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Final Report on the Safety Assessment of Nonoxynols -2, -4, -8, -9, -10, -12, -14, -15, -30, -40, and -50

Nonoxynols are chemically stable ethoxylated alkylphenols which are chemically foaming and solubilizing agents. Estimates of the acute oral LD50s of nine of the Nonoxynols (-2 to -15) range from 0.62 to 7.4 g/kg in several animal species. Acute dermal toxicity studies in rabbits produced an LD50 range of 1.8 ml/kg to 4.4 g/kg. Skin irritation tests on rabbits indicated that Nonoxynols are nonirritating to moderately irritating. Nonoxynol compounds with short ethoxylated chains are generally severe ocular irritants, whereas long-chained Nonoxynols are only slightly irritating to the rabbit eye. No evidence of carcinogenicity was observed when Nonoxynol-4 and -9 were fed to both dogs and rats. A mutagenicity study of these two compounds by the Ames test was negative.

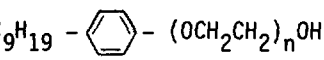
Undiluted Nonoxynol-4 and -9 were nonirritating and nonsensitizing in clinical studies. A 50% solution of Nonoxynol-15 and/or Nonoxynol-50 produced no irritation or sensitization when tested on 168 subjects, nor was there evidence of phototoxicity when tested on a subset of this population.

It is concluded that Nonoxynols -2, -4, -8, -9, -10, -12, -14, -15, -30, -40, and -50 are safe as cosmetic ingredients.

CHEMICAL AND PHYSICAL PROPERTIES

Structure

Nonoxynols (or nonylphenoxy polyethoxy ethanols) are ethoxylated alkylphenols which conform to the formula:



where n can vary from 1 to 100.[1-3] The nonyl group, a branched propylene trimer, is located in the para position to the polyethoxy side chain on the

benzene ring.[2] Nonoxynols are nonionic surface active agents in which the nonpolar alkyl chain has lipophilic properties and the polar polyoxyethylene portion of the molecule has hydrophilic properties.[4]

Many alkylphenols are synthesized commercially by the Fiedel–Crafts alkylation of a phenol with an olefin. Catalysts used in this reaction include boron trifluoride, boric, oxalic, sulfuric, tetraphosphoric, toluene sulfonic acids, and ferric chloride. The resulting monoalkylphenol contains over 90% of the adduct substituted in the para position. The product is then purified by distillation and ethoxylated, in the presence of trace amounts of NaOH catalyst; an appropriate number of moles of ethylene oxide (EO) must be added to produce the required alkylphenol ethoxylate.[2,5]

Nonoxynol-9 is manufactured by reacting commercial nonylphenol with EO. The number of moles of EO various from 5 to 18 with an average value of 9. Excess reactants are removed under a high vacuum manifold.[6] The preparation of other Nonoxynols has been described.[7]

Additional information on the chemistry, properties and methods of manufacture of the alkylphenol ethoxylates is reported elsewhere.[5]

Physical Properties

Nonoxynols are nonionic surfactants. Those which contain short EO chains are liquids (n = 1 to 13) or paste-like liquids (n = 14,15); those with longer chains (n > 20) are waxes (Table 1). Liquid Nonoxynols are usually sold at 100% concentrations; the waxy solids may be sold as 50%–70% solutions in water.[2]

As the length of the EO chain increases, the polarity of the nonoxynol molecule increases and water solubility is enhanced. Nonoxynols -1 through -6 are oil-soluble, whereas longer chain Nonoxynols are soluble in water and other polar substances. The hydrophile–lipophile balance (HLB) values range from 3.4 for Nonoxynol-1 to 19.0 for Nonoxynol-100. Specific gravities, viscosities, and other physical and chemical data of selected Nonoxynols can be found in Table 1.[8-10]

Aqueous Nonoxynols are adsorbed at greater than 90% when passed through a column of $ZnCl_2$-activated carbon, and follow Langmuir-type isotherms. Adsorption is enhanced as the alkyl chain is lengthened.[11]

The presence of inorganic and organic salts lowers the cloud point and adsorptivity of the Nonoxynols, and for Nonoxynol-10 increases its adsorption onto activated carbon. Inorganic salts which raise the cloud point hinder adsorption. For organic salts, adsorption of Nonoxynol-10 is lowered by competition and sorption between the salts and Nonoxynol-10. An increase in the hydrophobicity of the organic salts used hinders the adsorption of Nonoxynol-10.[12]

Adsorption properties of the Nonoxynols at the electrolyte-mercury boundary have been investigated by alternating current polarography (capacity-potential relationships).[13] The adsorption of Nonoxynols by polymer substrates has also been studied.[14] Surface interactions between submicroscopic pyrogenic silica and Nonoxynols have been studied by infrared spectroscopy.[15] Such anionic aggregating materials as sodium lauryl sulfate and sodium dioctylsulfosuccinate bind to the surface of colloidal silica in the presence of Nonoxynols. The presence of Nonoxynols decreases cationic surfactant absorption. The adsorp-

Table 1. Physicochemical Properties of Nonoxynols.

Nonoxynol	Conc. (%)	Phase	HLB	Solubility	Specific gravity at 25/25°C	Viscosity at 25°C (cps)	Other properties	Color
-1	100	Liquid	3.4	Oil	–	–	–	
-2	100	Liquid	–	Oil	0.984–0.986	–	–	
-4	100	Liquid	8.9	Oil, common org. solv.	1.020–1.030	–	–	White to light amber
-5	100	Liquid	10.0	Oil	–	–	C.P. 52–62	
-6	100	Liquid	10.9	Oil, H_2O, misc., common org. solv.	1.030–1.050	150–250	–	Colorless to light amber
-7	100	Liquid	11.7	Aromatic solv.	1.055 at 20/20°C	–	S.P. −6	
-8	100	Liquid	12.3	H_2O	1.05	–	C.P. 22–28	
-8.5	100	Liquid	–	H_2O, polar org. solv.	1.040–1.060	200–300	S.P. −1.0–1.1	Pale yellow
-9	100	Liquid	12.9	Aromatic solv.	–	–	C.P. 51–56	
-9	33	Liquid	13.0	H_2O	–	–	–	
-9.5	100	Liquid	12.9	H_2O, polar org. solv.	1.040–1.060	175–250	S.P. −2.5–4.0	Colorless to light amber
-10	100	Liquid	13.5	H_2O, aromatic solv.	–	–	–	
-11	100	Liquid	–	Highly H_2O	–	–	–	
-12	100	Liquid	14.1	Highly H_2O	1.07	–	–	
-13	100	Liquid	14.4	Highly H_2O	1.07 at 20/20°C	–	C.P. 90 S.P. 6	
-14	100	Vis. Liquid	14.7	Highly H_2O	–	–	–	
-15	100	Vis. Liquid	15.0	Highly H_2O, polar org. solv.	1.060–1.080	500–600	C.P. 96 S.P. 19–21	Opaque
-20	100	Wax	15.9	H_2O	–	–	C.P. >100 P.C. 68–72	

Table 1. (Continued.)

Nonoxynol	Conc. (%)	Phase	HLB	Solubility	Specific gravity at 25/25°C	Viscosity at 25°C (cps)	Other properties	Color
-30	100	Wax	17.1	H_2O	–	–	C.P. >100	
-30	70	Vis. Liquid	17.0	H_2O misc.	1.080–1.100	–	S.P. −5.0–−3.0 P.P. 0.0–2.0	Pale yellow to light amber
-40	100	Wax	17.8	Highly H_2O	1.082 at 58/25°C	–	S.P. 67	
-40	70	Vis. Liquid	–	Highly H_2O	–	–	–	
-50	100	Wax	18.1	Highly H_2O	–	–	C.P. >100	
-50	70	Vis. Liquid	–	Highly H_2O	–	–	–	
-100	100	Wax	19.0	Highly H_2O	1.08 at 57/20°C	–	C.P. Clear at 100°C	
-100	70	Vis. Liquid	–	Highly H_2O	–	–	–	
-100	50	Vis. Liquid	–	Highly H_2O	–	–	–	

Data from Refs. 2, 8–10.
S.P. = Solidification point (°C).
C.P. = Cloud point, 1% aqueous solution (°C).
P.P. = Pour point (°C).
P.C. = C.P., 1% in 10% NaCl (°C).

tion equilibrium at the silica surface is affected by mixed micellization between nonionic (Nonoxynols) and ionic surface active agents.[16]

Stability

Nonoxynol-9 is degraded in activated sludge waste treatment by slow oxidation and hydrolysis of the alkyl group, aromatic ring, and ethoxy chain, simultaneously.[17]

In river die-away tests, Nonoxynols were not degraded in clean water; the polyether chains were degraded slowly in polluted water.[18]

Analytical Methods

Some sampling and analytic techniques used to extract Nonoxynols from environmental and synthetic substances, to separate mixtures of nonionic surfactants, and to quantify pure Nonoxynol solutions are listed below.

