TO: Regulatory/Product Liability Team

FROM: T. G. Grumbles
DATE: January 14, 1988

Interoffice Communication

SUBJ: PROPOSED MEETING DATE/PROGRESS REPORT

VISTA

We are proposing to have our next meeting in Houston on one of the following dates:

Wednesday, February 17
Thursday, February 18
Tuesday, February 23

Please call me or Bill as soon as you get this memo to tell us which dates are acceptable.

Since our last meeting, we had an awareness training session in Ponca City for all R&D personnel. Training sessions are currently being planned for S&T management in late January, and other S&T personnel in mid-February. A session is scheduled for VALAMO on February 9. These training sessions have been a result of direct requests from the affected groups due to recent incidents involving the principles we discuss in the training sessions.

We still need your input on additional groups or persons you feel need the awareness training.

If you have thoughts on "points of control" for the system to be developed, and additional parts of the system that exist now, please feel free to call us before the meeting.

T. G. Grumbles

W. L. McClain

ajo

~~RE: ORG: RF~~
RE: VTAC

TO: Distribution

FROM: T. G. Grumbles
DATE: January 14, 1988

Interoffice Communication

SUBJ: FOLLOW-UP TO CARBIDE ALCOHOL ETHOXYLATE TESTING

VISTA

Enclosed are three items relating to the Union Carbide 8(e) filing regarding AE toxicity testing.

The first is EPA's response to the notice. This response is the typical EPA response to 8(e) filings and shows no particular interest at the agency regarding the filing.

The second attachment is a letter sent to the agency by Procter and Gamble. This is an "FYI" submittal in which P&G expresses their opinion on the relevance of the data. This is a good technical document that supports the general conclusion that the carbide data has little relevance to human safety.

The third attachment is a letter from Shell to SDA. The Shell letter supports our general situation in terms of testing protocol and retrospective data review. I've had further conversations with Shell regarding their testing protocol and they feel that the "limiting dose" is appropriate for evaluation of these materials. This is different from Carbide's approach of forcing the evaluation to an LD50 conclusion, which results in massive doses in the 4-8 g/kg range.

At this time SDA is considering formally surveying producers and users of AE's to gain more data or qualitative information supporting the safe use of AE's in consumer products, and the production industry populations. If the results are meaningful another "FYI" submittal would be sent to the agency by SDA

Tom

T. G. Grumbles

ajo
.302

Attachments

DISTRIBUTION: O. C. Kerfoot / A. M. Nielsen / C. M. Starks
T. P. Matson / W. H. Hilgers / W. L. McClain
C. J. Matson

VVV 000010065

Public File Copy

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV - 4 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

CERTIFIED MAIL

Dr. R. E. Bollinger
Director of Occupational Health
and Product Safety/Liability
Union Carbide Corporation
39 Old Ridgebury Road
Danbury, CT 06817-0001

Dear Sir:

With regard to:

TSCA Section 8(e) submission on: Alkoxylate Nonionic Surfactants

Submitted by: Union Carbide Corporation

Date submitted: October 13, 1987

EPA Document Control Number: 8EHQ-1087-0696

The Office of Toxic Substances (OTS) has completed a preliminary evaluation of the above referenced submission under Section 8(e), the "substantial risk" information reporting provision of the Toxic Substances Control Act (TSCA). The enclosed status report is the result of that preliminary OTS evaluation but does not necessarily represent EPA's conclusion concerning the reported findings.

With regard to the above referenced TSCA Section 8(e) submission, please ensure that EPA receives full copies of the final reports (including the actual experimental protocols, the exact identity, including the CAS Registry Number, if known, of each of the test materials, etc.) from the series of acute toxicity studies cited in the submission.

In view of EPA's general interest in corporate actions that are taken on a voluntary basis in response to chemical toxicity or exposure information, please describe the nature and results, if available, of Union Carbide's ongoing studies designed to clarify the reported toxicologic findings.

VVV 000010066

In responding to this request for information, or in otherwise communicating with EPA regarding this submission under Section 8(e), please refer to the EPA Document Control Number that has been assigned to the submission. As in the case of initial 8(e) submissions, all responses/correspondence will be placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA Section 8(e) policy statement ("Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk" 43 FR 11110; March 16, 1978). Any confidentiality claims should be supported by submission of information as described in the enclosed item entitled "Support Information for Confidentiality Claims."

