Nonanoic acid

Biocide for Use as Repellent

Dossier According to Directive 98/8/EC

Document III-A

Data on the Active Substance

Section A1 **Applicant**

Annex Point IIA1

1.1 Applicant

Name: W. Neudorff GmbH KG
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D-31860 Emmerthal
Germany

Telephone: +49- (0) 5155-624-126
Fax number: +49- (0) 5155-624-7122
E-mail: [redacted]

1.2 Manufacturer of Active Substance (if different)

[redacted]

Telephone: not available
Fax number: not available
E-mail: not available

Location of manufacturing plant:

[redacted]

Telephone: not available
Fax number: not available

1.3 Manufacturer of Product(s) (if different)

1) Product 1

Name: W. Neudorff GmbH KG
[redacted]

2) Product n

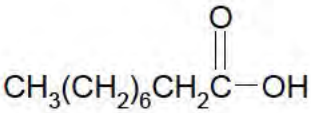
[redacted]

Location of manufacturing plant:

Name: W. Neudorff GmbH KG
[redacted]

[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Materials and methods	Applicant's version is acceptable
Conclusion	Adopt applicant's version
Reliability	n.a.
Acceptability	Acceptable
Remarks	-

Section A2		Identity of Active Substance				
Subsection (Annex Point)						**Official use only**
2.1	**Common name (IIA2.1)**	Nonanoic Acid				x
2.2	**Chemical name (IIA2.2)**	Nonanoic acid				
2.3	**Manufacturer´s development code number(s) (IIA2.3)**	[redacted]				
2.4	**CAS No and EC numbers (IIA2.4)**					
2.4.1	**CAS-No**	112-05-0				
	Isomer 1	No Isomers are formed				
	Isomer n	--				
2.4.2	**EC-No**	203-931-2				
	Isomer 1	No Isomers are formed				
	Isomer n	--				
2.4.3	**Other**	No other registration number (e.g. CIPAC) is available				
2.5	**Molecular and structural formula, molecular mass (IIA2.5)**					
2.5.1	**Molecular formula**	$C_9H_{18}O_2$				
2.5.2	**Structural formula**					
2.5.3	**Molecular mass**	158.2				x
2.6	**Method of manufacture of the active substance (IIA2.1)**	[redacted]				
2.7	**Specification of the purity of the active substance, as appropriate (IIA2.7)**	g/kg	g/l	% w/w	% v/v	x
		--	--	minimum declared 89.6%.	--	
		Based on the 5-Batch analysis the minimum purity of Pelargonic Acid is declared, analogue to Plant Protection Products, by subtracting 3 times the RSD from the mean content analysed.				x
2.8	**Identity of impurities and additives, as appropriate (IIA2.8)**	[redacted]				x
2.8.1	**Isomeric composition**	The technical product does not contain inactive isomers which have to be specified.				

Section A2	Identity of Active Substance
2.9 The origin of the natural active substance or the precursor(s) of the active substance (IIA2.9)	Oleic acid obtained from a natural source. [redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date May 2008

Materials and methods

2.1 Common name: synonym: Pelargonic acid

2.5.3 Molecular mass: 158.2 g/mol

2.7 Range of concentration: 89.6 – 100%w/w

Typical concentration from the five batch analysis: 90.5%w/w
min. and max. measured value from the 5 batch analysis: 89.98 – 90.74%

According to the five batch analysis, Nonanoic acid as manufactured is on hand with a minimum degree of purity of 89.6%w/w (mean value - 3 SD).

In general, also a maximum limit could be derived for the purity of the active substance as manufactured. However, as the active substance as manufactured stems form a natural source, only a minimum purity can be guaranteed by the supplier. The maximum purity could be considered up to 100%. This is acceptable for the following reasons:

In case of batches with a higher purity, the minimum degree of purity obtained with the new source is higher than the one obtained with the reference source. From the manufacturing process, no new impurity is expected to be present. The main impurities are heptanoic, octanoic and decanoic acid that are structurally and with regard to their physical-chemical properties and metabolic pathways and metabolic end-products comparable to nonanoic acid. Consequently it is to be expected that these impurities have (eco)toxicological properties comparable to nonanoic acid, minor quantitative changes of these impurities will not change the (eco)toxicological properties of the technical nonanoic acid.

Therefore it is acceptable that (eco)toxicological tests carried out with various purities within the range of 89.6 to 100%w/w are equally valid for the evaluation of (eco)toxicological properties of technical batches with purities in the range of 89.6 to 100%w/w.

In addition, according to the Company statement "Confirmation: Pelargonsäuregehalt in älteren Untersuchungen (Pelargonic acid content in older studies)", batches of Nonanoic acid (technical) prevalently show a purity of 93-94%w/w. Therefore 94%w/w is used as typical concentration of Nonanoic acid in the active substance as manufactured in this dossier.

2.8 [redacted]

Conclusion Adopt applicant's version with the amendments given above

Reliability 1

Acceptability Acceptable

Remarks -

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only
2.10.1 Human exposure towards active substance	The human exposure assessment considers the production of the active substance and the product, users handling the product at application (primary exposure) and an exposure of persons who might come into contact with the applied granules after application (secondary exposure). In the technical notes for guidance for human exposure estimation to biocidal products (TNG 2002) only sparse information concerning attractants and repellents not applied directly on human skin is available. As no specific guidance is available for the human exposure assessment of PT19, assessment of Pelargonic Acid and the biocidal product [redacted] follows in many aspects the proposals given for PT14 (rodenticides) as the exposure scenario for pellets and grain in open areas fits best to the use-concept of the repellent. The detailed exposure estimation is presented in a separate report (Kempernek, 2006a)	
2.10.1.1 Production of the active substance	Pelargonic Acid does not have any properties that make it more hazardous than other chemicals used in chemical manufacturing plants. In general Pelargonic Acid is manufactured in industrial production plants by trained professionals using a multi-step batch process. Exposure of worker to the active substance during manufacturing is very variable and depends strongly on the personal work hygiene of the individual worker. However, only a small fraction of the produced Pelargonic Acid is used in biocidal products marketed in Europe. Further main applications of Pelargonic Acid are lubricant base stocks, textile coning oils, polymerization initiators, corrosion inhibitors, metal cleaners, flotation agents for mineral refining, herbicides, fragrances, PVC plasticizers, cold water bleach activators and catalyst scavenger. However, as the active substance Pelargonic Acid is not produced in the European Union, European monitoring data are not available. Besides, as the production takes place outside Europe, exposure assessment during manufacturing of the active substance is not required.	
2.10.1.2 Production of the formulated product		
i) Description of process	The biocidal product "[redacted]" contains in general two main components. One is the plant protection product [redacted] that is contained in the BP at a concentration of 1% (w/w). The rest of the product (i.e. 99%) consists of pumice stone granule. The product is produced batch-wise in an automated processing facility. The batch size and frequency of the production are demand driven and thus variable. The amount of Pelargonic acid used for the production of the repellent "[redacted]" is expected to be approximately 100 kg/year. The active substance and the end products are only handled by industrial users with adequate training. Furthermore the production plant is DIN-ISO certified. This means that appropriate operating procedures do exist, which regulate different procedures to ensure that certain safety instructions and procedures are strictly followed by the workers (i.e. for example: Wearing of appropriate safety clothing and equipment, depending on the classification of the handled chemical).	

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC
	The BP is produced from Pelargonic Acid in a two step process. In the first step Pelargonic Acid is formulated with the appropriate formulants to result in the plant protection product [redacted] that contains 20% (w/w) Pelargonic Acid. The production takes place in an almost closed system of an automated facility. The liquid components, as for example Pelargonic Acid, are pumped out of drums into a closed reaction container, where the reaction takes place. The process of pumping out the liquid components takes place under a ventilated hood and is supervised by a single worker. This phase of the formulation process is considered as the only possibility where exposure of the worker via inhalation of evaporating active substance may occur, as all other steps of the production, including packaging, take place in a closed system. Via pipelines the finished emulsion concentrate is pumped into big-bags which serve as transport container to the next production step. The PPP [redacted] would be transported at this stage of the production to an automated filling facility. For the production of the BP, in a second step, the pumice stone granule is placed in a mixing container and the liquid emulsion concentrate is sprayed onto the granules under continuous mixing. The finished product is then transported to a closed automated filling facility where the end product is filled into plastic bags (PE-coex 6-fold) which are put into folding cardboard boxes. The only task of the workers at this stage of the production is to pile the cardboard boxes into big cartons for storage and transport, respectively. As also cleaning of the reaction containers and pipelines takes place in a closed system, where washing liquids are pumped, after their use, into separate containers for disposal, no further exposure of workers during the manufacture of the formulated product has to be considered.
ii) Workplace description	See above
iii) Inhalation exposure	As described above the only way workers may be exposed to Pelargonic Acid is during a short time period when the active substance is pumped out of drums into the closed reaction container. However, as this step takes place under a ventilated hood exposure is considered to be negligible. However, for exposure assessment it is assumed that the saturation concentration in air, which is limited by the vapour pressure, is reduced to less than 1% by the ventilation. Thus approximately 1% of the saturation concentration of Pelargonic Acid in air is assumed to be available for inhalation. Based on the vapour pressure of the active substance (0.9 Pa at 20°C, Franke 2001) the concentration in air can be calculated according to the following equation: x

$$W = \frac{(PxVxM)}{(RxT)}$$

W	amount of substance in g/m^3
P	vapour pressure of Pelargonic Acid at 20 C (0.9 Pa)
V	volume of air (1 m^3)
M	molecular weight of the active substance (158 2 g/mol)
R	gas constant (8 314 J/mol/K)
T	temperature (293.15 K)

x

$$W = \frac{(0.9x1x158.2)}{(8.314x293.15)} = 0.05842 g/m^3$$

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC	
	Assuming that the production takes place under a ventilated hood, the concentration is reduced to 1% of the saturation concentration, i.e. 0.5842 mg/m^3. The processing step of pumping out the active substance into the reaction container needs at maximum 30 minutes/day. Assuming an inhalation rate of 1.25 m^3/h and an adult of 60 kg, this would result in an inhalation exposure of 0.0061 mg Pelargonic Acid/kg bw/day if the worker wore no specific safety equipment.	x
iv) Dermal exposure	Based on the production process described above dermal exposure is not considered to be relevant	
2.10.1.3 Intended use(s) of the formulated product	Repellent against domestic cats. The product is intended to drive away cats from backyards, terraces, places where birds stay regularly and all places where territory marking is undesirable. The area that is to be protected is treated with 4-5 g granules/m^2. At application the granules should be distributed by hand evenly over an area of approximately 25 m^2.	x
1. Professional Users	Not relevant. The product is not intended for professional use.	
i) Description of application process	----	
ii) Workplace description	----	
iii) Inhalation exposure	----	
iv) Dermal exposure	----	
2. Non-professional Users including the general public		
(i) via inhalational contact	As the active substance exhibits only a medium volatility to air and due to the fact that the active substance is present in the product in its dissociated form as ammonium salt, volatility to air is expected to be lower for several orders of magnitude compared to the pure active substance. Furthermore the product is applied only outdoors at very low concentrations therefore the inhalation exposure during (primary exposure - user) or after (secondary exposure – non-user) application is considered to be negligible.	x

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC	
(ii) via skin contact	The detailed exposure estimation is presented in a separate report (Kempernek, 2006a) The following cases have been considered: ▪ Worst case: 100% of a.s. concentration in the recommended application rate (maximum value), no PPE (i.e.: granules applied with bare hand), 100% penetration of the skin. ▪ Reasonable worst case: 100% of a.s. concentration in the recommended application rate (maximum value), granules applied directly from the supplied sachet without touching the granules (this scenario is considered to reflect the application with PPE), 100% penetration of the skin (as no other data are available). ▪ Foreseeable misuse: the product is applied in a concentration of 3 times the recommended application rate, 100% of a.s. concentration in the recommended application rate (maximum value as no other data are available), no PPE (i.e.: granules applied with bare hand), 100% penetration of the skin. ▪ Normal use: as no industry data or survey data for the granular use of repellents do exist, specific values for the a.s. concentration to reflect a realistic exposure (usually: 95th percentile of data) are not available. As also no specific data on skin penetration are available a refinement of the reasonable worst case scenario is not possible at the moment. **Results** Exposure to Pelargonic Acid of non-professional users applying the granular formulation "[redacted]" according to label instructions is assumed to be low. Even for the case that the product is not used according to label instructions exposure can be assumed to be minimal.	x

Intended use (MG/PT)	Exposure scenario	Inhalational uptake	Dermal uptake (mg/kg bw/day)	Total systemic exposure (mg/kg bw/day)
PT19 Repellent against cats, outdoor use	**Worst case**	Negligible	0.0325	0.0325
	Reasonable worst case	Negligible	0.00325	0.00325
	Foreseeable misuse	Negligible	0.0977	0.0977

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC	
	Although in all exposure estimates the total systemic exposure is low, ranging from 0.00325 mg/kg bw/day to 0.09 mg/kg bw/day the values are likely to gross overestimate the real exposure as, due to the lack of other data, in all cases 100% absorption of the active substance was assumed. Considering all available toxicity data, this is considered to be a very unrealistic value.	
(iii) via drinking water	Not relevant	
(iv) via food	Not relevant	
(v) indirect via environment	Not relevant	
2.10.1.4 Secondary exposure	There are no industry generated experimental data available for the indirect exposure of humans to Pelargonic Acid when used in biocidal products as repellent and also no guidance is given for PT19 in the TNG on human exposure. Based on the use of the BP secondary exposure of adults to Pelargonic Acid used as repellent is not very likely. However to possible exposure scenarios for infants, which represent a more susceptible subpopulation, have been identified (i.e.: Oral and dermal exposure after application). Where appropriate, the modelled estimation of exposure is based on the recommendations given in the TNG on human exposure.	
(i) acute dermal uptake by a child	The detailed exposure estimation is presented in a separate report (Kempernek, 2006a) The following cases have been considered: ▪ Worst case — an infant with 10 kg body weight crawls on the treated soil surface. Exposure is dermal via the hands assuming a hand area of 200 cm^2, 100% hand contamination and 100% dermal uptake of the a.s. ▪ Reasonable worst case — an infant with 10 kg body weight crawls on the treated soil surface. Exposure is dermal via the hands assuming a hand area of 200 cm^2, 20% hand contamination and 100% dermal uptake of the a.s. (as no other data are available). **Results** Secondary exposure to Pelargonic Acid of infants crawling on the treated soil being exposed dermally via the hands is assumed to be low. Even for the highly unrealistic case that 100% of the hand surface is contaminated and 100% of the a.s. penetrates the skin total systemic exposure amounts only to 0.02 mg/kg bw/day.	x

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Intended use (MG/PT)	Exposure scenario	Inhalational uptake	Dermal uptake (mg/kg bw/day)	Total systemic exposure (mg/kg bw/day)
PT19 Repellent against cats, outdoor use	**Worst case**	Negligible	0.02	0.02
	Reasonable worst case	Negligible	0.004	0.004

(ii) acute oral uptake by a child

The detailed exposure estimation is presented in a separate report (Kempernek, 2006a) x

The following cases have been considered:

- Worst case: an infant with 10 kg body weight ingests 100 granules (only large granules with a higher a.s. content compared to small granules), 100% uptake of the ingested Pelargonic Acid
- Reasonable worst case: an infant with 10 kg body weight ingests 10 granules (large and small granules in a relation 50:50), 100% uptake of the ingested Pelargonic Acid (as no other data are available).

Results

Secondary exposure to Pelargonic Acid of infants playing at the site of application and ingesting Pelargonic Acid granules is assumed to be low. Even for the highly unrealistic case that 100 granules, that are neither visually attractive for infants nor by their taste, are ingested, assuming 100% systemic availability of the a.s., exposure amounts only to 0.00594 mg/kg bw/day.

Intended use (MG/PT)	Exposure scenario	Inhalational uptake	Oral uptake (mg/kg bw/day)	Total systemic exposure (mg/kg bw/day)
PT19 Repellent against cats, outdoor use	**Worst case**	Negligible	0.00594	0.00594
	Reasonable worst case	Negligible	0.000334	0.000334

2.10.2 Environmental exposure towards active substance x

2.10.2.1 Production

(i) Releases into water: Not relevant, as the active substance is not produced within the European Community.

(ii) Releases into air: Not relevant, as the active substance is not produced within the European Community.

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC
(iii) Waste disposal	Not relevant, as the active substance is not produced within the European Community.
2.10.2.2 Intended use(s)	Repellent against cats, outdoor use. The product is intended to drive away cats from backyards, terraces, places where birds stay regularly and all places where territory marking is undesirable. The area that is to be protected is treated with 4-5 g granules/m^2. At application the granules should be distributed by hand evenly over an area of approximately 25 m^2.
Affected compartment(s):	
water	30.04% (Estimation acc. to Mackay's EQC Level III Fugacity Model, more details are presented in a separate report, Kempernek, 2006c)
sediment	0.103% (Estimation acc. to Mackay's EQC Level III Fugacity Model, more details are presented in a separate report, Kempernek, 2006c)
air	3.09% (Estimation acc. to Mackay's EQC Level III Fugacity Model, more details are presented in a separate report, Kempernek, 2006c)
soil	66.4% (Estimation acc. to Mackay's EQC Level III Fugacity Model, more details are presented in a separate report, Kempernek, 2006c)
Predicted concentration in the affected compartment(s)	
water	$PEClocal_{water}$.= 9.65 x 10^{-6} mg/L $PEClocal_{water,ann}$.= 1.32 x 10^{-7} mg/L $PEC_{groundwater}$ = not relevant The detailed exposure estimation is presented in a separate report (Kempernek, 2006b)
sediment	$PEClocal_{sed}$.= 2.08 x 10^{-5} mg/kg The detailed exposure estimation is presented in a separate report (Kempernek, 2006b)
air	PEC_{air} = not relevant The detailed exposure estimation is presented in a separate report (Kempernek, 2006b)
soil	$PEClocal_{soil}$.= 0.059 mg/kg The detailed exposure estimation is presented in a separate report (Kempernek, 2006b)

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date April 2008

Materials and methods -

Conclusion Applicant's version is acceptable with the amendments given below

Reliability 2

Acceptability Acceptable

Remarks 2.10.1.3 Intended use(s) of the formulated product and 2.10.2.2 Intended use(s)

The available data do not allow the conclusions drawn by the applicant. The experimental data provide evidence that defecation by cats is massively reduced. This by itself is an interesting and positive effect of the product. As far as cat faeces are concerned, it will enable users to enhance hygienic conditions around sand tables and other places, where children play, as well as in back yards, on terraces etc. Any other product claim is not covered by the data provided in the dossier: Cats where not repelled, scent marking was not assessed at all, and the protection of birds or other potential prey has not been tested.

Furthermore the number of applications of the biocidal product as estimated by the applicant needed revision. It is based on the assumption that effects of the product will last for about four weeks. However, experimental evidence if provided for a period of only ten days. Efficacy was terminated by rain, which is common in central Europe. Thus, the estimated number of applications per year must be doubled compared to the applicants claim.

The estimate of the treated area also needs revision. If defecation of cats is to be reduced around housings, terraces, sand tables, back yards etc., the treated area will easily exceed 25 m^2. As a rough estimate 50 m^2 seems to be more adequate.

In addition, the application rate numbers need correction. Application rates in the course of the documented experiment were 10 g granules/m^2, equivalent to 0.02 g a.a/m^2, please see Doc. III-B 5.10.2/02.

Therefore the acceptable intended use is as follows:

Nonanoic acid is intended to be used in the biocidal product "[redacted]" (granules containing 0.2%w/w a.s.) which is to be applied as repellent (product type 19) via spreading by hand. The category of users is designated as general public. Although the biocidal product does not act as a repellent sensu strictu – cats are not driven away from the treated area – the behaviour of cats if modified such that defecation is massively reduced in treated areas. Thus, the field of use is to inhibit domestic cats from defecation in backyards, terraces, sand tables and other places where children play.

2.10.1.2, iii) Inhalation exposure:

For this scenario, 298.15 K and the respective vapour pressure of 1.4 Pa are used, giving a concentration in air of 89.4 mg/m^3 and resulting in an inhalation exposure of 0.93 mg/kg bw/day (without ventilation).

2.10.1.3, 2. Non-professional users including the general public

(i) via inhalational contact

Inhalation exposure is considered negligible compared to dermal exposure:

An assessment according to the scenario "Impregnated grains and pellets, application phase" as presented in "Human Exposure to Biocidal Products (TNsG June 2002), User Guidance version 1" was performed.

Assumptions: 500g of the product containing 0.2%w/w a.s. are used at once.

Thereby a fraction of 1% is released as dust / airborne particles. Although used outdoors, a room volume of 50 m³ is assumed. The inhalation rate of an adult is assumed with 1.25 m³/h, the body weight is 60 kg. Duration of exposure is 5 minutes per day. This scenario gives an inhalation exposure of 0.0003 mg/kg bw/day.

Analogous, inhalation exposure to volatilised Nonanoic acid is considered negligible: An estimation taking into account the ideal gas law, an inhalation rate of 1.25 m^3/h (default), a duration of exposure of 5 min. per day (default), an inhalation absorption of 100%, a body weight of 60 kg (adult, default), and reduction of the airborne concentration to 1% of saturated vapour concentration), the inhalative systemic uptake per day would be 0.002 mg/kg bw/day (Tier 1). As the scenario implies a closed, ventilated room and not the out-of-doors, the calculated value is likely to be an over-estimation (reasonable worst case).

(ii) via skin contact

The Austrian RMS believes that the presented scenario ("Technical Notes for Guidance, Human Exposure to Biocidal Products (TNsG June 2002)", part 3, section 7.2, application – wax block) is not quite reflecting the use of Katzenschreck.

Therefore, an estimation according to the scenario "Impregnated grains and pellets, application phase" as presented in "Human Exposure to Biocidal Products (TNsG June 2002), User Guidance version 1" is performed:

Assumptions: The pour density of the product is 340 mg/cm³, the product contains 0.2%w/w a.s. Dermal exposure is possible as a result of direct contact without gloves. Dusty formulations have the ability to spread/wander during handling, therefore the exposure of hands and forearms is considered in the scenario. The area of hands and forearms of an adult is assumed to be 2000 cm², the body weight is 60 kg, and dermal absorption is 100%. The thickness of layer of product in contact with skin is 0.01 cm (default).

This scenario gives a dermal exposure of 0.23 mg/kg bw/day.

It is acknowledged that the estimation might be rough and an overestimation. However, due to the lack of data for refinement, the scenario is defined as reasonable worst case.

2.10.1.4 Secondary exposure

(i) acute dermal uptake by a child

In the worst case scenario presented by the company the total systemic exposure is calculated by 200cm² x 0.001mg/cm² x 100/100 x 100/100 / 10kg = 0.02 mg/kg bw/day

with the following parameters: Hand area = 200 cm², Surface concentration = 0.001 mg/cm² (average concentration of the a.s. per cm² ground), Hand contamination = 100%, Dermal uptake = 100%, Body weight = 10 kg;

The worst case scenario and the reasonable worst case scenario are not accepted because using the average concentration of granules spread over the floor presumes that the product is applied evenly. However, it might be that on some spots the granules are applied accumulatedly and that the whole hand comes into contact with granules.

Therefore, an estimation according to the scenario "Impregnated grains and pellets, application phase" as presented in "Human Exposure to Biocidal Products (TNsG June 2002), User Guidance version 1" is performed using the following parameters:

The pour density of the product is 340 mg/cm³, the product contains 0.2%w/w a.s. Dermal exposure is possible during crawling. In this scenario, the exposure of hands is considered (hand surface: 200 cm²), the body weight is 10 kg, and dermal absorption is 100%. The thickness of layer of product in contact with skin is 0.01 cm (default).

This scenario gives a dermal exposure of 0.14 mg/kg bw/day.

If considering not only hands, but also legs and feet, dermal exposure is 1.20 mg/kg bw/day. (Surface area of hands, legs and feet for children = 1766 cm² according to H.J. Bremmer et al., CONSEXPO general factsheet, updated version for CONSEXPO 4, RIVM report 320104002/2006; this value represents a worst case as for infants, since the surface would be smaller for them.)

(ii) acute oral uptake by a child

The presented estimation is based upon the assumption that a child ingests 100 resp. 10 granules. This scenario is not presented in the "Technical Notes for Guidance, Human Exposure to Biocidal Products (TNsG June 2002)". This estimation might represent a realistic scenario. However, as this assumption is not supported by data, its acceptability cannot be assessed.