Methanol Extraction[19]
Thin-layer Chromatography[20]
Gel Chromatography[21]
Paper Chromatography[22]
Ion-exchange Chromatography[23]
Infrared Spectroscopy[19]
Mass Spectroscopy[24]
Ultraviolet Spectroscopy[4,23,25]
Proton Magnetic Resonance[26]
Spectrometric x-ray Fluorescence[27]

Nonoxynol molecular weight distributions and EO chain length determinations can be made by standard and circular thin-layer chromatography[28-30] and by infrared spectrophotometry.[31]

Impurities

There are no reports on the use of preservatives or antioxidant additives in the Nonoxynols.[2] There may exist in Nonoxynols trace amounts of ethylene oxide or its degradation product, 1,4-dioxane, which were not completely removed from the system.[32] Administration of 1% 1,4-dioxane in the drinking water to rats for 13 months induced hepatic lesions and hepatomas.[33]

USE

Cosmetic Uses

In cosmetic products Nonoxynols are used as emulsifying, wetting, foaming, and solubilizing agents and as protective colloids.[2] Nonoxynols are used in hair and skin care products, bath and shaving preparations, and personal cleanliness products.

Tables 2 and 3 list product types and the number of product formulations voluntarily reported to the Food and Drug Administration (FDA) in 1976 and

TABLE 2. Product Formulation Data.

Product category[a]	Total no. containing ingredient	No. of product formulations within each concentration range (%)[a]						
		>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
NONOXYNOL-2								
Hair sprays (aerosol fixatives)	10	–	–	–	–	–	1	9
Tonics, dressings, and other hair grooming aids	1	–	–	–	–	–	1	–
Personal cleanliness products	1	–	–	–	–	–	–	1
1976 TOTALS	12						2	10
NONOXYNOL-4								
Bath oils, tablets, and salts	14	–	–	–	–	14	–	–
Hair conditioners	1	–	–	–	–	1	–	–
Other hair preparations (noncoloring)	1	–	–	–	–	1	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	241	–	31	–	–	210	–	–
Hair bleaches	10	–	3	2	1	2	2	–
Face, body, and hand skin care preparations (excluding shaving preparations)	1	–	–	–	–	1	–	–
1976 TOTALS	268	–	34	2	1	229	2	–
NONOXYNOL-6								
Hair bleaches	3	3	–	–	–	–	–	–
Skin fresheners	2	–	–	–	–	2	–	–
1976 TOTALS	5	3	–	–	–	2	–	–
NONOXYNOL-8								
Bath oils, tablets, and salts	2	–	–	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	1	–	–	–	–	–	1	–
Skin fresheners	1	–	–	–	–	–	1	–
1976 TOTALS	4	–	–	–	–	–	4	–
NONOXYNOL-9								
Bath oils, tablets, and salts	8	–	–	–	–	6	2	–
Bubble baths	3	–	–	2	–	1	–	–
Other bath preparations	1	–	–	–	–	–	1	–
Fragrance preparations	3	–	–	3	–	–	–	–
Hair conditioners	1	–	–	–	–	–	1	–
Permanent waves	12	–	–	–	–	–	12	–
Hair shampoos (noncoloring)	8	–	–	–	1	6	1	–
Tonics, dressings, and other hair grooming aids	2	–	–	–	–	–	2	–
Wave sets	4	–	–	–	–	–	4	–
Other hair preparations (noncoloring)	2	–	–	–	–	2	–	–

TABLE 2. (Continued.)

Product category[a]	Total no. containing ingredient	No. of product formulations within each concentration range (%)[a]						
		>50	>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1
NONOXYNOL-9 (cont'd.)								
Hair dyes and colors (all types requiring caution statement and patch test)	52	–	43	9	–	–	–	–
Hair bleaches	6	–	1	3	–	2	–	–
Nail basecoats and undercoats	1	–	–	–	–	–	1	–
Bath soaps and detergents	2	–	–	2	–	–	–	–
Deodorants (underarm)	2	–	–	–	–	2	–	–
Douches	3	–	–	–	–	1	2	–
Other personal cleanliness products	4	–	–	–	–	2	2	–
Shaving cream (aerosol, brushless, and lather)	4	–	–	–	–	–	4	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	3	–	–	–	–	3	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	6	–	–	–	–	1	–	5
Night skin care preparations	1	–	–	–	–	–	1	–
Skin fresheners	9	–	–	–	–	3	5	1
Other skin care preparations	2	–	–	–	–	2	–	–
Suntan gels, creams, and liquids	1	–	–	–	–	1	–	–
1976 TOTALS	140	–	44	19	1	32	38	6
NONOXYNOL-10								
Hair conditioners	1	–	–	–	–	–	1	–
Permanent waves	3	–	–	–	–	–	3	–
Wave sets	1	–	–	–	–	–	1	–
Hair dyes and colors (all types requiring caution statement and patch test)	25	–	–	23	–	–	–	2
Hair bleaches	5	–	–	4	1	–	–	–
Bath soaps and detergents	1	–	–	–	–	1	–	–
Other personal cleanliness products	1	–	–	–	1	–	–	–
Shaving preparations	1	–	–	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	3	–	–	–	–	2	–	1
Paste masks (mud packs)	1	–	–	–	–	–	1	–
1976 TOTALS	42	–	–	27	2	3	7	3
NONOXYNOL-12								
Colognes and toilet waters	1	–	–	–	–	–	1	–
Hair conditioners	1	–	–	–	–	–	1	–
Hair shampoos (noncoloring)	4	–	–	–	–	3	1	–

TABLE 2. (Continued.)

Product category[a]	Total no. containing ingredient	No. of product formulations within each concentration range (%)[a]						
		>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
NONOXYNOL-12 (cont'd.)								
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	1	–	–	–	–	–	1	–
Paste masks (mud packs)	1	–	–	–	–	–	1	–
Skin fresheners	1	–	–	–	–	–	1	–
1976 TOTALS	9	–	–	–	–	3	6	–
NONOXYNOL-15								
Permanent waves	1	–	–	–	–	–	–	1
Hair shampoos (noncoloring)	1	–	–	–	–	–	–	1
1976 TOTALS	2	–	–	–	–	–	–	2
NONOXYNOL-30								
Hair bleaches	1	–	–	–	–	–	–	1
1976 TOTALS	1	–	–	–	–	–	–	1

[a]Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).

Data from Ref. 34.

1979 as containing the various Nonoxynols. In 1976, Nonoxynols -2, -4, -6, -8, -9, -10, -12, -15, and -30 were reported as ingredients in a total of 12, 268, 5, 4, 140, 42, 9, 2, and 1 cosmetic formulations, respectively, at concentrations ranging from ≤0.1% to >50%.[34] In 1979, Nonoxynols -2, -4, -6, -8, -9, -10, -12, -14, -15, -30, and -50 were reported as ingredients in 11, 66, 2, 3, 133, 10, 2, 8, 1, 2, and 1 cosmetic formulations, respectively, at concentrations ranging from ≤0.1% to >50%.[35]

Table 3. Number of Nonoxynol Products and Use Ranges.

Nonoxynol	≤0.1–0.1	>0.1–1.0	>1.0–5.0	>5.0–10	>10–25	>25–50	>50
-2	9	2	–	–	–	–	–
-4	1	10	19	1	1	34	–
-6	–	–	1	–	–	–	1
-8	–	3	–	–	–	–	–
-9	1	31	17	–	72	12	–
-10	3	2	5	1	24	–	–
-12	–	2	8	–	–	–	–
-14	–	2	–	–	–	–	–
-15	2	5	1	–	–	–	–
-30	1	–	–	–	–	–	–
-50	–	–	1	–	1	–	–

Data from Ref. 35.

