Human & Environmental Risk Assessment

on ingredients of

European household cleaning products

Fatty Acid Salts

Human Health Risk Assessment

Draft for Public Comment

June, 2002

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2. Executive Summary

Fatty acid salts (soap) are a widely used class of anionic surfactants. They are used in household cleaning products, cosmetics, lubricants (and other miscellaneous industrial applications) and coatings. Uses in household cleaning products, the scope of this HERA assessment, include fabric washing products, fabric conditioners, laundry additives, and surface and toilet cleaners.

According to data received from a survey conducted among detergent formulator companies, an overall annual tonnage of 71306 tonnes of fatty acid salts for use in HERA applications was estimated. This was compiled using data from 4 out of the 6 main formulator companies.

Fatty acid salts are of low acute toxicity. Their skin and eye irritation potential is chain length dependent and decreases with increasing chain length. They are not skin sensitisers. The available repeated dose toxicity data demonstrate the low toxicity of the fatty acids and their salts. Also, they are not considered to be mutagenic, genotoxic or carcinogenic, and are not reproductive or developmental toxicants.

Accidental ingestion of fatty acid salt containing detergent products is not expected to result in any significant adverse health effect. This assessment is based on toxicological data demonstrating the low acute oral toxicity of fatty acid salts and the fact that not a single fatality has been reported in the UK, following accidental ingestion of detergents containing fatty acid salts.

The estimated total human exposure to fatty acid salts, from the different exposure scenarios for the handling and use of detergent products containing fatty acid salts, showed a margin of exposure (MOE) of 258,620. This extremely large MOE is large enough to be reassuring with regard to the relatively small variability of the hazard data on which it is based. Also, in the UK, the recommended dietary fatty acid intake by the Department of Health is about 100 g of fatty acids per day or 1.7 g (1700 mg) of fatty acids per kilogram body weight per day. This exposure is several orders of magnitude above that resulting from exposure to fatty acid salts in household cleaning products. .

Based on the available data, the use of fatty acid salts in household detergent and cleaning products does not raise any safety concerns with regard to consumer use.

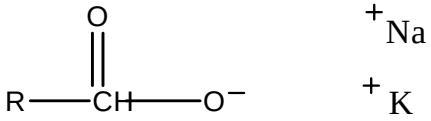
3. Substance Characterisation

Fatty acid salts are a widely used class of anionic surfactants. The applications which are covered by the scope of HERA include use in fabric washing products, fabric conditioners, laundry additives, and surface and toilet cleaners. In addition, there are a number of uses which are not covered by HERA. These include cosmetics, lubricants (and other miscellaneous industrial applications) and use in coatings.

3.1. CAS No and Grouping information

The category for this assessment is defined as the salts of monocarboxylic acids bearing a straight, even numbered fatty acid chain, ranging in number of carbon atoms from 10 to 22. The C16 to C22 members of the group may be saturated or unsaturated (unsatd) with a carbon-carbon double bond.

The fatty acids salts grouping consists of both discrete chemicals with an incremental and constant change across its members (carbon chain length) and commercial mixtures that are composed of fatty acids salts with a range of carbon chain lengths. The chemical structure of the category is:



where R contains from 9 to 21 carbon atoms and the higher fatty acid chain lengths may be saturated or unsaturated, with potassium or sodium salts included.

3.2. Chemical structure and composition

Table 1 covers the CAS numbers provided by 4 out 6 formulator companies. Although clearly important from a Regulatory perspective, the environmental assessment is not based on CAS Nos., but on the product composition and specifically carbon chain length distribution - which is key to the environmental profile of this family. Whilst fatty acids are used in the initial starting list of materials, the final formulation of products covered through this assessment can be expected to contain only fatty acid salts. Thus, the salts of fatty acids only are considered here. Data for fatty acids have been used only for (comparative) read across purposes in the absence of data for the salts.

Table 1 – Chemicals, CAS Numbers, Synonyms, and Structural Composition

CAS No.	Compound	Synonyms	Chain length
Fatty Acid Salts			
629-25-4	Dodecanoic acid, sodium salt	Sodium laurate	12
143-18-0	9-Octadecenoic acid, potassium salt	Oleic acid, potassium salt; Potassium oleate	18
143-19-1	9-Octadecanoic acid, sodium salt	Oleic acid, sodium salt; Sodium oleate	18
822-16-2	Octadecanoic acid, sodium salt	Stearic acid, sodium salt; Sodium stearate	18
2272-11-9	9-Octadecanoic acid (Z)-, compd with 2-aminoethanol (1:1)	Monoethanolamine oleate	20
85408-69-1	Fatty acids, C8-C18 and C16-18 unsatd. Sodium salts	-	16-18
Fatty Acids			
143-07-7	Dodecanoic acid	Lauric acid	12
90990-09-3	Fatty acids, C10-14	-	10-14
67701-01-3	Fatty acids, C12-18	-	12-18
67701-03-5	Fatty acids, C16-18	-	16-18
67701-06-8	Fatty acids, C14-18 and C16-18 unsatd	-	14-18
85711-54-2	Fatty acids, rape oil	-	18-22
68424-37-3	Fatty acids C14-C22	-	14-22

Due to the limited availability of measured physical-chemical data for the fatty acid salts, these data have been generated mostly using predicted values from the EPIWIN program (see Appendix I).

The available data demonstrate that the melting point increases with increasing chain length. Unsaturation results in decreased melting points in comparison to the saturated analogue. The salts of the fatty acids generally have higher melting points compared to their corresponding fatty acid.

The relevance of the boiling point endpoint for the salts of the fatty acids is questionable, as these chemicals are expected to decompose prior to reaching boiling temperatures. For saturated linear fatty acids, the boiling point increases with increasing carbon chain length.

The vapour pressure of the salts of single or mixed fatty acids are expected to be low. Due to lack of measured data for the fatty acid salts predicted values based on estimated log Kow have been generated by EPIWIN. Available data for members of the fatty acids themselves indicate that these chemicals have very low vapour pressures. Among the fatty acids, vapour pressure decreases with increasing chain length.

For fatty acids the partition co-efficient increases with increasing chain length.

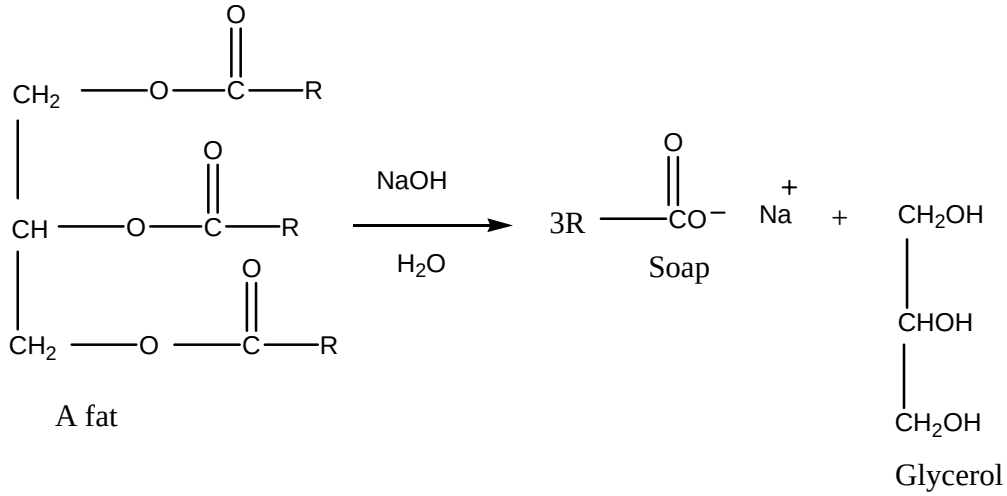
Available data for the salts of the fatty acids indicate that the salts, not unexpectedly, have much greater water solubility than the free acids, which demonstrate that water solubility decreases with increasing chain length.

Physical-Chemical data are provided in Appendix I.

3.3 Manufacturing Route and Production/Volume Statistics

According to data received from AISE the estimated annual tonnage of fatty acids salts produced for use in household cleaning products in Europe is 71306 tons. This has been compiled from 4 out of the 6 main formulator companies.

Soaps are produced by the saponification of fat with alkali. The production process was invented by Leblanc in 1791, when he found a process for producing soda (Na_2CO_3) and thus NaOH became commercially available for the saponification of fatty acids (Moreno *et al.* 1993; Bruschweiler *et al.* 1988). The saponification of fats is given in figure 1.



Where R = C9 – C21 aliphatic chains

Figure 1: Saponification of fats (from BKH, 1994)

The crude soap curds contain glycerol and excess alkali but purification can be effected by boiling with a large amount of water, followed by precipitation of the pure sodium carboxylate salts on addition of sodium chloride (McMurry, 1984 *cited in* BKH, 1994).

3.4. Use applications summary

Tonnage used in HERA applications (HERA Tonnage)

To determine the total fatty acid salt tonnage used in products falling within the scope of HERA (i.e., household detergents and cleaning products), a survey was conducted among detergent formulator companies (data from members of AISE). The data received from the 4 of the 6 major fatty acid salt formulators provided an overall estimated annual tonnage of 71306 tonnes for HERA applications. In addition, the data provided an estimated distribution between carbon chain lengths. This chain length distribution is not derived for a 100% of the total tonnage but for one which is greater than 80% of the total. The distribution is shown in Table 2.

Table 2. Tonnage of fatty acid salts within the scope of HERA, determined via AISE survey

	Estimated Carbon Distribution of Fatty acid salts (% weight)	Tonnage of fatty acid salts (tonnes/annum (tpa))*
C10	1.1	784
C12	37.2	26526
C14	11.8	8414
C16	17.3	12336
C18	31.8	22675
>C18 **	0.8	570
Total		71306

* These values are calculated from % chain distribution and total tonnage of 71306 tonnes per annum.

** This equates to predominantly C22

5. Human Health Assessment

5.1 Consumer Exposure

5.1.1 Product types

Data supplied by the formulating companies shows that fatty acid salts (soap) are used in fabric washing powders, tablets and liquids/gels, in fabric conditioners, laundry additives and in surface and toilet cleaner liquids. The salts of the fatty acids considered in this assessment are the sodium and potassium salts only. The level of soap found in fabric washing products ranges from approximately 0.1-10.5% in regular powder, 2-20% in regular liquid, 0.1-3.4% in compact powder, 4-10% in compact liquid, 0.7-2% in tablets and 13.1-15.1% in compact gels. The maximum level found in fabric conditioners is 0.75%, while levels of 0.1-3.0% can be found in surface cleaners (with the gel containing potentially the highest levels) and 0.55-1.9% in toilet cleaners. Table 1 in Section 3.2 (and Table 1 in Appendix II) gives the chemical names, synonyms and carbon chain lengths of the chemicals considered in this assessment.

5.1.2 Consumer Contact Scenarios

Fabric washing powders and liquids as well as fabric conditioners are used in two ways, either in the washing machine or in a bowl for hand washing. Surface and toilet cleaner liquids are applied directly onto the surface or into the toilet bowl. Hence, the potential for consumer contact is identified as follows:

- Dermal contact:-
  - Contact with the washing solution
  - Contact with concentrated paste of product used in fabric pre-treatment
  - Contact with clothes containing deposited product
- Contact via inhalation:-
  - Pouring the product from the container into the machine/bowl (does not apply to liquid, tablets or gel)
  - Inhalation of aerosols generated by spray cleaners
- Oral ingestion:-
  - Direct accidental or intentional ingestion of product
  - Indirect exposure via the environment
- Other Exposures – eye exposure:-

- Splashing of products into eye

5.1.3 Consumer contact estimates

There is a consolidated overview concerning the habits and uses of detergents and surface cleaners in Western Europe, which was tabulated and issued by the European Soap and Detergent Industry Association, AISE (AISE, 2002). This list reflects the consumer's use of detergents in g/cup, tasks/week, duration of task and other uses of products and is relevant in providing data reflecting consumer exposure. It can be used in calculating the following:

5.1.3.1 Dermal contact

Consumers may be exposed to fatty acid salts via skin contact with washing solutions, which contain fatty acid salts. Relevant exposure scenarios are direct contact with the product, hand washing of clothes, contact with the concentrated paste of products used in fabric pre-treatment and contact with clothes containing deposited product.