All available information requested by this letter should be transmitted to the EPA Document Processing Center at the address provided below within 20 working days of your receipt of this letter; any requested information or supplemental information that becomes available following your response to this EPA letter should be sent to EPA immediately upon your company's receipt of such information.

Document Processing Center (TS-790)
(Attn: Section 8(e) Coordinator)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

Should you have any questions or comments prior to responding to the Agency's request for additional information, please contact Mr. David R. Williams of the Chemical Screening Branch/ECAD at (202)-382-3468.

The Environmental Protection Agency looks forward to continued cooperation with Union Carbide in its ongoing efforts to evaluate and minimize the potential risks posed by chemical substances to health or the environment.

Sincerely,

Frank D. Kover, Chief
Chemical Screening Branch
CSB/ECAD/OTS/OPTS (TS-778)

Enclosures

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

PUBLIC FILE COPY

DATE: OCT 30 1987

SUBJECT: Status Report* 8EHQ-1087-0696

Approved: 11/02/87

FROM: James F. Darr, Section Head
Chemical Risk Identification Section/CSB

TO: Frank D. Kover, Branch Chief
Chemical Screening Branch/ECAD/OTS/OPTS

Submission Description

The Union Carbide Corporation provided the following information with regard to the preliminary results of acute toxicity studies conducted by Union Carbide over the last year-and-a-half on a series of 18 different alkoxylate nonionic surfactants:

> "The acute lethal toxicity of these materials, as expressed by peroral or 24-hour percutaneous LD50, varied between moderate to very low (i.e., LD50 values ranged between 0.4 to >16 ml/kg by peroral administration and between 0.8 to >16 ml/kg by percutaneous application). An unusual pattern of toxicity, however, was observed in the 24-hour occluded cutaneous application in the rabbit portion of these studies. The pattern was characterized by delayed deaths and macroscopic evidence of lung injury. Microscopic examination of lung tissue was recently conducted on animals treated with the last 7 of the 18 of these materials, these tissues being saved only after recognizing that this pattern of toxicity had emerged. Microscopic findings included bronchopneumonia, pneumonitis, alveolar histiocytosis, edema, congestion and necrosis. In almost all cases, the injury was associated with the presence of foreign vegetable matter in the lower respiratory tract and lung. The foreign vegetable matter was presumably feed particles which had been aspirated.

==========

* NOTE: This status report is the result of a preliminary evaluation of information submitted to EPA pursuant to Section 8(e), the substantial risk information reporting provision of the Toxic Substances Control Act (TSCA). The statements made in this report should not be regarded as expressing final EPA policy or intent with respect to the subject chemical(s). Any review of this status report should take into account the fact that the report may be based on incomplete information.

VVV 000010068

> "No one of these studies by itself would trigger a concern regarding substantial risk of adverse health effects. However, when these results are considered together, and taken across the entire family of these surfactants, there appears to be a consistent pattern of toxicity. A review of acute toxicity studies conducted over the past 40 years on various alkoxylated nonionic surfactants further substantiates a pattern of delayed deaths and visual evidence of lung injury. Based upon this review and the recent studies, . . . [Union Carbide believes] that not only do long chain alcohol ethoxylates and ethoxy/propoxy copolymer surfactants produce this pattern of toxicity, but that nonylphenol ethoxylates may also exhibit a similar pattern of toxicity. However, the relevance of these studies to human health is unknown."

In submitting this information to EPA under Section 8(e) of TSCA, Union Carbide stated that copies of the final reports from the recently conducted studies will be provided to EPA as soon as those reports are issued. According to Union Carbide, these final reports will "describe in detail the toxic response (days to death), macroscopic and microscopic observations on the recent surfactant acute toxicity and primary irritancy studies."

Submission Evaluation

An EPA evaluation of the overall significance of the reported findings should be possible upon the Agency's receipt of complete copies of the final reports of the performed studies.

Comments/Recommendations

In its Section 8(e) notice, Union Carbide stated that the company is "advising employees and customers who handle, use or otherwise may be potentially exposed to these types of surfactants" about the results of these studies and the fact that the study findings had been reported to EPA. In addition, Union Carbide stated that "studies are currently being conducted and further information is being sought to clarify this toxic response and better place it in perspective to potential human health risks."

a) The Chemical Screening Branch will ask Union Carbide to ensure that EPA receives complete copies of the final reports (including the actual experimental protocols, the exact identity, including CAS Registry Number (if known), of each of the test materials, etc.) from the series of acute toxicity studies cited in the company's TSCA Section 8(e) submission.

