Committee for Risk Assessment

RAC

Annex 1

Background document

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

nonanoic acid

EC number: 203-931-2
CAS number: 112-05-0

CLH-O-0000002588-64-03/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: Nonanoic Acid

EC Number: **203-931-2**

CAS Number: **112-05-0**

Index Number: **607-197-00-8**

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.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Nonanoic Acid***
EC number:	***203-931-2***
CAS number:	***112-05-0***
Annex VI Index number:	***607-197-00-8***
Degree of purity:	***Min. 89.6 % 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	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Skin Corr. 1B – H314	C; Corrosive R34
Current proposal for consideration by RAC	Skin Irritation 2 – H315 Eye Damage 1 – H318 Aquatic Chronic 3 – H412	Xi; Irritating R38 R41
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Irritation 2 – H315 Eye Damage 1 – H318 Aquatic Chronic 3 – H412	Xi; Irritating R38 R41

1.3 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			None	conclusive but not sufficient for classification
2.2.	Flammable gases			None	data lacking
2.3.	Flammable aerosols			None	data lacking
2.4.	Oxidising gases			None	data lacking
2.5.	Gases under pressure			None	data lacking
2.6.	Flammable liquids			None	conclusive but not sufficient for classification
2.7.	Flammable solids			None	data lacking
2.8.	Self-reactive substances and mixtures			None	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids			None	data lacking
2.10.	Pyrophoric solids			None	data lacking
2.11.	Self-heating substances and mixtures			None	data lacking
2.12.	Substances and mixtures which in contact with water emit flammable gases			None	conclusive but not sufficient for classification
2.13.	Oxidising liquids			None	conclusive but not sufficient for classification
2.14.	Oxidising solids			None	data lacking
2.15.	Organic peroxides			None	conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals			None	data lacking
3.1.	Acute toxicity - oral			None	conclusive but not sufficient for classification
	Acute toxicity - dermal			None	conclusive but not sufficient for classification

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
	Acute toxicity - inhalation			None	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	H315: Causes skin irritation Skin Irrit. 2		H314 – Causes severe skin burns and eye damage	
3.3.	Serious eye damage / eye irritation	H318: Causes serious eye damage Eye damage 1		H314 – Causes severe skin burns and eye damage	
3.4.	Respiratory sensitisation			None	data lacking
3.4.	Skin sensitisation			None	conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity			None	conclusive but not sufficient for classification
3.6.	Carcinogenicity			None	conclusive but not sufficient for classification
3.7.	Reproductive toxicity			None	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity – single exposure			None	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure			None	conclusive but not sufficient for classification
3.10.	Aspiration hazard			None	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	None	
5.1.	Hazardous to the ozone layer	n.a.	n.a.	None	data lacking

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

Labelling:

Labelling			Justification
GHS Pictograms			Weight of evidence evaluation supporting skin irritation and risk for serious eye damage, see Doc II-A 3.3 Specification of Prevention Phrases according to Regulation (EC) No 1272/2008 Rapidly degradable substance for which adequate chronic toxicity data are available. Lowest chronic value is NOE_rC from algae is 0.568 mg/L.
Signal words		Danger	
Classification		Serious eye damage – Hazard Category 1 Skin irritation- Hazard Category 2 Aquatic Chronic 3	
Hazard statements		H318: Causes serious eye damage H315: Causes skin irritation H412: Harmful to aquatic life with long lasting effects	
Precautionary Statements	General	-	
	Prevention	P264: Wash thoroughly after handling P273: Avoid release to the environment P280: Wear protective gloves/protective clothing/eye protection/face protection.	
	Response	P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P310: Immediately call a POISON CENTER or doctor/physician P302+P352: IF ON SKIN: Wash with plenty of soap and water. P332 + P313: If skin irritation occurs, get medical advice/attention P362: Take off contaminated clothing and wash before reuse.	
	Storage	-	
	Disposal	P501: Dispose of contents/container in accordance with local/regional/national/ international regulations (to be specified).	

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				conclusive but not sufficient for classification
Oxidising properties				conclusive but not sufficient for classification
Flammability				conclusive but not sufficient for classification
Thermal stability				conclusive but not sufficient for classification
Acute toxicity				conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure				conclusive but not sufficient for classification
Repeated dose toxicity				conclusive but not sufficient for classification
Irritation / Corrosion	Xi; R38 Irritating to skin R41 Risk of severe damage to eyes		C; R34 corrosive	
Sensitisation				conclusive but not sufficient for classification
Carcinogenicity				conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity				conclusive but not sufficient for classification
Toxicity to reproduction – fertility				conclusive but not sufficient for classification
Toxicity to reproduction – development				conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation				conclusive but not sufficient for classification
Environment	n.c.	n.a.	n.c.	conclusive but not sufficient for classification

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

Labelling:

Classification and Labelling proposal		Justification
Hazard symbol		Weight of evidence evaluation supporting skin irritation and risk for serious eye damage; Specification of Prevention Phrases according to Directive 67/548/EEC
Indication of danger	Xi Irritating	
R phrases	R38 Irritating to skin R41 Risk of severe damage to eyes	
S phrases	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	
Classification	Xi; R38-R41	
Labelling	Xi; R: 38-41 S: 26-36/37/39	

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Table 5: Current classification according to Directive 67/548/EEC

Classification	C; R34
Class of danger	Corrosive
R phrases	R34
S phrases	S1/2 S26 S28 S36/37/39 S45

2.2 Short summary of the scientific justification for the CLH proposal

Human health

The animal data from Unichema/Notox 1984 and Hoechst 1990 submitted by OXEA GmbH are in agreement with the animal data presented in this CLH Dossier and confirm the borderline to corrosive properties. However giving more weight to the later animal studies (Celandese/RCC 2001 from OXEA GmbH and Otterdijk 2001 from this CLH report) that include in contrast to the earlier studies also a 14 day post exposure period and giving also more weight to the human data (Jirova et al. 2008 and Wahlberg 1983 and Robinson 1999) presented in this CLH Dossier the overall weight of evidence supports a classification as skin irritant rather than skin corrosion.

Based on the literature data for octanoic acid and decanoic acid indicating eye corrosion and reading across these data to the structurally and physico-chemically related Nonanoic acid classification for risk of severe damage to eye (R41) or eye irritant category I (H318) according to CLP Regulation is proposed.

Environment:

Acute aquatic toxicity: L(E)C_{50} values between 1 - >100 mg/L; lowest acute value LC_{50} (fish) >7.2 mg/L;

Chronic Aquatic toxicity: NOEC values between 0.1 – 100 mg/L; lowest chronic NOEC (algae) =0.568 mg/L;

Fate & behaviour: rapidly biodegradable; calculated log P_{ow} =3.52; BCF estimated for fish 195.88;

REACH registration dossier for Nonanoic acid:

Acute aquatic toxicity: L(E)C_{50} values between 10 - >100 mg/L; lowest acute value E_rC_{50} (algae) =60 mg/L;

Chronic Aquatic toxicity: NOEC values between 10 – 100 mg/L; lowest chronic NOEC (crustacea) =18 mg/L;

Fate & behaviour: rapidly biodegradable; measured log P_{ow} =3.42; BCF estimated for fish 3.2;

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.

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 value from algae with 0.568 mg/L in combination with rapid biodegradability.

DSD:

- No classification. Nonanoic acid is readily biodegradable and the log P_{ow} is given with 3.42 (measured) – 3.52 (calculated). All available L(E)C_{50} values are between 10 and >100 mg/L. The only exception is the lowest LC_{50} for fish with >7.2 mg/L. 7.2 mg/L was the highest concentration

tested at which no effects could be observed. In the REACH dossier 3 different acute studies with fish are presented with LC_{50} values between 96 - >105 mg/L. In addition a chronic NOEC value for fish with 19.2 mg/L is available in the CAR for biocides and a LC_{50} for fish from Octanoic acid with 68 mg/L is available in the respective CAR.

2.3 Current harmonised classification and labelling

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

Skin Corr. 1B

H314

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

C; Corrosive

R34

S1/2, 26, 28, 36/37/39, 45

2.4 Current self-classification and labelling

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

Not available

2.4.2 Current self-classification and labelling based on DSD criteria

Xi; Irritating

R36/38, 41, 52

S26, 36/37/39, 60, 61

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Biocide – 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 evaluated were those of skin irritation/corrosion, eye irritation

and the environment.

Please note that references cited here can be found in the CLH report and/or the background document to the pinion; references not quoted in the above docuemnts are included at the end of this opinion for the sake of convenience.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

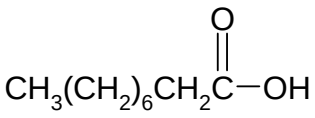
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6: Substance identity

EC number:	203-931-2
EC name:	
CAS number (EC inventory):	
CAS number:	112-05-0
CAS name:	
IUPAC name:	Nonanoic acid
CLP Annex VI Index number:	Not available
Molecular formula:	$C_9H_{18}O_2$
Molecular weight range:	158.2

Structural formula:



1.2 Composition of the substance

Table 7: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Nonanoic acid	89.6 % w/w	89.6 – 100 % w/w	

Current Annex VI entry: not available

Table 8: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
See confidential Annex			

Current Annex VI entry: not available

Table 9: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
See confidential Annex				

Current Annex VI entry: not available

1.2.1 Composition of test material

See confidential Annex

1.3 Physico-chemical properties

Table 10: Summary of physico - chemical properties

Property	Purity/Specification	Results	Reference
Melting point	Nonanoic acid (99.5%)	11.7°C - 12.5°C	**Doc. III-A 3; Study A 3.1.1/01**
Boiling point	Nonanoic acid (99.5%)	258.4°C	**Doc. III-A 3; Study A 3.1.2/01**
Relative density	Nonanoic acid (99.5%)	Density: ρ=0.90588kg/L (19.8°C)	**Doc. III-A 3; Study A 3.1.3/01**
Relative density	NEU 1170H (19.98% Nonanoic acid)	Relative density: $\rho^{20}_{4.0}$= 0.99	**Doc. III-A 3; Study A 3.1.3/02**
Vapour pressure	Nonanoic acid (~100%)	0.9 Pa (20°C) 1.4 Pa (25°C) 10.6 Pa (50°C)	**Doc. III-A 3; Study A 3.2/01**
Henry´s Law Constant	-	Calculated: 0.33 Pa x m^3/mol (20°C)	**Doc. III-A 3; Study A 3.2.1/01**
Physical state	Nonanoic acid	Oily colourless liquid	**Doc. III-A 3; Study A 3.3/01**
Colour	Nonanoic acid technical	Slightly yellow to colourless	**Doc. III-A 3; Study A 3.3/01**
Odour	Nonanoic acid, technical	Strongly rancid	**Doc. III-A 3; Study A 3.3/01**
Absorption spectra: UV/VIS	Nonanoic acid	UV/VIS extinction occurs in the range of 200 to 340 nm.	**Doc. III-A 3; Study A 3.4/01**
Absorption spectra: IR	Nonanoic acid (99.5%)	IR spectrum is consistent with the proposed structure of Nonanoic acid.	**Doc. III-A 3; Study A 3.4/02**
Absorption spectra: NMR	Nonanoic acid (93%)	NMR spectrum is consistent with the proposed structure of Nonanoic acid.	**Doc. III-A 3; Study A 3.4/03,** **Doc. III-A 3; Study A 3.4/05**
Absorption spectra: MS	Nonanoic acid	MS spectrum is consistent with the proposed structure of Nonanoic acid.	**Doc. III-A 3; Study A 3.4/04**

Table 10: Summary of physico - chemical properties

contd.

Property	**Purity/Specification**	**Results**	**Reference**
Water solubility	Nonanoic acid (98.5%)	0.164 g/L (10°C; pH 3); 0.169 g/L (20°C; pH 3); 0.184 g/L (30°C; pH 3); 0.203 g/L (20°C; pH 4); 0.415 g/L (20°C; pH 5) Remarks/Justification: At pH > 5.5 Nonanoic acid forms Nonanoates. The water solubility of Sodium nonanoate is between 205.5 and 277.7 g/L at pH 13-14 and 260.4 g/L at pH between 7 and 13.	**Doc. III-A 3; Study "Water_solubility_ PelargonicAcid_ 2007"**
Dissociation constant	Nonanoic acid (92.0%)	pK_a=4.9 at 20°C	**Doc. III-A 3; Study A 3.6/01**
	Ammonium Salt of Nonanoic acid (36.8%)	pK_a=4.8 at 20°C	**Doc. III-A 3; Study A 3.6/02**
Solubility in organic solvents, including the effect of temperature on solubility	Nonanoic acid (99.5%)	The solubility of Nonanoic acid in n-heptane, p-xylene, 1,2-dichloroethane, methanol, acetone and ethylacetate was determined to be >250 g/L(T=20 ± 1°C). Octanol and Nonanoic acid are miscible in any proportion. OECD 105; EU A.6	**Doc. III-A 3; Study A 3.7/01**
Stability in organic solvents used in b.p. and identity of relevant breakdown products		The active substance / biocidal product do not contain any organic solvent.	-
Partition coefficient n-octanol/water	-	Estimated log P_{ow}: 3.52 (Calculated with KOWWIN Version 1.66) (pH 7, T=25°C) Remarks/Justification: In the Guidance for the implementation of REACH Chapter R.7A – Endpoint specific guidance as well as in OECD Guideline for the testing of chemicals No.107 , 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. So the calculated log P_{ow} can be accepted.	**Doc. III-A 3; Study A 3.9/01**
Thermal stability	Nonanoic acid (~100%)	No exothermal decomposition up to 350°C.	**Doc. III-A 3; Study A 3.2/01**
Flammability	Nonanoic acid (90%)	Self-ignition temperature: 220°C	**Doc. III-A 3; Study A 3.11/01**

Table 10: Summary of physico - chemical properties

contd.

Property	Purity/Specification	Results	**Reference**
Flash-point	Nonanoic acid (90%)	132.9°C – 133.9°C	**Doc. III-A 3; Study A 3.12/01**
Surface tension	90% saturated aqueous solution of Nonanoic acid	34.6 mN/m (20.1°C)	**Doc. III-A 3; Study A 3.13/01**
Viscosity	Nonanoic acid (93%)	20°C 8.7 mPas 40°C 5.2 mPas	**Doc. III-A 3; Study A 3.14/01; Company statement "Analysenzertifikat Viskosität (analysis certificate viscosity)"**
Explosive properties	-	Based on its structure Nonanoic acid is not considered explosive.	**Doc. III-A 3; Company Statement**
Oxidising properties	-	Based on its structure Nonanoic acid is not considered oxidising.	**Doc. III-A 3; Company Statement**
Reactivity towards container material	-	Metal barrels coated with lacquer on the inside have been used since many years without having negative influence on the contained product.	**Doc. III-A 3; Company Statement**

2 MANUFACTURE AND USES

2.1 Manufacture

See confidential Annex

2.2 Identified uses

Biocide for use as: PT 2 Private area and public health area disinfectants and other biocidal products
PZ 10 Masonry preservatives
PT 19 Repellent

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 11: Summary table for relevant physico-chemical studies

Property	Purity	Results	Reference
Thermal stability	Nonanoic acid (~100%)	No exothermal decomposition up to 350°C	**Doc. III-A 3; Study A 3.2/01**
Flammability	Nonanoic acid (90%)	Self-ignition temperature: 220°C	**Doc. III-A 3; Study A 3.11/01**
Flash-point	Nonanoic acid (90%)	132.9°C – 133.9°C	**Doc. III-A 3; Study A 3.12/01**
Explosive properties	-	Based on its structure Nonanoic acid is not considered explosive.	**Doc. III-A 3; Company Statement**
Oxidising properties	-	Based on its structure Nonanoic acid is not considered oxidising.	**Doc. III-A 3; Company Statement**
Reactivity towards container material	-	Metal barrels coated with lacquer on the inside have been used since many years without having negative influence on the contained product.	**Doc. III-A 3; Company Statement**

Based on its structure Nonanoic acid displays neither explosive nor oxidizing properties. Its flash point is in the range of 132.9 to 133.9°C and its self ignition temperature was determined to be 220°C. The substance was proved to be stable up to 350°C. (Please see table 5-1)

In conclusion, no physico-chemical hazards could be identified for the active substance. Hence no classification is required on the base of physico-chemical properties.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

As all fatty acids, Pelargonic acid is present in nature. It has been found to occur naturally in soil (**Doc III-A 7.2.1/02**) and has been found in various plants as well as in a variety of animal fats and foods of animal origin (Stewart, 2000).