Direct Skin Contact: Hand-washed Laundry

The concentration of laundry detergent in hand washing solutions is approximately 1% (10 g/l) (AISE, 2002). The highest concentration of fatty acid salts in laundry detergents is 20% (for liquid detergent). For this reason in a worst case assumption, the hands and forearms of the consumer could be exposed to an estimated fatty acid salts concentration of up to 2.0 g/l (= mg/ml). The estimated surface of the hands and forearms, exposed to the washing solution is 1980 cm^2 (EU Technical Guidance Document (EU TGD), Part I, Annex VI).

Soap is a surface active agent and soap anions will form a film on the surface. Therefore, the concentration on the surface will be different from the body of the suspension. However, assuming a film thickness of 100 µm (0.1 mm or 0.01 cm) (EU TGD, Part I, Annex VI) on the hands and a percutaneous absorption of 1% (0.01) for ionic substances (Schaefer and Redelmeier, 1996) (the ionised acid form of the fatty acids is less easily absorbed than the non-ionised form, therefore the 1% (0.01) used here is a worst case assumption) in a 24 hour exposure period, the following amount of fatty acid salts absorbed via skin can be calculated:

Surface area of hands and forearms x film thickness x fraction absorbed x fatty acid salt concentration = amount absorbed

$$1980\ cm^2 \times 0.01\ cm \times 0.01 \times 2.0\ mg/ml\ (cm^3) = 0.40\ mg$$

0.40 mg fatty acid salts absorbed in 24 hours

Assuming 10 minutes contact time per task and a very conservative maximum task frequency of 21 washes per week (3 per day) (AISE, 2002), the total daily contact time is 30 minutes. Therefore, a correction factor of [(0.40 mg/day) x (1/24 day/hr) x (30/60hr)] is used yielding an assumed absorption of **8.3×10^{-3} mg.**

Based on a body weight of 60 kg the estimated systemic dose of fatty acid salts would be equal to:

$Exp_{sys\ (direct\ skin\ contact)}$ = 1.4 x 10^{-4} mg/kg body weight per day

Direct skin contact: Contact with laundry tablets/powder/liquid

Contact with laundry tablets may occur during unwrapping the tablets and placing them into the washing machine. However, the contact time is very low (<1 min) and only the tips of thumb and index finger of one hand are exposed so the amount absorbed percutaneously is considered insignificant. Some parts of the body, mainly the hand, might also come into contact with washing powder/liquid when transferring the product from the container into the machine. Contact time during these scenarios is very low and can be assumed to be a few seconds, the skin area affected is small and exposure occurs only occasionally and not regularly with product use. Hence, the systemic fatty acid salts exposure resulting from this scenario is also considered to be negligible.

Direct skin contact: Contact via pre-treatment of clothes

Commonly, clothing stains are spot-treated by hand with detergent. If a powdered detergent is used, a paste of about 60% [600 mg/ml powder] (AISE, 2002) will be used or a liquid will be applied directly. The highest concentration of fatty acid salts in laundry powder (laundry regular) is 10.5%. Therefore, the highest concentration of fatty acid salts in hand washing paste will be 63 mg/ml. The highest concentration of fatty acid salts in liquid laundry detergents amounts to 20% (200 mg/ml). Because liquid detergents may be used for pre-treatment, the worst case value of 200 mg/ml will be used in the calculation. The skin surface area exposed will be the hands only (840 cm^2) (EU TGD, Part I, Annex VI).

Again assuming a film thickness of 100 µm on the hands and a percutaneous absorption of 1% for ionic substances in 24 hour exposure time, the following amount of fatty acid salts absorbed via skin can be calculated:

Surface area of hands x film thickness x fraction absorbed x fatty acid salt concentration = amount absorbed

840 cm^2 x 0.01 cm x 0.01 x 200 mg/ml (cm^3) = 16.8 mg

16.8 mg fatty acid salts absorbed in 24 hours

Under the very conservative assumptions of 10 min highest contact time per task and a maximum task frequency of 1 wash pre-treatment per day, the total daily contact time adds to 10 minutes. Assuming such very conservative daily duration of exposure the amount of absorbed fatty acid salts per day can be calculated as [(16.8 mg/day) x (10/60 hr) x (1/24 day/hr)] = **0.12 mg.**

Based on a body weight of 60 kg the estimated systemic dose of fatty acid salts would be equal to:

$Exp_{sys\ (direct\ skin\ contact)}$ = 2.0 x 10^{-3} mg/kg body weight per day

This exposure estimate can be regarded as very conservative. Typically, consumers pre-wet the laundry before applying the detergent for pre-treatment or conduct pre-treatment under running tap water. Both practices lead to a significant dilution which is not reflected in this exposure estimate. It should also be considered that only a fraction of the two hands' surface will actually be exposed. The assumption that both hands will be fully immersed leads to a likely overestimate of the true exposure.

Indirect skin contact: Transfer of FAS from clothing

Residues of components of laundry detergents may remain on textiles after washing and can transfer from the textile to the skin. Rodrgiuez *et al.* (1994) determined that the amount of fatty acids deposited on fabric after 10 repeats of a typical washing process with a typical laundry detergent was in the order of 13.4 g of fatty acids per kg of fabric.

The indirect dermal exposure resulting from the transfer of fatty acid salts from clothing can be calculated using the equation as described in Appendix D of the HERA guidance document:-

$$\mathbf{EXP_{sys} = F_1 \times C' \times S_{der} \times n \times F_2 \times F_3 \times F_4 / BW}$$

Where F_1 percentage (%) weight fraction of substance in product: **20%** (0.2)

C' product load in [mg/cm^2]: **1.34×10^{-1} mg/cm^2***

S_{der} surface area of exposed skin [cm^2]: **17,600 cm^2 (excludes heads and hands)**

n product use frequency [events/day]: 1 (not used)

F_2 percentage (%) weight fraction transferred from medium to skin: **1%** (Vermeire *et al.*1993)

F_3 percentage (%) weight fraction remaining on skin: **100%** (worst case assumption)

F_4 percentage (%) weight fraction absorbed via skin: **1%** (Schaefer and Redelmeier, 1996)

BW body weight in kg: **60 kg**

* C' was determined by multiplying the experimental value of the amount of fatty acids deposited on fabric after a typical wash (i.e. 13.4 g/kg) (Rodriguez *et al.* 1994) times an estimated value of the fabric density (FD = 10 mg/cm^2) (P&G unpublished internal data, 1996)

$$\mathbf{EXP_{sys} = F_1 \times C' \times S_{der} \times n \times F_2 \times F_3 \times F_4 / BW}$$

$$\mathbf{EXP_{sys}} = 0.2 \times (1.34 \times 10^{-1}) \times 17{,}600 \times 0.01 \times 1 \times 0.01 / 60$$

$$EXP_{sys\ (indirect\ skin\ contact)} = 7.9 \times 10^{-4} \text{ mg/kg body weight/day}$$

5.1.3.2 Oral exposure

There is no significant source of oral contact from the recommended use of soaps in detergent products.

Accidental Ingestion

The accidental or intentional overexposure to fatty acid salts directly is not considered to be a likely occurrence for consumers, but it may occur via household detergent products containing fatty acid salts. In the UK, the Department of Trade and Industry (DTI) produce an annual report of the home accident surveillance system (HASS). The data in this report summarises the information recorded at accident and emergency (A & E) units at a sample of hospitals across the UK. It also includes death statistics produced by the Office for National Statistics for England and Wales. The figures for 1998 show that for the representative sample of hospitals surveyed, there were 33 reported accidents involving detergent washing powder (the national estimate being 644) with none of these resulting in fatalities (DTI, 1998). In 1996 and 1997, despite their being 43 and 50 reported cases, respectively, no fatalities were reported either.

Also, considering the high levels of fatty acids that are present in the diet, it is extremely unlikely that accidental ingestion of a household cleaning product would result in over exposure to fatty acids or their salts, and any adverse effects seen are unlikely to be due to these chemicals.

Indirect Exposure

There are no data available on the levels of soap present in drinking water. However, in an environmental hazard assessment of soaps by BKH (1994), it is reported that "due to strong adsorption and poor water solubility of calcium salts, soaps are almost completely removed from raw sewage by normal sewage treatment plants". Any soap remaining will be further removed by drinking water treatment processes so the amount of soap present in drinking water is likely to be insignificant.

Indirect Exposure via the diet

By far the most significant exposure to fatty acids and their salts is via the diet as fatty acids are present in large quantities in the diet. In the UK, the Department of Health have set dietary reference values for fat and recommend that total fatty acid intake should average 30 per cent of total dietary energy including alcohol (DoH, 1991). This equates to about 100 g of fatty acids per day or **1.7 g of fatty acids per kg body weight (1700 mg/kg body weight per day)**.

5.1.3.3 Inhalation Exposure

Inhalation exposure from pouring the product from the container into the machine/bowl

Fabric washing powders are manufactured to rigorous specifications of particle size, enhanced by the exclusion of particles small enough to be inhaled into the lungs. Tests on fabric washing powders over many years have shown a very low level of dust in these products, and within the dust, the level of respirable particles is extremely low. It has been estimated that a cup of fabric washing powder (200 g) can generate 0.27µg of dust (Van de Plassche *et al.*

1998), giving rise to a maximum exposure by inhalation of **0.028 µg of fatty acid salts** (assuming 10.5% of material in product).

Hence, intake via inhalation = $0.028 \times 10^{-3}/60 \times 3^{*}$ = **1.4×10^{-6} mg/kg body weight/day**

*Assuming 21 washes per week (21/7 = 3) (AISE, 2002)

Lint formation during drying of fabrics in tumble-driers which vent indoors is not considered to contribute to inhalation exposure to fatty acid salts, since washed fabrics do not contain any significant amount of fatty acid salts (see above).

Inhalation of aerosols generated by spray cleaners

Fatty acid salts are also present in surface cleaning sprays at a maximum concentration of 0.1%. The HERA guidance document specifies the algorithm to be used for calculation of consumers' worst-case exposure to aerosols generated by the spray cleaner:

$$\mathbf{Exp_{sys} = F_1 \times C` \times Q_{inh} \times t \times n \times F_7 \times F_8 / BW}$$

F_1 percentage weight fraction of substance in product **0.1%** (worst case)

C` product concentration in air: **0.35 mg/m^3** * (P&G unpublished data)

Q_{inh} ventilation rate -**0.8 m^3/h** (EU TGD)

t duration of exposure - **10 min** (0.17h) (AISE, 2002)

n product use frequency (tasks per day) - **1** (AISE, 2002)

F_7 weight fraction of respirable particles - **100%**

F_8 weight fraction absorbed or bioavailable - **75%** (EU TGD)

BW body weight **60 kg** (EU TGD)

* this value was obtained by experimental measurements of the concentration of aerosol particles smaller than 6.4 microns in size which are generated upon spraying with typical surface cleaning spray products [Note is the value of 6.4 microns acceptable; sometimes a cut-off value of 10 micron is used.

$$\mathbf{Exp_{sys} = F_1 \times C` \times Q_{inh} \times t \times n \times F_7 \times F_8 / BW}$$

$Exp_{sys\ (inhalation\ of\ aerosols)} = [(0.001) \times (0.35\ mg/m^3) \times (0.8\ m^3/hr) \times (0.17\ hr) \times (0.75)] \ / \ 60\ kg$

$Exp_{sys\ (inhalation\ of\ aerosols)} = 6.0 \times 10^{-7}$ mg /kg body weight per day

5.1.3.4 Other exposures (eye exposure)

Accidental exposure of the eyes to fatty acid salts will occur in consumers only via splashes or spills with a formulated product. Therefore, the eye irritation potential has to be considered in the context of accidental exposure.

Table 3 - Total Consumer Exposure (All Routes) from household cleaning products

Route	Exposure to soap (mg/kg/day)
1. Dermal	
Hand laundry	1.4×10^{-4}
Fabric pre-treatment	2.0×10^{-3}
Wearing laundered fabric	7.9×10^{-4}
TOTAL DERMAL	$\boldsymbol{2.9 \times 10^{-3}}$
2. Oral	
Accidental Ingestion	**--**
Indirect Exposure via Drinking Water	Negligible
TOTAL ORAL	***Negligible***
3. Inhalation	
Pouring product	1.4×10^{-6}
Spray cleaner	6.0×10^{-7}
TOTAL INHALATION	$\boldsymbol{2.0 \times 10^{-6}}$
TOTAL (ALL ROUTES)	$\mathbf{2.9 \times 10^{-3}}$

5.2 Hazard Assessment

5.2.1 Summary of available toxicological data

Introduction

The acid and alkali salt forms of the same chemical are expected to have many similar physicochemical and toxicological properties when they become bioavailable; therefore, data read across is used for those instances where data are available for the acid form but not the salt, and vice versa. This position is based on experimental studies that have clearly demonstrated a high degree of similarity between the toxicokinetics and toxicodynamics of acid and salt forms of the same chemical (BASF, 2001).