An estimation according to the scenario "Impregnated grains and pellets, use phase" from the "Human Exposure to Biocidal Products (TNsG June 2002), User Guidance version 1" is performed using the following parameters:

An infant (body weight: 10 kg) eats 5 grams of the biocidal product containing 0.2%w/w active substance. Oral absorption is 100%.

This results in 1.00 mg/kg bw/day.

A further estimation considering hand-to-mouth contact was performed: It is assumed that the entire product that ends up on the hands is taken in orally, which results in 0.14 mg/kg bw/day.

2.10.2 Environmental exposure towards active substance

This document represents the applicant's exposure assessment. In the course of detailed evaluation content of environmental exposure assessment was amended by the competent authority.

Please refer to the following appendix for detailed description of all assumptions, calculations and results (PECs) which were considered acceptable.

APPENDIX :

PREDICTED ENVIRONMENTAL CONCENTRATIONS

PEC in air

This scenario applies to ground surface consisting of non permeable materials as well as to unpaved soil.

The PEC of Nonanoic acid in air from its outdoor use as granular formulation as repellent against cats may be considered negligible because the active substance exhibits only a volatility to air of 0.9 Pa at 20°C (**Study A 3.2/01, Doc. III-A 3**) and due to its Henry's Law constant of 0.33 Pa x m^3/mol (20°C) (**Study A 3.2.1/01, Doc. III-A 3**) also exhibits only a slight fugacity from water to air.

Besides, Nonanoic acid is not expected to display adverse effects on the atmospheric environment, but is destroyed by photochemical oxidative degradation with a half-life of 13.15 to 39.44 hours (**Study A 7.3.1/01, Doc. III-A 7.3.1/01**).

STP

This scenario only applies to the ground surface consisting of non permeable materials.

Since the use patterns are comparable, an adaptation of the scenario developed in the framework of the EU Biocides Directive for the assessment of exposure to insecticides in Gel application is used (OECD, 2008).

For this use scenario, it is considered that releases are collected in a Sewage Treatment Plant (STP), which will act as a point source.

Therefore, the direct emission rate of active substance to the facility drain ($Elocal_{facilitydrain}$) is estimated as follows:

$$Elocal_{\text{facilitydrain}} = Q_{prod} \times F_{AI} \times N_{sites} \times N_{appl} \times F_{release,\text{facilitydrain}}$$

According to the use recommendations the product "[redacted]" is applied at a maximum rate of 10 g/m^2. A typical treated area covers 50 m^2. This results in an amount of product used per treatment (Q_{prod}) of 500 g. The fraction of Nonanoic acid that is contained in the biocidal product (F_{AI}) is given to be 0.2% (w/w). As the product is applied once per treatment to a broad area (in contrary to the estimations for insecticides), the number of application (N_{appl}) is set to 1. As no data or estimations are available for the fraction of the product released to the facility drain during application and use ($F_{relrase,facilitydrain}$) this factor is also set to 1, assuming as a worst case scenario that the total amount of product is discharged into the sewage system.

Estimation is needed for the number of houses that apply the product and are connected to the STP (N_{sites}). Here no standard simultaneity factor can be applied, as the moment of emission is not independent and random (as assumed for a simultanity factor), but the result of a rain event.

For this scenario, it is proposed to consider an STP catchment of 10000 inhabitants. The default number of houses per STP catchment is proposed to be 4000.

Assuming that 50% of the houses have a cat and that 20% the houses who don't have a cat, may buy the product "[redacted]", the use pattern can be described as 400 users within the group of 4000 houses connected to the STP. Therefore, a factor of 10% as estimate for the number of houses that apply the product (i.e. 400 houses) is used.

$$Elocal_{\text{facilitydrain}} = 0.5\ kg \times 0.002 \times 400 \times 1 \times 1 = 0.4\ kg\ a.s.$$

<u>Concentrations and emissions of a sewage treatment plant (STP)</u> are estimated using TGD on Risk Assessment Part II model (chapter 2.3.7.1).

Concentrations and emissions of Mixed waste/rain water systems (STP is not by-passed):

For calculation of the concentration of Nonanoic acid in the STP effluent (0.024 mg/L) dimension of the waste water treatment plant (2000 m³ per day) and the fraction of the substance reaching the effluent of the STP (12%) are taken from the Technical Guidance Document.

To evaluate the risk posed by a substance to micro-organisms (PEC_{STP}) it is necessary to estimate which concentrations microorganisms are exposed. For this purpose, it is assumed that only the dissolved concentration is bioavailable. It is also assumed that homogeneous mixing in the aeration tank occurs, which implies that dissolved concentration of a substance is equal to the effluent concentrations.

PEC_{STP} = 0.024 mg/L

Emissions of separate rain water systems (STP is by-passed):

For separate systems (rain water), it can be considered that no removal takes place at this point source, that would mean that STP is by-passed. The concentration in the untreated waste water (0.2 mg/L) can be calculated from the direct emission rate of active substance to the facility drain ($Elocal_{facilitydrain}$) and the flow to the STP. The influent flow equals the effluent discharge (2000 m³ per day).

PEC in surface water

This scenario only applies to the ground surface consisting of non permeable materials.

The local concentrations in surface water, resulting from the emissions to a sewage treatment plant can be calculated according to TGD on Risk Assessment Part II model (chapter 2.3.8.3).

Concentrations and emissions of Mixed waste/rain water systems (STP is not by-passed):

For principles of estimation of the concentration of the substance in the STP effluent (0.024 mg/L) see chapter STP. The concentration of suspended matter in the river (15 mg/L) and the dilution factor (10) to the surface water are taken from the Technical Guidance Document. The solids-water partitioning coefficient of suspended matter (Kp_{susp}=6.31 L/kg) is calculated from the partitioning coefficient organic carbon-water value (K_{oc}=63.1 L/kg) and the fraction of organic carbon in the compartment (Foc_{susp}=0.1).

Predicted environmental concentrations of Nonanoic acid in surface water are:

$PEC_{localwater\ STP\ is\ not\ by\text{-}passed} = 2.40 \times 10^{-3}$ mg/L

As the product "[redacted]" is recommended to be applied at maximum 10 times per year the annual concentration in surface water can be estimated according to the TGD on risk assessment Part II (equ. 47) as follows:

$$\text{Clocal}_{\text{water,ann STP is not by-passed}} = \frac{\text{Temission}}{365} \times Clocal_{water}$$

$$\text{Clocal}_{\text{water,ann STP is not by-passed}} = \frac{10}{365} \times 2.40 \times 10^{-3} = 6.57 \times 10^{-5}\, mg/L$$

$PEClocal_{water,ann\ STP\ is\ not\ by\text{-}passed} = 6.75 \times 10^{-5}$ mg/L

Emissions of separate rain water systems (STP is by-passed):

For principles of estimation of the concentration of the active substance in the concentration in the untreated waste water (0.2 mg/L) see chapter STP. of this document. The solids-water partitioning coefficient of suspended matter (Kp_{susp}=6.31 L/kg) is calculated from the partitioning coefficient organic carbon-water value (K_{oc}=63.1 L/kg) and the fraction of organic carbon in the compartment (Foc_{susp}=0.1).

Predicted environmental concentrations of Nonanoic acid in surface water are:

$PEC_{localwater\ STP\ is\ by\text{-}passed} = 2.00 \times 10^{-2}$ mg/L

As the product "[redacted]" is recommended to be applied at maximum 10 times per year the annual concentration in surface water can be estimated according to the TGD on risk assessment Part II (equ. 47) as follows:

$$\text{Clocal}_{\text{water,ann STP is by-passed}} = \frac{\text{Temission}}{365} \times Clocal_{water}$$

$$\text{Clocal}_{\text{water,ann STP is by-passed}} = \frac{10}{365} \times 2.00 \times 10^{-2} = 5.48 \times 10^{-4}\, mg/L$$

$\text{PEClocal}_{\text{water,ann STP is by-passed}}$ = 5.48 x 10^{-4} mg/L

As worst case assumption **$\text{PEC}_{\text{localwater}}$** is equaled to **$\text{PEC}_{\text{localwater STP is by-passed}}$ = 2.00 x 10^{-2} mg/L** for further calculations.

PEC in sediment

This scenario only applies to the ground surface consisting of non permeable materials.

The PEClocal in sediment can be derived from the $\text{PEClocal}_{\text{water}}$ (2.00 x 10^{-2} mg/L) considering the properties of suspended matter. According to the TGD on risk assessment Part II (equ. 50) the $\text{PEClocal}_{\text{sed}}$ is estimated as follows:

$$PEClocal_{sed} = \frac{\text{K}_{\text{susp-water}}}{\text{RHO}_{\text{susp}}} \times PEClocal_{water} \times 1000$$

For the determination of the suspended matter-water partitioning coefficient ($K_{\text{susp-water}}$), equ. 23 and 24 of the TGD on risk assessment Part II and the recommended default values of table 5 of this document are used. Considering a K_{OC} value of 63.1 for Nonanoic acid (**Study A 7.1.3/01, Doc. III-A 7.1.3**), the solid-water partition coefficient in suspended matter (Kp_{susp}) is 6.31. After application of equ. 24 the $K_{\text{susp-water}}$ value is calculated to be 2.4775 m^3/m^3.

$$PEClocal_{sed} = \frac{2.4775}{1150} \times 2.00 \times 10^{-2} \times 1000 = 4.31 \times 10^{-2}\, mg/kg$$

$\text{PEClocal}_{\text{sed}}$ = 4.31 x 10^{-2} mg/kg

PEC in soil

This scenario applies to ground surface consisting of non permeable materials as well as to unpaved soil. Entry via aerial deposition on soil is considered not relevant (chapter PEC in Air).

Ground surface: non permeable materials

For the calculation of the concentrations of Nonanoic acid in soil and pore water resulting from the treatment of ground consisting of non permeable materials, the exposure route is given by the application of sewage sludge in agriculture (according to TGD on Risk Assessment Part II model; chapter 2.3.8.5).

To fulfil the requirements of the TWA Guidance document[1], a scenario without removal by degradation following the recommendations given in the Technical Guidance Document is applied.

For sludge application to agricultural soil an application rate of 5000 kg/ha dry weight per year is assumed while for grassland a rate of 1000 kg/ha/yr should be used. Sludge application is treated as a single event once a year. The deposition is averaged over the whole area.

[1] Technical Notes for Guidance on "Assessment of environmental effects of biocidal active substances that rapidly degrade in environmental compartments of concern" endorsed during the 29th CA-Meeting (2008)

For this assessment, a simple model is used. The top layer of the soil compartment is described as one compartment (box), with an influx through sludge application (1 time per year), without removal from the box by degradation, volatilisation, leaching, and other processes if relevant. The concentration in this soil box can now be described with the simple equation:

$$C_{local,soil} = C_{sludge,soil1(0)} = \text{concentration in soil due to a single sludge application}$$

The concentration just after a single sludge application is calculated according to TGD on Risk Assessment Part II model; chapter 2.3.8.5 (equ. 60)

The mixing depth of soil (agricultural soil: 0.2 m; grassland 0.1 m) and the bulk density of soil (1700 kg/m^3) are taken from the Technical Guidance Document.

The concentration in dry sewage sludge (90.14 mg/kg) is calculated from the emission rate to water, the fraction of the emission sorbed to sludge (16%) and the rate of sewage sludge production.

$Clocal_{soil;\ arable\ wwt} = PEClocal_{soil;\ arable\ wwt} = 0.133\ mg/kg_{dwt}$

$Clocal_{soil;\ grassland\ wwt} = PEClocal_{soil;\ grassland\ wwt} = 0.053\ mg/kg_{dwt}$

The conversion to dry weight can be performed by using a conversion factor of 1.13 kg_{wwt}/kg_{dwt}.

$\mathbf{Clocal_{soil;\ arable\ dwt} = PEClocal_{soil;\ arable\ dwt} = 0.150\ mg/kg_{dwt}}$

$\mathbf{Clocal_{soil;\ grassland\ dwt} = PEClocal_{soil;\ grassland\ dwt} = 0.060\ mg/kg_{dwt}}$

The concentration in pore water is derived using equation 67 of the TGD on risk assessment Part II.

$$PEClocal_{soil,porew} = \frac{PEClocal_{soil} \times RHO_{soil}}{K_{soil\text{-}water} \times 1000}$$

For the determination of the soil-water partitioning coefficient equation 22, 23 and 24 of the TGD on risk assessment Part II and recommended default values of table 5 of this document are used. Considering a K_{oc} value of 63.1 (**Study A 7.1.3/01, Doc. III-A 7.1.3**) and a Henry´s Law Constant of 0.33 Pa x m^3/mol (20°C, **Doc. III-A 3; Study A 3.2.1/01**), the soils-water partitioning coefficient in soil is 1.26 and $K_{air\text{-}water}$ is calculated to be 0.0001. After application of equation 24 the $K_{soil\text{-}water}$ value is calculated to be 2.093 m³/m³.

$\mathbf{Clocal_{soil,porew\ arable\ dwt} = PEClocal_{soil;\ arable\ dwt} = 0.122\ mg/L}$

$\mathbf{Clocal_{soil,porew\ grassland\ dwt} = PEClocal_{soil;\ grassland\ dwt} = 0.049\ mg/L}$

It should be noted that this concentration of Nonanoic acid does not consider accumulation of the substance when the product is applied several years. In addition, it is questioned if a soil depths up to 20 cm should be considered relevant for substances like fatty acids, which adsorb very weakly onto soil (K_{oc} values for Nonanoic acid are 63.1 and 100.0 L/kg) and are therefore transported rapidly through soil.

Furthermore, if rapid degradation (DT50 for Nonanoic acid 2.1 days at 12°C) is regarded in the calculations, the amount of Nonanoic acid will go down. This finding is confirmed by the calculation of the average concentrations in soil according to TGD.

It is calculated as the average concentrations over certain time-periods in agricultural soil fertilized with sludge from a STP.

Two different soil types are distinguished: arable land and grassland. For the terrestrial ecosystem, the concentration is averaged over 30 days, for human indirect exposure a period of 180 days is used for a worst case

approach. It is assumed that sludge is applied for 10 continuous years. A full description of the default values used for calculation can be found in table 5.2.5-1. Calculated concentrations are listed in table 5.2.5-2.

Table 5.2.5-1: Parameters and default values used for calculations of Nonanoic acid in soil and pore water

Parameter	**Value**
Averaging time	30 days (terrestrial ecosystem) 180 days (agricultural soil and grassland)
Dry sludge application rate	0.5 kg/m² (arable soil) 0.1 kg/m² (grassland soil)
Mixing depth of soil	0.2 m (arable soil) 0.1 m (grassland soil)
Bulk density of soil	1700 kg/m³
Fraction of emission directed to sludge by STP	16% = 0.16
Concentration of suspended matter in STP influent	0.45 kg/m³
Effluent discharge rate of STP	2000 m³/day
Surplus sludge per inhabitant equivalent	0.011kg/eq and day
Capacity of the STP	10000 eq
Partial mass transfer coeff. at air-side of the air-soil interface	120 m/day
Partial mass transfer coeff. at soilair-side of the air-soil interface	0.48 m/day
Partial mass transfer coeff. at soilwater-side of the air-soil interface	4.8×10^{-5} m/day
Gas constant	8.314 Pa x m³/mol/k
Temperature at the air-water interface	285 K
Fraction air in compartment soil	0.2
Fraction water in compartment soil	0.2
Fraction solids in compartment soil	0.6
Density of the solid phase	2500 kg/m³
Weight fraction of organic carbon in compartment soil	0.02
Adsorption coefficient of Nonanoic acid, experimentally determined (**Study A 7.1.3/01, Doc. III-A 7.1.3**).	63.1 L/kg
Fraction of rain water that infiltrates into soil	0.25
Rate of wet precipitation (700 mm/year)	1.92×10^{-3} m per day
Half-life for biodegradation in soil (**Study 7.2.1/02, Doc. III-A 7.2.1/02,**)	2.1 days
Number of days per year that the emission takes place	365 days
Standard deposition flux of aerosol-bound compounds at a source strength of 1 kg per day	0.01 mg/m² per day
Deposition flux of gaseous compounds as a function of Henry's Law constant, at a source strength of 1 kg per day	4×10^{-4} mg/m² per day
Vapour pressure of Nonanoic acid (**Study A 3.2/01, Doc. III-A 3**)	0.9 Pa at 20°C

Table 5.2.5-2: Calculated concentrations in soil and pore water resulting from the exposure route given by the application of sewage sludge

Local Concentration in wet soil	Local Concentration in dry soil	Local Concentration in pore water soil
Arable soil 1.33×10^{-2} mg/kg (30 days) 2.22×10^{-3} mg/kg (180 days)	Arable soil 1.51×10^{-2} mg/kg (30 days) 2.51×10^{-3} mg/kg (180 days)	Arable soil 10.8 µg/L (30 days) 1.80 µg/L (180 days)
Grassland 8.85×10^{-4} mg/kg (180 days)	Grassland 1.00×10^{-3} mg/kg (180 days)	Grassland 0.71 µg/L (180 days)

Steady state concentrations in soil and in pore water have been calculated in terms of wet soil. The conversion to dry weight can be performed by using a conversion factor of 1.13 kg_{wwt}/kg_{dwt}

Ground surface: unpaved soil

For the exposure estimation in soil the proposals published in the ESD (Larsen, 2003) are followed as the exposure scenario for pellets and grain in open areas in this document fits best to the use-concept of the repellent.

According to the use recommendations the product "[redacted]" is applied at a maximum rate of 10 g/m^2. A typical treated area covers 50 m^2. This results in an amount of product used per treatment (Q_{prod}) of 500 g. As the product is applied once per treatment to a broad area (in contrary to the estimations for rodenticides), the number of refilling times (N_{refil}) and application sites (N_{sites}) are set to 1. As no data or estimations are available for the fraction of the product released to soil during application and use ($F_{relrase,soil,appl}$) this factor is also set to 1, assuming as a worst case scenario that the total amount of product is mixed into soil.

Based on this use scenario, the amount of Nonanoic acid that is contained in the biocidal product at a concentration (Fc_{pod}) of 0.2% (w/w) can be calculated to be 1.0 g a.s. per treatment

$$Elocal_{soil} = Q_{prod} \times Fc_{prod} \times N_{sites} \times N_{refil} \times F_{release,soil}$$

$$Elocal_{soil} = 500\ g \times 0.002 \times 1 \times 1 \times 1 = 1.0 g\ a.s.$$

For the calculation of the exposed soil volume ($Vsoil_{exposed}$) and the local concentration in soil ($Clocal_{soil}$) the default values given in the emission scenario document are used (i.e.: 10 cm soil depth, 1700 kg/m^3 for the density of wet exposed soil).

$$Vsoil_{exposed} = AREA_{exposed} \times DEPTH_{soil}$$

$$Vsoil_{exposed} = 50\ m^2 \times 0.1\ m = 5\ m^3$$

$$Clocal_{soil} = \frac{\mathrm{Elocal}_{soil} \times 10^3}{\mathrm{Vsoil}_{exposed} \times \mathrm{RHO}_{soil}}$$

$$Clocal_{soil} = \frac{1.0 \times 10^3}{5 \times 1700} = 0.118\ mg/kg$$

$Clocal_{soil}$ = $PEClocal_{soil\ wwt}$ = 0.12 mg/kg_{wwt}

The conversion to dry weight can be performed by using a conversion factor of 1.13 kg_{wwt}/kg_{dwt}.

$Clocal_{soil}$ = $PEClocal_{soil\ dwt}$ = 0.13 mg/kg_{dwt}

It should be noted that this concentration of Nonanoic acid does not consider accumulation of the substance when the product is applied several times. However, Nonanoic acid is rapidly eliminated from soil, with a DT_{50} value of 2.1 days and a DT_{90} value of 3.4 days. Application is intended to occur not more than 10 times per year. Therefore no assessment considering accumulation is performed.

The concentration in pore water is derived using equation 67 of the TGD on risk assessment Part II.

$$PEClocal_{soil,porew}, = \frac{PEClocal_{soil} \times RHO_{soil}}{K_{soil\text{-}water} \times 1000}$$

For the determination of the soil-water partitioning coefficient equation 22, 23 and 24 of the TGD on risk assessment Part II and recommended default values of table 5 of this document are used. Considering a K_{oc} value of 63.1 (**Study A 7.1.3/01, Doc. III-A 7.1.3)** and a Henry´s Law Constant of 0.33 Pa x m^3/mol (20°C, **Doc. III-A 3; Study A 3.2.1/01**), the soils-water partitioning coefficient in soil is 1.26 and $K_{air\text{-}water}$ is calculated to be 0.0001. After application of equation 24 the $K_{soil\text{-}water}$ value is calculated to be 2.093 m^3/m^3.

$$PEClocal_{soil,porew}, = \frac{0.12 \times 1700}{2.093 \times 1000} = 0.096 mg/kg$$

$PEClocal_{soil,porew}$ = 0.096 mg/L

However it is questioned if a soil depth of 10 cm should be considered relevant for substances like fatty acids, which adsorb very weakly onto soil (K_{oc} values for Nonanoic acid are 63.1 and 100.0 L/kg) and are therefore transported rapidly through soil.

Therefore, in a refined approach higher leaching distances (soil depths) for the soil receiving compartment are considered. The distances used are in steps of ten up to 50 cm.

Table 5.2.5-3: Calculated concentrations in soil and pore water for several leaching distances

Soil depth	Local PEC wet soil	Local PEC dry soil	Local PEC pore water soil
10 cm	0.118 mg/kg	0.133 mg/kg	96 µg/L
20 cm	0.059 mg/kg	0.067 mg/kg	48 µg/L
30 cm	0.039 mg/kg	0.044 mg/kg	32 µg/L
40 cm	0.029 mg/kg	0.033 mg/kg	24 µg/L
50 cm	0.023 mg/kg	0.027 mg/kg	19 µg/L

In addition, if rapid degradation (DT_{50} for Nonanoic acid 2.1 days at 12°C) is applied to the calculated PECs, the amount of Nonanoic acid will drop to half of the calculated concentrations within 2 days at environmentally relevant conditions (e.g.: at a soil depth of 10 cm to 0.067 mg/kg dry soil).

PEC in ground water

This scenario applies to ground surface consisting of non permeable materials as well as to unpaved soil.

The concentration in groundwater can be calculated for indirect exposure of humans through drinking water.

In a first tier scenario, the concentration in pore water of soil can be taken as indication for potential groundwater levels. It should be noted, that this is a worst-case assumption, neglecting transformation and dilution in deeper soil layers.

Both, the concentrations in pore water, resulting from sludge application, and the concentrations in pore water, resulting from the treatment of unpaved soil are calculated in chapter PEC in Soil of this document.

Nonanoic acid is hydrolytically stable and it is not susceptible to phototransformation in water. However, Nonanoic acid is shown to be readily biodegradable (**Study A 7.1.1.2.1/01, Doc. III-A 7.1.1.2.1**). The results in two soil degradation studies (**Study A7.2.1/01 and /02, Doc. III-A 7.2.1/01 and /02**) revealed DT_{50} values of approximately 3.8 and 5.7 days at 12°C (2 and 3 days at 20°C) for fatty acids (C14-C20) and a DT_{50} value of approximately 2.1 day at 12°C (1.1 days at 20°C) for Nonanoic acid in soil.

Based on the results of the adsorption/desorption study (**Study A7.1.3/01, Doc. III-A 7.1.3**) it can be assumed that the mobility characteristics of Nonanoic acid, both in the ionised and non-ionised forms are not very different from each other. Nonanoic acid adsorbs weakly onto soil as K_{oc} values between 63.1 and 100.0 are determined. However according to the experimentally determined DT_{50} values (**Study A7.2.1/01 and /02, Doc. III-A 7.2.1/01 and /02**), it is anticipated that the fatty acid salt is metabolized before it can enter the ground water and run off.

In a second tier scenario, this finding is confirmed by the FOCUSPELMO calculation (**Study B 7.1/01, Doc. III-B 7.1**) that is prepared under Directive 91/414/EEC for the herbicidal use of Nonanoic acid. The predicted environmental concentrations in ground water (PEC_{gw}) for Nonanoic acid after post-emergence application of NEU 1170 H is derived from a calculation using the model software FOCUSPELMO 2.2.2. This calculation is performed assuming an application of the emulsion concentrate formulation NEU 1170 H, that is contained in the biocidal product at a concentration of 1%, with eight yearly applications of 31.74 kg a.s./ha over a period of 26 years. The results show that there will be no contamination of ground water with Nonanoic acid after 26 years simulation of a treatment with NEU 1170 H at a rate corresponding to 31.74 kg Nonanoic acid/ha.