Pelargonic acid rarely will be ingested as free fatty acid but more likely is taken up as salt (primarily as sodium, potassium or ammonium salt) or as a component of lipids (mostly fats). The conduction of new studies on this subject is not required, since absorption, distribution, metabolism and excretion of non-esterified or esterified fatty acids in men are basic knowledge and as such are

presented in all relevant handbooks of biochemistry. The more important ones were consolidated to give a brief summary (**Doc III-A 6.2_non-sub**).

Absorption

Non-esterified short-chain fatty acids, like Pelargonic Acid, are rapidly absorbed from the lumen of the intestine directly into the portal blood stream. This entry is sodium-dependent and can take place against concentration gradient by a process of active transport (Bell et al. 1976).

Fats, however, are not able to pass as such the intestine brushborder cells. They must be emulsified by bile salts and then undergoe lipolysis under the influence of pancreatic lipase (Bell et al.). By the breakage of the triglyceride at the two primary positions, fatty acids and monoglycerides will be formed. They are able to shape into watersoluble micells, with the hydrophilic hydroxyl- and carboxyl-groups facing outwards and the hydrophobic monoglycerides directed inwards. In this form, the micells under participation of bile salts are passively transported into cells, either by dissolving in the membrane or by pinocytosis.

Most triglycerides are between 95 and 100% digestable. Longer-chain fatty acids are less well absorbed than shorter-chain fatty acids (Guthrie and Andrews 1975). In the case of Pelargonic Acids complete and rapid absorption (see above) can be expected, therefore 100% oral absorption is assumed for the exposure calculations. A profound description of the involved enzymatic processes is given by Orten and Neuhaus 1975.

In the absence of any absorption tests and considering the physical-chemical properties dermal and inhalation absorption is assumed to be 100% for the purpose of exposure and risk assessment.

Distribution

About 70% of the absorbed micells are resynthesized immediately to form triglycerides (Guthrie and Andrews 1975). The resynthetisation follows by fatty acid activation to fatty acyl-CoA derivatives. These react with L-alpha-glycerophosphate to yield glyceride phosphates which then are hydrolyzed to form the corresponding glycerides. The enzymatic steps are described in detail by Orten and Neuhaus 1975.

Further transportation follows in at least three forms, as

- chylomicrons (aggregates of triglycerides (80%), phospholipids (7%) and cholesterol (9%) which are “coated” with lipoproteins)
- lipids associated with proteins as lipoproteins
- non-esterified fatty acids (NEFA) loosely bound to albumin.

Chilomicrons and lipoproteins predominantly are transported from the intracellular fluid into the lactals and the lymphatics, and finally into the systemic blood stream (Orten and Neuhaus 1975).

Non-esterified fatty acids (NEFAs) are mainly transported through the portal blood system loosely bound to plasma albumin (Orten and Neuhaus 1975). While the amount of NEFAs in the plasma is very small (0.1-0.3 g/L in fasting adults), they apparently represent the form mobilized for oxidation to meet energy needs. They have an exceedingly high turnover rate, with a half-life of 2 to 3 minutes only (Orten and Neuhaus 1975).

A large proportion of absorbed fat is carried to the liver, the chief site for its metabolic disposal. Triglycerides entering the liver as chilomicrons are hydrolyzed to their constituent fatty acids and glycerol. Both compounds may be utilized to form phospholipids and lipoproteins. The lipoproteins which can obtain 55 to 90% fat facilitate the transport of fat throughout the body where it is used as a source of energy or may be stored in the fat depots of each cell or in special adipose cells for future use (Guthrie and Andrews 1975). Fat is either oxidized - mainly in the liver and muscles – or is stored – mainly in the subcutaneous or retroperitoneal adipose tissues (Bell et al. 1972).

Metabolism and excretion

The oxidative degradation of fatty acids is a universal biochemical capacity among living organisms. Fatty acids are the form in which fat is liberated from the depots. Albumin carries the fatty acids in the bloodstream to other tissues, like liver, heart, and kidneys (Zubay 1983). Intracellularly, 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). The pathway for the oxidation of fatty acids is indicated in Fig. 3.1-a. The parent even-numbered fatty acid is activated by conversion to the fatty acyl-CoA, oxidized to the alpha, beta-unsaturated compound, hydrated, oxidized to the beta-keto derivative, and finally subjected to a thiolytic cleavage yielding acetyl-CoA and the fatty acyl-CoA containing two less carbonatoms, which, in turn, undergoes the same series of reactions (Mahler and Cordes 1971). Each of these steps is exhaustively described by the a.m. authors and by Bell et al. 1972. A detailed chapter on the enzymology of beta-oxidation is written by Zubay 1983.

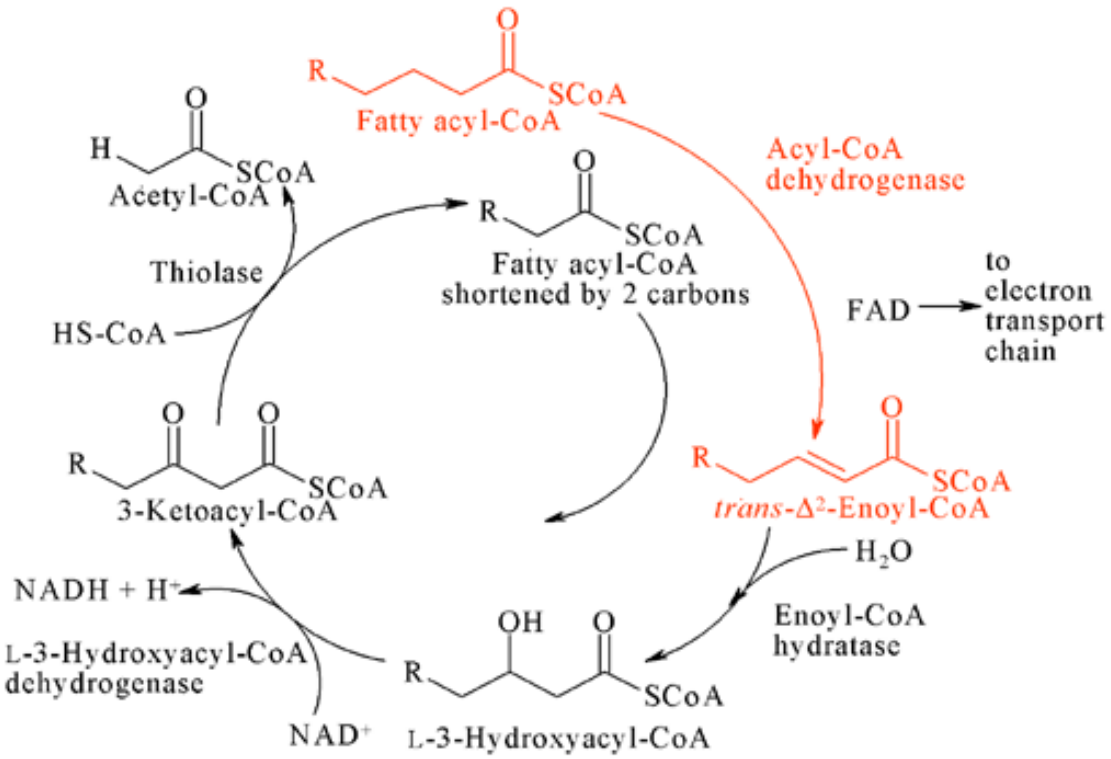


Figure 3.1-a: β-oxidation of fatty acids (Lamm et al. 2002)

Oxidation of fatty acids with an odd number of carbons: The sequence of reactions as summarized above for the oxidation of even-numbered fatty acids is also applicable to the oxidation of those with an odd number of carbon atoms. 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:

CH_3CH_2C-CoA

The propionyl-CoA is converted to succinyl-CoA as indicated in Fig. 3.1-b. Succinyl-CoA can be further metabolized in the tricarboxylic acid cycle, finally to yield CO_2 and water. Two other pathways for the utilization of propionyl-CoA finally to form acetyl-CoA have been described by Mahler and Cordes 1971 and are similarly shown in Figure 3.1-b.

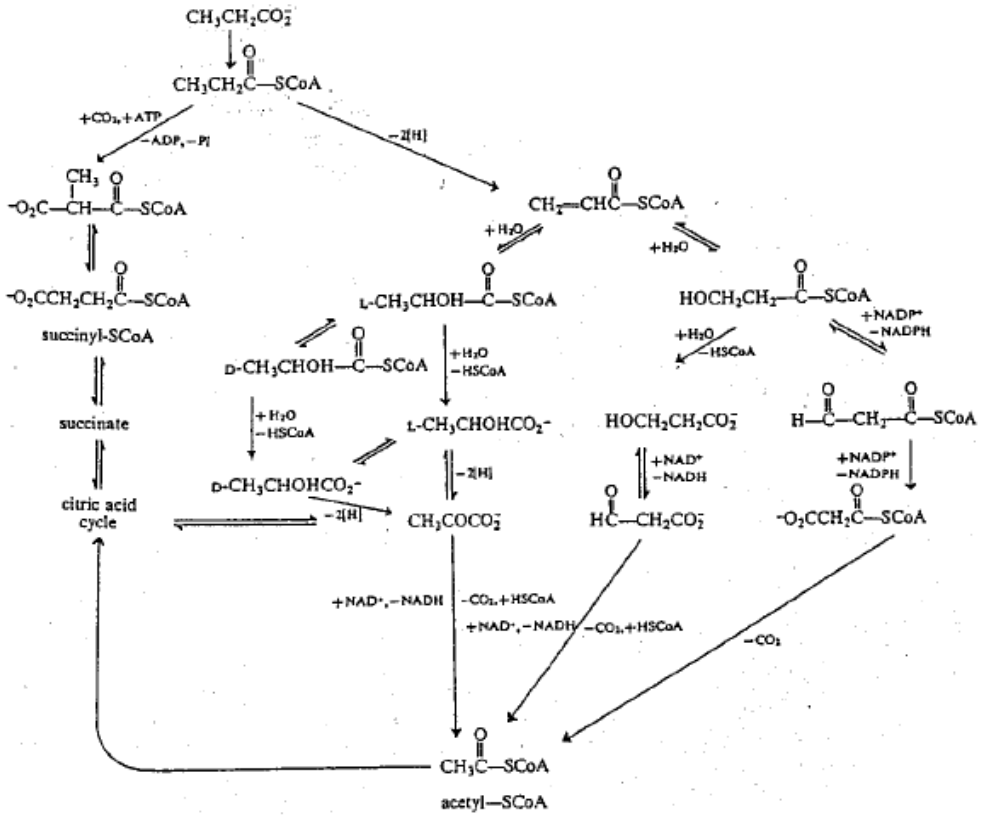


Figure 3.1-b: Fate of propionate and propionyl-SCoA (Mahler and Cordes 1971)

Although ß-oxidation is quantitatively the most significant pathway for catabolism of fatty acids, alpha-oxidation and omega-oxidation are still to be mentioned (Zubay 1983).

As a result of the in details complicated degradation steps of fatty acids the final products are CO_2 and acetyl-CoA resp. succinyl-CoA which as such are further metabolized to CO_2 and water. Finally no other excretion products than these ones are formed.

Omega-oxidation has been observed as a minor pathway for the oxidation of the fatty acids in rat liver microsomes. This involves oxidation of the terminal methyl of adjacent methylene carbon of fatty acids by NADPH and molecular oxygen:

Fatty acids when absorbed through the intestinal lumen or released from fat depots are readily utilized and step-wise metabolized, finally generate energy by degradation to carbondioxide and water. After complete oxidation, no other degradation products than mentioned above will be excreted.

4.1.2 Human information

Not available

4.1.3 Summary and discussion on toxicokinetics

See discussion above

4.2 Acute toxicity

Table 12: Summary table of relevant acute toxicity studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels, duration of exposure	Value LD_{50}/LC_{50}	Remarks	Reference
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	LD_{50} >2000 mg/ kg bw	Test substance: Nonanoic acid	**Doc III-A 6.1.1/01**
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	LD_{50} >2000 mg/ kg bw	Test substance: Nonanoic acid Hunched posture, piloerection, chromod-acryorrhoea, lethargy, uncoordinated movements and/or shallow respiration were noted among all animals between days 1 and 5. Swelling, general erythema, scales and scabs were seen on the treated skin-area of the animals during the observation period.	**Doc III-A 6.1.2/01**
Inhalation	No information available	Rat, no information available for strain, sex and number of animals used	No information available for dose levels used, 4 h duration of exposure	LC_{50} (4 h) >5.3 mg/L	Test substance: Nonanoic acid	Copping L.G. 1998 (Bio-pesticide Manual) Doc III-A 6.1.3/01
Inhalation	No information available	No information available for species, strain, sex and number of animals used	No information available for dose levels used, 4 h duration of exposure	LC_{50} (4 h) >5.53 mg/L and LC_{50} (4 h) >5.9 mg/L	Test substance: C9 and C10 fatty acids: 60% formulation and C9 fatty acids: 80% formulation	Anonymous (Safer Inc), date not stated Doc. III-A 6.1.3/02
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	LC_{50} (4 h) >0.55 mg nonanoic acid as ammonium salt/L air (measured)	Test substance: Formulation containing 33% nonanoic acid. as ammonium salt/L; results calculated for nonanoic acid. No macroscopic pathological effects observed, clinical signs were food refusal at day 1 (grade	**Doc III-B 6.1.3/01**

Route	Method Guideline	Species Strain Sex no/group	Dose levels, duration of exposure	Value LD_{50}/LC_{50}	Remarks	Reference
			acid./L air] 4 h exposure		3 from 3) and day 2 (grade up to 2) and apathy at day 1 and 2 (grades up to 3).	
Inhalation	OECD No. 403 GLP	Sprague-Dawley Rat, 5 males and 5 females per dose group	Measured 1 [mg a.s./L air] 4 h exposure	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	Study B 6.1.3/02

4.2.1 Non-human information

The acute toxicity of Nonanoic acid has been investigated in rats by the oral and dermal routs. For the inhalation route a key study with NEU 1170 H containing Nonanoic acid as ammonium salt is available.

4.2.1.1 Acute toxicity: oral

Rats received a single oral dose of 2000 mg tech. a.i./kg bw in propylene glycol by gavage. No mortalities occurred. Clinical signs included lethargy and uncoordinated movements at the beginning of the study. The mean body weight gain was normal. No abnormalities were observed at macroscopic post mortem examination (**Doc III-A 6.1.1/01**). These results are in agreement with the data cited in the BioPesticide Manual (Copping 1998, rats and mice >5000 mg/kg, Doc. III-A 6.1.3/01).

