EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

octanoic acid

EC number: 204-677-5

CAS number: 124-07-2

CLH-O-0000002589-62-03/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

6 June 2013

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: Octanoic acid

EC Number: **204-677-5**

CAS Number: **124-07-2**

Index Number: **not available**

Contact details for dossier submitter:

Umweltbundesamt GmbH

on behalf of

AT Competent Authority

Federal Ministry of Agriculture, Forestry, Environment and Water Management

Version number: 2 **Date: 22. Dec. 2011**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Octanoic acid***
EC number:	***204-677-5***
CAS number:	***124-07-2***
Annex VI Index number:	***n.a.***
Degree of purity:	***99.3%w/w***
Impurities:	***see confidential Annex***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation (including criteria according to 2nd ATP of CLP)	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Not currently in Annex VI, Table 3.1 of the CLP Regulation	Not currently in Annex VI, Table 3.2 of the CLP Regulation
Current proposal for consideration by RAC	Skin Irritation 1C – H314 Aquatic Chronic 3 – H412	C; corrosive N; Dangerous for the environment R34 R 51/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Irritation 1B – H314 Aquatic Chronic 3 – H412	C; corrosive N; Dangerous for the environment

		R34 R 51/53

Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation (including criteria according to 2nd ATP of CLP)

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	n.a.	n.a.	currently not classified	Data lacking
2.3.	Flammable aerosols	n.a.	n.a.	currently not classified	Data lacking
2.4.	Oxidising gases	n.a.	n.a.	currently not classified	Data lacking
2.5.	Gases under pressure	n.a.	n.a.	currently not classified	Data lacking
2.6.	Flammable liquids	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.7.	Flammable solids	n.a.	n.a.	currently not classified	Data lacking
2.8.	Self-reactive substances and mixtures	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	n.a.	n.a.	currently not classified	Data lacking
2.10.	Pyrophoric solids	n.a.	n.a.	currently not classified	Data lacking
2.11.	Self-heating substances and mixtures	n.a.	n.a.	currently not classified	Data lacking
2.12.	Substances and mixtures which in contact with water emit flammable gases	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.13.	Oxidising liquids	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.14.	Oxidising solids	n.a.	n.a.	currently not classified	Data lacking
2.15.	Organic peroxides	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	n.a.	n.a.	currently not classified	Data lacking
3.1.	Acute toxicity - oral	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
	Acute toxicity - dermal	n.a.	n.a.	currently not	conclusive but not sufficient for

				classified	classification
	Acute toxicity - inhalation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Skin Irrit. 1C H314: Causes severe skin burns and eye damage.	n.a.	currently not classified	n.a.
3.3.	Serious eye damage / eye irritation	n.a.	n.a.	currently not classified	n.a.
3.4.	Respiratory sensitisation	n.a.	n.a.	currently not classified	Data lacking
3.4.	Skin sensitisation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.6.	Carcinogenicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
3.10.	Aspiration hazard	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic Chronic 3 H412: Harmful to aquatic life with long lasting effects.	None	currently not classified	n.a.
5.1.	Hazardous to the ozone layer	n.a.	n.a.	currently not classified	Data lacking

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

<table>
<tr><th colspan="3">Labelling</th><th>Justification</th></tr>
<tr><td colspan="2">GHS Pictograms</td><td></td><td rowspan="8">Weight of evidence evaluation supporting skin corrosion. Specification of Prevention Phrases according to Regulation (EC) No 1272/2008

Rapidly degradable substance for which adequate chronic toxicity data are available for algae. Lowest chronic values are the geometric mean NOE_rCs from algae with 0.47 and 0.2 mg/L.

For fish and crustacea only reliable short term toxicity values in the range of 10 – 100 mg/L are available, which in combination with ready biodegradability, measured BCF_{fish} values from 234 – 249 and a log P_{ow} of 3.03 – 3.05 don’t lead to any classification.</td></tr>
<tr><td colspan="2">Signal words</td><td>Danger</td></tr>
<tr><td colspan="2">Classification</td><td>Skin irritation – Hazard Category 1C

Aquatic Chronic 3</td></tr>
<tr><td colspan="2">Hazard statements</td><td>H314: Causes severe skin burns and eye damage

H412 : Harmful to aquatic life with long lasting effects</td></tr>
<tr><td rowspan="5">Precautionary Statements</td><td>General</td><td>-</td></tr>
<tr><td>Prevention</td><td>P260: Do not breathe dust/fume/gas/mist/vapours/spray.

P264: Wash thoroughly after handling.

P273: Avoid release to the environment

P280: Wear protective gloves/protective clothing/eye protection/face protection.</td></tr>
<tr><td>Response</td><td>P301 + P330 + P331: IF SWALLOWED rinse mouth, do NOT induce vomiting.

P303 + P361 + P353: IF ON SKIN (or hair) remove/take off immediately all contaminated clothing, rinse skin with water/shower.

P304 + P340: IF INHALED remove victim to fresh air and keep at rest in a position comfortable for breathing.

P310: Immediately call a POISON CENTER or doctor/physician.

P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.</td></tr>
<tr><td>Storage</td><td>P405: Store locked up.</td><td></td></tr>
<tr><td>Disposal</td><td>P501: Dispose of contents/container in accordance with local/regional/national/international regulations (to be specified).</td><td></td></tr>
</table>

Proposed notes assigned to an entry:

None

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1]	Reason for no classification [2]
Explosiveness	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Oxidising properties	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Flammability	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Other physico-chemical properties	n.a.	n.a.	currently not classified	Data lacking
Thermal stability	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Acute toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Repeated dose toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Irritation / Corrosion	C; R34 causes burns.	n.a.	currently not classified	n.a.
Sensitisation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Carcinogenicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Toxicity to reproduction – fertility	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Toxicity to reproduction – development	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	n.a.	n.a.	currently not classified	conclusive but not sufficient for classification
Environment	N; R51/53 Dangerous for the environment; Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	n.a.	currently not classified	n.a.

[1] Including SCLs
[2] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger:
C – corrosive;
N - dangerous for the environment

R-phrases:
R34 – causes burns
R51/53 - toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S-phrases:
S20/21 When using do not eat, drink or smoke
S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S36/37/39 Wear suitable protective clothing, gloves and eye/face protection
S2 Keep out of the reach of children
S61 - avoid release to the environment. Refer to special instructions/safety data sheets

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

There is no current classification according to Annex I of Council Directive 67/548/EEC

There is also no current classification according to Table 3.1 of Annex VI of Regulation (EC) No 1272/2008.

2.2 Short summary of the scientific justification for the CLH proposal

Human Toxicology:

Weight of evidence evaluation supporting skin corrosion: The chemical safety report for octanoic acid submitted to ECHA by Emery Oleochemicals GmbH contains also further non-published references: Nixon 1981 as well as Weterings 1984 provided in vivo rabbit skin irritation tests that result similar to the test results for nonanoic acid presented in this dossier, with alopecia and at least not fully reversible erythema and edema scores. Thus the in vivo data remain borderline with regard to skin irritation category 1 or 2. In contrast Whittle 1994 provided a rat in vitro skin corrosivity test on the basis of transcutaneous electrical resistance (TER) resulting in a TER reading value of < 5.0 kOhm/disc which is indicative for skin corrosion. This test is not directly comparable with the York 1996 in vitro TER data for decanoic acid (indicating non-corrosion), since the latter was carried out with human skin samples and a slightly different prediction model. However we consider that the Whittle 1994 data shift the overall evidence towards skin irritation category 1. Consequently on this basis classification for skin corrosion 1C is proposed (H314: Causes severe skin burns and eye damage). These data also support a specific classification limit of 70% for skin corrosion.

Environment:

Acute aquatic toxicity: $L(E)C_{50}$ values between 1 - 100 mg/L; lowest acute value E_rC_{50} (algae) =1.67 mg/L;

Chronic Aquatic toxicity: only one NOE_rC value for algae available =0.47 mg/L (geometric mean);

Fate & behaviour: rapidly biodegradable; log P_{ow} =3.03; BCF estimated for fish =75;

REACH registration dossier for Octanoic acid:

Acute aquatic toxicity: L(E)C_{50} values between 10 - 100 mg/L; lowest acute value EC_{50} (crustacea) >21 mg/L;

Chronic Aquatic toxicity: NOEC values between 0.01 – 10 mg/L; lowest chronic NOE_rC (algae) =0.007 mg/L (TWA), corresponding to 0.2 mg/L (geometric mean);

Fate & behaviour: rapidly biodegradable; log P_{ow} =3.05; BCF measured for fish 234 – 249;

On basis of these data in the CSA there was neither a classification proposed according to Annex VI, Table 3.1, nor according to Table 3.2 of the same Annex. But it has to be noticed, that the REACH dossier was submitted before the 2nd ATP to the CLP regulation was published.

Proposed C&L (according to the data summarised above):

CLP:

- No classification with Aquatic Acute 1, since all available acute toxicity values >1 mg/L.
- Classification with Aquatic Chronic 3 on the basis of the lowest available chronic NOE_rC values from algae (0.47 and 0.2 mg/L), calculated as geometric mean in combination with rapid biodegradability.

DSD:

- All available L(E)C_{50} values are between 10 and 100 mg/L. The only exception is the lowest E_rC_{50} from algae with 1.67 mg/L which leads to a classification with R51 and further on in combination with log P_{ow} values from 3.03 – 3.05 and measured BCF values from 234 – 249 to a classification with N; R51/53.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

No current classification and labelling.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

No current classification and labelling.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

No current classification and labelling.

2.4.2 Current self-classification and labelling based on DSD criteria

Classification

Class of danger	C (corrosive)
R phrases	R 34

S phrases	S 2, 24/25, 36/37/39

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Biocides: No need for justification.

Also conclusion for non-classification for the various endpoints is of utmost importance for European harmonisation. RMS proposals for classification and non-classification were not discussed in detail within the European Biocides Technical Meetings.

RAC general comment
The only hazard classes considered by RAC were those of skin irritation/corrosion, eye irritation, respiratory irritation and the environment. Please note that references cited here can be found in the CLH report and/or the background document to the opinion; references not quoted in the above documents are however included at the end of this opinion for the sake of convenience.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

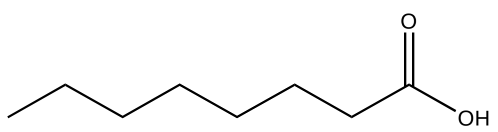
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	204-677-5
EC name:	octanoic acid
CAS number (EC inventory):	124-07-2
CAS number:	124-07-2
CAS name:	Octanoic acid
IUPAC name:	n-Octanoic acid
CLP Annex VI Index number:	not applicable
Molecular formula:	$C_8H_{16}O_2$
Molecular weight range:	144.21 g/mol

Structural formula:



1.2 Composition of the substance

See confidential Annex. (concerns Table 6-8)

Current Annex VI entry: No current Annex VI entry.

1.2.1 Composition of test material

See confidential Annex.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Purity/Specification	Results	Reference
Melting point	99.7 %	16.6 °C	Doc. III-A 3; Study A3/03 Doc. III-A 3; Study A3/17
Boiling point	100%	The result is 237±0.5°C at atmospheric pressure	Doc. III-A 3; Study A3/01
Density	99.5%	0.900 kg/L at 20°C. (This is a density and not a relative density).	Doc. III-A 3; Study A3/11_rev09
Vapour pressure	100%	$1.35*10^{-2}$ Pa (25°C) $8.90*10^{-3}$ Pa (20°C)	Doc. III-A 3; Study A3/01
Henry´s Law Constant	n.a.	0.237 Pa x m^3 x mol^{-1}(calculated)	Doc. III-A 3; Study A3/05
Physical state	n.a.	Liquid	Doc. III-A 3; Study A3/01
Colour	n.a.	Colourless liquid	Doc. III-A 3; Study A3/01
Odour	n.a.	Slightly unpleasant rancid	Doc. III-A 3; Study A3/01
Absorption spectra: UV/VIS	100%	There are no absorption maxima above 290 nm.	Doc. III-A 3; Study A3/01
Absorption spectra: IR	100%	IR, spectra in agreement with proposed structure	Doc. III-A 3; Study A3/01
Absorption spectra: NMR	100%	1H, 13C-NMR spectra in agreement with proposed structure	Doc. III-A 3; Study A3/01
Absorption spectra: MS	100%	mass spectra in agreement with proposed structure	Doc. III-A 3; Study A3/01

Property	Purity/Specification	Results	Reference
Water solubility	99% n.a.	Water: 0.88 g/L without a buffer (20°C) pH 4: 0.92 g/L (50°C) 0.75 g/L (20°C) pH 7: 3.18 g/L (50°C) 2.97 g/L (20°C) pH 9: 3.68 g/L (50°C) 3.35 g/L (20°C) OECD 105; EU A.6 0.68 g/L at 20 °C	Doc. III-A 3; Study A3/16 Doc. III-A 3; Study A3/03
Dissociation constant	n.a.	4.89 at 25°C (The reported dissociation constant (pK. value at 25°C) of n-Octanoic acid is 4.89 (Handbook of Chemistry and Physics, 79' edition 1998- 1999, pp. 8-46/56).	Doc. III-A 3; Study A3/02
Solubility in organic solvents, including the effects of temperature on stability	99.6%	Solubility in organic solvents of Octanoic acid is >1kg/L Hexane at 22°C and > 1kg/L Ethanol at 22°C	Doc. III-A 3; Study A3/19_rev09
Stability in organic solvents used in b.p. and identity of relevant breakdown products	n.a.	Not relevant. The active substance as manufactured does not include any organic solvent.	Doc. III-A 3.8; Study A3/06
Partition coefficient n-octanol/water	n.a.	Calculated with KOWWIN: Log Kow = 3.03 (undissociated acid)	Doc. III-A 3; Study A3/05
Thermal stability identity of relevant breakdown products	n.a. n.a	Octanoic acid is expected to be stable up to the boiling point. Octanoic acid will burn after ignition and produce water, carbondioxid, carbonmonoxid and unidentified hydrocarbons.	Doc. III-A 3; Study A 3/07_rev Doc. III-A 3; Study A 3/08
Flammability, including autoflammability and identity of combustion products	n.a.	The heat of combustion is -4799.9 kJ/mol (Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed. Volumes 1: 1991), therefore auto flammability is not expected.	Doc. III-A 3; Study A 3/08
Flash point	99.6 %	133.0 °C at 1005 mbar	Doc. III-A 3; Study A 3/17a
Surface tension	n.a.	mean 53.2 mN/M (20°C) at 0.61 g/L Octanoic Acid is surface active	Doc. III-A 3; Study A3/10_rev09

Property	Purity/Specification	Results	Reference
Viscosity	99%	result: 7.7 mPa.s (20 °C)	Doc. III-A 3; Study A3/10_rev09
Explosive properties	n.a.	Octanoic Acid does not contain structural elements such as peroxide, nitro-group known to cause explosions.	Doc. III-A 3; Study A 3/12
Oxidizing properties	n.a.	Octanoic acid is not it a strong acid, which may oxidize other materials in a situation as described in the EU method A.14. It is unlikely that Octanoic acid shows oxidizing properties under the condition of the test.	Doc. III-A 3; Study A 3/13
Reactivity towards container material	n.a.	Uncoated metal containers should be avoided. Plastic containers made of polyethylene or polypropylene and certified for use with acid are recommended.	Doc. III-A 3; Study A 3/14 Doc. III-A 3; Study A 3/15

2 MANUFACTURE AND USES

2.1 Manufacture

Biocides: Does not need to be specified for the CLH proposal.

2.2 Identified uses

Insecticide, product type 18

Food and feed area disinfectant, product type 4

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Property	Purity/Specification	Results	Reference
Thermal stability identity of relevant breakdown products	n.a. n.a	Octanoic acid is expected to be stable up to the boiling point. Octanoic acid will burn after ignition and produce water, carbondioxid, carbonmonoxid and unidentified hydrocarbons.	Doc. III-A 3; Study A 3/07_rev Doc. III-A 3; Study A 3/08
Flammability, including autoflammability and identity of combustion products	n.a.	The heat of combustion is -4799.9 kJ/mol (Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed. Volumes 1: 1991), therefore auto flammability is not expected.	Doc. III-A 3; Study A 3/08
Flash point	99.6 %	133.0 °C at 1005 mbar	Doc. III-A 3; Study A 3/17a
Explosive properties	n.a.	Octanoic Acid does not contain structural elements such as peroxide, nitro-group known to cause explosions.	Doc. III-A 3; Study A 3/12
Oxidizing properties	n.a.	Octanoic acid is not it a strong acid, which may oxidize other materials in a situation as described in the EU method A.14. It is unlikely that Octanoic acid shows oxidizing properties under the condition of the test.	Doc. III-A 3; Study A 3/13
Reactivity towards container material	n.a.	Uncoated metal containers should be avoided. Plastic containers made of polyethylene or polypropylene and certified for use with acid are recommended.	Doc. III-A 3; Study A 3/14 Doc. III-A 3; Study A 3/15

3.1 All hazard classes

3.1.1 Summary and discussion of all hazard classes

No classification is proposed based on available data.

3.1.2 Comparison with criteria

No classification is proposed based on available data.

3.1.3 Conclusions on classification and labelling

No classification is proposed based on available data.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Absorption

Oral

After oral ingestion of medium chain triglycerides (MCTs) they are hydrolyzed by lingual lipase in the stomach and then rapidly and efficiently by pancreatic lipase within the intestinal lumen (see e.g. Traul et al. 2000, Ref A 6.11). Free medium-chain fatty acids may be expected to be quickly and completely absorbed from the intestine (see e.g. Opdyke D.L.J. 1979). For oral application of Octanoic acid or MCTs 100% absorption can therefore be assumed.

Dermal

No studies on skin absorption are available. Undissociated Octanoic acid with a log P_{OW} of 3.03 as well as undissociated Decanoic acid with a log Pow of 4.09 is expected to easily penetrate and cross cell membranes. As it is found with absorption from the gut, it is appropriate to assume that the permeation through skin is easy. Also the skin irritating effects of the C8 and C10 fatty acids would support dermal absorption, on the other hand the low water solubility would limit dermal absorption. However after skin contact, the formation of a reservoir of the active substance in the stratum corneum and desquamation of the stratum corneum in time will result in less than 100% systemic availability.

Nevertheless in the absence of a dermal uptake study for the purpose of risk assessment 100% absorption of C8 and C10 fatty acids through the skin will be assumed.

Metabolism and distribution

After absorption from the gut C8 and C10 fatty acids are extensively metabolised in the liver. Only a minor fraction bypasses the liver and becomes distributed to peripheral tissues via the general circulation. C8 and C10 fatty acids are catabolised predominantly in the liver to C2 fragments, which are further converted to CO2 or used to synthesize longer-chain fatty acids.

C8 and C10 fatty acids not absorbed from the gut, but entering the body by dermal absorption can be expected to become absorbed into the blood stream and transported to the liver. A general overview of the digestion, absorption and transport of fats is shown in Figure 1 while the hepatic metabolism of fatty acids is shown in Figure 2.

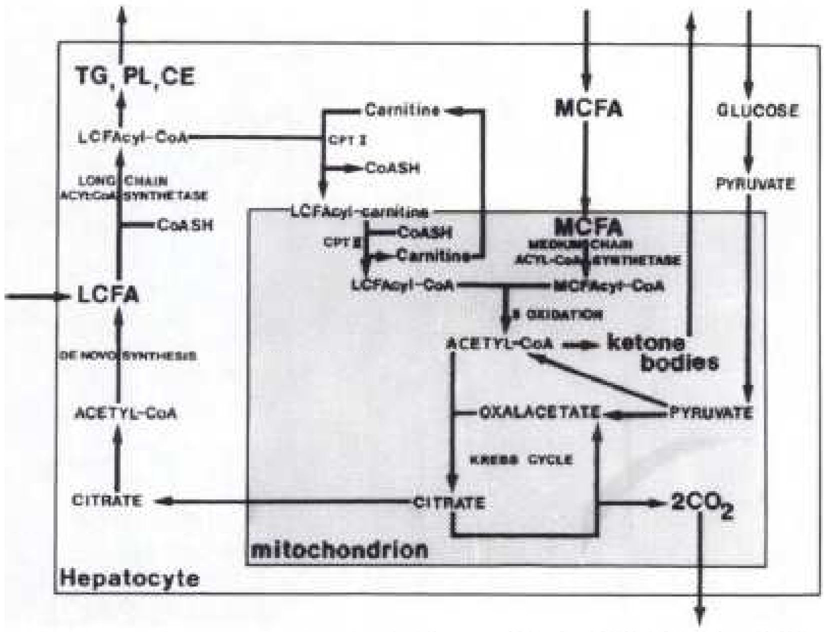


FIG. 2. Hepatic metabolism of fatty acids. *TG*, triacylglycerols; *PL*, phospholipids; *CE*, esterified cholesterol; CPT, carnitine palmityl transferase.

Figure 2 from Bach A.C. and Babayan V.K. (1982)

The metabolites formed in the liver from C8 and C10 fatty acids are also substances normally present and part of the physiological system.

For a more detailed summary of the absorption and metabolism of medium chain fatty acids also the CAR of Nonanoic acid may be consulted.

Decanoic acid and Octanoic acid are naturally present in many types of food in its free form or as triglyceride (see Gubler 2006, Ref A 6/05). Uptake as natural food source from cheese or coconut oil may be estimated to be significantly above 10 mg/ person day (=estimation from average Swiss cheese consumption; 178 mg Decanoic acid and 200 mg Octanoic acid per person and day = estimation from average coconut oil consumption; up to 2000 mg Decanoic acid and 750 mg Octanoic acid per person and day = estimation from 100 g sheep cheese; see Document III-A 6.5.1 and 2). The latter two estimates are in the range of the proposed Acceptable Exposure Level (AEL).

Free fatty acid consumption as food flavouring agent was estimated by JECFA (Joint Expert Committee on food additives, codex alimentarius, FAO/WHO) to be for Decanoic acid 0.980 mg/day (USA) or 1.4 mg/day (Europe) and for Octanoic acid 0.65 mg/day (USA) or 3.8 mg/day (Europe) (WHO 1998 Ref. A6/07, WHO 2005 Ref A6/13)

The daily human uptake of total fatty acids as food contents (mainly as fat) may be estimated e.g. based on the publications of Henderson et al 2003 and Ruston et al.2006. These publications contain details on average fatty acid consumption (Henderson et al 2003) and mean actual male and female body weight data (Ruston et al . 2006). In adults aged 19 to 64 years in the UK, the mean (± s) daily intake of total fat for men is 86.5 (± 28.2) g, which equates to a mean of 79.7 g total fatty acids and for women the daily intake of total fat is significantly lower at 61.4 (±21.7) g, which equates to a mean of 56.7 g total fatty acids (Henderson et al . 2003). Mean (± s) body mass is 84 (±15) kg for men and 69 (±15) kg for women (Ruston et al. 2006). These figures equate to 949 mg of fatty acids per kg body weight per day for men, and 821 mg fatty acids per kg body weight per day for women.

This estimation may further support the high AEL for the free fatty acids Decanoic acid and Octanoic acid (> 10 mg/kg bw day).

4.1.1 Non-human information

See chapter 4.1.

4.1.2 Human information

See chapter 4.1.

4.1.3 Summary and discussion on toxicokinetics

See chapter 4.1.