Section A3 **Physical and Chemical Properties of Active Substance**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.1 Melting point, boiling point, relative density (IIA3.1)								
3.1.1 Melting point								
Melting point	EEC A.1, OECD guideline 102 Capillary method	Pelargonic Acid (99.5%), batch no. 70728	11.7 °C - 12.5 °C		Y	1	Heintze, 2000a	x
3.1.2 Boiling point								
Boiling point	EEC A.2, OECD guideline 103 Method according to Siwoloboff	Pelargonic Acid (99.5%), batch no. 70728	The boiling point was found to be 258.39 °C		Y	1	Heintze, 2000b	x
3.1.3 Bulk density/ relative density								
Relative density	EEC A.3 Pycnometer method	Pelargonic Acid (90.0%), batch no. 70728	$\rho^{19\,8}{}_{4\,0}$= 0.90588 kg/L at 19.8°C		Y	1	Heintze, 2000c	x
3.2 Vapour pressure (IIA3.2)								
Vapour pressure 1	EEC A.4 OECD 104 Dynamic method	Pelargonic Acid (approx. 100%), batch no. 554800	0.9 Pa at 20°C		Y	1	Franke, 2001	x
Vapour pressure 2	EEC A.4 OECD 104 Dynamic method	Pelargonic Acid (approx. 100%), batch no. 554800	1.4 Pa at 25 °C		Y	1	Franke, 2001	x

Section A3 **Physical and Chemical Properties of Active Substance**

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
Vapour pressure3	EEC A.4 OECD 104 Dynamic method	Pelargonic Acid (approx. 100%), batch no. 554800	10.6 Pa at 50 °C		Y	1	Franke, 2001	x
3.2.1 Henry´s Law Constant (Pt. I-A3.2)	Calculation	Pelargonic Acid	0.33 Pa m^3 mol^{-1} at 20°C		N	1	Tiemann, 2003a	x
3.3 Appearance (IIA3.3)								
3.3.1 Physical state	Visual determination	Pelargonic Acid	Pelargonic acid is an oily colourless liquid		N	2	Anonymous, 1998	x
3.3.2 Colour	Visual determination	Pelargonic Acid, technical active ingredient	Slightly yellow		N	2	Anonymous, 1998	x
3.3.3 Odour	Olfactory determination	Pelargonic Acid, technical active ingredient	Strongly rancid		N	2	Anonymous, 1998	x
3.4 Absorption spectra (IIA3.4)								
UV/VIS	Spectroscopic method	Pelargonic Acid	UV/VIS extinction occurs in the range of 200 to 340 nm		N	2	Anonymous, 2003a	x
IR	BBA Part I, 1-2, B/2 Spectroscopic method	Pelargonic Acid (99.5%), batch no. 70728	Spectrum and table of signal characteristics are presented. IR spectrum is consistent with the proposed structure of Pelargonic Acid		Y	1	Heintze, 2000d	x

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Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
NMR	Spectroscopic method	Pelargonic Acid	NMR spectrum is presented. It is consistent with the proposed structure of Pelargonic Acid		N	2	Anonymous, 2003b	x
	Spectroscopic method	Pelargonic Acid (93%)	NMR spectrum is presented. It is consistent with the proposed structure of Pelargonic Acid		N	2	Krommen M. Zuniga y Rivero F., 2006	x
MS	Spectroscopic method	Pelargonic Acid	MS spectrum is presented. It is consistent with the proposed structure of Pelargonic Acid		N	2	Anonymous, 2003c	x
3.5 Solubility in water (IIA3.5)								
Water solubility	EEC A.6 OECD 105	Pelargonic Acid (92.0%), batch no. WE 547 605	The mean water solubility of the test item was calculated to be 202.7 mg/L at 20°C.		Y	1	Meinerling M., Herrmann S., 2006a	x
3.6 Dissociation constant (-)	OECD 112	Pelargonic Acid (92.0%), batch no. WE 547 605	The dissociation constant (pK_a) was determined to be: $pK_a = 4.9$		Y	1	Meinerling M., Herrmann S., 2006b	x

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	OECD 112	Ammonium salt of Pelargonic Acid (36.8% - corresponding to 312.3 g/L Pelargonic Acid), batch no. 606 070	The dissociation constant (pK_a) of the organic compound was interpolated from the titration curve. $pK_a = 4.8$		Y	1	Meinerling M., 2006a	x
3.7 Solubility in organic solvents, including the effect of temperature on solubility (IIIA3.1)	CIPAC Method MT 181	Pelargonic Acid (99.5%), batch no. 70728	Solubility (20±1°C) in: n-heptane, p-xylene, 1,2-dichloroethane, metha-nol, acetone and ethyl-acetate >250g/L Octanol and Pelargonic Acid are miscible in any proportion.		Y	1	Heintze, 2000e	x
3.8 Stability in organic solvents used in b.p. and identity of relevant breakdown products (IIIA3.2)				Not applicable. The active substance does not contain an organic solvent.				

Section A3 **Physical and Chemical Properties of Active Substance**

3.9	**Partition coefficient n-octanol/water (IIA3.6)** log Pow	EEC A.8, OECD guideline 107 Calculation method	Pelargonic Acid	log Pow: 3.52 (pH 7, 25 °C)	The partition coefficient could not be estimated from experimental data because the test substance is surface active. Thus log Pow was estimated by software calculation.	Y	1	Heintze, 2000f	x
3.10	**Thermal stability, identity of relevant breakdown products (IIA3.7)**	OECD 113	Pelargonic Acid (approx. 100%), batch no. 554800	No exothermal decomposition in the temperature range 25-350°C		Y	1	Franke, 2001 (Report submitted under point 3.2)	x
3.11	**Flammability, including auto-flammability and identity of combustion products (IIA3.8)**	EEC A.15	Pelargonic Acid (90%), batch no. 554800	Auto-flammability: The self-ignition temperature of the test substance is 220 °C	Flammability: Not required, because Pelargonic Acid is neither a solid or gas nor a substance that evolves highly flammable gases.	Y	1	Smeykal, 2000	x

Section A3 **Physical and Chemical Properties of Active Substance**

3.12 Flash-point (IIA3.9) Flash-point	EEC A.9 Flash point apparatus Pensky-Martens Semi Automatic Tester	Pelargonic Acid (90%), batch no. 554800	132.9°C – 133.9°C	The evolved vapour flashed at 133.4 °C	Y	1	Heintze, 2000g	x
3.13 Surface tension (IIA3.10) Surface tension	EEC A.5 OECD N°115	Pelargonic Acid (90%), batch no. 554800	Surface tension 34.6 mN/m at 20.1 °C. The substance was regarded to be surface active.	Because the test substance showed a surface tension lower than 60 mN/m, the test substance was regarded to be surface active.	Y	1	Heintze, 2000h	x
3.14 Viscosity (-)	OECD 114	Pelargonic Acid, batch no. 20060320-3	20°C 8.7 mPas 40°C 5.2 mPas		Y	1	Bär, 2006	x
3.15 Explosive properties (IIA3.11)				Not required, because Pelargonic Acid contains no explosive ingredients.				x

Section A3 **Physical and Chemical Properties of Active Substance**

3.16 Oxidizing properties (IIA3.12)				Not required, because Pelargonic Acid contains no oxidising ingredients.				x
3.17 Reactivity towards container material (IIA3.13)				Metal barrels coated with lacquer on the inside have been used since many years without having negative influence on the contained product				x

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date May 2008

Materials and methods Acceptable with the amendments given below.

Conclusion Agree with applicant's version with the amendments given below.

Reliability Please see single subsections

Acceptability Acceptable

Remarks

3.1.1 Melting point:

Reference: This corresponds to Study A 3.1.1/01.

3.1.2 Boiling point:

Reference: This corresponds to Study A 3.1.2/01.

3.1.3 Relative density of Nonanoic acid:

Purity/Specification: batch no. as described in DOC IV is 554800, 90%w/w a.s.

Results: density ρ^{198}_{40}= 0.90585 kg/L; relative density: ρ^{198}_{40}= 0.90588 [-]

Reference: Heintze, 2000c corresponds to Study A 3.1.3/01

Relative density of NEU 1170H:

Method: EEC A.3

Purity/Specification: batch no.0339-99; 19.98%w/w a.s.

Results: density ρ^{20}_{40}= 0.99 kg/L; relative density: ρ^{20}_{40}= 0.99 [-]

GLP: Y

Reliability: 1

Reference: Krips, 1999 corresponds to Study A 3.1.3/02

3.2 Vapour pressure:

Purity/Specification: content of the a.s. in batch 554800 is min. 90%w/w; additionally, the water (ca. 10%w/w) was removed by adding molecular sieves to the active substance.

Remarks: The test was carried out at temperatures from 142.6 to 249.6°C; the values for vp at 20, 25 and 50°C were calculated using Antoine constants.

Reference: This corresponds to Study A 3.2/01

3.2.1 Henry's Law Constant:

Results: The estimation considered a temperature of 25°C.

Reliability: n.a.

Reference: This corresponds to Study A 3.2.1/01

3.3.1 Physical state:

Reference: This corresponds to Study A 3.3/01

3.3.2 Colour:

Reference: This corresponds to Study A 3.3/01

3.3.3 Odour:

Reference: This corresponds to Study A 3.3/01

3.4 Absorption spectra UV/VIS:

Remarks: The UV/VIS study shows only absorption in the range of 200 to 290 nm, but not >290nm.

Reference: This corresponds to Study A 3.4/01

3.4 Absorption spectra IR:

Reference: This corresponds to Study A 3.4/02

3.4 Absorption spectra NMR:

Reference: Anonymous, 2003b corresponds to Study A 3.4/03

Reference: Krommen M. Zuniga y Rivero F., 2006 corresponds to Study A 3.4/05

3.4 Absorption spectra MS:

Reference: This corresponds to Study A 3.4/04

3.5 Solubility in water:

Method: Shake flask method

Results: The water solubility was calculated as mean value from 6 measurements (pH: 4)

Reference: This corresponds to Study A 3.5/01

Study 2:

Method: OECD guideline 105, Flask method

Purity/Specification: Nonanoic acid min. 98.5%w/w

Results: water solubility: 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.

GLP: Y

Reliability:1

Reference:"Study Water_solubility_PelargonicAcid_2007"

3.6 Dissociation constant

Results: The dissociation constant (pK_a) was determined to be pK_a=4.9 (20°C)

Reference: Meinerling M., Herrmann S., 2006b corresponds to Study A 3.6/01

Reference: Meinerling M., 2006a corresponds to Study A 3.6/02

3.7 Solubility in organic solvents, including the effect of temperature on solubility

Purity/Specification: content of the a.s. in batch 554800 is min. 90%w/w

Reference: This corresponds to Study A 3.7/01

3.9 Partition coefficient n-octanol/water

Method: Estimation with the Software SRC 2000 KOWWIN, Version 1.66; Syracuse Research Corporation

Reliability: n.a.

Reference: This corresponds to Study A 3.9/01

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.

3.10 Thermal stability, identity of relevant breakdown products

Purity/Specification: content of the a.s. in batch 554800 is min. 90%w/w; additionally, the water (ca. 10%w/w) was removed by adding molecular sieves to the active substance.

Method: DSC

Reference: This corresponds to Study A 3.2/01

3.11 Flammability, including auto-flammability and identity of combustion products

Method: DIN 51794

Reference: This corresponds to Study A 3.11/01

3.12 Flash-point

Method: DIN 51758

Reference: This corresponds to Study A 3.12/01

3.13 Surface tension

Purity/Specification: The study was performed with a 90% saturated aqueous solution of Nonanoic acid.

Reference: This corresponds to Study A 3.13/01

3.14 Viscosity

Purity/Specification: The batch contains 93%w/w Nonanoic acid.

Additional Reference: Company statement “Analysenzertifikat Viskosität (analysis certificate viscosity)”

Reference: This corresponds to Study A 3.14/01; Company statement “Analysenzertifikat Viskosität (analysis certificate viscosity)”

3.15 Explosive properties

Remarks/Justification: Furthermore there is no structural alert for explosive properties for Nonanoic acid.

Remarks: Company Statement

3.16 Oxidizing properties

Remarks/Justification: Furthermore there is no structural alert for oxidizing properties for Nonanoic acid.

Remarks: Company Statement

3.17 Reactivity towards container material

Remarks: Company statement

Section A4 (4.1_01) **Analytical Methods for Detection and Identification**

Annex Point IIA4.1

For pure substance

			Official use only
		1 REFERENCE	
1.1	**Reference**	Werle, H. (2003): Quantitative determination of water and fatty acids (C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12} fatty acid) in 5 lots [redacted] BioChem GmbH, Karlsruhe, Germany, unpublished report No. 03 50 40 108C – Dates of work October 2003-November 2003.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing [a.s.] submitted for first time [entry into Annex I/IA / authorisation]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	The study was performed analogous to the method "Methods of analysis NEU 11 40", ECO-Care Technologies Inc., Canada.	
2.2	**GLP**	Yes	
2.3	**Deviations**	----	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Enrichment	----	
3.1.2	Cleanup	About 265 mg [redacted] was weighed with an accuracy of 0.01 mg into a 100 mL volumetric flask. The sample was diluted with petroleum ether and the flask was made to volume (duplicate sample preparation). The relevant amount of the designated solution and 5.0 mL internal standard were pipetted into the same centrifuge vial. The tube was transferred into the solvent evaporating apparatus and the solvent was removed at 40°C. Thereafter 2 mL 1% sulphuric acid were pipetted into the tube and held for 2 H at 50°C in a water bath. After cool down to room temperature 1 mL n-hexane and 0.5 mL purified water were pipetted into the tube. After shaking and centrifugation at 3000 rpm the hexane layer was removed and filled into an autosampler vial.	
3.2	**Detection**		
3.2.1	Separation method	GC/FID	x
3.2.2	Detector	FID, temperature: 250°C	
3.2.3	Standard(s)	Addition of C12 fatty acid as internal standard (Addition was performed in such a strong concentration, that any C12 fatty acid amounts occurring in the [redacted] samples did not interfere with the standardisation).	
3.2.4	Interfering substance(s)	No interferences by other substances occurred	
3.3	**Linearity**		
3.3.1	Calibration range	Linear response in the range of 2.1 – 2.9 mg/mL.	
3.3.2	Number of measurements	6	x

Section A4 (4.1_01) Annex Point IIA4.1		Analytical Methods for Detection and Identification For pure substance	
3.3.3	Linearity	Correlation coefficient: R^2=0,9982	
3.4	**Specifity: interfering substances**	Not relevant, because no interfering substance occurred.	
3.5	**Recovery rates at different levels**	Mean recovery range: 96.7 –101.2%	
3.5.1	Relative standard deviation	Not stated in the report.	
3.6	**Limit of determination**	Not stated in the report.	x
3.7	**Precision**		
3.7.1	Repeatability	Mean RSD of [redacted] analysis: 1.3%	x
3.7.2	Independent laboratory validation	No data available	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	5 Batches from a manufacturing plant: 324202, 607102, 211302, 695603, 096801, produced and sampled in 2003, were used in the study. The method has been completely validated on these 5 different batches of Pelargonic Acid technical. The parameters linearity, precision, accuracy and specificity were checked.	
4.2	**Conclusion**	The method described above using GC/FID is suitable to determine the content of Pelargonic Acid in the technical material and was successfully validated.	
4.2.1	Reliability	2	
4.2.2	Deficiencies	Yes No recovery at different fortification levels was investigated. However the mean recovery range over three test runs at one fortification level was found to be acceptable (96.7 –101.2%).	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date

April 2008

Materials and methods

3.2.1 Separation method:

Gas chromatograph : HP 5890

Column : CP WAX 52 CB, 20m

Carrier gas : Helium, 100 k Pa

Injection temperature : 250°C

3.3.1 Calibration range:

Duplicate determinations at 6 concentrations

3.6 Limit of determination

Limit of determination can be omitted as the method serves only for the characterisation active substance in the formulation and was proven to be sensitive enough to do so.

3.7.1 Repeatability

Multiple samples (n=5) were prepared with technical grade Nonanoic acid, and each sample was injected twice.

The value given in this document is a mean value of the percental differences of the two repetitions of the five technical grade Nonanoic acid samples.

RSD from the mean content of the samples results in : 0.33%

Conclusion

Agree with the applicant´s version

Reliability

2

Acceptability

Acceptable

Remarks

A supplement concerning the concentrations corresponding to the recovery rates was written by the test laboratory and was added to the report.

Werle, H. (2005): 1st Supplement to the quantitative determination of water and fatty acids (C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12} fatty acids) in 5 lots emery 1202

In this document the concentrations corresponding to the recovery rates are given as follows:

Fatty Acid	Spiked set value in solution [mg/mL]	Analyzed content [mg/mL]	Recovery [%]	
			single values	mean
C9	1.2220	1.1816	96.7	98.9
	1.2220	1.2068	98.8	
	1.2220	1.2361	101.2	

Section A.4 (4.2_a) **Annex Point 4.2a**	**Analytical Methods for Detection and Identification** **For active substance in soil**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	The natural occurrence of Pelargonic Acid in our food supply and environment, and the rapid metabolism and degradation of Pelargonic Acid to background levels in soil eliminate the need to quantify Pelargonic Acid residues. Pelargonic Acid has been found to occur naturally in low concentrations in soil. The degradation of Pelargonic Acid applied to soil occurs very rapidly (DT_{50} = 2-3 days) by microbial means, not through hydrolysis or photolysis. Degradation occurs under aerobic conditions with beta-oxidation being the principal pathway of metabolism. Thus an analytical method for detecting and measuring the levels of Pelargonic Acid residue in soil is not necessary to protect the public health and the environment. The natural occurrence of Pelargonic Acid in our food supply and environment, and the rapid metabolism and degradation of Pelargonic Acid to background levels in soil eliminate the need to quantify Pelargonic Acid residue from applications as a biocide.	x
Undertaking of intended data submission [ ]	----	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	April 2008
Evaluation of applicant's justification	The justification is accepted. Nonanoic acid is a natural occurring active substance that degrades in soil very rapidly into substances of no concern. In addition an analytical method for the analysis of Nonanoic acid in soil is described in the aerobic degradation in soil screening study (document III A 7.2.1/01). This method can be used as a basis for monitoring and control of Nonanoic acid in soil.
Conclusion	Justification is accepted with the amendments given above
Remarks	-

Section A4 (4.2_b) **Analytical Methods for Detection and Identification**

Annex Point IIA4.2b

For active substance in air

Official use only

1 REFERENCE

1.1 Reference

[redacted] (1997a), NEU 1170 H - Acute inhalation toxicity, [redacted], Germany, unpublished report No. 97 10 42 026, dates of experimental work: 2 April to 24 April 1997

Submitted under Section B6.1.3

1.2 Data protection Yes

1.2.1 Data owner: Neudorff GmbH

1.2.2 Companies with letter of access: ----

1.2.3 Criteria for data protection: Data on existing [a.s.] submitted for first time [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study OECD Guideline for Testing of Chemicals No. 403

2.2 GLP Yes

2.3 Deviations For this study no deviations from the prescribed course of the test were ascertained.

3 MATERIALS AND METHODS

The determination of "NEU 1170 H" in this study was achieved by determining the fatty acid ingredients (ammonium salts of Pelargonic Acid) of the formulation after acidification followed by esterification with gas chromatography. Hence the described method is also considered to be adequate for the determination of the active substance in air.

3.1 Preliminary treatment

3.1.1 Enrichment: Aqueous samples of formulation were extracted with hexane.

3.1.2 Cleanup: The sample was evaporated with hexane, redissolved with hexane and methylated with methanol and sulphuric acid.

3.2 Detection

3.2.1 Separation method: GC

GC parameters (Pelargonic Acid)	
Carrier gas	Helium, 120 kPa
Column	J & W DB-5, 30 m x 0.25 mm
Injection	Split flow, 250 °C
Oven temperature program	60°C, ramp with 10 °C/min to 280°C, 10 min hold

3.2.2 Detector: FID, 250°C

3.2.3 Standard(s): Internal standard was used.

3.2.4 Interfering substance(s): No interferences affecting the chromatographic peaks of the active ingredient was observed.

Section A4 (4.2_b) Annex Point IIA4.2b		Analytical Methods for Detection and Identification For active substance in air	
3.3	**Linearity**		
3.3.1	Calibration range	Linearity was proved within the range of 0 to 10,52 mg NEU 1170 H/ mL measuring solution.	
3.3.2	Number of measurements	3	x
3.3.3	Linearity	R^2=0,99929	
3.4	**Specifity: interfering substances**	Not relevant, because no interfering substance occurs.	
3.5	**Recovery rates at different levels**	Determined formulation aerosol concentration: 1,75 mg NEU 1170 H /L air (i.e.: 0,64 mg/L ammonium salts of Pelargonic Acid - i.e.: 0,55 mg/L Pelargonic Acid based on a purity of 94%). Recovery rate: 8,75% Determined formulation aerosol concentration: 1,52 mg NEU 1170H/L air (i.e.: 0,56 mg/L ammonium salts of Pelargonic Acid - i.e.: 0,47 mg/L Pelargonic Acid based on a purity of 94%). Recovery rate: 7,6% Determined formulation aerosol concentration: 1,70 mg NEU 1170H/L air (i.e.: 0,63 mg/L ammonium salts of Pelargonic Acid - i.e.: 0,53 mg/L Pelargonic Acid based on a purity of 94%). Recovery rate: 8,5%	
3.5.1	Relative standard deviation	Not given in report	
3.6	**Limit of determination**	Not given in report	x
3.7	**Precision**		
3.7.1	Repeatability	Determination of repeatability (n=3) resulted in a standard deviation of 0, 49% for Pelargonic Acid.	
3.7.2	Independent laboratory validation	No data available	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	The formulation NEU 1170 H with a content of 36,8% ammonium salts of natural fatty acids (i.e. 332,2 g/L Pelargonic Acid technical) was used. Aqueous samples of NEU 1170 H were extracted with hexane, evaporated, redissolved with hexane and methylated with methanol and sulphuric acid. The fatty acid was analysed as fatty acid methyl ester by gas chromatography. Quantification was determined by internal standardization with heptadecanoic acid.	x

Section A4 (4.2_b)	**Analytical Methods for Detection and Identification**
Annex Point IIA4.2b	**For active substance in air**
4.2 Conclusion	The pure analytical method is sufficiently validated and qualified to determine Pelargonic Acid in aqueous air-collecting samples. The differences between the nominal content of Pelargonic Acid in air and the values analysed can be explained as follows. The aerosol consists of very small particles. Some of them will remain in the atmosphere such as they were generated. Some of them will join together and form bigger particles or drops which cannot be sampled. Other particles will precipitate on the walls and other parts of the inhalation chamber. These reasons will take influence on the percentage of aerosol available for inhalation purposes.
4.2.1 Reliability	2
4.2.2 Deficiencies	Yes No relative standard deviation given in the report. No limit of determination given in the report.

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	April 2008
Materials and methods	4.1 Materials and methods An old formulation containing 36.8% instead of 22% ammonium salts of pelargonic acid was used in this test. 3.3.2 Number of measurements Triplicate determinations at 7 concentrations 3.6 Limit of determination No limit of determination is given in the report. However, the report is accepted as the method serves for monitoring of toxicological relevant amounts of active substance in air. The acute inhalation study did not show any mortality but also no macroscopic pathological effects at 0.55 mg a.s./L air and the method proved sufficiently sensitive to detect at least these amounts.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The analytical method should be considered as additional information. Nonanoic acid is a naturally occurring compound and it would be impossible to distinguish between what occurs naturally and what occurs as a result of biocide usage. According to SANCO/825/00 rev. 7 no analytical method for the determination of residues in air has to be provided if relevant exposure according to application techniques is unlikely to occur and for naturally occurring non-toxic active substances.

Section A4 (4.2_c) **Analytical Methods for Detection and Identification**

Annex Point IIA4.2c

For active substance in water

Official use only

1 REFERENCE

1.1 Reference

Meinerling M., Mollandin G. (2007), Validation of an ANalytical Method for the Determination of Pelargonic Acid [redacted] in Water, Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany, unpublished report No. 31574101, dates of experimental work: 11 July to 2 August 2007

1.2 Data protection

Yes

1.2.1 Data owner

Neudorff GmbH

1.2.2 Companies with letter of access

1.2.3 Criteria for data protection

Data on existing [a.s.] submitted for first time [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study

SANCO/825/00 rev.7

2.2 GLP

Yes

2.3 Deviations

For this study no deviations from the prescribed course of the test were ascertained.