4.2.1.2 Acute toxicity: inhalation

For the characterisation of the acute inhalation toxicity three studies with Nonanoic acid are referenced here. Within the BioPesticide Manual (Copping 1998, Doc III-A 6.1.3/01) for nonanoic aicd an LC_{50} (4 h) >5.3 mg/L is stated. Safer Inc. (Anonymous without year, Doc III-A 6.1.3/02) conducted inhalation studies with a 60% C9/C10-formulation and an 80% C9-formulation which resulted in LC_{50} (4 h) values of >5.53 mg/L and >5.9 mg/L, respectively. A further study was conducted with a formulation containing 332.2 g Nonanoic acid as ammonium salt/L (**Doc III-B 6.1.3/01**). In this test a group of 5 male and 5 female Sprague-Dawley rats was exposed during a single continuous period of 4 hours to the highest achievable analytical concentration, that was 1.66 mg test formulation/L air which analytically corresponds to 0.55 mg Nonanoic acid technical/L air. Under the conditions of this experiment the test substance caused the following clinical signs: Complete food refusal at day 1 and partially at day 2 and apathy of various grades at day 1 and 2. Nevertheless the body weight loss observed till day 2 was partly compensated till the end of the 14 day observation period. No mortality was observed and also no macroscopic pathological alteration was detected at

the end of the 14 days observation period. A further study carried out with a formulation containing 18.7% nonanoic acid and 3% maleic hydrazide was submitted by the applicant (B6.1.3/02). The LC50 for this formulation is >5.3 mg/L which corresponds analytically to > 1 mg/L Nonanoic acid. No clinical or gross pathological findings were observed with this concentration. Two (expectedly data protected) inhalation toxicity studies are referenced in two EPA evaluations (A6.1.3/03 and /04). In the older evaluation (2004) a reference is cited indicating that an aerosol of Nonanoic acid at a concentration of 3.8 mg/L resulted in 80 % mortality while a concentration of 0.46 mg/L produced no mortality. In the newer evaluation (2006) only a new reference is cited indicating no deaths in 10 rats exposed for eight hours to saturated vapours of mixed isomers of Decanoic acid.

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 exposure. The RMS-AT did not independently assess these references since the available information seems sufficient also without these references.

4.2.1.3 Acute toxicity: dermal

Rats were exposed to a single dermal application of 2000 mg tech. a.i./kg bw as a 22% solution in propylene glycol for a period of 24 hours.. The following clinical signs were noted between days 1 and 5: Hunched posture, piloerection, chromod-acryorrhoea, lethargy, uncoordinated movements and/or shallow respiration. In 2 from 10 animals severe skin irritation was recorded as erythema, scales and scabs on the treated skin sites. In all animals some slight to moderate skin reaction was observed. The erythema was not reversible in 3 of 10 animals and the scabs and/or scales were not reversible in 6 of 10 animals within the 15 days of post-exposure observation. Nevertheless the body weight gains were within the normal range and no mortality occurred. (**Doc III-A 6.1.2/01**). These results are in agreement with data cited for the rabbit within a review by Safer Inc. (Anonymous without year, Doc. III-A 6.1.3/02, LD_{50} rabbit >2000 mg/kg) and with data for rats cited in the BioPesticide Manual (Copping 1998, LD_{50} >2000 mg/kg).

4.2.1.4 Acute toxicity: other routes

No data available.

4.2.2 Human information

Not available.

4.2.3 Summary and discussion of acute toxicity

See discussion above.

4.2.4 Comparison with criteria

On the basis of these acute oral and dermal toxicity studies Nonanoic acid does not need to be classified as harmful since the LD50 values are above 2000 mg/kg bw day.

Acute inhalation toxicity was not tested for the free acid, but only for the ammonium salt and just up to concentrations of 1 mg/L. This is below the maximum concentration that could trigger classification as harmful (5 mg/L). However at 1 mg/L no lethality was observed and also the LC50 literature values above 5 mg/kg bw day are available. In addition from knowledge of fatty acids as natural food components, absence of any structural alert and knowledge of metabolism it is to be expected that Nonanoic acid will not cause acute systemic toxicity. If at all, local irritation effects are to be expected. However, also in case severe, such effects should not lead to classification for acute systemic toxicity. Therefore no classification as harmful by inhalation is necessary.

4.2.5 Conclusions on classification and labelling

No classification for acute toxicity is necessary.

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

Not applicable

4.4 Irritation

4.4.1 Skin irritation

Table 13: Summary table of relevant skin irritation studies

Species, No of animals	Method	Conc.	Dose	Exposure time	Result		Reversibility 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		within 15 days Yes	Severely irritating to skin	**Doc III-A 6.1.4s/01**
					Erythema: 4	Oedema: No scoring possible due to eschar formation, fissuring and/or brown discolouration of the skin			
Rat, 5 males and 5 females	Acute dermal toxicity test with **Nonanoic acid** EEC B.3, OECD No. 402 GLP	22% in Polyethylene glycole (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	**Doc III-A 6.1.2/01**
Guinea pigs animals/group: 2 2 2 2 1	GPMT, EEC B.6, OECD No. 406; GLP; Epiderm. exp. with **Nonanoic acid**: Pretest	corn oil 100% 50% 20% 10% 5%	mg/cm^2 75 37.5 15 7.5 3.75	24 h	24 and 48h Eryt. grade 4 4 2 1 1	24 and 48h Oedema grade 1 1 0 0 0	n.a.	≥50% severely irritating 2-10% mildly irritating ≤1% not irritating	**Doc III-A 6.1.5/01**

Species, No of animals	Method	Conc.	Dose	Exposure time	Result		Reversibility yes/no	Conclusion	Reference
1 1 15	Main test	2% 1% 1%	1.5 0.75 0.15		1 0 0	0 0 0		to skin	
EpiDerm (reconstituted human epidermis model)	In vitro skin irritation test (Spielmann et al 2007); with **Nonanoic acid** and with **decanoic acid**	100%		15 minutes and 60 minutes	Prediction model: Tissue viability <50% or >50% and IL1α release 3x increased.		n.a.	At least irritating to skin	Jirova et al. 2008
n.a.	QSAR – Toxtree for **Nonanoic acid**	n.a.	n.a.	n.a.	n.a.		n.a.	Irritating or corrosive to skin	http://ecb.jrc.it/qsar/[1]
Human volunteer (author of publication)	Human patch test	100%, 60%, 40%, 20%, 10%, 5% in propanol	0.1 ml	repeated for 15 days	Increased skin thickness for concentrations ≥40%			Irritating to skin	Wahlberg 1983
Human skin ex vivo	Transcutaneous Elektrical Resistance Test (TER); OECD guideline 430 with **decanoic acid**	100%		24 h	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
Human, 72 volunteers	Human patch test with **octanoic** and **decanoic acid.** Patches applied with graded duration of exposure. Assessment after 24/48/72h	100%	200 mg/ch	≤4 graded: 0.5, 1, 2, 3, 4	% participants showing at least mild irritation: 37 to 56% after 1 hour 50 to 81% after up to 2 hours 81 to 89 after up to 3 hours 84 to 96% after up to 4 hours		Yes	At least mildly irritating to skin	Robinson et al. 1999

[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

Species, No of animals	**Method**	**Conc.**	**Dose**	**Exposure time**	**Result**	**Reversibility yes/no**	**Conclusion**	**Reference**
Human 8 volunteers	Human 24 hours exposure, measurement 20 minutes after patch removal	2.5%, 5%, 10%, 20% in propanol		24 hours	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

4.4.1.1 Non-human information

The potential of Nonanoic acid to irritate skin was tested in male New Zealand rabbits (**Doc III-A 6.1.4s/01**). 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 the 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 and the actual study is from 2001. Furthermore US-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.

Overall the severe skin reaction within the rabbit irritation test with Nonanoic acid seems to be borderline for classification as corrosive or as irritant.

Other tests are available that could inform on the corrosive/irritant properties of Nonanoic acid (see table 3.3.1):

Application of Nonanoic acid as a 22% solution in PEG (POLYETHYLENEGLYCOLE) for 24 hours within the acute dermal toxicity test (see **Doc III-A 6.1.2/01)** 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.

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

The dermal irritation test carried out with NEU 1170H containing the ammonium salt of Nonanoic acid, indicate that Nonanoic acid is expectedly not irritant at concentrations ≤ 19% when applied for 4 hours. After 24 hours of exposure to NEU 1170H containing 34% of Nonanoic acid temporary skin irritation was noted. Application of NEU 1170 H containing 20% of Nonanoic acid to the eye resulted eye irritant according to the OECD scores and the EU and GHS rules. Overall NEU 1170H containing the ammonium salt of Nonanoic acid at concentrations between 20 and 34% did not induce severe irritation effects.

4.4.1.2 Human information

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. 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 neat decanoic acid produced strong responses in some individuals already after 2 hours, but no further details are provided. However the same publication (York et al. 1996) presents results from an ex vivo transcutaneous electrical resistance (TER, see OECD guideline 430) test with human skin that did not indicate skin corrosion of neat decanoic acid. 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) 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 –at least without the raw data from the new EpiDerm test (in terms of % cell viability) - the published EpiDerm results (Jirova et al 2008) support that Nonanoic acid and Decanoic acid are at least skin irritant, but do not inform weather Nonanoic acid might be corrosive. However 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.

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.

4.4.1.3 Threshold for acute dermal irritation

For the **derivation of a threshold for acute dermal irritation** the guinea pig maximisation tests with Nonanoic acid (**Doc III-A 6.1.5/01)** and with NEU 1170 H (Doc III-B 6.3/01) could be engaged. A 24 hours application of a solution of Nonanoic acid ≤ 1% in corn oil to 750 µg/cm^2 skin did not show skin irritation in a total of more than 30 animals. The clinical publication from

Wahlberg et al. 1985 would be in agreement with this estimate. From 100 hospitalised patients with various skin diseases exposed to 1% Nonanoic acid in propanol for 48 hours only 3 showed some skin irritation. The same publication 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%. 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.

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 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 the sodium salt of SDS (salt of C12 carbonic acid) and the ammonium salt of Nonanoic acid and assuming that both substances induce irritation by direct cytotoxicity and consequent inflammatory reactions the data summarized for SDS support that also with (at least the ammonium salt of) Nonanoic 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 Nonanoic 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 Nonanoic 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 the dermal data basis includes mainly studies with Nonanoic acid in propylene glycol but also one animal test with NEU 1170H that is a solution of the ammonium salt in water with pH of 7. It may be assumed that the ammonium salt solution with pH 7 is less irritant compared to the acid in propylene glycol, though no significant differences are apparent in the guinea pig tests with Nonanoic acid and with NEU 1170H (irritation threshold with both tests about 1%). However the final product Katzenschreck contains 1% NEU 1170H (that is 20% solution of Nonanoic acid ammonium salt) in pumic stone, resulting in a Nonanoic acid content of 0.2% w/w. Probably the pumic stone may not be considered as dilution of Nonanoic acid, however it will reduce exposure in terms of µg/cm^2 of skin. Consequently the skin irritation threshold for Nonanoic acid likely overestimates the skin irritation with NEU 1170H and even more with the product Katzenschreck.

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 is based on animal test data (irritation NOAEC from 24 hour application in GPMTs) and human literature data (for up to 48 hour applications). The derivation of an acute local dermal AEC is not needed since acute effects should be addressed by respective classification and labelling. The derivation of longer

[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).

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.

4.4.1.4 Summary and discussion of skin irritation

The animal data from Unichema/Notox 1984 and Hoechst 1990 submitted by OXEA GmbH are in agreement with the animal data presented in this CLH Dossier and confirm the borderline to corrosive properties. However giving more weight to the later animal studies (Celandese/RCC 2001 from OXEA GmbH and Otterdijk 2001) that include in contrast to the earlier studies also a 14 day post exposure period and giving also more weight to the human data (Jirova et al. 2008 and Wahlberg 1983 and Robinson 1999) presented in this CLH Dossier the overall weight of evidence supports a classification as skin irritant rather than skin corrosion.

4.4.1.5 Comparison with criteria

See discussion above.

4.4.1.6 Conclusions on classification and labelling

Considering all available information the classification of Nonanoic acid with regard to skin corrosion or skin irritation Nonanoic acid should be classified as skin irritant, R38 according to EC criteria or as skin irritation category 2 (H315) according to GHS.

RAC evaluation of skin irritation/corrosion
Summary of the Dossier submitter's proposal The CLH report includes one rabbit dermal irritation study conducted with neat nonanoic acid (Otterdijk, 2001c). Animals were exposed for 4 hours and severe irritation (average erythema score 4 at 24, 48 and 72 hours, no oedema score possible), which was not fully resolved within 15 days, was reported. Application of 22% nonanoic acid in an acute dermal toxicity test (Otterdijk, 2001b) resulted in some clinical signs of irritation with 2/10 showing signs of severe irritation (erythema score of 3 and 4) not fully reversible after 15 days. A Guinea Pig Maximisation Test (GPMT) study revealed erythema scores or 4 and oedema scores of 1 for concentrations at and above 50% (Otterdijk, 2001d). Analysis using the ToxTree QSAR tool made available by the European Chemicals Bureau (ECB) suggested nonanoic acid, as well as its closely related substances octanoic and decanoic acid were borderline "irritating or corrosive to skin". The dossier submitter also mentions a dermal irritation study conducted with the ammonium salt of nonanoic acid in concentrations up to 34%, which showed little irritation properties. References or further analysis of this study were not included.

The dossier submitter includes several human patch test studies conducted with varying concentrations of octanoic, nonanoic and decanoic acid. Irritation was noted in most studies but no corrosion. However, exposure was terminated upon first sign of irritation in most studies (apart from those by Willis et al (1988) and Wahlberg et al (1985)). References are made to studies included in the REACH registration dossier (see ECHA web site) for nonanoic acid (Unichema/Notox, 1984, Hoechst, 1990 and Celanese/RCC, 2001). The dossier submitter argues that these studies confirm the results seen in the animal studies presented in the dossier but no further details are provided.

The dossier submitter concludes that nonanoic acid presents a borderline case for corrosion or irritation but based on a weight of evidence approach, they conclude that the current classification of Skin Corr. 1B – H314 should be changed to Skin Irrit. 2 – H315 according to CLP. The corresponding classification under DSD would be Xi; R38.

Comments received during public consultation

Comments were received from four Member States. Three agreed with the proposal for skin irritation while one disagreed and argued for classification as Skin Corr. 1C – H314. This is based on visible necrosis, scabs and/or fissures and alopecia, not fully resolved within 14 days, seen after 4h exposure in Otterdijk (2001c) and Unichema/Notox (1984). The lead registrant for nonanoic acid under REACH also submitted a comment arguing for Skin Corr. 1C – H314, based on the same results. The dossier submitter agreed that this is a borderline case, but argued the effects are fully reversible and requested RAC to conclude on this issue. A comment was submitted on behalf of the Fatty Acid Consortium (FAC) detailing two additional studies (Arcelin, 2001 and Weterings, 1984) which they claim support the proposed classification as Skin Irrit. 2 – H315. The study summaries were not available to the dossier submitter for an independent review but further details are available in the Response to comments document (RCOM).

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 classification and labeling for the individual substances. 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 noteed 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 explains the less clear irritating/corrosive effects of the three acids. Due to the close structural similarity and the very similar pK_a values, RAC supported the general evaluation approach of all three acids proposed by the dossier submitter.

The available information is briefly summarised below.

Assessment of human patch tests (HPT)

HPT 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 does 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 irritation. The ED_{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 4h 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, however 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. Through personal communication with the dossier submitter the 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, RAC supported the conclusion of the dossier submitter that the three organic acids are at least skin irritants, but does not consider that the studies provide evidence for a corrosive effects.