4.2 Acute toxicity

4.2.1 Non-human information

Table 11a: Summary table of relevant acute toxicity studies

Route	**Method Guideline**	**Species Strain Sex no/group**	**Dose levels duration of exposure**	**Substance tested**	**Value LD_{50}/LC_{50}**	**Remarks**	**Reference**
Oral	Similar to OECD 401	Rat Wistar, 5 rats/sex	Limit test 5 mg/kg bw	C8 fatty acid	> 5 mg/kg bw		**Kästner 1981** **Doc III-A 1.1**
Oral	Similar to OECD 401 non GLP	Rat, Carworth-Wistar, 5 rats/group	not reported	C8 fatty acid C10 fatty acid	1300 mg/kg bw (~ 1.41 ml/kg bw) 3800 g/kg bw (3,73 ml/kg bw) for		Smyth et al. 1962;
Oral	Not reported; non GLP	rat	Not reported	C10 fatty acid	4 entries from > 10 to > 10000 mg/kg bw		IUCLID 2000 (studies from 1975 to 1979 or date not given
Dermal	OECD 402; EU B.3 GLP study from 2006	Rat, HanRcc:WlST (SPF) rats 5m+5f/dose group	2000 mg/kg bw (diluted ~25% in PEG) 24 hours	C10 fatty acid	> 2000 mg/kg	Reversible skin irritation in all animals; on day 2: moderate sedation (4m, 3f), deep respiration (3m, 2f), hunched posture (3m, 1f)	**Talvioja K. 2006; Doc III-A 6.1.2,**
Dermal	Similar to OECD 402 non GLP	Rabbit, albino New Zealand, 4 rats/group	not reported	C8 fatty acid	640 mg/kg bw (~0.71 ml/kg bw)		Smyth et al. 1962
Inhalation	Not reported	Rat, no information available for strain, sex and number of animals used	No information available for dose levels used, 4 h duration of exposure	C9 fatty acid	LC50 (4 h) >5.3 mg/L for Nonanoic acid		Copping L.G. 1998 (Bio-pesticide Manual) Doc. III-A 6.1.3/3 nona
Inhalation	Not reported	No information available for	No information available for dose levels	C10 fatty acid	LC50 (2 h) >4.1 mg/L		Anonymous (Safer Inc), date not stated

Route	**Method Guideline**	**Species Strain Sex no/group**	**Dose levels duration of exposure**	**Substance tested**	**Value LD_{50}/LC_{50}**	**Remarks**	**Reference**
		species, strain, sex and number of animals used	used,	C9 and C10 fatty acids: 60% a.s. formulation and C9 fatty acids: 80% a.s. formulation	LC50 (4 h) >5.53 mg/L and LC50 (4 h) >5.9 mg/L		Doc. III-A 6.1.3/4
Inhalation	Similar to OECD 403 non GLP	Rat, albino, 6 rats/group	Approximately saturated vapour ("concentrated vapour", no analytical confirmation); 4 hours (C8) or 8hours (C10) whole body exposure	C8 fatty acid C10 fatty acid	Approximately saturated vapour	No mortality	Smyth et al. 1962
Inhalation	Not reported; non GLP	No information	Saturated vapour; 8 hours	C10 fatty acid	Saturated vapour	No mortality	IUCLID 2000 (study from 1979)

As additional information the data protected acute toxicity studies for Nonanoic acid (data owner W. Neudorff GmbH KG) are summarized in table 11b. The results are consistent with those reported for Octanoic acid and Decanoic acid.

Table 11b: acute toxicity studies for Nonanoic acid

Oral	EEC B.1 tris, OECD No. 423 GLP	Wistar rat, Crl:(WI) BR (outbred, SPF-Quality), 3 males and 3 females per dose group	0 and 2000 mg/kg bw, 14 days postexposure period	C9 fatty acid	LD_{50} >2000 mg/ kg bw		Otterdijk van F.M. 2001a, additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG
Dermal	EEC B.3, OECD No. 402 GLP	Wistar rat, Crl:(WI) BR (outbred, SPF-Quality), 5 males and 5 females per dose group	2000 mg/kg bw, 14 days postexposure period	C9 fatty acid	LD_{50} >2000 mg/ kg bw	Clinical signs were noted among all animals between days 1 and 5. Signs of severe skin irritation during the observation period.	Otterdijk van F.M. 2001b; additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG
Inhalation	OECD No. 403 GLP	Sprague-Dawley Rat, 5 males and 5 females per dose group	Nominal 6.6 [mg nonanoic acid/L air] Measured 0.5 [mg nonanoic acid/L air] 4 h exposure	C9 fatty acid	LC_{50} (4 h) >0.55 mg nonanoic acid as ammonium salt/L air (measured)	Test substance: Formulation containing 33% C9 fatty acid as ammonium salt/L; results calculated for C9 fatty acid No macroscopic pathological effects observed, clinical signs were food refusal at day 1 (grade 3 from 3) and day 2 (grade up to 2) and apathy at day 1 and 2 (grades up to 3).	Otterdijk van F.M. 2001c; additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG
Inhalation	OECD No. 403 GLP	Sprague-Dawley Rat, 5 males and 5 females per dose group	Measured 1 [mg nonanoic acid/L air] 4 h exposure	C9 fatty acid	LC_{50} (4 h) >1 mg nonanoic acid as ammonium salt/L air (measured)	Test substance: Formulation containing 19% nonanoic acid as ammonium salt and 3% Maleic hydrazid /L; results calculated for nonanoic acid No macroscopic pathological effects observed after 14 days of recovery, no clinical signs	Kramer H.J. (1997a) additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG

Within the draft assessment report for fatty acids (C7-C20) prepared by RMS Ireland in the context of 91/414/EEC reference is also given to secondary, non-GLP, though consistent literature (HERA

2002, Guest 1982) indicating that neither concentrated Octanoic acid nor Nonanoic acid nor Decanoic acid did cause mortality with 4 to 8 hours of inhalation exposure. The RMS-AT did not independently assess these references since the available information seems sufficient also without these references.

4.2.2 Human information

No information available.

4.2.3 Summary and discussion of acute toxicity

The acute toxicity data taken into consideration are summarised in the table 11a above. Most of the tests are older and not GLP approved. However the absence of adverse systemic effects is in line with the knowledge of its endogenous metababolism and the results of the available repeated dose studies. The results of the acute toxicity tests are consistent with each other. Furthermore WHO/ IPCS 1998 summarizes acute oral toxicity LD50 values for a series of carbonic acids including Octanoic and Decanoic acid, which are all above 1000 mg/kg bw. No classifications for acute oral, dermal or inhalation toxicity are required according to European Regulation 1272/2008/EC. Adverse local effects are to be expected from the potential of severe irritation.

4.2.4 Comparison with criteria

The acute oral toxicity studies indicate an LD50 above 2000 mg/kg bw, which is above the LD50 range that may lead to classification in category 4 (300 to 2000 mg/kg bw) or DSD category 3 (200 to 2000 mg/kg bw).

The acute dermal toxicity studies indicate an LD50 above 2000 mg/kg bw, which is above the LD50 range that may lead to classification in category 4 (1000 to 2000 mg/kg bw) or DSD category 3 (400 to 2000 mg/kg bw).

The acute inhalation toxicity studies indicate an LC50 above 5 mg/L, which is above the LD50 range that may lead to classification in category 4 (dust, mist 1 to 5 mg/L) or DSD category 3 (1 to 5 mg/L).

4.2.5 Conclusions on classification and labelling

No classification necessary.

4.3 Specific target organ toxicity – single exposure (STOT SE)

No classification necessary.

4.4 Irritation

4.4.1 Skin irritation

No specific guideline studies are available for Octanoic or Decanoic acid. However sufficient publications are available to assess the irritation potential by a total weight of evidence approach.

4.4.1.1 Human information

The publication from York et al 1996 reports that Decanoic acid showed non-corrosive in the ex vivo human skin based Transcutaneous Electrical Resistance Test. No full study report is available, but the brief method description is in line with the respective OECD guideline 430.

Jirova et al. 2008 reports new in vitro skin irritation data with the EpiDerm model with application times of 15 minutes and with 60 minutes. This new EpiDerm protocol (Spielmann et al. 2007) is designed and validated (ESAC 2007, adopted in EU, OECD process ongoing) to distinguish irritation from non-irritation. It differs from the EpiDerm protocol referenced by the OECD guideline 431 that differentiates corrosive from non-corrosive effects with regard to application time, recovery period and prediction model. Consequently the published EpiDerm results (Jirova et al 2008) support that Nonanoic acid and Decanoic acid are skin irritant (but do not inform weather these medium chain fatty acids might be corrosive).

Several human patch tests are available with the structurally related Decanoic and Octanoic acid, they meet the criteria of the Helsinky Declaration from 1964 and further details on the ethical and scientific acceptability are discussed in Robinson et al. 2001. Within a human patch test (see Robinson et al 1999) 72 human volunteers were exposed to 0.2 ml of Octanoic acid and 0.2 g of Decanoic acid in 0.2 ml distilled water, each to different skin areas. The patches were applied to the arms subsequently with increasing duration of 0.5, 1, 2, 3 and 4 hours. As soon as an individual participant showed at least mild, unequivocal erythema he was not further exposed for increasing duration. 37 to 56% of the participants (for Octanoic and Decanoic acid, each 2 test sites) showed at least mild irritation already after up to 1 hour of exposure and 84 to 96% of the participants showed at least mild irritation after up to 4 hours of application. For Octanoic acid 10 from 69 individuals (ca. 15%) showed moderate skin reactions already at 3 hours, with these 10 participants no longer exposure was tested. For Decanoic acid 1 from 70 individuals showed moderate skin reactions and another one showed strong skin reactions, each after 2 hours. From an earlier publication (York et al. 1996) it also appears that within the human patch test Decanoic acid produced strong responses in some individuals already after 2 hours, but no further details are provided.

In addition Jirova et al. 2008 reports also a new human patch test that showed reversible irritation only after 4 hours of exposure, with 19 from 29 volunteers for Nonanoic acid and with 28 from 29 volunteers for melted Decanoic acid. (The fact that irritation was observed only after 4 hours and not after 0.25, 0.5, 1,2 or 3 hours of exposure is not explicit in the publication but personally communicated upon request of the RMS).

In addition, when Wahlberg 1983 applied 0.1 ml neat Nonanoic acid repeatedly for 15 days to his volar forearm he also did not report any corrosion.

Willis et al. 1988a reports the application of 40, 60, 70 and 80% Nonanoic acid to 48 hours to a total of 70 human volunteers with the aim to determine the optimum concentration of a number of irritants for use within clinical studies. For 26 volunteers at the concentration of 80% no corrosion but up to moderate skin reactions defined as erythema with oedema and papules were reported For similar clinical objectives Wahlberg et al. 1980 presented test results from the application of 5, 10, 20, 40% Nonanoic acid for 48 hours to healthy volunteers and dermatitis patients. 12 of the dermatitis patients received also 100% Nonanoic acid: With increasing concentration an increasing proportion of participants showed skin irritation, but no skin corrosion was reported for all concentrations. These latter 2 publications do not explicitly state the ethical standards that were applied; therefore this information is only reported for reasons of completeness.

4.4.1.2 Non-human information

Further indications for the evaluation with regard to corrosion could be derived from the Toxtree QSAR tool provided by the ECB. It would result as borderline proposal “Irritating or corrosive to skin”.

The acute dermal toxicity test with Decanoic acid was carried out with a 25% solution in PEG for 24 hours on rats. All rats showed signs of skin irritation which were reversible within 15 days.

Following the total weight of evidence approach also the study results from the skin irritation study with Nonanoic acid has to be quoted as additional information. It shows borderline results between skin irritation and skin corrosion (see CAR Nonanoic acid on CIRCA from 2008-10-22): The potential of Nonanoic acid to irritate skin was tested in male New Zealand rabbits. The animals were exposed for 4 hours to 0.5 mL of the undiluted tech. a.i.. Observations were made 1, 24, 48 and 72 hours and 7 and/or 14 days after exposure. No mortality and no symptoms of systematic toxicity were observed. Exposure to Nonanoic acid resulted in severe erythema and (very) slight oedema in the treated skin-areas of the rabbits, which had resolved within 15 days after exposure. Oedema could not be scored on days 3, 4 and/or 8 due to fissuring, scab formation and/or brown discolouration of the treated skin. Brown discolouration (sign of necrosis) of the treated skin was observed among all animals between days 1 and 8. Scabs, eschar formation and/or fissuring of the skin were noted on days 3, 4 and/or 8 among the animals. In addition a bald skin and scaliness were observed at the end of the observation period, at day 14, in all 3 animals.

Though no scars were reported the overall skin irritation effects need to be considered as severe and with regard to bald skin and scaliness did not resolve within 15 days after exposure. According to GHS corrosive reactions are typified by ulcers, bleeding, bloody scabs, and by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology should be considered to evaluate questionable lesions. From these descriptors only “complete areas of alopecia” seem evident, which could –considering also the severe effects observed at the earlier time points- support classification as corrosive/category 1 according to GHS. The actual EU criteria for classification are not that explicit. Nevertheless within the 19th ATP Nonanoic acid was classified as corrosive. However this was in 1993, the respective data basis is not clear and not available and the actual study is from 2001. Furthermore EPA (2003) classified Nonanoic acid as Toxicity category II for irritation that would be in line with classification as irritant/category 2 according to GHS or irritant according to the EU criteria. Neither Octanoic acid nor Decanoic acid are actually classified in the EU.

Also the acute dermal toxicity test of Nonanoic acid as 22% solution in PEG for 24 hours led to some clinical signs and in 2 from 10 animals to severe irritation effects. However if we would calculate a medium score for erythema and scaling/scabs or swelling for 24, 48 and 72 hours (according to OECD scores) it would remain below 2 (see CAR Nonanoic acid on CIRCA from 2008-10-22, the study is data protected)

4.4.1.3 Summary and discussion of skin irritation

Considering all the information reported above and available to the RMS for the biocides CAR Octanoic acid and Decanoic acid seemed to result as skin irritant.

Table 12a: Summary of skin irritation data for Octanoic, Nonanoic and Decanoic acid (public available or data protected and property of applicant)

Species, No of animals	Method	Conc.	Dose	Exposure time	Substance tested	Result	Reversibility yes/no	Conclusion from RMS	Reference
Human skin ex vivo	Transcutaneous Elektrical Resistance Test (TER); OECD guideline 430	100%		24 h	C10 fatty acid	29.9 ± 5.4 kΩ/disc (a value of ≤11 kΩ/disc indicates that a substance could produce a corrosive effect on human skin in vivo)	n.a.	Not-corrosive to skin	York et al. 1996
EpiDerm (reconstituted human epidermis model)	In vitro skin irritation test (Spielmann et al 2007);	100%		15 minutes and 60 minutes	C9 and melted C10 fatty acid	irritant Prediction model: Tissue viability <50% or >50% and IL1α release 3x increased.	n.a.	At least irritating to skin	Jirova et al. 2008
Human volunteers	Human patch test	100%	200ml/ chamber	4 h	melted C10 fatty acid C9 fatty acid	irritant with 18/29 volunteers irritant with 19/29 volunteers	Yes	irritating to skin	Jirova et al. 2008
Human, 72 volunteers	Human patch test Patches applied with graded duration of exposure. Assessment after 24/48/72h	100%	200 mg/chamber	≤4 graded: 0.5, 1, 2, 3, 4	C10 fatty acid C8 fatty acid	% participants showing at least mild irritation: 50 to 56% after 1 hour 78 to 82% after up to 2 hours 90 to 94 after up to 3 hours 92 to 97% after up to 4 hours 14 to 38% after 1 hour 50 to 62% after up to 2 hours 81 to 84% after up to 3 hours	Yes	At least mildly irritating to skin	Robinson et al. 1999 Doc-III A6.1.4.s/02

						85 to 89% after up to 4 hours			
Human volunteer (author of publication)	Human patch test	100%, 60%, 40%, 20%, 10%, 5% in propanol	0.1 ml	repeated for 15 days	C9 fatty acid	Increased skin thickness for concentrations ≥40%		Irritating to skin	Wahlberg 1983
Human 8 volunteers	Human 24 hours exposure, measurement 20 minutes after patch removal	2.5%, 5%, 10%, 20% in propanol		24 hours	C9 fatty acid	2.5% or 5%: None of the measured endpoints indicated skin irritation: visual irritation score, skin reflectance spectrophotometer, transepidermal water loss and laser Doppler flowmetry	Yes	At least irritating to skin	Andersen et al 1995
n.a.	QSAR – Toxtree	n.a.	n.a.	n.a.	C8, C9, C10 fatty acid	Irritating or corrosive to skin	n.a.	Irritating or corrosive to skin	http://ecb.jrc.it/qsar/[1]
Rabbit	Primary skin irritation in albino rabbits, 5/group, Non GLP study from 1962	100%	0.01 ml/animal	24	C8 and C10 fatty acid	Severely irritating (no standard test, score 5 from 10)	Not reported	severely Irritating to skin	Smyth et al. 1962; Doc-III A6.1.4.s/01
Rat, 5 males and 5 females	Acute dermal toxicity test with Decanoic acid EEC B.3, OECD No. 402 GLP study from 2006	25% in PEG	ca 30 (m); 27 (f) mg/cm^2	24 h	C10 fatty acid	Skin reactions during daily observation for 15 days post exposure: All animals erythema grade 1 to 2 after application, developed into scaling and scabs (grade 1 to 2), completely reversible after 14 days of observation.	Yes within 15 days	irritating to skin	TalviOja K. 2006; Doc III-A 6.1.2,
Mouse, 4 per dose group	LLNA, With Decanoic acid	In acetone:olive oil 4:1	25µl/ear	3 times in 3 consecutive days	C10 fatty acid				Weber 2006, Doc-III A6.1.5

[1] Model according to Gerner et al. 2004. QSAR Comb. Sci. 23: 726-733; Walker et al. 2005. QSAR Comb. Sci. 24:378-384; Hulzebos et al. 2005. QSAR Comb. Sci. 24 : 332-342

	OECD 427 EEC B.42	70% 50% 25%				slight irritation no irritation no irritation	Not within 6 days	Mildly irritant	

Table 12b: Summary of data with C9 fatty acid as additional information for the evaluation of C8 and C10 fatty acids (data protected and not property of applicant for Octanoic and Decanoic acid)

Species, Number	Method	Conc.	Dose	Exp. time	Result		Revers. yes/no	Conclusion	Reference
Rabbit, 3 males	Dermal irritation test with Nonanoic acid EEC B.4, OECD No. 404 GLP	100%	75 mg/cm^2	4 h	Average Score 24, 48, 72 hours Erythema: 4 Oedema: No scoring possible due to eschar formation, fissuring and/or brown discolouration of the skin		within 15 days Yes	Severely irritating to skin	Otterdijk van F.M. 2001c; additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG
Rat, 5 males and 5 females	Acute dermal toxicity test with Nonanoic acid EEC B.3, OECD No. 402 GLP	22% in PEG	ca 30 (m); 27 (f) mg/cm^2	24 h	Skin reactions during daily observation for 15 days post exposure: All animals erythema 2/10 animals erythema up to grade 3 and 4 on single days (scale 1-4) All animals scabs and/or scales 7/10 animals scabs and/or scales up to grade 2 on single days (scale 1-3) Clinical signs: Hunched posture, piloerection, chromod-acryorrhoea, lethargy, uncoordinated movements and/or shallow respiration were noted among all animals between days 1 and 5		within 15 days: Erythema not reversible in 3/10 animals (grade 1 at day 15) Scabs and/or scales not reversible in 6/10 animals (grade 1 at day 15)	Severely irritating to skin	Otterdijk van F.M. 2001b; additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG
Guinea pigs animals/group: 2 2 2 2 1 1 1 15	GPMT, EEC B.6, OECD No. 406; GLP; Epiderm. exp. with Nonanoic acid: Pretest Main test	corn oil 100% 50% 20% 10% 5% 2% 1% 1%	mg/cm^2 75 37.5 15 7.5 3.75 1.5 0.75 0.15	24 h	24 and 48h Eryt. grade 4 4 2 1 1 1 0 0	24 and 48h Oedema grade 1 1 0 0 0 0 0 0	n.a.	≥50% severely irritating 2-10% mildly irritating ≤1% not irritating to skin	Otterdijk van F.M. 2001d; additional information only since data owned by C9 fatty acid applicant W.Neudorff GmbH KG

However the chemical safety report for octanoic acid submitted to ECHA by Emery Oleochemicals GmbH contains also further non-published references: Nixon 1981 as well as Weterings 1984 provided in vivo rabbit skin irritation tests that result similar to the test results for nonanoic acid, with alopecia and at least not fully reversible erythema and edema scores. Thus the in vivo data remain borderline with regard to skin irritation category 1 or 2. In contrast Whittle 1994 provided a rat in vitro skin corrosivity test on the basis of transcutaneous electrical resistance (TER) resulting in a TER reading value of < 5.0 kOhm/disc which is indicative for skin corrosion. This test is not directly comparable with the York 1996 in vitro TER data for decanoic acid (indicating non-corrosion), since the latter was carried out with human skin samples and a slightly different prediction model. However we consider that the Whittle 1994 data shift the overall evidence towards skin irritation category 1. Consequently on this basis classification for skin corrosion 1C is proposed (H314: Causes severe skin burns and eye damage). These data also support a specific classification limit of 70% for skin corrosion.

4.4.1.4 Threshold for acute dermal irritation

For the **derivation of a threshold for acute dermal irritation** some studies from literature are summarized:

The clinical publication from Wahlberg et al. 1985 would be in agreement with an NOAEC estimate of 1%. From 100 hospitalised patients with various skin diseases exposed to 1% of the structurally related Nonanoic acid in propanol for 48 hours only 3 showed some skin irritation. The same publications reports that exposure of these 100 patients to a 5% solution resulted skin irritant in 35 patients. In Wahlberg et al. 1980 a 48 hours patch with 5% Nonanoic acid in propanol resulted skin irritant in 11 from 116 healthy human volunteers.

When Wahlberg 1983 applied 0.1 ml of 5, 10, 20, 40, 60 and 100% Nonanoic acid repeatedly for 15 days to his volar forearm, he did not find oedema development (as measured by skin-thickness) for concentrations up to 20% (in propanol). The same publication reports application of 5% Nonanoic acid in propanol to 3 guinea pigs for 15 consecutive days without oedema formation, but the application to one rabbit resulted in significant oedema. However these publications do not address at all if erythema was visible.

Within the Local Lymph Node Assay Decanoic acid was applied to the mouse ear for 3 consecutive days. It induced mild irritation only at concentrations of 70%. A GPMT carried out with Nonanoic acid showed skin irritation after epidermal application for 24 hours only with concentrations above 1%.

Andersen et al 1995 reports test results that aim to contribute to the development of objective tests for human skin irritation. Eight healthy Caucasian volunteers were (after informed consent) exposed for 24 hours to the structurally related Nonanoic acid in concentrations of 2.5%, 5%, 10% and 20% in propanol. Skin irritation was measured 20 minutes after patch removal by visual irritation score, skin reflectance spectrophotometer, transepidermal water loss and laser Doppler flowmetry. None of the endpoints mentioned above indicated skin irritation for concentrations of 2.5% or 5%.

Branco et al 2005 investigated hypo- or hyperreactivity to skin irritants after repeated exposure. The sodium-salt of the structurally related C12 carbonic acid (Sodium-dodecyl-sulfate, SDS) was applied to seven healthy Caucasian volunteers (after informed consent) in concentrations of 0.025%, 0.05% and 0.075% in water continuously for 5 days per week, 3 consecutive weeks, then 3 weeks of break and again 3 weeks of the same exposure regime. After each day of exposure the skin was analysed and the substance was renewed. Also after the first exposure break and 2 and 5 weeks after the last exposure the skin was analysed. Skin reaction was analysed by visual scoring, transepidermal water loss, capacitance, skin colour reflectance and laser Doppler flowmetry. Skin reactions increased with repeated exposure but after the exposure breaks of 3 or 2 weeks all endpoints returned to basal levels. Considering the structural similarity of SDS (salt of C12 carbonic acid) and Octanoic and Decanoic acid and assuming that both substances induce irritation by direct cytotoxicity and consequent inflammatory reactions the data summarized for SDS support that also with Octanoic and Decanoic acid adaptive reactions after repeated exposure are unlikely.

In summary there is evidence (in terms of incidence, magnitude and reversibility of skin irritation effects) that a Octanoic and Decanoic acid concentration of 1% may be a suitable point of departure for the derivation of an acceptable exposure level, at least for acute, dermal local effects. However, according to TM

2009 no acute local AECs are necessary for risk assessment. The respective risk is considered to be sufficiently assessed and managed by the respective assignment of R- and S-phrases, or H- and P- statements (GHS).

The uncertainty of this point of departure for quantitative estimation of medium or long term dermal local thresholds lies within the question if or how much lower this point would be with daily repeated dermal exposure (actual database does not exceed 48 hours of application). The RMS-AT is not aware of data based assessment factors to address this uncertainty. However at least there is some evidence that it is unlikely that adaptive reactions will develop after repeated exposure to Octanoic or Decanoic acid (endpoints return to basal levels after some weeks of break)

The uncertainty of a point of departure derived from new dermal repeated dose studies in animals would lie within the question if and how semi-occlusive conditions in the animal test can be translated to realistic human exposure situations and if the amount per treated skin area is realistic. Furthermore interspecies uncertainty would need to be accounted; TM 2009 proposes as a general rule an assessment factor (AF) of 1 for local dermal effects but also indicates that uncertainty of local AF can be very high and adjustments should be done with caution. The respective empirical database is very limited. Therefore it may be interesting that several publications are available indicating that acute dermal irritation studies in rabbits show a sensitivity of about 100% but specificity of or below 50% for the prediction of 4h-human-patch-test data. The new in vitro human skin method EU-B46 (full replacement of in vivo method) seems to perform superior (see e.g. Jirova et al. 2007, Basketter et al. 2004[2]). However the RMS is not aware of any discussion of the implications of these data for interspecies uncertainty estimates for local dermal repeated dose NOAECs.