A general premise in regulatory toxicology is that testing an acid form of a chemical is representative of the testing that chemical as an alkali salt. In the gastrointestinal tract, acids

and bases are absorbed in the undissociated (non-ionised) form by simple diffusion or by facilitated diffusion. In general, the amount of dissociation of acids and bases is determined by the pKa values of the substance and the pH of the environment. The pH of the stomach varies between 1-3 and in the intestines, pH values between 5 and 8 are reported. In an acidic environment, acids will be present mainly in the non-ionised form. The amount of dissociation depends on the strength of the acid. Strong acids may be dissociated to some extent in very acidic environments like the stomach, but weaker acids will occur mainly undissociated (BASF, 2001).

It is expected that both the acids and the salts will be present in (or converted to) the acid form in the stomach. This means that for both types of parent chemical (acid or salt) the same compounds eventually enter the small intestine, where equilibrium, as a result of increased pH, will shift towards dissociation (ionised form). Hence, the situation will be similar for compounds originating from acids and therefore no differences in uptake are anticipated (BASF, 2001).

5.2.1.1 Acute Toxicity

As all the data below have been taken from secondary published sources and not from the original studies, the data have been rated as class 4 (i.e. not assignable) using the method described by Klimisch *et al.* (1997), unless otherwise stated.

Acute oral toxicity

Given the assumption that the salts of fatty acids will exhibit a similar toxicity profile as the comparable free acids, the available data on the fatty acids in Table 4 can be used to estimate the toxicity for the salts for which data are lacking. For example, both stearic acid and sodium stearate (C18) have reported LD50 values of >5,000 mg/kg body weight.

The available data for fatty acids provide a clear picture of low acute toxicity for this class of chemicals. All oral LD50 values were greater than 2,000 mg/kg, with little mortality being observed even at the highest doses tested in the studies (IUCLID, 2000c, 2000e, 2000f, 2000g; Clayton & Clayton, 1982; CIR, 1987).

The available data for the fatty acid salts also indicate that these are of low acute toxicity. For example, an acute oral LD50 value of >5,000 mg/kg (highest dose tested) has been reported for sodium soap. This test was done according to GLP and OECD Guideline 401 (IUCLID, 2000f), while in another study also done to GLP and according to Directive 84/449/EEC, B.1, an LD50 value of >2,000 mg/kg (highest dose tested) was reported for fatty acids, C16-18 and C18-unstad., sodium salts (IUCLID, 2000f).

Any toxic effects, such as excessive salivation, diarrhoea, central nervous system depression, loss of reflex actions or coma, shown at higher doses, decrease in severity with an increase in the chain length of the fatty acid (Pi-Sunyer *et al.*, 1969). These reported effects are a result of the high doses administered and the fact that unlike humans rats don't have a vomiting reflex. Therefore, these high dose effects are not considered relevant for human exposure.

Summary: The available data indicate that the fatty acid salts exhibit a very low order of toxicity following acute exposure via the oral route.

Acute Inhalation Toxicity

The physical/chemical properties of fatty acid salts and their normal usage scenarios dictate that the primary route of exposure will be dermal which is consistent with the available data, with very limited data on the effects of acute inhalation of fatty acids or their salts located. In a study in which rats were exposed for 8 hours to saturated vapours of mixed isomers of decanoic acid (C10) no deaths were observed (IUCLID, 2000c).

Summary: The very limited data do not indicate that adverse effects would be expected following inhalation of fatty acid salts. In addition, this is not expected to be a significant route of exposure to these chemicals.

Acute Dermal Toxicity

As with the acute oral data, the available acute dermal toxicity data for the fatty acids (and their salts) provide a clear picture of low acute toxicity for this group of chemicals. All dermal LD50 values were greater than >2,000 mg/kg (BIBRA, 1996; IUCLID, 2000e; Clayton & Clayton, 1982; CIR, 1982, 1987).

In a dermal study in which concentrations of sodium stearate (C18) ranged between 10-25% in a 20% bath soap detergent form, the LD50 was >3000 mg/kg (highest dose tested) (CIR, 1982). In a dermal study in guinea pigs, application of commercial grade oleic acid (3,000 mg/kg) produced no deaths and no signs of toxicity. The number of applications was not stated (CIR, 1987).

Summary: The available data indicate that fatty acids (and their salts) are of low acute toxicity by the dermal route.

Table 4 – Acute toxicity of fatty acids and their salts

Test Material	CAS No.	Chain Length	Species /route	LD50 (mg/kg bw)	Reference
Decanoic acid (capric acid)	334-48-5	10	Rat/oral Rat/dermal Rat/inhal.	3,320 >5,000 No deaths with 8hr conc. vapour	IUCLID, 2000c BIBRA, 1996 BIBRA, 1996
Dodecanoic acid (lauric acid)	143-07-7	12	Rat/oral	12,000	Clayton & Clayton, 1982
Hexadecanoic acid (palmitic acid)	57-10-3	16	Rat/oral Rabbit/dermal	>10,000 >2,000	CIR, 1987 CIR, 1987
Octadecanoic acid (stearic acid)	57-11-4	18	Rat/oral Rabbit/dermal	>5,000 >5,000	Clayton & Clayton, 1982

Octadecanoic acid, Na salt (sodium stearate)	822-16-2	18	Rat/oral Rabbit/dermal Rabbit/dermal	>5,000 >10 ml/kg (formulation) >3,000	CIR, 1982 CIR, 1982 CIR, 1982
9-Octadecenoic acid (oleic acid)	112-80-1	18	Rat/oral Guinea pig/dermal	>19,243 >3,000	IUCLID, 2000e IUCLID, 2000e
Fatty acids, C14-18 and C16-18 unsat'd.	67701-06-8	16-18	Rat/oral Rat/oral	>5,000 >2,000	IUCLID, 2000f IUCLID, 2000f
Fatty acids, C18-22	90990-11-7	18-22	Rat/oral	>5,000	IUCLID, 2000g

5.2.1.2 Corrosiveness/Irritation

As all the data below have been taken from secondary published sources and not from the original studies, the data have been rated as class 4 (i.e. not assignable) using the method described by Klimisch *et al.* (1997), unless otherwise stated.

Skin Irritation

General

The primary concern with fatty acids is usually of an acute nature arising from the primary irritant effect, particularly of the short chain length acids (carbon chain lengths of C_{16} to C_{18} contribute to a low skin irritation effect). As the molecular weight increases and the water solubility decreases, the irritating capacity in general decreases (Clayton & Clayton, 1982; Madsen *et al.,* 2001).

Human Data

Studies in humans on the relative irritancy of free fatty acids (under occlusive patches) have revealed that the even numbered chain saturated free fatty acids of C_8 through C_{14} chain lengths are the most irritating (Stillman *et al.* 1975). With 0.5 M fatty acids, in most males (total of 10 subjects) there was an erythematous response by the tenth day at the sites of application of C_8 through C_{12}. There was a negligible response to the other fatty acids (C_{14} through C_{18}). By the eighth day of application of the 1.0 M saturated fatty acids, there was an erythematous response in all subjects at the sites of C_8 through C_{12}. There was a negligible response to fatty acids C_{14} through C_{18} (Stillman *et al.* 1975).

Approximately 0.5% aqueous solutions of the sodium salts of decanoic acid (C10) proved irritant to 3-40% of an unstated number of volunteers (no other details available) (BIBRA, 1996), while covered contact (22-24 hr) with 0.25% aqueous sodium decanoate caused weak reactions (presumably of an irritant nature) in two of 25 volunteers. Similar tests with 0.1% apparently elicited no responses (no other details available) (BIBRA, 1996).

Several soap bar formulations with concentrations of myristic acid (C14) of 10, 22.1 and 91.0% were tested for skin irritation using 16 human subjects. A 0.2 ml volume of 8%

aqueous preparations was applied to the ventral skin of the forearm under occlusive patches once daily for 5 days using the Frosch-Kligman soap chamber test. The formulations were considered "slightly" to "moderately irritating", and erythema scores were 1.41, 1.73 and 1.95 on a scale from 0 to 5 for the formulations containing 10, 22.1 and 91% myristic acid, respectively (CIR, 1987).

In a single insult occlusive patch test (SIOPT), commercial grade myristic acid produced no irritation in 17, mild erythema in 2, and moderate erythema in 1 of 20 panellists. The primary irritation index was 0.2 and myristic acid was considered "practically non-irritating" (CIR, 1987).

A single insult, 24 hour, occlusive patch test was conducted on 20 human subjects to determine the skin irritation potential of 0.5% sodium stearate in aqueous solution. The test solution produced no irritation in 16 subjects, and minimal to moderate erythema in four. The investigators concluded that sodium stearate (C18) "exhibited an acceptable and typical soap response" (CIR, 1982).

Animal Data

Tests in animals show that the skin irritation potential of fatty acids decreases with increasing chain length, such that the very short chain acids are corrosive, the medium chain length C10 is irritant, and C12 is minimally irritant. The longer chain lengths, C14 and above, are not irritant (CIR, 1987; Madsen *et al.* 2001). Also, the existence of unsaturated carbon chains and carbon chain lengths of C_{16} to C_{18} contribute to a low skin irritation effect (Madsen *et al.*, 2001).

In a study evaluating the toxicity of nine of the most commonly used commercial grades of fatty acids, both grades of octadecanoic acids (70% stearic acid, 30% palmitic acid; 45% stearic acid, 55% palmitic acid), myristic acid (C14) and palmitic acid (C16) gave a primary irritation index (PII) of 0. Capric acid (C10) proved to have higher irritancy with a PII of 4.60 (Briggs *et al.* 1976).

A SIOPT of commercial grade lauric acid (C12) (0.5 ml) to intact and abraded sites of the skin of 6 albino rabbits produced slight erythema at both sites after 24 hours which subsided by 72 hours, minimal oedema after 72 hours and a PII of 1.12. Blanching and some coriaceous tissue were noted at a few abraded sites (CIR, 1987).

A 50% solution of a coconut soap (for which lauric acid is the dominant acid) was patch tested in rabbits, guinea pigs and humans. Skin responses were graded at 4, 24 and 48 hours after each patch application. Irritancy judged at 4 hours was negligible in humans, slight in the guinea pig and moderate in the rabbit (Nixon *et al.* 1975).

Sodium soap (composition not stated) was not irritating (concentration used not stated) to rabbits in the acute dermal irritation/corrosion test conducted to GLP and according to OECD Guideline 404 (IUCLID, 2000f).

Pure fatty acid sodium soap was applied to the uncovered skin of rabbits, "hairless" mice and guinea pigs for prolonged periods (five days a week for four and a half weeks – that is 23 applications) in order to represent the exposure of skin during normal working conditions. Following the tests, the skin was removed from the animals and subjected to histological examination. No histological changes were noted and the test material was at the low end of

the irritancy scale. However, in patch tests, the fatty acid sodium salt had shown a medium irritancy grade, indicating that, given different conditions of exposure, the same chemical may behave in a different manner in contact with the skin (Brown, 1971). However occlusive patches were used, which is not relevant to the household cleaning product exposure conditions and so is of limited relevance.

In a SIOPT, commercial grade myristic acid (C14) (0.5 ml) was applied to intact and abraded sites on the skin of 6 albino rabbits and the PII was 0. In a "repeat open patch" test using commercial grade myristic acid (0.5 g), all 6 treated albino rabbits developed mild to moderate erythema from 24 to 72 hours. One rabbit developed very slight oedema after the 72-hour scoring (CIR, 1987).