Assessment of animal and in vitro studies

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

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

Van Otterdijk (2001c), 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 and (very) slight oedema, 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 (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, bald skin and scaliness were observed at the end of the observation period, at day 14 in all 3 animals.

According to CLP, corrosive reactions are typified as 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. Of these, only the alopecia at day 14 meets the criteria for corrosion, therefore the dossier submitter considers these effects borderline

for classification as corrosive.

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 an OECD 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 a local lymph node assay (LLNA) in mice, 25 µL/ear of 70% decanoic acid applied 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. However, RAC concluded that the outcomes of these in vitro tests are overruled by the weight of evidence form the various in vivo tests, including the human data, which did not show corrosion.

Comparison with the classification 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 except one test on octanoic acid, which showed no full reversibility of full thickness necrosis at day 14.

When determined, there was reversibility within 15 days in animal studies in all other studies. Unfortunately, the reports do not provide information on the severity of the effects. Irritation was also seen in the HPT in most of the volunteers exposed up to 48 h at concentrations of 20% and higher.

RAC noted that the evidence for skin corrosion of nonanoic acid is borderline. Since the available information on decanoic acid does not indicate skin corrosion and considering their similar pKa values, RAC does not consider that there is sufficient evidence to classify nonanoic acid as corrosive.

Based on a weight of evidence approach and in agreement with the dossier submitter, RAC concludes that nonanoic acid should be considered as irritating to the skin and warrants classification as Skin Irrit. 2 - H315 according to CLP (Xi; R38 according to DSD).

4.4.2 Eye irritation

4.4.2.1 Non-human information

For the estimation of **eye irritation hazard** no studies are available for Nonanoic 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 a publication was identified (see Smyth et al. 1962) attributing score 9 from 10 for corneal necrosis to Ocantoic and Decanoic acid, which also rises concern for severe eye damage by Nonanoic acid.

4.4.2.2 Human information

Not available

4.4.2.3 Summary and discussion of eye irritation

Based on the literature data for octanoic and decanoic acid indicating eye corrosion and reading across these data to the structurally and physico-chemically related Nonanoic acid classification for risk of severe damage to eye (R41) or eye irritant category I (H318) according to CLP Regulation.

The conclusion from the Draize et al. 1944 data presented in the dossier of OXEA GmbH are not clear enough to counterbalance the Smith et al. 1962 data for octanoic and decanoic acid indicating eye corrosion.

This classification proposal is in disagreement with the actual U.S. EPA classification as eye irritant Toxicity Category II. In contrast the R41/category I classification proposal is supported by the actual EU classification as corrosive (R34). However neither the data basis for the EPA nor for the EU classification is available to the RMS.

Classification as irritating to eyes, R36 according to EU scheme or category II according to GHS, would need new negative (in vitro) eye corrosion test data.

4.4.2.4 Comparison with criteria

See discussion above

4.4.2.5 Conclusions on classification and labelling

Nonanoic acid should be classified for risk of severe damage to eye (R41) or eye irritant category I (H318) according to CLP Regulation.

RAC evaluation of eye irritation

Summary of the Dossier submitter's proposal

No studies estimating the eye irritation properties of nonanoic acid are made available in the CLH report. The dossier submitter argues that a severe skin irritation classification would exclude further eye irritation testing (OECD TG 405) and result in classification as severely eye damaging. Nevertheless, one non GLP-compliant study (Smyth et al., 1962) conducted with octanoic and decanoic acid in rabbits, is mentioned in the CLH report. This study indicated corneal necrosis (score of 9 out of 10 is reported) from exposure to octanoic and decanoic acids which would raise concerns for eye damaging properties of nonanoic acid. The dossier submitter proposes to classify nonanoic acid as Eye Dam. 1 – H318 under CLP and R41 under DSD.

Comments received during public consultation

Two Member States and one industry commenter supported the classification proposal for Eye Dam. 1 – H318. One Member State argued that the substance should be classified as corrosive, which covers eye damage and this would therefore be superfluous. One Member State argued that classification for eye damage is not warranted due to lack of data and proposes classification as Eye Irrit. 2 – H319. The FAC argues in their comment that the database is not sufficient to conclude on classification for eye effects.

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 very similar structutres, the similar pK_a values of octanoic and nonanoic acid and the proposed classification and labelling of the three organic acids as irritants to the skin , the RAC used the sparse information available on the individual compounds to evaluate the three organic acids.

Regarding octanoic and decanoic acid, 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 corneal effects (severity grade 9), 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.

During the public consultation 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 supported this proposal although the study was not made available to them. RAC evaluated the Leoni and Riedel (2011) study. In accordance with the OECD 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 scores of 1, 1.67 and 2. In two animals, lesions of the iris (average score 1 for both animals) and the cornea (average 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 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 the same public consultation for octanoic acid, 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 TG 437 compliant study which concluded that based on the criteria of the guideline, a 20% dilution of decanoic acid was 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 compound is considered to be corrosive or a severe irritant.

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

Comparison with classification 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 were irreversible effects resulting from exposure to 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.

Based on the data on octanoic and decanoic acid, RAC concluded that classification as Eye Irrit. 2 H313according to CLP (Xi; R36 according to DSD) for nonanoic acid was warranted.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

Considering the strong skin and eye irritation properties of Nonanoic 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 chapter 4.2. of this report. 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.

4.4.3.2 Human information

Not available

4.4.3.3 Local respiratory irritation threshold

The data are **insufficient to derive a local respiratory AEC**. However Nonanoic acid has a strongly rancid odour and in an acute inhalation study, no evidence of respiratory irritating potential were observed in rats exposed to 1 mg/L of the ammonium salt of nonanoic acid: 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 Nonanoic acid indicates a respiratory LC50 > 5 mg/L (see Doc II-3.2). 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 2010 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 2010 proposal 10 or less).

Considering these uncertainties and that there is no need for a medium or long term risk assessment with regard to local respiratory effects for the intended use of the representative product for PT 19, no respective AECs is derived.

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.

4.4.3.4 Summary and discussion of respiratory tract irritation

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.

4.4.3.5 Comparison with criteria

See discussion above

4.4.3.6 Conclusions on classification and labelling

No classification for respiratory irritation required.

4.5 Corrosivity

See discussion in chapter 4.4

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 14: Summary table of relevant skin sensitisation studies

Species	Method	Number of animals sensitized/total number of animals	Result	Reference
Albino Guinea pigs, Dunkin Hartley strain (SPF-quality), 10 females per test item group	EEC B.6, OECD No. 406	0/10	No skin sensitisation	**Doc III-A 6.1.5/01**

4.6.1.1 Non-human information

In a Maximisation test according to Magnusson and Kligman 15 female guinea pigs were used to study the sensitising properties of Nonanoic acid. The guinea pigs were grouped into a test compound group (10 animals) and a vehicle group (5 animals). The test substance was intradermally injected with a 2% concentration and 7 days later epidermally exposed with a 20% concentration. The control animals were similarly treated with corn oil (vehicle) alone. Two weeks after the epidermal applications of all animals were challenged with a 1% test substance concentration and the vehicle. There was no evidence that Nonanoic acid had caused skin hypersensitivity in the guinea pig, since no responses were observed in the animals in the challenge

phase. The concentrations for induction and challenge were substantiated by pretests indicating necrosis at 5% with intrademal injection (therefore selected 2%), severe irritation at 50% apical application (therefore selected 20% for apical induction) and erythema grade 1 at 2% apical application (therefore selected 1% for challenge). The study is considered to be fully valid also with regard to results from positive controls (Klimisch score 1). (**Doc III-A 6.1.5/01**).

This result is in agreement with the Guinea-Pig-Maximisation-Test (GPMT) according to Magnusson and Kligman carried out with NEU 1170 H, a formulation containing 20% Nonanoic acid (see document IIB 6.4 and III-B 6.3, Huygevoort 2000).

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). Similar difficulties were observed for the structurally tightly related Octanoic and Decanoic acid that were also submitted for evaluation for inclusion into Annex I of Directive 98/8/EC.

Considering the negative GPMT for Nonanoic acid and giving preference the consideration that these linear carbonic acids do not contain structural alerts necessary for protein interaction, the purity of technical Nonanoic acid (see confidential section) and the high concentrations of 50 or 100% needed for positive response in the LLNA, Nonanoic acid should not be classified as skin sensitising.

4.6.1.2 Human information

Not available

4.6.1.3 Summary and discussion of skin sensitisation

Considering the negative GPMT for Nonanoic acid and giving preference the consideration that these linear carbonic acids do not contain structural alerts necessary for protein interaction, the purity of technical Nonanoic acid (see confidential section) and the high concentrations of 50 or 100% needed for positive response in the LLNA, Nonanoic acid should not be classified as skin sensitising.

4.6.1.4 Comparison with criteria

See discussion above

4.6.1.5 Conclusions on classification and labelling

No classification for skin sensitization is required.

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 there are no metabolites of concern.

4.7 Repeated dose toxicity

Table 15 Repeated dose toxicity tests with Nonanoic acid

Route	Duration of study	Species Strain Sex no/group	Dose levels, frequency of application	Results	LOAEC/ LOAEL	NOAEC/ NOAEL	Reference
Oral	28 days	Wistar rat, Crl:(WI) BR (outbred, SPF-Quality), 5 males and 5 females per dose group	Dose level per gavage 0, 50, 150 or 1000 mg/kg bw/day with 0, 1, 3, 20% in propylene glycol	**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)	20% / 1000 mg/kg/day	3% / 150 mg/kg/day	**Doc III-A 6.3.1/01**

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

In a subacute 4-week oral toxicity study male and female Wistar rats received Nonanoic acid by gavage at doses of 0, 50, 150 or 1000 mg/kg bw/day in concentrations of 1%, 3% and 20% in Propylene glycol 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 6.3/01**).

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 (Doc III-A 6.3/02).

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.

Within the rat teratogenicity study (see chapter 3.8.) Nonanoic acid was applied by gavage for 10 days (day 6 to 15 post mating) at a dose of 1500 mg/kg bw day as 30% solution in corn oil. However no maternal toxicity including no maternal gross pathological effects in the thoracic, abdominal and pelvic viscera were observed.

In addition as mentioned above within the 14 days study (Kuhn 1995, Doc III-A 6.3.1/02, Study summary from EPA, no letter of access for the applicant available) the macroscopic effect on the forestomach was also not observed even at higher doses of up 1834 mg/kg bw/day administered at concentrations of 20000 ppm (corresponding to 2%) in food.

The difference between the three study results cited above might be explained by the different application periods that were 10 days and 14 days for the studies showing no effects but 28 days for the study showing the forestomach irritation. Also 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 14 day study (Doc III-A 6.3/02). In addition the lack of effects within the 10 and 14 day studies was not verified by histological analysis. Finally within the 14 day study Nonanoic acid was applied in much lower concentrations, that is 2% compared to 20% in the 28 day study.

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.

In addition further studies with medium chain triglycerides are available that support the assumption of low risk for systemic effects from Nonanoic acid:

Webb et al. 1993 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, C9 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.

Harkins et Sarett 1968 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.

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.

A publication from Mori 1953 indicates 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.

4.7.1.2 Repeated dose toxicity: inhalation

No data

4.7.1.3 Repeated dose toxicity: dermal

No data

4.7.1.4 Repeated dose toxicity: other routes

No data

4.7.1.5 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].

Nonanoic acid is a linear saturated fatty acid and ubiquitous like other similar fatty acids in nature

The metabolic pathways are similar for all fatty acids: complete catabolism for energy supply or conversion to fat suitable for storage (see chapter 3.1.1).

Consumption data available for total fatty acids as food contents (~950 mg/kg bw/day, Henderson et al 2003 and Ruston et al. 2006)

Fatty acids are consumed mainly as triglyceride-esters (fat), however before resportion the esters are split and free fatty acids are temporarily available.

4.7.1.6 Other relevant information

None

4.7.1.7 Summary and discussion of repeated dose toxicity

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 Nonanoic acid as such is ubiquitous in nature, it has been reported in plants, several essential oils, in algae and in animal products like milk (Stewart 2000).

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 studies. 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.

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

- The nature of Nonanoic acid, that is a linear saturated fatty acid and the ubiquity of Nonanoic acid and other similar fatty acids in nature
- 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 3.1.1).
- Consumption data available for total fatty acids as food contents (~950 mg/kg bw/day, Henderson et al 2003 and Ruston et al. 2006)
- 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 just concern for skin and eye irritation of the a.s.
- The rapid degradation of Nonanoic acid in the environment through oxidative degradation pathways common for fatty acids
- The expected low human exposure in terms of level and frequency due to the intended use of the representative biocidal product.

Accepting to waive the studies is in agreement with the evaluation of US EPA (US EPA Anonymous 1998 and 2003). Besides the US FDA permits use of Nonanoic acid as food additive for direct addition to food for human consumption (21 CFR 172.515), as secondary food additive used in washing or to assist in the peeling of fruits and vegetables (21 CFR 173.315) and in sanitising solutions (21 CFR 178.1010).

4.7.1.8 Local oral acceptable exposure concentration

A somewhat different approach may be necessary for the derivation of a local-oral AEL: In the available 28 day rat gavage study 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 the rat forestomach irritation 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 the oral data were generated

with Nonanoic acid in propylene glycol but the product Katzenschreck (to which oral exposure might occur) contains 1% NEU 1170H (that is a 20% solution of the ammonium salt in water with pH of 7) in pumic stone resulting in a Nonanoic acid content of 0.2% w/w. Probably the pumic stone may not be considered as dilution of Nonanoic acid, however it will expectedly reduce exposure in terms of µg/cm^2 of mucosa. Consequently the irritation threshold for Nonanoic acid likely overestimates the irritation with NEU 1170H and even more with the product Katzenschreck (see also Doc II-A 3.11.2 and 3.11.3).

No studies for medium or long term dermal or respiratory exposure are available. However for the representative biocidal product and intended use respective AECs are not necessary (see document IIC). For discussion of the data to be consulted for a qualitative risk assessment with regard to local dermal and local respiratory effects see Doc. II-A3.3.

For the derivation of AELs and oral AEC see chapter 3.11.2 and 3.11.3.

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

No systemic adverse effects were observed up to dose levels above 1000 mg/kg bw day. No adverse effects are to be expected due to the ubiquitous nature of fatty acids and consideration of their nutritional role within fats.

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

See discussion above

4.7.1.11 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)

Table 16: Summary table of relevant in vitro mutagenicity studies

Test system Method Guideline	Organism/ strain(s)	Concentra-tions tested	Result		Remark	Reference
			+ S9	- S9		
Gene mutation in bacteria EEC B.13/14, OECD No. 471	S. typhi-murium: TA1535, TA1537, TA98, TA100	93-5000 µg a.i./plate	-	-	No increase in the number of revertants was observed upon treatment with Nonanoic Acid under all conditions tested.	**Doc III-A 6.6.1/01**

Test system Method Guideline	Organism/ strain(s)	Concentra-tions tested	Result		Remark	Reference
			+ S9	- S9		
	E. coli: WP_2uvrA					
Cytogenicity in mammalian cells EEC B.10, OECD No. 473	Human lymphocytes	100-750 µg a.i./mL (with S9 activation) 10-750 µg a.i./mL (without S9 activation)	-	-	In the absence and presence of S9-mix, Pelargonic Acid did not induce a statistically significant relevant increase in the number of cells with chromosome aberrations up to concentrations of 520 µg a.i. per mL. "Pseudo-positive" results are obtained at cytotoxic concentrations of 750 µg a.i. per mL (mitotic index = 38%).	**Doc III-A 6.6.2/01**

4.9.1 Non-human information

4.9.1.1 In vitro data

One bacterial gene mutation test and one mammalian in vitro chromosomal aberration test are available for the characterisation of the genotoxic potential of Nonanoic acid.

