A Review on Toxicological Properties of Fatty Acids, Fatty Alcohols, and Their Derivatives

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INTRODUCTION

Natural oils and fats are triglycerides or esters of glycerines and a mixture of fatty acids, formed by the reaction between glycerine and three molecules of fatty acids. The fatty acid part represents around 90% by weight, the glycerine part around 10% of the fat molecule (Dieckelmann *et al.*, 1988). Basic oleochemicals are produced from natural oils and fats by hydrolysis or methylation. The end-use markets for basic oleochemicals are extensive for either the direct uses of fatty acids, methyl esters, and glycerine or for the intermediate uses of their derivatives *(Table 1)* (Kaufman *et al.*, 1991).

Oils and fats are nontoxic. This is evident from their LD_{50} value of over 10g/kg. The LD_{50} is the statistically derived single dose of a substance that can be expected to cause death in 50% of dosed animals (Hoyng, 1991).

THE TOXICOLOGY OF FATTY ACIDS

Fatty acid mixture is obtained from oils and fats by hydrolysis under high pressure and temperature. Fractional distillation of the mixture separate the shorter chain fatty (≤C14) acids from the longer one (≥C14). Depending on the distillation conditions, fatty acids of different grades and purities are produced.

TABLE 1. THE END-USE MARKETS FOR BASIC OLEOCHEMICALS AND THEIR DERIVATIVES

Basic oleochemicals	Oleochemical derivatives	End-use markets
Fatty acids	Fatty amides	Building auxiliaries
Fatty acid methyl esters	Dimer and trimer acids	Candles
Fatty alcohols	Epoxidized oils and esters	Cleaning agents
Fatty amines	Ethoxylates	Cosmetics
Glycerine	Fatty acid sulphates	Detergents
	Fatty acid sulphonates	Fire extinguishing agents
	Fatty esters soaps and salts	Flotation
		Food emulsifiers
		Insecticides
		Leather
		Lubricants
		Paints
		Paper
		Pesticides
		Pharmaceuticals
		Plastics
		Rubber
		Soaps
		Textile
		Tyres

Fatty acids are nontoxic with a LD_{50} in excess of 2g/kg. The short chain fatty acids can cause one or more of the following: corrosion, skin/eye irritation or foul smell. But even these are safely used as ingredients in soap and cosmetic formulations (Hoyng, 1991). This review collates information on the toxicology of fatty acids, esters of fatty acids and fatty alcohols.

Table 2 shows the toxicology of fatty acids (Kabara, 1979). The acids used in this study were a composite of materials obtained from 12 member companies of the Fatty Acid Producers Council. The saturated fatty acids (C_{10} to C_{18}) were given at 10.0 g/kg while octadecanoic ($C_{18:1}$) and octadecadienoic ($C_{18:2}$) were given at 21.5 ml/kg. Caprylic acid was given at the higher dosage.

Tables 3, 4 and *5* show a summary of primary skin irritation, patch test for corrosivity and acute eye application, respectively, for some of the fatty acids (Kabara, 1979).

As a summary, caprylic and capric acids produced blanching, necrosis (mortification of piece of tissue) and coriaceousness (leather-like tissue). No corrosive effects were noted in any animal which was tested with lauric acid, myristic acid, palmitic acid, stearic acid and oleic acid.

The LD_{50} oral ingestion values for common commercial fatty acids are in the range which are considered nontoxic;

a) 24-hr primary skin irritation is considered positive for octanoic acid but negative for decanoic acid and upwards;

b) 4-hr skin corrosivity is considered positive for decanoic acid and lower, negative for lauric acid and higher; and

c) eye irritation is considered positive for lauric acid and lower, negative for myristic acid and higher.