Also intraspecies uncertainty would need to be accounted. TM 2009 proposes as general rule an AF of 10 or less for local dermal effects, depending on the knowledge of mechanism and knowledge on respective human variation. Fluhr et al. 2008 reviews that dermal irritation is not an immunologic inert process but involves different cytokines and intercellular interactions but provides just qualitative information on individual and environment related variables. Basketter et al. 1996 reports substantial human intraspecies differences for acute local effects with SDS.

However Fluhr et al. 2008 references also the importance of the barrier function of the skin for irritation effects and the necessity to consider synergistic effects with mechanical or physical stress or other substances.

The latter also means that the product formulation (including pH adjustment and solvent selection) may have a significant impact on the dermal irritation potential, which means that data for the active substance may contain high uncertainty for product risk assessment. In the specific case of Nonanoic acid (considered relevant for Octanoic acid and Decanoic acid by read across) the dermal data basis includes mainly studies with Nonanoic acid in propylene glycol. However the final representative products contain Octanoic acid and Decanoic acid in concentrations between 3% and 10% in water or -with higher concentrations- in water/ethanol/isopropanol mixture. All products contain emulgators, some products contain a preservative, some are pH neutralized others contain high amounts of strong acids rendering the product corrosive.

It should also be considered that skin irritation may be quantified by various methods and endpoints showing different sensitivity. Fluhr et al. 2008 discusses several approaches to quantify skin irritation covering endpoints of heat, redness, swelling, pain and dysfunction and he regards a multiparametric approach in the evaluation of irritant reaction as adequate.

In summery the actual point of departure (1%) for the estimation of local dermal effects of Octanoic acid and Decanoic acid is based on human literature data with Nonanoic acid and SDS (for up to 48 hour applications) which is in agreement with guinea pig test data for Nonanoic acid (irritation NOAEC from 24 hour application in GPMTs) and conservative when considering mouse data with Decanoic acid (LLNA application for 3 consecutive days, irritation threshold ≥ 50%, Doc III-A 6.1.5). The derivation of an acute

[2] For the 4h-HPT 30 human volunteers are exposed to the substance with 0.2g/25mm plain Hill chamber for up to 4 hours. As soon as weak but unequivocal erythema is observed exposure is stopped in the respective individual and counted as positive response. The substance is considered as skin irritant (R38), when the incidence of positive irritation reactions to the undiluted test substance is statistically significantly ≥ the level of reaction in the same panel of volunteers to 20% SDS (see Basketter et al. 1997, York et al. 1996, Robinson et al. 2001).

local dermal AEC is not needed since acute effects should be addressed by respective classification and labelling. The derivation of longer term local dermal AECs from these data would contain uncertainty with regard to the necessity to extrapolate from acute to longer term scenarios and with regard to the fact that the product composition may have a substantial influence. However new dermal repeated dose data from animals (expectedly achievable only for a.i.) would contain other uncertainties with regard to exposure-design and inter- and intraspecies differences and would not reduce the uncertainty with regard to differences between active substance and product formulation. Therefore – in case necessary and adequate- a qualitative risk assessment with regard to local skin effects may be preferred. The available data may be taken into consideration including the uncertainties described.

Furthermore for all wet-work places integrated skin protection programmes including prevention, early recognition and medical care should be regular practice in order to control risk for dermal irritation.

4.4.1.5 Comparison with criteria

Nixon 1981 as well as Weterings 1984 (see CSR for octanoic acid by Emery Oleochemicals GmbH) provided in vivo rabbit skin irritation tests that result similar to the test results for nonanoic acid, with alopecia and at least not fully reversible erythema and edema scores. Smith et al. 1962 skin irritation data with octanoic acid would support skin irritation category 2 and the human patch test data from Robinson et al. 1999 do not indicate that octanoic acid is a more potent skin irritant than decanoic acid. Further in vitro and human data are available data for on nonanoic and decanoic acid supporting rather irritant than corrosive properties. Thus the in vivo data remain borderline with regard to skin corrosion or irritation. In contrast Whittle 1994 (see CSR for octanoic acid by Emery Oleochemicals GmbH) provided a rat in vitro skin corrosivity test on the basis of transcutaneous electrical resistance (TER) resulting in a TER reading value of < 5.0 kOhm/disc which is indicative for skin corrosion. This test is not directly comparable with the York 1996 in vitro TER data for decanoic acid (indicating non-corrosion), since the latter was carried out with human skin samples and a slightly different prediction model. However we consider that the Whittle 1994 data shift the overall evidence towards skin corrosion. Consequently on this basis classification for skin irritation category 1C is proposed (H314: Causes severe skin burns and eye damage). The data presented in the CSR for octanoic acid by Emery Oleochemicals GmbH also support a specific classification limit of 70% for skin corrosion.

4.4.1.6 Conclusions on classification and labelling

Considering all available information with regard to skin corrosion or skin irritation Octanoic acid should be classified as skin irritant category 1, R34 according to EC criteria or as skin irritation category 1C, H314 according to GHS.

RAC evaluation of skin irritation/corrosion
Summary of the Dossier submitter's proposal No specific guideline studies on irritation or corrosion with octanoic acid are reported in the CLH report. The dossier submitter presents a weight of evidence approach to derive a classification, based onevidence from human experiments, QSAR analysis and from the structurally similar nonanoic and decanoic acid. Several human volunteer, patch-test studies conducted with Octanoic, Nonanoic and Decanoic acid are described in the CLH report (Jirova et al., 2008, Robinson et al., 1999, Wahlberg, 1983 and Andersen et al., 1995). These all indicated that the substances were at least irritating to skin but most studies terminated exposure when volunteers showed signs of irritation. A transcutaneous electrical resistance test (TERT, York et al., 1996) indicated that decanoic acid was non-corrosive (29.9 kΩ/disc) while Jirova et al. (2008), using the EpiDerm in vitro skin irritation test, concluded that nonanoic and decanoic acid were at least irritant to skin. The ToxTree QSAR tool developed by the European

Chemicals Bureau (ECB) indicates that octanoic, nonanoic and decanoic acids are borderline irritating or corrosive to skin.

One non-GLP compliant skin irritation study in rabbits using octanoic acid and indicating severe irritation was reported in the CLH report (Smyth et al., 1962) but this study was not conducted using a standardised design. In addition, several studies using dermal application of nonanoic or decanoic acid in rats, rabbits, guinea pigs and mice are reported as supportive information. These studies apply different concentrations of the test substance and are reported to indicate mild to severe irritation (Talvioja, 2006, Weber 2006, Otterdijk, 2001b, c and d).

The dossier submitter also referenced three studies included in the REACH registration dossier for octanoic acid (see the ECHA web-site). Of the two in vivo rabbit skin irritation studies, one (Nixon, 1981) is inconclusive regarding skin corrosion, whereas the 2nd (Weterings, 1984) indicated borderline corrosivity. The in vitro transcutaneous electrical resistance test (Whittle, 1994) produced resistance below 5.0 kΩ/disc (3.6 kΩ/disc), indicating corrosion. These studies were not reported further in the CLH report but subsequently, the dossier submitter included a summary of them in the Response to comments document (RCOM) document.

Taking into account the data from the registration dossier, in particular the results of the TERT study reported in Whittle (1994), the dossier submitter argues that the overall evidence points towards corrosivity and proposes a classification of Skin Corr. 1C – H314 according to CLP (C; R34 according to DSD). They also propose a specific concentration limit of Skin Corr. 1C – H314; C ≥ 70% based on the studies presented in the REACH registration dossier.

Comments received during public consultation

Two Member States provided comments during the public consultation. One agreed with the proposed classification but the other requested study summaries for the studies included in the REACH registration dossier for octanoic acid but not summarised in the CLH report (Nixon, 1981; Weterings, 1984 and Whittle, 1994). The summaries were provided by the dossier submitter in the RCOM.

Several industry representatives provided identical statements on behalf of the Fatty Acid Consortium (FAC). With regard to the corrosion/irritation classification, the FAC agreed with the proposed classification and SCL. Another industry commenter highlighted that for linear unbranched saturated organic acids, corrosion and irritation are associated with chain length. Shorter chain organic acids (such as acetic acid) are considered corrosive while longer chain acids (e.g. C16-C18 acids) are not considered irritant. Octanoic acid (along with nonanoic and decanoic acids) would fall in the middle of this range. The commenter requests that the reporting of corrosion/irritation studies be more detailed. The Whittle (1994) study only reports resistance values of <5.0 kOhm/disc but does not report skin disc damage or mean disc dye content. The human volunteer 4 h test study showed octanoic acid to be irritant but not corrosive. The dossier submitter maintains that the Whittle (1994) study is valid and notes that exposure was terminated immediately upon signs of irritation being observed in the human test studies.

Assessment and comparison with the classification criteria

Since there is insufficient data on the individual organic acids, the dossier submitter used the available information on octanoic, nonanoic and decanonic acid to derive a classification and labeling for the individual compounds. The RAC supported this approach because the pK_a values of the three acids are similar (octanoic acid 4.89, nonanoic acid 4.96, decanoic acid no pK_a, because it is a solid). These values are similar to the pK_a of 4.76 of acetic acid, which is corrosive to the skin (Category 1A, H314). However, RAC notes that the pK_a and pH values are based on molarity. Since there are large differences in the molecular weights between acetic acid (60) and the three organic acids (octanoic acid 144, nonanoic acid 158, decanoic acid 172) their acidity per weight is lower than that of acetic acid. This may explain the less clear irritating/corrosive effects of the three acids. Due to the close structural similarity and the very similar pK_a values, the RAC supported the general evaluation approach of all three acids proposed by the dossier submitter.

The available information is briefly summarised below.

Human patch tests (HPT)

AHPT on 72 human volunteers reported by Robinson et al. (1999) using octanoic and decanoic acid revealed at least mild irritation in 37 to 56% of the participants up to 1 h and in 84 to 96% after up to 4 h exposure. For ethical reasons, exposure was terminated at the first sign of irritation before 4 h of exposure.

In contrast to the dossier submitter, RAC did not see evidence from the York et al. (1996) study that decanoic acid produced strong responses in some individuals at 2 h. The report only states that as the concentration was increased, eventually 100% of the volunteers responded and that labelling with R38 was justified.

Irritation by nonanoic acid has also been reported by Wahlberg (1983) (0.1 ml neat nonanoic acid repeatedly for 15 days on the forearm, 1 person).

The studies by Willis et al. (1988) and Wahlberg et al. (1985) continued exposure even after signs of irritation were noted. Willis et al. (1988) applied up to 80% nonanoic acid for 48 h to 42 healthy non-atopic male volunteers (not 70 as reported in the CLH report). In 28 volunteers exposed to the 80% solution, up to moderate skin reactions (erythema with oedema and papules) but no corrosion was observed. In a similar study, Wahlberg et al. (1985) reported skin irritation with increasing concentration but no corrosion. In this study up to 40% nonanoic acid was applied to 100 hospitalised patients with various skin diseases. At 20% and 40% nonanoic acid, all the 25 exposed patients reacted with skin irritation. The ID_{50} for irritation was about 6%.

Since the EU classification of chemicals for irritation is based on the available rabbit data, Jirova et al. (2008) used the data from 25 compounds to compare the outcome of studies with the EpiDerm model, applying 15 and 60 min exposure times and the 4 h human patch test (HPT 0.2 g nonanoic and decanonic acid for 4 h, observation time up to 72 h) with data on rabbits. Whereas decanoic acid showed irritation in all three tests, nonanoic acid resulted in irritation from the EpiDerm and HPT test data, and borderline corrosion or irritation from the rabbit study. When compared with the 4h HPT results, the rabbit in vivo test provided 100% sensitivity (5/5), but only 50% specificity (10/20). The EpiDerm protocol with 15 min exposure corresponded better to the response seen in man – sensitivity 80% (4 of 5 irritants classified correctly), while the optimized EpiDerm protocol with 60 min exposure time reached higher concordance with the rabbit test.

The authors concluded that although the rabbit test exhibited 100% sensitivity, but only 50% specificity, the rabbit test identifies irritants reliably, whereas 50% of non-irritants are wrongly labelled as irritants.

However, the RAC noted that no information on the rabbit tests or on the reason for corrosion/irritation for nonanoic acid is provided. Following a personal communication with the dossier submitter's study authors reported that the HPT on nonanoic and decanoic acids showed irritation after 4 h, not at shorter times of exposure.

Based on the human patch test studies alone, the RAC supported the conclusion of the dossier submitter that the three organic acids are at least skin irritants, but do allow conclusions to be drawn on a possible corrosive effect.

Animal and in vitro studies

The rabbit study reported by Jirova et al. (2008) cannot be used to support classification because no information on the test procedure or outcome is provided.

The three studies reported in the REACH registration on octanoic acid have not been available to the dossier submitter and to RAC. The dossier submitter summarises them as follows: (see Annex I)

In a dermal irritation test, Nixon et al. (1981) applied 30, 50, 60, 70 and 100% 0.8 ml octanoic acid/2 cm^2 to 6 rabbits for 3 h. Whereas erythema and oedema induced by 30-70% were fully reversible after 24 h, at 100% they were not fully reversible in 5/6 animals within 48 h. There was no observation at day14.

In an OECD TG 404 compliant dermal irritation test, Weterings (1984) applied 0.5 ml 100% octanoic acid to 3 rabbits for 4 h. Full thickness necrosis occurred at 48 h in all animals, which was not fully reversible within 14 days, therefore the conclusion was that octanoic acid was skin corrosive.

In the in vitro transcutaneous electrical resistance test using 100% octanoic acid (Whittle 1994) it was reported that the test substance displayed properties which may be corrosive to animal skin in vivo.

Smyth et al. (1962), using 5 albino rabbits exposed to 0.1 ml 100% octanoic or decanoic acid for 24 h, reported severe irritation. Reversibility was not determined.

Van Otterdijk (2001), using 3 male rabbits exposed to 75 mg/cm^2 100% nonanoic acid for 4 h and observation up to 72 h, also reported severe irritation, which was reversible within 15 days.

Irritation has also been observed in the acute dermal toxicity test in rats (25% decanoic acid for 24 h), which was reversible within 15 days (Talvioja, 2006). The acute dermal toxicity study in rats with 22% nonanoic acid for 24 h showed severe irritation (van Otterdijk, 2001). The erythema was not reversible in 3/10 animals within 15 days.

In the OECD TG 4OECD TG 406 skin sensitisation test in Guinea pigs, 24 h exposure to nonanoic acid at concentrations above 50% was reported as severely irritating but with an oedema grade of 1 at 24 and 48 h. Reversibility was not investigated (Talvioja, 2006).

In the local lymph node assay (LLNA) in mice, 25 µl/ear of 70% decanoic acid 3 times in 3 consecutive days was mildly irritant, which did not reverse within 6 days (Weber et al., 2006).

Since the dossier submitter considered the findings borderline to corrosion they used the Toxtree QSAR evaluation of the three organic acids (which revealed irritating or corrosive to skin) and the in vitro rat skin corrosivity test on the basis of transcutaneous electrical resistance (TER), which indicated skin corrosion. RAC agrees with the dossier submitter that these tests support the corrosive effect seen in two rabbit studies.

Comparison with criteria

When tested in rabbits, guinea pigs and mice, the three organic acids induced mild to severe skin irritation in a high percentage of the animals. Where determined, there was reversibility within 15 days in animal studies, except in two tests using 100% octanoic acid, which showed necrosis. Irritation was also seen in the HPT in most of the volunteers exposed up to 48 h at concentrations of 20% and higher. For ethical reasons most human studies were not continued when irritation was observed (apart from Willis et al. (1988) and Wahlberg et al. (1985)).

The RAC noted that two studies in rabbits on octanoic acid resulted in skin corrosion. Thus, the RAC supports the dossier submitter's proposal that octanoic acid should be considered as corrosive to the skin and warrants classification as Skin Corr. 1 C - H314 according to CLP (C; R34 according to DSD). RAC however, does not support the proposed specific concentration limits as the available data do not allow for their determination.

4.4.2 Eye irritation

For the estimation of **eye irritation** hazard no studies are available for Octanoic acid or for Decanoic acid. A severe skin irritation would, according to OECD guideline 405, exclude further eye irritation testing with animals and result in classification as severely eye damaging. Furthermore two publications were identified (see table 13 below) attributing score 9 from 10 for corneal necrosis or indicating corneal opacity and no reversibility up to 72 hours for Decanoic acid as well as Octanoic acid.

In addition, if classification for skin irritation category 1, “H314: Causes severe skin burns and eye damage” is supported classification and labelling for eye corrosion is already included.

Consequently Octanoic acid as well as Decanoic acid needs to be classified for risk of severe damage to eye (R41) according to EC criteria or eye irritant category I (H318) according to GHS.

New in vitro eye corrosion test data would be needed to classify Octanoic acid and/or Decanoic acid as irritating to eyes, R36 according to EU scheme or category II, H318 according to GHS

Several in vitro tests for severe eye damage are validated and recommended in the European Manual of Decisions for Classification and Labelling (BCOP, ICE, RRET-IRE, HET-CAM) and the Bovine Cornea Opacity Test (BCOP) and the Isolated Chicken Eye Test (ICE) are also adopted as OECD TG. Since it is clear from the available data that the substance is at least eye irritating, a negative e.g. BCOP test should be sufficient to conclude on classification of Octanoic and Decanoic acid as eye irritant (R36 or Cat II H319).

Table 13: Summary of octanoic acid eye irritation for Octanoic and Decanoic acid

Species	Method	Scoring System			Result	Reversibility yes/no	Reference
Rabbit, 5/group	Not reported Non-GLP publication from 1962	Grade 1	Grade 5	Grade 10	Grade 9, indicating risk for serious damage to eye (R41 or H318)	Not reported	Smyth et al. 1962; Doc-III A6.1.4.e/1
		very small area of necrosis	burn	severe burn			
rabbit	Not reported Non-GLP publication from 1976	-	-	-	corneal opacity and moderate conjunctivitis	No reversibility up to 72 hours	Briggs et al. 1976

4.4.2.1 Comparison with criteria

Not necessary, octanoic acid shall be classified for skin irritation category 1 which includes already severe eye damage.

4.4.2.2 Conclusions on classification and labelling

See above.

RAC evaluation of eye irritation

Summary of the Dossier submitter's proposal

No guideline specific eye irritation studies are reported in the CLH report. Two older, non-GLP compliant studies (Smyth et al., 1962 and Briggs et al., 1976) indicate damage to eyes. As the dossier submitter proposes classification for Skin Corr. 1C – H314 (causes skin burns and eye damage) and C; R34 (causes burns), they conclude that classification for eye damage is implicitly covered.

Comments received during public consultation

Several industry commenters submitted an identical paper from FAC. They agreed with the classification but requested addition of SCLs for eye irritation (Eye Irrit. 2 – H319: 1% < C ≤ 70%), based on results from Leoni and Riedel (2011). The dossier submitter agreed to the setting of SCLs for eye irritation based on the summaries provided by FAC but stressed that they do not have access to the study summary for an independent evaluation. Another industry commenter referenced a Bovine Corneal Opacity and Permeability (BCOP) test for decanoic acid which indicates non-corrosivity of decanoic acid. They therefore concluded that octanoic acid should be classified as Eye Irrit. 2 – H319. The dossier submitter did not have access to the study results and did not comment on the validity of the study. The two studies mentioned by industry during the public consultation were made available to RAC and are assessed below

Assessment and comparison with the classification criteria

There are no guideline specific eye irritation studies on octanoic-, nonanoic-, or decanoic acid reported in the CLH dossiers. Due to the C&L of the three organic acids as irritants to the skin and the similar pK_a values of octanoic and nonanoic acid, RAC used the sparse information available on the individual compounds for evaluation of the three organic acids.

Regarding <u>octanoic and decanoic acid,</u> two older, non-GLP compliant studies in rabbits (Smyth et al., 1962 and Briggs et al., 1976) were available to the dossier submitter. The Smyth et al. (1962) study in 5 rabbits per group resulted in grade 9 corneal effects , indicating risk for severe damage to the eye for both octanoic and decanoic acid. No information on the concentration or on the reversibility was provided. The Briggs et al. (1976) study revealed corneal opacity, with no reversibility over up to 72 h. No information on the number of rabbits or on the concentrations of the test compounds is provided and no scoring has been applied.

For octanoic acid, industry provided information from a study by Leoni and Riedel (2011). In 2 out of 3 rabbits tested, lesions of the iris with a score equal to 1 have been induced using 70% octanoic acid. The effects were fully reversible within 6 – 11 days. The test would result in classification as Eye Irrit. 2 - H319 at 70%. The dossier submitter supports this proposal although the study was not made available to them. RAC has evaluated the Leoni and Riedel (2011) study. In accordance with the OECD TG 4OECD TG 403 test guideline, 0.1 ml of 70% octanoic acid was applied for 24 h to 3 rabbits. The animals were observed over 72 h and at 6, 9, and 11 days after dosing. Conjunctival redness, chemosis and discharge were observed in all animals, with average score of 1, 1.67 and 2. In two animals, lesions of the iris (average score 1 in both animals) and the cornea (average 72 h scores 1.33 and 0.67, respectively) were observed. At the end of the prolonged observation period of 9 days no corneal, iris or other lesions were seen in any of the three animals. According to the CLP criteria, this corresponds to a classification as Eye Irrit. 2 – H319 (Xi; R36 according to DSD). This more recent study does not confirm the results of the older non-guideline studies.

During public consultation, industry also referred to a Bovine Corneal Opacity and Permeability (BCOP) test for decanoic acid, which indicates non-corrosivity. RAC has evaluated this OECD TG 437 study and supports the conclusion of the report that based on the criteria of the guideline, a 20% dilution of decanoic acid is not corrosive or a severe irritant to the eye. The in vitro opacity score was 16.83 as compared to a score of ≥ 55.1, at which a substance is considered to be corrosive or a severe irritant.

For nonanoic acid no eye damage or eye irritation data are available.

Comparison with criteria

The available information is inconsistent and does not allow a clear differentiation between irreversible and reversible effects on the eyes. The poorly described Smyth et al. (1962) study indicates that there are irreversible effects resulting from treatment with octanoic and decanoic acid, which is not supported by the study of Briggs et al. (1976) and the more recent study by Leoni and Riedel (2011) on octanoic acid, from which classification as Eye Irrit. 2 - H313 at 70% could be derived. The study by Briggs et al. (1976) does not provide sufficient information to evaluate the irritating potencies of octanoic and decanoic acids.

RAC concluded that classification as Eye Irrit. 2 H313 according to CLP (DSD: Xi; R36 DSD) for octanoic acid would be warranted. However, the Guidance to the CLP Criteria clearly states that when a substance is classified as skin corrosive category 1 then serious damage to the eyes is implicit. Since octanoic acid is classified as skin corrosive, there is no need to proceed with a separate classification for eye effects.

4.4.3 Respiratory tract irritation

4.4.3.1 Summary and discussion of respiratory tract irritation

Considering the strong skin and eye irritation properties of Octanoic acid and Decanoic acid also respiratory irritation hazard has to be assumed. However the only available quantitative information for effects via inhalation stems from acute inhalation studies and is summarized in document IIA, chapter 3.2. The available data are not sufficient for classification for respiratory irritation (STOT – single exposure, category 3) since the European CLP regulation 1272/2008 supports respective classification only when largely based on human respiratory data.

The data are **insufficient to derive a local respiratory AEC**. However it is likely that with an acute exposure of 1mg/L Nonanoic acid as ammonium salt (relevant for Octanoic acid and Decanoic acid by read across) no severe respiratory irritation occurred in the rat: Within rats no clinical signs and no macroscopic pathological effects were observed after 4 hours of exposure to 1 mg/L Nonanoic acid as ammonium salt within a formulation (pH 7) containing additionally Maleic hydrazid with 3%. The overall database for Octanoic acid, Nonanoic acid and Decanoic acid indicates a respiratory LC_{50} > 5 mg/L (see chapter 4.2). As mentioned the data are insufficient for classification for respiratory irritation (STOT –SE).