A bacterial mutagenicity assay was performed on *Salmonella typhimurium* strains TA1535, TA1537, TA100 and TA98, and on *Escherichia coli* strain WP_2uvrA, with and without liver microsomal S9-activation. A dose range finding test and three mutation assays were conducted, with and without 5% and 10% S9-mix and maximum concentrations of 4650 and 5000 µg a.i./plate. Nonanoic acid did not induce a dose-related two-fold increase in the number of revertant (His^+) colonies in each of the four tester strains (TA1535, TA1537, TA98, TA100) and in the number of revertant (Trp^+) colonies in tester strain WP_2uvrA both in absence and presence of S9-metabolic activation. These results were confirmed in independently repeated experiments. It is concluded that Nonanoic acid is not mutagenic in the *Salmonella typhimurium* reverse mutation assay and in the *Escherichia coli* reverse mutation assay (**Doc III-A 6.6.1/01**).

As additional information it should be mentioned that these results are in agreement with another reverse gene mutation assay with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 exposed to concentrations ranging from 100 to 5000 µg Nonanoic acid /plate (Doc III-A 6.6.1/02, EPA study summary, letter of access of the applicant not available).

The effects of Nonanoic acid on the number of chromosome aberrations in cultured peripheral human lymphocytes was tested at different concentrations, exposition times and times of fixation. The first cytogenetic assay was conducted with concentrations ranging from 100 to 750 µg a.i./mL with 3 hours exposure time with and without S9-mix activation. In the second cytogenetic assay, lower concentrations of 10 to 300 µg a.i./mL with exposure times of 24 and 48 hours were used without activation, whereas in the case of activation the cultures were exposed to 333-520 µg a.i./mL for 3 hours only. In the first assay the highest concentration of 750 µg a.i./mL induced a statistically significant increase in the number of cells with chromosome aberrations in the absence and presence of S9-mix. As this concentration was very cytotoxic (mitotic index = 38%) and highly precipitating, the next lower concentration of 520 µg a.i./mL was scored as well. However, this concentration did not induce chromosome aberrations. Similarly, all scores of the second assay did

not show any statistically significant increases in cells with chromosome aberrations. It is concluded that the observed positive effects of the highest concentration in the first assay are due to cytotoxicity related secondary mechanisms. Therefore, Nonanoic acid may be considered as not clastogenic in human lymphocyte cultures (**Doc III-A 6.6.2/01,** Neurath 2002).

Another EPA evaluation, only available in form of a study summary, for a mouse lymphoma forward mutation assay is available as additional background information (No letter of access is available for the applicant): L5178TK+/- cells were exposed for 4 hours to non- activated doses ranging from 150 to 1600 µg Nonanoic acid per mL and to S9-activated concentrations ranging from 37.5 to 600 µg a.i./mL. Nonanoic acid was not considered to be mutagenic under the conditions of this study without exogenous metabolic activation. Nonanoic acid, in the presence of S9 metabolic activation, induced a weak mutagenic response. Increases in the numbers of mutants per plate were seen at all test material concentrations, and doubled at ≥ 300 µg/mL in trial 1, and at doses ≥ 100 µg/mL in trial 2. This occurred only in the presence of increasing moderate to severe cytotoxicity and small colony development and may indicate damage to the chromosome carrying the TK locus, rather than actual mutagenicity within the TK gene locus. Therefore EPA concludes that the results do not reflect intrinsic mutagenicity. However the study is of limited value since the purity of the substance tested is not available in the study summary and there is no access to the fully study (Cifone M.A., 1993).

4.9.1.2 In vivo data

A further EPA evaluation also only available in form of a study summary of an in vivo mouse micronucleus assay is available as additional background information: Groups of 15 male and 15 female ICR mice were administered single oral doses of 1250, 2500, or 5000 mg Nonanoic acid/kg bw. The bone marrow cells were harvested 24, 48 and 72 hours post treatment. No significant increases in the frequency of micronucleated polychromatic erythrocytes (PECs) were observed in either sex at any dose. Thus EPA concluded that Nonanoic Acid was negative in the micronucleus assay (Doc III-A 6.6.4/01). However the study is of limited value since the purity of the substance tested is not clear and there is no access to the full study.

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 3.5. - bullet points) seems sufficient also without this reference.

4.9.2 Human information

See chapter 4.7.1.5

4.9.3 Other relevant information

None

4.9.4 Summary and discussion of mutagenicity

It is concluded that Nonanoic acid is not mutagenic in vitro.

The available evidence based essentially on the two in vitro genotoxicity studies submitted as well as the absence of structural alerts, consideration of human consumption data of fatty acids as fats and knowledge of metabolism and finally the description of the purity (see confidential section) suggests that no further testing is required and Nonanoic acid can be considered as non-genotoxic.

4.9.5 Comparison with criteria

See discussion above.

4.9.6 Conclusions on classification and labelling

No classification for genotoxicity is necessary.

4.10 Carcinogenicity

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Within the 28 day gavage study 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 Nonanoic acid (single chain saturated fatty acid) and the knowledge about kinetics and metabolism of fatty acids (Wester and Kroes 1988, Harrison 1992, IARC 1999, ECETOC 2006, Proctor 2007).

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 3.5.)

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 3.5. - bullet points) seems sufficient also without this reference.

4.10.1.2 Carcinogenicity: inhalation

No data available.

4.10.1.3 Carcinogenicity: dermal

Furthermore as additional information an EPA study summary is available for a dermal repeated dose study (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 Nonanoic 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.

4.10.2 Human information

See chapter 4.7.1.5

4.10.3 Other relevant information

Not available

4.10.4 Summary and discussion of carcinogenicity

No carcinogenicity study with the free fatty acid is available. Local GI effects may be expected from high concentrations, which could result in an unspecific tumor promoting effect, but these effects should not result in classification for carcinogenicity.

Available nutritional studies with medium chain triglycerides as well as human information on ubiquity, consumption data as fat and metabolism support that no adverse systemic effects are to be expected even with high doses.

A dermal carcinogenicity study is available which indicates no dermal carcinogenicity. However these data are of limited value since it is unclear why no skin irritation was reported.

4.10.5 Comparison with criteria

See discussion above

4.10.6 Conclusions on classification and labelling

No classification necessary.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Table 17 Summary of Decanoic acid and Octanoic acid data for potential fertility effects

Route of exposure	Testtype Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	LOEL 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

Harkins et Sarett 1968 (see Doc III-A 6.8.2 add RMS) 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 acid 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. It is also apparent that the rats fed MCT were required to synthesize a large portion of the fatty acids secreted in the milk fat, since about 80% of the dietary fatty acids were C8 and C10 in the MCT group, but these constituted only 24% of the milk fatty acids. In contrast, the fatty acids in the milk secreted by the low oil group were similar to those contained in the dietary fat. Fatty acid composition of these milks show appreciably higher levels of saturated fatty acids C8 to C16 in the milk of the MCT group and markedly more C16:1, C18 and C18:1 in

the milk of the rats fed oleo oil. 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 LOEL of ≥ 8000 mg/kg bw day is apparent in this study. Read across of this result to Nonanoic acid is considered appropriate based on intermediate structure and comparable metabolism.

Taking furthermore into consideration the arguments listed in chapter 4.7.1.7 (bullet points) there is no concern for reproductive toxicity.

4.11.1.2 Human information

See chapter 4.7.1.5

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4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Table 18 Teratogenicity test with Nonanoic acid

Route of exposure	Testtype Method Guideline	Species Strain Sex no/group	Ex-posure period	Doses	Critical effects dams fetuses	NO(A)EL maternal toxicity	NO(A)EL Teratogenicity Embryotoxicity	Reference
Oral	EPA FIFRA Guideline § 152-23	Rat, Crl: COBS CD (SD) BR, 22 females per group	during days 6 through 15 of gestation	1500 mg/kg bw/day and a vehicle control	--	1500 mg/kg bw/day	1500 mg/kg bw/day	**Doc III-A 6.8.1.1/01**

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 (**Doc III-A 6.8.1.1/01**).

Taking furthermore into consideration the arguments listed in chapter 4.7.1.7 (bullet points) there is no concern for developmental toxicity.

4.11.2.2 Human information

See chapter 4.7.1.5

4.11.3 Other relevant information

Not available

4.11.4 Summary and discussion of reproductive toxicity

A teratogenicity study is available with the free nonanoic acid. No adverse effects were observed.

An nutritional study intended to allow observation of potential fertility effects from medium chain triglycerides as well as human information on ubiquity, consumption data as fat and metabolism support that no adverse systemic effects are to be expected even with high doses.

4.11.5 Comparison with criteria

See discussions above.

4.11.6 Conclusions on classification and labelling

No classification is necessary.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

There are no indications from the standard systemic toxicity studies that the active substance Nonanoic acid has neurotoxic properties. The subacute gavage study included also a functional analysis without positive findings. No studies on neurotoxicity were considered necessary.

4.12.1.2 Immunotoxicity

No data available.

4.12.1.3 Specific investigations: other studies

Not available

4.12.1.4 Human information

See chapter 4.7.1.5

4.12.2 Summary and discussion

See discussions above

4.12.3 Comparison with criteria

See discussions above

4.12.4 Conclusions on classification and labelling

No classification necessary.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

5.1.1 Stability

Hydrolysis

A justification for non-submission of data (**Doc. III-A 7.1.1.1.1**) has been submitted stating that hydrolysis of the active substance can be excluded by its structure, as free carbon acids cannot be hydrolysed in the absence of further functional chemical groups.

Conclusion: As we agree with the applicant no further data were asked for.

Photolysis in water

Aqueous photolysis can occur for substances which have UV/visible light absorption maxima in the range of 290 to 800 nm. Nonanoic acid does not display chromophore properties at wavelengths above 290 nm. (**Doc. III-A 3, Study A 3.4/01**). Therefore, photolytic degradation in water is excluded.

Photo-oxidation in air and abiotic effects on the atmosphere

The photochemical degradation of Nonanoic acid in air was estimated using the model AOPWIN (version 1.9, Epi Suite, Syracuse Research Corporation, see **Doc. III-A 7.3.1, Study A 7.3.1**).

The specific degradation rate constant of Nonanoic acid with OH-radicals was estimated to be k_{OH} = 9.76 x 10^{-12} cm³/molecule/s, mainly due to hydrogen abstraction (ca. 92%) and reaction with the hydroxyl-group (ca. 5%). 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:

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

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

$\underline{k_{deg, air} = 0.42\ d^{-1}, T_{1/2} = 39.4\ h}$ (TGD)

The half-life of Nonanoic acid is estimated to be 39.4 h. Based on this result an accumulation of Nonanoic 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 3.4/01**), short atmospheric lifetime (**Doc. III-A 7.3.1, Study A 7.3.1**), absence of Cl, F, N or S substituents in the molecule (**Doc. III-A 2**), Nonanoic 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. Finally no other products are formed.

5.1.2.1 Biodegradation estimation

No data available

5.1.2.2 Screening tests

The biodegradation of Nonanoic acid was investigated in a ready biodegradability test **(Study A 7.1.1.2.1/01 including 1st amendment, Doc. III-A 7.1.1.2.1)** according to OECD guideline 301 F. At the end of the 10-day window on day 11, 64% and 67% biodegradation were found. At the end of the 28-day exposure period degradation rates of 77% and 76% were found. The percentage biodegradation exceeded 60% after 28 days and within the 10-day window.

Conclusion: Nonanoic acid is “readily biodegradable”.

Therefore no further studies on biodegradation (inherent or simulation tests) have been asked for.

Table 19 Biodegradability, STP

Guideline /	Test	Test	Inoculum	Addi-	Test	Degradation	Reference

Test method	type	para-meter	Type	Concen-tration	Adap-tation	tional sub-strate	substance concentr.	Incu-bation period	Degree [%]	
EEC C.4-D, OECD 301-F / Manometric respirometry test	ready	Oxygen demand	Activa-ted sludge	30 mg suspend-ded solids/L	No	No	103-106 mg Nonanoic acid/L	11 days (10 day window) 28 days	64-67% 76-77%	**Study A 7.1.1.2.1/ 01 including 1st amendment, 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

Nonanoic acid is readily biodegradable. Dissipation of fatty acids (C14-C20) in soil is very rapid with DT_{50} values of 3.8–5.7 days at 12°C (2-3 days at 20°C). The principal way of degradation of fatty acids under aerobic conditions is the microbial shortening by C2 pieces (β-oxidation of fatty acids). Dissipation of Nonanoic acid from soil is even faster with a DT_{50} value of approximately 2.1 days at 12°C (1.1 days at 20°C). Nonanoic acid has been found to be present in untreated soil at naturally occurring background levels (range found in the degradation study: 0.35–0.65 mg/kg soil).

Hydrolysis can be excluded by its structure, as free carbon acids cannot be hydrolysed in the absence of further functional groups.

Photolytic degradation in water is excluded for Nonanoic acid, as it does not display chromophore properties at wavelengths above 290 nm.

An estimation of photochemical degradation of Nonanoic acid in air according to TGD resulted in a half-life of 39.4h ($k_{deg, air} = 0.42d^{-1}$; $c(OH)^{air} = 5x10^5$ molecules/cm^3).

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

In a screening test according to OECD guideline 121 the adsorption characteristics of both the ionised and non-ionised form of Nonanoic acid was determined **(Study A 7.1.3/01, Doc. III-A 7.1.3)**, which resulted in K_{oc} values of 63.1 L/kg and 100.0 L/kg, respectively.

The adsorption coefficient K_{oc} was interpolated from a calibration curve using 6 reference items. The linearity of the method was proven in the log K_{oc}-range from 1.25 to 3.2.

Conclusion: Nonanoic acid is not strongly adsorbed to soil.

Table 20 Adsorption onto / desorption from soils

Guideline / Test method	Soil	Substance	Koc_{ads}	Koc_{des}	Reference
OECD 121 / Estimation of the Adsorption Coefficient (K_{oc}) on Soil and on Sewage Sludge using HPLC	Cyanopropyl stationary phase	Nonanoic acid in Methanol/pure water Methanol/buffer solution pH 4	Log K_{oc}:1.8 K_{oc}: 63.1 L/kg Log K_{oc}: 2 K_{oc}: 100.0 L/kg	-	**Study A 7.1.3/01, Doc. III-A 7.1.3**

5.2.2 Volatilisation

Table 20b vapour pressure

Property	Purity/Specification	Results	Reference
Vapour pressure	Nonanoic acid (~100%)	0.9 Pa (20°C) 1.4 Pa (25°C) 10.6 Pa (50°C)	**Doc. III-A 3; Study A 3.2/01**

Henry´s Law Constant	-	Calculated: 0.33 Pa x m^3/mol (20°C)	**Doc. III-A 3; Study A 3.2.1/01**

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) = 0.0001393

With HENRY [Pa * m3 *mol-1], R = 8.314 Pa * m3 –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

Table 21 Estimations on aquatic bioconcentration

Estimation (**log P_{OW}**) with the Software SRC 2000 KOWWIN, Version 1.66; Syracuse Research Corporation

Basis for estimation	log P_{OW}	Estimated BCF for Nonanoic acid	Reference

Calculation	3.52	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 3.52, the log BCF_{fish} can be calculated as: log BCF_{fish}=0.85 x 3.52 – 0.70 = 2.292 BCF_{fish}=195.88	TGD on Risk Assessment

The calculated BCF_{fish} for Nonanoic acid is 195.88. In addition to the facts and arguments given above, together with the knowledge on metabolism and biological properties of fatty acids, sufficient evidence is given of the non-bioaccumulating properties of Nonanoic acid.