TABLE 2. THE TOXICOLOGY OF FATTY ACIDS

Fatty Acid	*Effect*
Caprylic acid	While no deaths occured at the 10.0 ml/kg dose, all rats given 21.5 ml/kg of this fatty acid died within 2 hours after ingestion. The acute oral LD_{50} for the male albino rat is 14.7 ml/kg.
Capric acid	Since no death occur at the highest level tested, the oral LD_{50} for capric acid is greater than 10.0 g/kg.
Lauric acid	The oral LD_{50} for lauric acid is greater than 10.0 g/kg since none of the animals died.
Myristic acid	No mortalities occurred at any dosage level tested. Therefore, the acute oral LD_{50} is greater than 10.0 g/kg.
Oleic and Linoleic acids	When the rats given 21.5 ml/kg of these fatty acids, the toxic signs persisted for 2-3 days after which the rats appeared normal.

Source: Kabara (1979).

TABLE 3. PRIMARY SKIN IRRITATION

Fatty acid	*Effect*
Caprylic acid	Produced necrotic tissue at each intact and abraded site at the 24 hour reading. Very slight to moderate edema was observed. All intact and abraded sites were coriaceous at the 72 hour reading. The Primary Irritation Index (PII) was 5.46.
Capric acid	Produced necrosis or blanching in 5 or 6 intact sites and in all of the abraded sites at the 24 hour reading. Very slight edema was noted at some of the intact and abraded sites. The PII was 4.60.
Lauric acid	Produced very slight erythema or blanching in some of the intact and abraded sites. No edema was present at this reading. The PII was 1.12.
Myristic, Palmitic and Stearic acids	All had PII of 0.0. No signs of irritation or corrosivity were observed.
Oleic acid	Produced very slight erythema in some of the intact and abraded sites at the 24 hour reading. No edema was observed. The PII was 0.50.

Source: Kabara (1979).

TABLE 4. PATCH TEST FOR CORROSIVITY

Fatty acid	*Effect*
Caprylic acid	Produced necrosis or spotted and/or entire blanching of each site at the 4 hour reading. At the 24 hour and 48 hour readings, entire or spotted coriceousness was noted at each site.
Capric acid	Produced blanching of one site and necrosis of one site at the 4 hour reading. The remaining sites exhibited no corrosive effects.
Lauric, Myristic, Palmitic, Stearic and Oleic acids	No corrosive effects were noted at any site in any rabbit tested at any time during the study.

Source: Kabara (1979).

TABLE 5. ACUTE EYE APPLICATION

Fatty acid	*Effect*
Caprylic acid	Produced corneal opacity and moderate or marked conjunctivitis in all rabbits, and iritis in 3 rabbits. Blanching of the conjunctival tissues were noted in one rabbit. Irritative signs did not subside appreciably during the 72 hour observation period.
Capric acid	Produced corneal opacity and moderate conjunctivitis in each rabbit, and iritis in some rabbits. There was no decrease in irritation during the observation period.
Lauric acid	Produced corneal opacity and moderate conjunctivitis in all rabbits, and iritis in some rabbits. Irritative signs did not subside appreciably during the 72 hour observation period.
Myristic acid	Mild conjunctival erythema in some rabbits.
Palmitic acid	Produced no signs of eye irritation in any rabbit.
Stearic acid	No sign of eye irritation was observed at any time during the study.
Oleic acid	Produced mild conjunctivitis in some rabbits. No other irritative sign was observed.

Source: Kabara (1979).

Based on these results, caprylic acid and capric acid were classified as corrosive, and together with lauric acid, were determined to be eye irritants. The toxicity and irritability caused by oleic acid and linoleic acid may be due to the presence of their peroxides which are known to be toxic.

ECOLOGICAL EFFECTS OF FATTY ACIDS

The release of substances into the environment during manufacturing, processing, distribution, use or disposal can have an adverse impact on both natural and man-modified ecosystems and their components. *Table 6* summarized the effects of fatty acids on some organisms found in the aquatic environment (Verschueren, 1996).

THE TOXICOLOGY OF FATTY ALCOHOLS

Commercial production of natural fatty alcohols is currently achieved by either the hydrogenation of methyl esters or of fatty acids obtained from the glycerides (Kaufman *et al.*, 1991). The C_{12} and higher fatty alcohols are of prime interest for the surfactant industries.

