SURFACTANT EFFECTS ON HUMANS AND OTHER MAMMALS

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FOREWORD

Collecting, organizing, and interpreting the toxicity data on the surfactants certainly in our environment and possibly included in traces in our diet or water supply is such an obviously timely contribution we can only feel grateful to the author for his labors buttressed by data garnered from over 140 references. The possible hazard to the human population is estimated from summaries of (a) the acute toxicities of more than 30 surfactants; (b) the effects on human volunteers in 7 studies; (c) the chronic toxicity studies of more than a score of surfactants consumed by animals in feeding periods of a few days to 2 years; (d) the 10 fertility and reproduction studies in animals; (e) the investigations of the role of surfactants in tumor production, in infections, and in the promotion of intestinal absorption processes. As the basis for comparisons, careful estimates of average human consumption of surfactants are made. The environmental hazard from surfactants is shown to be reassuringly negligible.

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Summary

This review is a guide to the original scientific literature (through 1965) pertinent to possible effects of our exposure to the trace amounts of surfactants which may enter our environment via sewage. The data show beyond any reasonable question that the margin of safety is very great, and there is no indication that hazard exists.

The review is divided into the following sections:

1. *Introduction.* Background of the problem and scope of the review.
2. *Exposure Levels in Our Environment.* The amounts of surfactant which might be ingested by the individual in the normal course of events.
3. *Acute Toxicity.* Lethal dose data for surfactants in animals.
4. *Chronic Toxicity.* Absence of toxic effects of surfactants upon prolonged feeding below the lethal dose limit, in man and in up to three generations of animals.
5. *Solubilization and Synergy.* Experiments indicating the negligible degree of hazard associated with surfactants at environmental levels through promotion of (a) activity of carcinogenic substances, (b) bacterial or viral infectivity, or (c) intestinal absorption.

1. Introduction

A surfactant intended for commercial sale, either as such or as a component in a detergent or cleaning formulation, should first undergo exhaustive tests to establish that there is no direct hazard to the health of the user. The detergent industry is particularly careful in this regard because many of its products come into intimate contact with the skin, and are also used in the washing of wearing apparel, food, and food utensils.

In recent years a whole additional area of potential hazard has come into view as a consequence of increasing population densities: contamination of water supplies by sewage and other wastewaters. One of the minor but (by virtue of its foaming properties) more obvious components of sewage was tetrapropylene-derived alkylbenzene sulfonate (tpABS), the surfactant in major use during the years 1950-1964. Detergents based on this material have been in almost universal use in our nation's households, so that it has been present in our domestic sewage at levels averaging around 10 parts per million (ppm). Most of our sewage ultimately finds its way into rivers or ground waters. Our rivers have averaged perhaps 0.1 ppm or less of tpABS except in the cases where they are made up largely of raw or treated sewage, where they have occasionally run up to 1 ppm or higher. Ground waters have ranged from zero to several parts per million, depending upon the proximity to sewage entry points.

Use of tpABS was discontinued by the United States detergent industry in mid-1965 in favor of linear alkylate sulfonate (LAS) and other surfactants more easily decomposed by bacterial action. Thus surfactants originating from detergents

will be a diminishing factor in the problems of sewage contamination still facing us. Nevertheless it seems appropriate at this time to bring together data relevant to the margin of safety which we can expect.

In this particular context we will primarily consider the anionic and the nonionic surfactants. Cationics are used in relatively small quantities, mainly as bactericides and sanitizers rather than as detergents, and the quantity appearing in wastewaters is completely insignificant. Furthermore, cationic surfactants are neutralized, chemically and functionally, by an equivalent amount of anionic surfactant, so that they do not exist in free form in the presence of excess anionic.

Anionic and nonionic surfactants are relatively non-toxic to mammals, falling in the same general range as sodium chloride or sodium bicarbonate. Prolonged ingestion of hundreds or thousands of milligrams per day has been found harmless to humans, thousands of times the amounts which would enter through use of municipal drinking water where tpABS levels have averaged well below 0.1 ppm (one-tenth of a milligram per liter).

The references forming the basis for the above generalization are listed in full in the following sections. Tabulations of much of the data is beyond our scope, because a multitude of experimental details and variables and qualifying circumstances would have to be enumerated for intelligent use and comparison of the exact numerical results; direct consultation of the original publication is advisable. In some cases complete information is not given even in the original, particularly with respect to the exact chemical nature or structure of the surfactant used.

Literature coverage in this survey is intended to be reasonably complete. Two main handicaps were encountered: first, it is not possible to define rigidly the exact limits of the subject matter; and second, the broad interdisciplinary interest has resulted in papers scattered through a multitude of peripheral journals.

2. Exposure Levels in Our Environment

To establish a frame of reference for the toxicity data which follow, we shall first consider the typical amount of surfactant of detergent origin ingested by the average person. The indications are that this is somewhere in the vicinity of one milligram per day.

Municipal drinking waters of 32 U.S. cities have shown tpABS levels from zero to 0.14 ppm, averaging about 0.025 ppm (AASGP 1961). An upper limit of 0.5 ppm for anionic surfactant content was established for aesthetic (rather than toxicity) reasons in the U.S. Public Health Service Drinking Water Standards (1962), although well water may occasionally be grossly contaminated with sewage and show tpABS levels of 1 ppm or more. Assuming that a person drinks two liters of water per day, the tpABS intake would be 0.05 milligrams from the average municipal water, or 1 milligram at the upper limit of the USPHS Standards.

Krüger (1960, p. 291) reports that intake of surfactant through imperfect rinsing of dishes and utensils has been estimated at around 100 milligrams per year, or 0.3 mg. per day. A study by the British Committee on Synthetic Detergents indicated that unrinsed vessels imparted 0.2 to 1 ppm of surfactant to the water when refilled (Ministry of Housing, 1956, p. 10). Assuming a water use of 2 liters per day this would correspond to 0.4 to 2 milligrams per day. Borneff (1957, p. 592) estimates the average intake as about 0.01 milligram per kilogram per day, or 0.5 to 1 milligram per person. Measurements by Wedell (1964) led to a value of about 0.4 milligrams per day.