In view of EPA's general interest in corporate actions taken on a voluntary basis in response to new chemical toxicity or exposure information, Union Carbide will be asked to describe the nature and results, if available, of the company's ongoing studies designed to clarify the reported toxicologic findings.

b) The Chemical Screening Branch will review the reported information in order to determine the need for further OTS assessment.

c) The Chemical Screening Branch will transmit copies of this status report to NIOSH, OSHA, CPSC, FDA, NTP, OSWER/EPA, OW/EPA, OAR/EPA, ORD/EPA and OPP/OPTS/EPA. In addition, copies of this status report will be sent to the TSCA Assistance Office (TAO/OTS/OPTS/EPA) for further distribution.

THE PROCTER & GAMBLE COMPANY
[illegible] CENTER
[illegible] CINCINNATI, OHIO 45217-1087

December 22, 1987

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460

ATTENTION: 8(e) Coordinator

Dear Sir or Madam:

This submission is in response to a recent Notice of Substantial Risk filed by Union Carbide under Section 8(e) of the Toxic Substances Control Act for Alkoxylate Nonionic Surfactants, dated October 13, 1987. These surfactants have been safely used in laundry detergents and other consumer products for approximately 20 years. During this time, Procter & Gamble and others have published results of tests conducted on these surfactants which support the safe manufacture and consumer use of products containing them. This extensive existing data base and long-term history of safe marketing of alkoxylate surfactants leads to the conclusion that use of alkoxylate surfactants in consumer products does not represent a substantial risk to human health.

Information provided here supports the conclusion that the Union Carbide laboratory animal findings are not relevant to human exposures and demonstrates the safety of alkoxylate surfactants for consumers and employees; anticipated consumer exposures are at least 150,000 fold less than the acute rabbit exposure described in the filing. This requests that EPA consider this additional information and perspective when evaluating the Union Carbide findings. Furthermore, please share our document with any other regulatory agency to which the Union Carbide Notice of Substantial Risk is forwarded for review.

The following summarizes published results of safety tests conducted by Procter & Gamble on the alkoxylate nonionic surfactants. Alcohol ethoxylates are the most thoroughly studied of the alkoxylate surfactants and will be referred to as AE. Where possible, we have attempted to draw parallels between this extensive body of information, other pertinent literature, and the observations made by Union Carbide in their recent filing.

Acute Toxicity

Acute toxicity data available for AE in laboratory animals demonstrate that AE are not unusually toxic and are comparable to other commonly used surfactants in this regard. AE can produce irritant and anesthetic effects when large volumes of undilute material are dosed. However, these effects are dose-dependent and do not occur at expected human exposures because of differences in dose, duration of exposure, and pharmacokinetics.

Union Carbide reported that the 18 different alkoxylates had a rat oral LD_{50} between 0.4 to >16 ml/kg and a rabbit percutaneous LD_{50} between 0.8 to >16 ml/kg. This is not unexpected for these or other types of surfactants according to the published literature[1,2,3]. Table I summarizes these data and supports the conclusion that AE surfactants have an acute toxicity which is comparable to other types of common surfactants.

The primary signs of AE acute oral toxicity observed in rats are central nervous system (CNS) depression, loss of righting reflex, diarrhea, piloerection, gastrointestinal irritation, and loss of electrolytes and fluid. Deaths, if they occur, are usually delayed (2-6 days)[2]. Acute dermal AE toxicity in rabbits is associated with hypoactivity, severe skin irritation and sometimes delayed deaths [2]. These findings are consistent with those reported by Union Carbide in the 8(e) submission.