The cosmetic product formulation computer printout which is made available by the FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[36] The ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

As components of at least nine major cosmetic product categories, Nonoxynols may come into contact with the skin of the face, scalp, hair, nails, and axillae, and the skin of the body.[34,35]

Products containing Nonoxynols can be used daily or occasionally and their use may extend over a period of years. Contact with such products may last from seconds to hours.

Noncosmetic Uses

The nonionic surfactant properties of Nonoxynols permit their use in a wide variety of industrial, household, agricultural, and pharmaceutical products (Table 4).

In Switzerland, the dairy industry uses iodophors containing Nonoxynol-15 in sanitizing processes; therefore, milk can become contaminated with Nonoxynol-15. Government officials in that country have established the tolerance level of Nonoxynol-15 in milk at 2.0 ppm.[37]

The FDA Panel on Review of Contraceptives has concluded that Nonoxynol-9 is safe and effective for over-the-counter (OTC) use as a vaginal contraceptive. The Panel reviewed several animal toxicology studies (including subacute feeding, excretion, acute oral toxicity, skin penetration, and primary eye irritation tests) in its determination of Nonoxynol's safety. The review included the safety and effectiveness of Nonoxynol-9 as a contraceptive for intravaginal use in humans at daily exposures of 124 mg.[38]

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

The metabolism of Nonoxynols takes place by shortening the ethylene oxide chain and some carboxylation of the alkyl chain by omega-oxidation. No metabolic formation of free phenolic groups has been reported.[39,40]

Knaak et al.[6] fed 67 mg/kg of ethylene-^{14}C oxide-labeled Nonoxynol-7, -10, -12, or -15 to groups of four rats each. Seven days cumulative ^{14}C levels in urine, feces, and expired air were determined. With increasing ethoxy chain length,

TABLE 4. Noncosmetic Uses of Specific Nonoxynols.

Nonoxynol	*Detergent*	*Emulsifier*	*Dispersant*	*Wetting*	*Others*
-1	X	X	–	–	Antifoaming agent, dry cleaning
-2	X	X	X	–	Foam stabilizer, mfg. of anionic surfactants
-4	X	X	X	X	Foam suppressor, agric. toxicants, plasticizer, freeze-thaw, stabilizer, chemical intermediate, antistatic agent
-5	X	X	X	X	Dry cleaning, HC solvent, fuel de-icer, silicone emulsifier
-6	X	X	X	X	Dry cleaning, HC solvent, paint stabilizer, petr. additive
-7	X	X	X	X	Textile scouring, pig. dispersant, sanitizers, emulsion polymerization
-8 and -8.5	X	X	X	X	Low foaming agent, textile deterg., corrosion inhibitor
-9 and -9.5	X	X	X	X	Textile, paper, paint, and metal processing, pesticides, pig. wetting
-10	X	X	X	X	Textile assistant and processing, pesticides, scouring agent
-11	X	X	X	X	Corrosion inhibitor, lime dispersant, sanitizers, metal cleaner
-12	X	X	X	X	Metal degreasing, sanitizers, home and ind. cleaner
-13	X	X	–	X	Textile scouring, emulsion polymerization, home and ind. cleaner
-14	X	X	X	X	General detergency, emulsifier for oils, waxes, and fats
-15	X	X	X	X	Metal cleaner, bottle washing, veg. and mineral oil emulsifiers
-20	X	X	–	X	Stabilizer for synthetic latices, de-emulsifier for crude petr., emulsifier for oils, waxes, fats, organic solvents and polyester resins
-30	X	X	X	X	Solubilizer, textile scouring, emulsion polymerization, synthetic latices, stabilizer, sanitizer, leveling agent, dyeing assistants
-40	X	X	X	X	Stabilizer for synthetic latices, solubilizers, leveling agent, emulsion polymerization, dyeing assistants, sanitizers
-50	X	X	X	X	Stabilizer, solubilizer and emulsifier for floor waxes and polishes, leveling agent, emulsion polymerization
-100	X	X	X	X	Stabilizer, solubilizer, leveling agent, sanitizers

Data from Refs. 9, 10.

urinary and pulmonary excretion of radiocarbon decreased and fecal excretion of label increased, indicating decreased intestinal absorption.

Chvapil et al.[41] reported that Nonoxynol-9 is absorbed through the vaginal wall of rabbits and rats, and is excreted by liver–bile–feces and kidney–urine routes.

Animal Toxicology

Acute Effects

Oral toxicity

Studies of various Nonoxynols, administered by gavage to rabbits, rats, guinea pigs, or mice indicate that ingested Nonoxynols are slightly toxic to relatively harmless (Table 5). Necropsy findings in animals that had died included

TABLE 5. Acute Oral Toxicity.

Nonoxynol	Animals (no. and species)	Concentration (%)	Dose	LD50	Comment[a]	Ref.
-2	30 rats (M + F)	100	2.96–4.26 g/kg	3.55 g/kg	Slightly toxic	44
-4	25 rats (M)	100	5.6–9.7 g/kg	7.4 g/kg	Practically nontoxic	46
-4	15 rats (M)	100	3.1–6.0 g/kg	4.3 g/kg	Slightly toxic	45
-6	30 rats (M + F)	100	1.45–2.67 g/kg	1.98 g/kg	Slightly toxic	44
-7	20 rats (M)	100	2.42–5.57 ml/kg	3.67 ml/kg	Slightly toxic	45
-9	80 rats	100	1.0–50 g/kg	3.0 g/kg	Slightly toxic	47
-9	80 guinea pigs	100	0.5–15 g/kg	2.0 g/kg	Slightly toxic	47
-9	12 rabbits	100	2.59–7.48 g/kg	4.4 g/kg	Slightly toxic	47
-9	15 rats (M)	100	1.67–3.25 ml/kg	2.33 ml/kg	Slightly toxic	45
-9	15 rats (M)	100	1.88–3.23 ml/kg	2.46 ml/kg	Slightly toxic	45
-9	15 rats (M)	100	–	1.41 ml/kg	Slightly toxic	45
-9	15 rats (M)	100	1.28–3.13 ml/kg	2.00 ml/kg	Slightly toxic	45
-9	20 rats (F)	100	1.77–4.53 ml/kg	2.83 ml/kg	Slightly toxic	45
-9	15 rats (F)	100	1.68–3.38 ml/kg	2.38 ml/kg	Slightly toxic	45
-9	20 mice	100	3.07–5.98 ml/kg	4.29 ml/kg	Slightly toxic	45
-9	12 guinea pigs (M)	100	0.60–1.18 ml/kg	0.84 ml/kg	Slightly toxic	45
-9	12 rabbits (M)	100	0.25–1.57 ml/kg	0.62 ml/kg	Slightly toxic	45
-9	8 rabbits (F)	100	0.28–1.37 ml/kg	0.62 ml/kg	Slightly toxic	45
-9	5 rats	100	2.1–3.2 ml/kg	2.6 ml/kg	Slightly toxic	48
-9	5 rats	100	0.25–8.0 g/kg	1.8 g/kg	Slightly toxic	49
-10	20 rats (M)	100	1.0–1.7 g/kg	1.3 g/kg	Slightly toxic	45
-10	20 rats (F)	10 (aq.)	1.0–1.6 g/kg	1.3 g/kg	Slightly toxic	45
-12	34 rats (M + F)	100	2.80–9.20 ml/kg	5.10 ml/kg	Slightly toxic	44
-13	15 rats (M)	100	2.68–5.21 ml/kg	3.73 ml/kg	Slightly toxic	45
-15	50 rats	25 (aq.)	1.9–3.3 g/kg	2.5 g/kg	Slightly toxic	50
-30	50 rats	25 (aq.)	4–64 ml/kg	Not Determined	Relatively harmless	50
-40	25 rats	100	10.14–26.01 g/kg	Not Determined	Relatively harmless	46
-40	10 rats	100	34–64 ml/kg	Not Determined	Relatively harmless	45

[a]Classified according to Hodge and Sterner.[51]

congested and hemorrhagic lungs, pale or mottled kidneys, gastrointestinal congestion, and congested kidneys. Animals which survived had diarrhea, tremors, prostration and narcosis.