Use of tpABS for washing foods has been approved by the U.S. Food and Drug Administration (1964a). However, published data are scanty on amounts of surfactant residues remaining after rinsing, presumably because this is not a common household practice. Shinoda (1962) reports 0.1 to 0.2 milligrams of tpABS remaining per 100 grams of cabbage, and if we assume this to be typical we again may estimate a daily intake in the order of magnitude of one milligram.

Another entry route for surfactants into the human system is via toothpaste. The usual formulation contains 1-2% of surfactant, which would amount to perhaps 10-20 milligrams per use. If 1-2% of this is swallowed or absorbed that would amount to 0.1 to 0.4 milligrams.

Summing up all of these, we can estimate that the average intake of surfactants of detergent origin may range between about 0.3 and 3 milligrams per person per day.

There is another class of surfactant compounds which has no detergency properties and does not properly fall into the scope of the present discussion because they are not used in commercial detergent formulations. These are the emulsifiers used in certain foods at levels up to around 0.5%. Pratt (1952) has estimated an average intake around 500 milligrams per person per day; their harmless nature has, of course, been demonstrated (page 5).

3. Acute Toxicity

The toxic level of a substance for human beings is ordinarily estimated from the results of animal experimentation. Table 1 shows data on the acute oral toxicity of various surfactants when fed to various mammals, expressed as the LD_{50}, the lethal dose of substance per kilogram of body weight which in a single administration will on the average kill half of the animals in the test group. Such data are only semi-quantitative, depending on many experimental variables as discussed by Treon (1962) and Griffith (1964). Furthermore, extrapolation from other animals to human beings introduces some further uncertainty; for example see Brodie (1965). Nevertheless, extreme precision is unnecessary for our present purpose, since it will be evident that the margin of safety is very great when we are considering environmental exposures to surfactants.

For example, the first section of Table 1 shows that the LD_{50} of alkylbenzene sulfonates is in the range of 500 to 3000 milligrams per kilogram. The lower figure corresponds to a dose of about one ounce for an individual weighing 120 pounds, some 25,000 times greater than the daily intake estimated in Section 2. The higher figure is in the same order of magnitude as sodium chloride (3100 mg./kg.) or sodium bicarbonate (4300 mg./kg.) as reported by Snyder (1964).

Other anionic surfactants, the sulfates and sulfonates listed in Table 1, fall in this same toxicity range. Some of the nonionics do also, while others exhibit still lower toxicity. The cationic surfactants listed in the table likewise overlap the anionics, but they are in general somewhat more toxic. The only human fatality that has been reported resulted from ingestion of a cationic — less than one ounce of an alcoholic disinfectant containing 10% of a quaternary ammonium derivative. It was determined that alcohol increased the toxicity of the cationic (Adelson, 1952).

4. Chronic Toxicity

Although the probability of acute poisoning by detergent type surfactants is vanishingly small, prolonged ingestion of smaller amounts of surfactants should also be examined for undesirable effects.

Controlled observations upon humans are possible at levels below the acute toxicity limit, and the potential usefulness of surfactants in medicine has led to many investigations, such as those reviewed by Borneff (1957). Table 2 lists several experiments in which surfactants were fed to human volunteers over long periods at levels 100 to 10,000 times as great as the 1 milligram per day estimated normal ingestion. No harmful effects could be found as judged by the many criteria listed in Table 2.

Exposure of workmen in surfactant manufacturing plants over long periods of time has also been cited as evidence for their lack of toxicity, for example by Benaglia (1943) for dialkyl sulfosuccinate. Sakabe (1962) measured the amount of tpABS dust inhaled by workmen as about 4.5 milligrams per hour; no clinical effects were found, although skin irritation did result from the prolonged external contact.

The use of surfactants at extremely high levels in medicated sprays or aerosols has been examined. Hall (1950) studied four different anionic surfactants and found that aerosols produced from water containing 1000 ppm of surfactant had no adverse effects on guinea pigs when inhaled 8 hours per day for 6 days, but that at 5,000 ppm there was difficulty in breathing and at 10,000 ppm some deaths resulted. Histological changes in the lungs were noted at the two higher levels. Hall's four anionics were two alkyl sulfates, an alkylaryl sulfonate and a dialkyl sulfosuccinate. Grubb (1960) reported that lauryl alcohol EO(7) showed no harmful effects when inhaled from a vaporizer by rats or humans.

Numerous prolonged animal feeding experiments are listed in Table 3. Perhaps the most significant are the two-year rat studies (which encompass the entire lifetime of the experimental animals). Typical results include those of Bornmann (1963) who administered both tpABS and LAS in the drinking water at 100 ppm. The daily consumption of water was 20-30 ml. of water per animal, making the ABS dose 2-3 mg. This is the same order of magnitude as the estimated daily human intake, but since a rat weighs half a kilogram or less the rat dose per kilogram was more than 100 times the human. Tusing (1960) and Paynter (1960) used dose levels up to ten times higher yet. All of these studies showed no significant difference between the alkylbenzene sulfonate fed animals and the controls. Similar results were obtained in most of the other studies in Table 3. Even in the case of the cationic surfactants no effects were noted except for doses very much higher than can be anticipated in the general human environment.

Daily doses of alkylbenzene sulfonates as high as 50% of the LD_{50} were administered to rats by Hine (1953) up to 45 days with no noticeable effect, and up to 10% by Garshenin (1963) with little effect. On the other hand, Hopper (1949) tested 17 different surfactants at 10% of the LD_{50} in daily doses and found significant mortality for many of them within a month. Needless to say, these exposures are many orders of magnitude higher than found in our environment.

In addition to tests over one lifetime, experiments have been carried still further to determine any possible effect upon reproduction or offspring. Table 4 lists a number of studies which show that alkylbenzene sulfonates and several other surfactants in the diet of rats had no detectable effects at least into the second generation of offspring. Petri (1961) mentions a harmful effect upon pregnant guinea pigs when their drinking water contained 2% (20,000 ppm) of various unspecified detergents; details of this work do not appear to have been published but its significance in terms of actual environmental exposures is questionable.