3 MATERIALS AND METHODS

An analytical method for the determination of Pelargonic Acid [redacted] in water based on LC with MS-detection and external standard was established and validated.

3.1 Preliminary treatment

3.1.1 Preparation of stock solution

Approximately 50 mg of the reference item were weighed precisely to 0.1 mg into a 50 mL volumetric flask, respectively. It was filled up to the mark using acetonitrile

3.1.2 Working standard solution

Appropriate volumes of the stock solution were diluted with tap water to obtain standard solutions in concentration range of 2 to 75 µg/L.

3.2 Detection

3.2.1 Separation method

LC (Perkin Elmer Series 200 pump and autosampler)

GC parameters (Pelargonic Acid)	
Column	RP 18 (125*3 mm)
Mobile Phase	A: acetonitrile containing 0.05% acetic acid B: water containing 0.05% acetic acid 0 min: 50% A/ 50% B 4 min: 95% A/ 5% B 6 min: 95% A/ 5% B 7 min: 50% A/ 50% B 10 min: 50% A/ 50% B
Flow Rate	0.3 mL/min
Injection Volume	30 µL
Temperature	Room temperatur

Section A4 (4.2_c) Annex Point IIA4.2c		Analytical Methods for Detection and Identification For active substance in water
3.2.2	Detector	Mass Spectrometer Sciex API 2000 Ion Source: Turbo Ion Spray, negative mode Mass Ion: 157 amu (parent ion)
3.2.3	Standard(s)	External standard Nonanoic Acid (CAS: 112-05-0) Lot No.: 1111337 Purity: 99.5%
3.2.4	Interfering substance(s)	The blank values of the control samples were more than 30% of the LOQ. Water samples of different sources as well as water for chromatographic purpose showed the same interference. The reason for the blank value could not be identified. By the applied LC-MS method only one mass ion of the parent compound was used for identification and quantification. Different analytical methods (HPLC-UV detection, gas chromatographic methods) were evaluated to find an appropriate confirmatory technique to demonstrate the specificity of the method. However, no appropriate confirmatory technique could be developed without extraordinary effort.
3.3	**Linearity**	
3.3.1	Calibration range	2 – 75 µg/L. Although the regression coefficient seems to demonstrate linearity the calculation of the response / mass ratio indicates a deviation from linearity. This deviation is caused by the blank value which has an effect on the response of the lower concentrations. The calibration range was restricted to concentrations from 7.5 to 75 µg/L.
3.3.2	Number of measurements	7 concentrations were measured.
3.3.3	Linearity	R^2=0,996
3.4	**Specifity: interfering substances**	The identity of the analyte was established by use of MS technique and by comparison of the retention time obtained from sample solutions and standard solutions. The retention time of the analyte in the samples solution did not differ by more than 1% from that for the standard solution. The blank values of the control samples were more than 30% of the LOQ. Water samples of different sources as well as water for chromatographic purpose showed the same interference. The reason for the blank value could not be identified.

Section A4 (4.2_c) Annex Point IIA4.2c		Analytical Methods for Detection and Identification For active substance in water	
3.5	**Recovery rates at different levels**	Three different fortification levels were analysed. To fortify water at different concentrations appropriate volumes of a solution containing the test item were poured into tap water. Stock solutions of approximately 50 mg of the test item/50 mL in acetonitrile were prepared. It was diluted in tap water. Untreated tap water without addition of the test item served as blank sample. At each fortification level 5 independent replicates and two blank control samples were made. Fortification level 5µg/L: Mean recovery = 68% (n = 5, SD = 30%) Fortification level 10µg/L: Mean recovery = 81% (n = 5, SD = 9%) Fortification level 50µg/L: Mean recovery = 96% (n = 5, SD = 4%)	
3.5.1	Relative standard deviation	Fortification level 5µg/L: RSD 44% Fortification level 10µg/L: RSD 11% Fortification level 50µg/L: RSD 4%	
3.6	**Limit of determination**	LOD = 8 µg/L (calculated from calibration data)	x
3.7	**Precision**		
3.7.1	Repeatability	Repeated injection of a sample solutions resulted in a coefficient of variation which was better than 2%	
3.7.2	Independent laboratory validation	No data available	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	An analytical method for the determination of Pelargonic Acid [redacted] in water based on LC with MS-detection and external standard was established and validated. Preliminary tests for the validation of the chromatographic method were carried out for the decision which conditions had to be used. The identity of the analyte was established by use of MS technique and by comparison of the retention time obtained from sample solutions and standard solutions.	

Section A4 (4.2_c) **Analytical Methods for Detection and Identification**

Annex Point IIA4.2c

For active substance in water

4.2 Conclusion

In non-GLP pre-experiments different methods were investigated for their applicability for determination of perlagonic acid from aqueous solution.

HPLC-UV:

The test substance is an aliphatic carboxylic acid and does not contain other functional groups than the carboxylic group. Liquid chromatography with UV-detection is applicable for quantification in concentration range above 50 mg/L. Enrichment factors of more than 1000 have to be applied to quantify the substance at concentration level of low µg/L range.
For further refinement of the quantification limit enrichments techniques were tested. Solid phase extraction as well as liquid-liquid extraction approach was performed. Prior extraction the samples were acidified. Using both enrichment techniques the recovery rates were approximately 200% of the nominal value. The high recovery rate is assumed to be the consequence of a blank value in water.

GC-method:

A method for determination of pelargonic acid using gas chromatography includes an extraction and derivatisation step. The acid has to be transformed to its ester to reduce the polarity and to increase the volatility of the compound.

Pelargonic acid methyl ester was used as reference compound. For determination a GC-method with MS-detection was established. The GC-MS spectrum of the ester indicates several mass peaks. For quantification of the ester the molecule peak 172 and the fragment peaks 74 and 87 were used. The detection limit is estimated to be approximately 5 µg/L.

To quantify the test item pelargonic acid from aqueous samples the acid has to be transformed to the ester. Thus the substance has to be esterified and extracted.

A sample preparation procedure is going to be established based on four main steps. In a first step the sample is esterified. Therefore, 50 mL sample volume and 25 mL reagent for esterification (alkaline methanol) were heated to 100°C in a water bath. Afterwards the methylation followed by addition of 50 acidic methanol. It was heated again. Then the solution was extracted two times with organic solvent (n-hexane/diethyl ether). The extract was concentrated using a rotary evaporator. Different approaches were performed.

Fortified samples at a concentration level of 10, 2.5 and 1 µg/L were analysed using the described method. Recovery rates of 50 to 200% were obtained. Analysis of untreated blank samples resulted in a blank value of 0.5 µg/L. Corrected for the blank value the recovery was in range from 35 to 156% of the nominal values. Extraordinary additional efforts had to be made for optimization of the method.

LC-MS:

The proposed LC-MS method allows the determination of pelargonic acid at concentration levels of approx. 10 µg/L without complex sample preparation steps. The LC-MS method is straightforward and can be easily established in other laboratories whereas in case of the GC-MS method the sample preparation procedure is complex.

Section A4 (4.2_c)	**Analytical Methods for Detection and Identification**
Annex Point IIA4.2c	**For active substance in water**
4.2.1 Reliability	1
4.2.2 Deficiencies	Yes A remarkable blank value was observed in the control samples. As the blank value was in the same magnitude also for the solvent which was used to prepare the standard solutions concentration of 10 µg/L could be determined with sufficient accuracy.

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	April 2008
Materials and methods	Agree with applicant´s version
Conclusion	Agree with applicant´s version
Reliability	1
Acceptability	Acceptable
Remarks	3.6 Limit of determination 8 µg/L is the limit of detection (LOD) and was calculated from the calibration data. However, 10µg/L is the limit of Quantification (LOQ) and can be determined with sufficient precision and accuracy. The value doses not meet the criteria of Directive 98/83/EC (EU drinking water limit). However, due to the fact Nonanoic acid is a natural occurring active substance that degrades in water very rapidly the test is considered sufficient at this stage.

Section A.4 (4.2_d) **Annex Point 4.2d**	**Analytical Methods for Detection and Identification** **For active substance in animal and human body fluids and tissues**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	As the active substance Pelargonic Acid is not classified as toxic or very toxic an analytical method for the determination of residues in animal and human body fluids and tissues is not required.	
Undertaking of intended data submission [ ]	----	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Evaluation of applicant's justification	The justification is acceptable according to TGD on data requirements, chapter 2 Pert A, point 4.2.d
Conclusion	Agree with applicant´s version
Remarks	-

Section A4 (4.3) **Annex Point IIIA-IV.1**	**Analytical Methods for Detection and Identification** **For active substance in food/feedstuffs**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [...]**	
Limited exposure [X]	**Other justification [ ]**	
Detailed justification:	No analytical method for the determination of Pelargonic Acid in plant material is presented, because the formulation is not designed for the application on crops intended for food or feed. The formulation will not directly contact desirable food commodities since exposure will be intentionally avoided by the user. In addition, fatty acids, including Pelargonic Acid, are metabolized in mammalian systems and plants to produce energy. The oxidative degradation of fatty acids is a metabolic pathway in humans, animals and plants. Fatty acids of varying chain lengths are metabolized into two-carbon fragments through a sequence of enzyme-catalyzed reactions. The metabolic products are then incorporated into fats, carbohydrates and amino acids. Because of the non-toxic properties of Pelargonic Acid in several plant and animal toxicity studies the US EPA additionally established an exemption from the requirement of a tolerance for residues of Pelargonic Acid when used as a herbicide in or on all food commodities (US EPA, 2003).	
Undertaking of intended data submission [ ]	----	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Evaluation of applicant's justification	The justification is acceptable, based on the intended use of the substance and the recommendations in the TGD on data requirements, chapter 3, point 4.3.
Conclusion	Agree with applicant´s version
Remarks	The intended areas of use are backyards, terraces and all places where territory marking is undesirable. Hence there is no contamination of food and feedstuff expected.

Section A5	Effectiveness against target organisms and intended uses	
Subsection (Annex Point)		**Official use only**
5.1 Function (IIA5.1)	Repellent	
5.2 Organism(s) to be controlled and products, organisms or objects to be protected (IIA5.2)	Repellent against domestic cats	x
5.2.1 Organism(s) to be controlled (IIA5.2)	Domestic cat (*Felis catus*)	
5.2.2 Products, organisms or objects to be protected (IIA5.2)	The repellent drives away cats from backyards, terraces, places where birds stay regularly and all places where territory marking is undesirable.	x
5.3 Effects on target organisms, and likely concentration at which the active substance will be used (IIA5.3)		
5.3.1 Effects on target organisms (IIA5.3)	The scent of the biocidal product (scent originating from plant material bound to clay minerals) masks the territory marks of cats and gets the cats to avoid the treated area. Due to the lack of appropriate test-guidelines for repellents and as no guidance, concerning the efficacy testing of products of PT19, was provided, a pre-test on principle repellent effect of Pelargonic Acid and a field study were conducted. For details see table 5.3.	x
5.3.2 Likely concentrations at which the A.S. will be used (IIA5.3)		
PT19	The active substance is contained in the product at a concentration of 0.2 % (w/w).	
5.4 Mode of action (including time delay) (IIA5.4)		
5.4.1 Mode of action	The scent of the biocidal product masks the territory marks of cats and gets the cats to avoid the treated area.	x
5.4.2 Time delay	The effect of the biocidal product occurs often with a time delay of several days. This is based on the species typical behaviour of cats. As cats that have marked their territory do not accept foreign scents in their territory they occur in the beginning more often on treated areas. However, due to the long lasting effect of the biocidal product cats give up their territory and avoid from now on the treated areas.	x

Section A5		Effectiveness against target organisms and intended uses	
5.5	**Field of use envisaged (IIA5.5)**		
	MG01: Disinfectants, general biocidal products	----	
	MG02: Preservatives	----	
	MG03: Pest control	Product type PT19 (Repellent), out-door use	
	MG04: Other biocidal products	----	
	Further specification	----	
5.6	**User (IIA5.6)**		
	Industrial	Not intended for industrial use.	
	Professional	Not intended for professional use.	
	General public	The area that is to be protected is treated with 4-5 g granules/m^2. At application the granules should be distributed evenly over an area of approximately 25 m^2. Aggregated application is recommended for highly frequented places as wall- and roof projections as well as near to bird nesting and feeding sites.	x
5.7	**Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA5.7)**	[redacted] is a repellent that is effective against cats by smell. Therefore no typical resistance or cross-resistance mechanisms can be expected.	x
5.7.1	**Development of resistance**	Based on its mode of action no development of resistance is expected.	
5.7.2	**Management strategies**	Not required	
5.8	**Likely tonnage to be placed on the market per year (IIA5.8)**	At present the amount of Pelargonic acid used for the production of the repellent [redacted] for the EU market is expected to be approximately 100 kg/year.	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date

May 2008

Materials and methods

5.2 Organism(s) to be controlled and products, organisms or objects to be protected: The conducted experiments do not allow for the conclusions drawn in the dossier submitted by the applicant. Basically, the applicant has shown that the active substance Nonanoic acid reduces the amount of solid excrements in a treated area compared to an untreated control area. Further claims regarding effects of the active substance are neither supported by the applied experimental methods nor by the reported results or references to scientific literature.

The reduction of cat faeces by itself would allow for applications of the a.s. around human housings like terraces and, e.g., sand tables for children, who should in any case not play around with excrements.

Revised version: Domestic cats, areas around human housings

5.2.2 Products, organisms or objects to be protected: Territorial marking was not tested. Consequently, such an effect can not be claimed for the active substance.

Revised version: The active substance deters cats from depositing faeces in the treated areas, e.g. backyards, terraces, sand tables, where faeces are undesirable.

5.3.1 Effects on target organisms: Masking of territorial marks has not been tested. Suggested rewording: The scent of the active substance deters cats from defecating in the treated area.

Revised version: The scent of the biocidal product (scent originating from plant material bound to clay minerals) deters cats from defecating in the treated area. For details see table 5.3.

5.3.2 Likely concentrations at which the a.s. will be used: The application rate of the active substance was 0.02 g/m^2 during the field experiment. Since efficacy testing was not performed at other application rates, the value 0.02 g/m^2 will be applied for risk assessment. The estimate of the treated area seems to low. The product was evenly spread over the treated area. Therefore, the treatment of a protective belt around can't be assumed. Overall, terraces, sand tables, children play grounds and backyards easily exceed 25 m^2 around human housings. An average treated area of 50 m^2 around a human housing seems much more realistic.

Revised version: The active substance will be applied at a rate of 0.02 g/m^2. The surface of treated areas is estimated to range around 50 m^2.

5.4.1 Mode of action: The term masking is inappropriate, see above.

Revised version: The smell of the active substance deters cats from defecating in the treated area.

5.4.2 Time delay: Statements on delay are not covered by experimental data or references to the scientific literature.

Revised version: A time delay was not observed during the conducted experiment.

5.6 User: Statements on protection of birds etc. are not covered by the experimental data.

Revised version: Outdoor use around human housing by the general public

5.7 Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies:

Revised version: [redacted] is effective against cats by smell. Therefore no typical resistance or cross-resistance mechanisms can be expected.

Conclusion	The application contains product claims, which are neither supported by experimental data, nor references to the scientific literature. However, the experimental data provide some evidence that defecation of cats is widely reduced in areas treated with the active substance Nonanoic acid. It is therefore concluded that treatment of, e.g., backyards, sand table, terraces etc. will protect these from cat faeces and provide hygienic benefits.
Reliability	2: The obtained experimental results are not suitable for rigorous statistical testing; the character of the data allows only very limited conclusions. However, the main effect observed throughout the experimental period allows concluding that "[redacted]" will hinder cats to deposit faeces in treated areas.
Acceptability	The study is acceptable under the perspective of the above stated revisions regarding product label claims, mode of action, and effects of the active substance.
Remarks	The applicant may submit data regarding his original product claims (e.g. protection of birds, prevention of territory marking) at the stage of national product authorisation. However, he is strongly advised to gain expertise from behavioural ecologists, ethologists, or chemical ecologists to implement experimental procedures, which ultimately allow for the intended conclusions.

Section 5.3: Summary table of experimental data on the effectiveness of the active substance against target organisms at different fields of use envisaged, where applicable

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
Repellent	PT 19, outdoor use	[redacted] containing Pelargonic acid at a concentration of 0.2 % w/w	Domestic cat (*Felis catus*)	The test substance was applied on cat litter and the avoidance of the treated place by the cat compared to an untreated place was investigated.	Pre-test on principle repellent effect of Pelargonic Acid: For quantification of repellence a correction coefficient has been calculated by comparing the time the cat spent in or near the comparative pan with that spent in or near at the repellence pan. concentration: 0.02 g a.s./m^2	The cat used only the litter pan without repellent product for excretion. The repellent litter pan was unused. The litter pan without test substance was accepted instantly as excretion place. In contrast the repellent litter pan was visited three times by the cat – each time for 10-20 seconds. In this time the cat just sniffed at the litter tentatively and withdrew very quickly without touching any part of the litter pan. Comparison of webcam records gave a factor of 4.4 which means that the cat was present in or at the comparative litter pan > 4 times more frequently compared to the presence in or at the repellent litter pan.	[redacted] (2006) **submitted under B 5.10.2/01**
Repellent	PT19, outdoor use	[redacted] containing Pelargonic acid at a concentration of 0.2 % w/w	Domestic cat (*Felis catus*)	Within a fenced area a test field, which was treated with the repellent and a control field, which remained untreated during the test were defined. Excretion and behaviour of 58 cats was investigated in the fenced area over a period of 23 days.	Excrements were counted each day in the test and the control field and the behaviour of the cats was recorded by two cameras during the whole test period over 24 hours. concentration: 0.02 g a.s./m^2	The application of [redacted] did not change the cat's initial pathways. On contrary, the test field was frequented more often than before application and the new substance was examined thoroughly by the cats, which was proved by the picture processing results. However, solid excretion was reduced by 94% in the test field compared to the control field during the examination period.	[redacted] (2007) **submitted under B 5.10.2/02**

*) References:

[redacted] (2006), Efficacy of Neudorff [redacted] 618 070 Proof of principle repellence against cats, LHS Institut für Hygieneforschung und Schädlingsbekämfung in Labor und Praxis, Wr. Neustadt, Austria, unpublished report No. 2060717-R

[redacted] (2007), Efficacy of Neudorff [redacted], Repellence against Cats – Field Test, LHS Institut für Hygieneforschung und Schädlingsbekämfung in Labor und Praxis, Wr. Neustadt, Austria, unpublished report No. 20070516-N

Section A6.1.1.	**Acute Toxicity**
Annex Point IIA6.1.1.	**Oral**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2001a), Assessment of acute oral toxicity with Pelargonsäure in the rat (acute toxic class method), [redacted], unpublished report No. 321547, dates of experimental work: 11 April to 27 April 2001	
1.2	**Data protection**	Yes	
1.2.1	Data owner	W. Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EEC B.1 tris, OECD No. 423	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	799800	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Clear yellow liquid	
3.1.2.2	Purity	93% C-9 fatty acids	
3.1.2.3	Stability	Not indicated	
3.2	**Test Animals**		
3.2.1	Species	Wistar rat	
3.2.2	Strain	Crl:(WI) BR (outbred, SPF-Quality)	
3.2.3	Source	Charles River Deutschland, Sulzfeld, Germany	
3.2.4	Sex	3 males and 3 females	
3.2.5	Age/weight at study initiation	Age: 6 weeks Weight: males 275g (mean), females 186 g (mean)	
3.2.6	Number of animals per group	3 animals of one sex in each dose group	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	**Oral**	
3.3.1	Postexposure period	14 days	
3.3.2	Type	Gavage	
3.3.3	Concentration	2000 mg/kg bw	
3.3.4	Vehicle	Propylene glycol	

Section A6.1.1.	Acute Toxicity
Annex Point IIA6.1.1.	Oral

3.3.5	Concentration in vehicle	Not stated
3.3.6	Total volume applied	10 mL/kg bw
3.3.7	Controls	----
3.4	**Examinations**	Mortality/viability, body weight, clinical signs, necropsy at the end of the observation period and description of macroscopic abnormalities
3.5	**Method of determination of LD_{50}**	Not applicable. LD_{50} greater than the highest concentration tested.
3.6	**Further remarks**	----

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	No mortality occurred. Lethargy and uncoordinated movements were shown by the animals on days 1 and/or 2. Piloerection was shown by one female on day 1
4.2	**Pathology**	No abnormalities were found at macroscopic post mortem examination of the animals.
4.3	**Other**	The mean body weight gain shown by the animals over the study period was considered to be similar to that expected of normal untreated animals of the same age and strain
4.4	**LD_{50}**	Oral LD_{50} for males > 2000 mg/kg bw for females > 2000 mg/kg bw combined > 2000 mg/kg bw

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	B.1 tris, OECD No. 423
5.2	**Results and discussion**	The oral LD50 value of Pelargonic Acid in Wistar rats was found to exceed 2000 mg/kg body weight. Pelargonic Acid does not warrant classification as being toxic or harmful on the basis of this study
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Materials and Methods	Agree with applicant's version
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	

Table A6_1-1. Table for Acute Oral Toxicity

Dose [mg/kg bw]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
2000	0/6	Animals were sacrificed at study termination	No mortality occurred
LD_{50} value	> 2000 mg/kg bw		

Section A6.1.2	**Acute Toxicity**
Annex Point IIA6.1.2.	**Dermal**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2001b), Assessment of acute dermal toxicity with Pelargonsäure in the rat, [redacted], unpublished report No. 321558, dates of experimental work: 11 April to 25 April 2001	
1.2	**Data protection**	Yes	
1.2.1	Data owner	W. Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EEC B.3, OECD No. 402	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	799800	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Clear yellow liquid	
3.1.2.2	Purity	93% C-9 fatty acids	
3.1.2.3	Stability	Not indicated	
3.2	**Test Animals**		
3.2.1	Species	Wistar rat	
3.2.2	Strain	Crl:(WI) BR (outbred, SPF-Quality)	
3.2.3	Source	Charles River Deutschland, Sulzfeld, Germany	
3.2.4	Sex	5 males and 5 females	
3.2.5	Age/weight at study initiation	Age: 10 weeks Weight: males 369 g (mean), females 239 g (mean)	
3.2.6	Number of animals per group	5 animals of one sex in each dose group	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	**dermal**	
3.3.1	Postexposure period	14 days	
3.3.2	Area covered	10% of body surface	
3.3.3	Occlusion	Semi-occlusive	
3.3.4	Vehicle	Propylene glycol	

Section A6.1.2 Annex Point IIA6.1.2.		Acute Toxicity Dermal
3.3.5	Concentration in vehicle	Not stated
3.3.6	Total volume applied	10 mL/kg bw (corresponding to 2000 mg/kg bw)
3.3.7	Duration of exposure	24 h
3.3.8	Removal of test substance	Tissue moistened with water
3.3.9	Controls	No control animals used
3.4	**Examinations**	Mortality/viability, body weight, clinical signs, necropsy at the end of the observation period and description of macroscopic abnormalities
3.5	**Method of determination of LD_{50}**	Not applicable. LD_{50} greater than the highest concentration tested.
3.6	**Further remarks**	----
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	No mortality occurred. Hunched posture, piloerection, chromodacryorrhoea, 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.
4.2	**Pathology**	No abnormalities were found at macroscopic post mortem examination of the animals.
4.3	**Other**	The changes noted in body weight gain in males and females were within the range expected for rats used in this type of study and were considered not indicative of toxicity.
4.4	**LD_{50}**	Dermal LD_{50} for males > 2000 mg/kg bw for females > 2000 mg/kg bw combined > 2000 mg/kg bw
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	EEC B.3, OECD No. 402
5.2	**Results and discussion**	The dermal LD50 value of Pelargonic Acid in Wistar rats was found to exceed 2000 mg/kg body weight. Pelargonic Acid does not warrant classification as being toxic or harmful on the basis of this study.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Materials and Methods	Agree with applicant's version
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	

Table A6_1-2. Table for Acute Dermal Toxicity

Dose [mg/kg bw]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
2000	0/10	Animals were sacrificed at study termination	No mortality occurred
LD_{50} value	> 2000 mg/kg bw		