The derivation of a local respiratory AEC from these data would contain uncertainties with regard to the extrapolation from acute to medium or long term exposure and the fact that necropsy was not carried out at the end of exposure but after 14 days of observation and no respiratory histology and/or functional tests are available for the acute study. Furthermore extrapolation from rat to human has to be accounted (airway anatomy, respiratory rate, deposition patterns and consequently local and total clearance rates). From Kalberlah et al 2002 and ECETOC 2003 and as concluded in TM 2009 humans may be considered on average marginally more sensitive than rats and an uncertainty factor of 2.5 may be adequate. However the empirical data base for this interspecies uncertainty factor for local respiratory effects is very weak, just as it is the case for the human intraspecies variability (TM 2009 proposal 10 or less).

Furthermore product formulation may have a very significant influence on irritation thresholds. In the specific case of Octanoic, Nonanoic and Decanoic acid the inhalation data basis includes studies with the free acids and with the ammonium salt. However the final representative products contain Octanoic acid and Decanoic acid in concentrations between 3% and 10% in water or -with higher concentrations- in water/ethanol/isopropanol mixture. All products contain emulgators, some products contain a preservative, some are pH neutralized others contain high amounts of strong acids rendering the product corrosive.

Since new repeated dose inhalation tests can usually only be obtained for active substances but not for individual products and considering the significant influence that product formulation may have on local irritancy it is proposed that – in case needed and appropriate- a qualitative risk assessment with regard to local respiratory effects of the product may be preferred. The available data may be taken into consideration including the uncertainties described.

4.4.3.2 Comparison with criteria

The available data are not sufficient for classification for respiratory irritation (STOT – single exposure, category 3) since the European CLP regulation 1272/2008 supports respective classification only when largely based on human respiratory data.

4.4.3.3 Conclusions on classification and labelling

No classification necessary.

4.5 Corrosivity

See chapter 4.4

4.6 Sensitisation

4.6.1 Skin sensititsation

4.6.1.1 Non-human information

Species	Method	Substance tested	Result	Conclusion	Reference
Mouse	Local lymph node assay	C8 fatty acid	Dose/ SI 10 /0.7 25 / 1.0 50 / 1.6 Vehicle acetone-olive oil	Not sensitizing	Gerberick et al. 2004 Doc III-A 6.1.5/1
Mouse	Local lymph node assay OECD 429, EU B.42 Vehicle acetone:olive oil	C10 fatty acid	Dose / SI 25% / 3.3 50% / 2.7 70% / 4.9 erythema Control HCA 25% / 12.2	Weight of evidence evaluation: not sensitizing	Weber 2006; Doc-III-A 6.1.5/2

4.6.1.2 Human information

Species	Method	Substance tested	Result	Conclusion	Reference
Human	25 volunteers, 1% concentration; occlusive application for 5 alternate 48 hour periods. 10-14 day after treatment, challenge was performed.	C8 fatty acid	0/25 volunteers sensitized	Not-sensitizing, but low relevance because of low test concentration and since no information about ethical criteria explicit.	Cited in BIBRA 1988
Human	Human maximisation test, 28 volunteers, 1% concentration Occlusive application of test material for 5 alternate 48 hour periods. 10-14 day after treatment, challenge was performed.	C10 fatty acid	0/28 volunteers sensitized	Not-sensitizing, but low relevance because of low test concentration and since no information about ethical criteria explicit.	Cited in Opdyke 1979 and IUCLID 2000 (probably identical reference)

4.6.1.3 Summary and discussion of skin sensitisation

Sensitisation tests with Octanoic acid and with Decanoic acid performed with human volunteers (referenced in Bibra 1988, Opdyke 1979) did not indicate a skin sensitisation potential. However the tests were carried out with 25 or 28 human volunteers, respectively and just a 1% solution, which is very low. Moreover neither study reports nor full publication and no information on the coherence with ethical principles for human testing is available. Therefore these references are of very limited value for hazard assessment.

Gerberick et al. 2004 reports a negative LLNA for Octanoic acid. However no full publication or study report is available and Octanoic acid was tested only up to concentrations of 50%.

Consequently a new LLNA study according to OECD 429/EU B.42 and GLP was performed with 70% of Decanoic acid in acetone: olive oil. Since this study resulted borderline to positive a total weight of evidence evaluation was proposed by the applicant.

The evaluation concludes that neither Octanoic acid nor Decanoic acid are sensitizing based on the following considerations:

- The LLNA conducted with Decanoic acid (GLP study from 2006) at concentrations of 25%, 50% and 70% in acetone: olive oil (AOO, 4:1 v/v) resulted in a stimulation index (SI) of 3.3., 2.7, 4.9 respectively. The positive control with 25% hexyl-cinnamic-aledehyde (HCA) resulted in an SI of 12.2. The EC3 value is 53%, indicating that Decanoic acid is according to the LLNA –if at all- a very weak sensitizer.
- The Health& Safety Executive Report 399/2001 on "Development of the local lymph node assay for risk assessment of chemicals and formulations" contains information on the inter-laboratory and temporal stability of SI values of 25% HCA (positive reference used) and the influence of vehicle and formulation on LLNA response. The reported SI for the three laboratories are 7.2 to 13.9 (mean 9.0), 4.0 to 8.8 (mean 6.5) and 3.8 to 8.5 (mean 6.6) showing that the positive reference SI of 12.2 is on the high side. The laboratory conducting the LLNA with Decanoic acid showed comparable historical reference data indicating that the negative control dpm (disintegration-per-minute) values are within the lower 5th percentile of the historical control range resulting in a higher SI. That results shows that the test is likely on the very sensitive side.
- The example of dimethylamino-propylamin (DMAPA) results in the LLNA (as provided in the presentation of Peninks 2007) and the report cited above show that the vehicle can have enough influence on the SI to reach a slightly elevated level exceeding 3.0 by influencing the skin permeation. AOO (recommended in the validated LLNA as first choice and used in the test for decanoic acid) like ethanol is known to lessen the skin barrier for lipophilic substances.
- The purity of the active substance Decanoic acid tested and the purity of Octanoic acid and Decanoic acid marketed is relatively high (within the LLNA: 99.6% C10 and 0.2 % C8; in 5-batch analysis: 99 % C10, 0.67 % C8, 0.08 % C6, 0.04 % C12) indicating that it is very unlikely that impurities cause a positive response.
- There are no reports that medium chain fatty acids have caused skin sensitisation in humans, though the applicant states that Decanoic acid is used in cosmetics and biocides (Octanoic acid or Decanoic acid are not part of Annex III (list of skin sensitizers) of the Cosmetic Directive; concentrations of use are not public available - the biocidal products on the market contain up to 20 % decanoic acid.
- Published results indicate that octanoic acid is non-sensitizing in the LLNA up to a concentration of 50% (higher concentrations not tested, Gerberic et al 2004).
- Octanoic acid and Decanoic acid lacks structural properties, which would cause interactions with proteins. That opinion is supported by the results of the OECD Toolbox. The results on the skin metabolism (only simulated data are available) also do not indicate that a metabolite would cause the observed elevated SI. (However, the acetone part of the solvent (acetone/olive oil, 4:1) has structural properties which are known to cause protein binding through nucleophilic addition to ketones.)
- Octanoic acid and Decanoic acid are ubiquitously present in most species including humans and a fast natural metabolism into other medium chain fatty acids is textbook knowledge.

- The chosen concentrations in the LLNA (low dose, 714 mg/kg/day, total 2143 mg/kg, mid dose, 1366 mg/kg/day, total 4098 mg/kg and high dose, 1975 mg/kg/day, total 5924 mg/kg) do lead to high body burden (for a 60 kg adult person to about 120 g) which are not expected to stay for a significant time on human skin because of the irritating properties of the medium chain fatty acids.
- In literature positive results with the local lymph node assay (LLNA) are reported for Nonanoic acid (Montelius et al. 1998), but at the same time these results are described as false positive (Montelius et al. 1998); further discussion of false positive and negative results from LLNAs and GPMTs are in line with this perception (see e.g. Basketter et al. 1998, 2007a and b, Kreiling et al. 2008) and further methodical improvements of the LLNA are under discussion (see e.g. Ku et al. 2008, Loveren et al. 2008) which should be fostered by other research aimed at improving the mechanistic understanding of sensitisation (see e.g. Aeby et al. 2008).
- The RMS has a guinea pig-maximisation-test (GMPT, OECD-GLP study from 2001, data owned by different applicant) in hands for Nonanoic acid (that was submitted for the biocides review for PT 19 as cat-repellent) which is clearly negative.

Considering the negative LLNA for Octanoic acid up to 50%, the high concentrations of 50 or 100% needed for positive response in the LLNA for Decanoic acid and giving preference to the consideration that these linear carbonic acids do not contain structural alerts necessary for protein interaction as well as the high purity of technical Octanoic acid and Decanoic acid (see confidential Annex) none of these two medium chain fatty acids should be classified as skin sensitising. This decision is in agreement with the negative results of the Guinea Pig Maximisation Test with Nonanoic acid.

4.6.1.4 Comparison with criteria

See chapter 4.6.1

4.6.1.5 Conclusions on classification and labelling

No classification is necessary.

4.6.2 Respiratory sensitisation

No data are available to estimate the hazard for repiratory sensitisation. However it is assumed that the main toxicological mechanism of action is irritation by direct membrane destruction and consequent inflammatory reactions and there are no metabolites of concern.

4.6.2.1 Comparison with criteria

See discussion above.

4.6.2.2 Conclusions on classification and labelling

No classification necessary.

4.7 Repeated dose toxicity

4.7.1 Non-human information

No standard guideline studies are available for this endpoint. However toxicological information is available from several nutritional studies performed with medium-chain triglycerides (MCT). As described in chapter 4.1 MCTs easy absorption and endogenous metabolism represents textbook knowledge that should be taken into account for discussion of potential adverse effects.

For repeated dose oral exposure two studies are summarised in more details (see table 17a below):

Webb et al. 1993 (see Doc III-A 6.4.1.1/01) published a sub-chronic feeding study in rats with caprenin, a randomized triglyceride primarily comprising caprylic (octanoic) acid (C8:0), capric (decanoic) acid (C10:0) and behenic acid (C22:0). Caprenin was administered in a semi-purified diet to weanling rats (25/sex/group) at dose levels of 5.23, 10.23 and 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. Corn oil alone (12.14%) and a blend of medium-chain triglyceride (MCT) oil plus corn oil (11.21 and 3.13%, respectively) served as controls. All diets were formulated to provide about 4000 kcal/kg of diet and 26.8% of digestible calories from fat by assuming that corn oil, MCT oil, and caprenin provided 9,7 and 5 kcal/g, respectively. Survival, clinical signs, body weight, feed consumption, feed efficiency, organ weights, organ-to-bodyweight 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 corn oil and MCT oil control groups as well as the high-dose caprenin group. Additional rats (n = 5/sex/group) were included in the study to determine whether there was marked storage of C22:O in heart, liver or perirenal fat at the end of the 91-day feeding period. 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, nor were significant amounts of C22: 0 present in the fat extracted from the selected fat depot sites. These 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. Considering that C8 and C10 fatty acids are structurally tightly related and share the same metabolism this may be translated to a common NOAEL of ≥ 7000 mg/kg bw for Decanoic acid and Octanoic acid.

Harkins et Sarett 1968 (see Doc III-A 6.4.1.1/02) published a nutritional evaluation of a medium chain triglyceride (MCT) preparation. A casein diet, containing 18.5% MCT and 2.5% safflower oil, the latter to supply essential fatty acids, was compared with similar diets containing conventional dietary fats. The MCT contained about 51% octanoic acid and 35% decanoic arid resulting in an octanoic acid dietary dose of about 4700 mg/kg bw day and a decanoic acid dietary dose of about 3200 mg/kg bw day. Data obtained in a 47-week study showed that the MCT diet supported normal growth and development. At autopsy carcass composition (without liver, heart, epididymal fat pads, GI) in terms of weight, fat, protein and ash levels were similar to those in rats fed with conventional fats. Also organ weights of liver, kidney, spleen, heart, adrenals, femurs and testes were similar in all groups. Histological study showed that intestinal and liver sections were normal after 47 weeks on the MCT-containing diet. In general, rats fed MCT had slightly lower growth rates and caloric efficiency values, less carcass fat and smaller epididymal fat pads than animals fed conventional dietary fats. Little C8 and Cl0 were found in depot fat that is 0.5 and 4.9%, respectively, though these fatty acids comprised about 85% of the dietary fat. The MCT diet also supported normal reproduction, as indicated by litter size and number. For Decanoic acid and Octanoic acid a common NOAEL of ≥ 8000 mg/kg bw day is apparent in this study.

Table 17a Summary of Decanoic acid and Octanoic acid repeated dose toxicity data

Route	duration of study	Species Strain Sex no/group	dose evels [g/kg bw day] frequency of application	Results	LO(A)EL	NO(A)EL	Reference
Oral (feeding of caprenin (triclyceride) consisting to 26.6% of Decanoic acid and 23.2% Octanoic acid)	91 days	Rat Sprague-Dawley, 25 sex/group	Low dose C10: 1.17 (m); 1.3 (f) Low dose C8: 1.02 (m); 1.14 (f) mid-dose C10: 2.3 (m); 2.5 (f) mid-dose C8: 2.02 (m); 2.25 (f) high-dose C10: 3.5 (m); 3.9 (f) high-dose C8: 3.06 (m); 3.39 (f)	No adverse effects caused by Decanoic acid or Octanoic acid in form of caprenin	-	≥ 7000 mg/kg bw/day	Webb, 1993 Doc III A6.4.1.1/01
Oral (feeding of medium-chain triglycerides (MCT) containing 35% Decanoic acid and 51% Octanoic acid)	2 generatio ns	Rat, Wistar, 15 sex/group	40% of daily calories in food supplied by MCT (assuming default food conversion factor between 0.1 and 0.05 equivalent to ca. 8 g/kg bw/day Decanoic+Octanoic acid)	No adverse effects caused by Decanoic acid and Octanoic acid in form of medium-chain triglycerides	-	≥ 8000 mg/kg bw/day	Harkins, 1968 Doc III-A6.4.1.1/02

Traul et al 2000 references also several other animal studies with MCT: a 3 week dietary toxicity study in chicks, a 30 day oral gavage study in rats, a 90 day parenteral study in rabbits, another 3 months dietary study in rats and three six week studies in rats. Most of these studies are performed for the purpose of nutrition and special attention to changes in the fatty acid metabolism, weight gain or blood parameters like cholesterols were given. Compared to a diet containing long-chain fatty acids, which represent a higher caloric value, reduced weight gain has been reported, but if corrected for caloric intake no significant derivations are observed. The results are in line with those detailed above.

Traul et al 2000 references also human studies which indicate no toxicological symptoms from MCT repeatedly applied for up to 10 days with doses up to about 1000 mg MCT/kg bw day. Traul et al 2000 discusses also the potential for ketosis but concludes that there is no risk, even with high dietary MCT doses [~ g/kg bw].

The applicant provided also a publication from Mori 1953 indicating that dietary doses of 5000 - 10000 mg Octanoic acid and Decanoic acid per kg bw for 150 days did not induce any pathological changes in the rat forestomach or glandular stomach. However the study does not indicate that also other endpoints were analysed. WHO/IPCS 1998 gives also reference to this publication and others indicating repeated dose NOAELs for hexanoic, decanoic and lauric acid of higher than 1000 mg/kg bw day.

For the evaluation of Nonanoic acid in the context of the BPD 98/8/EC the respective applicant W. Neudorff GmbH KG submitted a subacute 4-week oral toxicity study. The study is owned by W. Neudorff GmbH KG and data protected, however since the data requirement for repeated dose studies is fulfilled with the references provided above and the study is not used for the advantage of the applicant of decanoic and octanoic acid (Fatty Acid Consortium) it may be cited and discussed also for the evaluation of Decanoic acid and Octanoic acid: Male and female Wistar rats received Nonanoic acid at doses of 0, 50, 150 or 1000 mg/kg bw/day by gavage in concentrations of 1%, 3% and 20% in Propylene glycol as vehicle. Propylene glycol was used as vehicle. No test substance related mortalities occurred. In week 3 on some occasions breathing difficulties in the form of rales and/or gasping were evident for most animals of the high dose group. In animals of the two other dose groups, no treatment related clinical signs of toxicity were observed. Body weight and body weight gain of treated animals remained in the range of control animals. There was only slightly lower food consumption for the high dose females in week 3, however since food intake was normal again in week 4 this was considered to be without toxicological relevance. No treatment related changes were observed with the functional examinations of hearing ability, papillary reflex, static righting reflex and grip strength and within the motor activity test. Haematological and clinical chemistry findings did not reveal any treatment related differences. Absolute and relative organ weights showed no dose-related changes. An irregular surface of the forestomach was noted at all high dose animals. In this dose group, histopathological examination showed slight to marked hyperplasia of the squamous epithelium of the forestomach. These latter effects were also noticed at 2 from 10 animals of the mid-dose group but these were considered to be without any toxicological relevance since they were minimal and occurred in the absence of (other) functional/morphological disturbances or clinical signs. Therefore a local oral NOAEC of 3% at a dose of 150 mg/kg bw/day was established (Doc III-A 6.3.1).

Table 17b: Repeated dose toxicity tests with Nonanoic acid (read across to Decanoic and Octanoic acid)

Route	Dura-tion of study	Species Strain Sex no/group	Dose levels, frequency of application	Results	NOAEL	Reference
Oral	28 days	Wistar rat, Crl:(WI) BR (outbred, SPF-Quality), 5 males and 5 females per dose group	Dose level of either 50, 150 or 1000 mg/kg bw/day, per gavage	1000 mg/kg bw day macroscopically irregular surface of the forestomach confirmed by microscopic hyperplasia of the respective squamous epithelium. 150 mg/kg bw day minimal hyperplasia of squamous epithelium of fore stomach (2 males, no other effects observed)	≥ 1000 mg/kg/day	Doc III-A 6.3.1; Otterdijk 2002, GLP Study, data protected; owned by W. Neudorff GmbH KG

As additional information a study summary of a range finding study from U.S. EPA may be referenced (no study report or letter of access available): Nonanoic acid was administered in the diet for 14 days to male and female Sprague-Dawley rats at 0, 1500, 2500, 4000, 6300, 7500 or 20000 ppm, corresponding to 0, 145, 267, 423, 633, 753 or 1834 mg/kg bw/day, respectively. No systemic toxicity was seen in either sex at any dose level; treatment had no adverse effect on survival, clinical signs, body weight, body weight gain, food consumption, haematology, clinical chemistry or gross pathology, but no histopathology was carried out.

The effects on the squamous epithelium of the forestomach, which were a macroscopic irregular surface and a microscopic hyperplasia, were induced at the highest tested dose of 1000 mg/kg bw/day when applied daily for 28 days by gavage as a 20% solution in propylene glycol.

However as mentioned above within the 14 days study (Kuhn 1995, Study summary from EPA, no letter of access for the applicant available) the macroscopic effect on the forestomach was not observed even at higher doses of up 1834 mg/kg bw/day administered at concentrations of 20000 ppm (corresponding to 2%) in food. Also Mori 1953 did not find any pathological effects in the forestomach or glandular stomach for Octanoic and Decanoic acid dietary applied in concentrations of 5000 to 10 000 mg/kg bw day for 150 days.

The difference between the three study results cited above may be explained by the way of application (dietary vs. gavage): The capacity of the chow pulp to buffer the irritation property of Nonanoic acid could have contributed to the lack of forestomach effects in the Kuhn 1995 and Mori 1953 publication. In addition the lack of effects within these two studies was not verified by histological analysis.

However the effect on the forestomach was the only potentially toxicologically relevant effect observed in the oral repeated dose studies. This effect is assumed to be associated with its local irritant property rather than by systemic action. Therefore the LOAEL of 1000 mg/kg bw day based on the hyperplasia of the squamous epithelium of the forestomach in the 28-day gavage study and the respective NOAEL of 150 mg/kg bw day are not suitable for the derivation of a systemic AEL.

4.7.2 Human information

Traul et al 2000 references also human studies which indicate no toxicological symptoms from MCT repeatedly applied for up to 10 days with doses up to about 1000 mg MCT/kg bw day. Traul et al 2000 discusses also the potential for ketosis but concludes that there is no risk, even with high dietary MCT doses [~ g/kg bw].

4.7.3 Summary and discussion of repeated dose toxicity

In summary- though medium chain fatty acids (including C8, C9, C10) were applied as repeated dose up to 10 000 mg/kg bw day no systemic LOAEL can be derived from the toxicological studies. The assumption of a low toxicological concern for systemic effects of medium chain fatty acids is plausible. Daily human uptake of fatty acids as food contents is, e.g. according to Henderson et al 2003 about 900 mg/kg bw day and the metabolic pathways are similar for all fatty acids, that is complete catabolism for energy supply or conversion to fat suitable for storage (see also chapter 3.1.1). In addition estimates of uptake as natural food content specific for Decanoic acid and Octanoic acid were submitted (see chapter 4.1.).

In the absence of a systemic LOAEL from toxicological studies and taking into consideration the ubiquitous nature of fatty acids and their common metabolic pathways it seems appropriate to estimate the systemic AEL based on the highest systemic NOAEL from the longest available repeated dose study. The publications from Webb 1993, Harkins 1968, Traul et al 2000 for medium chain triglycerides (MCTs) as well as the publications from Mori 1953 and WHO/IPCS 1998 for the free fatty acids would support NOAELs above 1000 mg/kg bw day. However the 28 day study with Nonanoic acid indicating a NOAEL of ≥ 1000 mg/kg bw day is more robust, since it was carried out with the free fatty acid and with GLP and OECD test guideline standards. Consequently a systemic NOAEL of 1000 mg/kg bw day is proposed.

4.7.4 Other relevant information

Local AECs

A somewhat different approach may be necessary for the derivation of a local-oral AEL: In the available 28 day rat gavage study with the structurally related Nonanoic acid local-oral effects were observed as forestomach irritation with a NOAEL of 150 mg/kg bw day at a concentration of 3% in propylene glycol.

In principle the relevance of this finding for human risk assessment is questionable (Wester et al. 1988, IARC 1999, ECETOC 2006, Proctor 2007). A human counterpart for the rodent forestomach does not exist: The epithelia of the rodent forestomach are not identical to the epithelia of the human oesophagus or stomach. The rodent forestomach is a cornified stratified squamous epithelium without glands. In contrast the human oesophagus is a non-keratinizing stratified squamous epithelium with submucosal glands (providing some protection of the epithelium by mucus secretions) and the human stomach is lined by columnar epithelial cells with diverse glands. The rodent forestomach has a medium pH between 4.5 and 6, the human esophagus has a pH of 7 and the human stomach a pH of 1 to 2 (fasting). But probably most important, the contact time between the oesophagus epithelium and Nonanoic acid is negligible in humans when compared to the rodents' forestomach, which functions as a storage organ. The contact time in the human stomach and intestine may be significant, as is the contact time in the rodent glandular stomach and intestine. Therefore, it was suggested that no-observable-effect levels should be determined in those parts of the gastro-intestinal tract having a counterpart in humans, such as pharynx and oesophagus (Harrison 1992) or glandular stomach or intestine. No effects were observed in these tissues within the rat 28 day gavage study.

Consequently it is assumed that the 28 day NOAEC for forestomach irritation in the rat is – if at all relevant- at least a conservative point of departure for estimating local oral effects in humans. Therefore a local-oral AEC may be derived from the local NOAEC without the application of kinetic and dynamic interspecies factors and without a kinetic intraspecies factor. However local irritation effects may be significantly influenced by product composition attributing additional uncertainty to the local oral AEC. In the specific case of Nonanoic acid (relevant for Octanoic acid and Decanoic acid by read across) the oral data were generated with Nonanoic acid in propylene glycol. However the final representative products contain Octanoic acid and Decanoic acid in concentrations between 3% and 10% in water or -with higher concentrations- in water/ethanol/isopropanol mixture. All products contain emulgators, some products contain a preservative, some are pH neutralized others contain high amounts of strong acids rendering the product corrosive. Consequently there may be high uncertainty in the threshold extrapolation from the carbonic acid to the final product.

No studies for the derivation of local-dermal or local-inhalation AELs for medium or long term exposure situations are available. For discussion of the data to be consulted for a qualitative risk assessment with regard to local dermal and local respiratory effects see chapter 4.4.