In addition to the long term feeding studies on mammals listed in Table 3, there are many papers in the literature on the use of surfactants at the 0.1 to 1% level in the diet of poultry to improve their rate of growth and efficiency of feed utilization; for example see Bolton (1961), Havermann (1957), Knauth (1964), Ney (1954), Ringrose (1959), Stern (1953). Although there is considerable disagreement as to achieving the desired effects, there is no indication that surfactants are harmful to the birds at these relatively high levels.

Certain nonionic products have been used for many years as food additives to impart a variety of desirable properties, and much of the toxicity data on nonionics were originally determined with such use in mind. Not having been designed with good washing and cleaning properties, in general these products are not used in commercial detergents. The Food Protection Committee of the National Research Council (1956) has reviewed surfactants as food additives with the conclusion that surface activity itself is not a measure of toxicity and that the safety of each surfactant for use in food must be determined separately as with every other material regardless of type. Keyworth (1956) has also contributed a review of this subject. Recent approvals by the U.S. Food and Drug Administration (1960, 1964b, c) include the use of fatty acyl sorbitan ethoxylates at levels up to about 0.5% in certain foods and beverages.

5. Solubilization and Synergy

In addition to the preceding data which show quite conclusively that surfactants themselves present no particular hazard to mammals, one further area has been studied: can surfactants enhance the activity of other potentially harmful agents in our environment? Such effects might arise (1) simply from their surfactant properties which conceivably might influence the solubility, dispersion, mobility or penetration of other materials, or (2) from synergy, the enhancement (or repression) of activity of two or more compounds together compared to the activity of either alone.

a. Cancer

Borneff (1959a) has discussed the possible interaction of surfactants with the carcinogenic hydrocarbons which may be present in soot, engine exhaust fumes, asphalt and the like, suggesting that surfactants might increase the concentration of such materials dissolved in water supplies. Subsequently, Borneff (1960, 1963) experimentally demonstrated the incidence of stomach tumors, including carcinomas, in mice which had been given water containing 3% (30,000 ppm) detergent and 10 ppm of a carcinogenic hydrocarbon (benzopyrene) in their drinking water for most of their lifetime, about 400 days. When the benzopyrene was given in the food the incidence of tumors was considerably lower and there were no carcinomas; here the presence or absence of detergent in the water made no difference. Without benzopyrene but with detergent the total tumor incidence was still lower (again no carcinomas); this group showed a somewhat higher incidence of hyperkeratosis and somewhat lower incidence of lung adenoma than did the corresponding controls. The detergent used was a proprietary formulation, not characterized as to chemical nature or content of surfactant. Borneff (1959b) elsewhere stated that it contained both anionic and nonionic surfactants.

Borneff concluded in view of these results that the household use of and resulting ingestion of detergents presents no hazard, either from enhancement of carcinogenic action of other materials in the diet or from toxicity of the detergent itself. His question, not completely answered in this study, as to whether

drinking water made from detergent-containing river water presents a hazard has been subsequently answered. He recognized that the solubilization of carcinogenic hydrocarbons should not occur at surfactant concentrations found in sewage and rivers since these are far below the critical micelle concentration. Experimental evidence has since been presented by Böhm-Gössl (1965) for benzopyrene. Its solubility in water is well below 0.01 ppm and remains at that level in the presence of increasing amounts of tpABS or LAS up to above the critical micelle concentration. Only when the surfactant concentration exceeds about 300 ppm in hard water or 500 ppm in distilled water does solubilization begin to occur. Thus although Borneff was able to dissolve 10 ppm of benzopyrene in his 30,000 ppm detergent water for his feeding experiments, it is evident that this could not have been accomplished with surfactant concentrations of 1-10 ppm and that the hazard from this source is negligible.

Borneff (1960) suggested further that if the solubilization hazard does indeed exist, the preferred way to eliminate it would be the development of biodegradable surfactants by the detergent industry. As indicated in Section 1, this has now been accomplished.

Not only is the danger of enhancement negligible, as suggested by the above work; there is indeed some indication that at the same high surfactant levels used in the other studies, an actual inhibiting action may be exerted. Hodes (1960) reported growth inhibition of Ehrlich ascites tumor cells caused by in vitro treatment with sodium lauryl sulfate or with a nonylphenol polyethoxylate prior to inoculation into mice. Surfactant concentrations were not specified but were presumably in the range of 1000-5000 ppm judging by other work cited. Experiments with the cationic lauryl pyridinium chloride were inconclusive because the animals died before tumor growth occurred. Unfortunately, there was no inhibition of tumor growth when untreated cells were injected, followed a week later by injection of surfactant. A similar reduction of infectivity was noted by Guerritore (1959) in Rous sarcoma extracts upon addition of sodium dodecyl sulfate.

Although it does not fall directly within the scope of this review because unrelated to sewage-borne waste detergents and because it does not involve detergent type surfactants, one other area of cancer research may be mentioned briefly. Certain materials exhibit a tumor-promoting action, although not tumorigenic themselves. That is, continued application to the skin will cause the development of tumors in animals which have previously been treated with a small dose of carcinogenic material, insufficient to cause tumors unaided. This phenomenon is not a causative factor in our environment because repeated applications of massive amounts of the tumor promoter are required for its action to be exhibited; its major significance is that it provides another research tool useful in developing an understanding of the fundamental biochemical principles and processes of cancer origin and development.

In his review of tumor-promotion, Setälä (1961) points out that there is a whole spectrum of such agents now known, and that new ones are being continually discovered. One of the earliest known was oleic acid, and one of the most useful is a surfactant, a fatty acyl sorbitan ethoxylate containing about 20 EO units. The irrelevance of these tumor-promoting properties to hazards in ordinary use has been pointed out by Shubik (1958b), Della Porta (1960), Saffiotti (1963) and Poel (1963) (in fact Poel was unable to induce tumors at all), and is attested by the continued approval of use of the fatty acyl sorbitan ethoxylates as food additives given by the U.S.

Food and Drug Administration (1960, 1964b, c).