Table 22 Estimations on terrestrial bioconcentration

Basis for estimation	**log P_{OW}**	**Estimated BCF for Nonanoic acid**	**Reference**
Calculation	3.52	The $BCF_{earthworm}$ can be calculated according to the following formula: $BCF_{earthworm} = \frac{0.84 + 0.012 \times P_{OW}}{RHO_{earthworm}}$ P_{ow} is the partition coefficient of Nonanoic acid and is equal to 3311.3. $RHO_{earthworm}$ is the bulk density of earthworm $BCF_{earthworm} = \frac{0.84 + 0.012 \times 3311.3}{1} = 40.57$ $BCF_{earthworm}$=40.57	TGD on Risk Assessment

The calculated BCF of Nonanoic acid in earthworms is 40.57. In addition to the arguments given above, Nonanoic acid can be assumed not being bioaccumulative.

5.3.1.2 Measured bioaccumulation data

Not available

5.3.2 Summary and discussion of aquatic bioaccumulation

Based on its chemical structure, Nonanoic 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 Pow can be determined for Nonanoic 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 Nonanoic acid is a very simple molecule (nine-carbon straight-chain fatty acid (C9H18O2)) the model calculations can be assumed to be a reliable estimate. For comparison, the log Pow from other fatty acids are mentioned (Octanoic acid 3.03, Decanoic acid 4.02, both estimated with QSAR methods).

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

Nonanoic acid is also a substance with high surface activity (surface tension 34.6 mN/m). As surface active molecules could have a potential for bioaccumulation, the testing of the bioaccumulation in an appropriate species of fish might be necessary.

For Nonanoic acid, bioaccumulation is not an important issue, because

- Nonanoic acid is as rapidly biodegradable
- Nonanoic acid is a fatty acid. Fatty acids are ubiquitous available in the environment and important naturally occurring biological molecules, found in all living organisms. They may be regarded as having fundamental roles (i.e. they are the building blocks of structurally important molecules in cellular membranes and also serve as sources of energy for biological systems).
- Nonanoic acid is metabolized via ß-oxidation. This is quantitatively the most significant pathway for catabolism of fatty acids and results in the final products CO_2 and acetyl-CoA which as such are further metabolized to CO_2 and water (for details of the degradation steps see Doc. II-A, 1.1 Toxicokinetics, Metabolism and Distribution).

As no study on bioconcentration in aquatic organisms is necessary and available, the BCF is calculated according to formula 74 of the TGD for completeness.

5.4 Aquatic toxicity

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

Tables 23 - 28: Summary of relevant information on aquatic toxicity

See chapters 5.4.1.1, 5.4.1.2, 5.4.2.1, 5.4.2.2, 5.4.3, 5.4.4.

In the toxicity tests in fish, daphnia and algae the test substance was NEU 1170 H. For information concerning NEU 1170 H and the way to express the data in Nonanoic acid please see Document II-A, Effects Assessment for the Active Substance, Appendix Confidential Data and Information, 1.2 Definition of the active substance.

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

The acute toxicity of NEU 1170 H was investigated on rainbow trout and golden ide in a semi-static study for 96 hours (Study B 7.7.1.1.1/01 and **B 7.7.1.1.1/02, Doc. III-A 7.4.1.1**). The LC_{50} values could not be calculated because no mortality up to the highest tested concentration of 100 mg NEU 1170 H/L was observed. So the LC_{50} values are higher than the highest concentration tested (given in mean measured values) and calculated for the ai. For the results given as Nonanoic acid see table 23 below:

Table 23 Acute toxicity to fish

Guideline / Test method	Species	Endpoint/ Type of test	Exposure		Results in mg Nonanoic acid/L, mean measured			Remarks	Reference
			design	duration	LC_0	LC_{50}	LC_{100}		
EEC C.1, OECD No. 203	*Oncorhynchus mykiss* (rainbow trout)	mortality/ acute	Semi-static	96h	13.66	>13.66	>13.66	No effects up to the highest concentration tested	Study B 7.7.1.1.1/01 Doc. III-A 7.4.1.1
EEC C.1, OECD No. 203	*Leuciscus idus* (golden ide)	mortality/ acute	Semi-static	96h	7.2	>7.2	>7.2	No effects up to the highest concentration tested	**Study B 7.7.1.1.1/02 Doc. III-A 7.4.1.1**

5.4.1.2 Long-term toxicity to fish

In a 28-day flow-through study with NEU 1170 H (**Study A 7.4.3.1/01, Doc. III-A 7.4.3.1**), the fish showed no toxic effects and there were no mortalities during the test up to the highest concentration tested. Data on size and weight of the fish at the beginning as well as at the end of the study were statistically evaluated, so the test considers chronic effects also. No statically significant influence on the fish growth could be observed.

For the results given as Nonanoic acid see table 24 below:

Table 24 Effects on reproduction and growth rate of fish

Guideline/ Test method	Species	Endpoint/ Type of test	Exposure		Results in mg Nonanoic acid/L nominal confirmed		Remarks	Reference
			design	duration	NOEC	LOEC		
OECD No. 204	*Oncorhynchus mykiss* (rainbow trout)	mortality and non-lethal effects/ chronic	flow-through	28 days	19.2	>19.2	-	**Study A 7.4.3.1/01 Doc. III-A 7.4.3.1**

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Acute toxicity of NEU 1170 H to daphnids (*Daphnia magna*) was investigated in a semi-static study (Study **B 7.7.1.1.2/01 Doc. III-A 7.4.1.2)**. The highest tested nominal concentration causing no mortality after 48 hours was 10 mg NEU 1170 H/L. For the results given as Nonanoic acid see table 25 below:

Table 25 Acute toxicity to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results in mg Nonanoic acid/L, mean measured			Remarks	Reference
			design	duration	EC_0	EC_{50}	EC_{100}		
OECD 202-I	*Daphnia magna*	immobilisation/ acute	Semi-static	48h	1.98	23.63	62.16	----	**Study B 7.7.1.1.2/01 Doc. III-A 7.4.1.2**

5.4.2.2 Long-term toxicity to aquatic invertebrates

The effects of a 21 day exposure of *Daphnia magna* to NEU 1170 H on the immobility and reproduction was investigated in a semi-static study (**Study A 7.4.3.1/01, Doc. III-A 7.4.3.1**). EC_{50} values on toxicity could not be calculated because a maximum of 20% mortality was observed in the highest concentration tested at the end of the test after 21 days. For the results given as Nonanoic acid see table 26 below:

Table 26 Effects on reproduction and growth rate with an invertebrate species

Guideline/ Test method	Species	Endpoint/ Type of test	Exposure		Results in mg Nonanoic acid/L, mean measured		Remarks	Reference
			design	duration	NOEC	LOEC		
OECD No. 211	*Daphnia magna*	mortality and reproduction/ chronic	semi-static	21 days	9.93	>9.93	-	**Study A 7.4.3.4/01 Doc. III-A 7.4.3.4**

5.4.3 Algae and aquatic plants

A static study was conducted on the toxicity of NEU 1170 H to the algae *Scenedesmus subspicatus* (**Study B 7.7.1.1.3/01, 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 20.0 mg NEU 1170 H/L (NOE_rC). Because of poor measurements of the test item, the EC values could only be given in nominal values.

In a further study the toxicity of NEU 1170 H to the alga *Anabaena flos-aquae* under static conditions was investigated for 96 hours (Study B 7.7.1.1.3/02 Doc. III-A 7.4.1.3). No EC values

could be calculated for NEU 1170 H, because the NOEC is equal to 100 mg NEU 1170 H/L, the highest concentration tested.

The exposure of *Lemna gibba* to NEU 1170 H over a period of 7 days under semi static conditions showed E_rC_{50} (µ) >100 mg NEU 1170 H/L. The EC_{50} (frond numbers) was 83.47 mg NEU 1170 H/L and the E_bC_{50} was 51.41 mg NEU 1170 H/L. For growth rate and for biomass production the NOEC was found to be 50 mg NEU 1170 H/L and the LOEC 100 mg NEU 1170 H/L (Study A 7.4.3.5.2/01).

For the results given as Nonanoic acid see table 27 below:

Table 27 Growth inhibition on algae and on aquatic plants

Guideline/ Test method	Species	End-point	Exposure		Results in mg Nonanoic acid/L, mean measured			Remarks	Reference
			design	duration	NOE_rC	E_bC_{50}[1]	E_rC_{50}[2]/EC_{50}		
OECD 201	*Scenedesmus subspicatus*	growth and biomass inhibition	static	72h	**0.568**	15.19*	103.4*	----	**Study B 7.7.1.1.3/01** **Doc. III-A 7.4.1.3**
ASTM Designation: E 1218-90 EPA, Ecological Effect Test Guidelines, OPPTS 850.5400.	*Anabaena flos-aquae*	growth and biomass inhibition	static	96h	3.48	>3.48	>3.48	No effects up to the highest concentration tested	Study B 7.7.1.1.3/02 Doc. III-A 7.4.1.3
Draft Guideline after the 1st Lemna expert meeting in Ispra 6-7 March 1997	*Lemna gibba*	frond number, growth rates, biomass production	semi static	7 days	9.6*	9.87*	>19.2* (growth rate) 16.02* (frond numbers)	----	Study A 7.4.3.5.2/01

[1] - calculated from the area under the growth curve; [2] - calculated from growth rate

*nominal values

5.4.4 Other aquatic organisms (including sediment)

Inhibition of microbial activity (aquatic)

The inhibitory effects of Nonanoic acid against aquatic micro-organisms were investigated in an activated sludge respiration inhibition test according to OECD guideline 209 **(Study A 7.4.1.4/01, Doc. III-A 7.4.1.4),** which resulted in an EC_{20} of 360.5 mg a.s./L (nominal) and in an EC_{50} of 565.2

mg a.s./L (nominal). In this test, in comparison to the inoculum controls, the respiration rate of the activated sludge was slightly activated by 7.1% at the lowest concentration of 10 mg a.s./L. At the next higher concentrations of nominal 32, 100 and 320 mg/L, the respiration rate was slightly inhibited by a maximum of 14.3% at a plateau. At the highest test concentration of 1000 mg/L (nominal), the respiration activity was inhibited by 85.7%.

Further information: The additionally submitted literature (US EPA, 1992, Reregistration Eligibility Document-Soap Salts) states that fatty acids and their salts are excellent substrates for microbial growth and it gives a very short summary of the detailed information given in chapter 3.1.

Conclusion: Inhibitory effects against aquatic micro-organisms are not expected up to 360.5 mg Nonanoic acid/L (nominal), the EC_{50} is 565.2 mg a.s./L (nominal).

Table 28 Effects on microbial activity (aquatic)

Guideline / Test method	Species / Inoculum	Endpoint / Type of test	Exposure		Results			Re-marks	Reference
			design	duration	EC_{20}	EC_{50}	EC_{80}		
OECD 209 / Activated Sludge, Respiration Inhibition Test	Activated sludge	Oxygen measurement / Respiration inhibition	static with aeration	3h	360.5 mg a.s./L (nominal)	565.2 mg a.s./L (nominal)	Not determined	--	**Study A 7.4.1.4/01 Doc. III-A 7.4.1.4**

Sediment dwelling organisms

There are no effect data available from tests with sediment dwelling organisms.

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 >1 mg/L;

Lowest $L(E)C_{50}$ value: LC_{50} (fish) >7.2 mg/L

➔ **No classification**

Studies used:

- Doc. III-A 7.4.1.1: Heintze A. (1999b), OECD 203, Acute Toxicity testing of NEU 1170 H in Golden ite (*Leuciscus idus*) (Teleostei, Salmonidae) -> **LC_{50} (fish) >7.2 mg/L**

- Doc. III-A 7.4.1.2: Kleiner R. (1998), OECD 202, Acute immobilisation test Daphnia, *Daphnia magna*, NEU 1170 H -> **EC_{50} (crustacea) =23.63 mg/L**
- Doc. III-A 7.4.1.3: Kleiner R. (1999), OECD 201, Algae growth inhibition test, *Scenedesmus subspicatus*, NEU 1170 H -> **E_rC_{50} (algae) =103.4 mg/L**

Aquatic Chronic Categories:

Rapidly degradable substance for which adequate chronic toxicity data are available for all three trophic levels; NOECs between 0.1 mg/L and 100 mg/L; lowest chronic value is the NOE_rC from algae with 0.568 mg/L, which in combination lead to a classification with Aquatic Chronic 3.

Aquatic Chronic 1:

➔ **No classification**

Aquatic Chronic 2:

➔ **No classification**

Aquatic Chronic 3:

➔ **Classification with Aquatic Chronic 3**

Studies used:

- Doc. III-A 7.1.1.2.1: Hertl J. (2002), OECD 301 F, Ready biodegradability of Pelargonic acid in a manometric respirometry test including 1st amendment from July 2006 -> **76-77% degradation in 28 days**
- Doc. III-A 7.4.3.1: Heintze A. (1999c), OECD 204, 28-day prolonged toxicity test of NEU 1170 H in Rainbow trout (*Oncorhynchus mykiss*) (Teleostei, Salmonidae) -> **NOEC (fish) ≥19.2 mg/L**
- Doc. III-A 7.4.3.4: Heintze A. (1999d), OECD 211, Assessment of toxic effects of NEU 1170 H on *Daphia magna* using the 21 day reproduction test -> **NOEC (crustacea) =9.93 mg/L**
- Doc. III-A 7.4.1.3: Kleiner R. (1999), OECD 201, Algae growth inhibition test, *Scenedesmus subspicatus*, NEU 1170 H -> **NOE_rC (algae) =0.568 mg/L**

DSD:

Readily biodegradable substance; log P_{ow} =3.52, $BCF_{fish.\ calculated}$ =195.88; acute aquatic toxicity values available for all three trophic levels; $E(L)C_{50}$ values between 1 - >100 mg/L; lowest $L(E)C_{50}$ value from fish > 7.2 mg/L;

R50/53:

➔ **No classification**

R50:

➔ **No classification**

R51/53:

The lowest LC_{50} value (fish) is >7.2 mg/L, which would lead to a classification with R51 and in combination with a calculated log P_{ow} of 3.52 further on to a classification with N; R51/53, although the substance is readily biodegradable.

7.2 mg/L was the highest concentration tested in the respective study. No effects were observed at that concentration. In contrast to this value the long term NOEC (fish) for Nonanoic acid was found to be 19.2 mg/L. There is also a LC_{50} (fish) available from Octanoic acid (C8 fatty acid) with 68 mg/L (Draft Competent Authority Report, Document I, Octanoic acid, Product Type 4 and 18, 2011).

Therefore as a weight of evidence decision it is proposed not to classify Nonanoic acid with R51/53.

➔ **No classification**

R52/53:

This criterion only applies, if the substance is not readily biodegradable. Therefore no classification is proposed.