An antidandruff shampoo containing 17.5% Nonoxynol-9 and a foaming bath oil containing 20% Nonoxynol-12 were tested for acute oral toxicity in fasted female rats. When 5 g/kg were administered by stomach tube to five animals per formulation, both formulations resulted in LD50 values of >5.0 g/kg, indicating that these products are "practically nontoxic."[42,43]

Dermal toxicity

One diluted and five undiluted Nonoxynols were tested in rabbits for dermal toxicity (Table 6). In each study, the sample was applied once under occlusion to shaved, abraded skin. The patches were removed at 24 h, the exposed sites rinsed and the animals observed for 14 days. The LD50 values resulting from these studies indicate that Nonoxynols-4, -7, -9, -10, and -13 ranged from 1.8 ml/kg to 4.4 g/kg. A 50% Nonoxynol-40 applied in a similar manner was reported to have an LD50 of greater than 10 g/kg. Table 6 documents the associated toxic effects observed during the testing.[44,45]

Nonoxynols-5 to -11.5, when applied topically to rabbits, resulted in minimum lethal doses of 2 to 10 g/kg. Toxicity decreased as ethoxylation increased.[39]

Inhalation toxicity

Groups of six male rats were placed in inhalation chambers and exposed once to Nonoxynol-4, -7, or -9 for either four or eight hours (Table 7). Animals were observed for 14 days following exposure. Inhalation of these Nonoxynols did not cause toxic effects in rats (normal weight gains and no mortalities).[45]

Parenteral toxicity

Three groups of female rats were injected with Nonoxynol-9, intraperitoneally (undiluted), subcutaneously (undiluted), or intravenously (1% solution in saline). The corresponding LD50 values determined were 210 mg/kg, 1000 mg/kg, and 44 mg/kg.[45]

Primary skin irritation

Eleven Nonoxynols were tested in rabbits for skin irritation according to the following protocols: (A) 0.01 ml of the test substance was applied undiluted to the clipped intact skin of each rabbit and examined 24 h later; (B) 0.5 ml of the test material was applied under occlusion to clipped intact and abraded skin. The sites were individually examined at 24 h and scored separately from erythema and edema at 24 and 72 h. The mean scores for 24- and 72-h gradings were averaged to determine the Primary Irritation Index (PII) (Table 8). The results indicated that Nonoxynols -7, -9, -10, -12, -13, -15, -30, and -40 were nonirritating to mildly irritating, whereas Nonoxynols -2, and -6 were moderately to severely irritating to the skin. Undiluted Nonoxynol-4 was reported to be nonirritating in one study but was found to be a primary irritant in another. In the latter study,

TABLE 6. Acute Dermal Toxicity of Nonoxynols.

Nonoxynol	*Concentration (%)*	*Dosage*	*No. of rabbits*	*Dermal LD50*	*Comments*	*Ref.*
-4	100	1.0–6.6 ml/kg	5	2.5 ml/kg	Erythema and necrosis of skin at various doses. Lung congestion and hemorrhages in dead animals.	45
-7	100	0.5–6.0 ml/kg	5	1.8 ml/kg	Erythema and necrosis of skin at various doses. Lung congestion, hemorrhages, and liver congestion.	45
-9	100	2.0–8.0 ml/kg	12	4.4 g/kg	Diarrhea, liver lesions and erythema at 50 and 8.0 g/kg.	44
-9	100	1.75–4.57 ml/kg	5	2.83 ml/kg	Necrosis of skin.	45
-10	100	1.4–3.0 ml/kg	5	2.0 ml/kg	–	45
-13	100	2.13–5.37 ml/kg	8	3.97 ml/kg	Lung hemorrhages, mottled liver and kidneys in dead animals.	45
-40	50	10 g/kg	3	>10 g/kg	Erythema and necrosis of skin.	45
-40	50	5 g/kg	3	>5 g/kg	Erythema and necrosis of skin.	45

TABLE 7. Acute Inhalation Toxicity.

Nonoxynol	Test concentration	Concentration in chamber	Hours of exposure	No. of rats	Comment
-4	1% aerosol aqueous dispersion	0.0213 ml/l in chamber	8	6 (M)	No mortality Normal weight gains
-7	1% aerosol aqueous dispersion	0.025 ml/l in chamber	8	6 (M)	No mortality Normal weight gains
-9	Concentrated vapor (Ambient temp.)	–	8	6 (M)	No mortality
-9	Vapor (179 °C)[a]	–	4	6 (M)	No mortality

Data from Ref. 45.
[a]Decomposition products of Nonoxynol-9 assayed.

well defined to severe erythema and slight to severe edema, which in most cases worsened by 72 h, were observed in all animals at both intact and abraded sites.

Nonoxynols -9 and -10 were applied under occlusion to the abraded and intact skin of the rabbit abdomen and ear. Ten applications to intact areas were made over a period of 14 days insuring continuous contact with sample for the 14 days. Three applications to abraded areas were made over three days. Five ml per exposure of 1%, 5%, or 25% aqueous preparation were used. All concentrations caused very slight erythema.[49]

Nonoxynols -5 to -11.5 were evaluated for skin irritancy according to the Draize procedure. Irritation scores ranged from 2.0 to 4.3 (indicating mild to moderate irritation) after 24 h; no irritation remained after 120 h.[39]

TABLE 8. Skin Irritation.

Nonoxynol	Concentration (%)	No. of rabbits	Protocol[a]	PII or Grade[b]	Comment	Ref.
-2	100	6	B	2.0	Moderately irritating	44
-4	100	6	B	5.58	Primary irritant	46
-4	100	5	A	NI[b]	Nonirritating	45
-6	100	6	B	3.00	Severely irritating	44
-7	100	5	A	NI[b]	Nonirritating	45
-9	100	5	B	–	Practically nonirritating	47
-9	100	–	A	Grade 2	Minimal capillary injection	45
-10	100	5	A	NI[c]	Nonirritating	45
-12	100	6 (M + F)	B	0.75	Slightly irritating	44
-13	100	5	A	Grade 3	Marked capillary injection	45
-15	100	6	B	0.45	Slightly irritating	44
-30	70 (aq.)	6	B	1.83	Mildly irritating	47
-40	100	6	B	1.46	Mildly irritating	47
-40	100	5	A	Grade 2	Minimal capillary injection	45

[a]Described in text.
[b]PII max. = 8.00; Grade max. = 10.
[c]NI = Not recorded as an irritant.

Primary eye irritation

Five Nonoxynols were tested in rabbits for ocular irritation according to the Draize method. Six other Nonoxynols were tested according to the following protocol: single doses of 0.005, 0.02, 0.10, or 0.5 ml of undiluted Nonoxynol or 0.5 ml of 40%, 15%, 5%, or 1% dilutions were placed in the conjunctival sacs of five rabbits per group. Eyes were examined within 1 h unstained and at 24 h after fluorescein staining and were scored. The results (Table 9) indicated that Nonoxynols -2 (undiluted), -15 (10% and 15%), -30 (25%), and -40 (undiluted) were nonirritating to minimally irritating, and that undiluted Nonoxynols -4, -6, -7, -9, -10, -12, -13, and -15 are severely irritating to the eyes of rabbits.

In another test, 0.1 ml of a 20% solution of Nonoxynol-9 at pH 6.1 was applied directly onto the cornea of one eye of each of 10 rabbits, 14 guinea pigs, 8 rats, and 11 mice. Corneal changes and lesions were evaluated at 1, 4, 7, and 30 h; scores were 34.4, 41.4, 30.8, and 70.7 (maximum score = 100) for rabbits, guinea pigs, rats, and mice, respectively. In rabbits the effect of rinsing the treated eye with 20 ml of water 4 sec after instillation of the sample was also studied. The results of this study indicated that Nonoxynol-9 is a moderate to severe eye irritant.[52]

Marzulli and Ruggles[57] reported a study on the ocular irritancy of Nonoxynol using the Draize rabbit eye irritation test. They concluded that, when compared with the 70% isopropanol control, Nonoxynol caused considerable eye irritation.