Shubik (1958a) examined two alkylbenzene sulfonates and three types of nonionic surfactant and found no tumor-promotion by any of them, and Opdyke (1964) reported absence of tumor-promotion by a detergent formulation containing 20% tpABS. This is consistent with the view expressed by Setälä (1961) that surface activity has no necessary relationship with tumor-promoting properties. Saffiotti (1962) reported that commercial alkylbenzenes, alkylbenzene sulfonates and petroleum ether extracts of the sulfonates were themselves all without carcinogenic activity, but that the unsulfonated alkylbenzenes did have a small degree of tumor-promoting activity when applied in conjunction with a carcinogen. Tusing (1962) examined two other anionic surfactants for skin tumorigenicity in mice, also with negative results.

Altogether the evidence is quite conclusive that environmental exposure to surfactants introduces no cancer hazards.

b. Infections, Toxins and Bacterial Travel

It has been found that surfactants do not aid bacteria or viruses in penetrating body membranes or other defenses against infection, despite their wetting and dispersing powers. This question has been investigated by Borneff for several infective agents as tabulated in Table 5. The first two entries in the table indicate some infections, but this was attributed to the general poor health of the animals caused by the high levels of surfactant fed rather than to any promoting activity of the surfactant. At the lower levels, still much higher than found in the normal human environment, no differences in infectivity were found between the surfactant-fed animals and the controls.

Gershenfeld (1941) investigated the influence of surfactants upon antiseptics in the protection of rabbits against infection by *Staphylococcus aureus* culture applied in skin puncture wounds. Addition of 10,000 ppm of surfactant (several dozen varieties, most of them anionic sulfates or sulfonates) had no effect, either positive or negative, upon infection or healing of the wound. (Nor did the antiseptics themselves; all wounds, with or without antiseptic or surfactant, healed in the same period of time and without infection.)

Bacterial toxins from many species are inactivated by natural and synthetic surfactants (Glassman, 1948). For example, Macfarlane (1941) found that 250-2500 ppm solutions of sodium dodecyl sulfate inhibited the activity of *Clostridium welchii* toxin to the extent of 80-100%, and Glassman (1950) inactivated type B botulinum toxin with either anionic or cationic, but not nonionic, surfactants. One exception has been noted by Pannell (1955), who reported that 5000 ppm solutions of several anionics and cationics enhanced several fold the toxicity of plague toxin (from *Pasteurella pestis*), as determined by injection into mice. Several nonionics were inactive. The concentrations and other conditions, for either enhancement or inactivation, are of course not at all pertinent to the environmental exposures which are under consideration in this review.

Surfactants do not facilitate the movement of bacteria through soil, and hence do not influence the spread of infections via groundwater. This question was investigated by Robeck (1962), who found that tpABS at 10 ppm had no influence on the travel of coliform bacteria through soil.

c. Promotion of Absorption

Woodard (1945) reported that various anionic surfactants "when reasonable concentrations were used" had no influence on intestinal absorption of glucose, nor on the acute toxicity of ethanol,

chloracetic acid or hydroquinone. At higher concentrations, very much higher than encountered in our environment, Table 6 indicates that surfactants may promote the absorption of various materials through the walls of the gastrointestinal tract. This may arise in part from supplementing the body's own surfactants, the bile acids, but still does not seem to be entirely a consequence of surface activity per se. It has been applied to improving the efficiency of nutrition and medication mentioned above (pp. 4, 5), but cannot be considered as contributing to any environmental hazard.

ABBREVIATIONS

ABS – Alkylbenzene sulfonate. This is properly a generic term covering any benzene sulfonate with alkyl substituents. The term is used in the field of detergent technology in a more restricted sense to designate those with detergent or surfactant properties, for which the alkyl group is usually in the range from 10 to 15 carbon atoms. It has often been improperly used without qualifying modifier to designate one specific type of ABS, that derived from tetrapropylene.

tpABS – ABS in which the alkyl group is derived from tetrapropylene.

LAS – Linear alkylate sulfonate. ABS in which the alkyl groups are linear, ordinarily in the range from 10 to 15 carbon atoms.

ppm – parts per million. One milligram per liter of water is almost exactly one part per million, and the terms are used interchangeably in this review.

EO – used here to indicate ethylene oxide condensates in which the numerical designation indicates mols of EO per mol of base.

TABLE 1
Acute Oral Toxicity of Surfactants to Mammals

Surfactant	LD_{50} mg/kg	Animal	Reference
ALKYLBENZENE SULFONATE (Note 1)			
tpABS	1220	Rat	Bornmann 1961
LAS	1260	Rat	Bornmann 1961
	2500	Rat	Cabejszek 1963
	2200	Rat	Drachev 1965
Dodecylbenzene	2300	Rat	Drachev 1965
	2300	Rat	Garshenin 1963
	2000	Mouse	Hopper 1949
Decylbenzene	2100	Mouse	Hopper 1949
	2000	Mouse	Hine 1953
	2320	Rat	Hine 1953
	1130	Hamster	Hine 1953
	1730	Rabbit	Hine 1953
	1400	Mouse	Okahara 1963
(Note 2)	1400	Rat	Olson 1962
tpABS	520	Rat	Oser 1965
LAS	650	Rat	Oser 1965
	1400	Rat	Smyth 1941
(Note 3)	2200-3200	Rat	Snyder 1964
(Note 3)	4600	Mouse	Snyder 1964
	1500	Rat	Woodard 1945
	2800	Mouse	Woodard 1945
Decylbenzene	2000	Mouse	Woodard 1945
ALKYL SULFATE			
Lauryl	1300	Rat	Olson 1962
Lauryl	2730	Rat	Smyth 1941
Lauryl	1000	Rat	Woodard 1945
2-Ethylhexyl	4125	Rat	Smyth 1941
2-Ethylhexyl	1520	Guinea pig	Smyth 1941
7-Et-2-Me-undecyl-4	1250	Rat	Smyth 1941
7-Et-2-Me-undecyl-4	650	Guinea pig	Smyth 1941
3, 9-diEt-tridecyl-6	1430	Rat	Smyth 1941
3, 9-diEt-tridecyl-6	425	Guinea pig	Smyth 1941
SULFATED NONIONIC			
Lauryl alcohol EO (3)	1820	Rat	Tusing 1962
Octylphenol EO	3700-5400	Rat	Finnegan 1953
MISCELLANEOUS SULFONATES			
Alkane	2700	Rat	Drachev 1965
Alkane	3000	Rat	Garshenin 1963
Hydrocarbon	4000+	Rat	Woodard 1945
Lauryl glyceryl ether	1820	Rat	Tusing 1962

