Amended Safety Assessment of Octoxynols as Used in Cosmetics

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ABBREVIATIONS

BVDV	back vertex distance variability
Caco2	human colon adenocarcinoma cell line
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CTFA	Cosmetic, Toiletry, and Fragrance Association
DTH	delayed-type hypersensitivity
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EC_{50}	half-maximal effective concentration
ECHA	European Chemicals Agency
ELISA	enzyme linked immunosorbent assay
EPA	Environmental Protection Agency
EPP	ethylphenyl proprionate
ET_{50}	exposure time that reduces tissue viability to 50%
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
FOU	frequency of use
FSDC	fetal skin dendritic cells
GRASE	generally recognized as safe and effective
H4IIE	rat liver hepatoma cell line
HeLa	human cervical carcinoma cells
HepG2	human liver hepatoma cell line
HIV	human immunodeficiency virus
HRIPT	human repeat insult patch test
IgM	immunoglobulin M
IL	interleukin
IP-10	gamma interferon inducible protein 10
LDH	lactate dehydrogenase
LD	lethal dose
l.o.	leave-on
MDCK	Madin-Darby canine kidney
MDSS	maximal primary Draize irritation score
MIP-3α	macrophage inflammatory protein 3α
MMAD	mass mean aerodynamic diameter
MoCRA	Modernization of Cosmetics Regulation Act
MOE	margin of exposure
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	molecular weight
NOEL	no-observed-effect-level
NOAEL	no-observed-adverse-effect-level
NoG	Notes of Guidance
NRU	neutral red uptake
OECD	Organisation for Economic Co-operation and Development
OTC	over-the-counter
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered solution
PEG	polyethylene glycol
PFC	plaque-forming cells
PII	primary irritation index
RLD	Registration and Listing Data
r.o.	rinse-off
SCCS	Scientific Committee on Consumer Safety
SED	systemic exposure dose
SRBC	sheep red blood cells
SLS	sodium lauryl sulfate
TG	test guideline
TK6	human lymphoblastoid cell line
TNF-α	tumor necrosis factor alpha

TPA	12-*O*-tetradecanoylphorbol-13-acetate
US	United States
UV	ultraviolet
VEC-100	reconstructed human vaginal-ectocervical epithelium
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of 25 octoxynol ingredients, which are reported to function as surfactants in cosmetics. The Panel reviewed the available data to determine the safety of these ingredients. Industry should minimize impurities that could be present in cosmetic formulations, such as heavy metals and ethylene oxide impurities, according to limits set by the US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA). The Panel issued an amended report with a revised conclusion stating the octoxynols reviewed in this report are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

This assessment reviews the safety of the following 25 octoxynol ingredients as used in cosmetic formulations:

Octoxynol-1	Octoxynol-12	Octoxynol-9 Carboxylic Acid
Octoxynol-3	Octoxynol-13	Octoxynol-20 Carboxylic Acid
Octoxynol-5	Octoxynol-16	Potassium Octoxynol-12 Phosphate
Octoxynol-6	Octoxynol-20	Sodium Octoxynol-2 Ethane Sulfonate
Octoxynol-7	Octoxynol-25	Sodium Octoxynol-2 Sulfate
Octoxynol-8	Octoxynol-30	Sodium Octoxynol-6 Sulfate
Octoxynol-9	Octoxynol-33	Sodium Octoxynol-9 Sulfate
Octoxynol-10	Octoxynol-40	
Octoxynol-11	Octoxynol-70	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), these ingredients are reported to function in cosmetics as surfactants (Table 1).[1] The Panel first reviewed these octoxynol ingredients in a safety assessment that was published in 2004.[2] The Panel issued a final report with the conclusion that Octoxynol-9, -10, -11, -12, -13, -16, -20, -25, -30, -33, -40, -70, and Octoxynol-9 Carboxylic Acid, Octoxynol-20 Carboxylic Acid, Potassium Octoxynol-12 Phosphate, and Sodium Octoxynol-9 Sulfate are safe as used in rinse-off and leave-on cosmetic products. The Panel also concluded that Octoxynol-1, -3, -5, -6, -7, and -8, and Sodium Octoxynol-2 Ethane Sulfonate, Sodium Octoxynol-2 Sulfate, and Sodium Octoxynol-6 Sulfate are safe as used in rinse-off cosmetic products and safe at concentrations of ≤ 5% in leave on cosmetic products.

In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since the original assessment was issued. At its June 2023 meeting, the Panel determined that this safety assessment should be reopened to explore the irritation potential of these ingredients in products which come in contact with mucous membranes (suspected use of Octoxynol-9 in vaginally applied products). Furthermore, the report was also reopened due to the newly reported use of Octoxynol-9 at 0.1% in baby products.[3]

Of note, the Panel has also published reviews on the safety of nonoxynols, which are structurally similar, slightly longer chain (1 carbon longer) ingredients in 1983, 1999, and in 2015, which are available on the Cosmetic Ingredient Review (CIR) website (https://cir-reports.cir-safety.org).[4-6] During the 2015 review, the Panel concluded that the nonoxynols are safe in the present practices of use and concentration in cosmetics as described in the safety assessment, when formulated to be non-irritating.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted January 2025. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website ((https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline)). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Summarized excerpts from the previous report on these octoxynol ingredients are included in this document, as indicated by *italicized text*. Because the original (2004) octoxynols report included supporting data from the 1983 and 1999 nonoxynols reports; accordingly, those data, as well as data from the final report on nonoxynols that was published in 2015,[6] are also disseminated throughout the text of this re-review document as read-across sources, as appropriate, and are also identified by *italicized text*. (This information is not included in the tables or the summary section.)

Much of the published data in the literature has been identified under the name "Triton X-100." According to different sources, this name corresponds to several different octoxynol ingredients named in this report (e.g., Octoxynol-1, Octoxynol-9). Because it is unknown which octoxynol ingredient is being referred to, studies using Triton X-100 have been placed under the subheading "an octoxynol (number of ethoxy repeat units unknown)" and the test substance is referred to as "an octoxynol" throughout the study summaries. It should be noted, however, that during the previous review of this report, it was thought that Triton X-100 referred only to Octoxynol-9. Therefore, data on Triton X-100 was included in those reports as Octoxynol-9 (and thus are included in this report, in italicized text, also as Octoxynol-9). It should also be noted that all

octoxynols are mixtures with varying averages of ethoxy repeat units. Triton X-100 is generally considered to have an average of 9.5 ethoxy units.[7]

CHEMISTRY

Definition and Structure

According to the *Dictionary*, these octoxynols are ethoxylated alkyl phenols which generally conform to the structure in Figure 1.[1]

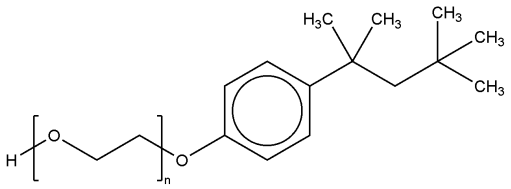


Figure 1. General formula for octoxynols, wherein "n" is the average number of ethoxy repeat units (e.g., n = 3 for Octoxynol-3)

These ingredients are mostly identified by the generic CAS Nos. 9002-93-1; 9036-19-5; and 9004-87-9. Specific CAS Nos. are assigned to several of the octoxynol ingredients. The definitions, idealized structures, and reported functions of the ingredients included in this review, as well as the CAS Nos., are provided in Table 1.[1]

Chemical Properties

Octoxynols, or polyoxyethylene octylphenyl ethers, are ethoxylated alkylphenols with the chemical formula, $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$*, where n in the formula represents the number of moles of ethylene oxide, average value.*[2] *The average value for n in chemicals of this class is evident in the ingredient name (e.g. Octoxynol-1, Octoxynol-3, etc.). For cosmetic ingredients, n can vary from 1 – 70. By contrast, the nonoxynols have the formula* $C_9H_{19}C_6H_4(OCH_2CH_2)_nOH$.

These ingredients are water white to light amber liquids.[2] Octoxynol-9 has a water solubility of 4.55 mg/l (at 20° C) and has an average molecular weight of 647 Da.[8] Chemical properties of the octoxynols included in this report are presented in Table 2.[9-20]

Method of Manufacture

Octoxynol-9 is reportedly prepared by reacting p-(1,1,3,3-tetramethylbutyl)phenol with ethylene oxide, at elevated temperature and under pressure, in the presence of sodium hydroxide.[2] *In general, the semi batch process is commonly used for the production of polyoxyethylated nonionic surfactants. A reaction vessel is charged with alkylphenol and an appropriate catalyst (not specified). The catalyzed alkylphenol is heated to reaction temperature and purged with nitrogen to reduce the water generated during the catalysis step; water removal is integral to minimize polyethylene glycol formation. After drying, ethylene oxide is added. When the alkylphenol has been polyoxyethylated to the desired extent, the reaction mixture is held at reaction temperature until the residual ethylene oxide concentration in the liquid product has been reduced to an acceptable level. The product is then neutralized, post-treated, and filtered for removal of insoluble salts formed during neutralization. The raw materials used in the production of Octoxynol-11 are exclusively from petrochemical origin.*

Impurities

At the time of the original report, Cosmetic, Toiletry, and Fragrance Association (CTFA [now known as the Personal Care Products Council (Council)]) specifications stated that Octoxynol-1 has a minimum purity of 99%, and that Ocyoxynol-5 and Octoxynol-9 contain sulfated ash (0.25% maximum) and water (0.5% maximum).[2] *The National Formulary stated Octoxynol-9 may contain arsenic (2 ppm), heavy metals (0.002%), and no more than 5 ppm ethylene oxide as impurities. A sample of Octoxynol-11 was reported to contain < 1% water; specifications for the following impurities included sulfated ashes (< 0.2%), heavy metals (< 10 ppm Pb), and arsenic (< 2 ppm). The percentage of volatiles in a sample of Octoxynol-13 was reported to be 0.5%, including < 0.0002% ethylene oxide.*

Ultraviolet (UV) Absorption

An ultraviolet (UV) spectral analysis of a 0.32 mM aqueous solution of Octoxynol-9 demonstrated an absorption maximum at 276 nm and slight absorbance at 290 nm, as a tail on the peak at 276 nm.[2] *No detectable absorbance was observed above 295 nm. It was concluded that Octoxynol-9 had no significant absorbance in the UVA and UVB regions of the spectrum.*

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US FDA the cosmetics industry on the expected use of these octoxynols in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption.[21] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to RLD submitted to CIR in 2024, Octoxynol-9 is reported to have the greatest number of uses (it is reported to be used in 38 formulations; Table 3).[22] VCRP (2023) data indicated Octoxynol-11 had the greatest reported frequency of use (8 total formulations).[23] In 2001, Octoxynol-9 was reported to have the highest number of uses (131 total formulations).[2] The results of the concentration of use surveys conducted by the Council in 2022 (performed using VCRP categories) and 2025 (performed using MoCRA categories) indicate Octoxynol-9 has the highest maximum reported concentration of use; it is used at 2% in skin cleansing preparations.[3,24] The highest concentration reported in leave-on products in 2022 was for Octoxynol-12; it is reported to be used at a maximum of 1.5% in face and neck products (not spray). Previous concentration of use data (1999/2001) indicated that Octoxynol-10 had the highest concentration of use (it was used at up to 25% Octoxynol-10 in hair bleaches). The ingredients not in use according to the VCRP, RLD, and industry survey are listed in Table 4.

VCRP (2023) data indicated that some of these ingredients may be used near the eye (e.g., Octoxynol-11 is used in eye lotions and other eye makeup preparations; concentrations not stated) and in products that may be incidentally ingested (Octoxynol-12 is used in lipsticks; concentration not stated). These uses, however, were not reported in RLD submitted to CIR in 2024. RLD indicate that mucous membrane exposure to Octoxynol-9 may occur, as it is used in bath soaps and body washes and disposable wipes (at 0.36%). According to 2022 concentration of use data, Octoxynol-9 is used at 0.1% in other baby products; however, this use was not reported in 2024 RLD or 2025 concentration of use data. These ingredients are also used in formulations that may be incidentally inhaled (e.g., Octoxynol-9 is used in cologne and toilet waters; concentration not stated). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Some products containing these ingredients may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. Some of the reported product categories for these ingredients as listed in the RLD do require designation if airbrush application is used (e.g., Octoxynol-9 is used in indoor tanning preparations), but no airbrush use was indicated. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available, when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The octoxynol ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[25] However, according to the European Chemicals Agency (ECHA), these ingredient are considered "substances of very high concern" based on toxicity to aquatic life with long lasting effects.[26] Therefore, in Europe, use of these ingredients, including in cosmetics, requires authorization.

Non-Cosmetic

Octoxynol-1, -3, -5, -7, -9, -8, -10, -11, -12, -13, -16, -20, -25, -30, -33, -40, and -70, Potassium Octoxynol-12 Phosphate, and Sodium Octoxynol-2 Ethane Sulfonate have been approved for indirect food uses as surfactants in pesticide dilutions applied to crops (21CFR172.710); components of paper products that come in contact with dry food (21CFR176.180); and components of defoaming agents (21CFR176.210) and emulsifiers (21CFR178.3400) used in the production of paper goods utilized for food transport. Octoxynol-30, -33, -40, and -70 are listed in 40CFR180.960 as polymers that are exempt from the requirement of tolerance.

In 2002 (67FR31123), the FDA issued a final rule stating that the use of Octoxynol-9 in over-the counter (OTC) drugs is not deemed generally recognized as safe or effective (GRASE), and therefore that any drug product containing Octoxynol-9 labeled for OTC use as a vaginal contraceptive or spermicide will be considered misbranded (and will require a drug application), which was reiterated in 21CFR310.545.

Octoyxnol-1 is commonly employed as a detergent in the manufacture of biotherapeutics, such as vaccines.[27,28] Octoxynol-40 has an FDA-approved drug use in ophthalmic solution drops at a maximum potency per unit dose of 0.05% w/v.[29]Additionally, Octoyxnol-40 is utilized in various (nanomicellar) ocular drug delivery formulations.[30-32]

In accordance with a 2020 Amendment to Article 56(1) of Regulation (EC) No. 1907/2006, uses of the substance group 4(1,1,3,3-tetramethylbutylphenol, ethoxylated (covering well-defined substances and substances of unknown or variable composition, complex reaction products or biological materials, polymers and homologues) require authorization for use in pharmaceuticals after January 2021.

TOXICOKINETIC STUDIES

Percutaneous Absorption

nonoxynols

The in vitro skin penetration of nonoxynol-2, -4, and -9 (10% w/w in isopropyl myristate) was evaluated using heat-separated human epidermal membranes in an experiment designed to mimic in-use conditions relative to ingredient use in "on-head" rinse-off products such as an oxidative hair color. Each nonoxynol solution (10 µl) was dispensed over the surface of the stratum corneum and rinsate samples (obtained with isopropyl myristate) were removed from the receptor medium at 2, 4, 6, 8, 25, and 48-h post application of the vehicle. Most of the applied nonoxynols were recovered in the 1 and 48-h rinsates and no quantifiable amounts were present in the receptor phase, indicating that none of the nonoxynols permeated through the skin to any great extent. In a third experiment, the in vitro skin penetration of nonoxynol-2, -4, and -9 (10% w/w in isopropyl alcohol per solution; volume = 15 µl) was evaluated in heat-separated human epidermal membranes (n =3) to mimic the in-use conditions relative to nonoxynols in leave-on products. Solutions remained in contact with the skin for 48 h, after which the entire receptor media was analyzed by high performance liquid chromatography. The total skin permeation for the nonoxynols was as follows 6.17 µg/cm^2, corresponding to 0.57% of the applied dose for nonoxynol-2, 7.10 µg/cm^2, corresponding to 0.66% of applied dose for nonoxynol-4, and 4.73 µg/cm^2, corresponding to 0.49% of the applied dose for nonoxynol-9. Based on these data, the researchers stated that the total skin penetration for nonoxynol-9 was slightly lower than that for nonoxynol-2, and -4, and, that the levels of nonoxynols absorbed followed a brief exposure period would be very low. Therefore, the potential for systemic exposure to the lower molecular weight nonoxynols was considered to be extremely low under conditions of rinse-off application to the scalp (500 – 750 cm^2) in products such as hair dyes.