The effects of AE are due to interactions with cell membranes, as predicted by physicochemical properties (surface activity, nonionic and lipophilic character)[4]. The type of effects produced depends on dose, route of administration, and species. Local and general anesthetic effects are likely when the rate and quantity of a membrane-active material systemically absorbed is sufficient to interact with peripheral and/or central neuronal membranes[5]. Anesthetic doses of AE in laboratory animals produce a progressive syndrome of early CNS excitation (ataxia, irregular breathing) followed by CNS depression (loss of righting reflex, slow regular breathing). Deaths occurring within minutes to a few hours are a result of respiratory depression or cardiovascular collapse. Effects are dose-dependent and completely reversible in animals receiving non-lethal doses[6]. Anesthetic effects do not often occur following oral or dermal administration of AE. This is due to slow systemic absorption by these routes, hepatic metabolism (detoxification), and the emetic properties of AE in some species via the oral route[2,7].

As stated, delayed deaths (within days) have been described in laboratory animals[2]. Dose-related membrane effects at the site of administration are the likely cause[8]. Observed effects vary according to route of administration and include severe gastritis (oral), peritonitis (IP), and skin irritation (dermal)[2]. Hemolysis occurs after IV dosing.

Dermal Penetration

As stated above, dermal penetration of AE is not usually sufficient to produce systemic toxicity. Drotman reported that only 1-2% of an AE was absorbed in vivo through human skin after 8 hr non-occluded exposure[7]. Larger amounts of surfactant probably were absorbed across rabbit skin in the Union Carbide studies based on the following:

1) The exposure was of 24 hr duration.
2) The application sites were occluded which generally enhances skin permeability about 10-fold[9]. 1618-65 applicability!
3) Neat surfactant produces severe skin irritation which can further increase skin permeability[10]. ← can carbide confirm?
4) The skin of laboratory animals is generally more permeable than human skin; it increases in the order man<rat<rabbit[11].

Dermal penetration of AE has been studied in experimental animals but not in rabbits under occlusive conditions. Percutaneous absorption generally increases with increasing length of the alcohol chain and decreasing degree of alkoxylation and branching[12,13,14]. When AE were applied to rat skin under anticipated consumer use conditions (<2% solutions, 1-15 min contact followed by rinsing), less than 5% of the applied dose was absorbed through the skin within two days. A maximum permeability constant of 2.13×10^{-4} cm/min was calculated for the alkoxylate surfactants under these conditions (Attachment I). Under more exaggerated conditions (up to 72 hr exposure and/or occlusive application), 25%-50% of applied alkoxylates are absorbed in rats[7,14].

The dermal absorption of AE under exaggerated exposure conditions suggests that systemic AE exposure in the Union Carbide rabbit dermal studies may have been sufficient to produce anesthetic effects. However, dermal AE penetration in humans under anticipated use conditions will result in negligible sytemic exposure.

Subchronic and Chronic Safety Studies

Eleven subchronic percutaneous toxicity studies were conducted with two different AE or formulations containing them[15]. The AE had the general formula:

$H_3C(CH_2)_nO(CH_2CH_2O)_mH$ n=11-14 and m=average of 6 or 7.

Application of 50 mg/kg/day (2.5% aqueous solutions) of the AE to rabbit skin for 4 and 13 weeks (5 days/week) produced no evidence of systemic toxicity. Skin irritation was the only treatment-related effect observed. Occasional deaths were attributed to septicemia and were observed in control animals as well. Similar results were obtained with formulations containing 33% AE and applied at a dose of 60 or 200 mg/kg.

Guinea pigs were immersed in 10% aqueous solutions of AE (n=13-14; m=7) four hours/day for five days. No systemic toxicity was observed. Fissured skin, evidenced by hyperkeratosis, acanthosis, and dermal infiltration, was the only effect observed[15].

A chronic skin painting study has been conducted with an AE. Repeated dermal application of 0, 0.2, 1.0, or 5.0% aqueous AE solutions (n=11-12; m=6.5) to mice three times/week for 18 months produced no treatment-related effects[16]. This study and the other subchronic dermal studies demonstrate that the acute toxic effects observed with large doses of undilute AE does not occur under conditions more comparable to expected human exposures.

Relevance to Worker Exposures

AE are received, stored, and processed into product under closed systems in our manufacturing facilities. Direct skin contact does not occur under normal conditions. In the event of an accidental spill, exposure is self-limiting due to safe handling practices and the inherent irritancy of the neat material. Workers are instructed to wash exposed areas immediately and thoroughly and to use impervious clothing for any subsequent clean-up effort. The neat

surfactants are skin irritants[2] and are not likely to be kept on the skin for prolonged periods of time under occluded conditions. The percutaneous toxicity studies conducted by Union Carbide involved high volume (up to 16 ml/kg) occluded exposures of 24 hr duration. It can be assumed that 10% or greater of the rabbit surface area was exposed in these studies based on the volumes employed, e.g. up to 48 ml/3 kg rabbit. This is in contrast to anticipated worker exposures of short duration (minutes), non-occlusive, and over a smaller percent of total body surface area (less than 5%)[17]. For these reasons we believe that the reported acute rabbit dermal studies are not relevant to worker exposures to AE in our manufacturing facilities.

