate silicon.

Type A Zeolite is not a teratogen and is not carcinogenic orally or via the inhalation route of exposure. The negative mutagenic activity noted in other silicates make it highly unlikely that Type A Zeolite poses a mutagenic hazard.

As with other builders, based on present knowledge and using current state-of-the-art techniques of toxicological assessment, it is concluded that the use of Type A Zeolite in detergents will not pose a health hazard to humans.

Summary

Aluminosilicates are widely utilized in the food industry and in treating drinking water, not posing a human health hazard under current conditions of use. Cubic Type A Zeolite, with a Na:Si:Al ratio of 1:1:1 is thermodynamically less stable than food grade aluminosilicate, with its corresponding ratio of 1:1:13 rapidly forming insoluble aluminates and soluble silicates in aqueous suspensions at a pH <8, hence rarely being found in the environment.

Type A Zeolite is essentially non-toxic in acute and chronic toxicity tests on animals, the behaviour being representative of the silicates formed on hydrolysis. No carcinogenic or teratogenic effects were noted after
exposure of experimental animals to high levels of Type A Zeolite and it is unlikely to produce mutagenic effects.

Considering the normal exposure of man to natural silicon compounds without evident health hazards and the miniscule increase in silicon levels in drinking water resulting from the proposed use of Type A Zeolite in detergents, the Task Force concludes that use of this zeolite in detergents is not anticipated to lead to adverse human health effects.

References


The Science Advisory Board, formerly the Research Advisory Board, has previously investigated and made recommendations regarding the environmental and human health impact of the use of NTA as a detergent builder. A task force is now working on the environmental impact of the non-NTA detergent builders. The Task Force on the Health Effects of Non-NTA Detergent Builders should review the approaches used by the Task Force on Health Effects of NTA and the Task Forces on the Environmental Effects of NTA and Non-NTA Detergent Builders, respectively, in order to maintain some consistency in approach.

The Task Force on the Health Effects of Non-NTA Detergent Builders is charged to:

A. (1) determine the chemicals which are currently in use as detergent builders;

   (2) determine those chemicals which are likely to be used in the near future; and

   (3) appraise what is known and what is unknown about the health effects of the substances listed in 1 and 2.

B. The task force will advise the Science Advisory Board regarding their overall appraisal of the impact on human health of the non-NTA detergent builders and any specific areas which require additional research.

C. These tasks are to be completed by January 1, 1979, with an interim report on May 1, 1978.
APPENDIX A

TECHNICAL REPORT
for the
SECRETARY OF DEFENSE

HEALTH EFFECTS OF NON-IONIZING RADIATION
ON MAN

The Secretary of Defense and the Secretary of Health, Education, and Welfare have determined that non-ionizing radiation poses a potential threat to human health. This report is intended to provide a comprehensive examination of the effects of non-ionizing radiation on human health.

The Task Force on the Health Effects of Non-Ionizing Radiation was established to conduct a thorough study of the potential health effects of non-ionizing radiation. The Task Force was composed of experts in various fields, including biology, medicine, and engineering.

The Task Force's findings were based on extensive research and analysis. Their conclusions are summarized in the following sections:

1. Biological effects of non-ionizing radiation
2. Evidence of adverse health effects
3. Recommendations for future research

These findings are intended to provide a comprehensive understanding of the potential health effects of non-ionizing radiation.
APPENDIX B

MEMBERSHIP, TASK FORCE ON THE
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APPENDIX C

TERMS OF REFERENCE FOR THE SCIENCE ADVISORY BOARD

1. As used herein, "research" includes development, demonstration and research activities, but does not include regular monitoring and surveillance of water quality.

2. The functions and responsibilities of the Science Advisory Board relating to research activities in Canada and the United States concerning the quality of the waters of the Great Lakes System shall be as follows:

(a) to review at regular intervals these research activities in order to:

(i) examine the adequacy and reliability of research results, their dissemination, and the effectiveness of their application;
(ii) identify deficiencies in their scope, and inadequacies in their funding and in completing schedules;
(iii) identify additional research projects that should be undertaken;
(iv) identify specific research programs for which international cooperation will be productive;

(b) to provide advice and consolidations of scientific opinion to the Commission and its boards on particular problems referred to the Advisory Board by the Commission or its boards;

(c) to facilitate both formal and informal international cooperation and coordination of research; and

(d) to make recommendations to the Commission.

3. The Science Advisory Board on its own authority may seek analyses, assessments and recommendations from other professional, academic, governmental or intergovernmental groups about the problems of Great Lakes water quality research and related research activities.

4. The IJC shall determine the size and composition of the Science Advisory Board. The Commission should appoint members to the Advisory Board from appropriate Federal, State and Provincial Government agencies and from other agencies, organizations and institutions involved in Great Lakes research activities. In making these appointments the Commission should consider individuals from the academic, scientific and industrial communities and the general public. Membership should be based primarily upon an individual's qualifications and potential contribution to the work of the Advisory Board.

5. The Science Advisory Board should work at all times in close cooperation with the Great Lakes Water Quality Board.
APPENDIX D

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