The percutaneous absorption of nonoxynol-4 and nonoxynol-9 was studied in vitro using human, pig, and rat skin samples in flowthrough diffusion cells.[33] Topical solutions of 0.1, 1, or 10% ^{14}C-nonoxynol-4 (each in polyethylene glycol (PEG-400)) and 0.1, 1, or 10% aqueous ^{14}C-nonoxynol-9 were applied, and radioactivity in the perfusate was monitored over an 8-h period. Skin penetration was generally less than 5% of the applied dose, most of which was found in the stratum corneum. For both ^{14}C-nonoxynols in all skin samples, the fraction of dose absorbed was highest for the lowest applied concentration. Dermal absorption was similar across all concentrations. In rat skin, penetration, but not absorption, was greater when water was used as the vehicle compared to PEG-400 as the vehicle. The results of the study suggested that ^{14}C-nonoxynol-9 and ^{14}C-nonoxynol-4 were minimally absorbed across the skin.

Absorption, Distribution, Metabolism, and Excretion

Dermal

Octoxynol-9 was administered at doses ranging from 5 to 20 ml/kg to 3 guinea pigs in an acute dermal toxicity study.[2] No evidence of dermal absorption was observed. No further details were provided.

Oral

The absorption, distribution, and excretion of Octoxynol-40 was evaluated using 4 rats and 2 dogs.[2] Tritium-labelled Octoxynol-40 ([^{3}H]Octoxynol-40; specific activity = 5.85 mC/g) was fed, via gavage, to 4 rats; 2 additional rats served as controls. Feces and urine were collected and analyzed in 2 rats and both dogs, whereas only urinalyses was performed for the other 2 rats. Essentially all of the radioactivity that was fed was recovered in the feces of rats (up to 92.2%) and dogs

(up to 86.4%). Urine (2 dogs and 2 rats) and carcass (2 rats) were said to contain minor amounts of radioactivity. The percent recovery of radioactivity in the urine was 0.59 – 2% (4 rats) and 1.17% and 1.46% (2 dogs, respectively).

Intravaginal

Octoxynol-9 was stated to be rapidly and quantitatively absorbed from the vaginal wall into the systemic circulation of rabbits and rats.[2] *This statement was based on a study in which nonoxynol-9 was absorbed through the vaginal wall of rabbits and rats and excreted by liver-bile-feces and kidney-urine routes (details not reported).*

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Octoxynol-9 was evaluated using 3 guinea pigs.[2] *Single doses of the test substance were administered via a cuff at doses ranging from 5 - 20 ml/kg. Slight to moderate edema and scattered erythema (at periphery) were observed 24 h post-application. At 1 wk, desquamation and slight alopecia were observed. There was no evidence of dermal absorption; the LD_{50} was greater than 20 ml/kg.*

an octoxynol (number of ethoxy repeat units unknown)

The acute dermal toxicity of a leather cream was evaluated in Wistar albino rats (3/sex/group) according to Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 402.[34] The cream comprised of white beeswax, carnauba wax, and distilled water, as well as an octoxynol, silicone oil, linseed oil, Sudan black dye, and nigrosine black dye (amounts not specified). Animals received either no treatment (controls), wax base, laboratory-based sample of the leather cream, or the marketed leather cream on a shaved area of the back and were observed for signs of irritation, general signs of toxicity, and mortality for 14 d; animals were necropsied on day 15 and treated tissue underwent histopathological examination. No mortality, signs of erythema or edema, significant changes in body weights, or food consumption was observed. No damage in skin tissue was observed in the treated groups, compared to controls, indicating that no dermal toxicity was caused by the leather cream samples. No further details were provided.

Oral

Several acute oral toxicity studies were performed in rats using short-chain octoxynols.[2] *A mean acute oral LD_{50} value of 7.1 ± 0.1 ml/kg was reported for rats (number not stated) dosed orally with Octoxynol-1. Following the single oral administration of Octoxynol-3 to rats (number not stated), a mean acute oral LD_{50} of 4.0 ± 0.2 ml/kg was reported. A mean acute oral LD_{50} of 3.8 ± 0.2 ml/kg was reported for rats (number and strain not specified) that received a single oral dose of Octoxynol-5. No further details were provided for these studies.*

The acute oral toxicity of undiluted Octoxynol-9 was evaluated using a total of 10 mice.[2] *A single dose of the test substance was administered at doses ranging from 200 – 3200 mg/kg. Weakness and diarrhea were observed; the LD_{50} was determined to be approximately 1600 mg/kg. In another acute oral toxicity study, groups of 10 Charles River SCD rats were administered a single oral dose of undiluted Octoxynol-9 at doses ranging from 0.678 – 1.86 ml/kg. The mortality rate per group was dose-dependent; 9 out of 10 of the animals administered the highest dose died. The acute oral LD_{50} was determined to be 1.06 ml/kg (confidence limits = 0.989 – 1.29 ml/kg). Ten adult rats were given a single oral dose of 200 – 3200 mg/kg Octoxynol-9. Slight to moderate weakness, diarrhea, ataxia, and prostration were noted at the highest dose; the LD_{50} was determined to be in the 800 – 1600 mg/kg range.*

Four groups of 6 Wistar-derived albino rats (3/sex/group; weights = 150 – 300 g) were used to evaluate the acute oral toxicity of Octoxynol-13.[2] *The animals received a single graded dose (from 691 – 1400 mg/kg) by gavage and were then observed for signs of pharmacologic activity and toxicity at 1, 3, 6, and 24 h after dosing. Following a 14-d non-treatment period, the animals were killed and subjected to necropsy. Gross changes included reddening of the gastrointestinal mucosa and fibrous tissue encasing the heart or lungs. An LD_{50} of 985 mg/kg Octoxynol-13 was reported.*

Fasted male albino rats were administered a single dose of either Octoxynol-16 (30%), Octoxynol-16 (70%), Octoxynol-20 (70%), Octoxynol-30 (70%), or Octoxynol-40 (70%) via gavage.[2] *Ten animals were used per group and 4 groups were used per test article, with the exception of Octoxynol-40 (70%), for which only one group was used. Octoxynol-16 (30%) was administered at up to 6 g/kg, Octoxynol-16 (70%) and Octoxynol-20 (70%) at up to 7 g/kg, Octoxynol-30 (70%) at up to 28 g/kg, and Octoxynol-40 (70%) at 28 g/kg. Eight of the 10 rats dosed with 6 g/kg Octoxynol-16 (30%) and 7/10 rats dosed with 7 g/kg Octoxynol-16 (70%) died; the LD_{50} values for these groups were 2.68 and 2.78 g/kg, respectively. Only one rat dosed with 28 g/kg Octoxynol-40 (70%) died. The LD_{50} values for the Octoxynol-20 (70%) and Octoxynol-30 (70%) groups were 3.64 and 21.20 g/kg, respectively. Diarrhea was reported with the groups given Octoxynol-16 and Octoxynol-20. An analysis of variance test using the LD_{50} values for 70% Octoxynol-16, 70% Octoxynol-20, and 70% Octoxynol-30 indicated that the difference between these values was significant at the 5% level.*

Inhalation

Two Swiss mice were exposed, nose-only, to airborne concentrations of 4.4, 15, 36, or 38 mg/l Octoxynol-9 at a rate of 30 l/min.[2] *The airborne exposure resulted in a concentration-related decrease in respiratory rate; Octoxynol-9 was*

classified as a sensory irritant. In another study, the acute inhalation toxicity of Octoxynol-9 was evaluated using 50 Syrian hamsters that were exposed to aerosolized Octoxynol-9 with a mass mean aerodynamic diameter (MMAD) of 1.5 µm and a concentration of 2.8 mg/l (estimated lung burden: 203 – 835 µg/g lung), or by bronchopulmonary lavage with 0.01 – 0.10% Octoxynol-9 in isotonic saline (estimated lung burden: 302 – 3180 µg of Octoxynol-9). In the inhalation study, animals died from laryngeal obstruction, with moderate pulmonary edema and pneumonitis, and the LD_{50} was 501 µg/g lung. In the lavage study, animals died from pulmonary edema and acute pneumonia, and the LD_{50} was 2060 µg/g. The lungs of Syrian hamsters were treated with 0.05% Octoxynol-9 in 0.9% saline, or only saline, via lavage (80% lung volume). Lung cell [^{3}H]thymidine uptake was evaluated after animals received a 2-h pulse of the radioactive label before they were killed at 2, 18, 24, 48, or 72 h after lavage was initiated. The researchers stated that the increased [^{3}H]thymidine uptake into the alveolar macrophages of lungs lavaged with Octoxynol-9, compared to saline controls, was not attributed to an altered distribution of type I, type II, or endothelial cells, but to an increased incorporation of label into the alveolar macrophages and injured ciliated airways. Six male and 6 female Syrian hamsters (Sch:(SYR) strain) were treated by lavage (1 lung per animal; two consecutive washes) with 0.01, 0.05, 0.075, or 0.1% Octoxynol-9 (in saline) via bronchopulmonary lavage and anesthetized. Lactate dehydrogenase (LDH) release into the alveolar fluid during lavage was measured as an indication of immediate injury. The increase of LDH activity in the cell-free portion of the lavage fluid was correlated with increasing concentrations of Octoxynol-9 (correlation coefficient = 0.98). No deaths occurred in the control group or in groups dosed with 0.01 or 0.05% Octoxynol-9. All the animals treated with 0.075 or 0.1% Octoxynol-9 died anywhere from 7 h to 3 d post lavage. Atelectasis (focal and mild) and severe pulmonary edema were noted at microscopic examination. Histopathologic findings in animals that died at days 2 and 3 post lavage included focal necrosis associated with hemorrhagic areas of the lung and an acute generalized pneumonia with polymorphonuclear leukocyte and macrophage exudation. Tritiated Octoxynol-9 was administered to groups of male and female Syrian hamsters (4 – 8/group; 32 total), via lavage, at weight percentage concentrations of 0.01, 0.05, 0.06, 0.075, or 0.1% in isotonic saline. Twenty-four hamsters treated with isotonic saline were used as controls; none of the controls died. Mortality rates in test animals were as follows: 0.01% (0/4), 0.05% (1/8), 0.06% (4/8), 0.075% (8/8), and 0.1% Octoxynol-9 (4/4). Congested lungs, focal areas of peripheral atelectasis, and blood-tinged fluid in the trachea and large bronchi were noted at necropsy. Several pulmonary and bronchial histopathologic changes were observed and varied as a function of survival time; no evidence of residual injury was observed in animals which survived until necropsy. An LD_{50} of 2100 µg (estimated mean lung burden of Octoxynol-9) was reported. In another experiment, groups of 50 hamsters (95-d or 419-d old) were exposed, nose-only, to an Octoxynol-9 aerosol. The 95 d-old hamsters were exposed to a nebulized aerosol of Octoxynol-9 with an MMAD of 1.47 µm while 419-d-old hamsters were exposed to a nebulized aerosol of Octoxynol-9 with an MMAD of 1.51 µm; in each group a mass concentration of 3 mg/l was produced by nebulization of 10% solution of Octoxynol-9 (in ethanol). Groups of 10 animals were removed from the exposure chamber at different time intervals (not specified) in order to provide initial respiratory tract burdens, which ranged from 800 – 3100 µg. Ten hamsters from each age group which were exposed to aerosolized ethanol for 37 min served as controls. Death was attributed to obstructive asphyxia; laryngeal and epiglottic edema were the most prominent gross features. No abnormalities were observed in the lower trachea, major bronchi, lungs, or in the large or small bronchi. Upon microscopic examination, mucosal ulcerations with necrotic bases were observed in laryngeal secretions and were present in single alveoli.

Short-Term Toxicity Studies

Dermal

Multiple octoxynols were applied to the skin of rabbits (strain and number not specified) over a period of 4 wk (20 applications total).[2] *Ingredients were applied at the following concentrations: 1% Octoxynol-1, 1% Octoxynol-3, 0.1% Octoxynol-9, and 0.1% Octoxynol-13. No histopathologic changes were noted for each ingredient tested. No further details were provided.*

Inhalation

In a short-term inhalation toxicity study, Sprague-Dawley CD rats (5/sex) were exposed to an ethoxylated para-tert-octyl phenol (an octoxynol, number of moles of ethylene oxide not stated; target concentration: 10 mg/m^3) in an inhalation chamber for 5 d/wk (6 h/d) for 2 wk.[2] *The MMAD of the test substance was 1.8 µm. None of the animals died. Lung-to-body weight ratios in test animals were significantly greater when compared to controls. Reddening of the lung was observed grossly in 4 males and 3 females. Upon histopathologic examination, inflammatory changes in the alveolar walls/perivascular space were noted. Compared to air-exposed controls, both the incidence and severity of this finding were greater. Alveolar/bronchiolar epithelial hyperplasia was observed only in treated animals, and therefore, was considered treatment-related.*

Intravaginal

<u>nonoxynols</u>

Groups of 6 Sprague-Dawley female rats were treated intravaginally with nonoxynol-9 in a short-term toxicity study.[2] *Instillations of 5 mg of nonoxynol-9/100 g bw, in saline, were made to the upper aspect of the vagina daily for 5, 10, 15, or 20 d, after which blood samples were also obtained. Controls were intravaginally injected with saline. Animals were exsanguinated at 5-d intervals and the liver, kidneys, and lungs were removed. Total hydroxyproline and deoxyribonucleic*

(DNA) content were determined in hepatic and renal tissues. Lesions of nonspecific inflammation with destruction of normal lobule architecture, increased density of rough endoplasmic reticulum, and a significant increase in serum glutamic oxaloacetic transaminase activity were observed in liver specimens after 15 injections. DNA content and total hydroxyproline were significantly increased in kidneys after 15 d.

Subchronic Toxicity Studies

Oral

Male and female rats (15/sex) received 5% Octoxynol-40, in the diet daily for 3 mo.[2] Another group of 15 male and 15 female rats served as controls. Three test animals (all males) and 2 controls (1 male and 1 female) died. Test animal deaths were not related to dosing with Octoxynol-40. No effects on growth or food consumption were noted and urinary concentrations of sugar and protein were comparable between test and control animals. Results of hematologic evaluations indicated no definite effects of Octoxynol-40 dosing. No statistically significant differences between the organ-to-body weight ratios of heart, spleen, kidney, liver, and testes were observed between test and control animals. Mean testes/body weight ratios x 10-3 were 8.7 ± 1.1 g (test animals) and 9.2 ± 1.1 g (controls). No test substance-related lesions were observed at histopathologic examination.

In another study, groups of young albino rats (30/sex/group) were administered 0.035, 0.35, or 1.4% Octoxynol-40 in daily diet for 3 mo. Controls received basic diet only. Compared to controls, no adverse effects on the testes/body weight ratio were noted at any of the 3 administered doses. In another study, Octoxynol-40 was administered to groups of 4 purebred Beagle dogs (2/sex/group) at concentrations of 0.35 or 5%, in the diet for 3 mo. An additional group of 4 dogs served as controls. No adverse effects on body weight, food consumption, hematocrit, hemoglobin, total and differential white cell counts, urinary concentrations of sugar and protein, organ-to-body weight ratios (including testes/body weight ratios), or test substance-related lesions were observed.

Chronic Toxicity Studies

Oral

The chronic oral toxicity of Octoxynol-40 was evaluated in groups of young albino rats (30/sex/group).[2] Octoxynol-40 was administered at concentrations of 0.035, 35, or 1.4% in the daily diet for up to 2 yr. Controls received basic diet only. After the third month of dosing, 5 males and 5 females from each dose group were killed, and tissues (heart, lung, liver, kidney, and gonads + other tissues) were subjected to histopathologic examination. The remaining animals (20/group) continued to receive treatment till the end of the 2-yr study, after which surviving animals were killed and necropsied. No adverse effects on survival, growth, food consumption, hematocrit, hemoglobin, total and differential leukocyte counts, urinary concentrations of sugar and protein, organ-to-body weight ratios, or pathological lesions were observed.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

The sperm immobilization potential of Octoxynol-9 was evaluated in vitro.[2] The effective concentration of Octoxynol-9 for totally immobilizing all spermatozoa (human) within 20 s was 0.24 mg/ml.