Fatty alcohols are among the materials of low acute toxicity. The toxicity generally decreases with increasing number of carbon atoms. *Table 7* summarizes the acute toxicity data for a number of fatty alcohols (Potokar *et al.*, 1982). Values which are at times conspicuously different for the same material are caused by different test methods, varying sensitivities of the test animals and different product manufacturing processes.

Higher fatty alcohols are well tolerated by the human skin and therefore have a long tradition as constituents of cosmetics and pharmaceuticals. Undiluted fatty alcohols, especially those of low molecular weight (C_6-C_8), display some mucous membrane irritating properties (Potokar *et al.*, 1982). Hexadecyl and octadecyl alcohol are, the alcohols with the best mucous

TABLE 6. EFFECTS OF FATTY ACIDS ON AQUATIC ORGANISMS

Fatty acid	*Ecological effects*
Caproic acid (Hexanoic acid)	*Daphnia magna*: 24h LC_{50} = 22 mg/l Gammarus (*Hyale plumulosa*): 96h LC_{50} = 235 mg/l Red killifish (*Oryzias latipes*): 96h LC_{50} = 80 mg/l
Caprylic acid (Octanoic acid)	*Daphnia magna*: 24h EC_{50} = 550 mg/l Red killifish (*Oryzias latipes*): 96h LC_{50} = 57 mg/l
Capric acid (Decanoic acid)	Gammarus (*Hyale plumulosa*): 96h LC_{50} = 41 mg/l Red killifish (*Oryzias latipes*): 96h LC_{50} = 20 mg/l
Lauric acid (Dodecanoic acid)	Gammarus (*Hyale plumulosa*): 96h LC_{0} = no mortality at saturation conc. Red killifish (*Oryzias latipes*): 96h LC_{50} = 8.6 mg/l
Myristic acid (Tetradecanoic acid)	Gammarus (*Hyale plumulosa*): 96h LC_{50} = no mortality at saturation conc.
Palmitic acid (Hexadecanoic acid)	Goldfish : lethal dose = 11 mg/l (sodium salt) Red killifish (*Oryzias latipes*): 96h LC_{50} = 150 mg/l (sodium salt)
Stearic acid (Octadecanoic acid)	Goldfish : lethal dose = 14 mg/l (sodium salt) Red killifish (*Oryzias latipes*): 96h LC_{50} = 125 mg/l (sodium salt)
Oleic acid (9-Octadecanoic acid)	Goldfish : lethal dose = 8 mg/l (sodium salt) Red killifish (*Oryzias latipes*): 96h LC_{50} = 217 mg/l (sodium salt)

Source: Verschueren (1996).

membrane compatibility.

FATTY ALCOHOL POLYGLYCOL ETHERS

Fatty alcohol polyglycol ethers with 4-30 moles of ethylene oxide have a higher acute systemic toxicity than do fatty alcohols *(Table 8)* (Potokar *et al.*, 1982).

Fatty alcohol polyglycol ethers, as nonionic detergent raw materials, do not present a toxicological risk if appropriately used. Toxic effects of these materials are mostly limited to local irritations.

FATTY ALCOHOL ETHER SULPHATES AND FATTY ALCOHOL SULPHATES

Among the fatty alcohol derivatives, the fatty alcohol ether sulphates are probably the most important cosmetics raw materials. Since these materials are preferentially used in foam and bath preparations, they are generally in contact with the human body only for a short time. The mean lethal dose is in a range which can hardly be reached by man even upon intentional consumption *(Table 9)* (Potokar *et al.*, 1982).

TABLE 7. TOXICOLOGICAL PROPERTIES OF SOME HIGHER FATTY ALCOHOLS AFTER A SINGLE ADMINISTRATION.