Section A6.1.3_01 **Acute Toxicity**

Annex Point IIA6.1.3. **Inhalation**

					Official use only
		1 REFERENCE			
1.1	**Reference**	Copping L.G. (1998), The BioPesticide Manual, British Crop Protection Council, 1st edition, p. 25			
1.2	**Data protection**	No			
1.2.1	Data owner	----			
1.2.2	Companies with letter of access	----			
1.2.3	Criteria for data protection	----			
		2 GUIDELINES AND QUALITY ASSURANCE			
2.1	**Guideline study**	No information available			
2.2	**GLP**	No information available			
2.3	**Deviations**	No information available			
		3 MATERIALS AND METHODS			
3.1	**Test material**	No information available			
3.1.1	Lot/Batch number	No information available			
3.1.2	Specification	No information available			
3.1.2.1	Description	No information available			
3.1.2.2	Purity	No information available			
3.1.2.3	Stability	No information available			
3.2	**Test Animals**				
3.2.1	Species	Rat			
3.2.2	Strain	No information available			
3.2.3	Source	No information available			
3.2.4	Sex	No information available			
3.2.5	Age/weight at study initiation	No information available			
3.2.6	Number of animals per group	No information available			
3.2.7	Control animals	No information available			
3.3	**Administration/ Exposure**	**Inhalation**			
3.3.1	Postexposure period	No information available			
3.3.2	Concentrations	Nominal concentration	[mg/m³]	No information available	
		Analytical concentration	[mg/m³]	No information available	
3.3.3	Particle size	No information available			
3.3.4	Type or preparation of particles	No information available			
3.3.5	Type of exposure	No information available			

Section A6.1.3_01 Annex Point IIA6.1.3.	Acute Toxicity Inhalation
3.3.6 Vehicle	No information available
3.3.7 Concentration in vehicle	No information available
3.3.8 Duration of exposure	4 h
3.3.9 Controls	No information available
3.4 Method of determination of LC_{50}	No information available
3.5 Further remarks	----
	4 RESULTS AND DISCUSSION
4.1 Clinical signs	No information available
4.2 Pathology	No information available
4.3 Other	No information available
4.4 LC_{50}	>5.3 mg/L
	5 APPLICANT'S SUMMARY AND CONCLUSION
5.1 Materials and methods	No information available
5.2 Results and discussion	The LC_{50} (4 h) in the rat was found to be > 5.3 mg/L.
5.3 Conclusion	
5.3.1 Reliability	2
5.3.2 Deficiencies	Yes As only the end point of the study is given in the reference no information on possible deficiencies regarding methodology is available.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Materials and Methods	Agree with applicant's version
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	4 ("studies or data....which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."
Acceptability	Acceptable as additional information, acute oral and acute dermal data are available.
Remarks	

Section A6.1.3_02 **Acute Toxicity**

Annex Point IIA6.1.3. **Inhalation**

					Official use only
		1 REFERENCE			
1.1	**Reference**	Anonymous (date not stated), Toxicological Similarity of Straight Chain Saturated Fatty Acids of Greater Than 8 Carbon Chain Length by Various Routes of Exposure, Safer Inc, Eden Prairie MN 55334-3585, USA			
1.2	**Data protection**	No			
1.2.1	Data owner	----			
1.2.2	Companies with letter of access	----			
1.2.3	Criteria for data protection	----			
		2 GUIDELINES AND QUALITY ASSURANCE			
2.1	**Guideline study**	No information available			
2.2	**GLP**	No information available			
2.3	**Deviations**	No information available			
		3 MATERIALS AND METHODS			
3.1	**Test material**	C9 and C10 fatty acids: 60% a.s. formulation C9 fatty acids: 80% a.s. formulation			
3.1.1	Lot/Batch number	No information available			
3.1.2	Specification	No information available			
3.1.2.1	Description	No information available			
3.1.2.2	Purity	No information available			
3.1.2.3	Stability	No information available			
3.2	**Test Animals**				
3.2.1	Species	No information available			
3.2.2	Strain	No information available			
3.2.3	Source	No information available			
3.2.4	Sex	No information available			
3.2.5	Age/weight at study initiation	No information available			
3.2.6	Number of animals per group	No information available			
3.2.7	Control animals	No information available			
3.3	**Administration/ Exposure**	**Inhalation**			
3.3.1	Postexposure period	No information available			
3.3.2	Concentrations	Nominal concentration	[mg/m³]	No information available	
		Analytical concentration	[mg/m³]	No information available	
3.3.3	Particle size	No information available			

Section A6.1.3_02 Annex Point IIA6.1.3.		Acute Toxicity Inhalation
3.3.4	Type or preparation of particles	No information available
3.3.5	Type of exposure	No information available
3.3.6	Vehicle	No information available
3.3.7	Concentration in vehicle	No information available
3.3.8	Duration of exposure	4 h
3.3.9	Controls	No information available
3.4	**Method of determination of LC_{50}**	No information available
3.5	**Further remarks**	----
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	No information available
4.2	**Pathology**	No information available
4.3	**Other**	No information available
4.4	**LC_{50}**	C9 and C10 fatty acids 60% formulation: >5.53 mg/L C9 80% formulation: >5.9 mg/L
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	No information available
5.2	**Results and discussion**	The LC_{50} (4 h) of a 60% formulation of C9 and C10 fatty acids was found to be > 5.53 mg/L and the LC_{50} (4 h) of a 80% formulation of C9 fatty acids was found to be > 5.53 mg/L.
5.3	**Conclusion**	
5.3.1	Reliability	2
5.3.2	Deficiencies	Yes As only the end points of the studies are given in the reference no information on possible deficiencies regarding methodology is available.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	4 ("studies or data....which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."
Acceptability	Acceptable as additional information, acute oral and acute dermal data are available.
Remarks	Publication on homepage of informagen.com seems not to be online any more.

Section A 6.1.4.e
Annex Point IIA6.1.4

Acute Eye Irritation

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	According to OECD Guideline 405, materials which have demonstrated severe skin irritancy in a dermal study need not be further tested for eye irritancy. It is presumed that such substances will produce similarly severe effects on the eyes. With reference to the results of the primary skin irritation study conducted with the active substance (see section A 6.1.4.s) and based on information of further literature data the company refrained from conducting an eye irritation study and agrees that Pelargonic Acid is to be classified as Xi-irritating to eyes (R36).	
Undertaking of intended data submission [ ]	----	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	March 2008
Evaluation of applicant's justification	Since skin irritation is severe corrosive effects on the eye should not be excluded. Furthermore a publication is available from Smyth et. al 1962. (*Range finding toxicity data: List VI. American Industrial Hygiene Association journal 23, 95-107)* indicating eye corrosion for octanoic and decanoic acid. Therefore we propose to stop the decision logic of the OECD testing and classification scheme at step 1a (existing data showing effects on eyes) and classify nonanoic acid with R41, risk for serious damage to the eye. An in vitro test like the BCOP test may be carried out to prove the absence of corrosive effects in the eye.
Conclusion	We propose classification with R41.
Remarks	The validation of further in vitro models for eye corrosion and irritation is ongoing. The decision to carry out a new test could be postponed to a later stage when new in vitro tests will be available that can reliably identify not only eye corrosion but also eye irritation.

Section A6.1.4.s. **Acute Dermal Irritation**

Annex Point IIA6.4.

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2001c), Primary skin irritation/corrosion study with pelargonsäure in the rabbit (4-hour semi-occlusive application), [redacted] unpublished report No. 321604, dates of experimental work: 12 June to 1 August 2001	
1.2	**Data protection**	Yes	
1.2.1	Data owner	W. Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EEC B.4, OECD No. 404	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	799800	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Clear yellow liquid	
3.1.2.2	Purity	93% C-9 fatty acids	
3.1.2.3	Stability	Not indicated	
3.2	**Test Animals**		
3.2.1	Species	Albino rabbit	
3.2.2	Strain	New Zealand White rabbit (SPF-quality)	
3.2.3	Source	Charles River Deutschland, Kisslegg, Germany	
3.2.4	Sex	3 males	
3.2.5	Age/weight at study initiation	Age: at least 6 weeks Weight: 1.4 – 1.8 kg	
3.2.6	Number of animals per group	3 animals of one sex	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Application		
3.3.1.1	Preparation of test substance	The test substance was applied undiluted as delivered by the sponsor	

Section A6.1.4.s. **Acute Dermal Irritation**

Annex Point IIA6.4.

3.3.1.2	Test site and Preparation of Test Site	Approximately 24 hours before treatment, the dorsal fur was clipped with electric clippers, exposing an area of approximately 150 cm^2. The test substance was applied to the skin of one flank, using a metalline patch of 2x3 cm. The patch was mounted on Micropore tape, which was wrapped around the abdomen and secured with an elastic bandage.
3.3.2	Occlusion	Semiocclusive
3.3.3	Vehicle	----
3.3.4	Concentration in vehicle	----
3.3.5	Total volume applied	0.5 mL test substance/animal
3.3.6	Removal of test substance	With water
3.3.7	Duration of exposure	4 h
3.3.8	Postexposure period	14 days
3.3.9	Controls	No control animals used
3.4	**Examinations**	
3.4.1	Clinical signs	No
3.4.2	Dermal examination	Yes
3.4.2.1	scoring system	<u>Erythema and eschar formation:</u> No erythema 0 Very slight erythema (barely visible) 1 Well-defined erythema 2 Moderate to severe erythema 3 Severe erythema (beet redness) 4 <u>Oedema formation:</u> No oedema 0 Very slight oedema (barely visible) 1 Slight oedema (edges of area well defined by definite raising 2 Moderate oedema (raised approximately 1 mm) 3 Severe oedema (raised more than 1 mm and extending beyond the area of exposure) 4
3.4.2.2	Examination time points	1h, 24h, 48h, 72h, 7 days, 14 days after removal of the dressings and test substance
3.4.3	Other examinations	No histopathology was performed, since the skin reaction was not masked by test substance staining.
3.5	**Further remarks**	----

Section A6.1.4.s. **Acute Dermal Irritation**

Annex Point IIA6.4.

4 RESULTS AND DISCUSSION

4.1 Average score

4.1.1 Erythema

Average score of all 3 animals:

24h	4
48h	4
72h	4

4.1.2 Oedema

Average score of all 3 animals:

24h	1,33
48h	No scoring possible due to eschar formation, fissuring and/or brown discolouration of the skin
72h	No scoring possible due to eschar formation, fissuring and/or brown discolouration of the skin

4.2 Reversibility

Yes

Eschar formation:	reversible after 7-14 days
Fissuring of the skin:	reversible after 7-14 days
Brown discolouration (a sign of necrosis):	reversible after 7-14 days

4.3 Other examinations

Colouration: No staining of the treated skin by the test substance was observed.

Toxicity: No symptoms of systemic toxicity were observed in the animals during the test period and no mortality occurred.

4.4 Overall result

4 hours exposure to 0.5 mL of Pelargonic acid resulted in severe erythema and slight oedema in the treated skin-areas of the three rabbits. Oedema could not be scored on days 3, 4 and/or 8 due to fissuring, eschar 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 was noted on days 3, 4 and/or 8 among the animals. In addition, a bald skin and/or scaliness were observed on day 8 and/or day 15. The skin irritation had resolved within 15 days after exposure in the surviving animals.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

EEC B.4, OECD No. 404

5.2 Results and discussion

No evidence of full thickness destruction of the skin or scar tissue was observed during the observation period, indicating that no corrosion of the skin had occurred by dermal application of Pelargonic acid to the intact rabbit skin.

Based on the test results and according to EC criteria for classification and labelling requirements for dangerous substances and preparations Pelargonic acid has to be labelled as : Irritating to skin (R38).

5.3 Conclusion

5.3.1 Reliability

1

5.3.2 Deficiencies

No

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date March 2008

Materials and Methods Agree with applicant's version

Results and discussion Agree with applicant's version

Conclusion Agree with applicant's version

Reliability 1

Acceptability acceptable

Remarks TABLE 1: INDIVIDUAL SKIN IRRITATION SCORES

Animal #	644 (sentinel)*			684			685		
Time after exposure	Erythema	Oedema	comments	Erythema	Oedema	comments	Erythema	Oedema	comments
1 hour	4	1	k	4	2	k	4	1	k
24 hours	4	2	k	4	1	k	4	1	k
48 hours	4	-	g k	4	-	d k	4	-	g k
72 hours	4	-	d g	4	-	d k	4	-	g k
7 days	1	1	h l	2	-	d k l	2	-	e g k
14 days				0	0	h l	0	0	h l

* This animal was sacrificed after the observation on day 8, since sufficient information was obtained from this animal for the purpose of this study and for classification of the test substance.

Comments:
-. No scoring possible due to eschar formation, fissuring and/or brown discolouration of the skin.
d. Eschar formation.
e. Scabs.
h. Reduced flexibility of the skin.
g. Fissuring of the skin.
h. Bald skin.
k. Brown discolouration, a sign of necrosis.
l. Scaliness.

Table A6_1-4S-1. Table for skin irritation study

score (average of animals investigated)	time	Erythema	Oedema
average score Draize scores (0 to maximum 4)	1 h	4	1.33
	24 h	4	1.33
	48 h	4	--#
	72 h	4	--#
	7 d	1.66	--#
	14 d	0	0
average score	24h, 48h, 72h	4.0	--#
reversibility: *		c	c
average time for reversibility:		7-14 days	7-14 days

No scoring possible due to eschar formation, fissuring and/or brown discolouration of the skin

* c : completely reversible
n c : not completely reversible
n : not reversible

Section A6.1.5	**Skin sensitisation**
Annex Point IIA6.1.5	Guinea pig maximisation test (GPMT)

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2001d), Assessment of contact hypersensitivity to Pelargonsäure in the Albino Guinea Pig (Maximisation-Test), [redacted] unpublished report No. 321615 dates of experimental work: 10 April to 8 June 2001	
1.2	**Data protection**	Yes	
1.2.1	Data owner	W. Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EEC B.6, OECD No. 406	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	799800	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Clear yellow liquid	
3.1.2.2	Purity	93% C-9 fatty acids	
3.1.2.3	Stability	Not indicated	
3.1.2.4	Preparation of test substance for application	for induction: used with corn oil as vehicle for challenge: used with corn oil as vehicle	
3.1.2.5	Pretest performed on irritant effects	Yes	
3.2	**Test Animals**		
3.2.1	Species	Albino Guinea pigs	
3.2.2	Strain	Dunkin Hartley strain (SPF-quality)	
3.2.3	Source	Charles River Deutschland, Kisslegg, Germany	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	Age: Approx. 5 weeks Weight: 386 g (mean)	
3.2.6	Number of animals per group	Experimental group: 10 females Control group: 5 females	
3.2.7	Control animals	Yes	

Section A6.1.5 Annex Point IIA6.1.5	Skin sensitisation Guinea pig maximisation test (GPMT)	
3.3 Administration/ Exposure	Study type: Adjuvant	
3.3.1 Induction schedule	day 0 – day 8	
3.3.2 Way of Induction	Induction 1: intradermal Induction 2: topical, semi-occlusive	
3.3.3 Concentrations used for induction	Intradermal: B) 2% test substance in corn oil C) 1:1 mixture of 4% test substance in corn oil with Freunds' Adjuvant Topical: 20% test substance in corn oil	
3.3.4 Concentration Freunds Complete Adjuvant (FCA)	50% in water	
3.3.5 Challenge schedule	day 22; see table in appendix	
3.3.6 Concentrations used for challenge	1% test substance in corn oil	
3.3.7 Rechallenge	No	
3.3.8 Scoring schedule	24h, 48h after end of exposure	
3.3.9 Removal of the test substance	24 hours after exposure removal with water	
3.3.10 Positive control substance	α-hexylcinnamic aldehyde	
3.4 Examinations		
3.4.1 Pilot study	No	
3.5 Further remarks	----	
	4 RESULTS AND DISCUSSION	
4.1 Results of pilot studies	No pilot studies conducted	X
4.2 Results of test		
4.2.1 24h after challenge	Negative control group: 0/5 Test substance group: 0/10 Positive control group: 10/10	
4.2.2 48h after challenge	Negative control group: 0/5 Test substance group: 0/10 Positive control group: 10/10	
4.2.3 Other findings	----	
4.3 Overall result	No skin reactions were evident after the challenge exposure in the experimental and control animals. No mortality occurred and no symptoms of systemic toxicity were observed in the animals of the main study. Body weights and body weight gain of experimental animals remained in the same range as controls over the study period.	

Section A6.1.5	**Skin sensitisation**
Annex Point IIA6.1.5	Guinea pig maximisation test (GPMT)

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	EEC B.6, OECD No. 406
5.2	**Results and discussion**	There was no evidence that Pelargonic acid had caused skin hypersensitivity in the guinea pig, since no responses were observed in the experimental animals in the challenge phase. This result indicates a sensitisation rate of 0%.
5.3	**Conclusion**	Based on the results of the test and according to EC criteria for classification and labelling Pelargonic acid does not have to be classified as skin sensitizer.
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date

Materials and Methods

4.1. Results of pilot studies

A preliminary irritation study was conducted indicating that intradermal injection of a 2% solution causes erythema grade 3 after 24 and 48 hours, higher concentrations resulted in necrosis. Epidermal exposure of a 20% solution resulted in erythema grade 2, higher concentrations resulted in erythema grade 4 and oedema grade 1 after 24 hours and after 48 hours additionally scabs were observed with the higher concentrations. Epidermal exposure of 10%, 5% and 2% still lead to erythema grade 1. Epidermal exposure to 1% and 0.5% did not result in any erythema.

SKIN REACTIONS AFTER INTRADERMAL INJECTION

Animal number	Conc %	24 hours after injection Erythema (grade)	24 hours after injection Necrosis (mm)	48 hours after injection Erythema (grade)	48 hours after injection Necrosis (mm)
593	100		9		9
	50		7		7
594	20		8		8
	10		6		6
650	5		4		3
	2	3		3	

SKIN REACTIONS AFTER EPIDERMAL EXPOSURE

Animal number	Body weight (gram)	Conc. %	24 hours after exposure Erythema (grade)	24 hours after exposure Oedema (grade)	48 hours after exposure Erythema (grade)	48 hours after exposure Oedema (grade)
591	380	100	4	1	4 k	1
		50	4	1	4 k	1
592	414	100	4	1	4 k	1
		50	4	1	4 k	1
593	398	20	2	0	2	0
		10	1	0	1	0
594	396	20	2	0	2	0
		10	1	0	1	0
650	463	5	1	0	1	0
		2	1	0	1	0
685	399	1	0	0	0	0
		0.5	0	0	0	0

k. Scabs

Results and discussion Agree with applicant´s version.

Conclusion Agree with applicant´s version.

Reliability 1

Acceptability acceptable

Remarks

Table A6_1_5-1. Detailed information including induction/challenge/scoring schedule for skin sensitisation test

Inductions	GPMT		Observations/Remarks
	day of treatment	application	
Induction 1	1	intradermal	3 Pairs of intradermal injections (0.1 mL/site) A) 1:1 mixture of Freunds' Adjuvant with water B) Test substance at 2% concentration C) 1:1 mixture of test substance at 4% concentration with Freunds' Adjuvant Control animals: Treated as above except that no test substance but vehicle alone was administered
Assessment of dermal reactions caused by intradermal injection	3	--	Control Group: Mean score (5 animals): A): 3 (Erythema) B): 1.4 (Erythema) C): 2.8 (Erythema) Experimental group: Mean score (10 animals): A): 3 (Erythema) B): 2.7 (Erythema) C): 4 (Erythema) 3.9 (Necrosis in mm)
Induction 2	8	topical	0.5 mL of a 20% test substance concentration
Assessment of dermal reactions caused by topical application	10	--	Control Group: Mean score (5 animals): 0.8 (Erythema) 0 (Oedema) Experimental group: Mean score (10 animals): 2.3 (Erythema) 0 (Oedema)
challenge	22	topical	0.1 mL of a 1% test substance concentration in the vehicle
scoring 1	24	--	
scoring 2	25	--	

Table A6_1_5-2. Result of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	**Test group**	**Positive control**
scored after 24h	0 / 5	0 / 10	10 / 10
scored after 48h	0 / 5	0 / 10	10 / 10

Section A6.2 **Metabolism, toxicokinetic and percutaneous absorption (in vivo test)**
Annex Point IIA6.2

JUSTIFICATION FOR NON-SUBMISSION OF DATA

Official use only

Other existing data [ ] **Technically not feasible [ ]** **Scientifically unjustified [x]**

Limited exposure [ ] **Other justification [ ]**

Detailed justification:

As all fatty acids, Pelargonic acid is present in nature and has been found in various plants as well as in a variety of animal fats and foods of animal origin.

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 (Zschinttzsch 2003).

1. 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 water soluble 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 fats 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. A profound description of the involved enzymatic processes is given by Orten and Neuhaus 1975.

2. 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).

3. 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. A6.2-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.

Section A6.2 **Metabolism, toxicokinetic and percutaneous absorption (in vivo test)**
Annex Point IIA6.2

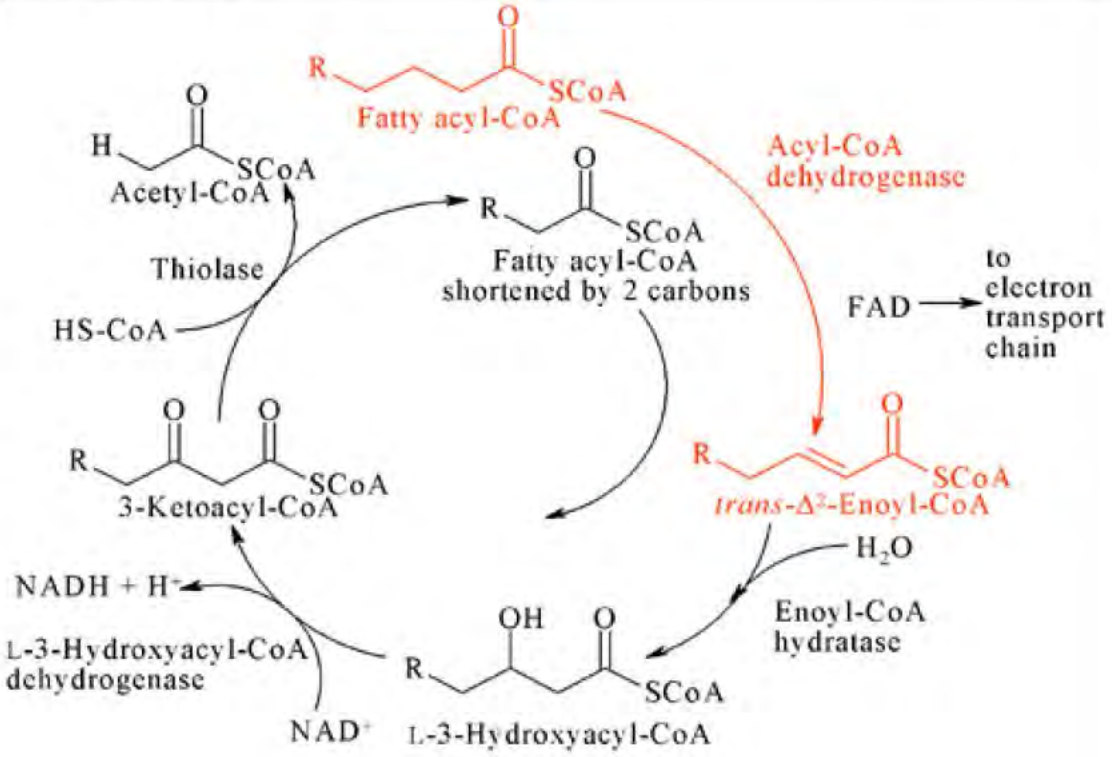

Figure A6.2-a: β-oxidation of fatty acids (Lamm et al. 2002)

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. A6.2-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 Fig. A6.2-b.