Dermal

Groups of 25 Sprague-Dawley CD rats were dermally dosed with 530, 1600, or 4270 mg/kg/d Octoxynol-9, at a constant dose volume of 4 ml/kg, from gestation day 6 to day 15.[2] Controls received dermal applications of deionized and filtered water. Each test article application was made under occlusion to a clipped, 20 cm^2 area of the back for 6 h. One rat in the highest dose group was found dead on gestation day 7; the cause of death was not determined. Body weight gain over the entire gestational period was reduced only in the highest dose group. No statistically significant differences in lung, liver, or kidney weights were noted between test (all dose groups) and control groups. No dams aborted or delivered early and no effects on gravid uterine weights, number of ovarian corpora lutea, number of total, viable, or nonviable implantations/litter, or preimplantation loss were observed, compared to controls. The incidence of atelectasis (lung collapse) was significantly increased in dams in the 1600 and 4270 mg/kg/d groups. A significant decrease in the incidence of dilated renal pelvis was noted in the 530 mg/kg/d group. An increased incidence of vestigial fourteenth thoracic rib was noted in pups from all 3 dose groups. The following statistically significant skeletal variations were observed only in pups from the highest dose group: poorly ossified lumbar arches, unossified and poorly ossified sternebrae, unossified cervical centrum, rudimentary bone island, poorly ossified hyoid, poorly ossified zygomatic arch, and poorly ossified supraoccipital. The researchers concluded that dermal exposure to Octoxynol-9 produced a low order of maternal toxicity, while having a pronounced effect on fetal skeletal development. The toxicological significance of these abnormalities seen in this study were unclear; the increased incidence of supernumerary thoracic ribs was considered a common developmental variation. The no-observed-effect-level (NOEL) for Octoxynol-9 related to maternal toxicity was 1600 mg/kg/d, while the NOEL related to developmental toxicity was determined to be 70 mg/kg/d.

Oral

No signs of maternal or fetal toxicity were observed in 50 female CD-1 mice that received 800 mg/kg/d Octoxynol-9, via gavage, on days 6 through 13 of gestation.[2] In another developmental toxicity study, groups of 27 Sprague-Dawley CD rats

received 0, 70, or 340 mg/kg/d Octoxynol-9, in the diet, from days 6 through 16 of gestation. A control group received untreated feed. On gestation day 17, the test diet was withdrawn and replaced with the control diet. None of the animals died, and no clinical signs were reported. No effects on gravid uterine weights were noted in any dosage group. When corrected for gravid uterine weight, body weight gains over the entire gestational period were reduced in the 70 mg/kg/d group; these results were not considered toxicologically significant. No effect on the number of ovarian corpora lutea, the number of total, viable, or nonviable implantations per litter, or preimplantation loss were observed, compared to controls. However, a statistically significant increase in the incidence of displaced testes in fetuses was noted in the 340 mg/kg/d group. Statistically significant skeletal variations observed only in the 340 mg/kg/d group included: vestigial fourteenth rib, accessory ribs on cervical vertebra 7, and both cervical and fourteenth thoracic rib, and decrease in the incidence of poorly ossified hyoid. The authors concluded that oral exposure to Octoxynol-9 produced a low order of maternal toxicity, while having a pronounced effect on fetal skeletal development. The toxicological significance of these abnormalities seen in this study was unclear; the increased incidence of supernumerary thoracic ribs was considered a common developmental variation.

Intravaginal

In a developmental and reproductive toxicity study, groups of pregnant Sprague-Dawley COBS CD rats were intravaginally administered either 0.5 or 5 mg/kg/d Octoxynol-9 (in contraceptive jelly) from gestation day 6 to gestation day 15.[2] Three additional groups of 25 rats served as untreated controls, sham controls, and vehicle controls (contraceptive jelly excipients). Statistically significant reductions in body weight were observed in sham controls ($p = 0.05$) and the 5 mg/kg/d group ($p = 0.01$) on gestation day 6 to 16. The biological significance of the reduced body weight was questionable, given that body weights were comparable for all groups after the treatment period and for the entire duration of the observation period. Malformations were observed in 2 female fetuses from 2 different litters of dams dosed with 0.5 mg/kg/d. These malformations consisted of a threadlike tail in one fetus and the following in the other fetus: cleft palate, cleft lip, misplaced pinna, open eye lid, brachygnathia, and aglossia. Skeletal malformations were not observed. The incidence of developmental variations ranged from 70 (untreated controls) to 114 (sham controls) per group and consisted of the following: malaligned sternebrae, variations in the number of ribs, and, mainly, ossification retardation of the skull, hyoid, os coxae, sternebra, and vertebral centra. These variations were considered to be evenly distributed among test and control groups; visceral variations were not observed. One nonviable fetus from the 5 mg/kg/d group was examined. No malformations or developmental variations were noted and no other dead fetuses or late resorptions were observed. It was concluded that Octoxynol-9 was not embryotoxic or teratogenic when administered intravaginally to rats during organogenesis.

GENOTOXICITY STUDIES

In Vitro

Octoxynol-1 was not mutagenic in an Ames test using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 at test concentrations ranging from 0.0031 – 0.1 µl/plate with metabolic activation and from 0.0063 – 0.1 µl/plate without metabolic activation.[2] The mutagenic effect of several known mutagens in combination with Octoxynol-9 was tested using S. typhimurium strain TA100. Concentrations of the following mutagens, which were known to produce 500 – 1000 revertants/plate, were added to top agar: sodium azide in water (0.5 µg/plate); N-aminomorpholine in water (5.2 µmol/plate); ethyl methanesulfonate in dimethyl sulfoxide (DMSO) (42.3 µmol/plate); benzo(a)pyrene in DMSO (3 µg/plate, with metabolic activation); 2-aminoanthracene in DMSO (2 µg/plate); and styrene oxide in DMSO (4 µmol/plate). Octoxynol-9 (unspecified amount) was applied directly to the hardened agar, as crystals, or as a liquid to sterile, filter paper discs. Octoxynol-9 caused toxicity (background lawn appeared less dense compared to control plates) in the presence of sodium azide, styrene oxide, or N-aminomorpholine; the addition of Octoxynol-9 did not affect the mutagenicity of ethyl methylsulfonate, benzo(a)pyrene, or 2-aminoanthracene.

Two successive treatments with Octoxynol-9 (to remove cytoplasmic contamination) preserved the integrity of DNA in a rat liver cell suspension.[2] Three successive treatments resulted in DNA breakage and further decrease in ribonucleic acid and protein content. In a study evaluating the effect of Octoxynol-9 on chromatin in rat liver, thymus, and ascites hepatoma cells, treated cells had rough nuclear structure compared to controls and some compaction of chromatin was seen; no changes in DNA content were observed. Unscheduled DNA synthesis in a nontumorigenic adult rat hepatocyte cell line exposed to 10, 25, or 50 µg/ml Octoxynol-9 and 5µCi/ml [^{3}H] for 18 h was evaluated in a DNA repair assay; Octoxynol-9 did not induce DNA damage. No increases in single strand DNA were observed in mouse lymphoma L5178Y/TK $^{+/-}$ cells treated with 3, 10, 25, 30, or 100 µl/l Octoxynol-9 in an DNA alkaline unwinding test. The induction of DNA double-strand breaks in cultured human lung epithelial cells treated with 5% Octoxynol-9 only occurred after cell viability reduced to < 60% and was considered extragenomic damage.

Octoxynol-9 was not mutagenic when tested in a nontumorigenic T51B rat hepatocyte cell line at up to 40 µg/ml in a hypoxanthine guanine phosphoribosyl transferase mutation assay and at up to 50 µg/ml in a malignant transformation assay.[2] In a chromosomal aberration assay, Octoxynol-9 enhanced the induction of abnormalities in Chinese hamster ovary cells, when tested in conjunction with known clastogens, dimethylnitrosamine, benzo[a]pyrene, and aniline, but was not

clastogenic alone. No significant mutagenic activity was observed in mouse lymphoma LT178Y TK $^{+/-}$ 3.7.2.C cells treated with 1 – 45 ug/l Octoxynol-9 in a mouse lymphoma thymidine kinase forward mutation assay.

an octoxynol (number of ethoxy repeat units unknown)

An octoxynol (6.25, 12.5, 25, 50, 100 and 200 µg/ml) was used as a known non-genotoxic agent in a comet and micronucleus assay (assays performed using human lymphoblastoid cell line TK6).[35] In the comet assay, no significant increase in the comet tail was observed at up to 100 µg/ml (irrelevant positive responses observed at 200 µg/ml). In the micronucleus assay, no increase in the frequency of micronucleated cells was observed at any dose level.

CARCINOGENICITY STUDIES

Oral

nonoxynols

Groups of 50 B6C3F$_1$ mice received concentrations of 500, 1500, or 4500 ppm nonoxynol-10 in the diet for 104 wk.[33] *The mean daily intakes of nonoxynol-10 were 81.5, 254, and 873 mg/kg/d, respectively. A fourth group was fed a control diet. No pathological or microscopic changes were attributable to nonoxynol-10 upon examination and an increase in neoplastic or non-neoplastic lesions was not observed. It was concluded that nonoxynol-10 did not cause any increase in the incidence of neoplastic lesions in mice; nonoxynol-10 was not considered a carcinogen.*

Intravaginal

nonoxynols

In a lifetime exposure study, rats (number and strain not specified) were dosed with 6.7 or 33.6 mg/kg nonoxynol-9, intravaginally, 3 times per wk for a total of 24 mo.[2] *The low and high doses represented approximately 4 times and 20 times the clinical dose, respectively. Two groups of rats served as sham and untreated controls. No significant differences were observed between experimental and control groups. This was true for all of the measured parameters, which included palpable masses and mortality, with the exception of histopathologic tissue examination. Any positive findings observed in the experimental group at necropsy were considered related to the process of aging and were not related to the test substance.*

OTHER RELEVANT STUDIES

Effect on Stratum Corneum

The effect of Octoxynol-9 on intercellular adhesion was evaluated in stratum corneum samples obtained from the back of guinea pigs.[2] *Samples (10 mm^2) were immersed in 10 ml of Octoxynol-9 solution (0.1 M and 0.1%) for 1 – 30 d without mechanical stimulation. There was no splitting of the stratum corneum into fragments; only rolling or curling. Corneocytes were rarely observed and differences in elasticity values between distilled water controls and Octoxynol-9-treated samples were slight. In another study, in vitro damage to the stratum corneum following exposure to 1% Octoxynol-9 was evaluated. Three suction blisters were obtained from the volar forearms of young adult males and viable epidermis was removed from the blister roofs with a saline-moistened cotton swab. Discs of stratum corneum were agitated in a 1% solution of Octoxynol-9 in distilled water for up to 6 h. Octoxynol-9 caused slight swelling, vacuolization, and moderate loss of staining intensity. Corneocytes which released into the distilled water had no discernable changes in size or shape and stained well with rhodamine.*

Comedogenicity

Octoxynol-9 was used as the vehicle control in two studies evaluating the comedogenicity of sulfur.[2] *Subjects had severe acne and a pronounced propensity for comedo formation. In the first study, an occlusive patch containing 0.25% Octoxynol-9 was applied to the back of 6 subjects 3 times per wk for 6 wk. A blank, dry occlusive patch was applied to an additional 6 subjects that served as controls. Comedones were observed in 3 of the 6 subjects tested with Octoxynol-9 and in 1 of the 6 controls. Two of 6 biopsy specimens from the Octoxynol-9-treated sites contained definite comedones; 1 of 6 biopsy specimens from the control sites contained definite comedones. In a separate study, 40 subjects were treated in a similar fashion. Twenty subjects had a history of acne but were free of active disease; the remaining 20 had active acne on their backs, either comedonal or comedonal with some small pustules. Comedones were observed in 2 out of 20 subjects, both tested with, or without, Octoxynol-9. Four out of 20 biopsy specimens from the Octoxynol-9-treated sites contained definite comedones, while 2 out of 20 control biopsy specimens contained definite comedones. The authors concluded that Octoxynol-9 was comedogenic.*

Immune System Effects

The effect of Octoxynol-9 dosing on humoral and cell-mediated immune responses and autoimmune response was evaluated using 129/Ao Boy strain mice.[2] *Mice were administered 0.125% Octoxynol-9, in drinking water, for 4 wk, and in vitro and in vivo effects were evaluated. For the humoral response, mice were immunized with intraperitoneal (i.p). injection of 0.2 ml of 10% sheep red blood cells (SRBCs) in phosphate buffered solution (PBS). The number of anti-SRBC plaque-*

forming cells (anti-SRBC PFCs) in the spleen was determined after 4 d; Octoxynol-9 was shown to enhance the production of anti-SRBC PFCs.

For determination of the cellular response, anti-SRBC delayed type hypersensitivity (DTH) was evaluated.[2] *After 4 wk of dosing, mice were sensitized intravenously with 1 x 10^5 SRBCs in 0.1 ml PBS and after 4 d the reaction was elicited by intradermal introduction of 1 x 10^8 SRBCs into the left hind foot pad; Octoxynol-9 stimulated the cellular immune response to SRBCs. Octoxynol-9 did not affect the development of anti-SRBC DTH in mice that were dosed for 1 wk. In the in vivo study, Octoxynol-9 was shown to cause significantly greater stimulation of anti-hemoglobin plaque-forming cells (anti-Hb PFCs) in B lymphocytes isolated from treated mice, in the presence of thymocytes or T lymphocytes from control mice or from mice treated with Octoxynol-9. The immunotoxicity of Octoxynol-9 was evaluated in a double-blind study using 10 outbred CF-1 female mice. The animals received an i.p. injection of 0.2 ml Octoxynol-9 (concentration not stated), in sterile saline, for 24 d. Ten mice were dosed with saline (vehicle controls) and 5 mice were used as untreated controls. All mice were subcutaneously immunized with 0.05 ml of 5% SRBCs on day 11; immunization was repeated with 0.05 ml of 10% SRBCs on day 18. Animals were bled by caudal incision prior to treatment on days 16 and 25. No changes in organ or body weight, or changes in hematocrit, white blood cell counts, anti-red blood cell responses, or serum immunoglobin patterns were noted in treated animals, compared to saline-treated controls. Compared to the untreated controls, immunoglobin M (IgM) concentrations were significantly higher in the group injected with Octoxynol-9 and in the saline controls on day 16. The authors concluded that Octoxynol-9 had no significant effect on the immune or hematological system, and, thus, was nontoxic.*

Hormonal/Endocrine Effects

Alkylphenols, which include octoxynols, and related compounds have been reported to be estrogenic, both in vivo and in vitro because they mimic the effects of estradiol (concentrations at which effects seen not stated).[2] *In rats, nonoxynol-9 can be metabolized to para-nonylphenol, which has been described as estrogen-like because it mimicked the effects of estradiol (i.e., induction of the progesterone receptor and cellular proliferation) in the MCF-7 (estrogen-dependent breast cancer) cell line. Results from several studies indicate that several alkylphenols and related nonylphenol ethoxylate degradation products (4-nonylphenol, 4-tert-octylphenol, 4-tert-butylphenol, 4-nonylphenoldiethoxylate, nonoxynol-9, and 4-nonylphenoxycarboxylic acid) also can mimic the effect of estradiol.*

Barrier Disruption

nonoxynols

Cadaver epidermal membranes (n = 12) were placed between two halves of horizontal Franz-type glass diffusion cells and pretreated with nonoxynol-2, -4, and -9 (20% w/w solutions in isopropyl myristate; dose per nonoxynol = 10 ul/cm^2) for 60 min prior to rinsing with water.[2] *Water ($[^3H]_2O$) permeation rates were determined over an 8 h period; membranes treated only with isopropyl myristate served as controls. The permeability coefficients (cm/h) for each nonoxynol, in isopropyl myristate were as follows: 2.26 x 10^{-3} for nonoxynol-2, 2.40 x 10^{-3} for nonoxynol-4, 3.37 x 10^{-3} for nonoxynol-9 (compared to 1.34 x 10^{-3} for controls and 0.5 – 1.5 x 10^{-3} in normal skin). Four of the 12 nonoxynol-treated skin samples were compromised, while barrier disruption was reported in 2/12 controls. Based on these findings, nonoxynols were considered to minimally influence the skin barrier to water; however, it was not possible to assign a definite surfactant-induced damage claim.*

Age and Ocular Damage

an octoxynol (number of ethoxy repeat units unknown)

The effect of bovine age on the susceptibility to ocular damage was evaluated using lenses from calves (8 – 18 mo; n = 6) and cows (2 - 3 yr; n = 10).[36] Lenses were isolated aseptically and studied for 96 h following treatment with an octoxynol (tested at 1%). Control lenses were left untreated (n = 55 adult control lenses; n = 24 calf control lenses). Optical damage was evaluated via calculation of back vertex distance variability (BVDV). There was a significant difference in BVDV in the treated group, with calf lenses showing greater optical damage compared to adult cows ($p \leq 0.05$; this effect was not observed in control lenses). BVDV values were similar among control calf and adult lenses and adult lenses treated with the octoxynol (approximately 0.5 mm). The BVDV value of calf lenses treated with the octoxynol was approximately 3 mm.