Material	Acute toxicity			Eye irritation (rabbit)		Primary skin irritation[a]		
	Species	Administration	LD_{50} in g/kg	Dose in mg or test conc.	Symptom	Species	Dose in mg	Symptom
Hexyl alcohol C_6	rat mouse rabbit	oral oral dermal	0.7 1.9 3.1	250	strong irritation	rabbit	10	slight irritation
Octyl alcohol C_8	mouse	oral	1.7			rabbit	500	slight irritation
Octyl/decyl alcohol C_{8-10}	rat rabbit	oral dermal	>5.0 >1.0			rabbit, 2 hrs. contact	100	slight irritation
Decyl alcohol C_{10}	rat mouse rabbit	oral oral dermal	4.7 6.4 3.5	83	strong irritation	rabbit	2600/kg	median irritation
Lauryl alcohol C_{12}	rat rat rabbit guinea-pig	i.p.[b] oral oral dermal	0.8-1.6 >36.0 >36.0 >10.0			guinea-pig		no irritation
Lauryl/ myristyl alcohol C_{12-14}	rat	oral	>10.0	500	slight irritation	man, clinical test		without reaction
Myristyl alcohol C_{14}	rat	oral	>5.0	10%	tolerance limit	rabbit man	50% 25%	reddening without reaction
Cetyl alcohol C_{16}	rat mouse mouse rat rat guinea-pig	oral oral i.p.[b] i.p.[b] oral dermal	>10.0 3.2-6.4 1.6-3.2 1.6-3.2 6.4-12.8 <10.0	82	slight irritation	rabbit man guinea-pig	2600/kg 25% 25%	slight reaction without reaction slight reaction

Cont.

Material	Acute toxicity			Eye irritation (rabbit)		Primary skin irritation[a]		
	Species	Administration	LD_{50} in g/kg	Dose in mg or test conc.	Symptom	Species	Dose in mg	Symptom
	rat	inhalation 6 hrs. 2.22 mg/l air in 2 days deadly						
	rat	inhalation 6 hrs. 0.41 mg/l air survival						
	rat	oral	20.0	100	slight irritation			
Stearyl alcohol C_{18}	rat	oral	20.0 .	100	slight irritation			
	rat	oral	>5.0			man	5%	without irritation
	rabbit	dermal	>1.0					
	rat	inhalation 10% 2 hrs. no symptoms						
Oleyl alcohol	rat	oral	>25.0			man, clinical test with 2 hrs. contact time each		without irritation
Oleyl/ cetyl alcohol				500	slight irritation	man, as with oleyl alcohol		without irritation

[a] Contact time 24 hrs., otherwise the hours are given, administration of the undiluted product, otherwise the dilution is given in percent.
[b] Intraperitoneal, into the abdominal cavity.
Source: Potokar et al., (1982).

TABLE 8. EXAMPLES OF FATTY ALCOHOLS POLYGLYCOL ETHERS ON THE BASIS OF SATURATED FATTY ALCOHOLS. TOXICOLOGICAL DATA AFTER A SINGLE ADMINISTRATION.

Material	Acute oral toxicity		Eye irritation (rabbit)		Primary dermal irritation		
	Species	LD_{50} in g/kg	Test conc.	Symptom	Species	Test conc.	Symptom
Fatty alcohol C_{12}-C_{14}+2EO	rat rat	>5.0 14.9	1%	slight irritation	man, clinical test	1:100	without irritation
Fatty alcohol C_{12}-C_{14}+3EO	rat	8.2	10%	tolerance limit	man, 2x24 hrs.	10%	without irritation
Fatty alcohol C_{12}-C_{14}+4EO	rat	5.6	1%	without irritation			
Fatty alcohol C_{12}-C_{18}+3EO	mouse	>10.0					
Fatty alcohol C_{12}-C_{18}+10EO	mouse	4.7					
Cetyl stearyl alcohol C_{16}-C_{18}+12EO	rat	4.6			rabbit 1x appl. man, clinical study	10% 1:10	reddening without irritation
Cetyl stearyl alcohol C_{16}-C_{18}+20EO	rat	3.0			man, clinical study	10%	without irritation