TABLE 1 – (Continued)

Surfactant	LD_{50} mg/kg	Animal	Reference
Oleoyl methyl tauride	6600	Mouse	Hopper 1949
Oleoyl methyl tauride	4000+	Rat	Woodard 1945
Oleoyl methyl tauride	6300	Mouse	Woodard 1945
Isopropylnaphthalene	1900	Mouse	Hopper 1949
Butyl biphenyl	3400	Mouse	Hopper 1949
Butyl phenylphenol	2200-3800	Mouse	Hopper 1949
Ethyl phenylphenol	2000	Rat	Woodard 1945
Dodecyl diphenyl ether	700	Rat	Olson 1962
Alkylarylamine	2800	Mouse	Woodard 1945
Dioctyl succinate	4800	Mouse	Hopper 1949
Dioctyl succinate	1900	Rat	Olson 1962
Octylphenol EO (Note 4)	4900	Rat	Finnegan 1953
NONIONIC			
Stearoyl EO (8)	20,000–27,000	Hamster	Eagle 1956
Stearoyl EO (8)	53,000–64,000	Rat	Eagle 1956
Stearoyl EO (8)	12,000+	Rabbit	Eagle 1956
Fatty acyl EO	25,000+	Mouse	Hopper 1949
Lauryl alcohol EO (4)	5000-7600	Mouse	Treon 1962
Lauryl alcohol EO (4)	8600	Rat	Treon 1962
Lauryl alcohol EO (7)	1170	Mouse	Grubb 1960
Lauryl acohol EO (7)	4150	Rat	Grubb 1960
Lauryl alcohol EO (9)	3300	Mouse	Berberian 1965
Lauryl alcohol EO (23)	3500	Mouse	Treon 1962
Lauryl alcohol EO (23)	8600-9350	Rat	Treon 1962
Stearyl alcohol EO (2)	25,000+	Rat	Treon 1965
Stearyl alcohol EO (10)	2900	Rat	Treon 1965
Stearyl alcohol EO (20)	1900	Rat	Treon 1965
Oleyl alcohol EO (2)	25,800	Rat	Treon 1965
Oleyl alcohol EO (10)	2700	Rat	Treon 1965
Oleyl alcohol EO (20)	2800	Rat	Treon 1965
Fatty acyl sorbitan EO (20)	37,000–60,000+	Rat	Eagle 1956
Fatty acyl sorbitan EO (20)	18,000	Hamster	Eagle 1956
Fatty acyl sorbitan EO (20)	25,000+	Mouse	Hopper 1949
Fatty acyl sorbitan EO (20)	20,000+	Rat	Krantz 1951
Fatty acyl sorbitan EO (20)	20,000+	Rat	Treon 1965
Octyl phenol EO (1)	7000	Rat	Finnegan 1953
Octyl phenol EO (3)	4000	Rat	Finnegan 1953
Octyl phenol EO (5)	3800	Rat	Finnegan 1953
Octyl phenol EO (8-10)	1800	Rat	Finnegan 1953
Octyl phenol EO (12-13)	1900	Rat	Finnegan 1953
Octyl phenol EO (16)	2800	Rat	Larson 1963
Octyl phenol EO (20)	3600	Rat	Larson 1963

TABLE 1 – (Continued)

Surfactant	LD_{50} mg/kg	Animal	Reference
Octyl phenol EO (30)	21,000	Rat	Larson 1963
Octyl phenol EO (40)	28,000+	Rat	Larson 1963
Nonyl phenol EO (9-10)	1600	Rat	Olson 1962
Lauric diethanolamide	2700	Rat	Olson 1962
CATIONIC			
Quaternary ammonium	235	Rat	Alfredson 1951
Quaternary ammonium	390-1000	Rat	Finnegan 1953, 1954
Quaternary ammonium	340-2000	Mouse	Hopper 1949
Quaternary (Note 5)	230-730	Rat	Shelanski 1949
Quaternary (Note 5)	160-315	Guinea pig	Shelanski 1949
Quaternary ammonium	410-1600	Rat	Treon 1962
Quaternary ammonium	350	Rat	Woodard 1945
Quaternary pyridinium	470-2500+	Mouse	Hopper 1949
Quaternary pyridinium	200-250	Rat	Nelson 1946
Quaternary pyridinium	230	Rat	Shelanski 1949
Quaternary pyridinium	200	Guinea pig	Shelanski 1949
Quaternary pyridinium	400+	Rabbit	Warren 1942
Lauryl imidazoline	3200	Rat	Olson 1962

Note 1. Exact chemical structure of alkylbenzene sulfonate often unspecified; in such cases probably derived from kerosene or from tetrapropylene.

Note 2. Triethanolamine salt.

Note 3. Detergent formulation containing 20% surfactant.

Note 4. Octyl phenol ethoxylate sulfonate.

Note 5. Ammonium and pyridinium.

TABLE 2
Surfactant Feeding Experiments – Humans

Surfactant	Dose, mg/day	Duration	No. Subjects	(Note 1) Effect	Reference
ANIONIC					
Alkyl aryl sulfonate	100	4 mo.	6	o	Freeman 1945
Alkyl sulfate	1000	8 wk.	1	o	Fogelson 1944
Alkyl sulfate	1000	30 d.	34	o	Fogelson 1944
Alkyl sulfate	6000-9000	25-38 d.	4	o	Kirsner 1944
Hexadecyl sulfate	3600	15-80 d.	18	o, x	Prudden 1950
NONIONIC					
Stearoyl EO (40)	4500-6000	12 d.	8	o	Culver 1951
Oleoyl sorbitan EO (20)	4500-15,000	½-9 mo.	2+	o	Jones 1948
Oleoyl sorbitan EO (20)	4500-6000	1-4 yr.	100+	o	Krantz 1951

Note 1. o = no deleterious effects attributable to the surfactant.

x = no serious effects attributable to the surfactant.