Octoxynol-Induced Changes in Inflammatory Mediators in Ex Vivo Cervicovaginal Epithelium Model

Octoxynol-9

The impact of an Octoxynol-9 solution and a vaginal cleansing film (containing 1 and 3% Octoxynol-9, respectively) on inflammatory mediators (interleukin-1α (IL-1α) and IL-1β, evaluated with both substances; IL-6, tumor-necrosis factor alpha (TNF-α), IL-8, gamma interferon inducible protein 10 (IP-10) and macrophage inflammatory protein 3α (MIP-3α), evaluated only with the vaginal cleansing film) was studied.[37] Assays were performed using VEC-100 (reconstructed human vaginal-ectocervical epithelium) tissue equivalents. A significant increase ($p < 0.001$) in both IL-1α and IL-1β levels were observed in tissues treated with the Octoxynol-9 solution and the vaginal cleansing film compared to untreated controls. The vaginal cleansing film caused a significant several-fold increase ($p < 0.05$) of IL-8 and IP-10 compared to the untreated control. Significant changes were not observed regarding MIP-3α, IL-6, and TNF-α levels compared to the untreated control.

Cytotoxicity

An in vitro growth inhibition assay was performed using Octoxynol-9, sodium lauryl sulfate (SLS), phenol, ethylphenyl proprionate (EPP), and 12-O-tetradecanoylphorbol-13-acetate (TPA) in human epidermal keratinocytes.[2] *Each chemical was added to keratinocyte growth medium containing standard antimicrobials; no growth factors were added. Test substance concentrations were produced by 10-fold dilutions (volume = 10 µl) and ranged from 10^{-10} to 10^{-2} M. Morphological changes in the keratinocytes included marked rounding and shrinkage of cells. Growth inhibition induced by Octoxynol-9 occurred within less than an hour of exposure. The rank order for morphological changes was SLS > Octoxynol-9 >phenol >EPP > TPA, while the rank order for growth inhibition was TPA > EPP > SLS > Octoxynol-9 > phenol. TPA was considered the most potent irritant. The skin irritation potential of Octoxynol-9 and other surfactants (not specified) was evaluated in primary rat keratinocytes. Leaking of LDH into the medium, MTT reduction, and lysosomal uptake of neutral red dye were measured after treatment for 1 h, and after 24 h. Compared to controls, Octoxynol-9 caused less than a 2-fold increase in LDH release at 24 h. A dose-related increase in cellular LDH leakage in the medium was observed at concentrations of 10 – 100 µg/ml Octoxynol-9; most of the enzyme leakage occurred during the 1-h treatment period. Results from the MTT and NR assays were comparable to the LDH leakage results. An EC_{50} value was not calculated because the response to Octoxynol-9 treatment was below 50% of the maximal response. The cytotoxic potential of Octoxynol-9 was considered equivalent to that of the other tested surfactants.*

an octoxynol (number of ethoxy repeat units unknown)

The cytotoxic potential of an octoxynol (approximately 0.0001 – 2.7 mM) was evaluated in cell types that model the most vulnerable cells in human cervicovaginal mucosa (fully polarized columnar epithelial cells (Madin-Darby canine kidney (MDCK) and Caco-2 cells), human cervical non-polarized cells (HeLa), and dendritic cells (fetal skin dendritic cells (FSDC)).[38] Cytotoxicity was measured via a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, with cells exposed to the test substance for 20, 60, 180, and 540 min. The octoxynol was toxic to all evaluated cell types in a time- and concentration-dependent manner. Toxicity was observed at concentrations around the critical micelle concentration of the octoxynol (0.2 mM), which suggests a non-selective mode that involves destabilizing and/or damage to the cell membrane.

An octoxynol (0.002 – 0.16%) was used as a model irritant/cytotoxic agent in several assays evaluating cytotoxicity in cancer cell lines (rat liver hepatoma cell line (H4IIE), human colon adenocarcinoma cell line (Caco2), a human liver hepatoma cell line (HepG2)), and human melanoma cell lines (WM164, WM1366, and D24).[39,40] Cytotoxicity was observed in all evaluated cell lines.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

an octoxynol (number of ethoxy repeat units unknown)

In several studies, an octoxynol was used as a known dermal irritant, either as a positive control or as a well-defined model irritant to validate new in vitro dermal irritation/cytotoxicity models.[40-46] The test substance was evaluated in EpiDerm tissues (concentration not stated), an EpiDerm full thickness model (at 1%), reconstructed human epidermis (at 0.2 and 1%), immortalized human epidermal keratinocytes (at 0.005 and 0.1%), neonatal human epidermal keratinocytes (at 0.03 – 1%), and living skin equivalents (cultured human skin model; at 1 and 10%). In all studies, the octoxynol yielded expected (positive) results.

Animal

A peel-off mask product containing 0.25% Octoxynol-9 was classified as minimally irritating and non-irritating in 2 separate single-insult occlusive patch tests using rabbits (primary irritation index = 0 for both tests).[2] *A single dose of Octoxynol-9 (10% w/w aq.; 0.15 ml) was occlusively applied to shaved rabbit skin for 24 h and average values for skin irritation 1 and 24 h post-patch removal were utilized to obtain a maximal primary Draize irritation score (MDSS) score of 0.2 (scale = 0 – 8). In a developmental toxicity study, groups of 25 outbred Sprague-Dawley CD rats received dermal applications of Octoxynol-9 at doses of 530, 1600, or 4270 mg/kg/d, at a constant dose volume of 4 ml/kg from day 6 to 15 of gestation. Controls received applications of deionized and filtered water. Exfoliation/desquamation, excoriation, and erythema were observed in the 4270 mg/kg/d group. Only excoriation and erythema were observed in the low- and mid-dose groups.*

An aqueous solution of 20% Octoxynol-11 was classified as a moderate skin irritant.[2] *No further details were provided. An unspecified concentration of Octoxynol-13 (0.5 ml) was applied under an occlusive patch to intact or abraded, shaved rabbit skin. The average primary irritation index for reactions scored at 24 and 72 h was 0.50; Octoxynol-13 was not considered a primary dermal irritant.*

an octoxynol (number of ethoxy repeat units unknown)

The dermal irritation potential of a leather cream (laboratory and marketed) containing an octoxynol, white beeswax, carnauba wax, distilled water, silicone oil, linseed oil, Sudan black dye, and nigrosine black dye (concentrations of ingredients within cream not stated) was evaluated in rabbits (6/group; sex and strain not stated) according to OECD TG 404.[34] Creams were applied to the shaved back for 72 h and sites were evaluated 24, 48, and 72 h after exposure. Neither laboratory nor marketed creams were considered to be irritating.

Human

The skin irritation potential of Octoxynol-1, -3, -5, -9, and -13 (each undiluted) was evaluated in a 48-hr skin irritation test using 50 subjects.[2] *None of the test substances induced skin irritation. The skin irritation potential of 2 pairs of identical formulations (with and without 2% Octoxynol-9) was evaluated in 24-h single-insult occlusive patch tests. A PII of 0.55 (moderately irritating; with 2% Octoxynol) and 0.13 (minimally irritating; without 2% Octoxynol-9) were reported for the first pair of formulations. For the second pair of formulations (same composition except for presence or absence of 2% Octoxynol-9), a PII of 0.11 (minimally irritating; presence of Octoxynol-9 not indicated) was reported. These results were attributed to differences in the skin penetrability of Octoxynol-9 in one formulation compared to the other. Nine healthy female volunteers were tested with a daily application of 200 µl of 1% Octoxynol-9 in a polypropylene chamber for 4 d; Octoxynol-9 was classified as a nonirritant.*

Sensitization

Animal

nonoxynols

The skin sensitization potential of nonoxynol-6 was evaluated in a guinea pig maximization test.[2] *Groups of albino Hartley-Dalkin guinea pigs (5/group) were tested with 1.7, 3, 9, or 27 g % nonoxynol-6 (w/w) in propylene glycol during the induction phase. One animal in the 9% nonoxynol-6 group did not complete the study. On day 1 of induction, animals in each of the 4 groups received 3 pairs of injections of the following chemicals: (1) 0.1 ml nonoxynol-6, (2) 0.1 ml nonoxynol-6 mixed (50:50) with Freund's complete adjuvant (FCA), and (3) 0.1 ml FCA. On day 7, each injection site was shaved and an occlusive 48-h application of 100% nonoxynol-6 was made. During the challenge phase, an occlusive 24-h application of nonoxynol-6 (2.7% in petrolatum) was made and sites were scored at 48 h. A control group of 40 guinea pigs (20 exposed to deodorized kerosene and 20 exposed to tetraethylene glycol diacrylate during induction) were not exposed to nonoxynol-6 during the induction phase and were challenged with 2.7% nonoxynol-6. Challenge reactions in experimental animals were as follows: 2/5 (1.7% induction group), none in the 3% induction group, 1/4 (9% induction group), and 2/5 (27% induction group). The proportion of challenge reactions to 2.7% nonoxynol-6 in experimental groups was not significantly different from that in the control group; nonoxynol-6 was considered a non-sensitizer.*

an octoxynol (number of ethoxy repeat units unknown)

The dermal sensitization potential of a leather cream (laboratory and marketed; neat application over 25 cm^2 area) containing an octoxynol, white beeswax, carnauba wax, distilled water, silicone oil, linseed oil, Sudan black dye, and nigrosine black dye (concentrations of ingredients within cream not stated) was evaluated in rabbits (6/group; sex and strain not stated) according to OECD TG 406 (Buehler method).[34] Animals were treated on day 0 with 0.1% 1-chloro-2,4-dinitrobenzene (also used as positive control). No details regarding test substance application were provided. The test substance was considered to be non-sensitizing, and the positive control gave expected results.

Human

The skin sensitization potential of 0.1% Octoxynol-9 was evaluated in an assay using 84 men and 122 women.[2] *The test material was applied using a 1 in^2 cotton twill patch, and secured with adhesive tape, for 6 d to the arms of the men and to the arms and legs of the women. After a 2-wk nontreatment period, a 48-h challenge application was made. No reactions to the fabric treated with 0.1% Octoxynol-9 were observed. In a different sensitization assay, 9 consecutive, 24-h semi-occlusive applications of a foot gel containing 8% Octoxynol-9 (0.2 ml) were made to 20 males and 92 females over 3 wk. A challenge application was made after a 10 -14 d nontreatment period, which was scored 24 and 48 h post-application; no adverse reactions were observed and the foot gel containing 8% Octoxynol-9 was not considered to be a primary irritant or a sensitizer. A formulation containing 0.5% Octoxynol-9 was tested in an occlusive HRIPT using 102 subjects. Induction applications were made over 3 wk and reactions were scored 48 or 72 h post-application; after an unspecified nontreatment period, a 24-h challenge application was made and scored at 48 and 96 h post application. Seven subjects had a score of 1 or greater during induction and 1 subject had a score of 1 during the challenge phase; the test substance was not considered a sensitizer.*

Phototoxicity

In Vitro

nonoxynols

Photohemolysis of human red blood cell suspensions containing nonoxynol-9 (2×10^{-5} M) occurred after irradiation with ultraviolet light under aerobic conditions.[33] *Nonoxynol-9 was irradiated for 70 min under an oxygen and argon-*

enriched atmosphere in a photochemical reactor equipped with phosphorus lamps (emission maximum at 300 nm). Lysis was not observed after the red blood cells were irradiated for 80 min in the absence of 2 x 10^{-5} M nonoxynol-9 or when the cells were incubated with 2 x 10^{-5} M nonoxynol-9 in the dark. The researchers considered nonoxynol-9 was phototoxic in vitro.

OCULAR IRRITATION STUDIES

In Vitro

The ocular irritation potential of Octoxynol-9 was evaluated in an in vitro cytotoxicity assay, at concentrations ranging from 0.005 – 0.1%, using corneal cells from the fetal pig.[2] *Three corneal cell types were cultured (epithelial, endothelial, and stromal) and the mitochondrial capacity of these cells was assessed by monitoring the reduction of MTT reagent. Octoxynol-9 caused 50% reduction of MTT at a concentration of 0.006% (EC_{50} = 0.006%), which was said to correlate well with in vivo Draize test data (Draize score = 5, severe or extreme irritation). Concentrations higher than 0.01% completely inhibited the reduction of MTT.*

Animal

Several ocular irritation assays were performed to evaluate Octoxynol-9, mostly using the Draize method in rabbits.[2] *Octoxynol-9 (10%) was instilled in 1 eye of 6 rabbits (contralateral eyes served as controls); treated eyes were rinsed in 3 rabbits. Discrete to translucent areas of the cornea had not cleared in 2 of the 3 rabbits with unrinsed eyes; rinsed eyes were normal within 4 d. In a second study, Octoxynol-9 was instilled in 1 eye of each of 2 rabbits (and unrinsed). Moderate to severe erythema, slight to moderate edema, slight corneal opacity, and iridial injection were observed in the unrinsed eye; similar symptoms had cleared in the rinsed eye by 14 d post instillation. Signs of slight pannus and slight erythema on the nictitating membrane persisted in the unrinsed eye up to 14 d post-instillation; Octoxynol-9 was classified as a moderate permanent ocular irritant. A skin freshener formulation containing 0.25% Octoxynol-9 was instilled, and remained unrinsed, in rabbit eyes in 2 separate ocular irritation studies; the product was classified as minimally irritating. An unspecified concentration of Octoxynol-9 was instilled into the conjunctival sac (right eye; left eye served as control) in 2 young adult, male New Zealand white rabbits. Treated and untreated eyes were not rinsed until approximately 20 s post instillation. Moderate iritis, moderate conjunctival redness and chemosis, and copious blood-tinged discharge were observed in both treated eyes. Conjunctival redness had cleared by day 21 and corneal opacity and iritis persisted beyond day 21 post-instillation. Biomicroscopic examinations indicated moderate to severe corneal injury, which was evident from day 1 to day 3 post-instillation. Mild and moderate corneal opacity were observed in rinsed and unrinsed eyes, respectively; Octoxynol-9 was classified as a moderate ocular irritant. The maximum average Draize scores reported for rabbits (4 – 6/group) which had up to 10% Octoxynol-9 instilled in the conjunctival sac of 1 eye (unrinsed) were: 2 (minimally irritating) for 1% Octoxynol-9; 32 (moderately irritating) for 5% Octoxynol-9; 59 (severely irritating) for 10% Octoxynol-9. These results were correlated with mild, moderate, and severe corneal swelling, respectively. Octoxynol-9 (10% aq.) was classified as an ocular irritant when applied directly to the cornea and yielded a Draize eye irritation score of 55 when instilled directly in the eyes of rabbits (eyes remained unrinsed in both studies). A single, unrinsed instillation of 100 µl Octoxynol-9 (unspecified concentration) into the conjunctival sac of rabbit eyes was reported as being slightly irritating.*

The highest test concentrations of Octoxynol-1 (15%), -3 (15%), -5 (5%), -9 (0.5%), and -13 (1%) did not induce irritation in the eyes of 3 or more, rabbits from test groups comprising 5 animals.[2] *An aqueous solution of 20% Octoxynol-11 was classified as "very badly tolerated" in an ocular irritation test. No further details were provided. Three male and 3 female New Zealand white rabbits had 0.1 ml Octoxynol-13 instilled into the right eye; untreated eyes served as controls. Eyes remained unrinsed and reactions were scored at 1, 2, 3, and 7 d post-instillation (Draize scale: 0 – 110). Draize ocular irritation scores were 30.2 on day 1, 28 on day 2, 34.3 on day 3, 28.8 on day 4, and 33.8 on day 7; Octoxynol-13 was classified as severely irritating.*

an octoxynol (number of repeat ethoxy units unknown)

In several studies, an octoxynol was used as a known ocular irritant, either as a positive control or as a well-defined model irritant to validate new in vitro ocular irritation/cytotoxicity models.[47-50] Studies were performed using immortalized human corneal cells (0.0025 – 0.1 %), SV40T-transformed human corneal epithelial cells (at 0.005 – 0.1%), reconstructed human cornea-like epithelium (at 0.3%), and a reconstructed corneal epithelial model prepared from primary-cultured human limbal epithelial cells (at 5%). In all assays, the octoxynol gave expected (positive) results.