Waiving of chronic studies

The conduct of chronic toxicity studies was considered not to be necessary based on the following considerations:

- The detailed knowledge of the metabolic pathways that are similar for all fatty acids: complete catabolism for energy supply or conversion to fat suitable for storage (see chapter 4.1).
- The lack of toxicologically relevant effects also at the very high doses in the available oral repeated dose studies
- The results from the acute mammalian toxicology studies, indicating only concern for skin and eye irritation
- No genotoxicity supported by the evaluation of the three standard in vitro genotoxicity tests (see chapter 4.9) with Decanoic acid and with Octanoic acid.
- The nature of Decanoic acid and Octanoic acid that are linear saturated fatty acids and the ubiquity of these and other similar fatty acids in nature: Decanoic acid and Octanoic acid are naturally present in many types of food in its free form or as triglyceride (see Gubler 2006, Ref A 6/05). Uptake as natural food source from cheese or coconut oil may be estimated to be significantly above 20 mg/ person day (=estimation from average Swiss cheese consumption; 178 mg decanoic acid and 200 mg octanoic acid per person and day = estimation from average coconut oil consumption; up to 2000 mg decanoic acid and 750 mg octanoic acid per person and day = estimation from 100 g sheep cheese; see Document III-A 6.5.1 and 2). The latter four estimates are in the range of the proposed AEL. The daily human uptake of total fatty acids as food contents may be estimated - e.g. according to Henderson et al 2003 and Ruston et al. 2006 in the range of 900 mg/kg bw day (see Doc II-A 3.1). This may further support the high AEL for Decanoic acid and Octanoic acid (> 10 mg/kg bw day).

4.7.5 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

Though medium chain fatty acids (including C8, C9, C10) were applied as repeated dose up to 10 000 mg/kg bw day no systemic LOAEL can be derived from the toxicological studies.

4.7.6 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

See chapter 4.7.5.

4.7.7 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

No classification necessary.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

No classification necessary.

4.9 Germ cell mutagenicity (Mutagenicity)

4.9.1 Non-human information

Table 18: Summary of genotoxicity for Octanoic acid and Decanoic acid

Test system Method Guideline	organism/ strain(s)	concentrations tested (give range)	Substance tested	Result		Remark give information on cytotoxicity (MI= Mitotic Index in % of control) and other	Reference
				+ S9	- S9		
Bacterial gene mutation, OECD 471	S. typhimurium: TA 1535, TA 1537, TA 98, TA 100 E. coli: WP2 uvrA	62 – 5000 µg/plate	Decanoic acid	Neg.	Neg.	slightly reduced growth at 1666 and 5000 µg/plate (+S9; -S9)	Van Ommen 1999a; Doc III A6.6.1/1
Bacterial gene mutation, OECD 471	S. typhimurium: TA 1535, TA 1537, TA 98, TA 100 E. coli: WP2 uvrA	62 – 5000 µg/plate	Octanoic acid	Neg.	Neg.	reduced growth above 1500 µg/plate (+S9; -S9)	Van Ommen 1999b; Doc III A6.6.1/02
Cytogenetic test OECD 473	Chinese hamster Ovary K-1 line	5 – 500 µg/ml	Decanoic acid	Neg.	Neg.	Test 1: 200 µg/mL +S9 (MI= 48%) 50 µg/mL +S9 (MI=80%) 300 µg/mL -S9 (MI=48%) 100 µg/mL -S9 (MI=83%) Test 2: 350 µg/mL +S9 (MI=50%) 200 µg/mL +S9 (MI=80%) 50 µg/mL -S9 (MI=47%) 10 µg/mL -S9 (MI=82%)	De Vogel 1999a;Doc III A6.6.2/1

Table 18 Summary of genotoxicity for Octanoic acid and Decanoic acid (continued)

Cytogenetic test OECD 473	Chinese hamster Ovary K-1 line	25-1200 µg/ml	Octanoic acid	Neg.	Neg.	Test 1: 200 µg/mL +S9 (MI=48%) 50 µg/mL +S9 (MI=80%) 300 µg/mL -S9 (MI=48%) 100 µg/mL -S9 (MI=98%) Test 2: 350 µg/mL +S9 (MI=50%) 200 µg/mL +S9 (MI=80%) 50 µg/mL -S9 (MI=47%) 10 µg/mL -S9 (MI=82%)	De Vogel 1999b;Doc III A6.6.2/2
Gene mutation in mammalian cells OECD 476	Mouse lymphoma L5178Y cells	0.2 – 10 mM	Decanoic acid	Neg.	Neg.	Single positive response in presence of S9 at 2.2 mM. Effect not dose related and not reproducible. relative cell suspension growth < 10% of control with concentrations ≥3.4 mM	Steenwinkel 1999a; Doc III-A6.6.3/1
Gene mutation in mammalian cells OECD 476	Mouse lymphoma L5178Y cells	0.4 – 10 mM	Octanoic acid	Pos.	Neg.	Reproducible positive response at 10mM + S9 with relative total growth of 35% and pH of 6.9. - considered to result from cytotoxicity.	Steenwinkel 1999b; Doc III-A6.6.3/2

Furthermore within the draft assessment report for fatty acids (C7-C20) prepared by RMS Ireland in the context of 91/414/EEC reference is also given to a negative in vivo mammalian bone marrow chromosome aberration test in Chinese hamsters (Renner 1986, published). The RMS-AT did not independently assess this reference since the available information (see also chapter 4.7. - bullet points) seems sufficient also without this reference.

4.9.2 Human information

Detailed knowledge is available on the metabolic pathways that are similar for all fatty acids: complete catabolism for energy supply or conversion to fat suitable for storage (see chapter 4.1). Decanoic acid and Octanoic acid are linear saturated fatty acids and they as well as other similar fatty acids are ubiquitous in nature: Decanoic acid and Octanoic acid are naturally present in many types of food in its free form or as triglyceride (see Gubler 2006, Ref A 6/05). Uptake as natural food source from cheese or coconut oil may be estimated to be significantly above 20 mg/ person day (=estimation from average Swiss cheese consumption; 178 mg decanoic acid and 200 mg octanoic acid per person and day = estimation from average coconut oil consumption; up to 2000 mg decanoic acid and 750 mg octanoic acid per person and day = estimation from 100 g sheep cheese; see Document III-A 6.5.1 and 2). The latter four estimates are in the range of the proposed AEL. The daily human uptake of total fatty acids as food contents may be estimated - e.g. according to Henderson et al 2003 and Ruston et al. 2006 in the range of 900 mg/kg bw day (see Doc II-A 3.1). This may further support the high Acceptable Exposure Level (AEL) for Decanoic acid and Octanoic acid (> 10 mg/kg bw day).

4.9.3 Other relevant information

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4.9.4 Summary and discussion of mutagenicity

Decanoic acid acid did not induce genotoxicity in the standard bacterial mutation test, the in vitro cytogenicity test or the in vitro gene mutation test, neither with nor without metabolic activation by S9 mix.

The same is true for Octanoic acid with the exception of the in vitro gene mutation test that resulted reproducibly positive at a dose of 10 mM +S9. However actual ICH guidelines for genotoxicity testing propose to reduce the maximum dose within in vitro genotoxicity tests from 10 mM to 1 mM. This is supported by scientific data showing that by reducing the top concentration level to 1mM the number of substances being positive in the in vitro genotoxicity tests but negative in the carcinogenicity studies can be substantially reduced without reducing the sensitivity of the in vitro method (no increase of false negatives): Parry et al. 2010. Mutagenesis 25/6, 531-538; Kirkland et Fowler 2010. Mutagenesis 25/6, 539-553. In addition it is acknowledged that all other doses were negative and also the studies carried out with the structurally strongly related substance decanoic acid were negative.

The results from the in vitro chromosomal aberration test with decanoic acid may be considered borderline for the two highest doses of 300 and 500 µg/mL: at both doses 5 of 200 cells (2.5%) with aberrations were observed as compared to 0 of 200 cells in the negative control. The p-values is 0.03 (if one-sided test is considered). However this was not reproduced in the repeated test where a different fixation time was used (This was done since the study author applied a two sided test for the evaluation resulting in a p-value of 0.06 for the first test, that indicated a negative result). In addition these two higher concentrations are again above the concentrations actually recommended by ICH.

Considering all the negative genotoxicity results for Octanoic acid and for Decanoic acid and considering the absence of structural alerts of the active substances and the known impurities as well as all arguments listed in chapter 4.7 (bullet points) the overall conclusion is that neither Decanoic acid nor Octanoic acid are genotoxic.

4.9.5 Comparison with criteria

See chapter 4.9.4.

4.9.6 Conclusions on classification and labelling

No classification necessary.

4.10 Carcinogenicity

4.10.1 Non-human information

Within the 28 day gavage study with Nonanoic acid hyperplasia of the squamous epithelium of the forestomach was observed. However the effect is not considered to be of relevance for human cancer risk assessment. This conclusion is supported by the absence of genotoxic effects, the high doses applied (1000 mg/kg bw day) for achieving the hyperplasia and considering the nature of the active substance, a medium chain saturated fatty acid and the knowledge about kinetics and metabolism of fatty acids (see chapter 4.1). Clearly long term irritation is stimulating cell replication and presents as such a promoting effect that is increasing cancer risk, but such tumour promoting effects without tumour inducing effects are not warrant to classification. The same considerations are valid for the evaluation with regard to the dermal or inhalation exposure routes.

Therefore the conduct of a further carcinogenicity study was considered not to be necessary, no new toxicological information is expected (see also bullet points in chapter 4.7.)

Furthermore as additional information an EPA study summary is available for a dermal repeated dose study with Nonanoic acid (Barkley 1985; The applicant did not submit a letter of access). One control group (untreated), one vehicle control group (50 mg of mineral oil), one test substance group (50 mg of undiluted Nonanoic acid) and one positive control group (50 mg of a 0.05% solution of benzo(a)pyrene in mineral oil), each group consisting of 50 mice received the treatment twice a week for 80 weeks. At termination, a complete gross necropsy was performed and histopathological examinations of all tissues from all mice were conducted. No treatment-related clinical signs of toxicity were reported. Mean weight of mice treated with Nonanoic acid was similar to that of the untreated controls. No treatment-related non-neoplastic or neoplastic lesions were reported. No skin tumors were noticed in any mice treated with Nonanoic acid, vehicle or left untreated, whereas a total of 180 skin tumors were seen in the positive control group. The fact that no clinical signs and no lesions were reported with undiluted application of the medium chain fatty acid seems to be in contradiction with the strong irritant properties reported in the acute and repeated dose studies, however without the full study report this aspect cannot be further discussed.

Furthermore within the draft assessment report for fatty acids (C7-C20) prepared by RMS Ireland in the context of 91/414/EEC reference is also given to a comparative 2-year rat gavage study with corn oil, safflower oil and tricaprlyin in rats (GLP study). All substances caused in increase in pancreatic tumors and a decrease in mononuclear cell leukaemia. Male animals in the corn oil group also showed a distinct dose related increase in fatty liver. These were all considered as normal, well-known responses of male F344 rats to high fat diets. Doses above 2000 mg/kg bw were applied in this test. Clearly also RMS Ireland does not propose classification for carcinogenicity. The RMS-AT did not independently assess this reference since the available information (see also chapter 4.7. - bullet points) seems sufficient also without this reference.

4.10.2 Human information

See chapter 4.9.2.

4.10.3 Summary and discussion of carcinogenicity

Information on human dietary uptake of fatty acids as well as knowledge of human metabolism, negative genotoxicity studies as well as absence of any toxicological alerts from available repeated dose studies with medium chain triglycerides as well as nonanoic acid allow the conclusion that there is no concern for carcinogenicity.

4.10.4 Comparison with criteria

See chapter 4.10.3.

4.10.5 Conclusions on classification and labelling

No classification for carcinogenicity necessary.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Harkins et Sarett 1968 (see Doc III-A 6.4.1.1/02) published a nutritional evaluation of a medium chain triglyceride (MCT) preparation. A casein diet, containing 18.5% MCT and 2.5% safflower oil, the latter to supply essential fatty acids, was compared with similar diets containing conventional dietary fats. The MCT contained about 51% octanoic acid and 35% Decanoic arid resulting in an Octanoic acid dietary dose of about 4700 mg/kg bw day and a Decanoic acid dietary dose of about 3200 mg/kg bw day. Data obtained in a 47-week study showed that the MCT diet supported normal growth and development. The MCT diet supported normal reproduction, as indicated by litter size and number. However weight gain of F1 rats was highest with the oleo oil diet, lower with the MCT diet but lowest with the low-fat diet. Furthermore mortality was 7% or less in all groups except for the group receiving MCT for two generations (P and F1, 22%) and the group receiving low-fat diet in the P-generation and MCT in the F1 generation (20%). In contrast weight gain of the F2 generation fed on MCT for 2 generations was higher compared to all other groups. Determination of the amount of milk secreted by the mothers of each subgroup suggested that this may have affected weight gain and mortality: F1 generation rats that received the MCT diet in the P and F1 generation secreted a lower volume of milk with a lower level of fat compared to rats receiving an oleo oil diet. Furthermore it is reported that differences in weight gain is related in part to food intake since caloric efficiency were similar on all three diets. Consequently it may be concluded that the adverse effects observed stem from nutritional imbalances with high dose applications rather than from substance specific toxic mechanisms. Accordingly for Decanoic acid and Octanoic acid as medium chain triglycerides an overall NOAEL of ≥ 8000 mg/kg bw day is apparent in this study.

Taking furthermore into consideration the arguments listed in chapter 4.7 (bullet points) there is no concern for reproductive toxicity.

Table 20: Summary of octanoic acid information of fertility

Route of exposure	**Testtype Method Guideline**	**Species Strain Sex no/group**	**Exposure Period**	**Doses**	**NO(A)EL Parental; F1; F2 (male and female)**	**Reference**
Oral (feeding of medium-chain triglycerides containing 35% Decanoic acid and 51% Octanoic acid)	47 weeks	Rat, McCollum -Wisconsin	From 3 weeks prior to mating throughout the whole study	40% of daily calories in food supplied by MCT (assuming default food conversion factor between 0.1 and 0.05 equivalent to ca. 3 g/kg bw/day decanoic acid)	≥ 8000 mg/kg bw/day	Harkins, 1968; A6.8.2 and A6.4.1.1/ 02

4.11.1.2 Human information

See chapter 4.9.2.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

No specific teratogenicity study has been performed, but the following references were provided:

Scott et al. 1994 (A6.8.1/01 in reference list) reports that Octanoic acid was applied as single dose of 3228 mg/kg bw on day 12 of gestation, rats were killed and analysed on day 20 of gestation. No teratogenic effects were reported. The difference between octanoic acid and teratogenic valporic acid (= 2-propyl pentanoic acid) is explained to be related to the plasma level and half live that are magnitudes lower for octantanoic acid.

Mei-Jen Liu and Gary M. Pollack 1993 (A6.8.1/02 in reference list) reports the toxicokinetics and metabolism of valporic acid, cyclohexanecarboxylic acid, 1-methyl-1-cyclohexanecarboxylic acid and octanoic acid in Sprague-Dawley rats (4 animals per dose, 3 doses, intravenous application, analysis in serum and urine). It was shown that octanoic acid differs significantly from the other substances: Plasma half lives are very short (<5 minutes), no enterohepatic circulation and no recovery in urine, neither as parental substance nor as glucoronide-metabolites. This finding is explained by the fact that it is a naturally occurring substrate with a linear structure that allows easy mitochondrial ß-oxidation.

These data together with the considerations listed in chapter 4.7 (bullet points) sufficiently support that there is no concern for developmental toxicity of Decanoic acid.

It may also be acknowledged that a developmental toxicity study with Nonanoic acid was submitted in the context of the BPD 98/8/EC Annex I inclusion procedure. The study is owned by the respective applicant W. Neudorff GmbH KG and the data are protected. However since the data requirement for the evaluation of developmental toxicity is fulfilled with the references provided above and the study is not used to the advantage of the applicant of Decanoic and Octanoic acid (Fatty Acid Consortium) it may be cited and discussed also for the evaluation of Decanoic acid and Octanoic acid: In a developmental toxicity study, pregnant CD rats were administered Nonanoic acid in corn oil by oral intubation at 0 and 1500 mg/kg bw/day during days 6 through 15 of gestation. Treatment had no adverse effect on clinical signs, body weights, body weight gain, or food/water consumption and no maternal gross pathological effects were found in the thoracic, abdominal and pelvic viscera. Nonanoic acid did not cause any fetal toxicity; the mean numbers of viable foetuses, early or late resorptions, implantation sites, corpora lutea, pre- and post-implantation losses, sex ratios and fetal body weights in the treated group were comparable to those of the control group. No development toxicity was seen; Nonanoic acid did not increase the external, visceral, or skeletal malformations or variations in any of the foetuses. The NOAEL for maternal and developmental toxicity was 1500 mg/kg bw/day.

4.11.2.2 Human information

See chapter 4.9.2.

4.11.3 Summary and discussion of reproductive toxicity

Data for potential effects on fertility are available with medium chain fatty acid triglycerids. Data for potential effects on the development are available for octanoic acid and for nonanoic acid. None of these data indicate a concern for reproductive toxicity. However this is also not to be expected given the knowledge on metabolism in humans and daily exposure to fat as nutrient.

4.11.4 Comparison with criteria

See above.

4.11.5 Conclusions on classification and labelling

No classification necessary.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Neither the available studies and publications nor general considerations of structure and metabolism indicate a concern for neurotoxicity of Decanoic acid or Octanoic acid with oral, dermal or inhalation exposure (see also chapter 4.7.4, bullet points)

4.12.1.2 Immunotoxicity

No Data available.

4.12.1.3 Specific investigations: other studies

No Data available.

4.12.2 Human information

No Data available.

4.12.3 Summary and discussion

No data available.

4.12.4 Comparison with criteria

No data available.

4.12.5 Conclusions on classification and labelling

No classification necessary.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Preliminary note: The references to key studies are highlighted bold throughout this chapter.

5.1 Degradation

5.1.1 Stability

Hydrolysis

A justification for non-submission of data **(Doc. III-A 7.1.1.1.1)** was submitted stating that Octanoic acid does not contain any functional group or reactive centre, which can be hydrolysed by nucleofilic OH^- ions (at high pH values) or by electrophilic H_2O^+ ions (at low pH values). (See also **Study A 3/03 and A 3/16, Doc. III-A 3**). Therefore, Octanoic acid will not be able to react with water and will not be hydrolysed in water at the given pH values.

Conclusion:

Hydrolysis is not relevant for abiotic degradation of Octanoic acid.

Photolysis in water

Aqueous photolysis can occur for substances which have UV/visible light absorption maxima in the range of 290 to 800 nm. A justification for non submission of data **(Doc. III-A 7.1.1.1.2)** was submitted stating that Octanoic acid does not contain any functional group or reactive centre, which displays chromophore properties at wavelengths above 290 nm. (See also **Study A 3/01, Doc. III-A 3**). Therefore, photolytic degradation in water is excluded.

Conclusion:

Photolysis is not relevant for abiotic degradation of Octanoic acid.

Phototransformation in air

The photochemical degradation of Octanoic acid in air was estimated using the model AOPWIN (version 1.92, Epi Suite, Syracuse Research Corporation, see **Doc. III-A 7.3.1**).

The specific degradation rate constant of Octanoic acid with OH-radicals was estimated to be k_{OH} = 8.3499 x 10^{-12} cm³/molecule/s, mainly due to hydrogen abstraction (ca. 96%) and reaction with the hydroxyl-group (ca. 4%). Other mechanisms do not contribute to hydroxyl radical estimations. By relating k_{OH} to the average OH-radical concentration in the atmosphere $c(OH)_{air}$, the pseudo-first order rate constant for degradation in air $k_{deg, air}$ can be derived:

$$k_{deg, air} = k_{OH} \times c(OH)_{air} \times 24 \times 3600 \; [d^{-1}]$$

According to the TGD on Risk Assessment, $c(OH)_{air} = 5 \times 10^5$ molecules x cm^{-3}, which leads to

$k_{deg, air} = 0.361\ d^{-1}$, $T_{1/2} = 46.1$ h (TGD)

Conclusion:

The half-life of Octanoic acid is estimated to be 46.1 h. Based on this result an accumulation of Octanoic acid in air is not to be expected.

Substances which are contributing to degrading air quality (visibility, effects on human health, bad smell, effects on plants), global warming, ozone depletion in the atmosphere and ozone formation in the troposphere, acidification and/or long range transport, have the potential to display adverse abiotic effects on the atmospheric environment.

On the basis of its physical and chemical properties, as e.g. absence of absorption bands in the so-called atmospheric window (800-1200 nm; **Doc. III-A 3, Study A 3/01**), short atmospheric lifetime (**Doc. III-A 7.3.1**), absence of Cl, F, N or S substituents in the molecule (**Doc. III-A 2**), Octanoic acid is not expected to display adverse abiotic effects on the atmospheric environment.

5.1.2 Biodegradation

The oxidative degradation of fatty acids is a universal biochemical capacity among living organisms. Within cells, fatty acid oxidation occurs principally in the mitochondria; ß-oxidation is the normal mechanism, in which two-carbon units are sequentially removed beginning from the carboxyl-terminal end (Orten and Neuhaus 1975). A detailed chapter on the enzymology of beta-oxidation is written by Zubay 1983.Consequently, straight-chain fatty acids with e.g. 9 carbons are oxidized by the normal ß-oxidation sequence and give rise to 3 acetyl-CoAs and 1 propionyl-CoA.The propionyl-CoA is converted to succinyl-CoA. Succinyl-CoA can be further metabolized in the tricarboxylic acid cycle. As a result of the in details complicated degradation steps of fatty acids the final products are CO_2 and water. No other products than these ones are formed.

5.1.2.1 Biodegradation estimation

No data available.

5.1.2.2 Screening tests

The biodegradation of Octanoic acid was investigated in a Manometric resporometry test **(Study A 7.1.1.2.1/02, Doc. III-A 7.1.1.2.1)** according to OECD guideline 301 F. The biochemical oxygen demand of Octanoic acid in the test media significantly increased starting at day 4. After 8 days of exposure the mean biodegradation amounted to 62%. At the end of the 10-day window on day 11, 66% and 73% biodegradation were found. At the end of the 28-day exposure period a mean degradation rate of 84% was calculated. The percentage biodegradation exceeded 60% after 28 days and within the 10-day window.

Further information:

Additionally literature was submitted (Study A 7.1.1.2.1/01 “Fragrances and Biodegradation, Göteborgs Stad Miljö, ISSN 1401-2448 ISRN GBG-M-R—05/05—SE”) including a list of organic acids (e.g. Octanoic acid) which were found to be readily biodegradable. The report comes to the conclusion that saturated alkane carboxylic acids are readily biodegradable at least up to C18. Both statements are in line with the findings of the degradation study presented here and with the explanation of the metabolism of fatty acids (see above).

Conclusion:
Octanoic acid was found to be “readily biodegradable”.
Therefore the justification for non submission of data for inherent biodegradability **(Doc. III-A7.1.1.2.2)** was accepted and no further studies on biodegradation (simulation) tests have been asked for.

Table 21a: Biodegradability, screening tests

Guideline / Test method	Test type	Test para-meter	Inoculum			Addi-tional sub-strate	Test substance concentr.	Degradation		Reference
			Type	Concent ration	Ada ptati on			Incu-bation period	Degree [%]	
EEC C.4-D, OECD 301-F / Manometric respirometry test	ready	Oxygen demand (measurement of pressure drop)	Aerobic active-ated sludge	30 mg suspend-ded solids/L	No	No	100 mg Octanoic acid/L	11 days (10 day window) 28 days	66-73% 81-88%	**Study A 7.1.1.2.1/ 02** **Doc. III-A 7.1.1.2.1**

1 Test on *inherent* or *ready* biodegradability according to OECD criteria

5.1.2.3 Simulation tests

No data available.

5.1.3 Summary and discussion of degradation

Octanoic acid is readily biodegradable (84% at day 28; pass level reached at day 8). The principal way of degradation of fatty acids under aerobic conditions is the microbial shortening by C2 pieces (β-oxidation of fatty acids). In addition the DT_{50} soil from Nonanoic acid of 2.1 days at 12°C (Draft Competent Authority Report, Document I, Nonanoic acid, Product Type 19, 2008) was used for read across in order to refine the risk characterisation for the soil compartment of PT 4.

Hydrolysis can be excluded by its structure, since Octanoic acid does not contain any functional group or reactive centre, which can be hydrolysed by nucleophilic OH^- ions (at high pH values) or by electrophilic H_2O^+ ions (at low pH values).