Section A6.2 **Metabolism, toxicokinetic and percutaneous absorption (in vivo test)**
Annex Point IIA6.2

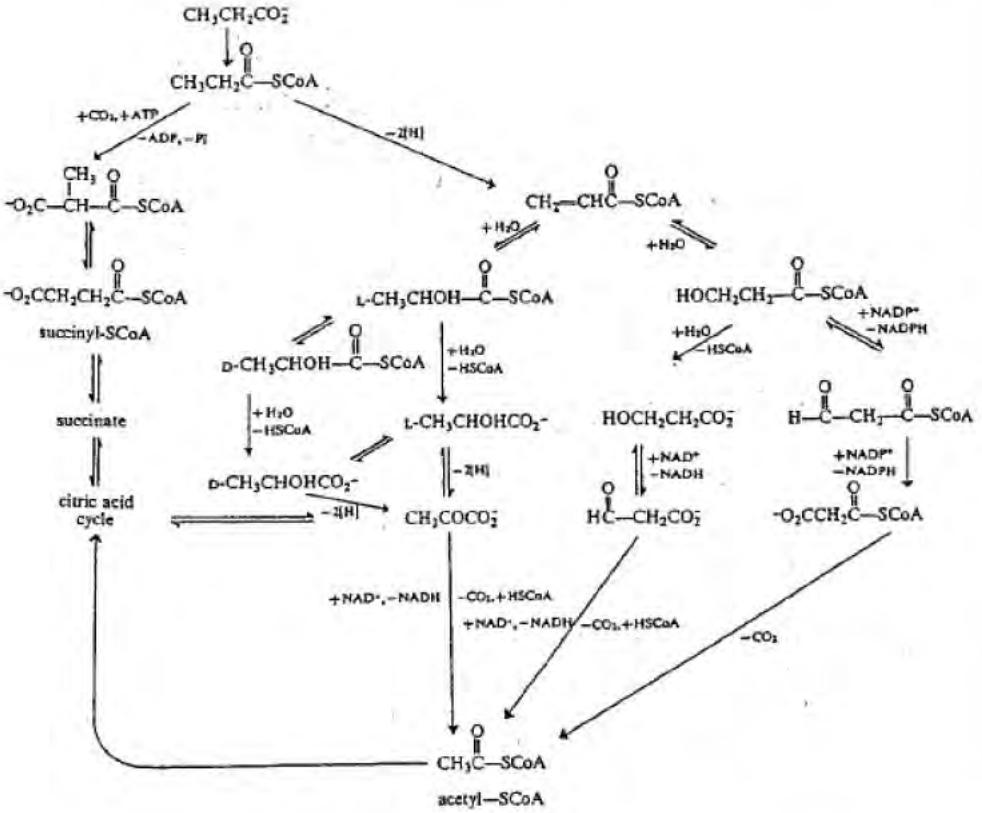

Figure A6.2-b: Fate of propionate and propionyl-ScoA (Mahler and Cordes 1971

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. Fatty acids, therefore, are regarded primarily as nutrients which yield a high amount of energy, contribute to various essential cell functions and do not have negative metabolic side-effects. After complete oxidation, no other degradation products than mentioned above will excreted.

Undertaking of intended data submission [ ] ----

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant´s version. Without any further information a dermal absorption rate of 100% is assumed for the purpose of risk assessment.
Conclusion	The justification for non-submission is acceptable.
Remarks	

Section A6.3.1_01 **28 days repeated dose toxicity in the rat**

Annex Point IIA6.3.1. **Oral**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2002), Subacute 28-day oral toxicity with Pelargonsäure by daily gavage in the rat, [redacted] unpublished report No. 321582, dates of experimental work: 24 August to 20 September 2001	
1.2	**Data protection**	Yes	
1.2.1	Data owner	W. Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EEC B.7, OECD No. 407	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	799800	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Clear yellow liquid	
3.1.2.2	Purity	93% C-9 fatty acids	
3.1.2.3	Stability	Not indicated	
3.2	**Test Animals**		
3.2.1	Species	Wistar rat	
3.2.2	Strain	Crl:(WI) BR (outbred, SPF-Quality)	
3.2.3	Source	Charles River Deutschland, Sulzfeld, Germany	
3.2.4	Sex	20 males and 20 females	
3.2.5	Age/weight at study initiation	Age: Approximately 6 weeks Weight: males 198-235 g, females 161-199 g	
3.2.6	Number of animals per group	5 animals of one sex in each dose group	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	**Oral**	
3.3.1	Duration of treatment	28 days	
3.3.2	Frequency of exposure	Daily	
3.3.3	Postexposure period	No postexposure period	

Section A6.3.1_01	28 days repeated dose toxicity in the rat
Annex Point IIA6.3.1.	Oral

3.3.4	**Oral**	
3.3.4.1	Type	Gavage
3.3.4.2	Concentration	Gavage dose level of either 50, 150 or 1000 mg/kg bw/day
3.3.4.3	Vehicle	Propylene glycol
3.3.4.4	Concentration in vehicle	Test group 2 50 mg in 5 mL propylene glycol/kg bw Test group 3 150 mg in 5 mL propylene glycol/kg bw Test group 4 1000 mg in 5 mL propylene glycol/kg bw
3.3.4.5	Total volume applied	5 mL/kg bw. Actual dose volumes were calculated weekly according to the latest body weight.
3.3.4.6	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes (once daily)
3.4.1.2	Mortality	Yes (twice daily)
3.4.2	Body weight	Yes (days 1, 8, 15, 22 and 28)
3.4.3	Food consumption	Yes (weekly)
3.4.4	Water consumption	Yes (subjective appraisal was maintained during the study, but no quantitative investigation introduced as no effect was suspected)
3.4.5	Ophthalmoscopic examination	No
3.4.6	Haematology	Yes All animals Time points: end of study Parameters: Haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count, clotting time, prothrombin time, thromboplastin time, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width
3.4.7	Clinical Chemisty	Yes All animals Time points: end of study Parameters: sodium, potassium, calcium, chloride, phosphorus, glucose, total cholesterol, urea, total bilirubin, creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase,
3.4.8	Urinalysis	No
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes Organs: liver, kidneys, adrenals, testes, epididymides, thymus, spleen, brain, heart

Section A6.3.1_01 Annex Point IIA6.3.1.		28 days repeated dose toxicity in the rat Oral	
3.5.2	Gross and histopathology	Yes Necropsy: All dose groups Organs: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, female mammary gland area, uterus, prostate, urinary bladder, lymph nodes, bone marrow, skin, eyes, cervix, clitoral gland, femur including joint, larynx, lacrimal gland, nasopharynx, preputial gland, sciatic nerve, seminal vesicles, skeletal muscle, tongue, uterus, vagina, all gross lesions Histopathology: Control and highest dose group, all animals that died spontaneously, all gross lesions of all animals Organs: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, oesophagus, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, uterus, prostate, urinary bladder, lymph nodes, bone marrow, sciatic nerve, all gross lesions	
3.5.3	Other examinations	Functional observations (during week 4 of treatment): Hearing ability, papillary reflex, static righting reflex and grip strength, motor activity test	
3.5.4	Statistics	If variables could be assumed to follow normal distribution, the Dunnett-test based on pooled variance estimates was applied. The Steel-test was applied when the data could not be assumed to follow a normal distribution. The exact Fisher-test was applied for frequency data. $P<0.05$	
3.6	**Further remarks**	**----**	
		4 RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	Breathing difficulties (rales and/or gasping) were shown by most high dose animals on some occasions in week 3 of the study. One of those females showed a hunched posture in week 3. No clinical signs were noted among the control and group 2 animals.	
4.1.2	Mortality	No test substance-related mortality occurred during the study period. One group 3 male was found dead on day 11. However detailed examination of the animal revealed that the death occurred due to misgavage.	X
4.2	**Body weight gain**	Body weight and body weight gain of treated animals remained in the same range as controls over the 4-week study period.	
4.3	**Food consumption and compound intake**	There were no differences in food consumption before or after allowance for body weight between treated and control animals that were considered to be of toxicological relevance.	
4.4	**Ophtalmoscopic examination**	No ophtalmoscopic examination was performed.	

Section A6.3.1_01 **28 days repeated dose toxicity in the rat**

Annex Point IIA6.3.1. **Oral**

4.5	**Blood analysis**	
4.5.1	Haematology	Haematological parameters of treated rats were considered not to have been affected by the treatment. Platelet counts of most treated males, and of some animals among control, group 2 and 3 females, were (generally) slightly low when compared to historical data (lower limit of reference range: male: $875x10^9$/L, n=865; female: $808x10^9$/L, n=915). This finding could not be explained. However, values of clotting parameters were within the range to be expected from untreated rats, and no treatment-related microscopic abnormalities were noted in the sternal bone marrow. Therefore, this finding was considered to be of no biological significance.
4.5.2	Clinical chemistry	There were no differences noted between control and treated rats that were considered to be related to treatment with pelargonic acid. The apparent increase of sodium values of group 2 males did not form a dose-related response and all individual values remained within the historical control range. This finding was therefore considered to be of no toxicological significance.
4.5.3	Urinalysis	No urinalysis was performed.
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	Organ weights and organ:body ratios of treated animals were considered to be similar to those of control animals. The statistically significant increase of mean heart weight of mid-dose males occurred in the absence of a dose-related response and was considered not to be a sign of toxicity.
4.6.2	Gross and histopathology	<u>Macroscopic examination:</u> An irregular surface of the forestomach was noted in all high dose animals. A thickened (glandular mucosa of the) stomach was occasionally observed among the treated animals. Since none of these cases could be confirmed microscopically, they were considered changes of no toxicological significance. Different incidental findings among control and/or treated animals were considered to be of no toxicological relevance. <u>Microscopic examination:</u> Slight to marked hyperplasia of the squamous epithelium of the forestomach was present in all high dose and at a minimal degree in two group 3 animals. All other microscopic findings noted among surviving animals were within the range of the background pathology encountered in Wistar rats of this age and strain and occurred at similar incidences and severity in both control and treated animals.
4.7	**Other**	Functional observations: No changes were observed in hearing ability, pupillary reflex, static righting reflex and grip strength. The variation in motor activity did not indicate a relation with treatment.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	EEC B.7, OECD No. 407

Section A6.3.1_01		**28 days repeated dose toxicity in the rat**	
Annex Point IIA6.3.1.		**Oral**	
5.2	**Results and discussion**	Breathing difficulties, in one case with hunched posture, were shown by most high dose animals. Although these signs were only present on some occasions in week 3, a relation to treatment with the test substance could not be entirely excluded. At macroscopy, an irregular surface of the forestomach was noted in all high dose animals, which was confirmed microscopically by hyperplasia of the squamous epithelium. There were no changes at performance of functional observations, at body weight, food consumption measurements, or alterations during clinical laboratory investigations and organ weight determination that were considered to be effect of the treatment. Since hyperplasia of the squamous epithelium of the forestomach in two animals dosed at 150 mg/kg/day occurred in the absence of functional/morphological disturbances or clinical signs and was of an incidental and minimal nature a No Observed Adverse Effect Level (NOAEL) of 150 mg/kg/day was established.	X
5.3	**Conclusion**		
5.3.1	LO(A)EL	1000 mg/kg/day At macroscopy, an irregular surface of the forestomach was noted in all high dose animals, which was confirmed microscopically by hyperplasia of the squamous epithelium.	X
5.3.2	NO(A)EL	150 mg/kg/day	X
5.3.3	Other	----	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	March 2008
Materials and Methods	**4.1.2. Mortality** Besides the male indicated also one female died from misgavage at day 9.
Results and discussion	**5.2.** Breathing difficulties of most animals of the high dose group on some occasions in week 3: Since these effects were not observed any more in week 4, a relation to treatment is unlikely. **5.3.1 LOAEL** Local oral LOAEL = 1000 mg/kg bw day; LOAEC = 20% in Propylene Glycol Systemic LOAEL > 1000 mg/kg bw day **5.3.2 NOAEL** Local oral NOAEL = 150 mg/kg bw day; LOAEC = 3% in Propylene Glycol Systemic NOAEL > 1000 mg/kg bw day
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	

Section A6.3.1_02	**28 days repeated dose toxicity in the rat**
Annex Point IIA6.3.1.	**Oral**

			Official use only
		1 REFERENCE	
1.1	**Reference**	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	
1.2	**Data protection**	No	
1.2.1	Data owner	----	X
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	----	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No information available.	X
2.2	**GLP**	Yes	
2.3	**Deviations**	No information available.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	4H006	
3.1.2	Specification	No information available	
3.1.2.1	Description	Pale yellow liquid	
3.1.2.2	Purity	93%	
3.1.2.3	Stability	Not indicated	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley	
3.2.3	Source	Harlan Sprague-Dawley, Houston, TX, U.S.A.	
3.2.4	Sex	21 males and 21 females	
3.2.5	Age/weight at study initiation	Age: No information available Weight: males 154-174 g, females 131-160 g	
3.2.6	Number of animals per group	3 animals of one sex in each dose group	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	**Oral**	
3.3.1	Duration of treatment	2 weeks	
3.3.2	Frequency of exposure	Daily	
3.3.3	Postexposure period	No postexposure period	

Section A6.3.1_02 **28 days repeated dose toxicity in the rat**

Annex Point IIA6.3.1. **Oral**

3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	Administered in the diet: 0, 1500, 2500, 4000, 6300, 7500 and 10000/20000 ppm (the dose of 10000 ppm in week 1 was increased to 20000 ppm during week 2) Dose level of either 0, 145, 267, 423, 633, 753 or 1834 mg/kg bw/day
3.3.4.3	Vehicle	No vehicle was used.
3.3.4.4	Concentration in vehicle	No vehicle was used.
3.3.4.5	Total volume applied	No vehicle was used.
3.3.4.6	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes (daily)
3.4.1.2	Mortality	Yes (daily)
3.4.2	Body weight	Yes (once prior to initiation and weekly through day 21)
3.4.3	Food consumption	Yes (was recorded twice weekly)
3.4.4	Water consumption	No
3.4.5	Ophthalmoscopic examination	No
3.4.6	Haematology	Yes All animals Time point: at termination Parameters: Haematocrit, haemoglobin concentration, erythrocyte count and leukocyte count
3.4.7	Clinical Chemisty	Yes All animals Time point: at termination Parameters: blood urea nitrogen, creatinine, serum alanine aminotransferase, total protein, albumin, alkaline phosphatase, total bilirubin, glucose and triglycerides
3.4.8	Urinalysis	No

Section A6.3.1_02 **28 days repeated dose toxicity in the rat**

Annex Point IIA6.3.1. **Oral**

3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	No
3.5.2	Gross and histopathology	Necropsy: Yes All dose groups Organs: no information available which organs and tissues were collected and examined Histopathology: No
3.5.3	Other examinations	No
3.5.4	Statistics	No information available
3.6	**Further remarks**	----
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	No treatment-related clinical signs of toxicity were seen at any dose level.
4.1.2	Mortality	All rats survived until termination of the study.
4.2	**Body weight gain**	Mean body weights of treated rats were comparable to those of the controls. Mean body weight gain was similar for all treatment groups and lowest for the control group.
4.3	**Food consumption and compound intake**	Mean food consumption was similar between treated and control groups. Mean compound consumption was 145, 267, 423, 633, 753, and 1834 mg/kg bw/day at 1500, 2500, 4000, 6300, 7500 and 20000 ppm, respectively.
4.4	**Ophtalmoscopic examination**	No ophtalmoscopic examination was performed.
4.5	**Blood analysis**	
4.5.1	Haematology	No treatment-related alterations in hematology parameters were seen at any dose level.
4.5.2	Clinical chemistry	There were no differences noted between control and treated rats at any dose level.
4.5.3	Urinalysis	No urinalysis was performed.
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	Organ weights were not determined.
4.6.2	Gross and histopathology	Macroscopic examination: No treatment-related gross pathology alterations were seen at terminal necropsy. Microscopic examination: Histopathological examinations were not conducted.

Section A6.3.1_02		28 days repeated dose toxicity in the rat	
Annex Point IIA6.3.1.		Oral	
4.7	**Other**	No other examinations were performed.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	No guidelines stated.	
5.2	**Results and discussion**	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, hematology, clinical chemistry or gross pathology. Inadequate numbers of animals were used, organ weights were not determined and histopathological examinations were not conducted. The results, however, were very uniform. It is not likely that increasing the number of animals from 3 to 5 per sex per dose and adding histopathology data would alter the toxicology profile.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	----	
5.3.2	NO(A)EL	> 1834 mg/kg bw/day Dietary administration of technical Pelargonic Acid to male and female rats at doses up to and including 20000 ppm (1834 mg/kg bw/day) did not cause any systemic toxicity.	
5.3.3	Other	----	
5.3.4	Reliability	2	X
5.3.5	Deficiencies	Yes (Inadequate numbers of animals were used, organ weights were not determined and histopathological examinations were not conducted.)	

Evaluation by Competent Authorities

	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2008
Materials and Methods	**1.2. Data protection** No study report but just a study summary from EPA evaluation is available. Therefore this study can only be used as additional information. **2.1. Guideline study** The study was carried out for the purpose of range finding, the protocol is similar to the OECD guideline 409 (28day study), but fewer animals were used (3 per sex instead of 4 per sex), no histopathology and no ophthalmological examination was carried out.
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	4 – No full study report but only a study summary was submitted. Furthermore no histology was conducted, however the NOAEL from the 28 day study was based on clinical signs and macroscopically and microscopically identified irritation effects on the forestomach. The means that the 2-week feeding study can be compared with the 28 day gavage study on the level of clinical signs and macroscopic analysis. The study can be used within the risk assessment of nonanoic acid as one contribution to discuss the effect of gavage application versus exposure via food.
Acceptability	Acceptable as additional information.
Remarks	

A6.4.2.1 **Annex Point IIA6.4.2**	**Subchronic toxicity (rodent)** **Dermal**

JUSTIFICATION FOR NON-SUBMISSION OF DATA

Official use only

Other existing data [ ] **Technically not feasible [ ]** **Scientifically unjustified [ ]**

Limited exposure [ ] **Other justification [x]**

Detailed justification:

Due to the lack of effects at extremely high doses up to 1834 mg/kg bw/day in the 14-day rat range finding study of Kuhn 1995 (see point 6.3.1/02) and due to the determination of low toxicity in the 28-day rat study of [redacted] (refer to point 6.3.1/01) a subchronic toxicity study in rodent by the oral route is not considered necessary.

Formatiert: Hervorheben

Besides also US EPA (Anonymous 1998) has stated that an oral 90-day study is not required due to the following reasons:

1) The lack of effects at extremely high doses in the range finding study of Kuhn 1995
2) The nature of Pelargonic Acid (i.e. fatty acid) and its ubiquity in nature
3) The use of Pelargonic Acid as a food additive
4) The results from the acute mammalian toxicology studies
5) The unlikelihood of prolonged human exposure via the oral route due to the proposed use patterns (no use in edible crops)
6) Further minimization of dietary exposure by plant metabolism and rapid degradation of Pelargonic Acid in soil and water through oxidative degradation pathways common for fatty acids.

As the oral route is expected to be the most relevant exposure and as the acute dermal toxicity study showed only local effects, due to the irritating potential of the active substance, and no systemic effects were noted a subchronic toxicity study by the dermal route in a rodent is not considered necessary.

Undertaking of intended data submission [ ] ----

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date September 2007

Evaluation of applicant's justification Agree with applicant's version.

Justification for non-submission of the oral subchronic toxicity study contained the same argument; therefore it was deleted for reasons of readability.

See also justification for non-submission document IIIA 6.5.

Toxicological concern might arise from the severely irritating properties of nonanoic acid. However a threshold concentration for this effect can be estimated based on the studies available. See discussion in document IIA 3.3 and IIB 6.3.

Conclusion The justification can be accepted taking also the arguments from document IIIA 6.5. into consideration.

Remarks The cited range finding study from Kuhn 1995 can only be used as additional information, since only the study summary from the EPA evaluation was submitted and not the full study report and without further information we need to assume that the study data are protected.

A6.5.1
Annex Point IIA6.5.1

Chronic toxicity (rodent)

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	As all fatty acids, Pelargonic acid is present in nature. It has been found to occur naturally in soil (Mozol V et al., 1986) 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). Based on the knowledge of fatty acid metabolism (see also **A6.2**), the non-toxic properties of Pelargonic acid, which were demonstrated in the acute toxicity tests as well as in repeated dose and genotoxicity tests, and the fact that exposure to the active substance will be very low when applied as biocidal product, no additional knowledge is considered to be gained if a chronic toxicity study in a rodent is conducted. Besides literature data on chronic toxicity in mice which were repeatedly treated by dermal application with 50 mg undiluted Pelargonic Acid twice a week for 80 weeks did not cause any dermal or systemic toxicity (Barkley, W. (1985)). Therefore a chronic toxicity study in a rodent by the oral route is not considered necessary.	
Undertaking of intended data submission [ ]	----	

Evaluation by Competent Authorities

	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant's version. See also justification for non-submission document IIIA 6.4. Toxicological concern might arise from the severely irritating properties of nonanoic acid. However a threshold concentration for this effect can be estimated based on the studies available. See discussion in document IIA 3.3 and IIB 6.3.
Conclusion	The justification is acceptable.
Remarks	The cited study from Barkley can only be used as additional information, since only the study summary from the EPA evaluation was submitted and not the full study report and without further information we need to assume that the study data are protected.

Section A6.6.1_01 **Genotoxicity in vitro**

Annex Point IIA6.6.1 **Gene mutation in bacteria**

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (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), [redacted] unpublished report No. 321569 dates of experimental work: 20 March to 14 May 2001
1.2	**Data protection**	Yes
1.2.1	Data owner	W. Neudorff GmbH KG
1.2.2		----
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes EEC B.13/14, OECD No. 471
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Pelargonic Acid
3.1.1	Lot/Batch number	799800
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Clear yellow liquid
3.1.2.2	Purity	93 % C-9 fatty acids
3.1.2.3	Stability	Not indicated
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	S. typhimurium: TA 1535, TA 1537, TA 98, TA 100 E. coli: WP2 uvr A
3.2.2	Deficiencies / Proficiencies	S. typhimurium: TA 1535: histidine deficient, crystal violet sensitive, UV-sensitive TA 1537: histidine deficient, crystal violet sensitive, UV-sensitive TA 98: histidine deficient, crystal violet sensitive, UV-sensitive, ampicillin resistant TA 100: histidine deficient, crystal violet sensitive, UV-sensitive, ampicillin resistant E. coli: WP2 uvr A: tryptophan deficient, UV sensitive

Section A6.6.1_01 Annex Point IIA6.6.1		Genotoxicity in vitro Gene mutation in bacteria	
3.2.3	Metabolic activation system	S9 mix S9 derived from male Wistar rats (Aroclor 1254 induced rat liver), own production. Before use, all S9-batches were characterized with the metabolic activation requiring positive control; benzo[a]pyrene (Sigma) in tester strain TA98 at the concentration of 5 µg/plate. S9-mix contained per 10 mL: 30 mg NADP and 15.2 mg glucose-6-phosphate in 5.5 ml Mill-Q water (first or second experiment respectively); 2 mL 0.5 M sodium phosphate buffer pH 7.4; 1 mL 0.08 M $MgCl_2$ solution; 1 mL 0.33 M KCl solution. The above solution was filter (0.22 µm)-sterilized. To 9.5 mL of S9-mix components 0.5 mL S9-fraction was added (5% /v/v) S9-fraction, respectively to 9.0 mL of S9-mix components 1.0 mL S9-fraction was added (10% (v/v) S9-fraction).	
3.2.4	Positive control	Non activation: For strain TA1535 — sodium azide For strain TA1537 — 9-aminoacridine For strain TA98 — daunomycine For strain TA100 — methylmethanesulfonate For strain WP_2uvrA — 4-nitroquinoline N-oxide Activation: For strains TA1535, TA1537, TA98 — 2-aminoanthracene For strain TA100 — 2-aminoanthracene For strain WP_2uvrA — 2-aminoanthracene	X
3.3	**Administration / Exposure; Application of test substance**		
3.3.1	Concentrations	Dose range finding: 3, 9, 31, 93, 310, 930, 3100, 4650 µg a.i./plate Experiment1: 100, 333, 1000, 3330, 5000 µg a.i./plate Experiment 2: 93, 310, 930, 3100, 4650 µg a.i./plate Experiment 3: 1000, 3330, 5000 µg a.i./plate	
3.3.2	Way of application	Top agar in top agar tubes was molten and heated to 45°C. The following solutions were successively added to 3 mL molten top agar: 0.1 mL of a dilution of the test substance in dimethyl sulfoxide (vehicle) and either 0.5 mL S9-mix (in case of activation assays) or 0.5 mL 0.1 M phosphate buffer (in case of non-activation assays). The ingredients were mixed and poured onto selective agar plate.	
3.3.3	Pre-incubation time	After solidification of the top agar, the plates were turned and incubated in the dark at 37±1°C for 48 h.	
3.3.4	Other modifications	----	
3.4	**Examinations**	*see tables in appendix for examinations and results*	
3.4.1	Number of cells evaluated	The revertant colonies were counted automatically if less than 40 colonies per plate were present. Plates with sufficient test article precipitate to interfere with automated colony counting were counted manually.	