MUCOUS MEMBRANE IRRITATION STUDIES

In Situ

The effect of Octoxynol-9 on the rat jejunum and colon was evaluated in a single-pass, in situ perfusion model using the release of LDH and solubilized mucus into luminal perfusate as potential markers of intestinal damage.[2] *Isolated jejunal and colonic segments of male Sprague-Dawley rats (4 -9/group) were perfused with 1% Octoxynol-9, polysorbate 80 (0.1 – 10% w/v in isotonic saline), or isotonic saline (controls) for 6 h. The LDH release rate was greatest in the Octoxynol-9 group and approximately 3 times lower in the colon than in the jejunum. Compared to controls, the release rate of LDH in the jejunum increased 2-fold after perfusion with 1% polysorbate, and 7-fold after perfusion with 1% Octoxynol-9. Mucous release rates*

for Octoxynol-9 and polysorbate 80 were similar and greater than in controls. The mucous and LDH release rates for Octoxynol-9-perfused rat colon segments returned to baseline values, suggesting that these effects were reversible. The following morphological changes which were observed after perfusion with 1% Octoxynol-9, were considered moderate: denudation of villous tips, desquamation of the epithelial surface, necrosis of the mucosal lamina propria, and intervillous adhesion. These changes were observed to a minimal degree after perfusion with saline or 1% polysorbate 80.

an octoxynol (number of repeat ethoxy units unknown)

An octoxynol (tested at 1%) was used as a positive control in 2 studies evaluating the irritation/cytotoxic potential in oral tissues models.[51,52] Application of the octoxynol to tissues yielded expected (positive) results. An octoxynol (1%) was used as a positive control in an in vitro assay evaluating the irritation potential of spermicides and feminine care products.[53] Vaginal tissue samples (n = 2) were obtained from healthy women undergoing hysterectomies for benign indications. An octoxynol (83 µl; 1% concentration) was applied to the samples for 0.5, 1, and 2 h, and the exposure times that reduced tissue viability to 50% (ET_{50}) was determined. The average ET_{50} was determined to be 1.25 h. Water, the negative control used in this assay, resulted in an ET_{50} of 18 h. Additionally, a full thickness VEC tissue model (VEC-100-FT) was exposed to a lubricant doped with 0.1 or 2% nonoxynol-9 for 18-h. Tissue viability and cytokine release of the VEC-100-FT model were evaluated via an MTT and enzyme linked immunosorbent assay (ELISA); 2 commercial lubricants were used as negative controls. Loss of tissue viability in the VEC-100-FT model was greater in the tissue treated with nonoxynol-9 (2% nonoxynol-9 > 0.1% nonoxynol-9 > lubricant 1 > lubricant 2); IL-α and interleukin-1β (IL-1β) concentrations increased as structural damage increased while tumor necrosis factor-α release decreased as structural damage and loss in tissue viability increased.

Animal

nonoxynols

In a mucous membrane irritation study, female Wistar rats (n= 9 -10) received a single dose of aqueous nonoxynol-9 (pH = 2; 5 mg/100 g) intravaginally; groups of 5 controls received distilled water.[2] Animals were killed over a period of 6 wk. Primary mucosal damage was observed for up to 24 h post administration, which included epithelial degeneration, necrosis and sloughing. A secondary acute inflammatory response, involving the entire vaginal wall and perivaginal tissues, was observed. The severity of vaginal wall inflammation was time-dependent; areas with minimal mucosal damage eventually returned to normal and areas with severe mucosal damage healed abnormally. In another study, a contraceptive cream containing 5% nonoxynol-9 was administered intravaginally (dose = 0.1 g/100 g body weight) to groups of female Wistar rats (3 – 8/group); controls received distilled water. The resulting lesions were not as severe as induced by exposure to aqueous nonoxynol-9 (5 mg/100 g); however, acute cervicovaginitis was observed in some of the rats. Groups of Sprague-Dawley rats (7/group) were administered 5, 12.5, 25, 50, or 75% nonoxynol-9, in distilled water, via vaginal lavage; 2 control groups received distilled water. Minimal irritation and inflammatory-cell infiltrate were observed in the vaginal mucosa of animals in the 5 and 12.5% groups. Mild irritation and epithelial exfoliation were observed in the 25% group. Epithelial exfoliation was more severe and persistent in animals that received 50 and 75% nonoxynol-9 concentrations; edema was noted in both groups. The inflammatory cell-infiltrate was the most severe and persistent in the 75% nonoxynol-9 group. Groups of New Zealand white female rabbits (3 – 4/group) had a collagen sponge containing 2.5, 5, 20, or 50 mg nonoxynol-9 in aqueous solution inserted into the vagina for 10 d. Six controls received just a collagen sponge. Moderate inflammatory changes were observed in the vaginas of rabbits in the 2.5 mg group. The most striking finding was a pronounced infiltration of polymorphonuclear leucocytes on the inserted sponge. Minimal changes were observed in 2 of the 6 controls. A dose-dependent increase in inflammatory changes, including cellular inflammatory infiltrate, edema of the connective tissue of the submucosal layer, and denudation of the mucosal epithelium were observed. No epithelial lining was observed in the 50 mg group, except in areas that were far removed from the medicated sponge. Concentration-dependent irritation of vaginal mucosa was observed in groups of New Zealand white rabbits (6/group) that received 2.5, 5. 12.5, or 25% nonoxynol-9 in 20 ml water, via vaginal lavage, once daily for 4 d. Lesions that were observed included epithelial exfoliation, submucosal edema, and inflammatory cell infiltrate; mild irritation was observed in the 2.5 and 5% dose groups, while moderate to severe irritation was observed in the 12.5 and 25% groups.

Female mice of the CF-1 strain were exposed to a spermicide containing 3.5% nonoxynol-9, either intravaginally or through intrauterine exposure.[33] Both modes of administration, with various exposure times, resulted in disruption of the uterine epithelium. Following intrauterine injection, the nonoxynol-9 spermicide caused rapid focal, uterine epithelial sloughing and complete epithelial loss within 24; regeneration of the uterine epithelium began 48 h after exposure and was completely restored within 72 h. However, the new epithelial layer was composed of cuboidal cells instead of the columnar cells that are normally present. The researchers concluded that nonoxynol-9 had a deleterious effect on uterine epithelium. The intravaginal dosing of female BALB/c mice with a commercial spermicide containing 3.5% nonoxynol-9 for 14 d induced an inflammatory response that was characterized by increased levels of cytokines and chemokines, the recruitment of neutrophils and monocytes into the genital tract, and the activation of the transcription factors nuclear factor kappa light chain enhancer of activated B cells and activator protein-1. Vaginal irritation, epithelial exfoliation, vascular congestion, and leukocyte infiltration were reported in a study on the toxicity of liposomal gels, in which 5 New Zealand white rabbits received 4% nonoxynol-9 (positive control) intravaginally at a dosage of 1 g/rabbit/d for 10 d.

CLINICAL STUDIES

Sixty women were instructed to use (in conjunction with a diaphragm) a spermicidal jelly containing 1% w/w Octoxynol-9 for 6 mo.[2] Twenty-seven women did not complete the study; 2 withdrew because of side effects. Of the 33 subjects who completed the study, vaginal irritation and excessive discharge were reported by 3 and 2 women, respectively. These side effects were described as minor and reversible in nature. No further details were provided.

nonoxynols

A clinical trial of nonoxynol-9 (in gel form) was performed using 40 healthy female volunteers.[33] Twenty women received the gel (20 mg/ml nonoxynol-9) and 20 received a placebo for 7 d; examinations were made on day 0, 7, and 14. Genital irritation, erythema, and histologic inflammation were observed in both the treatment and placebo groups. Inflammatory changes were characterized by patchy infiltration of the lamina propria, predominantly with CD^{8+} lymphocytes and macrophages; epithelial disruption was absent. The long-term effects of 5 spermicidal formulations containing nonoxynol-9, including 3 gels (52.5, 100, or 150 mg/dose), a film (100 mg/dose), and a suppository (100 mg/dose), were studied in groups of 30 women over 7 mo (subset of study performed in 1536 women summarized below). Overall, there was no increased risk for any new colposcopic lesion in any of the nonoxynol-9 groups, when compared to controls. However, women who had used any nonoxynol-9 product were more likely than controls to have genital lesions characterized by erythema or edema. A total of 34 serious adverse events occurred in 31 study participants either during or after spermicide use, but none was attributed to spermicide use. Seven-month probability data for vulvar or vaginal irritation did not differ between test groups; the researchers concluded that all 5 spermicide products were safe as used by the study participants. Histological findings of inflammation, a statistically significant increase in IL-IRA, and deep epithelial disruption were reported for 4 out of 20 women that applied 4% nonoxynol-9 spermicide gel twice a day for 13.5 consecutive days. The collective results of 2 separate clinical studies in which women applied a spermicide containing 3.5% nonoxynol-9 for 14 d (n = 179 subjects) or a vaginal suppository containing 150 mg nonoxynol-9 for 2 wk suggested that nonoxynol-9 does not elevate the incidence of lesions with epithelial disruption when these products are used no more than once per day. The incidence of lesions that were attributable to the use of these products were associated with an increased frequency of use.

Twelve contact dermatitis patients were patch tested with ingredients of a topical antiseptic preparation.[2] Ten of the patients had previously used various antiseptic preparations that contained nonoxynol-9. The remaining 2 patients had used antiseptic preparations that contained nonoxynol-8.3 and nonoxynol-10. Nonoxynol-8.3, -9, and -10 were patch tested at 2% in water. Patches remained in place for 48 h and reactions were scored at 48 h and at 72 or 96 h. All of the patients had ++ (strong, edematous or vesicular reaction) positive reactions either at 72 or 96 h. Epicutaneous test results for other ingredients of antiseptic preparations were negative, with the exception of 1 patient reaction to iodine. When 6 of the 12 patients in the study were tested with 2% aqueous nonoxynol-6, -8.3, -9, -10, -14, and -18 several months later, most of the reactions observed at 72 or 96 h were ++ reactions. However, in a couple of instances, a + (weak, non-vesicular), negative, or doubtful reaction was observed.

A multicenter study in Sweden was performed to evaluate the human sensitization potential of oxidized ethoxylated surfactants.[33] The 528 participants (196 males; 332 females) were identified as consecutive dermatitis patients with suspected allergic contact dermatitis. Patients were patch-tested with aqueous solutions of nonoxynol-10 (20%) and air-oxidized nonoxynol-10 (20%). None of the participants had reactions to nonxynol-10. Erythema was observed in 1 participant patch tested with oxidized nonoxynol-10, on day 7, which was noted as a non-allergic reaction.

A randomized trial was conducted in 1536 women across the US to evaluate the safety of 5 nonoxynol-9 spermicides.[33] The spermicides, used for a period of 7 mo, included 3 gels that contained nonoxynol-9 at doses of 52.5, 100, and 150 mg, respectively, and a film and suppository that each contained 100 mg nonoxynol-9. Papanicolaou smears and cervical cytology samples were obtained during follow-up visits done at 4, 17, and 30 wk after study initiation. Results for 640 women were included in a Papanicolaou smear analysis. No differences in the rates of cervical alterations among the women using different amounts or different formulations of nonoxynol-9 were found and no statistically significant evidence of a dose-response relationship between nonoxynol-9 and changes in cervical cytology was observed. Furthermore, duration, frequency, and total number of spermicide uses were not associated with any statistically significant changes in cervical cytology. Although a noted study limitation was the exclusion of more than half of the trial participants due to missing Papanicolaou smear data, there was no evidence that these exclusions were biased by spermicide group, and the group comparisons were deemed credible. The researchers concluded that exposure to different formulations and doses of spermicides containing nonoxynol-9 for 30 wk is unlikely to affect cervical cytology.

Case Reports

A patch test was performed in a 58-yr old uranium mill maintenance worker that used a waterless hand cleanser at work, containing 0.5% Octoxynol-9 and nonoxynol-6, in petrolatum.[2] Occlusive application of "A1 Test" strips were made to the upper back and sites were scored 48-h after application. No reaction to 0.5% Octoxynol-9 was observed. (Results for nonoxynol-6 were not provided.)

nonoxynols

A 72-yr-old male and 71-yr-old female presented with symptoms of photosensitization after being treated with an antiseptic preparation containing nonoxynol-10.[2,33] *A follow-up photosensitization study was conducted with 2 of the affected subjects and 32 controls (13 males and 19 females). Controls were suspected of having photodermatosis and had not used the antiseptic preparation. The 2 affected subjects and controls were patch tested with the antiseptic preparation, undiluted nonoxynol-10, 2% nonoxynol-10 in petrolatum, and 0.2 and 2% nonoxynol-10 in water. The 2 affected subjects were also patch tested with 1% nonoxynol-10% in water. The male affected subject exhibited photosensitization reactions to the antiseptic preparation and to 0.2, 1, and 2% aqueous nonoxynol-10. The female affected subject exhibited photosensitization reactions to the antiseptic preparation and to 2% nonoxynol-10 in petrolatum. No other reactions were observed in any of the remaining photopatch or nonirradiated sites. Of the 32 control subjects, 13 had photosensitization reactions to the antiseptic preparation and 4 had photosensitization reactions to aqueous nonoxynol-10. Undiluted nonoxynol-10 did not elicit photosensitization reactions in either affected subject or in controls.*

A woman (domestic cleaner) with a 5-mo history of acute severe dermatitis and a past history of atopic eczema was patch tested with nonoxynol-12, an ingredient of a polish utilized during work.[54] *The patient had severe dermatitis on the dorsa of the hands, forearms, and face. Positive patch test reactions to the following concentrations of nonoxynol-12 in petrolatum were reported: 0.01, 0.1, 0.5, and 1%. The reactions were classified as + on day 2 and ++ on day 4. Negative patch test results were reported for 30 control subjects.*

RISK ASSESSMENT

The diameters of anhydrous hair spray particles and pump hair spray particles were determined to be 60 – 80 µm and ≥ 80 µm, respectively, compared to respirable particles with a reported mean aerodynamic diameter of 4.25 ± 1.5 µm.[2] *Thus, the use of Octoxynol-9 in hair sprays was not expected to result in inhalation exposure.*

CIR staff applied the in silico tool, VERMEER Cosmolife (Ver. 0.24), previously named SpheraCosmolife[55] to estimate the daily exposure to octoxynols from cosmetic use. According to the Council's 2022 survey, the maximum reported concentration of use for this ingredient group is 2% (in skin cleansing formulas (rinse-off; reported for Octoxynol-9)).[3] As indicated by VERMEER Cosmolife, the following exposure parameters are sourced from the Scientific Committee on Consumer Safety (SCCS) Notes of Guidance (NoG)[56] and relevant published literature,[57-60] using 90th percentile exposure values:

Octoxynol-9 at 2% in skin cleansing formulas (e.g., makeup remover)

To utilize VERMEER Cosmolife for exposure estimation, a product category should be specified. Assuming the product type for "skin cleansing formulas (rinse-off)" is makeup remover:

Relative daily exposure of makeup remover: 5000 mg/d (8.33 mg/kg bw/d)
Body weight used for the product exposure: adult (60 kg)

Type of exposure: rinse-off
Retention factor applied: 0.1
Surface area involved: 565 cm^2 (½ area head - female)
Skin surface exposure: [5000 mg/d × 0.1 (retention factor) × 2% (use concentration)] ÷ 565 cm^2 = 0.018 mg/cm^2
External exposure of makeup remover for dermal uptake: 8.33 mg/kg bw/d × 2% (use concentration) = 0.17 mg/kg bw/d

The Systemic Exposure Dose (SED) assuming 10% dermal absorption was determined to be 0.0017 mg/kg bw/d. (An acute dermal toxicity study involving three guinea pigs showed no evidence of dermal absorption of Octoxynol-9.[2] An in vitro study using human skin demonstrated minimal penetration (< 0.5%) of applied Nonoxynol-9, with the majority of the dose retained in the stratum corneum.[33]) As the data suggest poor dermal bioavailability, a value of 10% dermal absorption has been considered here for a conservative estimation.