A 100% concentration of sodium stearate (C18) applied as a single dose under occlusive conditions (not relevant to product use conditions) to six albino rabbits caused no irritation (PII = 0.0) (CIR, 1982). In a Draize test, 10-25% sodium stearate in a bath soap and detergent form caused mild irritation in 6 rabbits (PII = 2.2) (CIR, 1982). In a SIOPT of commercial grade stearic acid, transient minimal erythema and no oedema were noted in 9 albino rabbits after a 2-hour exposure period (CIR, 1987).

Summary: Tests in animals and humans show that the skin irritation potential of fatty acids and their salts decreases with increasing chain length, such that the medium chain lengths (C10) are irritant, C12 is minimally irritant and the longer chain lengths, C14 and above, are not irritant.

Eye Irritation

Human Data

Accidental contact of the human eye with soap or soap powder followed by rapid rinsing of the eyes is not expected to cause severe reactions and reactions observed resolve quickly without any permanent damage (Madsen *et al.* 2001).

Animal Data

As with skin irritation, tests in animals also show that the eye irritation potential of fatty acids decreases with increasing chain length, such that chain lengths C10 and C12 are irritant and the longer chain lengths, C14 and above are not irritant (Briggs *et al.* 1976; CIR, 1987).

Instillation of commercial grade lauric acid (C12) into the eyes of 6 albino rabbits produced corneal opacity, mild conjunctivitis, and iritis throughout the 72 hour observation period. An aqueous dilution (8.0%) of a product formulation containing 8.7% lauric acid produced no occular irritation in 6 albino rabbits. A 1% aqueous preparation of a soap formulation containing 1.95% lauric acid was not irritating to treated unrinsed eyes of rabbits (CIR, 1987).

Administration of commercial grade palmitic acid (C16) to the eyes of 6 albino rabbits produced no irritation. Mild to moderate ocular irritation was produced in rabbits by product formulations containing 19.4% palmitic acid (CIR, 1987).

In occular irritation studies, fatty acids (lauric, myristic, palmitic, oleic and stearic acid) alone and at concentrations ranging from 1 to 19.4% in cosmetic product formulations produced no to minimal irritation after single and multiple (daily, 14-day) instillations into the eyes of albino rabbits. Irritation was primarily in the form of very slight conjunctival erythema. A

single instillation of lauric acid (as commercially supplied) also produced corneal opacity and iritis (CIR, 1987).

In a study evaluating the toxicity of nine commercial grades of fatty acids, stearic acid (55%-C16, 45%-C18) produced mild conjunctival erythema in two of six rabbits at 24 and 48 hours while all signs of irritation had subsided completely in 72 hours. The other acids fell roughly into the following levels of irritancy; stearic acid (unsaturated) and myristic acid (C14); mild conjunctivitis with complete clearing in 72 hours. Lauric (C12) and capric (C10); corneal opacity and moderate conjunctivitis which did not subside in 72 hours (Briggs *et al.* 1976).

In a Draize eye test, a 100% concentration of sodium stearate (C18) was applied to 6 rabbits and resulted in negligible irritation. On day one, 2/6 conjunctivae appeared necrotic and the irritation scores corresponded to moderate irritation initially, but negligible irritation was recorded by day 4 (CIR, 1982).

Sodium soap was not irritating to rabbits in the acute eye irritation/corrosion test conducted to GLP and according to OECD Guideline 405 (no other details available) (IUCLID, 2000f).

(Z)-Docos-13-enoic acid (C22) was moderately irritating in the rabbit eye in an acute eye irritation/corrosion test conducted to GLP and according to OECD Guideline 405 (no other details available) (IUCLID, 2000e).

Summary: As with skin irritation, tests show that the eye irritation potential of fatty acids and their salts decreases with increasing chain lengths, such that chain lengths C10 and C12 are irritant and the longer chain lengths, C14 and above are not irritant.

5.2.1.3 Sensitisation

As all the data below have been taken from secondary published sources and not from the original studies, the data have been rated as class 4 (i.e. not assignable) using the method described by Klimisch *et al.* (1997), unless otherwise stated.

Human Data

In a skin sensitisation study in 28 volunteers, five 48-hour covered applications of 1% decanoic acid (C10) in petrolatum were made over a 10 day period. The results were negative since none gave positive reactions when challenged 10-14 days after the induction phase with a final 48-hour closed patch test using 1% in petrolatum (IUCLID, 2000a).

No local reactions indicative of sensitisation were seen in 100 subjects patch tested [under unspecified conditions] with a bath soap and detergent formulation containing 0.3-0.75% sodium stearate (BIBRA, 1990).

De Groot *et al.* (1988) reported that 25 subjects showed no sensitisation reactions when exposed to 5% stearic acid (C18) in petrolatum and a 1% aqueous sodium stearate solution.

Animal Data

In two Magnusson and Kligman guinea pig maximisation tests, carried out in conformity with OECD Guideline No. 406 and EC test method B.6 as described in the Annex of EC Directive 84/449/EEC, using two different types of mixed fatty acid sodium salts, no skin sensitisation potential was demonstrated in either material (CIR, 1982).

Sodium soap (composition not stated) did not produce sensitisation reactions (concentration used not stated) in the guinea pig maximisation test which was conducted to GLP and according to OECD Guideline 406 (IUCLID, 2000f).

Summary: Based on the available data, fatty acids and their salts are not expected to have any skin sensitisation potential.

5.2.1.4 Repeated Dose Toxicity

Introduction

In the UK, the Department of Health have set dietary reference values for fatty acids and recommend that total fatty acid intake should average 30 per cent of total dietary energy including alcohol (DoH, 1991). This equates to about 100 g of fatty acids per day or 1.7 g (1700 mg) of fatty acids per kg body weight per day.

The available data demonstrate the low toxicity of fatty acids and their salts, which is consistent with the long history of safe use in foods for both fatty acids and glycerides. Further evidence of their safe use in foods is the fact that a number of regulatory bodies have reviewed data not available to us and concluded that fatty acids and their salts are of low toxicity.

For example, several of the fatty acids are Generally Recognised as Safe (GRAS) by the U.S. Food and Drug Administration (US FDA). Substances that are listed as GRAS include: stearic acid; oleic acid and sodium palmitate. Stearic acid is also included by the Council of Europe (1974), at a level of 4000 ppm, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. In those studies where adverse effects were observed at high doses, these effects were considered to be the result of dietary imbalance in fat intake. With respect to the salts of fatty acids, it is expected that these materials possess similar characteristics as the free acid, for the reasons outlined in 5.2.1.

When decanoic acid (C10) was reviewed by the Joint FAO/WHO Expert Committee on Food Additives, no specific ADI was established, because it was held that the compound's presence in food would not represent a human health hazard. This view was based upon the occurrence of the acid in edible fats and oils with long food-use history as well as data on total daily intakes and the toxicology of the acid (JECFA, 1986). Decanoic was also considered "safe in use" by the EU's Scientific Committee for food in their consideration of Chemically Defined Flavouring Substances (SCF, 1995).

The fatty acids as a group are permitted as direct food additives (21 CFR 172.210, 172.860, 173.340); There are no limitations other than the observance of current good manufacturing practice (21 CFR 174.5) on the use of oleic acid and stearic acids as indirect food additives (21 CFR 175.105, 176.200 and 21 CFR 175.105, 175.300, respectively) (CIR, 1987).

In 1974, the WHO set an unlimited ADI for the salts of myristic (C14), palmitic (C16) and stearic (C18) acids. They stated that myristic, palmitic and stearic acid and their salts are normal products of the metabolism of fats and their metabolic fate is well established. Provided the contribution of the cations does not add excessively to the normal body load there is no need to consider the use of these substances in any different light to that of dietary fatty acids (WHO, 1974; JECFA, 1986).

In Western Europe and North America, the estimated overall consumption of dietary sodium chloride is 5-20 g/day (2-8 g of sodium per day), the average being 10 g/day (4 g of sodium) (WHO, 1996). In the UK dietary reference values (DRV) have been published for potassium. The reference nutrient intake (RNI) for adults is 3.5 g daily (DoH, 1991). Considering the high intake of these individual cations in the diet, exposure to fatty acid salts in household cleaning products will not add excessively to the normal body load.

Oral Toxicity

As all the data below have been taken from secondary published sources and not from the original studies, the data have been rated as class 4 (i.e. not assignable) using the method described by Klimisch *et al.* (1997), unless otherwise stated.

It is worth noting when considering the oral toxicity of fatty acids and their salts, that due to their innocuous nature, fats and oils are commonly used as controls and as vehicles in animal toxicity studies. For example, OECD Guideline 408 (repeated dose 90-day oral toxicity study in rodents) recommends the use of "a solution/emulsion in oil (e.g. corn oil)" as a vehicle where an aqueous vehicle is not suitable (OECD, 1993).

Fitzhugh *et al.* (1960) fed lauric acid (C12) to five male rats at the 10% level of their diet for 18 weeks. A control group of 5 males was fed concurrently. There were no observable clinical effects, no adverse effects on weight gain, nor was there any mortality. Gross organ pathology and comparison of individual organ weights showed no significant differences between the controls and test animals.

In a 24-week oral study, rats were fed doses of 15% oleic acid (C18) (approximately 7.5 g/kg body weight per day). Normal growth and general good health was reported in the rats and the NOAEL was reported to be >7,500 mg/kg body weight per day (IUCLID, 2000e).

Caprenin, a randomised triglyceride primarily comprising caprylic (C8), capric (C10), and behenic (C22) acids, was administered in a semi-purified diet to weanling Sprague-Dawley rats (25/sex/group) at dose levels of 5.23, 10.23 or 15.00% (w/w) for 91 days. Corn oil was added at 8.96, 5.91 and 3.00%, respectively, to provide essential fatty acids and digestible fat calories. Survival, clinical signs, body weight, feed consumption, feed efficiency, organ weights, organ-to-body-weight ratios, organ-to-brain-weight ratios, haematological values and clinical chemistry parameters were evaluated in all groups. Histopathology of a full complement of tissues was evaluated in the control group as well as the high-dose caprenin group. No significant differences in body weight gain were measured with the balanced caloric diets, although feed conversion efficiency was reduced in the high-dose caprenin group. No adverse effects from the ingestion of caprenin were detected. The authors concluded that the results establish a no-observable-adverse-effect level (NOAEL) of more than 15% (w/w) caprenin in the diet (or more than 83% of total dietary fat), which is equal to

a mean exposure level of more than 13.2 g/kg/day for male rats and more than 14.6 g/kg/day for female rats (Webb *et al.* 1993).

Dermal toxicity

In a subchronic study, no adverse effects were produced from topical application of myristic acid (C14) to rabbit skin. One-half ml of a 30% preparation of myristic acid in ether and propylene glycol (solvents at a 1:1 ratio in concentration) was massaged into the depilated skin of the flanks of 5 rabbits daily for 30 days. The opposite flank of the rabbits was depilated and treated with solvent only. No significant macroscopic changes were observed. Microscopic lesions included thinning of collagen fibres in the superficial layer of the dermis after 10 days and a loose dermal infiltrate of lymphomononuclear cells and histocytes after 20 and 30 days (CIR, 1987).

A formulation "bath soap and detergent" containing 10-25% sodium stearate (C18) was used to conduct a dermal toxicity study in rabbits. Formulations at a dose of 2.0 g/kg were applied for 3 months to the skin by syringe daily, five days a week. No "untoward reactions" were observed (CIR, 1982).

Summary: The available data demonstrate the low toxicity of fatty acids and their salts, which is consistent with their long history of safe use in foods and the fact that many of the fatty acids are listed as GRAS.

5.2.1.5 Genetic Toxicity

In Vitro

Fatty acids are negative in *in vitro* bacterial systems used in the Ames test (BIBRA, 1988; BIBRA, 1996). In addition, saturated fatty acids up to and including C12, and the unsaturated acid C18:1, have shown inhibition of the mutagenic activity of N-nitrosodialkylamines on *Eschericha coli* (Negishi *et al.* 1984). Also, fatty acids from C12 up to C19 have shown anticlastogenic effects in the chromosome aberration test (Renner, 1986).

Capric acid (C10) produced negative results in the Ames test using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 at concentrations ranging from 0-666 µg/plate, with and without metabolic activation (IUCLID, 2000c). It also produced negative results in the *Escherichia coli* reverse mutation assay without activation (IUCLID, 2000c).

Lauric acid (C12) has shown negative results in the Ames test using *Salmonella typhimurium* with and without metabolic activation at concentrations up to 2500 µg/plate. (IUCLID, 2000a).