Section A6.6.1_01 **Genotoxicity in vitro**

Annex Point IIA6.6.1 **Gene mutation in bacteria**

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No
4.1.2	with metabolic activation	No
4.2	**Cytotoxicity**	No

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

EEC B.6, OECD No. 406

5.2 Results and discussion

Dose-Range finding assay:

Eight doses of the test substance ranging from 3 to 4560 µg a.i./plate were tested in the tester strains TA100 and WP_2uvrA in the absence and presence of 5% (v/v) S9-mix. Precipitation was observed at concentrations of 930 µg a.i./plate and upwards. In tester strain WP_2uvrA, no reduction of the bacterial background lawn and no biologically relevant decrease in the number of revertants were observed. In tester strain TA100 in the absence of S9-mix, a slight reduction in the number of revertant colonies was observed at the test substance concentration of 930 µg a.i./plate, a moderate reduction at 3100 µg/plate and an extreme reduction at 4650 µg a.i./plate. In the presence of S9-mix, a slight reduction in the number of revertant colonies was observed at the test substance concentration of 310 µg a.i./plate, a moderate reduction at 930 µg a.i./plate and an extreme reduction at 3100 and 4650 a.i./plate. A slight reduction of the bacterial background lawn was observed at 930, 3100 and 4650 µg a.i./plate in the absence and presence of S9-mix.

No increase in the number of revertants was observed upon treatment with Pelargonic Acid under all conditions tested.

Mutation assays:

Experiment 1: Based on the results of the dose range finding test, Pelargonic Acid was tested up to 5000 µg a.i./plate in the absence and presence of 5% (v/v) S9-mix with the strains TA1535, TA1537 and TA98. Precipitation occurred in the top agar at concentrations of 1000 µg a.i./plate and upwards. Precipitation on ten plates was observed at the start and at the end of the incubation period at the concentration of 5000 µg a.i./plate. Toxicity depended on dose and strain. Whereas TA1535 did no show reactions at 5000 µg a.i./plate, the reduction in the number of revertant colonies at only 3300 µg a.i./plate was moderate and extreme in strains TA98 and TA1537, respectively.

No increase in the number of revertants was observed upon treatment with Pelargonic Acid under all conditions tested.

Section A6.6.1_01	Genotoxicity in vitro
Annex Point IIA6.6.1	Gene mutation in bacteria

Experiment 2: To obtain more information about the mutagenicity of Pelargonic Acid, a second mutation experiment was performed in the absence and in the presence of 10% (v/v) S9-mix. Based on the results of the first mutation experiment, Pelargonic Acid was tested up to the dose level of 4650 µg a.i./plate in the tester strains TA1535, TA1537, TA98, TA100 and WP_2uvrA. The test substance precipitated in the top agar at concentrations of 930 µg a.i./plate and upwards.

No increase in the number of revertants was observed upon treatment with Pelargonic Acid under all conditions tested.

Experiment 3: In the dose range finding study and the second experiment, the concentrations tested were not corrected for the purity of the test substance (93% C-9 fatty acids). An additional experiment was performed in the absence of S9-mix and in the presence of 10% (v/v) S9-mix to overcome this error. Based on the results of the preceding mutation experiments, Pelargonic Acid was tested up to the dose level of 5000 µg a.i./plate in the tester strains TA1535, TA1537, TA98 and WP_2uvrA. Since TA100 showed severe toxicity in the preceding experiments, it was not necessary to test this strain at higher concentrations of Pelargonic Acid. Precipitation in the top agar occurred at concentrations of 1000 µg a.i./plate and upwards. Precipitation on the plates was observed at the start and at the end of the incubation period at the concentration of 5000 µg a.i./plate. In tester strains TA1535 and WP_2uvrA, no reduction of the bacterial background lawn and no biologically relevant decrease in the number of revertants were observed. In tester strain TA1535, an extreme or complete reduction in the number of revertant colonies was observed at test substance concentration of 3330 and 5000 µg a.i./plate in the absence and presence of S9-mix. In tester strain TA98 in the absence of S9-mix, an extreme reduction in the number of revertant colonies was observed at test substance concentrations of 3330 and 5000 µg a.i./plate. In the presence of S9-mix, a moderate or extreme reduction in the number of revertant colonies was observed at 3330 µg a.i./plate and 5000 µg a.i./plate, respectively.

No increase in the number of revertants was observed upon treatment with Pelargonic Acid under all conditions tested.

5.3 Conclusion

Based on the results of this study it is concluded that Pelargonic Acid is not mutagenic in the *Salmonella typhimurium* reverse mutation assay and in the *Escherichia coli* reverse mutation assay.

5.3.1 Reliability

1

5.3.2 Deficiencies

No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2006.05.09
Materials and Methods	3.2.4. Positive Control According to the study report (p9) all S9 batches were also characterized with the metabolic activation requiring positive control benzo[a]pyrene in tester strain TA98 at the concentration of 5µg/plate.
Results and discussion	
Conclusion	Agree with applicant's version.
Reliability	Agree with applicant's version.
Acceptability	acceptable
Remarks	

Table A6_6_1-1.Table for Gene Mutation Assay

Strain	Concentration [µg a.i./plate]	Mean number of revertant colonies		Comments
		— S9	+ S9	
Experiment 1				
Positive control		138±5		
Solvent control		13±2		
TA 1535	100	11±2		
	333	11±4		
	1000	11±1		
	3330	11±5		
	5000	12±6		
Positive control			874±134	
Solvent control			13±1	
TA 1535	100		12±1	
	333		9±2	
	1000		10±2	
	3330		7±1	
	5000		11±3	
Positive control		174±10		
Solvent control		6±2		
TA 1537	100	7±1		
	333	6±2		
	1000	5±1		
	3330	2±1		
	5000	--		Microcolonies, bacterial background lawn extremely reduced
Positive control			418±57	
Solvent control			5±1	
TA 1537	100		6±2	
	333		6±3	
	1000		4±1	
	3330		1±1	Bacterial background lawn slightly reduced
	5000		--	Microcolonies, bacterial background lawn extremely reduced
Positive control		339±71		
Solvent control		16±2		
TA 98	100	18±7		
	333	15±2		
	1000	13±1		
	3330	9±2		
	5000	7±2		

Positive control			419±25	
Solvent control			23±4	
TA 98	100		20±5	
	333		25±6	
	1000		15±3	
	3330		16±1	
	5000		11±3	
Experiment 2				
Positive control		461±24		
Solvent control		11±2		
TA 1535	93	13±4		
	310	13±4		
	930	6±1		
	3100	9±3		
	4650	6±2		Slight precipitate, bacterial background lawn slightly reduced
Positive control			125±28	
Solvent control			14±2	
TA 1535	93		13±5	
	310		10±1	
	930		13±8	
	3100		7±0	
	4650		8±3	Slight precipitate
Positive control		449±58		
Solvent control		8±3		
TA 1537	93	9±4		
	310	6±4		
	930	6±3		
	3100	1±2		
	4650	0±0		Slight precipitate
Positive control			86±18	
Solvent control			7±2	
TA 1537	93		6±1	
	310		8±3	
	930		6±4	
	3100		2±1	bacterial background lawn slightly reduced
	4650		1±1	Slight precipitate bacterial background lawn slightly reduced

Positive control		422±69		
Solvent control		18±1		
TA 98	93	17±2		
	310	18±6		
	930	17±5		
	3100	8±4		
	4650	5±1		Slight precipitate
Positive control			198±15	
Solvent control			23±1	
TA 98	93		29±8	
	310		20±2	
	930		18±5	
	3100		14±2	
	4650		10±2	Slight precipitate
Positive control		981±34		
Solvent control		99±10		
TA 100	93	90±12		
	310	81±3		
	930	70±13		
	3100	55±5		Slight precipitate
	4650	25±6		Slight precipitate, bacterial background lawn slightly reduced
Positive control			237±17	
Solvent control			79±12	
TA 100	93		61±7	
	310		49±13	
	930		29±2	Bacterial background lawn slightly reduced
	3100		13±2	Slight precipitate, bacterial background lawn slightly reduced
	4650		9±4	Slight precipitate bacterial background lawn slightly reduced
Positive control		1019±49		
Solvent control		15±5		
WP_2uvrA	93	13±4		
	310	10±1		
	930	12±5		
	3100	9±4		
	4650	9±2		Slight precipitate

Positive control			183±7	
Solvent control			10±2	
WP_2uvrA	93		10±2	
	310		10±4	
	930		10±2	
	3100		9±1	
	4650		12±1	Slight precipitate
Experiment 3				
Positive control		247±23		
Solvent control		15±5		
TA 1535	1000	10±2		
	3330	10±6		
	5000	10±3		Slight precipitate
Positive control			116±3	
Solvent control			13±1	
TA 1535	1000		9±1	
	3330		12±2	
	5000		15±8	Slight precipitate
Positive control		170±27		
Solvent control		5±2		
TA 1537	1000	7±3		
	3330	1±1		
	5000	0±0		Slight precipitate
Positive control			148±3	
Solvent control			7±3	
TA 1537	1000		7±2	
	3330		1±2	
	5000		1±1	Slight precipitate
Positive control		597±51		
Solvent control		27±2		
TA 98	1000	23±7		
	3330	9±3		
	5000	9±4		Slight precipitate
Positive control			306±14	
Solvent control			38±6	
TA 98	1000		26±4	
	3330		16±5	
	5000		14±1	Slight precipitate

Positive control		997±97		
Solvent control		12±1		
WP_2uvrA	1000	12±6		
	3330	9±5		
	5000	7±1		Slight precipitate
Positive control			286±49	
Solvent control			13±2	
WP_2uvrA	1000		10±3	
	3330		15±3	
	5000		12±2	Slight precipitate

Section A6.6.1_02	**Genotoxicity in vitro**
Annex Point IIA6.6.1	**Gene mutation in bacteria**

			Official use only
		1 REFERENCE	
1.1	**Reference**	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., report No. 15656-0-401R	
1.2	**Data protection**	No	X
1.2.1	Data owner	----	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	----	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EPA FIFRA Guideline § 152-17	
2.2	**GLP**	Yes	
2.3	**Deviations**	The lot number and the purity of the test material was not indicated in the study.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid (Technical Grade)	
3.1.1	Lot/Batch number	No information available	
3.1.2	Specification	No information available	
3.1.2.1	Description	Clear liquid	
3.1.2.2	Purity	No information available	
3.1.2.3	Stability	Not reported	
3.2	**Study Type**	Bacterial reverse mutation test	
3.2.1	Organism/cell type	S. typhimurium: TA 1535, TA 1537, TA 1538, TA 98, TA 100	
3.2.2	Deficiencies / Proficiencies	S. typhimurium: all test strains: histidine deficient	
3.2.3	Metabolic activation system	a. S9 Fraction: Commercially obtained microsomal fraction S9, derived from homogenates of livers from male Sprague-Dawley rats induced with Aroclor 1254 at a dose of 500 mg/kg, 5 days prior to sacrifice. b. Activation mixture composition:	

Water	0.70 mL
1M NaH_2PO_4/Na_2HPO_4	0.10 mL
0.25 M Glucose-6-phosphatase	0.02 mL
0.10 M NADP	0.04 mL
0.02 M $MgCl_2$ / 0.825 M KCl	0.04 mL
S9 homogenate	0.10 mL

Section A6.6.1_02 **Genotoxicity in vitro**

Annex Point IIA6.6.1 **Gene mutation in bacteria**

3.2.4	Positive control	Non activation:	
		For strain TA1535, TA100	sodium azide
		For strain TA1537	ICR-191
		For strain TA1538, TA98	2-nitrofluorene
		Activation:	
		For all strains	2-aminoanthracene (2.5 µg/plate)
3.3	**Administration / Exposure; Application of test substance**		
3.3.1	Concentrations	Dose range finding study:	6.7, 10, 33, 66.7, 100, 333, 667, 1000, 3300 and 5000 µg/plate
		Mutation assay:	100, 333, 667, 1000, 3330 and 5000 µg/plate
3.3.2	Way of application	The method used was a plate incorporation assay (Ames Test). Similar procedures were used for the range-finding and mutation assay. For the non-activated tests, 100µL of tester strain, 50 µL vehicle, positive control, or test substance was added to 13 x 100 mm tubes containing 2.5 mL molten selective agar. If S9 was used, 500 µL of S9 mix, 100 µL tester strain, and 50 µL of the vehicle, positive control, or test substance was added to 2.0 mL of the molten selective top agar. The mixture in the tubes were vortexed, then poured onto a layer of minimal bottom agar (25 mL) in a 15 x 100 mm Petri-dish.	
3.3.3	Pre-incubation time	After the overlay had solidified, the plates were inverted and incubated at 37±2°C for 48±8 h.	
3.3.4	Other modifications	----	
3.4	**Examinations**		
3.4.1	Number of cells evaluated	The plates were immediately counted after incubation, or stored at 5±3°C until counted. Revertant counts and the condition of the background lawn of growth (relative to the vehicle controls) was determined.	
		4 RESULTS AND DISCUSSION	
4.1	**Genotoxicity**		
4.1.1	without metabolic activation	No	
4.1.2	with metabolic activation	No	
4.2	**Cytotoxicity**	Yes Cytotoxicity was observed at 5000 µg per plate in the presence of S9 activation, and at 3300 and 5500 µg per plate in the non-activated cultures.	

Section A6.6.1_02	**Genotoxicity in vitro**
Annex Point IIA6.6.1	**Gene mutation in bacteria**

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	EPA FIFRA Guideline § 152-17
5.2	**Results and discussion**	Dose range finding assay: Cytotoxicity was observed at 5000 µg per plate in the presence of S9 activation, and at 3300 and 5500 µg per plate in the non-activated cultures. This was evidenced by a reduction in the numbers of revertants per plate and/or thinning of the bacterial background lawn. The six doses used in the mutagenicity assay were based on the range finding assay. Mutation assay: All validity criteria for a valid study were met, and no positive increases in the number of histidine revertants per plate were observed with any of the tester strains, with or without metabolic activation.
5.3	**Conclusion**	Under the conditions of this study Pelargonic Acid was negative for mutagenicity in all *Salmonella typhimurium* strains tested, with and without metabolic activation.
5.3.1	Reliability	2
5.3.2	Deficiencies	The lot number and the purity of the test material was not indicated in the study.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	September 2007
Materials and Methods	**1.2. Data protection** No study report but just a study summary from EPA evaluation is available. Therefore this study can only be used as additional information.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	4 – since no full report but only a study summary is available.
Acceptability	Acceptable as additional information
Remarks	

Section A6.6.2	**Genotoxicity in vitro**
Annex Point II6.6.2	**Cytogenicity in mammalian cells**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2001), Evaluation of the Ability of Pelargonsäure to induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes; (including Amendment No.1), [redacted], unpublished report No. 321571 dates of experimental work: 11 April to 26 September 2001	
1.2	**Data protection**	Yes	
1.2.1	Data owner	W. Neudorff GmbH KG	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	Data on existing a.s. for first entry to Annex I / IA / authorisation	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EEC B.10, OECD No. 473	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid	
3.1.1	Lot/Batch number	799800	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Clear yellow liquid	
3.1.2.2	Purity	93% C-9 fatty acids	
3.1.2.3	Stability	Not indicated	
3.2	**Study Type**	In vitro mammalian chromosome aberration test	
3.2.1	Organism/cell type	Human lymphocytes obtained from human venous blood from healthy adult male volunteers	
3.2.2	Deficiencies / Proficiencies	----	
3.2.3	Metabolic activation system	S9 mix S9 derived from male Wistar rats (Aroclor 1254 induced rat liver), own production. S9-mix contained per mL 1.63 mg $MgCl_2$ $6H_2O$; 2.46 mg KCl; 1.7 mg glucose-6-phosphate; 4.3 mg NADP; 4 µmol HEPES. The above solution was filter (0.22 µm)-sterilized. To 0.5 ml S9-mix components 0.5 mL S9-fraction was added (50% (v/v) S9-fraction) to complete the S9-mix. Metabolic activation was achieved by adding 0.2 mL S9-mix to 5.3 mL of a lymphocyte culture (containing 4.8 mL F10 complete culture medium, 0.4 mL blood and 0.1 mL (9 mg/mL) phytohaemagglutinin). The concentration of the S9-fraction in the exposuremedium was 1.8% (v/v).	
3.2.4	Positive control	Non activation: Mitomycin C (MMC) in water at 0.1, 0.2 and 0.5 µg/mL Activation: Cyclophosphamide (CP) in water at 15 µg/mL	

Section A6.6.2	Genotoxicity in vitro
Annex Point II6.6.2	Cytogenicity in mammalian cells

3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	First cytogenetic assay: without activation: 100, 333, 420, 480, 520, 750 µg/mL with activation: 100, 333, 420, 480, 520, 750 µg/mL Second cytogenetic assay: without activation: 10, 33, 100, 240, 300 µg/mL with activation: 333, 420, 480, 520 µg/mL
3.3.2	Way of application	Cell treatment Cells were exposed to test compound, solvent or positive control for 3 h (first trial) or 24 and 48 h (second trial) without activation, or for 3 hours with activation (both trials). Spindle inhibition 0.5 µg/mL colchicine was administered 2.5 h before cell harvest. Cell harvest Cells were exposed to test material, solvent or positive control and were harvested 20-22 h (first trial), or 44-46 h (second trial) after termination of treatment. Those cells which were treated for 24 and 48 h were fixed immediately. Slide preparation Slides were prepared by dropping the harvested cultures on clean slides. Two slides were prepared per culture. The slides were stained with 5% Giemsa solution. All slides were air-dried and cleared by dipping them in xylene before they were embedded in Micro Mount and mounted with a coverslip. Metaphase analysis Slides were coded prior to analysis. At least 200 metaphase chromosome spreads per concentration were examined for chromosome aberrations. In case the number of aberrant cells, gaps excluded, was ≥ 25 in 50 metaphases, no more metaphases were examined. Only metaphases containing 46 +/- 2 centromeres (chromosomes) were analysed.
3.3.3	Pre-incubation time	----
3.3.4	Other modifications	----
3.4	**Examinations**	The number of cells with aberrations and the number of aberrations were calculated. The following types of aberrations were recorded in the raw data: g` = chromatid gap, g" = chromosome gap, b` = chromatid break, b" = chromosome break, d` = chromatid deletion, m` = minute, m" = double minutes, dic = dicentric chromosome, tric = tricentric chromosome, r = ring chromosome, exch. = exchange figure, intra = chromosome intrachange, p = pulverized chromosomes, ma = multiple aberrations, poly = polyploidy, endo = endoreduplication (see tables in appendix for examinations and results)
3.4.1	Number of cells evaluated	200

Section A6.6.2	Genotoxicity in vitro
Annex Point II6.6.2	Cytogenicity in mammalian cells

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	Yes 750µg a.i./mL
4.1.2	with metabolic activation	Yes 750µg a.i./mL
4.2	**Cytotoxicity**	Precipation of Pelargonic Acid was noticed in both activated and non-activated cultures treated at 1000 µg a.i./mL. In both cultures treated for 3 h, a very high cytotoxicity (with a mitotic index of 0%) was observed, whereas lower concentrations of 333 µg a.i./mL and less were not cytotoxic at all. After an extended exposure time of 24 and 48 h without S9-mix activation, 333 µg a.i./mL produced a reduction of the mitotic index of more than 50%.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	EEC B.10, OECD No. 473
5.2	**Results and discussion**	<u>Dose range finding assay:</u> In the dose range finding assay Pelargonic Acid was tested at concentration levels of 10, 33, 100, 333 and 1000µg a.i./mL with metabolic activation (3 h exposure time, 24 h fixation time) and without metabolic activation (3, 24, 48 h exposure time and 24 or 48 h fixation time). Precipation of Pelargonic Acid was noticed in both activated and non-activated cultures treated at 1000 µg a.i./mL. In both cultures treated for 3 h, a very high cytotoxicity (with a mitotic index of 0%) was observed, whereas lower concentrations of 333 µg a.i./mL and less were not cytotoxic at all. After an extended exposure time of 24 and 48 h without S9-mix activation, 333 µg a.i./mL produced a reduction of the mitotic index of more than 50%. <u>First cytogenetic assay</u> In the first cytogenic assay, Pelargonic Acid was tested up to 750 µg a.i./mL for a 3 h exposure time with a 24 h fixation time in the absence of S9-mix and in the presence of S9-mix. In the absence and presence of S9-mix, 750 µg a.i./mL Pelargonic Acid induced a statistically significant increase in the number of cells with chromosome aberrations. Since this concentration was very toxic and highly precipitating, a less toxic and slight precipitating concentration of 520 µg a.i./mL was additionally scored. This concentration, however, did not induce a significant increase in the number of cells with chromosome aberrations.