Photolytic degradation in water is excluded for Octanoic acid, as it does not contain any functional group or reactive centre which displays chromophore properties at wavelengths above 290 nm.

An estimation of photochemical degradation of Octanoic acid in air according to TGD resulted in a half-life of 46.1h ($k_{deg,\ air}$ = 0.361 d^{-1}; $c(OH)_{air}$ = $5x10^5$ molecules/cm^3). Based on this result an accumulation of Octanoic acid in air is not expected.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

In a study according to OECD guideline 106 the adsorption characteristics of Octanoic acid were investigated (**Study A 7.1.3/01, Doc. III-A 7.1.3**).

Initially a preliminary test was conducted using soil I and II (table 21b) with three soil-to-solution ratios (1/1, 1/5 and 1/25). After 2, 5, 24 and 48 h of incubation no test substance was detected in the supernatants, except after 5h of incubation at the 1/5 ratio. Since strong adsorption of the test item to soil and complexation with Ca-ions were excluded, it was assumed that the test item degraded under the test conditions.

In a second step a screening test was performed using five soils sterilised by gamma-irradiation, a soil-to-solution ratio of 1/5 and an adsorption time of 4h. The test item disappeared completely from the supernatants, except for soil II and III. Only in the steril control (without soil), the test item was recovered.

The soils were extracted with acetonitrile solution. Virtually no test item could be detected in the extract solutions by LC/MS analysis. Extracts from untreated soil (blank estracts) were spiked with Octanoic acid and analysed by LC/MS. Again no test item could be detected. The same blank extracts sterilised by auroclaving showed complete recovery of the test item which confirms the microbial degradation of Octanoic acid.

Higher concentrations of Octanoic acid were measured after sterilisation of the soils at 120°C, but degradation could not be avoided for all samples. Desorption was performed for the same soils, but no test substance was detected in the desorption solutions.

Conclusion:

An adsorption equilibrium could not be reached since, Octcanoic acid rapidly degraded despite of soil sterilisation. For above-mentioned reasons no K_{oc} value could be calculated. At the same time the results show that there is negligible likelihood for leakage of Octanoic acid to groundwater due to rapid degradation.

In the risk characterisation a default K_{oc} value for the non-ionised form of Octanoic acid of 83.9 L/kg (calculated via EUSES) was used.

Table 21b: Adsorption onto / desorption from soils

Guideline / Test method	Soil	Substance	Koc_{ads}	Koc_{des}	Reference
OECD 106 / Adsorption – Desorption Using a Batch Equilibrium Method	Soil I: sandy loam Soil II: loam Soil III: sandy clay Soil IV: silty loam Soil V: silty clay	Octanoic acid	n.a.	n.a.	**Study A 7.1.3/01, Doc. III-A 7.1.3**

5.2.2 Volatilisation

Table 21c: Vapour pressure

Property	Purity/Specification	Results	Reference
Vapour pressure	100%	$1.35*10^{-2}$ Pa (25°C) $8.90*10^{-3}$ Pa (20°C)	Doc. III-A 3; Study A3/01
Henry´s Law Constant	n.a.	0.237 Pa x m^3 x mol^{-1}(calculated according to HENRYWIN 3.10)	Doc. III-A 3; Study A3/05

The transfer of a substance from the aqueous phase to the gas phase is estimated by means of its Henry´s Law constant.

K air-water = (HENRY) / (R*Temp) = $9.5*10^{-5}$

With HENRY [Pa * m^3 *mol^{-1}], R = 8.314 Pa * m^3 –mol^{-1}*K^{-1}; Temp [K]

5.2.3 Distribution modelling

No data available.

5.3 Aquatic Bioaccumulation

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The BCF is calculated with the program of EPI Suite and according to formula 74 of the TGD for completeness. The calculation of the BCF with the program of EPI Suite results in a BCF value of 120 when a biotransformation rate of zero is estimated. If biotransformation is taken into account, the BCF ranges from 58 to 84. This is in line with the BCF calculated according to the TGD (BCF=75, see below). So a BCF of 75 is applied.

Table 22: Estimations on aquatic bioconcentration

Basis for estimation	**log P_{OW}**	**Estimated BCF for Octanoic acid**	**Reference**
Calculation	3.03	The log BCF-value can be calculated using the log P_{ow} value log BCF=0.85 x log P_{ow} -0.7 Based on a calculated log P_{ow} of 3.03 the log BCF_{fish} can be calculated as: log BCF_{fish}=0.85 x 3.03 – 0.70 = 1.9 BCF_{fish}=75	TGD on Risk Assessment

The calculated BCF_{fish} for Octanoic acid is 75. This calculation also shows that the risk of bioaccumulation of Octanoic acid is low.

5.3.1.2 Measured bioaccumulation data

No study on bioconcentration in aquatic organisms is performed.

5.3.2 Summary and discussion of aquatic bioaccumulation

The calculated BCF_{fish} for Octanoic acid is 75. Based on its chemical structure, Octanoic acid is a so called amphiphile molecule. This is a term describing a chemical compound possessing both hydrophilic and lipophilic properties. As a result of having both lipophilic and hydrophilic portions, some amphiphilic compounds may dissolve in water and to some extent in non-polar organic solvents. When placed in an immiscible biphasic system consisting of aqueous and organic solvent, the amphiphilic compound will partition into the two phases. The extent of the hydrophobic and hydrophilic portions determines the extent of partitioning. This is the reason why no experimental log P_{ow} can be determined for Octanoic acid. Because the substance is completely miscible in Octanol, the Octanol/water coefficient cannot be calculated by the relation of water saturation concentration and Octanol saturation concentration. In the Guidance for the implementation of REACH, Chapter R.7A – Endpoint specific guidance, it is stated that the Shake Flask Method, which is a direct measurement method to estimate data on partition coefficient n-Octanol/water, is not suitable for surface active substances.

According to the TGD “Guidance document on data requirements for active substances and biocidal products” the value should be calculated if a test cannot be performed. Hence data from calculations using equations based on fragment contribution methods are only of limited validity. The validity of such QSAR methods decrease generally as the complexity of the molecule increases. However, as Octanoic acid is a very simple molecule (eight-carbon straight-chain fatty acid ($C_8H_{16}O_2$)) the model calculations can be assumed to be a reliable estimate. For comparison, the log P_{ow} from other fatty acids are mentioned (Decanoic acid 4.09, Nonanoic acid 3.52, both estimated with QSAR methods).

So the calculated log P_{ow} can be accepted.

Octanoic acid shows a surface tension of 53.2 mN/M. As surface active molecules with a surface tension of less than 50 mN/M could have a potential for bioaccumulation, this point is discussed further, highlighting the metabolism of the compound. Octanoic acid is a fatty acid and is therefore ubiquitous available in the environment. The metabolism takes place via ß-oxidation. Based on knowledge on metabolism and biological properties, sufficient evidence is given of the non-bioaccumulating properties of Octanoic acid.

5.4 Aquatic toxicity

Classification is based on the key studies (results and references highlighted bold).

Tables 23: Summary of relevant information on aquatic toxicity

See chapters 5.4.1, 5.4.2, 5.4.3, 5.4.4.

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

The acute toxicity of Octanoic acid was investigated in zebra fish (*Brachydanio Rerio*) in a semi-static study for 96 hours (Studies **A 7.4.1.1./02** and **A 7.4.1.1./03, Doc. III-A 7.4.1.1**). The NOEC was 22 mg/L as this was the lowest concentration where no effects could be estimated. At 46 mg/L abnormal fish could be seen. However, no mortalities occur at this test concentration. The calculated LC_{50} is 68 mg/L. For the results see table 23a below:

Table 23a: Acute toxicity to fish

Guideline / Test method	**Species**	**Endpoint**	**Exposure**		**Results in mg/L nominal confirmed**			**Remarks**	**Reference**
			design	duration	LC_0	LC_{50}	LC_{100}		
OECD 203 / EC C.1	Zebra fish (*Brachydanio rerio*)	Mortality	Semi-static	96 h	**46**	**68**	**100**		**Study A 7.4.1.1/02** and **Study A 7.4.1.1/03 Doc. III-A 7.4.1.1**

5.4.1.2 Long-term toxicity to fish

No data available

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

An older study, not fulfilling the validity criteria, as lacking in details on the actual concentrationes of the test substance, the number of immobile control animals and the dissolved oxygen as well is available and presented as supportive reference only (Study A 7.4.1.2/01). The read across to the new acute toxicity study in daphnids with Decanoic acid is supported as this can be seen as worst case.

Acute toxicity of Decanoic acid to daphnids (*Daphnia magna*) was investigated in a semi-static study (Study **A 7.4.1.2/02 D, Doc. III-A 7.4.1.2**). The highest tested nominal concentration causing no mortality after 48 hours was 10 mg/L. The calculated EC_{50} is 16 mg/L (corresponding to 13.4 mg/L Octanoic acid).

Conc. Octanoic acid [g/L] = conc. Decanoic acid [g/L] * MM Octa [g/mol] / MM Deca [g/mol], where: MM Octanoic acid = 144.21 g/mol and MM Decanoic acid = 172.27 g/mol

For the results given in Octanoic acid on equimolare basis see table 23b below:

Table 23b: Acute toxicity to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results in mg /L, nominal			Remarks	Reference
			design	**duration**	**EC_0**	**EC_{50}**	**EC_{100}**		
OECD 202	*Daphnia magna*	immobilisation / acute	Static	48h	300	550	1000	Added as supporting evidence	Study A 7.4.1.2/01
OECD 202-I	*Daphnia magna*	immobilisation / acute	Semi-static	48h	**8.4***	**13.4***	**38.5***	Read accross from Decanoic acid	**Study A 7.4.1.2/02 D Doc. III-A 7.4.1.2**

* nominal confirmed

5.4.2.2 Long-term toxicity to aquatic invertebrates

No data available

5.4.3 Algae and aquatic plants

A static study according to guideline OECD 201 was conducted to estimate the toxicity of Decanoic acid to the algae *Scenedesmus subspicatus* (**Study A 7.4.1.3/01 D, Doc. III-A 7.4.1.3**). The highest initial concentration tested at which the measured parameters do not show a significant inhibition of cell growth rate relative to control values is 0.57 mg/L (NOE_rC). As the test item decreases during the test period, the results are given in mean measured concentrations (calculated as geometric mean). The calculated E_rC_{50} is 2 mg/L (corresponding to 1.67 mg/L Octanoic acid).
Conc. Octanoic acid [g/L] = conc. Decanoic acid [g/L] * MM Octa [g/mol] / MM Deca [g/mol]; where: MM Octanoic acid = 144.21 g/mol and MM Decanoic acid = 172.27 g/mol

For the results given in Octanoic acid on equimolare basis see table 23c below:

Table 23c: Growth inhibition on algae

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results in mg/L mean measured			Remarks	Reference
			design	duration	NOE_rC	E_bC_{50}[1]	E_rC_{50}[2]		
OECD 201 / EC C.3	*Scenedesmus subspicatus*	Growth and biomass inhibition	static	72 h	**0.47**	**0.97**	**1.67**	Read accross from Decanoic acid	**Study A 7.4.1.3/01 D Doc. III-A 7.4.1.3**

[1] calculated from the area under the growth curve;

[2] calculated from growth rate

5.4.4 Other aquatic organisms (including sediment)

Inhibition of microbial activity (aquatic)

No data on the inhibition of the aquatic microbial activity were generated for Octanoic acid. To demonstrate the inhibition to microbial activity the data submitted for Decanoic acid were accepted for read across **(Doc. III-A7.4.1.4/01)**.

The inhibitory effects of Decanoic acid against aquatic micro-organisms were investigated in an activated sludge respiration inhibition test according to OECD guideline 209 (**Study A 7.4.1.4/02D, Doc. III-A 7.4.1.4/02**). In this study the nominal concentrations of 10, 32, 100, 320 and 1000 mg a.s./L were incubated for 3h.

Although Decanoic acid has limited water solubility in unbuffered tap water the test substance was directly mixed into tap water by ultrasonic treatment for fifteen minutes and intense stirring for 24h to dissolve a maximum amount of the test item and/or disperse it as homogeneously as possible. No emulsifier or solvent was used. Down to the lowest test concentration at least part of the test item was not dissolved. Finally the synthetic wastewater (buffered) and the activated sludge were added. It can be assumed that the test item was dissolved during the 3-hour incubation period since the test item was ready biodegradable (10% degradation within the first 24 hours and about 60% degradation after five days of incubation; RCC Study No. A86567 - Decanoic acid: Ready biodegradability in a manometric respirometry test; see Doc. III-A7.1.1.2.1). Furthermore it can be assumed that the test substance concentration was maintained throughout the test at >80% of the initial concentration, as was measured in the acute toxicity tests with daphnia and algae.

This point was also discussed with other member states during the commenting phase of the draft CAR and it was accepted to choose 1000mg/L as NOEC for micro-organisms.

At all tested concentrations Decanoic acid had no inhibitory effect on the respiration rate in comparison to the control, but it enhanced the respiration rates, due to the fact that it serves as a substrate for micro-organisms (10 mg a.s./L: +7.9%; 32 mg a.s./L: +13.9%, 100 mg a.s./L: +18.2%; 320 mg a.s./L: +42.3%; 1000 mg a.s./L: + 20.8%).

Conclusion:

The EC_{20}, EC_{50} and EC_{80} could not be calculated since no inhibition was observed throughout the test. The NOEC for Decanoic acid was therefore determined with ≥1000 mg a.s./L (nominal).

Taking into account the molecular weight of Octanoic acid (144.21 g/mol) and Decanoic acid (172.27 g/mol) the nominal NOEC for Octanoic acid was determined with ≥837.12 mg/L.

Conc. Octanoic acid [g/L] = conc. Decanoic acid [g/L] * MM Octa [g/mol] / MM Deca [g/mol]

where: MM Octanoic acid = 144.21 g/mol and MM Decanoic acid = 172.27 g/mol

Table 23d: Effects on microbial activity (aquatic)

Guideline /	Species /	Endpoint /	Exposure	Results	Re-	Reference

Test method	Inoculum	Type of test	design	duration	NOEC	EC_{20}, EC_{50} and EC_{80}	marks	
OECD 209 / Activated Sludge, Respiration Inhibition Test	Aerobic activated sludge	Oxygen measure-ment / Respiration inhibition	static with aeration and stirring	3h	Decanoic acid: ≥1000 mg /L (nominal) Octanoic acid: ≥837.12 mg/L (nominal)	n.a. no inhibition observed	Read accross from Decanoi c acid	**Study A 7.4.1.4/02D Doc. III-A 7.4.1.4**

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

CLP:

Aquatic Acute 1:

Aquatic acute toxicity: $L(E)C_{50}$ values for all three trophic levels (daphnia and algae: read across from Decanoic acid (C10 fatty acid)) >1 mg/L;

Lowest $L(E)C_{50}$ value: E_rC_{50} (algae) =1.67 mg/L

➔ **No classification**

Studies used:

- Doc. III-A 7.4.1.1: Bätscher R. (2006), OECD 203, Acute toxicity to Zebra fish (*Brachydanio rerio*) in a 96-hour semi-static test and first amendment to study plan -> **LC_{50} (fish) 68 mg/L**
- Doc. III-A 7.4.1.2: Bätscher R. (2006), OECD 202, Decanoic acid: Acute Toxicity to *Daphnia manga* in a 48-hour immobilization test -> **EC_{50} (crustacean, converted to Octanoic acid) =13.4 mg/L**
- Doc. III-A 7.4.1.3: Bätscher R. (2008), OECD 201, Decanoic acid: Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test -> **E_rC_{50} (algae, converted to Octanoic acid) =1.67 mg/L**

Aquatic Chronic Categories:

Octanoic acid is rapidly biodegradable, adequate chronic toxicity data are only available for algae (read across from Decanoic acid (C10 fatty acid)), NOE_rC =0.47 mg/L, which lead to a classification with Aquatic Chronic 3.

For fish and crustacea only short term toxicity values in the range of 10 – 100 mg/L are available, which in combination with rapidly biodegradability, a calculated BCF_{fish} of 75 and a calculated log P_{ow} of 3.03 don't lead to any classification.

Aquatic Chronic 1:

➔ **No classification**

Aquatic Chronic 2:

➔ **No classification**

Aquatic Chronic 3:

➔ **Classification with Aquatic Chronic 3**

<u>Studies used:</u>

- Doc. III-A 7.1.1.2.1**:** Seyfried B. (2006), OECD 301 F Octanoic acid: Ready biodegradability in a manomeatric respirometric respirometry test -> **81-88% degradation in 28 days**
- Doc. III-A 3: Partition coefficient of Octanoic acid, (Estimation with KOWIN v1.67) -> **log P_{ow} =3.03**
- Calculation according to TGD on Risk Assessment -> **BCF $_{fish. calculated}$ =75**
- Doc. III-A 7.4.1.1: Bätscher R. (2006), OECD 203, Acute toxicity to Zebra fish *(Brachydanio rerio)* in a 96-hour semi-static test and first amendment to study plan -> **LC_{50} (fish) 68 mg/L**
- Doc. III-A 7.4.1.2: Bätscher R. (2006), OECD 202, Decanoic acid: Acute Toxicity to *Daphnia manga* in a 48-hour immobilization test -> **EC_{50} (crustacea, converted to Octanoic acid) =13.4 mg/L**
- Doc. III-A 7.4.1.3: Bätscher R. (2008), OECD 201, Decanoic acid: Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test -> **NOE_rC_{50} (algae, converted to Octanoic acid) =0.47 mg/L**

<u>DSD:</u>

Octanoic acid is rapidly biodegradable. It has a log P_{ow} of 3.03 and a calculated BCF_{fish} of 75. Acute aquatic toxicity values are available for all three trophic levels (daphnia and algae: read across from Decanoic acid (C10 fatty acid)), $L(E)C_{50}$ values are all between 1 - 100 mg/L. Lowest value is the E_rC_{50} value from algae with 1.67 mg/L.

R50/53:

➔ **No classification**

R50:

➔ **No classification**

R51/53:

The lowest short term value is the E_rC_{50} from algae with 1.67 mg/L, which leads to a classification with R51 and in combination with a log P_{ow} of 3.03 and a calculated BCF_{fish} of 75 further on to a classification with N; R51/53, although the substance is rapidly biodegradable.

➔ **Classification with R51/53**

R52/53:

➔ **No classification**

Studies used:

- Doc. III-A 7.1.1.2.1**:** Seyfried B. (2006), OECD 301 F Octanoic acid: Ready biodegradability in a manomeatric respirometric respirometry test -> **81-88% degradation in 28 days**
- Doc. III-A 3: Partition coefficient of Octanoic acid, (Estimation with KOWIN v1.67 -> **log P_{ow} =3.03**
- Calculation according to TGD on Risk Assessment **->** **BCF $_{fish. calculated}$ =75**
- Doc. III-A 7.4.1.1: Bätscher R. (2006), OECD 203, Acute toxicity to Zebra fish *(Brachydanio rerio)* in a 96-hour semi-static test and first amendment to study plan -> **LC_{50} (fish) 68 mg/L**
- Doc. III-A 7.4.1.2: Bätscher R. (2006), OECD 202, Decanoic acid: Acute Toxicity to *Daphnia manga* in a 48-hour immobilization test -> **EC_{50} (crustacea, converted to Octanoic acid) =13.4 mg/L**
- Doc. III-A 7.4.1.3: Bätscher R. (2008), OECD 201, Decanoic acid: Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test -> **E_rC_{50} (algae, converted to Octanoic acid) =1.67 mg/L**

REACH registration dossier for Octanoic acid:

Acute aquatic toxicity: $L(E)C_{50}$ values for all three trophic levels available (daphnia: read across from Decanoic acid (C10 fatty acid)) between 10 - 100 mg/L; lowest acute value E_rC_{50} (crustacea) >21 mg/L;
Chronic aquatic toxicity: NOEC values for all three trophic levels available (fish: read across from Sodium laurate (C12); daphnia: read across from Decanoic acid (C10 fatty acid)) between 0.01 and 10 mg/L; lowest chronic NOE_rC (algae) =0.07 mg/L;
Fate & behaviour: rapidly biodegradable; log P_{ow} =3.05; BCF measured for fish 234 – 249;
The algae growth inhibition test is quoted with reliability 1. All other studies are quoted with reliability 2. The results of studies on fish acute and chronic toxicity are given as nominal values as well as the NOEC for daphnia from the chronic study. Only the acute toxicity for daphnia is given as geometric mean measured value. Whereas the acute and chronic toxicity values from algae are given as measured TWA values.
On basis of these data in the CSA there was neither a classification proposed according to Annex VI, Table 3.1, nor according to Table 3.2 of the same Annex. But it has to be noticed, that the REACH dossier was submitted before the 2nd ATP to the CLP regulation was published.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

CLP:

There are conflicting high quality data available for the algae growth inhibition test in the CAR on biocides with a NOE_rC (algae) of 0.47 mg/L (geometric mean) and the REACH dossier with a NOE_rC (algae) of 0.07 mg/L (TWA), which would, according to the 2^{nd} ATP to CLP, lead to different classifications of Octanoic acid according to long term aquatic hazards.
Based on the data given in IUCLID 5 it is clear that in the respective study the TWA was calculated, since the test substance concentration decreased below the detection limit. In the algae growth inhibition study which is presented in the CAR on biocides the test concentration also dropped below the detection limit.
For biocidal active substances there is a clear guidance how to handle such cases in the "Technical Notes for Guidance on Assessment of environmental effects of biocidal active substances that rapidly degrade in environmental compartments of concern, CA-May08-Doc.6.5". According to this guidance the measured concentration at the start and end (in this case the limit of detection) should be taken to derive the geometric mean value.
This approach was applied to calculate the NOE_rC (algae) of 0.47 mg/L which is presented in the biocides CAR. If the same approach is applied to the concentrations given in the IUCLID file of the algal growth inhibition test in the REACH dossier, then the NOE_rC (algae) is 0.2 mg/L (geometric mean), corresponding to 0.07 mg/L (TWA).

We therefore decided to propose the following classification and labelling based on the geometric mean NOE_rC values for algae:

Proposed classification and labelling according to Reg. (EU) No 1272/2008, Annex VI, Table 3.1 and Reg. (EU) No. 286/2011

<table>
<tr><th colspan="3">Classification and Labelling</th><th>Justification</th></tr>
<tr><td colspan="2">GHS Pictograms</td><td>-</td><td rowspan="7">Rapidly degradable substance for which adequate chronic toxicity data are available for algae. Lowest chronic values are the geometric mean NOE_rCs from algae with 0.47 and 0.2 mg/L.
For fish and crustacea only reliable short term toxicity values in the range of 10 – 100 mg/L are available, which in combination with ready biodegradability, measured BCF_{fish} values from 234 – 249 and a log P_{ow} of 3.03 – 3.05 don't lead to any classification.</td></tr>
<tr><td colspan="2">Signal words</td><td>-</td></tr>
<tr><td colspan="2">Classification</td><td>Aquatic Chronic 3</td></tr>
<tr><td colspan="2">Hazard statements</td><td>H412: Harmful to aquatic life with long lasting effects</td></tr>
<tr><td rowspan="5">Precautionary Statements</td><td>General</td><td>-</td></tr>
<tr><td>Prevention</td><td>P273: Avoid release to the environment</td></tr>
<tr><td>Response</td><td>-</td></tr>
<tr><td>Storage</td><td>-</td><td></td></tr>
<tr><td>Disposal</td><td>P501: Dispose of contents/container in accordance with local/regional/national/</td><td></td></tr>
</table>

		international regulations (to be specified).	

DSD:

Proposed classification and labelling according to Reg. (EU) No 1272/2008, Annex VI, Table 3.2

Classification and Labelling: N

R51/53

S61

Justification: Octanoic acid is readily biodegradable. The log P_{ow} is given with 3.05 (REACH dossier) – 3.03 (CAR). A calculated BCF_{fish} =75 (CAR) and measured BCF values from 234 - 249 (REACH dossier) are available. All available $L(E)C_{50}$ values are between 10 and 100 mg/L. The only exception is the lowest E_rC_{50} algae with 1.67 mg/L (CAR).

The E_rC_{50} algae with 1.67 mg/L in combination with a log P_{ow} of 3.03 – 3.05 and measured BCF values of >100 lead to a classification with N; R51/53 and S61.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The ecotoxicological tests on fish, crustaceans (read across from decanoic acid) and algae (read across from decanoic acid) presented in the CLH report show that the lowest short term value is the ErC_{50} for algae (= 1.67 mg/L). Since the $L(E)C_{50}$ values are all above 1 mg/L, the dossier submitter concluded that the criterion for classification for acute aquatic hazard Category 1 (CLP) and R50 (DSD) are not fulfilled. The dossier submitter considered octanoic acid to be readily biodegradable and rapidly degradable since in a manometric respirometric test (OECD TG 301F), a mean degradation rate of 84% at the end of the 28-days exposure period was observed.