Stearic acid (C18) was tested for mutagenicity using the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. Spot tests were performed using 50 mg/ml stearic acid suspensions in distilled water (50 µg/plate) with and without microsomal activation from hepatic S9 fractions from rats induced with Aroclor 1254 (50 µl/plate). Stearic acid had no mutagenic activity over background in the strains tested with and without metabolic activation (CIR, 1987).

A solution of 99.9% pure oleic acid (C18) was tested in the Ames test using *Salmonella typhimurium* strains TA98, TA100 and TA1535. It was tested at concentrations of 1, 5, 10, 50, 100, 500, 1000 and 5000 µg/plate with and without metabolic activation and produced negative results (IUCLID, 2000e). In the *Escherichia coli* reverse mutation assay using *E. coli* strain WP2uvrA, concentrations of 1, 5, 10, 50, 100, 500 1,000 and 5,000 ug/plate, with and without activation, a solution of 99.9% pure oleic acid also produced negative results. It has also produced negative results in *Saccharomyces cerevisiae* and in DNA and damage repair assays using *Bacillus subtilis* (BIBRA, 1986; IUCLID, 2000e).

Fatty acids, C18-22 produced negative results with and without metabolic activation in the Ames test at concentrations ranging between 4-1250 µg/plate using *Salmonella typhimurium* (IUCLID, 2000g).

In Vivo

No *in vivo* mutagenicity data was located. However, there is no association between the normal intake of large amounts of fatty acids in the diet and mutagenicity. Therefore, the small increase via exposure to fatty acids and their salts in household cleaning products would also be considered not to increase the risk of mutagenicity.

Summary: Based on the available data which show lack of mutagenicity under in vitro conditions, fatty acids and their salts are not mutagenic.

5.2.1.6 Carcinogenicity

Numerous mechanisms for the role of dietary fat in tumourigenesis have been studied and reviewed (e.g. Welsch and Aylsworth, 1983; Diamond *et al.* 1980; Woutersen *et al. 1999*).

In a two year study by Hiasa *et al.* (1985), groups of 50 male and 50 female F344 rats, initially 7 weeks old, were given sodium oleate (C18) for 108-weeks at concentrations of 2.5 and 5.0% in the drinking water. Control rats were given distilled water only. Sodium oleate slightly reduced the body-weight gain in the males, but not in the females, while water consumption was slightly depressed in the females, but not in the males. A slight depression in serum bilirubin of males in the 5.0% group was the only statistically significant finding ($p<0.05$) in the serum and urine analyses and in the haematological determinations of treated and control groups.

In the groups given 5% sodium oleate, the mean weights of the liver of males and of the heart, pancreas and adrenals of females were significantly lower ($p<0.05$) than those of the respective controls, while the weight of the thymus in the females was significantly higher ($p<0.05$).

Tumours developed in various organs, but there was no significant difference between their incidence in oleate-treated and control rats, apart from the pancreatic tumours (0% - 0/41M, 1/43F; 2.5% - 4/40M, 1/39F; 5% - 7/45M, 1/45F). However, the incidence of pancreatic tumours was within the normal background level for this strain of rat and the result was attributed to the unusual absence of pancreatic tumours in the control rat. Based on a weight of evidence approach including consideration of the historical range of pancreatic tumours in

these rats it was concluded that sodium oleate does not induce tumours when given orally to rats (Hiasa *at al.* 1985). *(Klimisch study rating – 2 i.e. reliable with restrictions)*

No evidence of carcinogenicity was seen in rats receiving 25% oleic acid (C18) in the diet (approximately 12.5 g/kg bodyweight per day) for 20 weeks (IUCLID, 2000e).

Also, due to their innocuous nature, fats and oils are commonly used as controls and as vehicles in animal toxicity studies. This along with the long history of safe use of the fatty acids and their salts, as well as the GRAS status for many of these chemicals, indicate no potential for carcinogenicity of these chemicals.

Summary: Based on the available data as well as the long history of safe use of these chemicals, it is not considered that the fatty acid salts possess carcinogenic activity, as a result of their use in household cleaning products.

5.2.1.7 Toxicity to Reproduction

15% oleic acid (C18) in the diet [approximately 7.5 g/kg bw/day] (the only dose tested) for 10 to 16 weeks did not affect the fertility of male rats but appeared to impair reproductive capacity in the females by interfering with parturition and mammary gland development. Mortality in the offspring was increased. No other information is available (BIBRA, 1986; IUCLID, 2000e).

Hendrich *et al.* (1993) conducted a study in which three generations of CBA/2 and C57Bl/6 mice were reared on semipurified diets containing 8.6% crude *Cuphea* oil. The *Cuphea* oil contained 76% capric acid (C10 fatty acid). Males of each generation were housed individually and fed for 13-weeks. Food intakes and body weights were measured weekly. Some males of each generation were fed for 5-12 months. Because *Cuphea* oil was in short supply, the F1 generation of the C57B1/6 strain were fed for 10 months, the F2 generation was fed for 8 months and the F3 generation was fed for 5 months; whereas in the CBA/2 strain, the F1 generation was fed for 11-12 months, the F2 generation was fed for 9-11 months and the F3 generation was fed for 6-8 months. The diet containing *Cuphea* oil did not impair reproductive parameters or cause any pathology in the mouse tissues examined. *Cuphea* oil moderately suppressed body weights and food intakes of mice in some groups between 4 and 13-weeks of age, but had no long-term effects on body weight, food intake or cholesterol status.

Again, the long history of safe use of these acids and their related glycerides and food oils, as well as the GRAS status for several of the fatty acids and their salts, indicate the low potential for reproductive toxicity of these chemicals.

Also, it is worth bearing in mind when considering the reproductive toxicity of fatty acids and their salts, that due to their innocuous nature, fats and oils are commonly used as controls and as vehicles in animal toxicity studies. For example, OECD Guideline 408 (repeated dose 90-day oral toxicity study in rodents) recommends the use of "a solution/emulsion in oil (e.g. corn oil)" as a vehicle where an aqueous vehicle is not suitable (OECD, 1993).

Summary: A three-generation reproductive study on a C10 fatty did not produce any reproductive effects. This along with the long history of safe use of the fatty acids indicate the low potential for reproductive toxicity of these chemicals.

5.2.1.8 Developmental Toxicity / Teratogenicity

Ishii *et al.* (1990) studied the effects of natural soap on the development of mouse embryos cultured *in vitro.* They found that there was no effect on embryo development at concentrations up to 0.05%. More than 0.05% natural soap gave rise to precipitates in the culture medium.

In a study by Palmer *et al.* (1975) 'soap' was examined for embryotoxic and teratogenic potential following percutaneous administration. Groups of rats and mice were treated with concentrations of 0.3, 3 and 30% of a standard soap solution. The formulated solutions were applied to the skin at the rate of 0.5 ml/rat or mouse per day with rats being dosed on days 2-15 and mice on days 2-13 of gestation. The concentrations of 0.3, 3 and 30% corresponded to nominal doses of 6, 60 and 600 mg/kg/day in rats and 50, 500, and 5000 mg/kg/day in mice.

In rats and mice treated with 30% soap solution the initial reaction consisted of erythema and oedema with peak response being attained by day 6 in mice and days 4 to 5 in rats. Clearly defined local reactions were not apparent at lower concentrations of soap. Weight loss, or marked retardation of bodyweight gain, reaching a peak at day 6 was observed for mice receiving soap at 3 or 30%. Rats were not conclusively affected by treatment as, even at the highest dose of 30%, weight gain was only slightly lower than that of controls. The marked reduction in numbers of litters containing viable young (due to non-pregnancy and/or total litter loss) recorded among mice treated with soap at 3 and 30% was considered secondary to maternal toxicity.

Effects on litter parameters were generally restricted to dosages causing marked maternal toxicity in mice, the principal effects being higher foetal loss (with consequent reduction in viable litter size) arising from an increased incidence of total litter loss. When dams showing total litter loss were excluded from the calculations, litter parameters were not unduly different from those of controls. At dosages that were non-toxic or only slightly toxic to the dam, litter parameters were not adversely affected as the only significant deviations from control values were in respect of the higher mean pup weights observed in rats at 0.3, 3 and 30% soap and the consequent higher litter weights at 0.3 or 30%. The incidences of major malformations, minor visceral or skeletal anomalies and skeletal variants were not statistically significant and produced no evidence of specific teratogenicity, even at maternally toxic dosages (Palmer *et al.* 1975).

It is important to bear in mind when considering the toxicity of fatty acids and their salts that due to their innocuous nature, fats and oils are commonly used as controls and as vehicles in animal toxicity studies. For example OECD Guideline 408 recommends the use of "a solution/emulsion in oil (e.g. corn oil)" where an aqueous vehicle is not suitable (OECD, 1993).

Summary: Available data do not provide evidence of significant developmental toxicity of fatty acid salts. Again, the long history of safe use of the fatty acids and their related glycerides and food oils, as well as the GRAS status for several members of the fatty acids and their salts, indicate the low potential for developmental toxicity of these chemicals.

5.2.1.9 Toxicokinetics

Fatty acids and their salts

Fatty acids are an endogenous part of every living cell and are an essential dietary requirement. They are absorbed, digested, and transported in animals and humans. Proposed mechanisms for fatty acid uptake by different tissues range from passive diffusion to facilitated diffusion or a combination of both (Abumrad *et al.* 1984; Harris *et al*., 1980). Radioactivity from labelled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph (CIR, 1987).

Fatty acids taken up by the tissues can either be stored in the form of triglycerides (98% of which occurs in adipose tissue depots) or they can be oxidised for energy via the β-oxidation and tricarboxylic acid cycle pathways of catabolism (Masoro, 1977). The β-oxidation of fatty acids occurs in most vertebrate tissues utilising an enzyme complex for the series of oxidation and hydration reactions resulting in the cleavage of acetate groups as acetyl CoA. β-oxidation essentially reduces the alkyl chain length by 2 carbon atoms with the release of acetic acid. This leaves another carboxyl group on the shortened alkyl chain for subsequent further β-oxidation. An additional isomerisation reaction is required for the complete catabolism of oleic acid. Alternate oxidation pathways can be found in the liver (ω-oxidation) and the brain (α-oxidation) (CIR, 1987).

Long chain, saturated fatty acids are less readily absorbed than unsaturated or short chain acids. Stearic acid is the most poorly absorbed of the common fatty acids (Clayton & Clayton, 1982; Opdyke, 1979). Several investigators have also found increasing fatty acid chain length slightly decreased their digestibility (CIR, 1987).

Howes (1975) examined the turnover of [^{14}C] surfactants in the rat and found that at 6h after administration, the C10 and C12 soaps were readily metabolised and the main route of excretion was as $^{14}CO_2$. The C14 soap was readily incorporated into the body and the ^{14}C excretion was slow. The C16 and C18 soaps showed some metabolism with subsequent $^{14}CO_2$ excretion but most of the ^{14}C was recovered in the carcass at 6 hours.

Sodium

Sodium is an essential element in the diet but a high intake of sodium has been associated with cardio-vascular diseases. Sodium is readily absorbed throughout the small intestine and is subject to rapid exchange by the large majority of cells in the body. The main regulation of the body concentrations of sodium takes place in the kidney. The consumer exposure to household cleaning products results in negligible exposure to sodium (compared to dietary uptake) and therefore elevation of the amounts of sodium are not expected to occur as a result of exposure to fatty acid sodium salts in cleaning products or their residues.

Potassium

Potassium salts are generally readily absorbed from the gastro-intestinal tract. Potassium is excreted by the kidneys; it is secreted in the distal tubules in exchange for sodium or hydrogen ions. The capacity of the kidneys to conserve potassium is poor and urinary excretion of potassium continues even when there is severe depletion. Some potassium is excreted in the faeces and small amounts may also be present in saliva, sweat, bile, and pancreatic juice (Martindale, 1996). Again, exposure to cleaning products containing potassium salts will not increase the body burden of potassium.

Dermal Penetration

It has been shown that the greatest skin penetration of the human epidermis was with C_{10} and C_{12} soaps and the rate of percutaneous absorption of sodium laurate is greater than that of most other anionic surfactants. (Prottey and Ferguson, 1975; Madsen *et al*., 2001; Howes, 1975).