Effects judged on the basis of such considerations as subject's feelings, body weight, metabolic rate, blood picture, liver function and kidney function. Tests included blood pressure; red and white cell count; hemoglobin; blood calcium, phosphorus, vitamin A, urea nitrogen, non protein nitrogen; serum albumin, globulin, bilirubin, cholesterol, cholesterol esters; differential blood smear; prothrombin time; intravenous hippuric acid test; cephalin flocculation; bromsulfalein retention; thymol turbidity; kidney concentrating action; urea clearance test; urine albumin; fecal fat, nitrogen.

TABLE 3
Surfactant Feeding Experiments – Animals

Surfactant	Animal	Dose (Note 1)	Duration	Effect (Note 2)	Reference
ALKYLBENZENE SULFONATE (Note 3)					
	Pig	2000 ppm-food	—	o	Beeson 1953
tpABS	Rat	2-3 mg/d	2 yr.	o	Bornmann 1963
LAS	Rat	2-3 mg/d	2 yr.	o	Bornmann 1963
	Rat	100 mg/kg/d	—	o	Cabejszek 1963
	Rat	10,000 ppm-food	4 mo.	o	Fitzhugh 1948
	Dog	80 mg/kg/d	6 mo.	o	Freeman 1945
	Rat	5000 ppm-food	65 d	o	Freeman 1945
	Rat	0.1 LD_{50}/day	45 d	x	Garshenin 1963
(Note 4)	Pig	9000 mg/day	206 d	o	Havermann 1954
	Rat	20 ppm-food	6 mo.	o	Hine 1953
	Rat	0.5 LD_{50}/day	45 d	o	Hine 1953
	Rabbit	100 mg/day	20 d	x	Hueper 1944
C_6, C_{10}, C_{12} alkyl	Rat, dog	5000 ppm-food	90 d	o	Kay 1965
tpABS	Dog	5000 ppm-food	2 yr.	o	Kay 1965
LAS	Rat	5000 ppm-food	90 d	o	Kay 1965
	Rat	30 mg/kg/d	6 mo.	o	Okahara 1963
tpABS	Rat	250 mg/kg/d	12 wk.	o	Oser 1965
LAS	Rat	250 mg/kg/d	12 wk.	o	Oser 1965
tpABS	Rat	2000 ppm-food	2 yr.	o	Paynter 1960
	Pig	2600 ppm-food	—	o	Perry 1953
	Rat	5000 ppm-food	13 wk.	o	Sanz Ibañez 1964
(Note 5)	Rat	5000 ppm-food	2 yr.	o	Snyder 1964
tpABS	Rat	5000 ppm-food	2 yr.	o	Tusing 1960
	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
ALKYL SULFATE					
Lauryl	Rat	30 mg/day	160 d.	o	Epstein 1939
Lauryl	Rat	10,000 ppm-food	2 yr.	o	Fitzhugh 1948
Lauryl	Dog	135 mg/kg/day	10 mo.	o	Fogelson 1944
Lauryl	Rat	60 mg/day	5 wk.	o	Hatton 1940
Lauryl	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
2-Ethylhexyl	Rat	175 mg/kg/day	30 d.	o	Smyth 1941
2-Ethylhexyl	Rabbit	100 mg/day	20 d.	x	Hueper 1944
7-Et-2-Me-undecyl-4	Rat	25 mg/kg/day	30 d.	o	Smyth 1941
3, 9-diEt-tridecyl-6	Rat	65 mg/kg/day	30 d.	o	Smyth 1941
SULFATED NONIONIC					
Lauryl EO (3)	Rat	5000 ppm-food	2 yr.	o	Tusing 1962
MISCELLANEOUS SULFONATES					
Alkane	Rat	0.1 LD_{50}/day	45 d.	o	Garshenin 1963

TABLE 3 – (Continued)

Surfactant	Animal	Dose (Note 1)	Duration	Effect (Note 2)	Reference
Lauryl glyceryl ether	Rat	5000 ppm-food	2 yr.	o	Tusing 1962
Oleoyl methyl tauride	Rat	20,000 ppm-food	4 mo.	o	Fitzhugh 1948
Oleoyl methyl tauride	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
Alkyl aryl	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
Butyl phenylphenol	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
Isopropyl-naphthalene	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
Lauryl benzoate	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
Dioctyl succinate	Rat	200-900 mg/kg/d	6 mo.	o	Benaglia 1943
Dioctyl succinate	Rabbit	500 mg/kg/d	24 wk.	xx	Benaglia 1943
Dioctyl succinate	Monkey	125 mg/kg/d	24 wk.	o	Benaglia 1943
Dioctyl succinate	Dog	250 mg/kg/d	24 wk.	o	Benaglia 1943
Dioctyl succinate	Rat	5000 ppm-food	2 yr.	o	Fitzhugh 1948
Dioctyl succinate	Rabbit	250 mg/day	5 mo.	o	Hueper 1944
Dioctyl succinate	Mouse	4 mg/day	7 mo.	o	Lorenz 1940
Dioctyl succinate	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
NONIONIC					
Stearoyl EO (8)	Hamster	50,000 ppm-food	—	o	Brush 1957
Stearoyl EO (8)	Mouse	50,000 ppm-food	—	o	Brush 1957
Stearoyl EO (8)	Dog	50,000 ppm-food	—	o	Brush 1957
Stearoyl EO (8)	Rat	250,000 ppm-food	21 wk.	x	Eagle 1956
Stearoyl EO (8)	Hamster	50,000 ppm-food	39 wk.	xx	Eagle 1956
Stearoyl EO (8)	Rat	20,000 ppm-food	2 yr.	o	Fitzhugh 1959
Stearoyl EO (8)	Dog	50,000 ppm-food	20 mo.	o	Fitzhugh 1959
Stearoyl EO (8)	Rat	110,000 ppm-food	1 yr.	o	Graham 1954
Stearoyl EO (8)	Rat	110,000 ppm-food	32 wk.	o	Graham 1955
Stearoyl EO (8)	Rat	250,000 ppm-food	59-70 d.	x	Harris 1951a
Stearoyl EO (8)	Hamster	50,000 ppm-food	68 d.	x	Harris 1951b
Stearoyl EO (8)	Rat	100,000 ppm-food	500 d.	o	Krehl 1955
Stearoyl EO (8)	Cat	200,000 ppm-food	1 yr.	o	Krehl 1955
Stearoyl EO (8)	Rat	200,000 ppm-food	2 yr.	o	Oser 1956
Stearoyl EO (8)	Rat	250,000 ppm-food	21 wk.	xx	Poling 1956
Stearoyl EO (8)	Hamster	50,000 ppm-food	39 wk.	xx	Poling 1956
Stearoyl EO (8)	Hamster	150,000 ppm-food	—	x	Schweigert 1950
Stearoyl EO (8)	Hamster	150,000 ppm-food	2-10 wk.	x	Wang 1950
Stearoyl EO (38)	Hamster	50,000 ppm-food	—	x	Brush 1957
Stearoyl EO (38)	Mouse	50,000 ppm-food	—	o	Brush 1957
Stearoyl EO (38)	Dog	50,000 ppm-food	—	o	Brush 1957
Lauryl alcohol EO (7)	Rat	3,400 ppm-food	4 wk.	o	Grubb 1960
Lauryl alcohol EO (9)	Rat	390 mg/kg/day	22 d.	o	Berberian 1965