Relevance to Consumer Exposures

Consumer dermal exposures to AE are expected to occur through non-occluded skin contact with dilute or full strength solutions of product or with fabric containing very low levels of surfactant as a consequence of the laundering process. A comparison of these exposures to the rabbit percutaneous exposures is presented in Attachment II. Anticipated consumer daily exposure is about 150,000 times less than that in the rabbit studies. This number is conservatively estimated and is likely to be several orders of magnitude greater since the permeability constant was calculated from in vivo rat studies. It has been found for a wide variety of materials that skin permeability increases in the following direction: man<rat<rabbit[11]. Therefore, the human systemic exposures are likely overestimated and the rabbit systemic exposures underestimated. Furthermore, the rabbit surface area exposed to neat AE was assumed to be 10% of the total surface area. The actual area exposed was probably larger in the Union Carbide rabbit studies which applied up to 16 ml/kg of AE. The acute rabbit percutaneous studies have no relevance to consumer exposures based on the extremely large differences in dose and exposure conditions. The safety of consumer exposures is supported by the AE dermal subchronic studies described earlier.

Carbide confirm?

Summary and Conclusions

AE are safe for consumer and worker dermal exposures. This is based on the lack of adverse findings in subchronic and chronic studies, the low rate of dermal penetration of AE under actual/realistic exposure conditions, and the safe usage history of these surfactants in marketed products. Effects observed in laboratory animals receiving large unrealistic, dermal doses of AE have no relevance to known human exposures. These effects are due to interactions of AE with membranes and are a function of dose, route of administration, and pharmacokinetic differences among species. No adverse effects would be expected or have been observed from human dermal exposures to AE other than transient, mild, skin irritation.

Please do not hesitate to contact me if we can be of any further assistance in terms of the existing data on AE animal toxicity or if you have any questions about the information and interpretations provided here.

Very truly yours,

The Procter & Gamble Company

T. W. Mooney, Manager
Technical Government Relations

TABLE I

Comparison of Rat Oral LD_{50} and Rabbit Percutaneous LD_{50} for Various Classes of Surfactants

Surfactant	Class	Rat Oral LD_{50} (ml/kg)	Rabbit Percutaneous LD_{50} (ml/kg)	Reference
Linear Alkylbenzene Sulfonates	Anionic	400-2500	200-1260	1
Alkyl Sulfates	Anionic	1000-4000	580	1,3
Alcohol Ethoxylates	Non-ionic	1600->25,000	1000-4000	1,2
Alcohol Ethoxy Sulfates	Anionic	1700->5000	4700-12,900	1,3
Alkylphenol Ethoxylates	Non-ionic	1000-25,000	2000-10,000	1
Alpha Olefin Sulfonate	Non-ionic	1300-2400	580-2200	1

ATTACHMENT I

Calculation of a Skin Permeability Constant for AE Surfactants

Reference: Black, J. G. and Howes, D.
Skin Penetration of Chemically Related Detergents, J. Soc. Cosmet. Chem., 30: 157-165, 1979.

Background: Four AE were evaluated in vivo on rat skin; the highest degree of penetration was observed with an alcohol carbon chain length of 15 and an average of three moles of ethylene oxide per mole of alcohol ($C_{15}E_3$).

The highest penetration value reported was for a 1% (10^4 ug/cm^3) solution of $C_{15}E_3$ applied to rat skin for 1 minute. Penetration was 2.13 ug/cm^2.