➔ **No classification**

Studies used:

- Doc. III-A 7.1.1.2.1: Hertl J. (2002), OECD 301 F, Ready biodegradability of Pelargonic acid in a manometric respirometry test including 1st amendment from July 2006 -> **76-77% degradation in 28 days**
- Doc. III-A 3: Study A 3.9/01 Partition coefficient of Nonanoic acid, (Estimation with the Software SRC 2000 KOWWIN) -> **log P_{ow} =3.52**
- Calculation according to TGD on Risk Assessment -> **$BCF_{fish.\ calculated}$ =195.88**
- Doc. III-A 7.4.1.1: Heintze A. (1999b), OECD 203, Acute Toxicity testing of NEU 1170 H in Golden ite (*Leuciscus idus*) (Teleostei, Salmonidae) -> **LC_{50} (fish) >7.2 mg/L**
- Doc. III-A 7.4.1.2: Kleiner R. (1998), OECD 202, Acute immobilisation test Daphnia, *Daphnia magna*, NEU 1170 H -> **EC_{50} (crustacea) =23.63 mg/L**
- Doc. III-A 7.4.1.3: Kleiner R. (1999), OECD 201, Algae growth inhibition test, *Scenedesmus subspicatus*, NEU 1170 H -> **E_rC_{50} (algae) =103.4 mg/L**

REACH registration dossier for Nonanoic acid:

Acute aquatic toxicity: $L(E)C_{50}$ values for all three trophic levels between 10 - >100 mg/L; lowest acute value E_rC_{50} (algae) =60 mg/L;

Chronic aquatic toxicity: NOEC values for two trophic levels (daphnia and algae; read across from Heptanoic acid (C7 fatty acid)) between 10 – 100 mg/L; lowest chronic NOEC (crustacea) =18 mg/L;

Fate & behaviour: rapidly biodegradable; measured log P_{ow} =3.42; BCF estimated for fish 3.2;
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.

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

CLP:

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

Classification and Labelling			**Justification**
GHS Pictograms		-	Rapidly degradable substance for which adequate chronic toxicity data are available for all three trophic levels. Lowest chronic value is NOE_rC from algae with 0.568 mg/L.
Signal words		-	
Classification		Aquatic Chronic 3	
Hazard statements		H412: Harmful to aquatic life with long lasting effects	
Precautionary Statements	**General**	-	
	Prevention	P273: Avoid release to the environment	
	Response	-	
	Storage	-	
	Disposal	P501: Dispose of contents/container in accordance with local/regional/national/ 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: No classification

Justification: Nonanoic acid is readily biodegradable. There is a measured log P_{ow} with 3.42 (REACH dossier) – and a calculated log P_{ow} with 3.52 (CAR) and there are calculated BCF_{fish} values with 95.88 (CAR) and 3.2 (REACH dossier) available. All available $L(E)C_{50}$ values are between 10 and >100 mg/L. The only exception is the lowest LC_{50} fish with >7.2 mg/L. 7.2 mg/L was the highest concentration tested at which no effects could be observed. In the REACH dossier 3 different acute studies with fish are presented with LC_{50} values between 96 - >105 mg/L. In addition a chronic NOEC value for Nonanoic acid for fish with 19.2

mg/L is available in the CAR and a LC_{50} fish for Octanoic acid (C8 fatty acid) with 68 mg/L is available from the CAR on Octanoic acid. Therefore the weight of evidence decision was taken not to classify the substance.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The ecotoxicological tests on fish, crustaceans and algae presented in the CLH report show that the lowest short term value is the LC_{50} for fish (> 7.2 mg/L). Since the L(E)C50 values are all above 1 mg/L, the dossier submitter concludes that the criterion for classification for acute aquatic hazard Category 1 (CLP) and R50 (DSD) are not fulfilled.

Long-term toxicity data are described in the CLH report for all three trophic levels. The lowest chronic value is the NOErC 0.568 mg/l for algae (*Desmodesmus Subspicatus*) .

The dossier submitter considered nonanoic acid as readily biodegradable and rapidly degradable, since in a manometric respirometry test (OECD TG 301F), degradation rates of 76-77% at the end of the 28-days exposure period were observed.

In the Competent Authority Report (CAR) for biocides, the calculated log Pow was given as 3.52 and the resulting calculated Bio Concentration Factor BCF on fish was 195.88. In the REACH registration dossier, the measured Pow was 3.42 and the calculated BCF for fish was 3.2.
The lowest value for aquatic acute toxicity in fish (> 7.2 mg/L) and the log Pow (≥ 3) would lead to a classification as R51/53 according to DSD. However, the dossier submitter discards this value and proposes not to classify with R51/53 following a weight of evidence assessment based on the following arguments:

a) 7.2 mg/L was the highest concentration tested in the study and no effects were observed at that concentration;
b) The long term NOEC for fish = 19.2 mg/L;
c) The LC_{50} for fish to octanoic acid = 68 mg/L.

In relation to the long term aquatic hazard, the dossier submitter proposed to use the NOEC value for algae which, together with the rapid degradability data, would result in classification as aquatic chronic Category 3 - H412, according to CLP and
'No classification' according to DSD.

Comments received during public consultation

During the public consultation, comments on hazards to the aquatic environment were received from five Member States Competent Authorities (MSCAs) and two industry organisations.
Three MSCAs supported the classification proposal, without providing further argumentation.

One MSCA supported the proposal, but claimed that the data presented in the CLH report did not allow conclusions to be drawn on the toxicity to fish and algae, since the test procedures used were not appropriate and a constant concentration of the test substance was not guaranteed. However, other valid data for fish and algae presented in the REACH registration dossiers for nonanoic acid support the proposed classification.

The remaining MSCA suggested that a wider set of ecotoxicity data relating to the homologous series (heptanoic, octanoic and decanoic acid) available from the REACH registration dossiers, should be considered, in order to address potentially conflicting aquatic chronic data.

In response to the latter two comments, the dossier submitter included in the RCOM a summary of all available chronic ecotoxicity data for fish and crustaceans from the CARs and REACH registration

dossiers for octanoic, nonanoic and decanoic acids. Based on all these data, the dossier submitter concludeed that the proposed classification was indeed appropriate.

One industry organisation considered that the evidence provided by the available data was not sufficient to justify classification as Aquatic Chronic 3, since the NOEC value of 0.568 is not supported by any other aquatic chronic value and the study was of poor quality. The dossier submitter responded to this comment by stating that being an algicide and herbicide, it is not surprising that it would have a low algae NOEC value andoreover, that the NOEC algae value for nonanoic acid was consistent with the values for decanoic and octanoic acids.

The second industry stakeholder organisation (Fatty Acids Consortium, FAC) proposed that nonanoic acid should not be classified as Aquatic Chronic 3, since the NOEC value of 0.568 mg/L was considered unreliable. They claimed that only the "nominal" NOEC value of 20 mg/l of the technical product, corresponding to 4.4 mg/L of the active ingredient, should be considered reliable. The Consortium supported this proposal by considering that, based on the data available in the REACH registration dossiers, an increase in aquatic toxicity can be expected as the chain length increases. Decanoic acid would therefore represent the worst case scenario.
The dossier submitter responded to this comment by confirming their view of the reliability of the chronic algae study and therefore supporting the proposed classification. More details, including the argumentation by FAC and the dossier submitter, are included in the RCOM.

Additional key elements

Nonanoic acid (C_9) belongs to a group of organic acids such as octanoic acid (C_8), decanoic acid (C_{10}) and lauric acid (C_{12}) therefore information about these structurally similar compounds is considered useful to classification for nonanoic 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.

				End points ***CAR for biocides***				***End points*** ***REACH registration dossier***			
	Species	**test**	**Design**	**Octanoic Acid**	**Nonanoic acid**	**Decanoic Acid**	**Lauric acid**	**Octanoic Acid**	**Nonanoic acid**	**Decanoic Acid**	**Lauric 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	-

	Pseudokirchnerella subcapitata	OECD TG 201	Static	-	-	-	-	31[5,6] mm (TWA) (120 nc)	-	-	-
	Desmodesmus subpicatus	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)	-	-	-
	*Desmodesmus Subspicatus*m	OECD TG 201	Static	0.21[3,4] mm (Gm) (2.68 nc) 0.52[7] mm (Gm) (3.62nc)	0.568mm (Gm) (3.97 nc)	0.25[4] mm (Gm) (3.2 nc)	0.079 mm (ErC10)	-	-	-	-
	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.

"-" = 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.

Nonanoic acid was readily biodegradable in an OECD TG 301F manometric respirometry test showing a degradation of 76 - 77% at 28 days and within the 10 d window 64 - 67%. Hydrolysis and photolytic degradation in water are excluded for nonanoic acid because organic acids cannot be hydrolysed in the absence of further functional groups and it do not display chromophore properties at wavelengths above 290 nm.

Additional information from the CAR of biocides showed the aerobic degradation of different mixtures of fatty acids in soil in two non GLP studies. Nonanoic acid rapidly dissipates from soil, with a DT_{50} value of approximately 2.1 days at 12ºC (1.1 days at 20ºC).

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

Bioaccumulation

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

Two different values of log Kow have been summarized in the CLH report: in the CAR for biocides the calculated log Kow is 3.52, and in the REACH registration dossier, the measured value is 3.42. This log Kow corresponds to an undissociated acid but at relevant environmental pHs, nonanoic acid is found in a dissociated form (pka = 4.9 nonanoic acid; pka = 4.8 ammonium salt of nonanoic acid) and therefore, the log kow is expected to be lower.

Nevertheless, nonanoic acid is a surface active substance (surface tension 34.6mN/m), and according to the Technical Guidance Document on Risk Assessment (EC 2003, part II, p. 24), for substances of this type it may not be advisable to use an estimated or measured Kow values as a predictor for Koc (soil, sediment, suspended organic matter and sludge) and 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 Kp and BCF.

For nonanoic acid, there is no BCF available; however, in the REACH registration dossier for octanoic acid, there is an experimental BCF performed with sodium laurate (dodecanoic acid), which can be used as a read-across for nonanoic acid. The measured BCF value for lauric acid is 255 L/kg, but it is based on total radio-labelled residues and therefore, this is an overestimate. 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 that 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 nonanoic acid itself. Dodecanoic acid is more hydrophobic than nonanoic acid, so a direct read across from its measured fish BCF is likely to be a worst case approach. The implication in the absence of any further evidence is that the BCF of nonanoic acid is below 500 L/kg, but it cannot be ruled out that the BCF is above 100 L/kg.

Aquatic toxicity

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

Regarding nonanoic acid, all tests (except testing of the effects on microbial aquatic activity) were conducted with the ammonium salt of nonanoic acid in the form of the "intermediate formulation" NEU 1170 H.

In these studies, the formulation NEU 1170 H, containing approximately 20% nonanoic acid (nominal), was tested. As in this formulation nonanoic acid is, apart from water, the main component and bioavailability of the active substance in the formulation is higher than for the technical active substance, these tests are considered to be appropriate for the evaluation of the active substance. The end-points of the tests were corrected according to the exact concentration of nonanoic acid.

The formulation NEU1170 H has been used under the Biocides Directive to study the toxicity of nonanoic acid (Competent Authority Report, CAR, 2007: Doc. II/III-A).
Furthermore, based on the concentration and DSD classification of the other components of the formulation, they are unlikely to contribute to its toxicity and if the toxicity obtained for nonanoic acid with this formulation is compared with other similar acids, it is consistent with a logical trend which shows an increase in toxicity with increasing hydrophobicity. Therefore, the use of the formulation NEU 1170H for the purpose of classification and labelling is considered appropriate.

As can be seen in table 1, when the toxicity to fish and *daphnia* is evaluated, the expected relationship between the toxicity and hydrophobicity of the acids can be seen and since water/fat solubility is related to chain-length of the acids, their toxicities follow the order: dodecanoic 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 potentially 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 (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 dodecanoic 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 dodecanoic acids 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. As can be seem 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 substances in the group. If this test is not considered, toxicity appears to increase with hydrophobicity as would be expected.

Furthermore, there are some deficiencies in the test from the REACH registration dossier, 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.

For nonanoic acid there is an algae test available with *Desmodesmus subspicatus*, the same species used for decanoic acid test, which is suitable to be used for classification purposes.

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 becomes 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 TG 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 72 h the growth inhibition is lower than at 48 h when the concentration was higher. Therefore, at least for this test, the criterion of using nominal concentrations is not met. For nonanoic acid it is not possible to check this due to the minimal data provided.

Moreover, under the Biocides Directive, the acute and chronic algae toxicity was based on mean measured concentrations" (CAR, 2007: Doc. II/III-A). Taking into account the deficiencies of the test submitted under REACH registration for octanoic acid and the justified use of measured concentrations in the algae tests conducted with nonanoic and decanoic acids, the classification is as follows.

Under CLP, the aquatic acute toxicity category is based on EC50 values, and for nonanoic acid these values are >1 mg/l, therefore nonanoic acid does not warrant classification for aquatic acute toxicity. This value is consistent with the acute toxicity of other structurally similar compounds (octanoic and decanoic acid) with EC50 values also higher than 1 mg/L.

Regarding chronic toxicity, two tests were reviewed, one in *Daphnia* with a NOEC of 9.93 mg/L, and one in algae (*Desmodesmus subspicatus)* which is the most sensitive species with a NOErC of 0.568 mg/L. Taking into account this value and its rapid degradation, nonanoic acid warrants classification as **Chronic category 3 (H412)** according to **CLP**. Although there are not chronic tests in fish, because the available OECD TG 204 prolonged toxicity study cannot be considered an aquatic chronic test, the surrogate approach is not relevant, since nonanoic acid is both readily biodegradable and has a fish BCF <500 L/kg Since this leads to no classification, it does not affect the proposal.

Considering the DSD classification, there is no measured ErC50 value from the test performed with *Desmodesmus subspicatus,* which is the most sensitive chronic species. However, for decanoic acid, which is a very similar substance with only one more carbon that nonanoic acid, the ErC50 value for this species was 2 mg/L; if read-across is then carried out to the nearest higher homologue, then the ErC50 for nonanoic acid would be 1.84 mg/L (Read across from decanoic acid: Conc. Nonanoic acid [g/L] = conc. Decanoic acid [g/L]*MM Nonanoic acid [g/mol] / MM Decanoic acid [g/mol], where: MM

Nonanoic acid = Molar Mass Nonanoic acid = 158.24 g/mol and MM Decanoic = Molar Mass Decanoic Acid = 172.27 g/mol)

) which would lead to a classification with R51 and in combination with a BCF >100 L/kg (the BCF > 100 L/kg cannot be ruled out) classification as N; R51/53 is therefore justified.

Supplemental information - In depth analyses by RAC

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

A recalculation of percentage reduction of growth rate [%] at 72 h has been done because the values which appear in the summary were wrongly calculated.

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 EC50>24 mg/L.

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

During the elaboration of the 2nd Draft Opinion of organic acids, the industry supplied three new tests, one of them was in Japanese, so it cannot be assessed.

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

The second test was a GLP Daphnia Magna reproduction test performed with decanoic acid and following the OECD TG 211, it is 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 hours 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 respective 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 fits the validity criteria of the guideline.

As well as for the algae test, the actual concentration is reduced along 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, 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 Alga, Growth Inhibition Test performed with octanoic acid and following 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 spaced 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 test start and in the test media after 72 h. The decrease of the test concentration was less than 20 % during the test period, and initial measured octanoic acid concentrations were used.

For the relevant parameter growth rate, the ErC50 and the ErC10 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 as the guideline establishes or without them. If the test has been performed according to the guideline it is difficult to understand why it is possible to maintain the concentration along the test for octanoic acid, and not for nonanoic, decanoic and lauric acid.