TABLE 3 – (Continued)

Surfactant	Animal	Dose (Note 1)	Duration	Effect (Note 2)	Reference
Oleyl alcohol EO (20)	Rat	70 mg/kg/day	6 mo.	o	Sweeney 1953
Fatty acyl sorbitan EO (20)	Hamster	50,000 ppm-food	—	x	Brush 1957
Fatty acyl sorbitan EO (20)	Mouse	50,000 ppm-food	—	o	Brush 1957
Fatty acyl sorbitan EO (20)	Dog	50,000 ppm-food	—	o	Brush 1957
Fatty acyl sorbitan EO (20)	Hamster	50,000 ppm-food	39 wk.	xx	Eagle 1956
Fatty acyl sorbitan EO (20)	Mouse	100,000 ppm-food	26 wk.	o	Ewing 1964
Fatty acyl sorbitan EO (20)	Mouse	100,000 ppm-food	22 mo.	o	Ewing 1964
Fatty acyl sorbitan EO (20)	Rat	20,000 ppm-food	2 yr.	o	Fitzhugh 1959
Fatty acyl sorbitan EO (20)	Dog	50,000 ppm-food	20 mo.	o	Fitzhugh 1959
Fatty acyl sorbitan EO (20)	Rat	250,000 ppm-food	59-70 d.	x	Harris 1951a
Fatty acyl sorbitan EO (20)	Hamster	50,000 ppm-food	68 d.	x	Harris 1951b
Fatty acyl sorbitan EO (20)	Rabbit	20,000 ppm-food	2 yr.	o	Krantz 1951
Fatty acyl sorbitan EO (20)	Monkey	1000 mg/day	10 mo.	o	Krantz 1951
Fatty acyl sorbitan EO (20)	Rat	200,000 ppm-food	2 yr.	o	Oser 1956
Fatty acyl sorbitan EO (20)	Rat	250,000 ppm-food	21 wk.	xx	Poling 1956
Fatty acyl sorbitan EO (20)	Hamster	50,000 ppm-food	39 wk.	xx	Poling 1956
Octyl phenol EO	Rat	10,000 ppm-food	4 mo.	o	Fitzhugh 1948
Octyl phenol EO (40)	Rat	14,000 ppm-food	2 yr.	o	Larson 1963
Octyl phenol EO (40)	Dog	50,000 ppm-food	3 mo.	o	Larson 1963
Alkylphenol EO	Rabbit	250 mg/day	5 mo.	o	Hueper 1944
Alkylphenol EO	G. pig	2000 ppm-water	180 d.	o	Woodard 1945
Fatty acyl sucrose	Rat	100,000 ppm-food	2 yr.	o	Chiancone 1963
Fatty acyl sucrose	Rat	2000 mg/kg/day	90 d.	o	Hara 1960

TABLE 3 – (Continued)

Surfactant	Animal	Dose (Note 1)	Duration	Effect (Note 2)	Reference
CATIONIC					
Quaternary ammonium	Rat	2500 ppm-food	2 yr.	o	Alfredson 1951
Quaternary ammonium	Dog	1200 ppm-food	15 wk.	o	Alfredson 1951
Quaternary ammonium	Rat	2500 ppm-food	2 yr.	o	Finnegan 1954
Quaternary ammonium	Dog	500 ppm-food	1 yr.	o	Finnegan 1954
Quaternary ammonium	Rat	625 ppm-food	2 yr.	x	Fitzhugh 1948
Quaternary ammonium	Rabbit	100 mg/day	12 d.	xx	Hueper 1944
Quaternary (Note 6)	Rat	25 mg/kg/d	2 yr.	o	Shelanski 1949
Quaternary (Note 6)	G. pig	25 mg/kg/d	1 yr.	o	Shelanski 1949
Quaternary pyridinium	Rat	60 mg/kg/d	60 d.	o	Nelson 1946
Quaternary pyridinium	Dog	20 mg/kg/d	90 d.	o	Nelson 1946
Quaternary pyridinium	Rat	20 mg/d	25 wk.	o	Vivino 1946
Quaternary pyridinium	Rabbit	100 mg/kg/d	4 wk.	o	Warren 1942
Quaternary pyridinium	G. pig	2000 ppm-water	40 d.	xx	Woodard 1945
"VARIOUS DETERGENTS"					
	Rats	100 mg/kg/d	2 yr.	o	Petri 1961
	Rabbits	1000 mg/kg/d	2 yr.	o	Petri 1961

Note 1. Many of these investigators have reported results at several feeding levels. Generally those tabulated here are the highest at which no significant effects were observed. If significant effects were observed at all levels fed, the lowest of these is given.

Note 2. o = no effects, or very slight; x = noticeable effect, e.g., poor growth rate; xx = some deaths, significantly more than in control group.

Note 3. Exact chemical structure often unspecified; probably usually derived from kerosene or tetrapropylene.