Howes (1975) studied the percutaneous absorption of some anionic surfactants and showed that sodium decanoate was reportedly poorly absorbed through the skin of rats when in uncovered contact for 15 minutes. Penetration through excised human skin proceeded at a rate similar to that for excised rat skin for up to 6 hours; thereafter absorption through human skin was slightly quicker. Also, for the three soaps which penetrated the skin (C10, C12 and C14) there was a lag time of 1 hour before any measurable penetration occurred, but after this the rate of penetration steadily increased. Howes also calculated from human epidermal studies *in vitro* that only small amounts of the C10, C12 and C14 soaps would be likely to penetrate the skin from a 15 minute wash and rinse *in vivo*. The low penetration rates of the C16 and C18 soaps suggests that little or none of these would penetrate from a 15 minute wash and rinse *in vivo*.

5.2.2 Identification of critical endpoints

5.2.2.1 Overview on Hazard identification

Fatty acid salts are considered to be of low toxicity after oral and dermal exposure. The estimated LD50 for chemicals in this class is greater than 2,000 mg/kg via the oral route and greater than 3,000 mg/kg via the dermal route. The acute inhalation data are limited but this is not expected to be a significant route of exposure to these chemicals.

The skin and eye irritation potential of fatty acids and their salts is chain length dependent. Tests in animals and humans show that the irritation potential decreases with increasing chain length such that C12 is minimally irritant and the longer chain lengths, C14 and above, are not irritant.

The available data support the hypothesis that fatty acid salts are not skin sensitisers.

The available oral and dermal repeated dose toxicity studies demonstrate the low toxicity of fatty acids and their salts. This is consistent with the long history of safe use in foods for both fatty acids and glycerides. Further evidence of their safe use in foods is the Generally Recognised As Safe (GRAS) status of several of the fatty acids. Provided the cation (sodium or potassium) does not add excessively to the normal body load, which will not be the case

following exposure to fatty acid salts in household cleaning products, then these substances are not considered hazardous.

Fatty acid salts are not considered to be mutagenic, genotoxic or carcinogenic, and are not expected to be reproductive or developmental toxicants, which again is consistent with their long history of safe use.

5.2.2.2 Rationale for identification of critical endpoints

Dermal exposure to fatty acid salts is the main exposure route for consumers using household cleaning products and subsequently, dermal effects such as skin irritation and sensitisation as well as long term dermal toxicity have to be considered with regard to the human risk assessment. A substantial amount of data are available addressing skin irritation and skin sensitisation potential for fatty acids and their salt solutions and fatty acid salts containing consumer product formulations. Dermal penetration studies have shown that soaps can penetrate the skin to varying extents and become available systemically and so the effects following long term exposure via the oral route have also been considered.

The eye irritation potential has to be considered, since accidental spillage may cause eye contact of fatty acid salts. For the assessment of accidental exposures via ingestion, the data on acute oral toxicity are considered.

5.2.2.3 Determination of NOAEL or quantitative evaluation of data

Considering the fact that the WHO felt it unnecessary to set an ADI for the salts of myristic, palmitic and stearic acids and since several of the fatty acids are listed as GRAS it was considered unnecessary to define a NOAEL that would be representative for the fatty acid salts as a group for use in the margin of exposure calculations.

5.3 Risk Assessment

5.3.1 Margin of Exposure Calculation

5.3.1.1 Exposure scenario: direct skin contact from hand washed laundry

From the exposure calculation (section 5.1.3.1), the dermal exposure to fatty acid salts as a result of hand washing was estimated to be 1.4×10^{-4} mg/kg body weight (0.1 μg/kg body weight). Given the fact that several of the fatty acids and their salts, including stearic acid, oleic acid and sodium palmitate are listed as GRAS, and since the WHO set an unlimited ADI

for the salts of myristic, palmitic and stearic acids, it is not expected that the limited exposure to fatty acids salts from hand washing will result in any adverse effects.

As stated in Section 5.2.1.2, tests in animals and humans show that the skin irritation potential of fatty acid decreases with increasing length such that the longer chain lengths, C14 and above are not irritant and the existence of unsaturated carbon chains and carbon chain lengths of C16 to C18 contribute to a low skin irritation effect. As the majority of the carbon chain lengths of the soaps considered in this assessment were C12 and above (98.9%) and considering the relatively short contact time and low exposure, it is not expected that direct skin contact with fatty acid salts from hand washed laundry will cause irritation in consumers.

5.3.1.2 Exposure scenario: direct skin contact from contact via pretreatment of clothes

From the exposure calculation (section 5.1.3.1), the dermal exposure to fatty acid salts as a result of contact via pretreatment of clothes was estimated to be 2.0×10^{-3} mg/kg body weight (2.0 μg/kg body weight). As stated above, the fact that several of the fatty acids and their salts are listed as GRAS, and since the WHO set an unlimited ADI for the salts of myristic, palmitic and stearic acids, it is not expected that the limited exposure to fatty acids salts from laundry pretreatment will result in any adverse effects.

As stated above, the majority of the carbon chain lengths of the soaps considered in this assessment were C12 and above (98.9%) which have low skin irritation potential. Therefore, considering the relatively short contact time and low exposure, it is not expected that direct skin contact with fatty acid salts from pretreatment of clothes will cause irritation in consumers.

5.3.1.3 Exposure scenario: indirect skin contact from transfer from clothing

From the exposure calculation (section 5.1.3.1), the dermal exposure to fatty acid salts as a result of transfer from clothing was estimated to be 7.9×10^{-4} mg/kg body weight (0.79 μg/kg body weight). Given the fact that several of the fatty acids and their salts are listed as GRAS, and since the WHO set an unlimited ADI for the salts of myristic, palmitic and stearic acids, it is not expected that the limited exposure to fatty acids salts from hand washing will result in any adverse effects.

The majority of the carbon chain lengths of the soaps considered in this assessment were C12 and above (98.9%) which have low skin irritation potential. Therefore, considering the relatively short contact time and low exposure, it is not expected that indirect skin contact with fatty acid salts from transfer from clothing will cause irritation in consumers.

5.3.1.4 Exposure scenario: Inhalation of laundry powder dust & inhalation of sprays generated by aerosols

From the exposure calculation (section 5.1.3.1), the total inhalation exposure to fatty acid salts as a result of pouring washing powder into a machine and inhaling aerosols generated by spray cleaners was estimated to be 2.0×10^{-6} mg/kg body weight (0.002 μg/kg body weight).

Although the inhalation data on fatty acid salts are limited, given the low order of toxicity of these chemicals and the fact that the exposure is orders of magnitude below the general threshold of no concern of 1.5 μg /day as defined by Munro (1998), then inhalation exposure to fatty acids will not be a concern.

5.3.1.5 Exposure scenario: Accidental Exposure

The acute oral toxicity data for a range of fatty acid salts have shown that the LD50 is greater than 2000 mg/kg. This level of toxicity is generally considered as low. Based on such an LD50 value, the uptake of fatty acid salts must be extremely high to reach acute lethal effects. Although fatty acid salts have been used for a very long time in a variety of applications, acute cases of oral poisoning have not been reported in the literature. Therefore, it appears as if occasional accidental ingestion of a few milligrams of fatty acid salts or intentional overexposure to fatty acid salts via the oral route does not result in adverse effects, which is not surprising given the low toxicity profile of these chemicals.

The available information show that the skin and eye irritation potential of fatty acids and their salts decreases with increasing chain length, such that C12 is minimally irritant and the longer chain lengths C14 and above are not irritant. As 98.9% of the carbon chain length distribution for chemicals in this assessment consist of C12 chain lengths and above (see Section 3.4), the fatty acid salts used in household cleaning products will not induce skin or eye irritation following the limited exposure to the products containing these materials. Also, fatty acid salts do not induce skin sensitisation in those exposed. Nevertheless, eye and prolonged skin contact with neat products should be avoided as other surfactants present in the formulations could induce irritation effects. In the case of eye contact, immediate rinsing with plenty of water is also recommended. This immediate action has been shown in animal experiments to minimise irritation effects.

Considering the fact that soaps are almost completely removed from wastewater the exposure via drinking water is expected to be insignificant.

5.3.1.6 Exposure scenario: Total Consumer Exposure

In a worst case scenario, the consumer exposure from direct and indirect skin contact of neat or diluted fatty acid salts containing product, inhalation of laundry powder dust and spray cleaners containing fatty acid salts and from accidental ingestion, results in an estimated systemic fatty acid salt dose of 2.9×10^{-3} mg/kg (2.9 μg/kg) body weight per day.

Although many of the fatty acids and their salts are listed as GRAS and the WHO set an unlimited ADI for the salts of myristic, palmitic and stearic acids, in order to illustrate the large margin of exposure between exposure to fatty acid salts in household cleaning products and adverse effects, a margin of exposure can be calculated for fatty acids using a LOAEL of approximately 7500 mg/kg body weight per day for oleic acid (C18) (BIBRA, 1986), as representative of this group for systemic toxicity. This was from a dietary study in which the fertility of male rats was not affected, but the reproductive capacity of females did seem to be impaired and the morality in the offspring was increased. Using this LOAEL and applying an

uncertainty factor of 10 to obtain a NOAEL, 750 mg/kg can be calculated as the NOAEL. Using this, the margin of exposure can be calculated as:-

MOE_{total}	**= systemic oral NOAEL / estimated total systemic dose**
	= 750 mg/kg bw per day / 2.9 x 10^{-3} mg/kg bw per day
MOE_{total}	= **258,620**

5.3.2 Risk Characterisation

The detailed consideration of the different exposure scenarios for the handling and use of detergent products containing fatty acid salts did not reveal any risk for consumers from the use of these materials. The estimated human exposure to fatty acid salts shows a Margin of Exposure of 258,620. This is an extremely large margin of exposure and was calculated from the total exposure scenarios, which is an unrealistic situation and will be unlikely in an "in-use" situation, making the margin of exposure even more conservative.

The determined MOE is certainly large enough to be reassuring with regard to the relatively small variability of the hazard data on which it is based. The MOE is based on worst case exposure assumptions and the true consumer exposure is highly likely to be significantly lower than presented here.

In the UK, the Department of Health have set dietary reference values for fatty acids and recommend that total fatty acid intake should average 30 per cent of total dietary energy including alcohol (DoH, 1991). This equates to about 100 g of fatty acids per day or 1.7 g of fatty acids per kg body weight (1700 mg/kg body weight per day). The total consumer exposure to fatty acids and their salts from the use of household cleaning products was calculated to be 2.9 x 10^{-3} (0.0029 mg/kg) body weight per day. This exposure is several orders of magnitude below that which is recommended via the diet, further illustrating the point that exposure to fatty acid salts in household cleaning products does not pose any risk to consumers.

Despite the fact that this assessment was based largely on secondary data, it is clear from the extremely large MOE that further experimental data are not required.

The available toxicological information indicates that fatty acid salts are of low acute toxicity after oral and dermal exposure.

The skin and eye irritation potential of fatty acids and their salts is chain length dependent and decreases with increasing chain length. They are not skin sensitisers. The available oral and dermal repeated dose toxicity studies demonstrate the low toxicity of fatty acids and their salts. This is consistent with the long history of safe use in foods for both fatty acids and glycerides. Also, the fatty acid salts are not considered to be mutagenic, genotoxic or carcinogenic, and are not expected to be reproductive or developmental toxicants, which again is consistent with their long history of safe use.

Accidental ingestion of a fatty acid salt containing detergent product is not expected to result in any significant adverse health effect. This assessment is based on toxicological data

demonstrating the low acute oral toxicity of fatty acid salts and the fact that not a single fatality has been reported in the UK, following accidental ingestion of detergents containing fatty acid salts.

In summary, the use of fatty acid salts in consumer products such as laundry and cleaning detergents does not raise any safety concerns with regard to systemic or local toxicity.

5.4 Discussion and Conclusions

Consumers are exposed to fatty acid salts through their presence in laundry and cleaning products mainly via the dermal route, and to a much lesser extent via the oral and inhalation routes. Skin exposure occurs mainly in hand-washed laundry, laundry pre-treatment and through fatty acid salt residues in the fabric after the washing cycle. Consumers may be orally exposed to fatty acid salts through accidental ingestion or via intentional over-exposure. The consumer aggregate exposure to fatty acid salts has been estimated to be 2.9×10^{-3} mg/kg (2.9 μg/kg) body weight per day.