Using the CORAL no-observed-adverse-effect-level (NOAEL) model implemented in VEGA software (NOAEL (IRFMN-CORAL) v.1.0),[26,27] VERMEER Cosmolife predicts a NOAEL of 28.11 mg/kg bw/d, while the it also indicates this prediction is considered to have a moderate reliability level. When experimental data on dermal absorption is lacking, a conservative 50% default value can be applied.[25] Consequently, the margin of exposure (MOE) is calculated as 337.5 when assuming 50% absorption, and 1687.27 when assuming 10% absorption. These values are greater than 100, and are therefore generally accepted for considering a cosmetic ingredient safe for use.

SUMMARY

The 25 octoxynol ingredients being reviewed in this report are reported to function in cosmetics as surfactants. The Panel first reviewed these octoxynol ingredients in a safety assessment that was published in 2004. At that time, the Panel issued a final report with the conclusion that Octoxynol-9, -10, -11, -12, -13, -16, -20, -25, -30, -33, -40, -70, Octoxynol-9 Carboxylic Acid, Octoxynol-20 Carboxylic Acid, Potassium Octoxynol-12 Phosphate, and Sodium Octoxynol-9 Sulfate are

safe as used in rinse-off and leave-on cosmetic products. Additionally, the Panel concluded that Octoxynol-1, -3, -5, -6, -7, and -8, Sodium Octoxynol-2 Ethane Sulfonate, Sodium Octoxynol-2 Sulfate, and Sodium Octoxynol-6 Sulfate are safe as used in rinse-off cosmetic products and safe at concentrations of ≤ 5% in leave on cosmetic products. In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. At its June 2023 meeting, the Panel determined that this safety assessment should be reopened to explore the irritation potential of these ingredients in products which come in contact with mucous membranes and due to the newly reported use of Octoxynol-9 at 0.1% in baby products.

According to 2023 VCRP survey data, Octoxynol-11 had the greatest reported frequency of use, in 8 formulations; frequency of use reduced from 131 uses reported in 2001. According to RLD submitted to CIR in 2024, Octoxynol-9 is reported to have the greatest number of uses (38 total formulations). Results from concentration of use surveys (2022 using VCRP product categories; 2025 using MoCRA product categories) conducted by the Council indicate that Octoxynol-9 has the highest reported maximum concentration of use, at 2% in skin cleansing preparations; in 2001, the highest reported concentration of use was Octoxynol-10 at 25% in hair lighteners with color.

The acute dermal toxicity of a leather cream comprised of white beeswax, carnauba wax, distilled water, an octoxynol, silicone oil, linseed oil, Sudan black dye, and nigrosine black dye was evaluated in Wistar albino rats (3/sex/group) according to OECD TG 402. No mortality, signs of erythema or edema, significant changes in body weights, or food consumption was observed, compared to controls.

An octoxynol (tested at up to 200 μg/ml) was used as a known non-genotoxic agent in a comet and micronucleus assay. The octoxynol gave expected results in both studies (positive results observed at the highest concentration in the comet assay; however, these results were considered irrelevant).

The effect of age on the ocular damage (from an octoxynol tested at 1%) susceptibility of bovine lenses was evaluated using calf and cow lenses. Ocular damage was statistically significantly greater in calf lenses compared to cow lenses.

The impact of an Octoxynol-9 solution and a vaginal cleansing film (containing 1 and 3% Octoxynol-9, respectively) on inflammatory mediators was evaluated in VEC-100 tissue equivalents. A statistically-significant increase in several of these inflammatory mediators were observed following application of the Octoxynol-9 solution (increase in IL-1α and IL-1β) and the cleansing film (increase in IL-1α and IL-1β, IL-8, and IP-10).

The cytotoxic potential of an octoxynol approximately (0.02 – 2.7 mM) was evaluated in cell types that model the most vulnerable cells in human cervicovaginal mucosa. Cytotoxicity was observed in all cell types in a time- and concentration-dependent manner. An octoxynol was used as a model irritant/cytotoxic agent in several cancer cell lines. Cytotoxicity was observed in all evaluated cell lines.

In several studies, an octoxynol was used as a known dermal irritant, either as a positive control or as a well-defined reference substance to validate new in vitro dermal irritation/cytotoxicity models. In all assays, the octoxynol gave expected (positive) results. A laboratory and marketed version of a cream containing an octoxyol (concentration of ingredient in cream not stated) was not considered to be irritating in a dermal irritation assay performed in rabbits. These creams were also considered to be non-sensitizing in an assay performed using guinea pigs.

In several studies, an octoxynol was used as a known ocular irritant, as either as a positive control or as a well-defined reference substance to validate new in vitro ocular irritation/cytotoxicity models. In all assays, the octoxynol gave expected (positive) results.

An octoxynol (tested at 1%) resulted in cytotoxicity to oral tissue models when used as a positive control in 2 assays. An octoxynol (tested at 1%) resulted in an average ET_{50} of 1.25 h when it was used as a positive control in an in vitro assay evaluating the irritation potential of vaginal products. A full thickness VEC tissue model was exposed to 0.1 or 2% nonoxynol-9 or 2 commercial lubricants for 18 h. Loss of tissue viability was from highest loss to lowest loss were as follows: 2% nonoxynol-9 > 0.1% nonoxynol-9 > lubricant 1 > lubricant 2.

MOE calculations were performed for Octoxynol-9 based on a NOAEL of 28.11 mg/kg bw/d and dermal absorption rates of 10 and 50%. The MOE calculations at 10 and 50% absorption rates were determined to be 1687.27 and 337.5, respectively.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusion of previously issued reports every 15 years. In 2004, the Panel published a final report on octoxynols, with the conclusion that Octoxynol-9, -10, -11, -12, -13, -16, -20, -25, -30, -33, -40, -70, and Octoxynol-9 Carboxylic Acid, Octoxynol-20 Carboxylic Acid, Potassium Octoxynol-12 Phosphate, and Sodium Octoxynol-9 Sulfate are safe as used in rinse-off and leave-on cosmetic products. The Panel also concluded that Octoxynol-1, -3, -5, -6, -7, and -8, and Sodium Octoxynol-2 Ethane Sulfonate, Sodium Octoxynol-2 Sulfate, and Sodium Octoxynol-6 Sulfate are safe as used in rinse-off cosmetic products and safe at concentrations of ≤ 5% in leave-on cosmetic products.

In June 2023, the Panel considered a re-review of these ingredients and re-opened this report to explore the irritation potential of these ingredients in vaginal douches, and a reported use of Octoxynol-9 in baby products. According to 2024 RLD and 2025 concentration of use data, these ingredients are not reported to be used in vaginal douches or baby products. However, 2022 concentration of use data indicated Octoxynol-9 was present at 0.1% in certain baby products.

After evaluation of previous and new data (including 2024 RLD), and in accordance with the product categories and concentrations of use identified in the Use section and Use table, the Panel issued a revised conclusion stating these ingredients are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating. The Panel was concerned that the potential exists for irritation due to evidence of dermal and ocular irritation in assays summarized in this report.

The Panel reviewed comments regarding use in vaginal and baby product formulations. Because such uses were not reported in the 2024 RLD or in response to the 2025 concentration of use survey, the Panel emphasized that unreported uses fall outside the scope of its safety conclusions. For the baby product use reported in 2022, the Panel stated that concluding "when formulated to be non-irritating" would mitigate concerns if use in baby products did occur.

The Panel also noted that octoxynols are used in products that may contact mucous membranes (e.g., disposable wipes). Such products should be formulated to be non-irritating to avoid adverse effects. In addition, while octoxynols can exhibit spermicidal activity, such activity is a non-cosmetic use and falls outside the purview of the Panel. The Panel does not expect spermicidal effects to occur from cosmetic use.

The Panel expressed concern regarding heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA. Furthermore, because these ingredients are ethoxylated, the Panel was also concerned about the possible presence of 1,4-dioxane and ethylene oxide impurities. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities from these octoxynols before blending them into cosmetic formulations.

It should be noted that although data on an in vitro unscheduled DNA synthesis assay have been provided herein (in italicized text, as this was reported in the original report), according to the Panel. this assay is no longer considered reliable and should not be used to determine the genotoxic potential of an ingredient. The lack of genotoxic potential for this ingredient group was supported by other more reliable assay types (e.g., Ames assay, micronucleus assay).

It has been reported that alkylphenol ethoxylates (including octoxynols) may be estrogenic. However, because octoxynol ingredients are used at low concentrations in cosmetics and dermal absorption is expected to be limited, concern for octoxynol-induced estrogenic effects was mitigated.

In addition, the Panel noted the incidence of increased supernumerary ribs observed in fetuses of rats given ≥1600 mg/kg Octoxynol-9 in a developmental and reproductive toxicity assay. This effect was not considered to be of concern as this finding is a common finding in rat teratology assays and is not necessarily a manifestation of a teratogenic effect. In addition, concern for developmental and reproductive toxicity was further mitigated as these effects were observed at doses much higher than what would be used in cosmetics.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients, and the acute/short-term inhalation assays indicating pulmonary edema, pneumonitis, and alveolar/bronchiolar hyperplasia in animals following inhalation exposure to Octoxynol-9 (MMAD = 1.5 or 1.8 μm). The Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concern, aside from the potential for sensory irritation, based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following octoxynols are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating:

Octoxynol-1	Octoxynol-12	Octoxynol-9 Carboxylic Acid*
Octoxynol-3	Octoxynol-13*	Octoxynol-20 Carboxylic Acid*
Octoxynol-5	Octoxynol-16*	Potassium Octoxynol-12 Phosphate*
Octoxynol-6*	Octoxynol-20*	Sodium Octoxynol-2 Ethane Sulfonate
Octoxynol-7*	Octoxynol-25*	Sodium Octoxynol-2 Sulfate*
Octoxynol-8*	Octoxynol-30	Sodium Octoxynol-6 Sulfate*
Octoxynol-9	Octoxynol-33*	Sodium Octoxynol-9 Sulfate*
Octoxynol-10	Octoxynol-40	
Octoxynol-11	Octoxynol-70	

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, idealized structures, and reported functions[1, CIR Staff]

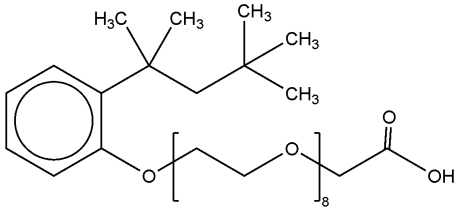
Ingredient/CAS No.	Definition	Function(s)
Octoxynol-1 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 2315-67-5	Octoxynol-1 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 1.	Surfactants – emulsifying agents
Octoxynol-3 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 27176-94-9 2315-62-0	Octoxynol-3 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in Figure 1, where n has an average value of 3.	Surfactants – emulsifying agents
Octoxynol-5 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 2315-64-2 27176-99-4	Octoxynol-5 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in Figure 1, where n has an average value of 5.	Surfactants – emulsifying agents
Octoxynol-6 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-6 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 6.	Surfactants- emulsifying agents
Octoxynol-7 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 27177-02-2	Octoxynol-7 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 7.	Surfactants – emulsifying agents
Octoxynol-8 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 3520-90-9 2638-43-9	Octoxynol-8 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 8.	Surfactants – emulsifying agents
Octoxynol-9 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 42173-90-0	Octoxynol-9 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 9.	Surfactants – emulsifying agents
Octoxynol-9 Carboxylic Acid 25338-58-3	Octoxynol-9 Carboxylic Acid is the organic acid that conforms generally to the following structure, where n has an average value of 8. 	Surfactants – emulsifying agents
Octoxynol-10 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 2315-66-4 27177-07-7	Octoxynol-10 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in Figure 1 where n has an average value of 10.	Surfactants – emulsifying agents
Octoxynol-11 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic) 108437-62-3	Octoxynol-11 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in Figure 1, where n has an average value of 11.	Surfactants – emulsifying agents
Octoxynol-12 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-12 is the ethoxylated alkyl phenol that conforms generally to chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 12.	Surfactants – emulsifying agents

Table 1. Definitions, idealized structures, and reported functions[1, CIR Staff]

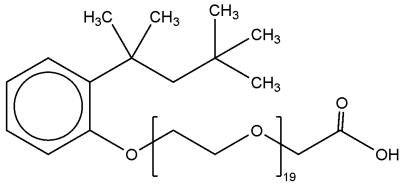
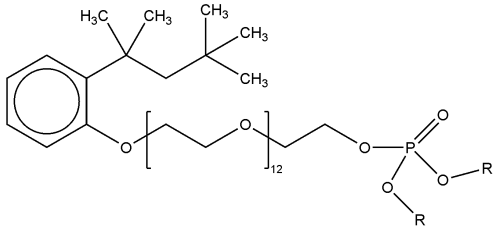
Ingredient/CAS No.	Definition	Function(s)
Octoxynol-13 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-13 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 13.	Surfactants – emulsifying agents
Octoxynol-16 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-16 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 16.	Surfactants – cleansing agents; Surfactants – emulsifying agents
Octoxynol-20 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-20 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 20.	Surfactants – emulsifying agents Surfactants – solubilizing agents
Octoxynol-20 Carboxylic Acid	Octoxynol-20 Carboxylic Acid is the organic acid that conforms generally to the following structure, where n has an average value of 19: 	Surfactants – cleansing agents
Octoxynol-25 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-25 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 25.	Surfactants – cleansing agents; Surfactants – solubilizing agents
Octoxynol-30 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-30 is the ethoxylated alky phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 30.	Surfactants – cleansing agents; Surfactants – solubilizing agents
Octoxynol-33 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-33 is the ethoxylated alky phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 33.	Surfactants – cleansing agents; Surfactants – solubilizing agents
Octoxynol-40 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-40 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 40.	Surfactants – cleansing agents; Surfactants – solubilizing agents
Octoxynol-70 9002-93-1 (generic) 9036-19-5 (generic) 9004-87-9 (generic)	Octoxynol-70 is the ethoxylated alkyl phenol that conforms generally to the chemical structure depicted in **Error! Reference source not found.**, where n has an average value of 70.	Surfactants – cleansing agents
Potassium Octoxynol-12 Phosphate	Potassium Octoxynol-12 Phosphate is the potassium salt of a complex mixture of esters of phosphoric acid and Octoxynol-12. This ingredient conforms to the following structure wherein R, in case, is hydrogen or potassium: 	Surfactants – cleansing agents; Surfactants – emulsifying agents; Surfactants – hydrotropes

Table 1. Definitions, idealized structures, and reported functions[1, CIR Staff]