In the CAR for biocides, the calculated log Pow is 3.03 and the resulting calculated BCF on fish is 75. In the REACH registration dossier, the Pow is 3.05 and the measured BCF for fish is 234 – 249.

Based on the values for aquatic acute toxicity stated above (1 mg/L < ErC_{50} for algae = 1.67 mg/L ≤ 10 mg/L), log Pow (≥ 3) and measured BCF (> 100), the dossier submitter proposed to classify as R51/53 according to DSD.

In relation to the long term aquatic hazard according to the changes to the CLP Regulation based on the 2nd ATP, only long term data on algae (*Desmodesmus Subspicatus*) are available, providing a geometric mean NOEC of 0.47 mg/L (72 h growth inhibition test, read across from decanoic acid, presented in the CAR for biocides). For fish and crustaceans, only acute toxicity values in the range 10-100 mg/l are available, which in combination with rapid degradability, measured BCF in fish < 500 and logPow < 4 does not lead to any classification. The dossier submitter proposed therefore to use the NOEC value for algae that, together with the rapid degradability, would determine a classification for aquatic chronic Category 3.

In conclusion, the dossier submitter proposes to classify octanoic acid as hazardous to the aquatic environment, aquatic chronic Category 3 - H412, according to the Regulation (EC) 1272/2008 (CLP), and R51/53 according to Directive 67/548/EEC (DSD).

However, following a remark raised in the public consultation, the dossier submitter has changed the proposed classification for long term aquatic hazard according to CLP to aquatic chronic Category 2. The dossier submitter justified the change on the basis of the algae TWA NOEC from the REACH registration dossier, (study conducted on *Pseudokirchnerella Subcapitata)*, which is equal to 0.07 mg/l. The dossier submitter has also changed the proposed classification according to DSD to "no classification", on the basis of the measured TWA ErC_{50} from the REACH registration dossier of octanoic acid (study conducted on *Pseudokirchnerella Subcapitata)*, which is equal to 31 mg/l.

Comments received during public consultation

During the public consultation, comments on hazards to the aquatic environment were received from four Member States Competent Authorities (MSCAs) and four companies.
Three MSCAs supported the classification proposal.
Another MSCA suggested that a wider set of ecotoxicity data be considered relative to the analogues (heptanoic, nonanoic and decanoic acid), available from the REACH registration dossiers, in order to understand and validate the read-across to octanoic acid.
In particular, this MSCA proposed that the TWA NOEC value relating to the study conducted on the algae *pseudokirchnerella subcapitata* be used from the REACH registration dossier instead of the read-across from decanoic acid.
In response to this comment, the dossier submitter included in the RCOM a summary of all available acute and chronic ecotoxicity data from CARS and REACH registration dossiers from heptanoic, octanoic, nonanoic and decanoic acids. On the basis of this extended dataset, the dossier submitter changed the proposed classification to Aquatic Chronic 2, according to CLP, and no classification, according to DSD.
The four companies referred to a report of the Fatty Acids Consortium (FAC) to propose no classification, on the basis of the general characteristics of fatty acids, naturally occurring and ubiquitously present in the aquatic environment, where they are readily biodegraded by microorganisms. They underpinned their justification with the argument that the logPow was inappropriate as a predictor of bioaccumulative properties and the fact that the calculated BCF (75) is < 100.
Moreover, they claimed that there were methodological deficiencies in the studies used to conclude on classification in the CLH report. They questioned the use of a 72h-NOEC instead of a 48h-NOEC in the algae test for decanoic acid under Biocide Directive, as well as the use of measured concentrations. (In their view, fatty acids act as nutrients for algae. Since the applied amount is not lost from the system but become part of the cells, nominal concentrations should be used). Therefore, they propose that the NOEC of 17.5 mg/l, which was obtained in a new algae study on octanoic acid, be considered. This value would warrant a "no classification" according to the CLP regulation.
Also, long term studies on aquatic invertebrates for decanoic acid are being conducted and test data were expected by October 2012.
The dossier submitter responded to this comment by supporting the classification as Aquatic Chronic 2 and describing the cause of the observed effects in the long term test on algae, and the lack of classification according to DSD.
For the full set of comments and responses, see the response to comments document (RCOM) in Annex 2.

Additional key elements

Octanoic acid (C8) belongs to a group of organic acids such as nonanoic (C9), decanoic (C10) and lauric (C12) acids, therefore information about these structurally similar compounds is considered useful to establish a classification for octanoic acid which is consistent with these other acids.
A consolidated set of all the available and reliable data from the CAR for biocides and other tests submitted more recently from REACH registration are shown in the next table in order to understand the classification and the comparison with other structurally similar organic acids.

Table 1. Ecotoxicity for organic acids.

Acute or chronic	**Species**	**test**	**Design**	***CAR for biocides***				***REACH registration dossier***			
				Octano	**Nonano**	**Decano**	**Lauri**	**Octano**	**Nonano**	**Decano**	**Lauri**

(L(E)C50 (mg/L))				**ic Acid**	**ic acid**	**ic Acid**	**c acid**	**ic Acid**	**ic acid**	**ic Acid**	**c acid**
Aquatic Acute Toxicity (L(E)C50 (mg/L))	*Danio rerio*	OECD TG 203	Flow-through	-	-	-	>10	-	-	-	-
	Pimephales promelas	OECD TG 203	Flow-through	-	-	-	-	-	104 mm	-	-
	Brachydanio rerio	OECD TG 203	Semi-static	68 nc	-	81.2[1]nc >8.6[9] nc	-	-	-	-	-
	Oncorhynchus mykiss	OECD TG 203	Semi-static	-	>13.66 mm (TWA)	-	-	-	-	-	-
	Leuciscus idus	OECD TG 203	Semi-static	-	>7.2 mm (TWA)	-	-	-	-	-	-
	Oncorhynchus mykiss	OECD TG 204[2]	Flow-through	-	19.2 nc	-	-	-	-	-	-
	Daphnia magna	OECD TG 202-I	Semi-static	13.4[3] nc 21.53[7] mm	23.63 mm	16 nc	1.9 mm	-	-	>21 mm (Gm) Static	-
	Pseudokirchneriella subcapitata	OECD TG 201	Static	-	-	-	-	31[5,6] mm (TWA) (120 nc)	-	-	-
	Desmodesmus subspicatus	OECD TG 201	Static	1.67[3] mm (26.79[3] – 94.23[7] nc)	1.84[8] Mm (103.4 nc)	2 mm (32 nc)	0.219 mm	-	-	-	-
	Anabaena flos-aquae	OPPTS 850.5400	Static	-	>3.48 mm (Gm)	-	-	-	-	-	-
	Lemna gibba	Draft guideline	Semi-static	-	> 9.77 mm	-	-	-	-	-	-
Aquatic Chronic Toxicity (NOEC (mg/L)	Daphnia Magna	OECD TG 211	Semi-static	9.05[7]	9.93 mm	-	-	-	-	-	0.47 mm (TWA)
	Pseudokirchnerella subcapitata	OECD TG 201	Static	-	-	-	-	0.07[6] mm (TWA) (10 nc)	-	-	-
	Scenedesmus subspicatus	OECD TG 201	Static	0.21[3,4] mm (Gm) (2.68	0.568mm (Gm)	0.25[4] mm (Gm)	0.079 mm (ErC10)	-	-	-	-

				nc) 0.52[7] mm (Gm) (3.62nc)	(3.97 nc)	(3.2 nc)					
	Anabaena flos-aquae	OPPTS 850.5400	Static	-	3.48mm (Gm)	-	-	-	-	-	-
	Lemna gibba	Draft guideline	Semi-static	-	4.86 mm	-	-	-	-	-	-

mm: mean measured, Gm: Geometric mean, nc: nominal concentration, TWA: time weight average.

"-" indicates no data.

[1] Read across from octanoic acid (MM = molar mass). Conc. Decanoic acid [g/L] = conc. Octanoic acid [g/L]*MM Deca [g/mol] / MM Octa [g/mol], where: MM Decanoic acid = 172.27 g/mol and MM Octanoic acid = 144.21 g/mol.

[2] Further information on possible short-term effects.

[3] Read across from decanoic acid. Conc. Octanoic acid [g/L] = conc. Decanoic acid [g/L]*MM Octa [g/mol] / MM Deca [g/mol], where: MM Decanoic acid = 172.27 g/mol and MM Octanoic acid = 144.21 g/mol.

[4] In the RCOM the DS recalculated the NOEC for decanoic acid from 0.57 mg/l (mentioned in the CLH report) to 0.25 mg/l. The value in the table for octanoic acid has been obtained by read-across from the recalculated value of decanoic acid.

[5] At the highest concentration tested the percentage reduction of growth rate was 42%.

[6] http://apps.echa.europa.eu/registered/data/dossiers/DISS-abdc6ece-790e-0db7-e044-00144f67d249/AGGR-14d1e708-b0d1-47bf-81ee-7bf28835d214_DISS-abdc6ece-790e-0db7-e044-00144f67d249.html#AGGR-14d1e708-b0d1-47bf-81ee-7bf28835d214. (See supplemental information section).

[7] Read across from nonanoic acid. Conc. Octanoic acid [g/L] = conc. Nonanoic acid [g/L]*MM Octa [g/mol] / MM Nonanoic [g/mol], where: MM Nonanoic acid = 158.24 g/mol and MM Octanoic acid = 144.21 g/mol.

[8] Read across from decanoic acid. Conc. Nonanoic acid [g/L] = conc. Decanoic acid [g/L]*MM Nona [g/mol] / MM Decanoic [g/mol], where: MM Nonanoic acid = 158.24 g/mol and MM Decanoic = 172.27 g/mol.

[9] Read across from lauric acid. Conc. Decanoic acid [g/L] = conc. Lauric acid acid [g/L]*MM Deca [g/mol] / MM Lauric [g/mol], where: MM Decanoic acid = 172.27 g/mol and MM Lauric acid = 200.32 g/mol.

Assessment and comparison with the classification criteria

Degradation.

Octanoic acid is readily biodegradable under Ready Biodegradability test conditions (OECD TG 301F); degradation was 81-88% at 28 days and within the 10 d window 66-73%. Hydrolysis and photolytic degradation in water are excluded for octanoic acid because organic acids cannot be hydrolysed in the absence of further functional groups and it does not display chromophore properties at wavelengths above 290 nm.

Octanoic acid degrades rapidly in the atmosphere by reaction with OH radicals ($T_{1/2}$: 46.1 h), therefore accumulation in air is not expected.

Based on the available data, RAC agrees with the dossier submitter that octanoic acid must be considered **rapidly degradable** according to CLP and **readily biodegradable** according to the DSD.

Bioaccumulation

No experimental log kow could be determined for decanoic acid, because the octanol /water coefficient cannot be accurately estimateded.

No experimental log kow can be determined for octanoic acid, because the octanol/water coefficient cannot be calculated by the relation of water saturation concentration and octanol saturation concentration.

A calculated log Kow value of 3.03 has been summarized in the CLH report. This log Kow corresponds to an undissociated acid; however at relevant environmental pHs, octanoic acid is found in a dissociated form (pka = 4.89) and, therefore, the log kow is expected to be lower.

Nevertheless, octanoic acid is a surface active substance (surface tension 53.2mN/m), and according to the Technical Guidance Document on Risk Assessment (EC 2003, part II, p. 24), for such substances it may not be advisable to use an estimated or measured Kow value as a predictor for BCF (fish, worm), because the predictive value of log Kow for such estimations may be too low. Instead, for surfactants it may be appropriate to obtain measured BCF values.

For octanoic acid, there is no BCF available; however, in the REACH registration dossier[i], there is an experimental BCF performed with sodium laurate, which can be used with caution as a read-across analogue for octanoic acid. The measured BCF value for lauric acid is 255 L/kg, but it is based on total radio-labelled residues and therefore, it is overestimated. Nevertheless, according to the guideline on the application of the CLP criteria (p. 506), if an experimental BCF based on the parent compound is not available, for classification purposes, the BCF based on radio-labelled residues can be used.

The test shows some deficiencies, such as the depuration phase was not determined, the fish were only sampled at the end of the exposure and furthermore the study was not GLP compliant; however, this test can indicate the bioaccumulation potential of similar substances and therefore it can be used as supportive information.

In conclusion, since the log kow may be an unreliable predictor of bioconcentration potential for this substance, it is not appropriate to compare it with the classification criteria. No measured BCF data are available for octanoic acid itself. The C_{12} analogue lauric acid is more hydrophobic than octanoic acid, so a direct read across of its measured fish BCF is likely to be a worst case scenario approach. The implication in the absence of any further evidence is that the BCF of octanoic acid is below 500 L/kg, but it cannot be ruled out that the BCF is above 100 L/kg.

<u>Aquatic toxicity</u>

A summary of ecotoxicological data of different structurally similar organic acids has been summarised in the additional key elements section, table 1.

As can be seen in this table, if the toxicity in fish and daphnia is evaluated without considering the read-across, as one would expect, there appears to be a direct relationship between the toxicity and hydrophobicity of the acids and since hydrophobicity is related to chain-length of the acids, their toxicities follow the order: lauric acid > decanoic acid > nonanoic acid > octanoic acid. However regarding the toxicity to algae, which is clearly the most sensitive taxonomic group, there are some data which are too inconsistent to enable a classification to be established.

Three different algae tests were included in the report, one performed with nonanoic acid with a NOEC of 0.57 mg/L (Competent Authority Report, CAR, of biocides), one more performed with decanoic acid and a NOEC of 0.21 mg/l (CAR of biocides) and finally another one with octanoic acid as the test substance and a NOEC of 0.07 mg/L (REACH registration dossier). Information on lauric acid has been also included in order to attempt to follow the trend of the toxicity, and the NOEC value used for algae is 0.079 mg/L (CAR of biocides). All these values were based on mean measured concentrations.

The tests for nonanoic, decanoic and lauric acid were performed with the same algae species (*Desmodesmus Subspicatus*) and for octanoic acid the selected algae species was *Pseudokirchnerella subcapitata*. These two species are recommended by the OECD TG 201 guideline.

As can be seen in the results, *Pseudokirchnerella Subcapitata* appears to be the most sensitive species and therefore octanoic acid the most toxic compound. This result from the REACH registration dossier is not consistent with the results obtained in daphnia and fish or with the trend observed in the algae tests carried out on the other substances in the group. If this test is not considered, toxicity appears to increase with hydrophobicity.

Furthermore, there are some deficiencies in the test from REACH registration, such as the inconsistency in dose-responsiveness at the lowest concentrations, the rapid loss of the test concentration and the fact that the highest effect is observed at 24 hours. Therefore, taking into account that the reliability of this test cannot fully be confirmed and that this test is not consistent with the results of the other taxonomic groups, it should not be used for classification purposes.

During Public Consultation, industry noted a new algae test performed with octanoic acid; this test was submitted during the preparation of the second draft opinion, however, according to the information included in the test report, it is not totally clear if, at the end of the test, the concentration has been measured with algae (as required by the guideline) or without them. On the other hand, if the test has been performed according to the guideline, it is difficult to understand why it is possible to maintain the concentration, for the duration of the test, for octanoic acid, and not for nonanoic, decanoic and lauric acids. So in analogy with the test that was registered under REACH, the reliability of this test can also not be confirmed, and therefore it should not be used for classification purposes (for more details, see the supplemental information section).

A read-across from nonanoic and decanoic acids is appropriate, if considering the worst case scenario, because the toxicity increases with increasing hydrophobicity.
As the test substance was not detectable at the end of the algae tests performed with nonanoic and decanoic acids, the 48 h time interval might be regarded as relevant. However, in the 72-hour algal growth inhibition test with decanoic acid, the following validity criterion given in OECD TG 201 is not fulfilled: "The test period may be shortened to at least 48 hours to maintain unlimited, exponential growth during the test as long as the minimum multiplication factor of 16 is reached". In the case of the algae test with decanoic acid, the multiplication factor is only approximately 10. Therefore, the total test duration of 72 h has to be used for effect assessment and to estimate chronic effects (by using a concentration equal to half of the limit of quantification when the test substance is not detectable). For nonanoic acid it is not possible to check this due to the minimal data provided.

There is a rapid loss of the test concentrations in the tests with nonanoic, decanoic and dodecanoic acids; this rapid loss also appears in fish and daphnia studies (semi-static tests), as well as in the algal tests without algae for nonanoic and dodecanoic acids. Furthermore, it is necessary to take into account that decanoic acid together with octanoic and nonanoic acids, are surface active substances and the critical micelle concentration is not mentioned in the dossier; so the presence of micelles and adsorption to hard surfaces could partly explain the technical difficulties associated with measuring the actual concentrations of these acids.

According to the OECD guideline 201, the use of nominal concentrations could be appropriate when a decrease in concentration of the test substance in the course of the test is not accompanied by a decrease in growth inhibition. In the algae test performed with decanoic acid it is observed that at 72h the growth inhibition is lower than at 48h when the concentration was higher. Therefore, at least for this test, the criterion for using nominal concentrations is not met.

Moreover, under the Biocides Directive, the acute and chronic algae toxicity was based on mean measured concentrations. Taking into account the deficiencies of the test submitted under REACH registration and the new test submitted by the industry and the justified use of measured concentrations in the algae tests conducted on nonanoic and decanoic acids, the classification is as follows.

Under CLP, the aquatic acute toxicity category is based on EC_{50} values, and for octanoic acid these values, considering also read-across from nonanoic and decanoic acids, are >1 mg/l, therefore octanoic acid does not warrant classification for aquatic acute toxicity. This value is consistent with the acute toxicity of other structurally similar compounds (nonanoic and decanoic acid) with EC_{50} values also higher than 1 mg/L.

Regarding chronic toxicity, the most sensitive species is the algae (*Desmodesmus subspicatus)* with a NOErC of 0.21mg/L (read across from decanoic acid) or 0.52 mg/L (read-across from nonanoic acid).

Taking into account these values and its rapid degradation, octanoic acid classifies as **Chronic category 3 (H412)** according to **CLP**. Although there are no chronic tests in fish, the surrogate approach is not relevant since octanoic acid is readily biodegradable and has a fish BCF <500 L/kg and therefore leads to no classification, and does not impact on the proposal. For chronic tests in *Daphnia*, please see the supplemental information section point 2 (read-across from decanoic acid) and table 1 from the additional information section (read-across from nonanoic acid). The read-across from decanoic acid is a worst case; nonanoic acid is more similar and therefore using read-across from nonanoic acid would be a more realistic approach, but both values trigger no classification.

Under **DSD**, the EC_{50} value for algae, *Desmodesmus subspicatus*, (read-across from decanoic acid) is 1.67 mg/L and although the substance is readily biodegradable, the BCF > 100 L/kg cannot be ruled out, therefore classification as R51/R53 is justified. It is not possible to carry out the read-across from nonanoic acid, because there is no reliable measured EC_{50} value for this species (*Desmodesmus subspicatus*).

Supplemental information - In depth analyses by RAC

1. REACH Registration dossier: Algae test (octanoic acid).

A calculation of percentage reduction of growth rate at 72 h has been conducted because the values which appear in the summary were calculated incorrectly.

Table 2: Percentage reduction of growth rate at 72h:

TWA concentrations (mg/l)	72h	Reduction [%]
control	0.05830	-
0.07	0.05399	7
0.09	0.03986	31.6
0.12	0.04715	19.1
4.9	0.03388	41.9
24	0.03382	42

Based on the data in the table above, it can be concluded that the EC_{50}>24 mg/L.

2. Additional information supplied by the industry: (see confidential section on CIRCA)

During the elaboration of the 2nd Draft Opinion for organic acids, the industry supplied three new tests; one of these was in Japanese, so it could not be assessed.

2nd test: *Effect of decanoic acid on the reproduction of Daphnia magna*

The second test was a GLP compliant *Daphnia Magna* reproduction test performed with decanoic acid and in accordance with the OECD TG 211. This was a limit test. The test item was prepared as a WAF and replaced daily alongside the control media. Samples were taken for chemical analysis from fresh and aged media during three representative 24 h exposure periods per week.

The effects on growth and reproductive performance were based on the time weighted average (TWA) measured concentration. The TWA concentration was 1.3 mg/L with respect to the nominal loading of 5 mg/L (25.9% recovery of nominal loading).

No immobilization occurred throughout the test. Age to first reproduction and growth (adult body length) were unaffected by the test loading. With a reproduction average of 76 for the control and 74 for the test loading, there was no significant inhibition of mean cumulative offspring. As there were no differences between the test loading and the control, the NOEC for all endpoints is reported as ≥1.3 mg/L (TWA).

The test meets the validity criteria of the guideline.

As was the case for the algae test, the actual concentration is reduced over the duration of the test; the TWA of the nominal loading of 5.0 mg/L was 1.3 mg/L (the TWA of the test item was 25.9% of nominal loading). According to the industry, a possible explanation for the decrease in concentration observed between fresh and aged test medium is the accumulation of decanoic acid by the test organism. However, taking into account the same losses of similar compounds were found in tests without organism, the causes of these losses are not clear.

The NOEC ≥1.3 mg/L (TWA) supports the conclusion that *Daphnia* is not the most sensitive species. This new test is not going to change the classification. This conclusion is also applicable to octanoic acid if a read-across from decanoic acid is used as a worst case scenario, providing NOEC values higher than 1 (NOEC (octanoic acid) >1.09 mg/L).

3rd test: *Effect of octanoic acid on the growth of Pseudokirchneriella subcapitata*

The third test was a GLP Freshwater Algae, Growth Inhibition Test performed with octanoic acid and followed the OECD TG 201.

The test item was dissolved in sterilised growth medium without a solvent. For the determination of algal growth, eight replicates for controls (test medium only) and four replicates for each test concentration were exposed to five different concentrations increasing by a factor of 2 (nominal 0, 5, 10, 20, 40, 80 mg test item/L).

The concentrations of octanoic acid were chemically analysed using GC-MS. Octanoic acid was analysed in the freshly prepared test solutions without algae at the start of the test and in the test media after 72 h. The decrease in the test concentration was less than 20 % during the test period, and therefore initial measured octanoic acid concentrations were used. For the relevant parameter growth rate, the ErC_{50} and the ErC_{10} values were 43.7 and 15.6 mg/L. The NOEC was calculated to be 17.5 mg/L. According to the information included in the test, it is not totally clear if, at the end of the test, the concentration has been measured with algae present, as required by the guidelines, or without algae. If the test has been performed according to the guidelines, it is difficult to understand why it is possible to maintain the concentration for the duration of the test for octanoic acid, and not for nonanoic, decanoic and lauric acid.