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Material	Acute oral toxicity		Eye irritation (rabbit)		Primary dermal irritation		
	Species	LD_{50} in g/kg	Test conc.	Symptom	Species	Test conc.	Symptom
Cetyl stearyl alcohol C_{16}-C_{18}+30EO	rat	>10.0	10% 35%	without irritation slight irritation	rabbit man, clinical study	25%	without irritation without irritation
Oleyl/Cetyl alcohol +7-8EO	mouse	4.7	25%	slight irritation	rabbit 1x appl.* man, 2hrs.	10%	reddening without irritation
Oleyl/Cetyl alcohol +5EO	rat	14.0					
Oleyl/Cetyl alcohol +10EO	rat	5.3					
Oleyl/Cetyl alcohol +10EO	rat	5.3					
Tallow alcohol+5EO	rat	5.7					
Tallow alcohol+12EO	mouse	2.1					
Tallow alcohol+14EO	rat	2.9					

* appl. = application

Source: Potokar et al., (1982).

TABLE 9. TOXICOLOGICAL DATA FOR FATTY ALCOHOL ETHER SULPHATES AFTER A SINGLE ADMINISTRATION

Material	Acute oral toxicity		Eye irritation (rabbit)		Primary dermal irritation (man)	
	Species	LD_{50} in g/kg	Test conc.	Symptom	Test conc. contact	Symptom
Sodium lauryl ether sulphate (25%), 1EO	mouse	3.9	0.5%	slight irritation		
Sodium lauryl ether sulphate (27%), 2EO	rat	>10.0	5.0%	reddening	1%	without irritation
Sodium lauryl ether sulphate (70%), 2EO	rat	4.5	10.0%	irritation	50%	without reaction
Sodium lauryl ether sulphate (70%), 3EO	rat	>5.0	1.0%	slight irritation		
Sodium lauryl ether sulphate (30%), 3.7EO	mouse	6.0	1.0%	slight irritation		
Ammonium lauryl ether sulphate (24%), 2EO	mouse	>10.0				
Magnesium lauryl ether sulphate (30%), 2EO	mouse	>10.0	1.0%	irritation		
Mixture of special fatty alcohol ether sulphates C_{12}-C_{18} (27%), 7-8EO	rat	>10.0	5.0%	slight irritation	50% 4hrs 1%	without irritation without irritation

Source: Potokar et al., (1982).

TABLE 10. EXAMPLES OF FATTY ALCOHOL SULPHATES. TOXICOLOGICAL DATA AFTER A SINGLE ADMINISTRATION

Material	Acute oral toxicity		Eye irritation (rabbit)		Primary dermal irritation	
	Species	LD_{50} in g/kg	Test conc.	Symptom	Test conc. contact	Symptom
Triethanolamine lauryl sulphate C_8-C_{14} (49%)	rat	7.9	50%	slight irritation	4 hrs.	without irritation
Ammonium lauryl sulphate C_8-C_{14} (34%)	rat	>5.0	1%	slight irritation	10%, 2hrs.	without irritation
Sodium lauryl sulphate (pure) C_{12}	rat	1.7	0.5%	without irritation	1%, 2hrs	without irritation
Lithium lauryl sulphate C_{12} (30%)	rat	5.1	1%[a]	irritation		
Monoethanolamine lauryl sulphate C_{12}-C_{14} (33%)	rat	5.6				
Diethanolamine lauryl sulphate C_{12}-C_{14} (31%)	rat	8.7	50%	slight irritation	50%, 2hrs	without irritation
Sodium lauryl sulphate C_{12}-C_{16} (29%)	mouse	2.9[a]	0.5%	slight irritation		
Sodium lauryl sulphate C_{12}-C_{16} (70%)	rat	7.7	1%[a]	irritation	1%[b], 8hrs	without irritation
Sodium lauryl sulphate C_{12}-C_{16} (90%)	mouse	2.3[a]			5%	without irritation
Sodium lauryl sulphate C_{12}-C_{18} (90%)	mouse	3.3	5%	irritation		
Sodium cetyl/stearyl sulphate C_{16}-C_{18}	rat	>10.0				

[a] test concentrations/values with respect to 100% Materials
[b] test concentration with respect to 30% materials
Source: Potokar et al., (1982).