Calculation:

$$\text{Permeability Constant} = \frac{\text{Penetration}}{\text{Concentration} \times \text{Time}}$$

$$= \frac{2.13 \text{ ug/cm}^2}{10^4 \text{ ug/cm}^3 \times 1 \text{ min.}} = 2.13 \times 10^{-4} \text{ cm/min.}$$

ATTACHMENT II

Comparison of Anticipated Consumer Percutaneous Exposure to AE in Liquid Detergent vs. Exposure in Rabbit Acute Percutaneous Toxicity Test

I. Consumer

Exposure	g/kg/day
Hand Laundry	1.0×10^{-5}
Laundry Pretreatment	1.1×10^{-3}
Fabric Deposition	1.4×10^{-6}
TOTAL	1.1×10^{-3} g/kg/day

II. Rabbit Percutaneous Test

Exposure	g/kg/day
24 hr. occlusion	163.6

III. $\frac{\text{Rabbit Exposure}}{\text{Consumer Exposure}} = \frac{163.6}{.0011} = 148,727$

I. Anticipated Percutaneous Exposure by Consumer to AE in a Liquid Detergent.

A. Hand Laundry

1). Assume maximum AE content of detergent is 35% w/w. (14)
2). Assume wash solution is 0.20% detergent. (18)
3). AE concentration in wash solution = (2 mg/ml)(.35) = 0.7 mg/ml = 7 x 10^{-4} g/cm^3.
4). Transcutaneous permeability constant 2.13 x 10^{-4} cm/min. (Attachment I).
5). Duration of daily exposure is 2.9 minutes. (18)
6). Surface area of exposed skin is 1680 cm^2. (19)
7). Adult body weight is 70 kg. (17)

$$\text{Exposure} = \frac{(7 \times 10^{-4} \text{ g AE}/\text{cm}^3)(2.13 \times 10^{-4} \text{ cm/min.})(2.9 \text{ min/day})(1680 \text{ cm}^2)}{70 \text{ Kg}}$$

$$= 1.0 \times 10^{-5} \text{ g/kg/day.}$$

B. Laundry Pretreatment

1). Assume maximum AE content of detergent is 35% w/w. (14)
2). Assume maximum detergent concentration for pretreatment = 100%.
3). AE concentration in pretreatment solution = 35 g/100 ml = 0.35 g/cm^3.
4). Trancutaneous permeability constant = 2.13 x 10^{-4} cm/min. (Attachment I).
5). Duration of daily exposure is 5.5 minutes. (18)
6). Surface area of exposed skin is 180 cm^2. (19)
7). Adult body weight is 70 Kg. (17)

$$\text{Exposure} = \frac{(0.35 \text{ g/cm}^3)(2.13 \times 10^{-4} \text{ cm/min.})(180 \text{ cm}^2)(5.5 \text{ min/day})}{70 \text{ Kg}}$$

$$= 1.1 \times 10^{-3} \text{ g/kg/day.}$$

C. Fabric Deposition

1). Assume maximum deposition of AE (100% cotton fabric) is 30 ug/cm^2. (18)
2). Covered body surface is 16020 cm^2/day. (19)
3). Assume 1% of AE is transferred from fabric to skin. (20)
4). 2% of AE transferred is absorbed. (7)

$$\text{Exposure} = \frac{(30 \text{ ug AE}/\text{cm}^2 \text{ fabric})(16020 \text{ cm}^2 \text{ fabric})(0.01 \text{ transfer})(0.02 \text{ absorption})}{(\text{cm}^2 \text{ fabric})(\text{day})(70 \text{ kg})}$$

$$= 1.4 \times 10^{-6} \text{ g/kg/day.}$$

II. Anticipated Percutantous Exposure by Rabbit to AE during Acute Dermal Toxicity Test.

A. Assumptions and Parameters

1). Density of neat surfactant is 1 g/ml or 1 g/cm^3.
2). Assume material applied to area corresponding to 10% body surface of 160 cm^2.(21)
3). Assume adult rabbit weighs 3 kg.(22)
4). Trancutaneous permeability constant is 2.13 x 10^{-4} cm/min (Attachment I).
5). Exposure is 24 hr = 1440 min.
6). Assume that occlusion increases absorption 10-fold. (9)

B. Calculation of Exposure

$$\frac{(1\ g\ AE)(2.13 \times 10^{-4}\ cm)(1440\ min)(160\ cm^2)(x10\ for\ occlusion)}{(\ cm^3\ )(\ \ min.\ \ )\ \ 3\ kg}$$

= 163.6 g/kg/day

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2) Benke, G., Brown, N., Walsh, M., and Drotman, R., Safety Testing of Alkyl Polyethoxylate Nonionic Surfactants. I. Acute Effects. Fd. Cosmet. Toxicol. 15: 309-318, 1977.