OTHER INFORMATION
No other information available

6 REFERENCES

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A6.1.3/06	2002	HUMAN AND ENVIRONMENTAL RISK ASSESSMENT ON INGREDIENTS OF EUROPEAN HOUSEHOLD CLEANING PRODUCTS: FATTY ACID SALTS, HUMAN HEALTH RISK ASSESSMENT: DRAFT FOR PUBLIC COMMENT, JUNE 2002. PUBLISHED.	N	-
A6.1.4s/01	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
A6.1.5/01	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
A6.2. non-sub	2000	THE NATURE OF DIETARY FATTY ACIDS AND THEIR NUTRIENT ROLE Source: Eco-Care Technologies Inc., Sidney, BC V8L 5L6, Canada Report-No. Not applicable Not GLP, Published	N	-
A6.2/01 non-sub	2003	THE ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF FATTY ACIDS INCLUDING PELARGONIC ACID IN MAMMALS - EXTRACT FROM LITERATURE GAB Consulting GmbH, Lamstedt, Germany Report-no. not stated	N	W. Neudorff GmbH KG

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A6.2/03 non-sub	1975	FATS OR LIPIDS Source: Introductory Nutrition, 3rd edition, pp. 37-51, C.V. Mosby Co., St. Louis, USA Report-no. not applicable Not GLP; Published	N	--
A6.2/04 non-sub	1971	BIOLOGICAL CHEMISTRY Source: Biological Chemistry, Harper & Row, New York, USA, 2nd edition, pp. 583-604, 712-755 Report-no. not applicable Not GLP; Published	N	--
A6.2/05 non-sub	1975	HUMAN BIOCHEMISTRY Source: Human Biochemistry, C.V. Mosby Company, St. Louis, USA, 9th edition, pp. 253-292 Report-no. not applicable Not GLP; Published	N	--
A6.2/06 non-sub	2001	BIOCHEMISTRY FOR CLINICAL MEDICINE Source: Greenwich Medical Media LTD, London, UK, pp. 85-109 Report-no. not applicable Not GLP; Published	N	--
A6.2/07 non-sub	1983	BIOCHEMISTRY Source: Biochemistry, Addison-Wesley Publishing Company, pp. 471-503 Report-no. not applicable Not GLP; Published	N	--
A6.2/08 non-sub	1976	TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY Source: Textbook of Physiology and Biochemistry, Churchill Livingstone, Edingburgh and London; pp. 124-130 Report-no. not applicable Not GLP; Published	N	--

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A6.2/09 non-sub	2002	RESEARCH Source: Arch. Biochem. Biophys. Vol 404, pp. 136-146 Report-no. not applicable Not GLP; Published	N	--
A6.3.1/01	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
A6.6.1/01	2001	EVALUATION OF THE MUTAGENIC ACTIVITY OF PELARGONSÄURE IN THE SALMONELLA TYPHIMURIUM REVERSE MUTATION ASSAY AND THE ESCHERICHIA COLI REVERSE MUTATION ASSAY (WITH INDEPENDENT REPEAT) Notox B.V, 's-Hertogenbosch, The Netherlands Report-No. 321569 GLP, Unpublished	Y	W. Neudorff GmbH KG
A6.6.2/01	2001	EVALUATION OF THE ABILITY OF PELARGONSÄURE TO INDUCE CHROMOSOME ABERRATIONS IN CULTURED PERIPHERAL HUMAN LYMPHOCYTES (INCLUDING AMENDMENT NO.1) Notox B.V, 's-Hertogenbosch, The Netherlands Report No. 321571 GLP, Unpublished	Y	W. Neudorff GmbH KG
A6.8.1.1/01	1994	TERATOLOGY SCREEN IN RATS Hazleton Washington Inc., Vienna, U.S.A. Report No. HWA 2689-101 Not GLP, Published	Y	Mycogen Corporation Dow Agrosciences LLC Data Compen-sation Department 9330 Zionsville Road IN 46268-1054

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A7.1.1.2.1/01	2002	READY BIODEGRADABILITY OF PELARGONIC ACID IN A MANOMETRIC RESPIROMETRY TEST INCLUDING 1ST AMENDMENT FROM JULY 2006 IBACON GmbH, Rossdorf, Germany Project 14737160, Report No.: 11841087 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.1.3/01	2006b	ESTIMATION OF THE ADSORPTION COEFFICIENT (K_{OC}) OF PELARGONIC ACID (EMERY 1202) USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC) IBACON GmbH, Rossdorf, Germany Project 31573195 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.2.1/01	1990	TESTING THE BIOLOGICAL DEGRADABILITY OF NEUDOSAN IN TWO SOILS Biochem GmbH, Daimlerstr. 5b, D-7500 Karlsruhe 21, Germany Report-no. not stated Not GLP, Unpublished	N	W. Neudorff GmbH KG
A7.2.1/02	1986	FATE OF CAPRIC AND PELARGONIC FATTY ACIDS IN SOIL Unpublished Report Report-no. not stated Not GLP, Unpublished	N	W. Neudorff GmbH KG
A7.3.1/01	2003b	PELARGONIC ACID - ESTIMATION OF THE PHOTOCHEMICAL OXIDATIVE DEGRADATION GAB Consulting GmbH, Lamstedt, Germany Report-No. 105155-A2-0210-01 Not GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.1.1/01-non-sub	1999a	NEU 1170 H – ACUTE TOXICITY TESTING OF NEU 1170 H IN RAINBOW TROUT (*ONCORHYNCHUS MYKISS*) (TELEOSTEI, SALMONIDAE) ArGe GAB Biotech/IFU, D-75223 Niefern-	Y	W. Neudorff GmbH KG

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		Öschelbronn Report No. 99024/01-AAOm GLP, Unpublished		
A7.4.1.1/02-non-sub	1999b	NEU 1170 H – ACUTE TOXICITY TESTING OF NEU 1170 H IN GOLDEN ITE (*LEUCISCUS IDUS*) (TELEOSTEI, SALMONIDAE) ArGe GAB Biotech/IFU, D-75223 Niefern-Öschelbronn Report No. 99024/01-AALi GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.1.2/01-non-sub	1998	ACUTE IMMOBILISATION TEST DAPHNIA – *DAPHINA MAGNA* ACCORDING TO OECD GUIDELINE 202-I (1984) NEU 1170 H (22 %) BioChem Agrar, Labor für biologische und chemische Analytik, D-04451 Cunnersdorf Report No. 981048039 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.1.3/01-non-sub	1999	ALGAE GROWTH INHIBITION TEST *SCENEDESMUS SUBSPICATUS* OECD GUIDELINE 201 (1984) NEU 1170 H (22%) BioChem Agrar, Labor für biologische und chemische Analytik D-04451 Cunnersdorf Report No. 981048040 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.1.3/02-non-sub	1999a	TESTING OF TOXIC EFFECTS OF NEU 1170 H ON THE BLUE-GREEN ALGA *ANABAENA FLOS-AQUAE* ArGe GAB Biotech/IFU, D-75223 Niefern-Öschelbronn Report No. 99024/01-AAAf GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.1.4/01	2006	TOXICITY OF PELARGONIC ACID (EMERY 1202) TO ACTIVATED SLUDGE IN A RESPIRATION INHIBITION TEST IBACON GmbH, Rossdorf, Germany Report-No. 31575171 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.3.1/01	1999c	28 – DAY PROLONGED TOXICITY TEST OF NEU 1170 H IN RAINBOW TROUT (*ONCORHYNCHUS MYKISS*) (TELEOSTEI, SALMONIDAE) ArGe GAB Biotech/IFU, D-75223 Niefern-Öschelbronn Report No. 99024/01-ACOm GLP, Unpublished	Y	W. Neudorff GmbH KG

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A7.4.3.4/01	1999d	ASSESSMENT OF TOXIC EFFECTS OF NEU 1170 H ON DAPHNIA MAGNA USING THE 21 DAY REPRODUCTION TEST ArGe GAB Biotech/IFU, D-75223 Niefern-Öschelbronn Report No. 99024/01-ARDm GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.4.3.5.2/01	1999b	ASSESSMENT OF TOXIC EFFECTS OF NEU 1170 H ON AQUATIC PLANTS USING THE DUCKWEED *LEMNA GIBBA* ArGe GAB Biotech/IFU, D-75223 Niefern-Öschelbronn Report No. 99024/01-AALG GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.5.1.2/01	1998	ACUTE TOXICITY OF NEU 1170 H ON EARTHWORMS, EISENIA FOETIDA USING AN ARTIFICIAL SOIL TEST Arbeitsgemeinschaft GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, D-75223 Niefern-Öschelbronn Report No. 97253/01-NLEf GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.5.1.3/01	2003	EFFECTS OF NEU 1170 H ON TERRESTRIAL (NON-TARGET) PLANTS: VEGETATIVE VIGOUR TEST IBACON GmbH, Rossdorf, Germany Report No. 15411087 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.5.3.1.1/01	1996	ACUTE ORAL TOXICITY STUDY IN BOBWHITE QUAIL WITH NEUDOSAN NEU NOTOX B.V., 's-Hertogenbosch , The Netherlands Report-no. 185052 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.5.3.1.2/01	2003	AVIAN DIETARY TOXICITY TEST OF "NEU 1170 H" IN JAPANESE QUAIL Harlan Bioservice for Science GmbH, Walsrode, Germany Report No. 10-16-0146-03 GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.5.3.1.2/02	2004	AVIAN DIETARY TOXICITY TEST OF "NEU 1170 H" IN THE MALLARD DUCK Harlan Bioservice for Science GmbH, Walsrode, Germany Report No. 10-16-0119-04	Y	W. Neudorff GmbH KG

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A7.5.4.1/01	1998	ASSESSMENT OF SIDE EFFECTS OF NEU 1170 H TO THE HONEY BEE, *APIS MELLIFERA* L. IN THE LABORATORY FOLLOWING THE EPPO GUIDELINE NO. 170 ArGe GAB Biotech/IFU, D-75223 Niefern-Öschelbronn Report No. 97253/01-BLEU GLP, Unpublished	Y	W. Neudorff GmbH KG
A7.5.4.1/02	2003	AN EXTENDED LABORATORY TEST TO DETERMINE THE EFFECTS OF NEU 1170 H ON THE GROUND-ACTIVE BEETLE, *POECILUS CUPREUS* Mambo-Tox Ltd., Southampton, U.K. Report No. NEU-03-5 GLP, Unpublished	Y	W. Neudorff GmbH KG
Company statement	2008	ANALYSENZERTIFIKAT VISKOSITÄT (ANALYSIS CERTIFICATE VISCOSITY) W. Neudorff GmbH KG, Emmerthal, Germany Report-No. not applicable, statement Not GLP, Unpublished	Y	W. Neudorff GmbH KG
Company statement	2007	GENERAL INFORMATION ON THE ACTIVE SUBSTANCE AND THE BIOCIDAL PRODUCT; active substance: Pelargonic Acid biocidal product: Katzenschreck W. Neudorff GmbH KG, Emmerthal, Germany Report-No. Not applicable (statement) Not GLP, Unpublished		W. Neudorff GmbH KG
Company statement	2006	MODE OF ACTION OF PELARGONIC ACID IN CAT REPELLENT PRODUCT W. Neudorff GmbH KG, Emmerthal, Germany Report-No. not applicable, statement Not GLP, Unpublished	N	W. Neudorff GmbH KG
Company statement	2008	CONFIRMATION: PELARGONSÄUREGEHALT IN ÄLTEREN UNTERSUCHUNGEN (PELARGONIC ACID CONTENT IN OLDER STUDIES) W. Neudorff GmbH KG, Emmerthal, Germany Report-No. not applicable, statement Not GLP, Unpublished	Y	W. Neudorff GmbH KG
Company statement	2008	MODE OF ACTION OF NONANOIC ACID (PELARGONIC ACID):	N	W. Neudorff GmbH KG

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		W. Neudorff GmbH KG, Emmerthal, Germany Report-No. not applicable, statement Not GLP, Unpublished		
Company statement	2007	Water solubility of Pelargonic acid; W. Neudorff GmbH KG, Emmerthal, Germany Report no:20061535/01-PCSB GLP, Unpublished	Y	W. Neudorff GmbH KG

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Anonymous	1998	PESTICIDE FACT SHEET (FOR PELARGONIC ACID, DATE ISSUED: JANUARY 1998 Source: US EPA Report-No.: Not applicable Not GLP, Published	N	--
Anonymous	2003	PELARGONIC ACID (NONANOIC ACID); EXEMPTION FROM THE REQUIREMENT OF A PESTICIDE TOLERANCE Source: US Environmental Protection Agency Report-No.: Not applicable Not GLP; Published	N	--
Barkley W.	1985	CHRONIC MOUSE DERMAL TOXICITY STUDY, TEST MATERIAL C-182 = PELARGONIC ACID Kettering Laboratory, Univ. Cincinnati, OH, U.S.A. Report No. not stated Not GLP, Published **Submitted in 6.5.1/01**	just EPA study summary, no letter of access from applicant available	?
Cifone M.A.	1993	MUTAGENICITY TEST ON PELARGONIC ACID (TECHNICAL GRADE) IN THE L5178Y TK +/- MOUSE LMPHOMA FORWARD MUTATION ASSAY WITH A CONFIRMATORY ASSAY Hazleton Washington, Vienna, VA, U.S.A. Report No. 15656-0-431R GLP, Published Submitted in A6.6.3 non-sub	just EPA study summary, no letter of access from applicant available	?
Harrison PT.	1992	PROPIONIC ACID AND THE PHENOMENON OF RODENT FORESTOMACH TUMORIGENESIS: A REVIEW BP group Occupational Health Centre, Guilford, Surrey, U. K. Food Chem Toxicol. 1992 Apr; 30(4): 333-40 Report-No. Not applicable Not GLP, Published	N	--
Kuhn J.O.	1995	PELARGONIC ACID-RANGE-FINDING FOR A 90-DAY RAT ORAL TOXICITY (DIET) Stillmeadow Inc., Sugar Land, Texas, U.S.A. Report No. 1941-95 GLP, Published Submitted as A6.3.1/02	just EPA study summary, no letter of access from applicant available	?
Lawlor T.E.	1993	MUTAGENICITY TEST ON PELARGONIC ACID (TECHNICAL GRADE) IN THE SALMONELLA/MAMMALIAN-MICROSOME REVERSE MUTATION ASSAY (AMES TEST) Hazleton Washington Inc., Vienna, VA, U.S.A.	just EPA study summary, no letter of access from applicant	?

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		Report No. 15656-0-401R GLP, Published Submitted as A6.6.1/02	available	
Li C.Y.	1978	SOIL FATTY ACIDS UNDER ALDER CONIFER STANDS OF COASTAL OREGON SOIL SCIENCE; Vol 125, No. 2, 92-94 Report-No.: not applicable, not GLP, Published	N	?
Murli H.	1993	MUTAGENICITY TEST ON N-PELARGONIC ACID IN VIVO MICRONUCLEUS ASSAY Hazleton Washington, Vienna, VA, U.S.A. Report No. 15656-0-455CO GLP, Published **Submitted as 6.6.4/01**	just EPA study summary, no letter of access from applicant available Draft CAR for fatty acids (C7-C20) prepared by RMS Ireland in the context of 91/414/EEC indicates no data protection	Mycogen Corp
US EPA, Anonymous	1992	THE REREGISTRATION ELIGIBILITY DOCUMENT (RED) ON SOAP SALTS Source: US EPA Report-No.: Not applicable Not GLP, Published	N	--
US EPA, Mycogen Corporation	1997	PELARGONIC ACID; PESTICIDE TOLERANCE PETITION 1/97 Source: Cornell University, 5123 Comstock Hall, Ithaca, New York Report-No.: not applicable, Not GLP, Published	N	?

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Basketter DA, Chamberlain M, Griffiths HA, Rowson M, Whittle E, York M.	1997	THE CLASSIFICATION OF SKIN IRRITANTS BY HUMAN PATCH TEST Food Chem Toxicol. 35(8):845-52	N	published
Basketter DA, Griffiths HA, Wang XM, Wilhelm KP, McFadden J.	1996	INDIVIDUAL, ETHNIC AND SEASONAL VARIABILITY IN IRRITANT SUSCEPTIBILITY OF SKIN: THE IMPLICATIONS FOR A PREDICTIVE HUMAN PATCH TEST. Contact Dermatitis 35(4), 208-13.	N	published
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7 ANNEXES

Confidential Annex