Two drops of 1%, 5%, or 25% Nonoxynols -9 and -10 were instilled into both eyes of each of three rabbits per concentration in another eye irritation study. Studies were performed with and without immediate irrigation. The lowest concentration tested caused very slight conjunctivitis; the middle concentration caused slight conjunctivitis and moderate corneal injury; the highest concentration caused moderate to severe corneal injury. Washing the eye lowered the average irritation index by 36.8%.[49]

Two shampoos, two bath oils, and one moisturizer containing 1.75%–2% Nonoxynols -4, -9, or -12 were tested for eye irritation potential according to the method of Draize. Results of these tests (Table 9) indicate that these products are minimally to moderately irritating when instilled in the eyes of rabbits.[42,43,54]

Subchronic Oral Toxicity

Two four-week feeding studies were conducted individually on four rats (2M, 2F). Animals were placed on diets containing 0.025%–2.5% Nonoxynol-9. At the end of the test, animals at the 2.5% dose level had scanty body fat deposits; carcasses were moderately thin to emaciated. The rats on a diet containing 0.025% Nonoxynol-9 were unaffected.[58]

Rats and dogs were fed diets containing either 0.04 to 5.0 g/kg or 0.01%–1% Nonoxynol-4, -6, -9, -15, -20, -30, or -40 for 90 days (Table 10). After 90 days, 1 or 5 g/kg/day Nonoxynol-20 caused focal myocardial necrosis in dogs but not in rats. In other studies with Nonoxynol-20 at 1 g/kg/day, six of eight dogs died between 4 and 14 days. Overall, dogs and guinea pigs showed evidence of cardiac lesions, but not rabbits, rats, and cats. In a 90-day study, Nonoxynol-20 at 0.04

TABLE 9. Ocular Irritation Studies.

Nonoxynol (product)	Conc. (%)	No. of rabbits	Wash (Y/N)	Grade[a]	Average Score[b] (Days)(Draize) 1	2	3	4	7	Comments	Ref.
-2	100	6 (M + F)	N	–	3.7	0.0	0.0	–	–	Minimally irritating	44
-4	100	6	N	–	39.7	36.7	21.2	–	11.0	Corneal, iridial and conjunctival effects observed. Moderately irritating.	53
-4	100	5 (M)	–	8	–	–	–	–	–	Moderately irritating	45
-4 (5% in moisturizing lotion)	100	6 (M + F)	N	–	1	0	0	0	0	Practically nonirritating	43
-6	100	6	N	–	28.8	26.0	30.3	30.7	16.0	Severe ocular irritant	44
-7	100	5	–	8	–	–	–	–	–	Moderately irritating	45
-9	5 (aq.)	10	–	–	–	–	–	–	–	All eye damage healed within 4 days	47
-9	100	5	–	8	–	–	–	–	–	Moderately irritating	45
-9 (1.75% in antidandruff shampoo)	25 (aq.)	6 (M + F)	N	–	14	7	2	0	0	Mildly irritating	54
-9	25 (aq.)	6 (M + F)	N	–	2	0	0	0	0	Practically nonirritating	54

(1.75% in antidandruff shampoo)											
-10	100	5	–	6	–	–	–	–	–	Severe corneal damage	45
-12	100	6	–	–	44.7	33.5	42.0	42.0	40.0	Severe ocular irritant	44
-12	100	6 (M + F)	Y	–	1	0	0	0	0	Practically nonirritating	42
(20% in foaming bath oil)											
-12	100	6 (M + F)	N	–	17	12	8	6	5	Mildly to moderately irritating	42
(20% in foaming bath oil)											
-13	100	5	–	8	–	–	–	–	–	Severe ocular necrosis	45
-15	100	1	N	–	39	20	18	14	0	Moderately irritating	55
-15	10	1	N	–	4	0	0	0	0	Minimally irritating	55
-15	15	1	N	–	6	2	0	0	0	Minimally irritating	55
-15	20	4	N	–	10.5	6.5	3	0.5	0	Slight to moderate conjunctival irritation	55
-30	25	3	N	–	2	0	0	0	0	Transitory conjunctival involvement	56
-30	25	3	Y – 2 sec	–	0	0	0	0	0	Nonirritating	56
-30	25	3	Y – 4 sec	–	0	0	0	0	0	Nonirritating	56
-40	100	5	–	1	–	–	–	–	–	No injury	45
-40	5	3	–	1	–	–	–	–	–	No injury	45
-40	100	6	–	–	1	0	0	–	–	Nonirritant	46

[a]Maximum grade = 60.
[b]Maximum score = 120.

TABLE 10. 90-Day Subchronic Oral Toxicity.

Nonoxynol	*Dose (g/kg) or concentration in diet*	*No. of Animals*	*Comments (effects were reported at lowest dose only)*[a]
-4	0.04–1 g/kg/day	60 rats	Retarded growth[b] and increased liver weight at 1 g/kg/day.
-4	0, 0.04, 0.2, 1.0 g/kg/day	4 dogs	Increased liver weight at 0.2 g/kg/day.
-6	0.04 to 1 g/kg/day	60 rats	Retarded growth[b] at 1 g/kg; increased liver weight at 0.2 g/kg.
-6	0, 0.04, 0.2, 1.0 g/kg/day	4 dogs	Increased liver weight at 1.0 g/kg/day.
-9	0.01–1.25%	80 rats	Retarded growth[b] and increased liver weight at 0.25%.
-9	0.01–5.0%	90 rats	Retarded growth[b] at 0.64 percent; 11/15 died at 5.0%.
-9	0.01–1.0%	50 rats	Increased liver, kidney and spleen weights at 0.3%.
-9	0.04, 0.64, 5.0%	3 dogs	Retarded growth[b] at 0.64%.
-15	0.04–1 g/kg/day	60 rats	Retarded growth[b] at 0.2 g/kg/day.
-15	0, 0.04, 0.2, 1.0 g/kg/day	4 dogs	No toxic effects.
-20	0.2–5 g/kg/day	60 rats	Retarded growth[b] at 5 g/kg/day.
-20	0.04, 0.2, 1.0, 5.0 g/kg/day	4 dogs	Death at 1 and 5 g/kg with myocardial degeneration and necrosis, emesis, altered organ weights, body weight loss, anorexia.
-30	0.2–5 g/kg/day	60 rats	No toxic effects.
-30	0, 0.04, 0.2, 1.0 g/kg/day	4 dogs	No toxic effects.
-40	0.03–3%	100 rats	Hepatic necrosis at 3% and slight central lobular granular degeneration.

[a]At a confidence level of 95% or higher.
[b]This effect was determined to be a result of Nonoxynol's poor palatability.
Data from Ref. 48.

g/kg/day produced cardiac lesions in dogs, whereas 5.00 g/kg/day had no effect in rats.[48]

Chronic Oral Toxicity

Nonoxynols -4 and -9 were administered to rats and dogs in two two-year feeding studies. Body weight and hematologic parameters were monitored in all studies. A number of rats at each dose level were sacrificed and necropsied after 12 months; all remaining rats were sacrificed and necropsied after 24 months. All dogs were sacrificed and necropsied after 720 days. The results of these tests at the dose levels shown in Table 11 indicate that these Nonoxynols have a low chronic toxicity.

Additional Studies

Mutagenesis

Four Italian trichomonacidal products containing Nonoxynol (n value not given) were evaluated for mutagenicity using the Ames test with *Salmonella*

TABLE 11. Chronic Oral Toxicity of Nonoxynols.

Nonoxynol	Dose or concentration in diet	No. of animals	Feeding duration	Comments
-4	0.04–1 g/kg/day	210 rats	2 years	No toxic effects except reduced body weights and enlarged liver at 1 g/kg.
-9	0.03–0.27%	216 rats	2 years	No toxic effects.
-4	0.04–1 g/kg/day	18 dogs	720 days	Reduced weight, emesis, increased serum alkaline phosphatase at 1 g/kg.
-9	0.03–0.27%	18 dogs	720 days	No toxic effects except increased liver:body weight ratio at 0.27%.