TABLE 11. TOXICOLOGICAL DATA FOR FATTY ALCOHOL ESTERS AFTER A SINGLE ADMINISTRATION

Material	Acute oral toxicity		Eye irritation, rabbit		Primary dermal irritation	
	Species	LD_{50} in g/kg	Test conc. or dose	Symptom	Species contact	Symptom
Oleic acid-decyl ester	rat	>20.0	50%	without irritation	rabbit, 6 hrs.	reddening
Oleic acid-oleyl ester	rat	>20.0				
Lauric acid-hexyl ester	rat	>20.0				
Stearyl stearate	rat	>20.0	100mg	without irritation		
Caprylic/caprinic acid, ester of Fatty alcohol C_{12}-C_{18}	rat	>20.0	10%	without irritation	man, clinical study	without irritation
Di-n-octyl phthalate	man	0.5g/kg =toxic dose	5mg	strong irritation		

Source: Potokar et al., (1982).

TABLE 12. EFFECTS OF FATTY ALCOHOLS ON AQUATIC ORGANISMS

Fatty alcohols	*Ecological effects*
n-Hexanol	*Alburnus alburnus*: 96h LC_{50} = 120 mg/l *Nitocra spinipes*: 96h LC_{50} = 317 mg/l
1-Octanol	*Daphnia magna:* 24h EC_{50} = 15-16 mg/l *Pimephales promelas:* 96h LC_{50} = 13-15 mg/l *Nitocra spinipes:* 96h LC_{50} = 60 mg/l
1-Decanol	*Daphnia magna:* 24h EC_{50} = 9.3 mg/l *Pimephales promelas:* 96h LC_{50} = 2.2-2.5 mg/l *Nitocra spinipes:* 96h LC_{50} = 3.1 mg/l (in water/acetone solution)
1-Dodecanol	*Pimephales promelas:* 96h LC_{50} = 1 mg/l *Nitocra spinipes:* 96h LC_{50} = 1 mg/l
1-Tetradecanol	n.a.
1-Hexadecanol	n.a.
1-Octadecanol	*Streptococcus mutans:* 24h NOEC = > 3.3 mg/l *Candida albicans:* 30h NOEC = 10 g/l
9-Octadecanol	n.a.

NOEC = No-observed-effect-concentration
n.a. = not available
Source: Veershueren (1996).

Mixtures of fatty alcohol sulphate homologues with carbon chains C_{12}-C_{18} may be ingested as residues on washed dishes or directly via water. Because of the low toxicity of these materials, they constitute no health risk for human beings (Potokar *et al.,* 1982). Fatty alcohol sulphates may cause irritation to mucous membranes depending on concentration *(Table 10)* (Potokar *et al.,* 1982).

FATTY ALCOHOL ESTERS

Of all the fatty alcohol derivatives, this class of compounds are acutely and parenterally the least toxic *(Table 11)* (Potokar *et al.,* 1982). Fatty alcohol esters which are contained in cosmetics are well tolerated in high concentrations. Lauric acid hexyl ester which was tested for its subacute toxicity toward rats did not cause any poisoning symptoms after oral application in the feed at 10,000 ppm level over a three week period.

ECOLOGICAL EFFECTS OF FATTY ALCOHOLS

The testing for toxicity toward water organisms in relatively simple screening tests constitute an important additional decision point, after biodegradability, in the ecological safeguarding of products (Fischer, 1982). *Table 12* summarizes the effects of fatty alcohols on some aquatic organisms.

CONCLUSION

The toxicological data summarized in this

review of natural fatty acids and fatty alcohols, and their derivatives show that these are classes of compounds of low toxicity.

It is known from tests for local compatibility that concentrates of fatty alcohols and derivatives may, depending on contact time, lead to reactions. They do not, however, lead to skin and mucous membrane damages as they are always employed in dilute solutions. Due to these favourable toxicological properties, they constitute suitable raw materials and auxiliaries for cosmetics, pharmaceuticals, and other applications.

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