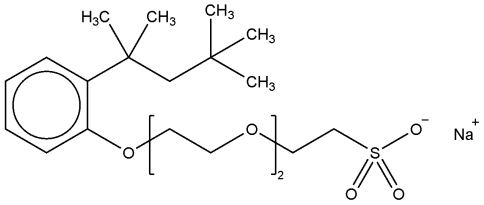
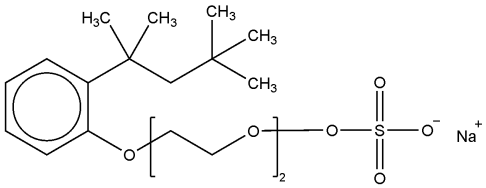
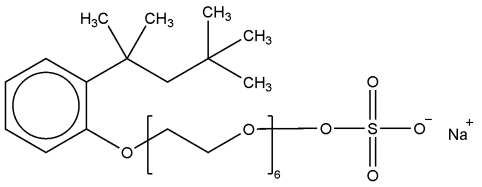
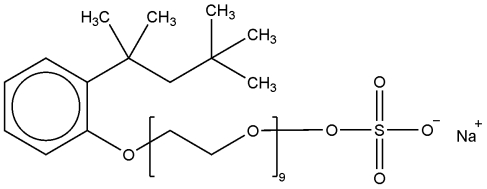
Ingredient/CAS No.	Definition	Function(s)
Sodium Octoxynol-2 Ethane Sulfonate 2917-94-4 55837-16-6 67923-87-9	Sodium Octoxynol-2 Ethane Sulfonate is the organic compound that conforms generally to the following structure: 	Surfactants – cleansing agents
Sodium Octoxynol-2 Sulfate	Sodium Octoxynol-2 Sulfate is the sodium salt of the sulfuric acid ester of Octoxynol-2 that conforms generally to the following structure, where n has an average value of 2: 	Surfactants – cleansing agents
Sodium Octoxynol-6 Sulfate	Sodium Octoxynol-6 Sulfate is the sodium salt of the sulfuric acid ester of Octoxynol-6 that conforms generally to the following structure, where n has an average value of 6: 	Surfactants – cleansing agents
Sodium Octoxynol-9 Sulfate	Sodium Octoxynol-9 Sulfate is the sodium salt of the sulfuric acid ester of Octoxynol-9 that conforms generally to the following structure, where n has an average value 9: 	Surfactants – cleansing agents

Table 2. Chemical properties

Property	Value	Reference
	Octoxynol-1	
Physical Form	slightly hazy, viscous liquid	2
Color	light amber	2
Molecular Weight (g/mol)	250.38	61
Specific Gravity (@ 25ºC)	0.980 – 0.990	2
Viscosity (CPS @ 25ºC)	740 – 840	2
Solubility	Soluble in organic solvents; insoluble in water	2
log P (@ 25 ºC)	4.73 (estimated)	11
	Octoxynol-3	
Molecular Weight (g/mol)	338.5	62
log K_{ow} (@ 25 ºC)	4.42 (estimated)	11
	Octoxynol-5	
Physical Form	slightly hazy, free-flowing liquid	2
Color	water white to light amber	2
Molecular Weight (g/mol)	426.59	11
Specific Gravity (@ 25ºC)	1.030 – 1.040	2
Solubility	Soluble in organic solvents; insoluble in water	2

Table 2. Chemical properties

Property	Value	Reference
log P (@ 25 ºC)	4.25 (estimated)	[11]
Octoxynol-6		
Molecular Weight (g/mol)	470.65	[11]
log P (@ 25 ºC)	3.95 (estimated)	[11]
Octoxynol-7		
Molecular Weight (g/mol)	514.70	[11]
log P (@ 25 ºC)	3.95 (estimated)	[11]
Octoxynol-8		
Molecular Weight (g/mol)	558.75	[11]
Specific Gravity (@ 25ºC)	1.054	[2]
Viscosity (CPS @ 25ºC)	260	[2]
log P (@ 25 ºC)	3.64 (estimated)	[11]
Octoxynol-9		
Physical Form	free-flowing liquid	[2]
Color	water white to light amber	[2]
Average Molecular Weight (Da)	647	[2]
Molecular Weight (g/mol)	602.81	[11]
Specific Gravity (@ 25ºC; water = 1)	1.057 – 1.069	[2]
Vapor pressure (mmHg @ 20ºC)	< 1	[2]
Vapor Density (air = 1)	> 1	[2]
Melting Point (ºC)	6	[2]
Boiling Point (ºC)	> 200	[2]
Solubility (mg/l at 20° C)	4.55	[8]
log P (@ 25 ºC)	3.70 (estimated)	[63]
Octoxynol-9 Carboxylic Acid		
Molecular Weight (g/mol)	616.79	[11]
log P (@ 25 ºC)	3.34 (estimated)	[11]
Octoxynol-10		
Molecular Weight (g/mol)	646.86	[11]
log P (@ 25 ºC)	3.53 (estimated)	[11]
Octoxynol-11		
Physical Form	viscous liquid	[2]
Color	Gardner scale < 3	[2]
Odor	Faint	[2]
Molecular Weight (g/mol)	690.91	[64]
Specific Gravity (@ 25ºC)	1.05 – 1.07	[2]
Solubility	Soluble in ethanol (96 °C, water, and vegetable oils); insoluble in water	[2]
log P (@ 25 ºC)	3.35 (estimated)	[63]
Octoxynol-12		
Molecular Weight (g/mol)	734.96	[11]
log P (@ 25 ºC)	3.18 (estimated)	[11]
Octoxynol-13		
Physical Form	free-flowing, viscous liquid	[2]
Odor	Aromatic	[2]
Molecular Weight (g/mol)	779.02	[63]
Specific Gravity (@ 25ºC; water =1)	1.06 -1.07	[2]
Vapor pressure	not volatile	[2]
Vapor Density	not volatile	[2]
Boiling Point (ºC)	200	[2]
Solubility	Soluble in water	[2]
log P (@ 25 ºC)	3.00 (estimated)	[63]
Octoxynol-16		
Molecular Weight (g/mol)	911.18	[65]
Specific Gravity (@ 25ºC)	1.080	[2]
Viscosity (CPS @ 25ºC)	540	[2]
log P (@ 25 ºC)	2.48 (estimated)	[63]
Octoxynol-20		
Molecular Weight (g/mol)	1086.89	[63]
Specific Gravity (@ 25 ºC)	1.088	[2]
Viscosity (kg/(CPS @ 25ºC)	420	[2]
log P (@ 25 ºC)	1.77 (estimated)	[63]

Table 2. Chemical properties

Property	Value	Reference
Octoxynol-20 Carboxylic Acid		
Molecular Weight (g/mol)	1101.37	[11]
log P (@ 25 ºC)	3.26 (estimated)	[11]
Octoxynol-25		
Molecular Weight (g/mol)	1307.65	[11]
log P (@ 25 ºC)	0.90 (estimated)	[11]
Octoxynol-30		
Molecular Weight (g/mol)	1527.92	[66]
Specific Gravity (@ 25ºC)	1.095	[2]
Viscosity (CPS @ 25ºC)	470	[2]
log P (@ 25 ºC)	0.02 (estimated)	[63]
Octoxynol-33		
Molecular Weight (g/mol)	1660.08	[67]
log P (@ 25 ºC)	-0.51 (estimated)	[63]
Octoxynol-40		
Molecular Weight (g/mol)	1968.45	[11]
log P (@ 25 ºC)	-1.74 (estimated)	[11]
Octoxynol-70		
Molecular Weight (g/mol)	3290.04	[63]
Potassium Octoxynol-12 Phosphate		
Formula Weight (g/mol)	859.00 – 935.18	[63]
Sodium Octoxynol-2 Ethane Sulfonate		
Formula Weight (g/mol)	424.5	[68]
Sodium Octoxynol-2 Sulfate		
Formula Weight (g/mol)	440.5	[69]
Sodium Octoxynol-6 Sulfate		
Formula Weight (g/mol)	572.7	[70]
Sodium Octoxynol-9 Sulfate		
Formula Weight (g/mol)	704.8	[71]

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Octoxynol-1					**Octoxynol-3**				
Totals*	**1**	**1**	**57**	**NR**	**0.06 - 5**	**1**	**NR**	**1**	**NR**	**NR**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*1*	*NR*	*NR*	*NR*	***	NR	1	NR	NR
Rinse-Off	***	*NR*	*57*	*NR*	*0.06 - 5*	***	NR	NR	NR	NR
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	NR	NR	NR	NR
Exposure Type										
Eye Area	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	NR	NR	NR	***	NR	1[a]	NR	NR
Incidental Inhalation-Powder	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Dermal Contact	***	1	1	NR	NR	***	NR	1	NR	NR
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	3	NR	1	***	NR	NR	NR	NR
Hair-Coloring	***	NR	53	NR	0.06 - 5	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products										
Bath Preparations										
Bath Oils, Tablets, and Salts										
Bubble Baths										
Eye Makeup Preparations (not children's)										
Eyebrow Pencil										
Eyeliner										
Eye Shadow										
Eye Lotion										
Eye Makeup Remover										
Mascara										
Other Eye Makeup Preparations										
Fragrance Preparations										
Cologne and Toilet Water										
Perfumes										
Other Fragrance Preparation										
Hair Preparations (non-coloring)						*1*				
Hair Conditioners	NR	NR	2	NR	1					
Hair Sprays (aerosol fixatives)										
Hair Straighteners										
Permanent Waves	NR	NR	1	NR	NR					
Rinses (non-coloring)										
Shampoos (non-coloring)						1	NR	NR	NR	NR
Tonics, Dressings, and Other Hair Grooming Aids										
Wave Sets										
Other Hair Preparations										

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Hair Coloring Preparations	***1***									
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	NR	53	NR	NR					
Hair Tints	1	NR	NR	NR	NR					
Hair Shampoos (coloring)										
Hair Lighteners with Color	NR	NR	NR	NR	5					
Hair Bleaches										
Other Hair Coloring Preparation	NR	NR	NR	NR	0.06 – 0.2					
Makeup Preparations (not eye; not children's)										
Blushers and Rouges (all types)										
Foundations										
Lipstick and Lip Glosses										
Makeup Bases										
Other Makeup Preparations										
Manicuring Preparations										
Other Manicuring Preparations										
Personal Cleanliness										
Bath Soaps and Body Washes										
Douches										
Disposable Wipes		NA	NA		NA		NA	NA		NA
Other Personal Cleanliness Products										
Shaving Preparations										
Aftershave Lotions										
Pre-shave Lotions (all types)										
Shaving Creams (aerosol, brushless, lather)										
Skin Care Preparations										
Cleansing	NR	NR	1	NR	NR					
Face and Neck (excluding shaving preparations)										
Body and Hand (excluding shaving preparations)										
Foot Powders and Sprays										
Moisturizing						NR	NR	1	NR	NR
Night										
Paste Masks (mud packs)										
Skin Fresheners										
Other Skin Care Preparations	NR	1	NR	NR	NR					
Suntan Preparations										
Suntan Gels, Creams, and Liquids										
Indoor Tanning Preparations										
Other Preparations (i.e., those preparations that do not fit another category)		NA	NA		NA		NA	NA		NA

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Octoxynol-5					**Octoxynol-6**				
Totals*	**2**	**NR**	**1**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Rinse-Off	***	*NR*	*1*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*1*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Powder	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Dermal Contact	***	NR	NR	NR	NR	***	NR	NR	NR	1
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair-Coloring	***	NR	1	NR	NR	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products										
Bath Preparations (diluted for use)										
Bath Oils, Tablets, and Salts										
Bubble Baths										
Eye Makeup Preparations										
Eyebrow Pencil										
Eyeliner										
Eye Shadow										
Eye Lotion										
Eye Makeup Remover										
Mascara										
Other Eye Makeup Preparations										
Fragrance Preparations										
Cologne and Toilet Water										
Perfumes										
Other Fragrance Preparation										
Hair Preparations (non-coloring)										
Hair Conditioners										
Hair Sprays (aerosol fixatives)										
Hair Straighteners										
Permanent Waves										
Rinses (non-coloring)										
Shampoos (non-coloring)										
Tonics, Dressings, and Other Hair Grooming Aids										
Wave Sets										
Other Hair Preparations										

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Hair Coloring Preparations	***2***									
Hair Dyes and Colors (all types requiring caution statements and patch tests)	2	NR	NR	NR	NR					
Hair Tints										
Hair Shampoos (coloring)										
Hair Lighteners with Color										
Hair Bleaches	NR	NR	1	NR	NR					
Other Hair Coloring Preparation										
Makeup Preparations (not eye; not children's)										
Blushers and Rouges (all types)										
Foundations										
Lipstick and Lip Glosses										
Makeup Bases										
Other Makeup Preparations										
Manicuring Preparations (Nail)										
Other Manicuring Preparations										
Personal Cleanliness Products										
Bath Soaps and Body Washes										
Douches										
Disposable Wipes		NA	NA		NA		NA	NA		NA
Other Personal Cleanliness Products										
Shaving Preparations										
Aftershave Lotions										
Pre-shave Lotions (all types)										
Shaving Creams (aerosol, brushless, lather)										
Skin Care Preparations										
Cleansing										
Face and Neck (excluding shaving preparations)										
Body and Hand (excluding shaving preparations)										
Foot Powders and Sprays										
Moisturizing										
Night										
Paste Masks (mud packs)						NR	NR	NR	NR	1
Skin Fresheners										
Other Skin Care Preparations										
Suntan Preparations										
Suntan Gels, Creams, and Liquids										
Indoor Tanning Preparations										
Other Tattoo Preparations		NA	NA		NA		NA	NA		NA
Other Preparations (i.e., those preparations that do not fit another category)		NA	NA		NA		NA	NA		NA

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Octoxynol-9					**Octoxynol-10**				
Totals*	**38**	**5**	**131**	**0.1 – 2**	**0.08 - 5**	**5**	**1**	**NR**	**NR**	**25**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*5*	*30*	*0.36*	*0.08 - 5*	***	*1*	*NR*	*NR*	*NR*
Rinse-Off	***	*NR*	*101*	*2*	*0.4 - 1*	***	*NR*	*NR*	*NR*	*25*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	1	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	1[a]	4; 11[a]; 2[b]	NR	0.1 – 5; 0.08 – 1[a]; 3b	***	NR	NR	NR	NR
Incidental Inhalation-Powder	***	NR	2[b]; 1[c]	NR	1; 3b	***	NR	NR	NR	NR
Dermal Contact	***	5	21	0.1 – 2	0.5 - 5	***	1	NR	NR	NR
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	48	NR	0.08 - 1	***	NR	NR	NR	NR
Hair-Coloring	***	NR	61	NR	0.4	***	NR	NR	NR	25
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	5	0.36	0.5 – 0.9	***	NR	NR	NR	NR
Baby Products	***	NR	1	0.1	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products	NR	NR	NR	0.1	NR					
Bath Preparations (diluted for use)										
Bath Oils, Tablets, and Salts	NR	NR	1	NR	NR					
Bubble Baths										
Eye Makeup Preparations										
Eyebrow Pencil										
Eyeliner	NR	1	NR	NR	NR					
Eye Shadow										
Eye Lotion										
Eye Makeup Remover										
Mascara										
Other Eye Makeup Preparations										
Fragrance Preparations	***1***									
Cologne and Toilet Water	1	NR	2	NR	5					
Perfumes	NR	NR	NR	0.7						
Other Fragrance Preparation	NR	NR	1	NR	NR					
Hair Preparations (non-coloring)	***3***									
Hair Conditioners	NR	NR	8	NR	0.4					
Hair Sprays (aerosol fixatives)	NR	NR	1	NR	0.1					
Hair Straighteners	NR	NR	1	NR	0.9					
Permanent Waves	NR	NR	17	NR	NR					
Rinses (non-coloring)										
Shampoos (non-coloring)	1 (r.o.)	NR	3	NR	0.7					
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	7	NR	0.08 – 1					
Wave Sets										