Data from Ref. 48.

typhimurium strains TA1535, TA100, TA1538, and TA98. Ten to 250 μg Nonoxynol added to cultures showed no mutagenic activity.[59]

Carcinogenesis

Nonoxynols -4 and -9 were not carcinogenic when fed for two years to rats at doses of 0.20 and 0.14 and to dogs at 0.04 and 0.03 g/kg/day.[48]

Nonoxynol (-7 and/or -10),[1] along with other surfactants, was tested at 2 g/L as a potential cocarcinogen with N-methyl-N'-nitro-N-nitrosoguanidine (NG) (0.1 g/l); both were supplied concurrently with the drinking water to 15 rats for 36 weeks. NG alone was supplied to 13 control animals. The overall incidence of stomach adenocarcinoma was 12 of 15 in the experimental group, and 8 of 13 for the controls. Neither negative control data nor a statistical analysis of the data were available. The author suggested that the surfactants may have a promoter effect because of their surfactant nature which enables the NG to penetrate the gastric barrier and come into contact with the gastric mucosa or to penetrate mucosal cells.[60,61]

Subcellular effects

When added to human or bovine serum, Nonoxynol-10 bound to serum albumin via hydrophobic interactions.[4] Nonoxynol-9 activates the respiration-dependent accumulation of potassium by isolated bovine heart mitochondria and increases the passive permeability of the membrane to potassium.[62] Nonoxynol-10 did not alter the activity of steroid 17,20-lyase derived from rat testis microsomes.[63] The prolongation of phenobarbital narcosis in mice by several Nonoxynols indicated that these compounds impaired the liver detoxification mechanism.[64]

Cellular effects

Several Nonoxynols and their derivatives have microbicidal properties.[9,10,65,66] When added at concentrations of 100 ppm to culture media, Nonoxynols -7, -9, and -10.5 each inhibited the growth of at least five species of fungi.[67,68] Nonoxynols potentiate the antibacterial effect of alkyldimethylbenzylammonium chloride against *Staphylococcus aureus* in culture.[69] Asculai et al.[70] tested the

in vitro effect of 5% Nonoxynol-9 on Herpes Simplex Viruses (HSV) Types 1 and 2. Nonoxynol-9 inactivated both HSV types by destroying the viral envelope and nucleocapsid.

Clinical Assessment of Safety

Skin Irritation

Cosmetic formulations containing Nonoxynol-4, -9, or -12 were tested for cumulative skin irritation. The test material was applied to the volar forearm surface and/or the inner aspect of the arm of the 20 test subjects and held under occlusive patches for 24 h. After patch removal and test site grading, fresh patches were reapplied to the same site. This procedure was repeated for a total of 10 applications. The concentration of the test material and results for the individual formulation containing the three Nonoxynols are given in Table 12. The results show a range of effects from slightly to mildly irritating to the human skin.[42,43,54,71]

Two cosmetic gels containing 2% and/or 4% Nonoxynol-9 were separately tested for irritation on 25 subjects. The gel was applied under an occlusive patch for 48 h before scoring. All sites were scored as zero.[72] (See Table 12.)

A gel containing 4% Nonoxynol-9 was tested on 212 subjects. The material was applied 11 times under occlusive patch. Neither the time interval between patch testing nor the quantity of gel applied was stated. A score of 11 out of a maximum possible score of 804 was reported. The investigator concluded that the "product showed no evidence of primary skin irritation or allergic sensitization"[72] (see Table 12).

When a spermicidal film containing 10% Nonoxynol was tested as a contraceptive in 30 women, two subjects experienced a mild local vaginal irritation and one noted some degree of pruritis.[73]

Skin Irritation and Sensitization

Undiluted Nonoxynol-4 was tested on 25 men and 25 women in a repeated insult patch test. Discs, 1.25 in in diameter, saturated with sample, were applied

TABLE 12. Skin Irritation Test of Product Formulations Containing Nonoxynol Compounds.

Nonoxynol	*Product*	*Ingredient concentration (%)*	*Patch conc. of product (%)*	*No. of subjects*	*PII*[a]	*Comment*	*Ref.*
-12	Foaming bath oil	20.0	1	20	0.30	Slightly irritating	42
-9	Antidandruff shampoo	1.75	2.5	20	1.7	Mildly irritating	71
-9	Antidandruff shampoo	1.75	5	20	1.7	Mildly irritating	71
-9	Antidandruff shampoo	1.75	1.25	20	0.50	Slightly irritating	54
-9	Antidandruff shampoo	1.75	1.25	20	0.35	Slightly irritating	54
-9	Cosmetic gel	2.0	100	25	0	Nonirritating	72
-9	Cosmetic gel	4.0	100	25	0	Nonirritating	72
-9	Cosmetic gel	4.0	100	212	–	Score of 11/804 nonirritating	72
-4	Moisturizing lotion	5.0	100	19	0.61	Slightly irritating	43

[a]Maximum score = 8.0.

TABLE 13. Skin Irritation and Sensitization.

Nonoxynol	Ingredient diluent	Concentration tested (%)	No. of subjects	Procedure	Results	Ref.
-4	None	100	50 (25M, 25F)	RIPT	No irritation No sensitization	47
-9	None	100	100 (50M, 50F)	RIPT	No irritation No sensitization	47
-15	Water	50	168 (53M, 115F)	RIPT	No irritation No sensitization	74
-50	Water	50	168 (53M, 115F)	RIPT	No irritation No sensitization	74

to the backs of the volunteers. The primary application was left in place for 48 h; the subsequent 14 induction patches were applied for 24 h each. After a two-week rest, challenge patches were applied for 24 h. None of the subjects showed immediate or delayed reactions to either the induction or challenge patches. Nonoxynol-4 appears to be "neither a primary irritant, a sensitizer, nor a fatiguing agent"[47] (see Table 13).

Undiluted Nonoxynol-9 was tested on 50 men and 50 women for skin irritation/sensitization potential. A single induction patch, applied to the back of each subject, was held in contact with the skin for five days. After a three-week rest, a challenge patch was applied to each subject for 48 h. There were no reactions to either patch. Nonoxynol-9 is "neither a primary irritant nor a sensitizer at 100% concentration"[47] (see Table 13).

A repeated insult patch test was performed on 168 subjects (115F, 53M) using 0.1 ml of a 50% water solution of Nonoxynol-15 and/or Nonoxynol-50. The test material was applied at 48 h intervals, three times per week for three weeks on the backs of the subjects. The test area was occluded for 24 h before removal, and washed with distilled water. The test sites were read at 48 h, after which fresh test material and the occlusive patch were reapplied. After a three-week non-treatment period, the test area, as well as an untreated site, were challenged using the same procedure as previously noted. The sites were scored for sensitization at 24, 48, and 72 h. The investigator noted that only transient reactions were observed during the test and that neither Nonoxynol-15 nor Nonoxynol-50 was an irritant or sensitizer[74] (see Table 13).

Phototoxicity and Photosensitization

Twenty-eight of the 168 subjects tested for irritation and sensitization previously discussed were randomly selected to test the ability of Nonoxynol-15 and Nonoxynol-50 to induce a phototoxic or photosensitization reaction following ultraviolet exposure. The test protocols were the same except that the forearm was used as a test site. The 28 subjects were divided into two groups, 19 received only UVA and nine received both UVA and UVB. The UVA (320–400 nm) light was applied for 15 min to the 19 subjects (4.4 $\mu W/cm^2$ at the skin surface measured at the 360 nm wave length peak). The UVB was applied at two times Mean Erythema Dose (MED) to nine subjects from a 150 watt Xenon Arc

Solar Simulator emitting at 280–320 nm. The subjects receiving the UVB exposure were also exposed for 5 min to UVA as previously described. The investigator noted that only transient reactions were observed, and that Nonoxynol-15 and Nonoxynol-50 are not photosensitizers.[74]

SUMMARY

Nonoxynols, ethoxylated alkylphenols containing 1–100 ethylene oxide groups, have a wide range of physical properties. Nonoxynols are chemically stable. They are used in cosmetic formulations as emulsifying, wetting, foaming and solubilizing agents in concentration ranges of ≤0.01%–50% (Nonoxynol-4 and -9); ≤0.01%–25% (Nonoxynol-10); and >0.1%–5.0% (Nonoxynol-12). Nonoxynol-containing products may come into contact with most of the external surfaces of the body and may be applied daily for a period of years.

Absorption and metabolism studies in the rat indicate that increasing the length of Nonoxynols' ethylene oxide chain decreases their intestinal absorption. Estimates of the acute oral LD50s of nine of the Nonoxynols (-2 to -15) ranged from 0.62 to 7.4 g/kg in several animal species. Nonoxynol-30 and -40 had higher LD50s. Acute dermal toxicity studies in rabbits on six undiluted Nonoxynols resulted in an LD50 range of 1.8 ml/kg to 4.4 g/kg. Acute inhalation by rats of aerosols of undiluted or 1% Nonoxynol-4, -7, or -9 for 8 h caused no deaths. Intraperitoneal, subcutaneous, and intravenous injections of Nonoxynol-9 resulted in LD50 values of 0.21 ml/kg, 1.00 ml/kg, and 0.044 g/kg, respectively.