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16) Human Safety and Environmental Aspects of Major Surfactants (Supplement), A. D. Little, Inc., February 20, 1981.

17) U. S. EPA, Handbook for Performing Exposure Assessments, May 6, 1982.

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20) Hollies, N., The Skin Barrier: How Does It Handle Materials Lost From Clothing? Text. Chem. Color. 12: 29, 1980.

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Shell Oil Company

One Shell Plaza
P.O. Box 4320
Houston, Texas 77210

23 DECEMBER 1987

Dr Keith Booman, Technical Director
Soap and Detergent Association
475 Park Avenue South
New York
N.Y. 10016

Dear Dr Booman,

As discussed with David Scharer of Shell at the 2nd December meeting of the Risk Assessment Subcommittee, we are providing the following information of rabbit acute dermal lethality studies of primary alcohol ethoxylates produced by Shell Chemical Company.

Shell has results of eighteen rabbit acute dermal lethality studies of alcohol ethoxylates performed between 1967 and 1981. Products tested ranged in alcohol carbon chain length from 9 - 15, and in ethoxylate mole ratio from an average of 2.5 - 13. Rabbits were generally exposed dermally to large amounts of the undiluted surfactant under occlusion for 24 hr; at the end of this period remaining surfactant was removed by washing, and the rabbits were observed for fourteen days. Animals which did not die during this period were sacrificed. All animals were examined by gross necropsy.

Delayed deaths and/or lung effects were reported in sixteen studies. Lung effects were observed on gross necropsy, and were generally described as "hyperemia; red patchy lungs; deep red lungs" etc. This is taken to imply congestion of the lungs with blood. No "creamy colored nodules", as reported by Carbide, were observed, although in older studies lung effects were often confounded by pus and other effects of intercurrent infection. No histopathological examination of the lung or other tissues was performed in these acute toxicity studies.

"Delayed death" in the context of these studies means that rabbits died other than during the first exposure day, i.e., during the fourteen day observation period. Lung effects were only observed in rabbits which had died during this period; in no animals which were sacrificed at the end of the study were lung effects reported at necropsy. Calculated LD50 values ranged from 2 g/kg to greater than 5 g/kg.

Skin irritancy, ranging from moderate to severe/corrosive was also reported in all these studies with undiluted alcohol ethoxylates. The skin irritancy may have caused profound stress, and markedly increased dermal absorption of administered alcohol ethoxylate over that which would have occured with non-irritant dilutions, i.e., use concentrations in formulations.

In more recent rabbit acute dermal lethality studies performed by Shell, limit doses of 2 g/kg have been used, as indicated by TSCA Health Effects Testing Guidelines [Federal Register 50, #188 pp 39390 - 39400]. In these studies, no lethality and no lung effects of undiluted alcohol ethoxylates or formulations have been reported.

Lung effects [but not delayed deaths] have also been reported in rats: in eight oral acute lethality studies with alcohol ethoxylates any deaths occurred within two days of dosing, but lung effects were reported in dead rats in about half the studies. However, in a study more relevant to potential human exposure, no deaths nor toxic effects [other than skin irritation] were reported when a 25% aqueous solution of NEODOL® 91-6 [0.5 ml/kg - a C9-11 alcohol, 6 mole average ethoxylate] was applied dermally for 13 weeks to rats.

Shell believes that the delayed deaths and lung effects in some of our rabbit acute dermal lethality studies of alcohol ethoxylates are unlikely to be relevant to human health: the effects were seen only after application for 24 hr under occlusion of high dose levels of undiluted surfactant. Under these conditions the alcohol ethoxylates were severely irritant to the skin, and at higher doses were often lethal to the rabbit. These conditions are highly unlikely to occur in occupational exposure to undiluted material, or in consumer use of formulated surfactants. However, further studies to elucidate the mechanism of this effect could be useful for definitive risk assessment.

I hope you find this information useful. I would be pleased to attend a meeting of the Risk Assessment Subcommittee of SDA to discuss these studies and exchange toxicologic information with representatives of the other member companies. Please call me at 713-241-0244 if you require further information.

Sincerely,

Ralph

Ralph Gingell
Senior Toxicologist

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