6 OTHER INFORMATION

Not available

7 REFERENCES

Section no/ reference no	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP (where relevant) / (Un)published**	**Data Protection**	**Owner**
A2/01	2009	Octanoic Acid: Complete Analysis of Four Batch Samples ChemService S.r.l. Study Number CH-627/2008 Unpublished	Y	SOPURA
A2.10/03	2006	Method to calculate the unavoidable residue Octanoic Acid SOPURA Unpublished	Y	SOPURA
A2.10/04	2006	Quantitative Evaluation Octanoic Acid Quantity likely to be found back in the Environment after Application Unpublished	Y	SOPURA
Company statement	2010	INFORMATION FOLLOWING THE REQUEST FROM THE AUSTRIAN RMS (information regarding calculations)	Y	SOPURA
A.3/01	1999	Determination of some physico-chemical properties of Octanoic acid TNO Prins Maurits Laboratory Report number: PML 1999-C109 Unpublished	Y	SOPURA
A3/02	1999	Expert statement: hydrolysis and dissociation constants of n-	Y	SOPURA

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
A3/04		octanoic acid and n-decanoic acid Report number: V99.846 TNO Voeding Unpublished		
A3/03	1989	Merck Index 11 th Edition – 1989; No. 1765	N	Published
A3/05	2006	Calculation of the Henry Law Constant and Log Kow for Octanoic acid with the Program HENRYWIN v3.10 Unpublished	Y	MCF-Consultancy GmbH
A3/06	2006	Expert statement Stability of octanoic acid in organic solvents Unpublished	Y	MCF-Consultancy GmbH
A3/07	2006	Expert statement Thermal stability of octanoic acid Unpublished	Y	MCF-Consultancy GmbH
A3/08	2006	Expert statement Flammability, including auto flammability and identity of combustion product of octanoic acid Unpublished	Y	MCF-Consultancy GmbH
A3/10_rev09a	2008	Octanoic acid Determination of the surface tension; Report No. 5474-OCTA-3 Sopura, Unpublished	Y	SOPURA
A3/11_rev09	2008	Octanoic acid Determination of the bulk density Report No. 5474-OCTA-5 Sopura Unpublished	Y	SOPURA
A3/12	2006	Expert statement Explosive properties of octanoic acid Unpublished	Y	MCF-Consultancy GmbH
A3/13	2006	Expert statement Oxidizing properties of octanoic acid Unpublished	Y	MCF-Consultancy GmbH
A3/14	2006	Expert statement Reactivity towards container material of octanoic acid Unpublished	Y	MCF-Consultancy GmbH
A3/15	2006	Expert statement Approval certificates Unpublished	Y	SOPURA
A3/16	2006	Edenor C 8 98-100 (octanoic acid): Determination of the water solubility considering also the effects of temperature and pH value ChemService S.r.l. Study nr CH-333/2006 Unpublished	Y	SOPURA
A3/17	2006	Analysis Certificate-Addendum SGS	Y	SOPURA

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
		Unpublished		
A3/17a	2009	Octanoic Acid: Determination of the Flash Point ChemService S.r.l. Study nr CH-623/2008 Unpublished	Y	SOPURA
A3/18_rev09a	2008	Octanoic acid Determination of the Viscosity Report No. 5474-OCTA-2 Sopura Unpublished	Y	SOPURA
A3/19_rev09	2009	Octanoic Acid: Determination of the Solubility in organic Solvents considering also the Effect of Temperature ChemService S.r.l. Study nr CH-624/2008 Unpublished	Y	SOPURA
A4.1/01	2009	Octanoic Acid: Validation of the Analytical Method for the Determination of the Active Ingredient Content ChemService S.r.l. Study nr CH-625/2008 GLP Unpublished	Y	SOPURA
A4.1/02	2009	Octanoic Acid: Validation of the Analytical Method for the Determination of the Significant Impurity Content ChemService S.r.l. Study nr CH-626/2008 GLP Unpublished	Y	SOPURA
A4.2/01	1998	In-situ methylation of strongly polar organic acids in natural waters supported by ion-pairing agents for headspace GC-MSD analysis Dresden University of technology Peter L. Neitzel, W. Walther, W. Nestler Fresenius J Anal Chem (1998) 361:318-323;	N	Published
A4.2/02	2006	Methodenvalidierung 0,1 µg/L for decanoic acid and octanoic acid Böhler Analytik Ges.m.b.H no GLP Unpublished.	Y	SolNova
A4.3/04	1990	Method for the Quantitative Analysis of Volatile Free and Total Branched-Chain Fatty Acids in Cheese and Milk Fat Kim J.H.A. and Lindsay R.C. J. Dairy Sci 73:1988-1999 Published	N	Published
A4.3/05	1990	Determination of Free Fatty Acids in Wort and Beer De Vries K. ASBC Journal	N	Published

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
		Published		
A4.3/06	1994	Analysis of Free Fatty Acids, Fusel Alcohols, and Esters in Beer: An Alternative to CS2 Extraction Alvarez P. and Malcorps P J. Am. Soc. Brew. Chem. 52(3):127-134 Published	N	Published
A4.3/07	1985	The Semi-Routine Use of Capillary Gas Chromatography for Analysis of Aroma Volatiles in Beer Stenroos L.E. et.al ASBC Journal:203-208 Published	N	Published
A4.3/08	1990	Extraction and Analysis of Volatile Compounds in White Wines Using Amberlite XAD-2 Resin and Capillary Gas Chromatography Edwards C.G. and Beelman R.B J. Agric. Food. Chem. 38:216-220 Published	N	Published
A5/01	2006	Microbiological performance of SEPTACID BN on beer spoiling bacteria Unpublished	Y	SOPURA
A5.3.1/01	2006	SOPURSEPT BN-8 + DT 6 in clean conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.1/02	2006	SOPURSEPT BN-8 + DT 6 in dirty conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.2/01	2006	SOPURSEPT BN-8 + DETAL HP in clean conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.2/02	2006	SOPURSEPT BN-8 + DETAL HP in dirty conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.2/03	2006	SOPURSEPT BN-8 + ATR B in clean conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.2/04	2006	SOPURSEPT BN-8 + ATR B in dirty conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
A5.3.3/01	2006	SOPURSEPT BN-8 + ATR F in clean conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.3/02	2006	SOPURSEPT BN-8 + ATR F in dirty conditions report assay Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.4/01	2010	SEPTACID BN without A.S.: Evaluation of the bactericidal and fungicidal activity according to the European standard test method EN1276 and EN1650. Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.4/02	2010	SEPTACID BN-PS without A.S.: Evaluation of the bactericidal and fungicidal activity according to the European standard test method EN1276 and EN1650. Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A5.3.4/03	2010	Decanoic acid.: Evaluation of the bactericidal and fungicidal activity according to the European standard test method EN1276 and EN1650. Haute école Lucia de Brouckère-Institut Meurice-Laboratoire de Microbiologie Unpublished	Y	SOPURA
A6/ 01	1976	Safety studies on a series of fatty acids. Briggs G.B; Doyler L.; Young J. A. American Industrial Hygiene Association Journal; April, 1976 Published	N	-
A6/02	1962	Range-finding toxicity data: List IV Smyth Jr.H.F., Carpenter C.P., Weil C.S., Pozzani U.C. and Striegel J.A. American Industrial Hygiene Association Journal (AIHAJ), 23, 95-107 Published	N	-
A6/03	1979	Capric acid, Opdyke D.L.J. Fd Cosmet. Toxicol. 17 735 (review article) Published	N	published

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protect ion	Owner
A6/04a	1996	Toxicity Profile , n-Decanoic acid (and its sodium and potassium salts) TNO BIBRA --- Published	N	published
A6/04b	1988	Toxicity Profile , n-Octanoic acid (and its sodium and potassium salts) TNO BIBRA --- Published	N	published
A6/05	2006	Riskassessments Gubler-Coaching, Pfäffikon, Switzerland Unpublished	Y	MCF-Consultancy GmbH
A6/07	1998	Safety evaluation of certain food additives and contaminants, saturated aliphatic acyclic linear primary alcohols, aldehydes, and acids the forty-ninth meeting of the JECFA, Joint FAO/WHO Expert Committee on Food Additives	N	Published
A6/08	2004	19,71 kg Käse ass Herr Schweizer im 2004 Anonymus Internet	N	Published
A6/09	2004	Sojaöl Spychiger Oil Trading AG,CH-6045 Meggen	N	Published
A6/10	2002	Fettsäurezusammensetzung wichtiger pflanzlicher und tierischer Speisefette und –öle Deutsche Gesellschaft für Fettwissenschaft	N	Published
A6/11	1999	Review of the Toxicologic Properties of Medium-chain Triglycerides Traul K.A., Driedger A., Ingle D.L., Nakhasi D. Food and Chemical Toxicology 38 (2000) Published	N	Published
A6/12	1982	Medium-chain triglycerides: an update Bach A.C., Babayan V.K. The American Journal of Nutrition 36 pages 950 – 962 Published	N	Published
A6/13	2005	Evaluation of certain food additives 63 report of the Joint FAO/WHO Expert Committee on Food Additives	N	Published
A6/14	2000	http://ecb.jrc.ec.europa.eu/esis/index.php IUCLID entry	Y	Not reported add. info.

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
A6/15	2004	A chemical dataset for evaluation of alternative approaches to skin-sensitization testing Gerberick G.F. et al. Contact Dermatitis, Vol 50, No 5, 2004 Published	N	Published
A6/16	1976	SAFETY STUDIES ON A SERIES OF FATTY ACIDS. Briggs G.B., Doyle R. L., Young J. A. American Industrial Hygiene Association Journal; April 1976	N	published
A6/17	1953	Production of gastric lesions in the rat by the diet containing fatty acids Mori K. GANN, Vol. 44; December Published	N	Published
A6/18	2007	ALTERNATIVE APPROACHES TO IMMUNOTOXICITY AND ALLERGY TESTING Presentation at EUROTOX Congress 2007 unpublished	N	Unpublished
A6.1.1/01	1981	Prüfung der akuten oralen Toxizität Henkel, Düsseldorf	Y	Cognis (LoA available)
A6.1.2/01	2006	Decanoic acid: Acute Dermal Toxicity Study in Rats; RCC Ltd, Itingen Switzerland Study Number A86556 Unpublished	Y	SOPURA
A6.1.3/02	1998	THE BIOPESTICIDE MANUAL Copping L.G. British Crop Protection Council, 1st edition, p. 25 Report-No. not applicable Not GLP, Published	N	Published
A6.1.3/03	--	TOXICOLOGICAL SIMILARITY OF STRAIGHT CHAIN SATURATED FATTY ACIDS OF GREATER THAN 8 CARBON CHAIN LENGTH BY VARIOUS ROUTES OF EXPOSURE Anonymous Safer Inc, Eden Prairie MN 55334-3585, USA Report-No. not applicable Not GLP, Published	N	Published
A6.1.4.s/02	1999	A two-center study of the development of acute irritation responses to fatty acids. Robinson M.K., Whittle E. and Basketter D.A. American Journal of Contact Dermatitis, Vol. 10, No 3 1999 Published	N	Published
A6.1.5/2	2006	Skin Sensitisation Study (Local Lymph Node Assay);	Y	SOPURA

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
		Austrian Research Centers GmbH – ARC Life Sciences Toxicology, Seibersdorf, Austria; Report Nr: ARC-L2241; Unpublished		
A6.1.5/1	2004	A chemical dataset for evaluation of alternative approaches to skin-sensitization testing Gerberick G.F. et al Contact Dermatitis, Vol 50, No 5, 2004 Published	N	published
A6.4.1.1/01	1993	A 91-day feeding study in rats with caprenin Webb D.R., Wood F.E., Bertram T.A. and Fortier N.E. Fd Chem. Tox. Vol 31, No 12 The Proctor & Gamble Company Published	N	published
A6.4.1.1/02 A6.8.2	1968	Nutritional Evaluation of Medium-Chain Triglycerides in the Rat Harkins R.W. and Sarett H.P. The Journal of the American Oil Chemists' Society Department of Nutritional Research, Mead Johnson Research Center, Evansville, Indiana Published	N	published
A6.6.1/1	1999a	Bacterial reverse mutation test with decanoic acid Netherlands Organisation for applied scientific research (TNO), Zeist, The Netherlands TNO-report V99.668 Ref nr A6.6.1/01	Y	SOPURA
A6.6.1/2	1999b	Bacterial reverse mutation test with octanoic acid Netherlands Organisation for applied scientific research (TNO) Zeist, Netherlands TNO-Report V99.668	Y	SOPURA
A6.6.2/1	1999a	Chromosomal aberration test with decanoic acid in cultured Chinese hamster ovary cells Netherlands Organisation for applied scientific research (TNO), Zeist, The Netherlands TNO-report V99.661 Ref nr A6.6.2/01	Y	SOPURA
A6.6.2/2	1999b	Chromosomal aberration test with octanoic acid in cultured Chinese hamster ovary cells Netherlands Organisation for applied scientific research (TNO) Zeist, Netherlands TNO-Report V99.660.	Y	SOPURA
A6.6.3/1	1999a	Gene mutation test at the TK-locus of L5178Y cells with Decanoic acid; Netherlands Organisation for applied scientific research (TNO), Zeist, The Netherlands TNO-report V99.715	Y	SOPURA

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
		Ref nr A6.6.3/01		
A6.6.3/2	1999b	Gene mutation test at the TK-locus of L5178Y cells with Octanoic acid Netherlands Organisation for applied scientific research (TNO) Zeist, Netherlands TNO-Report V99.715	Y	SOPURA
A6.8.1/01	1994	Pharmacokinetic Determinats of Embryotoxicity in Rats Associated with Organic Acids Scott et al. Environmental Health Perspectives 102 (suppl 11) Published	N	Published
A6.8.1/02	1993	Pharmacokinetics and pharmacodynamics of valproate analogs in rats. II. Pharmacokinetics of octanoic acid, cyclohexanecarboxylic acid, and 1-methyl-1-cyclohexanecarboxylic acid Mei-JenLiu and Pollack G. M. Biopharmaceutics & Drug Disposition, vol. 14 Published	N	Published
A6.8.2 A6.4.1.1/ 02	1968	Nutritional Evaluation of Medium-Chain Triglycerides in the Rat Harkins R. W. and Sarett H. P. The Journal of the American Oil Chemists' Society Department of Nutritional Research, Mead Johnson Research Center, Evansville, Indiana Published	N	published
A7.1.1.2.1/01	2005	Fragrances and Biodegradation Göteborgs Stad Miljö Anonymus ISSN 1401-2448 ISRN GBG-M-R—05/05—SE Published	N	Published
A7.1.1.2.1/02	2006	OCTANOIC ACID: READY BIODEGRADABILITY IN A MANOMETRIC RESPIROMETRY TEST; RCC LTD, Itingen, Switzerland; RCC Study Number: A86578 Unpublished	Y	SOPURA N.V.
A7.1.3/01	2008	ADSORPTION/DESORPTION OF OCTANOIC ACID ON SOILS; RCC Ltd, Itingen; RCC Report No. A86477 Unpublished	Y	SOPURA N.V.
A7.4.1.1/02	2006	Octanoic Acid: Acute Toxicity to Zebra Fish (Brachydanio Rerio) in a 96-hour semi-static Test RCC Ltd; Itingen, Switzerland RCC Study Number A86501	Y	SOPURA
A7.4.1.1/03	2006	First Amendment to Study Plan Octanoic Acid: Acute Toxicity to Zebra Fish (Brachydanio Rerio)	Y	SOPURA

Section no/ reference no	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)published	Data Protection	Owner
		in a 96-hour semi-static Test RCC Ltd; Itingen, Switzerland RCC Study Number A86501		
A7.4.1.2/01	2001	Octanoic acid Daphnia magna, Acute Toxicity; Henkel KgaA Department of Ecology; Final Report R-0100717 Unpublished	Y	Henkel KGaA
A.7.4.1.2/02 D	2006	DECANOIC ACID: ACUTE TOXICITY TO DAPHNIA MAGNA IN A 48-HOUR IMMOBILIZATION TEST; RCC Ltd, Itingen, Switzerland; RCC Study Number: A86488 Unpublished	Y	SOPURA
A7.4.1.3/01D	2008	DECANOIC ACID: TOXICITY TO SCENEDESMUS SUBSPICATUS IN A 72-HOUR ALGAL GROWTH INHIBITION TEST; RCC Ltd, Itingen, Switzerland RCC Study Number: A86523 (inclusive A86534) Unpublished	Y	SOPURA
A7.4.1.4/02D	2006	DECANOIC ACID: TOXICITY TO ACTIVATED SLUDGE IN A RESPIRATION INHIBITION TEST; RCC Ltd, Itingen Switzerland; RCC Study Number A86545 Unpublished; cross reference	Y	SOPURA N.V.
A7.4.2/01	2006	Calculation of the BCF for octanoic acid with the US-EPA program BCF Program	Y	MCF-Consultancy GmbH

Year	Title Source Institution; report nr GLP-, GEP-status Published or unpublished	Data Protection	Owner
2010	Agreement regarding the transfer of test reports between Octanoic and Decanoic acid Fatty acids consortium No GLP unpublished	Y	Fatty acids consortium
2010	Agreement regarding the transfer of documents between the product types Fatty acids consortium No GLP unpublished	Y	Fatty acids consortium
2008	The COLIPA strategy for the development of in vitro alternatives: Skin sensitisation	N	published

	Aeby P., Ashikaga T., Diembeck W.,, Eschrich D., Gerberick F.,, Kimber I, Marrec-Fairley M., Maxwell G., Ovigne J.M., Sakaguchi1H., Tailhardat M., Teissier S. AATEX 14, Special Issue, 375-379 http://altweb.jhsph.edu/wc6/		
1995	Skin irritation in man: a comparative bioengineering study using improved reflectance spectroscopy Andersen PH, Maibach HI Contact Dermatitis 33(5):315-22	N	published
1985	Chronic mouse dermal toxicity study, test material C-182 = Pelargonic Acid Barkley W. Kettering Laboratory, Univ. Cincinnati, OH, U.S.A. Report No. not stated Not GLP, Published	just EPA study summary, no letter of access from applicant available	published
1997	The classification of skin irritants by human patch test Basketter DA, Chamberlain M, Griffiths HA, Rowson M, Whittle E, York M. Food Chem Toxicol. 35(8):845-52.	N	published
2007a	Does irritation potency contribute to the skin sensitization potency of contact allergens? Basketter DA, Kan-King-Yu D, Dierkes P, Jowsey IR. Cutan Ocul Toxicol. 26(4): 279-86.	N	published
2007b	The Local Lymph Node Assay: Current Position in the Regulatory Classification of Skin Sensitizing Chemicals Basketter DA., Gerberick GF., Kimber I. Cutaneous and Ocular Toxicology 26:4, 293 - 301	N	published
1998	Strategies for Identifying False Positive Responses in Predictive Skin Sensitization Tests Basketter DA., Gerberick GF., Kimber I. Food and Chemical Toxicology 36: 327-333	N	published
2005	Long-term repetitive sodium lauryl sulfate-induced irritation of the skin: an in vivo study. Branco N, Lee I, Zhai H, Maibach HI. Contact Dermatitis 53(5):278-84	N	published
2006	Toxicological modes of action: relevance for human risk assessment ECETOC Technical Report No. 99, July 2006	N	published
2007	statement on the validity of in-vitro tests for skin irritation ESAC http://ecvam.jrc.it/index.htm	N	published
1992	Propionic acid and the phenomenon of rodent forestomach tumorigenesis: a review BP group Occupational Health Centre, Guilford, Surrey, U. K Harrison PT. Food Chem Toxicol. 1992 Apr; 30(4): 333-40	N	published

	Report-No. Not applicable Not GLP, Published		
1999	Predictive Value of Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risks to Humans IARC Technical Publication No. 39, 1999	N	published
2007	Comparison of human skin irritation and photo-irritation patch test data with cellular in vitro assays and animal in vivo data Jirova D., Liebsch M., Basketter D., Kandarova H., Kejlova K., Bendova H., Marriot M., Spiller E. AATEX 14, Special Issue, 359-365; Proc. 6th World Congress on Alternatives & Animal Use in the Life Sciences; August 21-25, 2007, Tokyo, Japan http://altweb.jhsph.edu/wc6/paper359.pdf	N	published
2008	Comparison of the skin sensitizing potential of unsaturated compounds as assessed by the murine local lymph node assay (LLNA) and the guinea pig maximization test (GPMT) Kreiling R., Hollnagel H.M., Hareng L., Eigler D., Lee M.S., Griem P., Dreeßen B., Kleber M., Albrecht A, Garcia C., Wendel A. Food Chem Toxicol. 46(6): 1896-1904	N	published
2008	Analysis of differential gene expression in auricular lymph nodes draining skin exposed to sensitizers and irritants Ku HO, Jeong SH, Kang HG, Pyo HM, Cho JH, Son SW, Ryu DY Toxicol Lett. 177(1):1-9.	N	published
2008	Skin sensitization in chemical risk assessment: report of a WHO/IPCS international workshop focusing on dose-response assessment Loveren van H, Cockshott A, Gebel T, Gundert-Remy U, de Jong WH, Matheson J, McGarry H, Musset L, Selgrade MK, Vickers C. Regul Toxicol Pharmacol. 50(2):155-99.	N	published
2007	McLean J. et al. Journal of Chemical Ecology 33:1997-2009	N	published
1998	Murine local lymph node assay for predictive testing of allergenicity: two irritants caused significant proliferation. Montelius J, Wahlkvist H, Boman A, Wahlberg JE. Acta Derm Venereol. 78(6): 433-7	N	published
2002	Subacute 28-Day Oral toxicity with Pelagonsäure by Daily Gavage in the Rat Notox B.V, 's-Hertogenbosch, The Netherlands Report-no. 321582 GLP, Unpublished	Y	W. Neudorff GmbH KG
2001a	Assessment of Acute oral Toxicity with Pelargonsäure in the Rat (Acute Toxic Class Method) Notox B.V, 's-Hertogenbosch, The Netherlands Report-No. 321547 GLP, Unpublished	Y	W. Neudorff GmbH KG
2001b	Assessment of Acute Dermal Toxicity with Pelargonsäure in the Rat Notox B.V, 's-Hertogenbosch, The Netherlands Report-No. 321558 GLP, Unpublished	Y	W. Neudorff GmbH KG

2007	Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment. Proctor DM, Gatto NM, Hong SJ, Allamneni KP. Toxicol Sci. 98(2):313-26 Report-No. Not applicable Not GLP, Published	N	--
2001	Validity and ethics of the human 4-h patch test as an alternative method to assess acute skin irritation potential Robinson MK, McFadden JP, Basketter DA. Contact Dermatitis 45(1):1-12	N	published
1991	Schilder M. Applied Animal Behaviour Science, 32:227-236	N	published
2007	The ECVAM international validation study on in vitro tests for acute skin irritation: report on the validity of the EPISKIN and EpiDerm assays and on the Skin Integrity Function Test. Spielmann H, Hoffmann S, Liebsch M, Botham P, Fentem JH, Eskes C, Roguet R, Cotovio J, Cole T, Worth A, Heylings J, Jones P, Robles C, Kandárová H, Gamer A, Remmele M, Curren R, Raabe H, Cockshott A, Gerner I, Zuang V. Altern Lab Anim. 35(6):559-601	N	published
2003	Nonanoic acid – an experimental irritant Wahlberg J, Lindberg M. Contact Dermatitis 49: 117–123	N	published
1983	Assessment of skin irritancy: measurement of skin fold thickness Wahlberg JE Contact Dermatitis 9(1):21-6	N	published
1980	Nonanoic acid irritation - a positive control at routine patch testing? Wahlberg JE, Maibach HI Contact Dermatitis 6(2):128-30	N	published
1985	Skin irritancy from nonanoic acid Wahlberg JE, Wrangsjö K, Hietasalo A. Contact Dermatitis 13(4):266-9	N	published
1988	Forestomach carcinogens: pathology and relevance to man. National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands Wester PW., Kroes R. Toxicol Pathol. 1988; 16(2): 165-71 Report-No. Not applicable Not GLP, Published	N	published
2005	Guidance document for the use of data in development of chemical-specific adjustment factors (CSAFs) for interspecies differences in human variability in dose/concentration-response assessment. IPCS harmonization project document ; no. 2 http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf		
1988b	Assessment of erythema in irritant contact dermatitis. Comparison between visual scoring and laser Doppler flowmetry Willis CM, Stephens CJ, Wilkinson JD.	N	published

	Contact Dermatitis 18(3):138-42		
1988a	Experimentally-induced irritant contact dermatitis. Determination of optimum irritant concentrations Willis CM, Stephens JM, Wilkinson JD Contact Dermatitis 18(1):20-4.	N	published
1996	Evaluation of a human patch test for the identification and classification of skin irritation potential. York M, Griffiths HA, Whittle E, Basketter DA. Contact Dermatitis 34(3):204-12.	N	published
2001c	Primary Skin Irritation/Corrosion Study with Pelargonsäure in the Rabbit (4-Hour Semi-Occlusive Application) Notox B.V, ‘s-Hertogenbosch, The Netherlands Report-no. 321604 GLP, Unpublished	Y	W. Neudorff GmbH KG
2001d	Assessment of Contact Hypersensitivity to Pelargonsäure in the Albino Guinea Pig (Maximisation-Test) Notox B.V, ‘s-Hertogenbosch, The Netherlands Report-no. 321615 GLP, Unpublished	Y	W. Neudorff GmbH KG
2003	The National Diet and Nutrition Survey: Adults Aged 19-64 years, Volume 2: Energy, protein, carbohydrate, fat and alcohol intake. Henderson L., Gregory J., Irving K., Swan G. London, HMSO	N	published
2006	The National Diet and Nutrition Survey: Adults Aged 19-64 years, Volume 4: Nutritional status (anthropometry and blood analytes), blood pressure and physical activity. Ruston D., Horare J., Henderson L., Gregory J., Bates C.J., Prentice A., Birch M., Swan G., Farron M. London, HMSO.	N	published

8 ANNEXES

Confidential Annex.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information).