PII values determined from skin irritation tests on rabbits ranged from 0.45 to 5.58; other tests indicated that Nonoxynols are nonirritating to moderately irritating when applied to the skin. Nonoxynol compounds with short EO chains are generally severe ocular irritants; Nonoxynol-15, -30, and -40 are only slightly irritating to the rabbit eye.

When fed subchronically or chronically in the diet to rats and dogs, at daily intakes of 0.2 to 1 g/kg or dietary concentrations of 0.27%, Nonoxynols -4 to -9 frequently increased liver weights. Nonoxynol-15 to -40 were less effective in this regard and were less toxic.

No evidence of carcinogenicity was observed when Nonoxynol-4 and -9 were fed for two years to both dogs and rats. A mutagenicity study of these two compounds by the Ames test was negative.

Undiluted Nonoxynol-4 and -9 were nonirritating and nonsensitizing to the skin of 50 and 100 human subjects, respectively. A 50% solution of Nonoxynol-15 and/or Nonoxynol-50 produced no irritation or sensitization when tested on 168 subjects. The latter two ingredients produced no indication of phototoxicity or photosensitivity when subjects were exposed to either UVA or UVB light after exposure to the compounds.

DISCUSSION

None of the 11 Nonoxynols discussed in this report has had complete toxicological testing; however, the total available test data for the entire group was

considered adequate. The differences in toxic effects among the various Nonoxynols are quantitative and most likely related to the rate of absorption as influenced by ethoxy groups. There was no evidence of qualitative differences in toxicity between the Nonoxynols; therefore, the Panel used the composite data to evaluate the safety of this group of ingredients.

CONCLUSION

On the basis of the available information presented in this report, the Panel concludes that Nonoxynols -2, -4, -8, -9, -10, -12, -14, -15, -30, -40, and -50 are safe as cosmetic ingredients in the present practices of concentration and use.

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REFERENCES

1. ESTRIN, N.F. (ed.). (1977). *CTFA Cosmetic Ingredient Dictionary.* Washington, DC: Cosmetic, Toiletry and Fragrance Assoc.
2. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (June 22, 1979). Submission of data by CTFA. CTFA Cosmetic Ingredient Chemical Descriptions and Specifications for the Nonoxynol group.*
3. WINDHOLZ, M. (ed.). (1976). *The Merck Index,* 9th ed. Rahway, NJ: Merck and Co.
4. GREEN, F.A. (1972). Interactions of a nonionic detergent. III. Hydrophobic interactions. J. Colloid. Interface Sci. **41**(1), 124–9.
5. ENYEART, C.R. (1967). Polyoxyethylene Alkylphenols, in: *Nonionic Surfactants.* Chapter 3. M.J. Schick (ed.). New York, NY: Marcel Dekker, Inc.
6. KNAAK, J.B., ELDRIDGE, J.M., and SULLIVAN, L.J. (1966). Excretion of certain polyethylene glycol ether adducts of nonylphenol by the rat. Toxicol. Appl. Pharmacol. **9**(2), 331–40.
7. MAYHEW, E. (1956). U.S. Patent No. 2,774,709, GAF.
8. CTFA. (June 11, 1980). Submission of data by CTFA. Summary of unpublished safety data on the Nonoxynol-4 Group.*
9. *McCUTCHEON'S DETERGENTS AND EMULSIFIERS,* International ed. (1973). Ridgewood, NJ: Allured Publishing Corp.
10. *McCUTCHEON'S DETERGENTS AND EMULSIFIERS,* North American ed. (1973). Ridgewood, NJ: Allured Publishing Corp.
11. ABE, I., HAYASHI, K., and KITAGAWA, M. (1976). Studies on the adsorption of surfactants on activated carbons. I. Adsorption of nonionic surfactants. Yukagaku **25**(3), 145–50.
12. ABE, I., HAYASHI, K., and KITAGAWA, M. (1976). Studies on the adsorption of surfactants on activated carbons. II. The effect of coexisting salts on the adsorption of nonionic surfactants. Yukagaku **25**(3), 151–5.
13. JEHRING, H. and WEISS, A. (1969). Alternating current polargraphy. VIII. Adsorption behavior of polyethylene glycol ethers at the mercury/electrolyte phase boundary. Tenside **6**(5), 251–7.
14. McCRACKEN, J.R. (1975). Adsorption of polyoxyethylated nonylphenol surfactants by selected polymer substrates. Diss. Abstr. Int. B **36**(2), 881.
15. RUPPRECHT, H. (1972). Infrared spectroscopic studies of surface reactions of Aerosil. Arch. Pharm. (Weinheim) **305**(2), 149–55.

*Available on request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., NW, Washington, DC 20005.

16. RUPPRECHT, H. and LIEBL, H. (1975). Sorption capacity of colloidal silica for homologous polyethylene glycol and polyethylene glycol derivatives. IV. Regulating medicinal binding on colloidal silica by nonionic surfactants. Pharm. Ztg. **120**(7), 179–82.
17. PATTERSON, S.J., SCOTT, C.C., and TUCKER, K.B.E. (1970). Nonionic detergent degradation. III. Initial mechanism of the degradation. J. Am. Oil Chem. Soc. **47,** 37–41.
18. KURATA, N. and KOSHIDA, K. (1975). Biodegradability of nonionic surfactants in river die-away tests using Tama River water. Yukagaku **24**(12), 879–81.
19. ANDERSON, C.A., GANLY, R.G., and WOOD, G.F. (1966). The determination of nonylphenol ethylene oxide detergents in wool grease. J. Pharm. Pharmacol. **18**(12), 809–14.
20. DARADICS, L. (1972). Separating surfactant mixtures by thin-layer chromatography. Chim. Anal. (Bucharest) **2**(1), 14–7.
21. BEREK, D. and NOVAK, L. (1973). Oligermeric polyethers characterized by gel chromatography. Chem. Prum. **23**(2), 91–4.
22. SELDEN, G.L. and BENEDICT, J.H. (1968). Identification of polyoxyalkylene-type nonionic surfactants by paper chromatography. J. Am. Oil Chem. Soc. **45**(10), 652–55.
23. KIKOLSKI, P., BARANOWSAK-GULIK, B., and ZNIEWIEROWSKA, W. (1971). Determination of monoethanolamides and polyoxyethylenated nonylphenols in washing powders by the combined technique of ion-exchange chromatography and ultraviolet spectrophotometry. Chem. Anal. (Warsaw) **16**(1), 31–41.
24. HARLESS, H.R. and CRABB, N.T. (1969). Mass Spectrometric study of nonylphenolethylene oxide adducts. J. Am. Oil Chem. Soc. **46**(5), 238–40.
25. EL-KHATEEB, S., HASSAN, S.M., AHMAD, A.K.S., and AMER, M.M. (1979). Spectrophotometric determination of some nonionic surfactants. Tenside Deterg. **16**(1), 27–9.
26. SHEIH, P.S. and FENDLER, J.H. (1977). Proton magnetic resonance investigations of nonionic polyoxyethylene nonylphenol surfactant aggregates in nonpolar solvents. J. Chem. Soc. Faraday Trans. 1 **73**(10), 1480–9.
27. KLIMA, Z., WINKLER, W., and GEGA, H. (1977). Determination of nonionic surfactants in technological baths and wastes by a spectrometric X-ray-fluorescence method. Przegl. Wlok. 297–9.
28. BUERGER, K. (1963). Thin-layer chromatographic method for determination of the molecular-weight distribution and the oxyethylation degree of poly(ethylene oxide) condensates. Frensenius' Z. Anal. Chem. **196**(4), 259–68.
29. FAVRETTO, L. (1970). Characterization of nonionic surfactants by means of thin-layer chromatography. Riv. Ital. Sostanze Grasse **47**(5), 187–91.
30. KONISHI, K. and YAMAGUCHI, S. (1966). Rapid determination of molecular weight distribution of poly(oxyethylene)-type nonionic surfactants by circular thin-layer chromatography. Anal. Chem. **38**(12), 1755–7.
31. FAVRETTO, L. and STANCHER, B. (1968). Determination of the number-average molecular weight of polyoxyethylene oligomers by infrared spectrophotometry. Univ. Studi Trieste, Fac. Econ. Copmmer. 1st **44,** 11.
32. BIRKEL, T.S., WARNER, C.R., and FAZIO, T. (1979). Gas chromatographic determination of 1,4-dioxane in polysorbate 60 and polysorbate 80. J. Assoc. Off. Anal. Chem. **62,** 931–6.
33. ARGUS, M.F., SOHAL, R.S., BRYANT, G.M., HOCH-LIGETI, C., and ARCOS, J.C. (1973). Dose response and ultrastructural alterations in dioxane carcinogenesis: influence of methylcholanthrene on acute toxicity. Europ. Cancer **9,** 237–73.
34. FOOD AND DRUG ADMINISTRATION (FDA). (Aug. 1976). Product formulation data. Computer printout. Washington, DC.
35. FDA. (June, 1979). Product formulation data. Computer printout.
36. CODE OF FEDERAL REGULATIONS. (1979). Title 21, Part 720.4.
37. SCHUMACHER, E. (1975). Residues of milk following teat dipping with iodophors, and their toxicologic evaluation. Wien. Tieraerztl. Monatsschr. **62**(6–8), 221–4.
38. FEDERAL REGISTER. (1980). Proposed Rule for Vaginal Contraceptive Drug Products for OTC Use. **45**(241), Dec. 12.
39. ARTHUR D. LITTLE INC. (1977). "Alkylphenol ethoxylates." Human Safety and Environmental Aspects of Major Surfactants. A report to the Soap and Detergent Assoc. Cambridge, MA. pp. 387–456.
40. OSBURN, Q.W. and BENEDICT, J.H. (1966). Polyoxylated alkyl phenols: relationship of structure to biodegradation mechanism. J. Am. Oil Chem. Soc. **43,** 141–6.