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Other Hair Preparations	2 (r.o.)	NR	11	NR	NR					
Hair Coloring Preparations	***3***									
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	NR	58	NR	NR					
Hair Tints	1	NR	NR	NR	NR					
Hair Shampoos (coloring)	NR	NR	1	NR	NR					
Hair Lighteners with Color										
Hair Bleaches	NR	NR	1	NR	NR	NR	NR	NR	NR	25
Other Hair Coloring Preparation	2 (l.o.)	NR	1	NR	0.4					
Makeup Preparations (not eye; not children's)	***1***									
Blushers and Rouges (all types)										
Foundations										
Lipstick and Lip Glosses										
Makeup Bases										
Other Makeup Preparations	1 (l.o.)	NR	NR	NR	NR					
Manicuring Preparations (Nail)	***1***									
Other Manicuring Preparations	1	NR	NR	NR	NR					
Personal Cleanliness Products	***4***									
Bath Soaps and Body Washes	3	NR	2	NR	NR					
Douches	NR	NR	1	NR	NR					
Disposable Wipes	1	NA	NA	0.36	NA		NA	NA		NA
Other Personal Cleanliness Products	NR	NR	2	NR	0.5 – 0.9					
Shaving Preparations	***1***									
Aftershave Lotions	NR	NR	1	NR	NR					
Pre-shave Lotions (all types)	1	NR	NR	NR	NR					
Shaving Creams (aerosol, brushless, lather)	NR	NR	NR	NR	1					
Skin Care Preparations	***23***					***5***				
Cleansing	3	NR	3	2	NR	2	NR	NR	NR	NR
Face and Neck (excluding shaving preparations)	18 (l.o.); 1 (r.o.)	NR	NR	0.22 (l.o.; not spray)	NR	1 (l.o.); 1 (r.o.)	NR	NR	NR	NR
Body and Hand (excluding shaving preparations)	NR	NR	2	NR	NR	1 (l.o.)	NR	NR	NR	NR
Foot Powders and Sprays	NR	NR	NR	NR	3					
Moisturizing	NR	1	2	NR	NR					
Night										
Paste Masks (mud packs)	NR	NR	3	NR	NR					
Skin Fresheners	NR	NR	2	NR	NR	1	NR	NR	NR	NR
Other Skin Care Preparations	3 (l.o.)	3	1	NR	NR	1 (l.o.); 1 (r.o.)	1	NR	NR	NR
Suntan Preparations	***3***									
Suntan Gels, Creams, and Liquids										
Indoor Tanning Preparations	3	NR	NR	NR	NR					
Other Preparations (i.e., those preparations that do not fit another category)	***1***	NA	NA	NR	NA		NA	NA		NA

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Octoxynol-11					**Octoxynol-12**				
Totals*	**1**	**8**	**19**	**NR**	**1**	**7**	**4**	**NR**	**1.5**	**NR**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*8*	*14*	*NR*	*1*	***	*3*	*NR*	*1.5*	*NR*
Rinse-Off	***	*NR*	*5*	*NR*	*1*	***	*1*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	2	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	2	NR	NR	NR
Incidental Inhalation-Spray	***	4[a]; 1[b]	1; 7[a]	NR	1a	***	1[b]	NR	NR	NR
Incidental Inhalation-Powder	***	1[b]	NR	NR	NR	***	1[b]	NR	1.5[c]	NR
Dermal Contact	***	8	15	NR	NR	***	2	NR	1.5	NR
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	4	NR	1	***	NR	NR	NR	NR
Hair-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	2	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products										
Bath Preparations (diluted for use)										
Bath Oils, Tablets, and Salts										
Bubble Baths										
Eye Makeup Preparations										
Eyebrow Pencil										
Eyeliner										
Eye Shadow										
Eye Lotion	NR	1	NR	NR	NR					
Eye Makeup Remover										
Mascara										
Other Eye Makeup Preparations	NR	1	NR	NR	NR					
Fragrance Preparations										
Cologne and Toilet Water										
Perfumes										
Other Fragrance Preparation	NR	NR	NR	NR	1					
Hair Preparations (non-coloring)						***3***				
Hair Conditioners										
Hair Sprays (aerosol fixatives)										
Hair Straighteners										
Permanent Waves										
Rinses (non-coloring)										
Shampoos (non-coloring)	NR	NR	NR	3	NR					
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	NR	NR	1					
Wave Sets										
Other Hair Preparations	NR	NR	NR	1	NR	3 (l.o.)	NR	NR	NR	NR

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Hair Coloring Preparations										
Hair Dyes and Colors (all types requiring caution statements and patch tests)										
Hair Tints										
Hair Shampoos (coloring)										
Hair Lighteners with Color										
Hair Bleaches										
Other Hair Coloring Preparation										
Makeup Preparations (not eye; not children's)										
Blushers and Rouges (all types)										
Foundations										
Lipstick and Lip Glosses						NR	2	NR	NR	NR
Makeup Bases	1	NR	NR	NR	NR					
Other Makeup Preparations										
Manicuring Preparations (Nail)										
Other Manicuring Preparations										
Personal Cleanliness Products						***2***				
Bath Soaps and Body Washes						2	NR	NR	NR	NR
Douches										
Disposable Wipes		NA	NA		NA		NA	NA		NA
Other Personal Cleanliness Products										
Shaving Preparations										
Aftershave Lotions										
Pre-shave Lotions (all types)										
Shaving Creams (aerosol, brushless, lather)										
Skin Care Preparations	***1***					***2***				
Cleansing	NR	NR	2	NR	1	NR	1	NR	NR	NR
Face and Neck (excluding shaving preparations)	NR	1	NR	NR	NR	NR	NR	NR	1.5 (not spray)	NR
Body and Hand (excluding shaving preparations)						NR	1	NR	NR	NR
Foot Powders and Sprays										
Moisturizing	NR	3	3	NR	NR	2	NR	NR	NR	NR
Night										
Paste Masks (mud packs)	NR	1	NR	NR	NR					
Skin Fresheners	NR	NR	2	NR	NR					
Other Skin Care Preparations	1 (r.o.)	1	4	NR	1					
Suntan Preparations										
Suntan Gels, Creams, and Liquids	NR	NR	2	NR	NR					
Indoor Tanning Preparations										
Other Preparations (i.e., those preparations that do not fit another category)		NA	NA		NA		NA	NA		NA

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Octoxynol-13					**Octoxynol-30**				
Totals*	**NR**	**NR**	**46**	**NR**	**0.1 - 2**	**NR**	**NR**	**NR**	**NR**	**1 - 2**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*NR*	*30*	*NR*	*0.1*	***	NR	NR	NR	1 - 2
Rinse-Off	***	*NR*	*14*	*NR*	*2*	***	NR	NR	NR	NR
Diluted for (Bath) Use	***	*NR*	*2*	*NR*	*0.8*	***	NR	NR	NR	NR
Exposure Type										
Eye Area	***	NR	5	NR	2	***	NR	NR	NR	1 - 2
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	14[a]; 3b	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Powder	***	NR	3b	NR	NR	***	NR	NR	NR	NR
Dermal Contact	***	NR	19	NR	0.8 - 2	***	NR	NR	NR	1
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	24	NR	0.1	***	NR	NR	NR	NR
Hair-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	2	NR	0.8	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products										
Bath Preparations (diluted for use)										
Bath Oils, Tablets, and Salts										
Bubble Baths	NR	NR	2	NR	0.8					
Eye Makeup Preparations										
Eyebrow Pencil										
Eyeliner						NR	NR	NR	NR	1
Eye Shadow										
Eye Lotion										
Eye Makeup Remover	NR	NR	2	NR	2					
Mascara	NR	NR	3	NR	NR	NR	NR	NR	NR	2
Other Eye Makeup Preparations										
Fragrance Preparations										
Cologne and Toilet Water										
Perfumes										
Other Fragrance Preparation										
Hair Preparations (non-coloring)										
Hair Conditioners	NR	NR	4	NR	NR					
Hair Sprays (aerosol fixatives)										
Hair Straighteners										
Permanent Waves										
Rinses (non-coloring)	NR	NR	4	NR	NR					
Shampoos (non-coloring)	NR	NR	2	NR	NR					
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	10	NR	NR					
Wave Sets	NR	NR	2	NR	NR					
Other Hair Preparations	NR	NR	2	NR	0.1					

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Hair Coloring Preparations										
Hair Dyes and Colors (all types requiring caution statements and patch tests)										
Hair Tints										
Hair Shampoos (coloring)										
Hair Lighteners with Color										
Hair Bleaches										
Other Hair Coloring Preparation										
Makeup Preparations (not eye; not children's)										
Blushers and Rouges (all types)	NR	NR	1	NR	NR					
Foundations	NR	NR	1	NR	NR					
Lipstick and Lip Glosses										
Makeup Bases										
Other Makeup Preparations										
Manicuring Preparations (Nail)										
Other Manicuring Preparations										
Personal Cleanliness Products										
Bath Soaps and Body Washes										
Douches										
Disposable Wipes		NA	NA		NA		NA	NA		NA
Other Personal Cleanliness Products										
Shaving Preparations										
Aftershave Lotions	NR	NR	1	NR	NR					
Beard Softeners										
Pre-shave Lotions (all types)										
Shaving Creams (aerosol, brushless, lather)										
Skin Care Preparations										
Cleansing										
Face and Neck (excluding shaving preparations)										
Body and Hand (excluding shaving preparations)	NR	NR	3	NR	NR					
Foot Powders and Sprays	NR	NR	3	NR	NR					
Moisturizing										
Night										
Paste Masks (mud packs)										
Skin Fresheners	NR	NR	1	NR	NR					
Other Skin Care Preparations	NR	NR	5	NR	NR					
Suntan Preparations										
Other Suntan Preparations										
Other Preparations (i.e., those preparations that do not fit another category)		NA	NA		NA		NA	NA		NA

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Octoxynol-40					**Octoxynol-70**				
Totals*	**2**	**2**	**18**	**NR**	**0.007 – 0.02**	1	NR	NR	NR	NR
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*NR*	*2*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Rinse-Off	***	*2*	*16*	*NR*	*0.007 – 0.02*	***	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Powder	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Dermal Contact	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	2	10	NR	0.007 – 0.01	***	NR	NR	NR	NR
Hair-Coloring	***	NR	8	NR	0.02	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products										
Bath Preparations (diluted for use)	*1*									
Bath Oils, Tablets, and Salts	1	NR	NR	NR	NR					
Bubble Baths										
Eye Makeup Preparations										
Eyebrow Pencil										
Eyeliner										
Eye Shadow										
Eye Lotion										
Eye Makeup Remover										
Mascara										
Other Eye Makeup Preparations										
Fragrance Preparations										
Cologne and Toilet Water										
Perfumes										
Other Fragrance Preparation										
Hair Preparations (non-coloring)	*1*					*1*				
Hair Conditioners	NR	NR	5	NR	0.01					
Hair Sprays (aerosol fixatives)										
Hair Straighteners	NR	2	NR	NR	NR					
Permanent Waves	NR	NR	1	NR	NR					
Rinses (non-coloring)										
Shampoos (non-coloring)	NR	NR	1	NR	0.007					
Tonics, Dressings, and Other Hair Grooming Aids										
Wave Sets	NR	NR	1	NR	NR					
Other Hair Preparations	1 (l.o.)	NR	2	NR	NR	1 (l.o.)	NR	NR	NR	NR

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Hair Coloring Preparations										
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	NR	1	NR	0.02					
Hair Tints										
Hair Shampoos (coloring)										
Hair Lighteners with Color										
Hair Bleaches	NR	NR	6	NR	NR					
Other Hair Coloring Preparation	NR	NR	1	NR	NR					
Makeup Preparations (not eye; not children's)										
Blushers and Rouges (all types)										
Foundations										
Lipstick and Lip Glosses										
Makeup Bases										
Other Makeup Preparations										
Manicuring Preparations (Nail)										
Other Manicuring Preparations										
Personal Cleanliness Products										
Bath Soaps and Body Washes										
Douches										
Disposable Wipes		NA	NA		NA		NA	NA		NA
Other Personal Cleanliness Products										
Shaving Preparations										
Aftershave Lotions										
Pre-shave Lotions (all types)										
Shaving Creams (aerosol, brushless, lather)										
Skin Care Preparations										
Cleansing										
Face and Neck (excluding shaving preparations)										
Body and Hand (excluding shaving preparations)										
Foot Powders and Sprays										
Moisturizing										
Night										
Paste Masks (mud packs)										
Skin Fresheners										
Other Skin Care Preparations										
Suntan Preparations										
Suntan Gels, Creams, and Liquids										
Indoor Tanning Preparations										
Other Preparations (i.e., those preparations that do not fit another category)		NA	NA		NA		NA	NA		NA

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
	Potassium Octoxynol-12 Phosphate					**Sodium Octoxynol-2 Ethane Sulfonate**				
Totals*	**NR**	**NR**	**18**	**NR**	**0.0008 – 0.5**	**NR**	**NR**	**NR**	**NR**	**1**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*NR*	*18*	*NR*	*0.0008 - 5*	***	*NR*	*NR*	*NR*	*NR*
Rinse-Off	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*1*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	NR	18	NR	0.002 – 0.5	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Powder	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Dermal Contact	***	NR	6	NR	NR	***	NR	NR	NR	1
Deodorant (underarm)	***	NR	NR	NR	0.0008 - 0.5	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Baby Products										
Other Baby Products										
Bath Preparations (diluted for use)										
Bath Oils, Tablets, and Salts										
Bubble Baths										
Eye Makeup Preparations										
Eyebrow Pencil	NR	NR	NR	NR	0.05					
Eyeliner	NR	NR	6	NR	0.02 – 0.05					
Eye Shadow	NR	NR	NR	NR	0.002					
Eye Lotion										
Eye Makeup Remover										
Mascara	NR	NR	12	NR	0.01 – 0.05					
Other Eye Makeup Preparations										
Fragrance Preparations										
Cologne and Toilet Water										
Perfumes										
Other Fragrance Preparation										
Hair Preparations (non-coloring)										
Hair Conditioners										
Hair Sprays (aerosol fixatives)										
Hair Straighteners										
Permanent Waves										
Rinses (non-coloring)										
Shampoos (non-coloring)										
Tonics, Dressings, and Other Hair Grooming Aids										
Wave Sets										
Other Hair Preparations										

Table 3. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[22]	**VCRP (2023)[23]**	**VCRP (2001)[2]**	**% (2022/ 2025)[3,24]**	**% (1999, 2001)[2]**	**RLD (2024)[22]**	**VCRP (2023)[23]**	**VCRP (1999, 2001)[2]**	**% (2022)[3]**	**% (1999, 2001)[2]**
Hair Coloring Preparations										
Hair Dyes and Colors (all types requiring caution statements and patch tests)										
Hair Tints										
Hair Shampoos (coloring)										
Hair Lighteners with Color										
Hair Bleaches										
Other Hair Coloring Preparation										
Makeup Preparations (not eye; not children's)										
Blushers and Rouges (all types)										
Foundations										
Lipstick and Lip Glosses										
Makeup Bases										
Other Makeup Preparations										
Manicuring Preparations (Nail)										
Other Manicuring Preparations										
Personal Cleanliness Products										
Bath Soaps and Body Washes										
Douches										
Disposable Wipes		NA	NA		NA		NA	NA		NA
Other Personal Cleanliness Products										
Shaving Preparations										
Aftershave Lotions										
Pre-shave Lotions (all types)										
Shaving Creams (aerosol, brushless, lather)										
Skin Care Preparations										
Cleansing										
Face and Neck (excluding shaving preparations)										
Body and Hand (excluding shaving preparations)										
Foot Powders and Sprays										
Moisturizing										
Night						NR	NR	NR	NR	1
Paste Masks (mud packs)										
Skin Fresheners										
Other Skin Care Preparations										
Suntan Preparations										
Suntan Gels, Creams, and Liquids	NR	NR	NR	NR	0.0008					
Indoor Tanning Preparations										
Other Preparations (i.e., those preparations that do not fit another category)		NA	NA		NA		NA	NA		NA

NR – not reported; NA – not applicable (this category was not part of the VCRP)
l.o. – leave-on; r.o. – rinse-off
*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.
**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
***In the RLD, each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 4. Octoxynol ingredients not reported to be in use [3,23]

Octoxnyol-6
Octoxynol-7
Octoxynol-8
Octoxynol-13
Octoxynol-16
Octoxynol-20
Octoxynol-25
Octoxynol-33
Octoxynol-9 Carboxylic Acid
Octoxynol-20 Carboxylic Acid
Potassium Octoxynol-12 Phosphate
Sodium Octoxynol-2 Sulfate
Sodium Octoxynol-6 Sulfate
Sodium Octoxynol-9 Sulfate

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