The available toxicological data demonstrates that fatty acid salts are neither genotoxic, mutagenic or carcinogenic, nor was there any evidence of reproductive toxicity (except at very high exposure levels) or developmental or teratogenic effects in animals. In addition, the fatty acids and their salts have a long history of safe use in foods. Further evidence of their safe use in foods is the GRAS status of several of the fatty acids. The WHO also set an unlimited ADI for the salts of myristic, palmitic and stearic acids and stated that myristic, palmitic and stearic acid and their salts are normal products of the metabolism of fats. Their metabolic fate after absorption is well established. Provided the contribution of the cations does not add excessively to the normal body load, which would not be the case following exposure to fatty acid salts in household cleaning products, then there is no reason to consider these substances more hazardous than dietary fatty acids.

The comparison of the aggregate exposure from the various scenarios with a NOAEL from a study on oleic acid, results in a MOE of 258,620. The study used to derive the NOAEL is from a secondary source preventing its quality to be checked. Also, the study reported a LOAEL (not a NOAEL), for which an uncertainty factor of 10 was applied to calculate the NOAEL, and the study was conducted on oleic acid (a C18 chain length fatty acid) and may not be totally representative of this group of chemicals. However, it nonetheless illustrates the large MOE that exists between exposure to a member of this group of chemicals and any adverse effects they may cause. Further reassurance is provided by WHO's decision to set "an unlimited ADI" for the salts of a number of specified fatty acids, as outlined above.

In the UK, the recommended total fatty acid intake is about 100 g of fatty acids per day or 1.7 g of fatty acids per kg body weight (1700 mg/kg body weight per day), while the total consumer exposure to fatty acids and their salts from the use of household cleaning products was calculated to be 2.9×10^{-3} (0.003 mg/kg) body weight per day. This extremely large difference in exposure further highlights the fact that exposure to fatty acid salts in household cleaning products is of no concern to the consumer.

Based on normal habits and uses, the consumer exposure to fatty acid salts by inhalation, oral uptake and skin contact is negligible and therefore the associated risk is also negligible.

In summary, the human health risk assessment has demonstrated that the use of fatty acid salts in household laundry and cleaning detergents is safe and does not cause concern with regard to consumer use.

6. References

Abumrad, N.A., Park, J.H. and Park, C.R. (1984) Permeation of long-chain fatty acids into adipocytes. Kinetics, specificity and evidence for involvement off a membrane protein. *J. Biol. Chem.* **259**(14): 8945-8953.

AISE (2002) HERA/Task Forces/Human/0011 Habits and Uses Table – Draft consolidated company data.

BASF (2001) High Production Volume Chemical Challenge Program. Robust summaries and test plan for Dicamba and Acifluorfen Intermediates category. Submitted by: BASF Corporation, December 20, 2001. Available at: http:www.epa.gov/chemrtk/dicambaa/c13451.pdf

BIBRA (1986) Toxicity Profile. Oleic acid. The British Industrial Biological Research Association. Surrey, UK.

BIBRA (1988) Toxicity Profile. n-Octanoic acid and its sodium and potassium salts. The British Industrial Biological Research Association. Surrey, UK.

BIBRA (1990) Toxicity Profile. Sodium stearate. The British Industrial Biological Research Association. Surrey, UK.

BIBRA (1996) Toxicity Profile. n-Decanoic acid (and its sodium and potassium salts). The British Industrial Biological Research Association. Surrey, UK.

BKH (1994). Environmental data review of soap. Final Report. Nederlandse Vereniging Van Zeepfabrikanten NVZ. NVZ in cooperation with European surfactant industry. BKH consulting engineers, bongaerts, Kuyper and huiswaard.

Briggs, G.B., Doyle, R.L. and Young, J.A. (1976) Safety studies on a series of fatty acids. *Am. Ind. Hyg. Assoc. J.*, **37**: 251-252.

Brown, V.K.H. (1971) A comparison of predictive irritation tests with surfactants on human and animal skin. *J. Soc. Cosmet. Chem.* **22**: 411-420.

Bruschweiler, H., Schwager, F., Gamperle, H. (1988) Seife – Waschveralten, Wascheffekte und Abbabarkeit, Seifen – Ole – Fette – Wasche, 114, 301-307.

CIR (1982) Final report of the safety assessment of lithium stearate, aluminum distearate, aluminum stearate, aluminum tristearate, ammonium stearate, calcium stearate, magnesium stearate, potassium stearate, sodium stearate, and zinc stearate. *JACT*, **1**(2): 143-177.

CIR (1987) Final report of the safety assessment for oleic acid, lauric acid, palmitic acid, myristic acid, stearic acid. Prepared by the Expert Panel of the Cosmetic Ingredient Review, Washington D.C.

Clayton, G.D. and Clayton, F.E. (1982) Patty's Industrial Hygiene and Toxicology. Volume 2C: Toxicology. 3rd Revised Edition. John Wiley & Sons: New York.

Council of Europe (1974) Natural Flavouring Substances, their sources and added artificial falvouring substances. Partial agreement in the Social and Public Health Field. List 1, No. 15, p127. Strasbourg.

De Groot, A.C., Van Der Meeren, H.L.M. and Weyland, J.W. (1988) Cosmetic allergy from stearic acid and glyceryl stearate. *Contact Dermatitis*, **19**(1): 77-78.

Diamond, L., O'Brien, T.G. and Baird, W.M. (1980) Tumour promoters and the mechanism of tumour promotion. *Adv. Canc. Res.* **32**: 1-74.

DoH (1991). Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO. 1991.

DTI (1998) Home accident surveillance system including leisure activities. 22nd Annual Report, 1998 Data. Department of Trade and Industry, UK.

European Economic Community (EEC), Directive 84/449/EEC, Annex V of the EEC Directive 67/548/EEC, Part B: Methods for Determination of Toxicity; B.4: "Acute Toxicity – skin irritation", EEC Publication No. L251, September 1984.

EU TGD (1996) Technical Guidance Document (Parts I-IV) in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No. 1488/94 on Risk Assessment for Existing Substances.

Fitzhugh, O.G., Schouboe, P.J. and Nelson, A.A. (1960) Oral toxicities of lauric acid and certain lauric acid derivatives. *Toxicology and Applied Pharmacology*, **2**: 59-67.

Harris, P., Gloster, J.A. and Ward, B.J. (1980) Transport of fatty acids in the heart. *Arch. Mal. Coeur* **73**(6): 595-598.

Hendrich, S. Lii, C.K. Myers, R. and Dupont, J. (1993) Effects of feeding *Cuphea* oil to three generations of CBA/2 and C57B1/6 mice. *JAOCS*, **70**(8): 797-802.

Hiasa, Y., Konishi, N., Kitahori Y. and Shimoyama, T. (1985) Carcinogenicity study of a commercial sodium oleate in Fischer rats. *Food and Chemical Toxicology*, **23**(6): 619-623.

Howes, D. (1975) The percutaneous absorption of some anionic surfactants. *J. Soc. Cosmet. Chem.* **26**: 47-63.

Ishii, Y., Samejima, Y., Saji, F. and Nomura, T. (1990) Effect of alcohol sulfate, linear alkylbenzene sulfonate and natural soap on the development of fertilised eggs of the mouse *in vitro*. *Mutation Research,* **242**: 151-155.

IUCLID (2000c) IUCLID Dataset on Decanoic acid. Creation Date 18 February 2000. European Chemical Bureau, Ispra, Italy.

IUCLID (2000e) IUCLID Dataset on Fatty acids, rape oil. Creation Date 19 February 2000. European Chemical Bureau, Ispra, Italy.

IUCLID (2000f) IUCLID Dataset on Fatty acids, C16-18 and C18-unsatd., sodium salts. Creation Date 19 February 2000. European Chemical Bureau, Ispra, Italy.

IUCLID (2000g) IUCLID Dataset on Fatty acids, C18-22. Creation Date 19 February 2000. European Chemical Bureau, Ispra, Italy.

JECFA (1986). 29th Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 733.

Klimisch, H.J., Andreae, M., Tillmann, U. (1997) A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*, **25**(1): 1-5.

Madsen, T., Buchardt Boyd, H., Nylén, D., Rathmann Pedersen, A., Petersen, G.I., and Simonsen, F. (2001) Environmental and Health Assessment of Substances in Household Detergents and Cosmetic Detergent Products. Environment Project No. 615, MiljØprojekt, MiljØstyrelsen.

Masoro, E.J. (1977) Lipids and lipid metabolism. *Ann. Rev. Physiol.* **39**: 301-321.

Martindale (1996) The Extra Pharmacopoeia. Evaluated information on the worlds drugs and medicines. Reynolds, J.E.F. (Ed). 31st Edition. The Royal Pharmaceutical Society.

McMurry, J., (1984) Organic Chemistry, Brooks/Cole Publishing Company, Monterey, California.

Moreno, A., Bravo, J., Ferrer, J., Bengoechea, C. (1993) Monitoring of soap in different environmental compartments, Petresa. Lecture presented at Giornate C.I.D. Venice.

Munro, I.C., Kroes, R. (1998) Application of thresholds of toxicological concern in the safety evaluation of certain flavouring substances. Annex 5, WHO Food Additive Series, No. 40.

Negishi, T. and Hayatsu, H. (1984) Inhibitory effect of saturated fatty acids on the mutagenicity of N-nitrosodimethylamine. *Mutation Research* **135**: 87-96.

Nixon, G.A. Tyson, C.A. and Wertz, W.C. (1975) Interspecies comparisons of skin irritancy. *Toxicol. Appl. Pharmacol.* **31**: 481-490.

OECD (1993) OECD Guidelines for the Testing of Chemicals. Volume 2, Organisation for Economic Co-Operation and Development, Paris.

Opdyke, D.L. (Editor) (1979) Monographs on fragrance raw materials. Stearic acid. *Food Cosmet. Toxicol.* **117**(4): 383-8.

Palmer, A.K., Readshaw, M.A. and Neuff, A.M. (1975) Assessment of the teratogenic potential of surfactants. Part III – Dermal application of LAS and soap. *Toxicology*, **4**: 171-181.

Pi-Sunyer, F.X., Hashim, S.A. and Van Itallie, T.B. (1969) Insulin and ketone responses to ingestion of medium and long-chain triglycerides in man. *Diabetes,* **18**(2): 96-100.

Prottey, C. and Ferguson, T. (1975) Factors which determine the skin irritation potential of soaps and detergents. *J Soc Cosmet Chem.* **26**: 29-46.

Renner, H.W. (1986) The anticlastogenic potential of fatty acid methyl esters. *Mutation Research* **172**: 265-269.

Rodriguez, C., Calvin, G., Lally, C. and LaChapelle, J.M. (1994) Skin effects associated with wearing fabrics washed with commercial laundry detergents. *J. Toxicol. – Cut. & Occular Toxicol.*, **13**(1): 39-45.

SCF (1995) Extracts from First Report on Chemically Defined Flavouring Substances. Scientific Committee for Food. Annex 6 to document III/5611/95.

Schaefer, H. and Redelmeier, T.E., (1996) Skin Barrier – Principles of Percutaneous Absorption. S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland), ISBN 3-8055-6326-4.

Stillman, M.A., Maibach, H.I. and Shalita, A.R. (1975) Relative irritancy of free fatty aids of different chain length. *Contact Dermatitis,* **1**(2): 65-69.

Van de Plassche, E., Bont, P., and Hesse, J. (1999) Exploratory Report: Fluorescent Whitening Agents (FWAs). National Institute of Public Health and the Environment. The Netherlands. Report No. 601503013.

Vermeire, T.G., van der Poel, P., van de Laar, R.T.H. and Roelfzema, H. (1993) Estimation of consumer exposure to chemicals: application of simple models. *The Science of the Total Environment,* **136**: 155-176.

Webb, D.R., Wood, F.E., Bertram, T.A., and Fortier, N.E. (1993) A 91-day feeding study in rats with caprenin. *Food and Chemical Toxicology,* **31**(12): 935-946.

Welsch, C.W. and Aylsworth, C.F. (1983) Enhancement of murine mammary tumourigenesis by feeding high levels of dietary fat: a hormonal mechanism. *J. Natl*

WHO (1974) Toxicological evaluation of some food additives, including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO Food Additive Series, No. 5, World Health Organisation, Geneva.