41. CHVAPIL, M., ESKELSON, C.D., STIFFEL, V., and DROEGEMUELLER, W. (1980). Studies on Nonoxynol-9. II. Intravaginal absorption, distribution, metabolism, and excretion in rats and rabbits. Contraception **22**(3), 325–39.
42. CTFA. (Feb. 5, 1976). Submission of data by CTFA. Unpublished safety data on a foaming bath oil (Nonoxynol-12).*
43. CTFA. (Feb. 15, 1979). Submission of data by CTFA. Unpublished safety data on a moisturizing lotion (Nonoxynol-4).*
44. CONSUMER PRODUCT TESTING CO. (CPTC). (1978). Submission of data by CTFA. GAF.*
45. MELLON INST. of IND. RES. (1963). Submission of data by CTFA. Union Carbide Corp.
46. M.B. RESEARCH LABS (MBRL). (1978). Submission of data by CTFA. GAF.*
47. INDUSTRIAL TOXICOLOGY LABS (ITL). (1960). Submission of data by CTFA. GAF.*
48. SMYTH, Jr. H.F. and CALANDRA, J.C. (1969). Toxicologic studies of alkylphenol polyoxyethylene surfactants. Toxicol. Appl. Pharmacol. **14**(2), 315–334.
49. OLSON, K.J., DUPREE, R.W., PLOMER, E.T., and ROWE, V.K. (1962). Toxicological properties of several commercially available surfactants. J. Soc. Cosmet. Chem. **13,** 469–79.
50. INDUSTRIAL BIOLOGY RESEARCH AND TESTING LABS (IBRTL). (Feb. 7, 1961). Submission of data by CTFA. Unpublished acute oral toxicity study on Nonoxynol-15 and -30.*
51. HODGE, H.C. and STERNER, J.H. (1949). Tabulation of toxicity classes. Am. Indus. Hyg. A. Quart. **10,** 93–6.
52. GERSHBEIN, L.L. and McDONALD, J.E. (1977). Evaluation of the corneal irritancy of test shampoos and detergents in various animal species. Food Cosmet. Toxicol. **15**(2), 131–4.
53. FOOD AND DRUG RESEARCH LABORATORIES (FDRL). (1977). Submission of data by CTFA. GAF.*
54. CTFA. (March 15, 1976). Submission of data by CTFA. Unpublished safety data on an antidandruff shampoo (Nonoxynol-9).*
55. INDUSTRIAL BIOLOGY LABS (IBL). (1961). Submission of data by CTFA. GAF.*
56. IBL. (1961). Submission of data by CTFA. GAF.*
57. MARZULLI, F.N. and RUGGLES, D.I. (1973). Rabbit eye irritation test: collaborative study. J. Assoc. Off. Anal. Chem. **56**(4), 905–14.
58. IBRTL. (Feb. 7, 1961). Submission of data by CTFA. Unpublished subchronic oral toxicity studies on Nonoxynol-9.*
59. TAMARO, M., BARAGGINO, E., and PILOTTO, A. (1979). Mutagenicity of some trichomonacides for *Salmonella typhimurium* (Ames test). Minerva Ginecol. **31**(4), 263–72.
60. TAKAHASHI, M., FUKUSHIMA, S., and HANANOUCHI, M. (1975). Induction of undifferentiated adeno carcinoma in the stomach of rats by n-methyl-n-nitro-n-nitroso guanidine with various kinds of surfactant, in: *Gann Monograph on Cancer Research,* No.17. Odashima Shigeyoshi et al. (eds.). Tokyo, Japan: Univ. of Tokyo Press. pp. 255–67.
61. TAKAHASHI, M., FUKUSHIMA, S., and SATO, H. (1973). Carcinogenic effect of n-methyl-n'-nitrosoguanidine with various kinds of surfactant in the glandular stomach of rats. Gann **64**(3), 211–8.
62. BRIERLEY, G.P., JURKOWITZ, M., MEROLA, A.J., and SCOTT, K.M. (1972). Ion transport by heart mitochrondria. XXV. Activation of energy-linked K^+ uptake by non-ionic detergents. Arch. Biochem. Biophys. **152**(2), 744–54.
63. BETZ, G. and MICHELS, D. (1973). Steroid 17,20-lyase. Effect of detergents on enzymic activity and microsomal composition. Steroids **21**(6), 785–800.
64. ZAJUSZ K. and ZYLKA, M. (1976). Effect of some detergents on the course of barbiturate narcosis. Bromatol. Chem. Toksykol. **9**(3), 295–9.
65. UCHIBORI, T., WATANABE, S., and ABE, Y. (1979). Studies on antimicrobial surface-active agents. 7. Preparation of derivatives of nonylphenyl poly(oxyethylene) ethers and determination of their antimicrobial activity. Yukagaku **28**(1), 31–5.
66. KAWADAM, J.M., UCHIBORI, T., and WATANABE, S. (1979). Studies on antimicrobial surface agents. 9. Preparations and antimicrobial activity of p-nonylphenyl poly (oxyethylene) ether derivatives containing nitrogen. Yukagaku **28**(1), 36–9.
67. MIYATA, Y., NAMIKI, T., TAKASHIMA, S., and MASAGO, H. (1973). A new aspect of protection method for phytophthora and phthium disease by nonionic surfactants. Part 2. Reinforcement effects by some fungicides. Sci. Rep. Kyoto Perfect/Univ. Agric. **25,** 31–6.
68. STEINER, G.W. and WATSON, R.D. (1965). The effect of surfactants on growth of fungi. Phytopathology **55**(9), 1009–12.

69. DELMOTTE, A. and GEERAERTS, R. (1964). Modifications of the antiseptic properties of alkyldimethylbenzylammonium chlorides, following the addition of various nonylphenol-ethylene oxide condensates. J. Pharm. Belg. **19**(3-4), 103-43.
70. ASCULAI, S.S., WEIS, M.T., RANCOURT, M.W., and KUPFERBERG, A.B. (1978). Inactivation of herpes simplex viruses by nonionic surfactants. Antimicrob. Agents Chemother. **13**(4), 686-90.
71. CTFA. (Nov. 22, 1972). Submission of data by CTFA. Unpublished safety data on antidandruff shampoo (Nonoxynol-9).*
72. CTFA. (Sept. 9, 1981). Submission of data by CTFA. Unpublished safety data on gels containing Nonoxynol-9.*
73. LICHTMAN, A.S. DAVAJAN, V., and TUCKER, D. (1973). C-Film: a new vaginal contraceptive. Contraception **8**, 291-7.
74. FDRL. (March 31, 1982). Submission of data by CTFA. Human irritation/sensitization and photosensitization data.*