Note 4. ABS + lauryl sulfate mixture.

Note 5. Detergent formulation containing 20% surfactant.

Note 6. Ammonium and pyridinium.

TABLE 4

Surfactant Feeding Studies – Fertility and Reproduction

Surfactant	Animal	Dose	Generations (Note 1)	Effect (Note 1)	Reference
ALKYLBENZENE SULFONATE					
tpABS	Rat	100 ppm-water	3	o	Bornmann 1963
tpABS	Rat	5000 ppm-food	3	o	Tusing 1960
LAS	Rat	100 ppm-water	3	o	Bornmann 1963
"alkylaryl"	Rat	5000 ppm-food	2	o	Freeman 1945
OTHER ANIONIC					
Lauryl EO (3) sulfate	Rat	1000 ppm-food	3	o	Tusing 1962
Lauryl glyceryl sulfonate	Rat	1000 ppm-food	3	o	Tusing 1962
NONIONIC					
Stearoyl EO (8)	Rat	200,000 ppm-food	3	o	Oser 1956
Stearoyl EO (40)	Rat	200,000 ppm-food	3	o	Oser 1956
Fatty acyl sorbitan EO (20)	Rat	20,000 ppm-food	3	o	Krantz 1951
Fatty acyl sorbitan EO (20)	Rat	200,000 ppm-food	3	o	Oser 1956
Fatty acyl sucrose	Rat	—	2	o	Colson 1964
CATIONIC					
Quaternary	Rat	25 mg/kg/d	3	o	Shelansky 1949
Quaternary pyridinium	Rat	20 mg/d	3	o	Vivino 1946
"VARIOUS DETERGENTS"					
	G. pig	20,000 ppm-water	—	M	Petri 1961

Note 1. 3-o: Parents fertile, F_1 fertile, F_2 normal; 2-o: Parents fertile, F_1 normal; M: Frequent miscarriage.

TABLE 5
Surfactants and Infection

Infective Agent	Animal	Surfactant	Surfactant Dose	Result (Note 1)	Reference
E. coli plus *Strep. mucosus*	G. pig	Hostapon	66-100 mg/kg/d	±	Borneff 1957
	G. pig	Hostapon	325 mg/kg/d	±	Borneff 1957
Salmonella typhi-murium	Mouse	Pril-flüssig	0.2 mg/day plus 330 ppm-water	o	Borneff 1957
Tubercle bacillus	G. pig	Hostapon	15 mg/kg/d	o	Borneff 1959b
Tubercle bacillus	G. pig	Pril-flüssig	0.25 mg/kg/d	o	Borneff 1959b
Encephalomyelitis (Theiler-virus)	Mouse	tpABS	12.5-125 mg/kg/d	o	Borneff 1962
Encephalomyelitis (Theiler-virus)	Mouse	Lauryl sulfate	12.5-125 mg/kg/d	o	Borneff 1962

Note 1. o = No significant difference between surfactant fed animals and controls.
± = Increased morbidity of surfactant-fed animals, but not necessarily linked to infection-promotion by surfactant.

TABLE 6
Surfactants and Gastro-Intestinal Absorption

Surfactant	Surfactant Dose	Material Absorbed	(Note 1) Result	Reference
ANIONIC				
Alkylbenzene Sulfonate	400 mg/kg	Mg^{++}ion	+	Opitz 1961
Alkylbenzene Sulfonate	20,000 ppm	Anionic dyes	+, o	Bornmann 1962
Alkylbenzene Sulfonate	20,000 ppm	Cationic dye	–	Bornmann 1962
Lauryl sulfate		Glucose	+	Kozlik 1956
Lauryl sulfate	25,000 ppm	Glucose	+	Mosinger 1956
Lauryl sulfate		Mg^{++}ion	+	Kozlik 1955
Lauryl sulfate		Calcium	+	Webling 1965
Lauryl sulfate		Iron	o	Brise 1962
Lauryl sulfate		Vitamin A ester	+, –	Fuchs 1954
Lauryl sulfate (Note 2)		Anionic dye	+	Lish 1959
Lauryl sulfate (Note 2)		Cationic dye	o	Lish 1959
Lauryl sulfate	100 ppm	Cationic dyes	+	Appel 1957
Lauryl sulfate		Strophanthin	+	Eybl 1957
Lauryl sulfate	10 mg	Strophanthin	+	Krause 1955
Dioctyl sulfosuccinate	250 mg/day	Cholesterol	–	Hueper 1944
Dioctyl sulfosuccinate		Iron	o	Brise 1962
Various Anionics		Glucose	–	Woodard 1945
NONIONIC				
Dodecyl alcohol EO	500 ppm	Digitalis	+	Nakano 1953b
Oleyl alcohol EO		Strophanthin, digitoxin	–	Nakano 1953a
Alkylphenol EO	250 mg/day	Cholesterol	+	Hueper 1944
Octylphenol-CH_2O EO	600 mg/kg	Corn oil	–	Tidwell 1965
Fatty-acyl sorbitan EO (20)	4500 mg/day	Fats, Vitamin A	+	Jones 1948
Fatty-acyl sorbitan EO (20)	3000 mg/day	Cholesterol	+	Kellner 1948
Fatty-acyl sorbitan EO (20)	<500 ppm	Strophanthin	+	Nakano 1953a
Fatty-acyl sorbitan EO (20)	>500 ppm	Strophanthin	–	Nakano 1953a
Fatty-acyl sorbitan EO (20)	10,000 ppm	Digitalis	+	Nakano 1953b
Fatty-acyl sorbitan EO (20)		Iron	o	Brise 1962
Fatty-acyl sorbitan EO (20)	50,000 ppm	Iron	+	Mori 1957
Fatty-acyl sorbitan EO (20)	16,000 mg/d	Penicillin	o	Schwartz 1949
Fatty-acyl sorbitan EO (20)	75,000 ppm	Salicylamide	–	Yamada 1965
CATIONIC				
Quaternary ammonium		Glucose	–	Nissim 1960

Note 1. + = Increased absorption. o = No effect. – = Decreased absorption.
Note 2. Similar results with dioctyl sulfosuccinate.

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