WHO (1996) Guidelines for Drinking Water Quality. Second Edition, Volume 2. Health criteria and other supporting information. World Health Organisation, Geneva.

Woutersen, R.A., Appel, M.J. van Garderen-Hoetmer A., and Wijands, M.V. (1999) Dietary fat and carcinogenesis. *Mutation Research,* **443**(1-2): 111-127.

Appendix I

Physical and Chemical Properties for the Sodium Salts of C10-C22 Fatty Acids

Chainlength : C10

Molecular weight	194.3	[g.mol-1]	
Melting point	203	[°C]	SRC
Boiling point	485	[°C]	SRC
Vapour pressure at 25 [°C]	1.1×10^{-7}	[Pa]	SRC
Octanol-water partition coefficient	0.2	[log10]	SRC
Water solubility	31000	[mg.l-1]	SRC

Chainlength : C12

Molecular weight	222.3	[g.mol-1]	
Melting point	217	[°C]	SRC
Boiling point	508	[°C]	SRC
Vapour pressure at 25 [°C]	2.0×10^{-8}	[Pa]	SRC
Octanol-water partition coefficient	1.2	[log10]	SRC
Water solubility {measured at 24oC}	3200 {22000}	[mg.l-1]	SRC{1}

Chainlength : C14

Molecular weight	250.4	[g.mol-1]	
Melting point	227	[°C]	SRC
Boiling point	532	[°C]	SRC
Vapour pressure at 25 [°C]	3.9×10^{-9}	[Pa]	SRC
Octanol-water partition coefficient	2.2	[log10]	SRC
Water solubility	330	[mg.l-1]	SRC

Chainlength : C16

Molecular weight	278.4	[g.mol-1]	
Melting point	238	[°C]	SRC
Boiling point	555	[°C]	SRC
Vapour pressure at 25 [°C]	1.8×10^{-10}	[Pa]	SRC
Octanol-water partition coefficient	3.2	[log10]	SRC
Water solubility {measured at 20oC}	33{2000}	[mg.l-1]	SRC{1}

Chainlength : C18 (Stearate)

Molecular weight	306.4	[g.mol-1]	
Melting point	250	[°C]	MSDS
Boiling point	578.0	[°C]	SRC
Vapour pressure at 25 [°C]	1.3×10^{-10}	[Pa]	SRC
Octanol-water partition coefficient	4.1	[log10]	SRC
Water solubility (at 20oC)	3.3	[mg.l-1]	SRC

Chainlength : C18 (Oleate)

Molecular weight	304.5	[g.mol-1]	
Melting point	251	[°C]	MSDS
Boiling point	582	[°C]	SRC
Vapour pressure at 25 [°C]	1.7×10^{-10}	[Pa]	SRC
Octanol-water partition coefficient	3.9	[log10]	SRC
Water solubility {measured at 20oC}	5.2{50000}	[mg.l-1]	SRC {1}

Chainlength : C22

Molecular weight	362.6	[g.mol-1]	
Melting point	271	[°C]	SRC
Boiling point	624	[°C]	SRC
Vapour pressure at 25 [°C]	4.5×10^{-12}	[Pa]	SRC
Octanol-water partition coefficient	6.1	[log10]	SRC
Water solubility	0.032	[mg.l-1]	SRC

Data Sources:

SRC) SRC data are calculated by the EPIWIN programme, supplied by the Syracuse Research Corporation.

1) Stephen, H Stephen T (1963). Solubilities of inorganic and organic compounds. Pergamon Press, New York

Physical and Chemical Properties for the Potassium Salts of C10-C22 Fatty Acids

Chainlength : C10

Molecular weight	210.36	[g.mol-1]	
Melting point	203.31	[°C]	SRC
Boiling point	485.18	[°C]	SRC
Vapour pressure at 25 [°C]	1.13×10^{-7}	[Pa]	SRC
Octanol-water partition coefficient	0.2	[log10]	SRC
Water solubility	2.6×10^{4}	[mg.l-1]	SRC

Chainlength : C12

Molecular weight	238.41	[g.mol-1]	
Melting point	216.51	[°C]	SRC
Boiling point	508.38	[°C]	SRC
Vapour pressure at 25 [°C]	2.03×10^{-8}	[Pa]	SRC
Octanol-water partition coefficient	1.19	[log10]	SRC
Water solubility (at 24 °C)	2.7×10^{3}	[mg.l-1]	SRC

Chainlength : C14

Molecular weight	266.47	[g.mol-1]	
Melting point	227.36	[°C]	SRC
Boiling point	531.59	[°C]	SRC
Vapour pressure at 25 [°C]	3.87×10^{-9}	[Pa]	SRC
Octanol-water partition coefficient	2.17	[log10]	SRC
Water solubility	268.8	[mg.l-1]	SRC

Chainlength : C16

Molecular weight	294.52	[g.mol-1]	
Melting point	238.20	[°C]	SRC
Boiling point	554.80	[°C]	SRC
Vapour pressure at 25 [°C]	7.26×10^{-10}	[Pa]	SRC
Octanol-water partition coefficient	3.15	[log10]	SRC
Water solubility {measured at 20oC}	26.91	[mg.l-1]	SRC

Chainlength : C18 (Stearate)

Molecular weight	322.58	[g.mol-1]	
Melting point	294.04	[°C]	SRC
Boiling point	578.01	[°C]	SRC
Vapour pressure at 25 [°C]	1.34×10^{-10}	[Pa]	SRC
Octanol-water partition coefficient	4.13	[log10]	SRC
Water solubility {measured at 20 °C }	2.67	[mg.l-1]	SRC

Chainlength : C18 (Oleate)

Molecular weight	320.56	[g.mol-1]	
Melting point	250.71	[°C]	SRC
Boiling point	581.58	[°C]	SRC
Vapour pressure at 25 [°C]	1.04×10^{-10}	[Pa]	SRC
Octanol-water partition coefficient	3.92	[log10]	SRC
Water solubility {measured at 20 °C }	4.19	[mg.l-1]	SRC

Chainlength : C22

Molecular weight	378.69	[g.mol-1]	
Melting point	270.72	[°C]	SRC
Boiling point	624.42	[°C]	SRC
Vapour pressure at 25 [°C]	4.47×10^{-12}	[Pa]	SRC
Octanol-water partition coefficient	6.10	[log10]	SRC
Water solubility {measured at 20 °C }	0.02	[mg.l-1]	SRC

Data Sources:

SRC) SRC data are calculated by the EPIWIN programme, supplied by the Syracuse Research Corporation.

Appendix II

Introduction

The following search strategy was used for an external literature search. This search was used alongside both internal searches and a data request spreadsheets sent to all relevant producer and formulator companies.

Table 1 - Chemicals used for data searching in HERA Fatty acid salts assessment:

Chemical Name	Synonyms	Carbon Chain Length	CAS Number
Decanoic acid, sodium salt**	Capric acid, sodium salt; sodium caprate	C10	1002-62-6
Dodecanoic acid*	Lauric acid	C12	143-07-7
Dodecanoic acid, sodium salt*	Lauric acid, sodium salt; Sodium laurate	C12	629-25-4
Tetradecanoic acid***	Myristic acid	C14	544-63-8
Tetradecanoic acid, sodium salt**	Myristic acid, sodium salt; Sodium myristate	C14	822-12-8
Hexadecanoic acid***	Palmitic acid	C16	57-10-3
Hexadecanoic acid, sodium salt**	Palmitic acid, sodium salt; Sodium palmitate	C16	408-35-5
Octadecanoic acid***	Stearic acid	C18	57-11-4
Octadecanoic acid, sodium salt*	Stearic acid, sodium salt; Sodium stearate	C18	822-16-2
9-Octadecanoic acid, potassium salt*	Oleic acid, potassium salt; Potassium oleate	C18	143-18-0
9-Octadecanoic acid, sodium salt*	Oleic acid, sodium salt; Sodium oleate	C18	143-19-1
9-Octadecanoic acid (Z-) cmpd with 2-aminoethanol (1:1)*	Monoethanolamine oleate	C20	2272-11-9
Fatty acids, C10-14***	--	C10-14	90990-09-3
Fatty acids, C12-18*	--	C12-18	67701-01-3
Fatty acids, C16-18*	--	C16-18	67701-03-5
Fatty acids, C14-18 and C16-18 unsat.d*	--	C16-18	67701-06-8
Chemical Name	Synonyms	Carbon Chain Length	CAS Number
Fatty acids, C14-22*	--	C14-22	68424-37-3
Fatty acids, C8-18 and C16-18 unsatd. Sodium salts*	--	C8-18	85408-69-1
Fatty acids, rape oil*	--	C22	85711-54-2

Note:-

*These chemicals are those which are used by the formulator companies (as provided to us by AISE)

**These chemicals are salts of fatty acids within the carbon chain lengths of interest to us, that may be useful for read across.

***The chemicals are fatty acids within the carbon chain length of interest to us and may be useful for read across data.

Keywords used in Search Strategy for Human Health Data

The following keywords were used with each of the chemicals listed above in the search strategy:-

HUMAN HEALTH

toxicity (or toxic?)	cancer
carcinogen? (or carcinogenic/carcinogenicity)	irritation
sensitisation	teratogen? (or teratogenic/teratogenicity)
Developmental	mutagen (or mutagenic/mutagenicity)
genotoxic? (or genotoxicity)	reproduction
skin penetration	Metabolism
Excretion	Absorption
ADME	

ENVIRONMENTAL

Ecotoxicity/ Ecotoxicology/ Ecotoxicological	Eco toxicity/ Eco toxicology/ Eco toxicological
Effects data	Acute toxicity /aquatic and/or

LC50 / EC50 / IC50 with each of the following:

Algae	Invertebrate
Daphnia	Fish
Acute toxicity / terrestrial and/or	

LC50 / EC50 / IC50 with each of the following:

Microorganism	Earthworm
Plant	Chronic toxicity / aquatic and/or

NOEC (No Observed Effect Concentration) with each of the following:

Algae	Invertebrate

Daphnia Fish

Chronic toxicity / terrestrial and/or

NOEC (No Observed Effect Concentration) with each of the following:

Microorganism Earthworm

Plant Mesocosm

Bioaccumulation Fate

Biodegradation / ready / inherent / SCAS (Semi Continuous Activated Sludge) / Zahn Wellens / MITI

Removal Degradation

Rate constants Aerobic

Anaerobic Abiotic

PHYSICAL – CHEMICAL

MW / Molecular Weight Mp / melting point

Bp / boiling point Vp / vapour pressure

Log P / log Kow / octanol water partition coefficient

Water solubility Koc – partition coefficient organic carbon water

Databases searched for Human health Data:

- IUCLID CD-ROM
- National Toxicology Program (NTP) website (http://ntp-server.niehs.nih.gov/)
- TOXNET website (http://toxnet.nlm.nih.gov/)

The TOXNET website contains links to the following databases:-

- Hazardous Substances Data bank (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB)
- TOXLINE abstracts database (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE)
- USEPA Integrated Risk Information System (IRIS) database (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?IRIS.htm)

  - DART/ETIC (Developmental and Reproductive toxicology) (http://toxnet.nlm.nih.gov/cgi-bin/sis/search)
  - GENE-TOX database (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX)
- Pubmed abstracts database website (http://www4.ncbi.nlm.nih.gov/PubMed/)
- IPCS Environmental Health Criteria (EHC)
- International Agency for Research on Cancer (IARC) evaluations
- Joint Expert Committee on Food Additives (JECFA) evaluations
- BIBRA Toxicity profiles

Databases searched search sites for environmental effects and fate data:

- IUCLID CD-ROM
- http://rpssnt021.ps.u1889.unilever.com/cc_remedy_open/area_msds
- http://psu18.ps.u1889.unilever.com:8889/seac/owa/test
- http://www.epa.gov/ecotox/
- http://esc.syrres.com/efdb/TSCATS.htm
- http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
- http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE.htm
- http://esc.syrres.com/efdb.htm
- http://wos.unilever.com/isicgi/CIW.cgi
- http://www.msdssolutions.com/en/
- http://library.dialog.com/bluesheets/html/bl0307.html
- http://physchem.ox.ac.uk/MSDS/#MSDS

Other search sites:

- BIOSIS previews (1969-present)
- Registry of Toxic Effects of Chemical Substances.