Section A6.6.2 Annex Point II6.6.2	Genotoxicity in vitro Cytogenicity in mammalian cells
	Second cytogenetic assay In the second cytogenic assay, Pelargonic Acid was tested at concentration levels of 333, 420, 480, 520 µg a.i./mL with metabolic activation (3 h exposure time, 48 h fixation time) and without metabolic activation at concentrations of 10, 33, 100, 240, 300 µg a.i./mL (24 or 48 h exposure time, 24 or 48 h fixation time). Both in the absence and presence of S9-mix, Pelargonic Acid did not induce a statistically significant or biologically relevant increase in the number of cells with chromosome aberrations. In all trials, the number of cells with chromosome aberration found in the solvent control cultures were within the laboratory historical control data range. The positive control chemicals mitomycin C and cyclophosphamide (MMC and CP) both produced statistically significant increases in the frequency of aberrant cells. Therefore, it is concluded that the test conditions were adequate and that the metabolic activation system functioned properly.
5.3 Conclusion	Evaluating all results, it is concluded that the observed increased number of cells with chromosome aberrations at the highly cytotoxic and severely precipitating concentration of 750 µg a.i./mL is due to cytotoxicity-related secondary mechanisms and does not reflect intrinsic mutagenicity mechanisms of the test substance. Therefore, the induction of chromosome aberration by Pelargonic Acid at the highest concentration tested may be considered biologically non-relevant and Pelargonic Acid may be considered as not clastogenic in human lymphocyte cultures.
5.3.1 Reliability	1
5.3.2 Deficiencies	No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Materials and Methods	Agree with applicant's version
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	

Table A6_6-2 **Table 1: Mitotic index and chromosome aberrations in human lymphocyte cultures treated with Pelargonic Acid (First cytogenetic trial)**

	Without S9-mix							*With S9-mix*					
	3 h exposure, 24 h fixation							*3 h exposure, 24 h fixation*					
Compound µg/ml	*DMSO 1% v/v*	*PA 100*	*PA 480*	*PA 520*	*PA 750*	*PA 750*	*MMC 0.5*	*DMSO 1% v/v*	*PA 100*	*PA 420*	*PA 520*	*PA 750*	*CP 15*
Mitotic Index (%)	100	86	70	73	38	*38*	72	100	108	85	93	38	38
No of cells scored	200	200	200	200	365[1)]	200[2)]	200	200	200	200	200	200	200
No of cells with aberrations (+ gaps)	5	5	3	4	24*	19**	54***	5	6	0	6	16*	75***
No of cells with aberrations (- gaps)	5	3	1	2	22	18**	45***	3	6	0	4	15*	72***

1) additional scoring of metaphases because of non-homogeneity in response

2) scored by another person

* significantly different from control group (Chi-square test): * P < 0.05, ** P < 0.01, *** P < 0.001

Table A6_6-2 **Table 2: Mitotic index and chromosome aberrations in human lymphocyte cultures treated with Pelargonic Acid, in dependence on exposure time (Second cytogenetic trial)**

	Without S9-mix									
	24 h exposure, 24 h fixation					*48 h exposure, 48 h fixation*				
Compound µg/ml	*DMSO 1% v/v*	*PA 10*	*PA 33*	*PA 100*	*MMC 0.2*	*DMSO 1% v/v*	*PA 10*	*PA 33*	*PA 100*	*MMC 0.1*
Mitotic Index (%)	100	94	85	56	53	100	107	86	50	83
No of cellsscored	200	200	200	200	200	200	200	200	200	200
No of cells with aberrations (+ gaps)	0	0	0	1	23***	0	1	0	1	42***
No of cells with aberrations (- gaps)	0	0	0	1	22***	0	1	0	0	40***

* significantly different from control group (Chi-square test): * P < 0.05, ** P < 0.01, *** P < 0.001

Table A6_6-2 **Table 3: Mitotic index and chromosome aberrations in human lymphocyte cultures treated with Pelargonic Acid (Second cytogenetic trial)**

	With S9-mix				
	3 h exposure, 48 h fixation				
Compound µg/ml	*DMSO 1% v/v*	*PA 333*	*PA 480*	*PA 520*	*CP 15*
Mitotic Index (%)	100	94	83	135	---[1)]
No of cells scored	200	200	200	200	200
No of cells with aberrations (+ gaps)	0	0	0	1	47***
No of cells with aberrations (- gaps)	0	0	0	1	44***

1) CP was fixed after 24 hours. Therefore, the mitotic index could not be calculated as percentage of control

* significantly different from control group (Chi-square test): * P < 0.05, ** P < 0.01, *** P < 0.001

A6.6.3 Annex Point IIA6.6.3	Genotoxicity in vitro Gene mutation in mammalian cells	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	No positive results were obtained in any of the in vitro genotoxicity tests conducted in S. typhimurium, E. coli or human lymphocytes. Based on these test results and on literature data on a mouse lymphoma forward mutation assay with Pelargonic acid, which did also not reveal any signs of genotoxicity (Cifone M.A. (1993)) a gene mutation assay in mammalian cells is not considered necessary.	
Undertaking of intended data submission [ ]	----	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant's statement. Furthermore nonanoic acid does not contain structural alerts for genotoxicity. The cited study was not submitted, only the corresponding evaluation of the study summary by EPA. Therefore the study can only be considered as additional information. Furthermore the purity and lot number for the substance tested is not available in the study summary.
Conclusion	The justification of non submission is acceptable.
Remarks	

Section A6.6.4	**Genotoxicity in vivo**	
Annex Point IIA6.6.4	Micronucleus test	

			Official use only
		1 REFERENCE	
1.1	**Reference**	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	
1.2	**Data protection**	No	X
1.2.1	Data owner	----	
1.2.2	Companies with letter of access	----	
1.2.3	Criteria for data protection	----	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EPA FIFRA Guideline § 152-17	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	n-Pelargonic Acid	
3.1.1	Lot/Batch number	n-Pelargonic Acid New Process Hoop	
3.1.2	Specification	No information available	
3.1.2.1	Description	Clear, colourless liquid	
3.1.2.2	Purity	Concentration in dosing sample (500 mg/mL) found to be 102% of target (by gas chromatography)	X
3.1.2.3	Stability	Stable for 24 hours at room temperature (tested in laboratory)	
3.1.2.4	Maximum tolerable dose	5000 mg/kg bw	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	ICR	
3.2.3	Source	Harlan Sprague Dawley, Inc., Frederick, MD	
3.2.4	Sex	75 females and males	
3.2.5	Age/weight at study initiation	Age: 8 weeks Weight: males 21.5-37.6 g and females 21.4-31.0 g	
3.2.6	Number of animals per group	15 males and 15 females per dose	
3.2.7	Control animals	Yes	

Section A6.6.4	**Genotoxicity in vivo**
Annex Point IIA6.6.4	Micronucleus test

3.3	**Administration/ Exposure**	**Oral**	
3.3.1	Number of applications	1	
3.3.2	Interval between applications	----	
3.3.3	Postexposure period	24, 48 and 72 h after treatment	
3.4	**Oral**	**Oral**	
3.4.1	Type	Gavage	
3.4.2	Concentration	0, 1250, 2500, 5000 mg/kg bw	
3.4.3	Vehicle	Corn oil	
3.4.4	Concentration in vehicle	No information available	
3.4.5	Total volume applied	10 mL/kg bw	
3.4.6	Controls	Negative control:	None
		Vehicle control:	Corn oil (dosing volume of 10 mL/kg bw) was administered by oral gavage
		Positive control:	Cyclophophamide dissolved in deionised water, dosed at 80 mg/kg
3.5	**Examinations**		
3.5.1	Clinical signs	No	
3.5.2	Tissue	Bone marrow	
		Frequency of PCEs (polychromatic erythrocytes) vs. NCEs (normochromatic erythrocytes) was determined by scoring the number per 1000 erythrocytes counted. Percentage or frequency of micronucleated cells (not individual micronuclei) was expressed as the% PCEs with micronuclei compared with the total PCEs (1000) counted.	
		Number of animals:	All animals except one female mouse which died during the study (5000 mg/kg bw group, 24 hour observation period); the cause of death was unknown.
		Number of cells:	Not reported
		Time points:	24, 48, 72 h after treatment
		Type of cells	Erythrocytes in bone marrow
		Parameters:	polychromatic/normochromatic erythrocytes ratio
3.6	**Further remarks**	----	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	No effects reported	
4.2	**Haematology / Tissue examination**	No effects reported	

Section A6.6.4		**Genotoxicity in vivo**
Annex Point IIA6.6.4		Micronucleus test
4.3	**Genotoxicity**	No
4.4	**Other**	----
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	EPA FIFRA Guideline § 152-17
5.2	**Results and discussion**	The test compound did not increase the% micronucleated PCEs at any dose or interval. X By contrast positive control induced a significant ($p \leq 0.05$) increase in the% micronucleated PCEs in both sexes.
5.3	**Conclusion**	Pelargonic Acid was adequately tested and found to be negative in this *in vivo* micronucleus assay.
5.3.1	Reliability	2
5.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Materials and Methods	**1.2. Data protection** No study report but just a study summary from EPA evaluation is available. Therefore this study can only be used as additional information. **3.1.2.2. Purity** The purity description is unclear. According to the 5-batch Analysis the purity of the substance as manufactured is ca. 90%.
Results and discussion	**5.2. Results and Discussion** No information on the PCE/NCE ratio is given in the study summary which does not allow to conclude if the active substance reached the bone marrow.
Conclusion	This EPA study summary evaluation is of limited value since the purity is unclear and the full study could not be submitted.
Reliability	4 – since no full study report but only a study summary is available.
Acceptability	Acceptable only as additional information.
Remarks	

A6.6.5 Annex Point IIA6.6.5	Genotoxicity in vivo Second in vivo test	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	Pelargonic Acid was not mutagenic in the reverse mutation assay conducted with Salmonella typhimurium and Escherichia coli with and without liver microsomal S9-activation. Pelargonic Acid did not induce chromosomal aberrations in human lymphocytes if tested at non-cytotoxic concentrations. The highest concentration of 750 µg a.i./mL induced an increase in the number of cells with chromosome aberrations. However, this concentration was highly cytotoxic and the result rather reflects toxicity related secondary mechanisms than intrinsic mutagenicity of the test substance. Therefore, the induction of chromosome aberration at the highest tested dose may be considered to be biologically non-relevant. Similar responses were obtained when Pelargonic Acid was tested in a mouse lymphoma forward mutation assay. Non-cytotoxic test substance concentrations did not influence the number of mutant colonies and the mutation frequency in L 5178 Y cells whereas cytotoxic concentrations caused positive effects. The same considerations as above lead to the conclusion that intrinsic mutagenicity cannot be assumed. In an in vivo mouse micronucleus assay with single oral doses of up to 5000 mg/kg bw/day no significant increases in the frequency of micronucleated polychromatic erythrocytes were observed. As no positive results were obtained in the in vitro genotoxicity tests and also not in the in vivo micronucleus test, no further genotoxicity testing is required.	
Undertaking of intended data submission [ ]	----	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Just the bacterial mutation test and an in vitro cytogenicity test with human lymphocytes is available or the evaluation of the genotoxicity of Nonanoic acid. For the other tests cited only study summaries from EPA and no full study reports are available, therefore they can be used only as additional information and not as basis for study waiving.
Conclusion	Considering also the nature of Nonanoic acid (linear carbonic acid) and the knowledge about kinetics and metabolism the 2 available in vitro tests are considered sufficient for evaluation of genotoxicity of Nonanoic acid.
Remarks	

A6.7.1
Annex Point IIA6.7.1

Carcinogenicity

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	As all fatty acids, Pelargonic acid is present in nature. It has been found to occur naturally in soil (Mozol V et al., 1986) 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). Based on the knowledge of fatty acid metabolism (see also **A6.2**), the non-toxic properties of Pelargonic acid, which were demonstrated in the acute toxicity tests as well as in repeated dose and genotoxicity tests, and the fact that exposure to the active substance will be very low when applied as biocidal product, no additional knowledge is considered to be gained if a carcinogenicity study in a rodent is conducted. Besides literature data on carcinogenicity in mice which were repeatedly treated by dermal application with 50 mg undiluted Pelargonic Acid twice a week for 80 weeks did not cause any dermal or systemic toxicity (Barkley W., 1985). Therefore a carciniogenicity study in a rodent by the oral route is not considered necessary.	
Undertaking of intended data submission [ ]	----	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant's version. The justification is identical with the justification for non-submission of the chronic toxicity study, document IIIA 6.5. See also justification for non-submission document IIIA 6.4. Toxicological concern might arise from the corrosive properties of nonanoic acid. However a threshold concentration for this effect can be estimated based on the studies available. See discussion in document IIA 3.3 and IIB 6.3.
Conclusion	The justification is acceptable.
Remarks	The cited study from Barkley can only be used as additional information, since only the study summary from the EPA evaluation was submitted and not the full study report.

Section A6.8.1.1 **Teratogenicity Study (rat)**

Annex Point IIA6.8.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	Wakefield A.E. (1994), Teratology screen in rats, Hazleton Washington Inc., Vienna, U.S.A., report No. HWA 2689-101	
1.2	**Data protection**	No	
1.2.1	Data owner	----	X
1.2.2	Companies with letter of access	----	X
1.2.3	Criteria for data protection	----	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes EPA FIFRA Guideline § 152-23	X
2.2	**GLP**	No	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Pelargonic Acid (Identification: C-182)	
3.1.1	Lot/Batch number	No information available	
3.1.2	Specification	No information available	
3.1.2.1	Description	Clear colourless liquid	
3.1.2.2	Purity	100% (assumed)	
3.1.2.3	Stability	Stability and concentration analyses of the dosing solutions were not assessed during the conduct of the study in 1982. Therefore, on February 7, 1994, one formulation of Pelargonic Acid in corn oil (300 mg/mL) was prepared in the same manner as the original dosing solution and evaluated for concentration and 7-day stability. Results: Concentration analyses indicated the formulation to be within 10% of target (day 0 and day 7) and the solution was stable at room temperature for 7 days.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Crl: COBS CD (SD) BR	
3.2.3	Source	Charles River, NY, U.S.A.	
3.2.4	Sex	44 females	
3.2.5	Age/weight at study initiation	Approximately 14 weeks at gestation Weight: females 199-292 g on gestation day 0	
3.2.6	Number of animals per group	22 females randomly assigned to 1 vehicle control group and 1 treatment group	
3.2.7	Control animals	Yes	
3.2.8	Mating period	Two females were paired with one male. Vaginal smears were taken daily during cohabitation, and the presence of a copulatory plug or sperm in the vaginal smear was considered evidence of mating. The day this evidence was seen was designated as day 0 of gestation, and the female was then removed from the male`s cage and housed individually.	

Section A6.8.1.1 **Teratogenicity Study (rat)**

Annex Point IIA6.8.1

3.3	**Administration/ Exposure**	**Oral**
3.3.1	Duration of exposure	The vehicle and the test substance were administered daily via gavage at a dose of 1500 mg/kg bw/day during days 6 through 15 of gestation. rat day 6-15 post mating
3.3.2	Postexposure period	All surviving dams were sacrificed on gestation day 20.
		Oral
3.3.3	Type	Gavage
3.3.4	Concentration	1500 mg/kg bw
3.3.5	Vehicle	Corn oil
3.3.6	Concentration in vehicle	A specific amount of test article was weighed into a pre-calibrated graduated beaker filled to a volume with appropriate amount of the vehicle (corn oil) and the mixture was kept homogenous by stirring on a magnetic stirrer during dosing. Dosing solutions were prepared fresh weekly and stored at room temperature between use.
3.3.7	Total volume applied	All groups received a dosing volume of 5 mL/kg body weight and the dose volumes were based on the most recent body weights except for the day 15 dose which was actually based on the day 12 body weight.
3.3.8	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Body weight	Yes (Body weights were obtained on days 0, 6, 9, 12, 15, and 20 of gestation.)
3.4.2	Food consumption	Yes (Food and water consumption were measured during days 6-9, 9-12, 12-15, 15-18, and 18-20 of gestation.)
3.4.3	Clinical signs	Yes (Animals were observed daily for clinical signs of toxicity.)
3.4.4	Examination of uterine content	The uterus was removed from the body, examined externally, weighed and then opened for internal examination. The following uterine parameters were examined/recorded: corpora lutea, number/placement of implantation sites, early/late resorptions and live/dead fetuses.
3.4.5	Examination of foetuses	
3.4.5.1	General	Each fetus was removed from the uterus and individually weighed and observed for gross external alterations. Approximately one-third of all fetuses from each litter was selected and processed for visceral examination by the Wilson Technique for soft-tissue alterations. The remaining fetuses were opened by longitudinal incision and the viscera were examined grossly; these fetuses were then eviscerated, stained with Alizarin red-S, and examined for skeletal alterations.
3.4.5.2	Skelet	Yes
3.4.5.3	Soft tissue	Yes
3.5	**Further remarks**	Gross pathologic alterations were recorded at termination.

Section A6.8.1.1 **Teratogenicity Study (rat)**

Annex Point IIA6.8.1

		4 RESULTS AND DISCUSSION	
4.1	**Maternal toxic effects**	No mortality, abortions, or premature deaths occurred during the study. No treatment-related clinical signs of toxicity were seen. No adverse effects were seen in body weight parameters. Mean body weight gains are presented in Table 1. Mean food and water consumption values of the treated group were similar to that of the vehicle control. No treatment-related macroscopical changes were observed in the dams sacrificed at termination.	X
4.2	**Teratogenic / embryotoxic effects**	Reproduction/fetal data are presented in Table 2. No biologically or statistically significant effects were seen on pregnancy rate, number of corpora lutea, number of implantations, total live fetuses per litter, resorption rate, number and percent of litters with resorption, fetal sex ratio, or fetal body weights. Fetal external, visceral and skeletal variations are presented in Table 3. Fetal external and visceral malformations are presented in Table 4; no skeletal malformations were seen. No treatment-related or statistically significant external, visceral or skeletal variations or malformations were seen in any of the fetuses.	
4.3	**Other effects**	----	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	EPA FIFRA Guideline § 152-23	
5.2	**Results and discussion**	In pregnant rats given oral administration of Pelargonic Acid during days 6 through 15 of gestation there were no mortality, abortions, or premature deliveries. Treatment had no adverse effect on clinical signs, body weights, body weight gain, or food/water consumption. Pelargonic Acid did not cause any fetal toxicity; the mean numbers of viable fetuses, 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; Pelargonic Acid did not increase the external, visceral, or skeletal malformations or variations in any of the fetuses. There were no distinct differences in the types or frequency of the findings seen between the control and treated group.	
5.3	**Conclusion**	Pelargonic Acid was not shown to be either a maternal or a developmental toxin at a dose of 1500 mg/kg bw/day.	
5.3.1	LO(A)EL maternal toxic effects	> 1500 mg/kg bw/day	
5.3.2	NO(A)EL maternal toxic effects	1500 mg/kg bw/day (higher than the limit dose)	
5.3.3	LO(A)EL embryotoxic / teratogenic effects	> 1500 mg/kg bw/day	
5.3.4	NO(A)EL embryotoxic / teratogenic effects	1500 mg/kg bw/day (higher than the limit dose)	
5.3.5	Reliability	2	
5.3.6	Deficiencies	No	

Evaluation by Competent Authorities

	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Materials and Methods	**1.2.1. Data owner** Mycogen Corporation Dow Agrosciences LLC Data Compensation Department 9330 Zionsville Road IN 46268-1054 Indianapolis US **1.2.2. Companies with letter of access** The applicant (W. Neudorff GmbH KG **2.1. Guideline Study** The study is in line with the OECD guideline No 414 with the exception that the exposure was carried out only for the period of organogenesis (day 6 to 15) instead of for the entire period of gestation and the the limit test was carried out at 1500 mg/kg bw day, instead of 1000 mg/kg bw day.
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version
Reliability	2: original study was carried out in 1982 with 10 compounds; the submitted study report represents a re-evaluation -also with regard to GLP compliance- and compilation of the data for nonanoic acid amended by a stability analysis. The writing of this new report and the stability test was carried out under GLP conditions, protocol and GLP deviations of the original study were evaluated and found to be minor. No analytic data confirming the assumed 100% purity of the substance are available.
Acceptability	acceptable
Remarks	**4.1. Maternal toxic effects** It might be relevant for risk assessment that at 1500 mg/kg bw day no gross pathological effects were found in the thoracic, abdominal and pelvic viscera, though in the 28 day oral study an irregular surface of the forstomach was noted in all high dose animals (1000 mg/kg bw day). In both studies the substance was applied by gavage.

Table A6_8-1 **Table 1: Body weight changes**

	Mean body weight gain (G)						
Dose mg/kg/day	*Days 0-6*	*Days 6-9*	*Days 9-12*	*Days 12-15*	*Days 6-15 (Dosing period)*	*Days 15-20 (Post-dosing)*	*Days 0-20 (Entire Study)*
0	20	5	9	11	25	60	105
1500	14	8	8	12	28	58	100

Table A6_8-1 **Table 2: Cesarean section observations**

Observations (Mean ± S.D.)	*Dose Level (mg/kg/day)*	
	0	*1500*
No. assigned	22	22
Females gravid	22	20
Died animals	0	0
Sacrificed animals	0	0
Aborted animals	0	0
Early delivery	0	0
Non pregnant animals	0	0
Total corpora lutea	349	295
Corpora lutea/dam	16 ± 2	15 ± 3
Total implantations	298	253
Implantation/dam	14 ± 2	13 ± 2
Total live fetuses	272	243
Live fetuses/litter	12 ± 3	12 ± 3
Total resorptions	26	10
Early resorptions	26	10
Late resorptions	0	0
Resorption/dam	1.2 ± 1.4	0.5 ± 0.8
Dead fetuses	0	0
Pre-implantation loss (%)	14.3 ± 9.2	13.0 ± 11.4
Post-implantation loss (%)	9.2 ± 11.2	4.6 ± 8.1
Gravid uterus weight (g)	69 ± 14	67 ± 15
Sex ratio male/female	53/47	52/48
Crown-rump length (cm)	3.76 ± 0.13	3.67 ± 0.27
Crown-rump length of males	3.80	3.74
Crown-rump length of females	3.71	3.60
Fetal weight	3.50 ± 0.21	3.44 ± 0.45

Table A6_8-1 **Table 3: Summary of fetal external, visceral and skeletal variations**

Observations	*Fetuses*		*Litters*	
	0	*1500*	*0*	*1500*
No. Examined Externally	272	243	22	20
Small fetus	1	0	1	0
Hydroureter(s)	1	1	1	1
Undulated ureter(s)	2	1	2	1
Dilated ureter(s)	16	10	8	7
Hindlimb appears oddly positioned	0	1	0	1
No. Examined Viscerally	81	73	22	20
Small fetus	0	2	0	1
Increased renal pelvic caviation	2	2	0	0
No. Examined Skeletally	191	170	22	20
Incomplete ossification of skull	26	29	10	13
Incomplete/nonossified hyoid body	25	24	9	9
Supraoccipital nonfused	0	1	0	1
Incomplete/unossified thoracic centrum	32	18	16	10
Bipartite thoracic centrum	11	11	8	6
Less than three caudal vertebrae ossified	0	4	0	2
Thoracic centrum missing	0	3	0	1
Lumbar centrum missing	0	3	0	1
Sacral arches and centra unossified	0	3	0	1
Sternebra(e) bipartite	1	0	1	0
Less than three sternbrae ossified	0	4	0	1
Wavy/bent ribs	2	3	2	1
13th rudimentary rib(s)	1	0	1	0
14th rudimentary rib(s)	1	2	1	2
Unossified pubis	1	4	1	2
Unossifies ischium	0	3	0	1
Incomplete ossification of pubis	0	1	0	1

Table A6_8-1 **Table 4: Summary of fetal external, visceral and skeletal malformations**

Observations	*Fetuses*		*Litters*	
	0	*1500*	*0*	*1500*
No. Examined Externally	272	243	22	20
Situs inversus	1	0	1	0
Cleft palate	0	4	0	1
Umbilical hernia	1	0	1	0
Total external malformations	**2** **0.7%**	**4** **1.6%**	**2** **9.1%**	**1** **5.0%**
No. Examined Viscerally	81	73	22	20
Cleft palate	0	2	0	1
Total visceral malformations	**0**	**2** **2.7%**	**0**	**1** **5.0%**
No. Examined Skeletally	191	170	22	20
Total skeletal malformations	**0**	**0**	**0**	**0**

Section 6.8.1.2
Annex Point IIA6.8.1.2

Teratogenicity (rabbit)

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	No study was considered necessary due to the maternal and developmental non-toxicity of Pelargonic Acid in the rat (see point 6.8.1.1).	
Undertaking of intended data submission [ ]	----	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant's version. A teratology screening test in rats is available (see document III A 6.8.1.1) See also the justification for non-submission document III A 6.4, 6.5. and 6.7.
Conclusion	The justification for non submission is acceptable taking into consideration also the arguments provided in document III A 6.5 and 6.7.
Remarks	

Section A6.8.2 Multigeneration Reproduction Toxicity Study
Annex Point IIA6.8.2 **Oral, rat**

Official use only

		1 REFERENCE
1.1	**Reference**	Harkins, R.W. & Sarett, H.P. (1968); nutritional evaluation of medium-chain triglyceride in the rat; The Journal of the American oil chemists' society, 1968, Vol. 45; page 26-30; No A6.4.1.1.b/01 and A6.8/01.
1.2	**Data protection**	No
1.2.1	Data owner	published
1.2.2	Companies with letter of access	none
1.2.3	Criteria for data protection	Data on existing a.s. submitted for the first time for entry into Annex I.
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No
2.2	**GLP**	No
2.3	**Deviations**	-
		3 MATERIALS AND METHODS
Test material		Medium-chain triglycerides (MCT) containing 51% octanoic acid (C8:0) **35% decanoic acid (C10:0)** 2% (C12:0) 0.9% (16:0)
3.1.1	Lot/Batch number	Not reported
3.1.2	Specification	A detailed analysis of all use materials is reported.
3.1.2.1	Description	Source and nature of the material are described in sufficient detail.
3.1.2.2	Purity	
3.1.2.3	Stability	Not reported
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	McCollum-Wisconsin
3.2.3	Source	Not reported
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	P: young adults (not further specified)
3.2.6	Number of animals per group	Not reported
3.2.7	Mating	P: 3 weeks after treatment started F1: 15 weeks of age
3.2.8	Duration of mating	Not reported
3.2.9	Deviations from standard protocol	-

Section A6.8.2 Annex Point IIA6.8.2		Multigeneration Reproduction Toxicity Study Oral, rat	
3.2.10	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Animal assignment to dosage groups	Not reported	
3.3.2	Duration of exposure before mating	P:3 weeks	
3.3.3	Duration of exposure in general P, F1, F2 males, females	P: exposure during pregnancy and lactation F1: after weaning rats were raised on same diets as fed to their mother At 12 weeks of age each F1 group was divided into 3 subgroups. One subgroup was continued on the same diet whereas the two other subgroups were switched to the diets containing one of the other two fats. After 3weeks the F1 females were mated. F2: after weaning rats were raised on same diets as fed to their mother Oral	
3.3.4	Type	in food	
3.3.5	Concentration	40% of the calories in food from or MCT (active ingredient) plus 2.5% safflower oil to supplement with essential fatty acids 38%of the calories in the food from carbohydrate 22% of the calories in food from protein mineral and vitamin mixture	X
3.3.6	Vehicle	-	
3.3.7	Concentration in vehicle	-	
3.3.8	Total volume applied	-	
3.3.9	Controls	Control-group 1: containing 40% of the calories in food from oleo oil otherwise as treatment group Control-group 2: low-fat diet containing 2.5% safflower oil otherwise as treatment group	X
3.4	**Examinations**		
3.4.1	Clinical signs	No effects reported	X
3.4.2	Body weight	Recorded after 4, 8, 47 weeks of treatment	X
3.4.3	Food/water consumption	7 days per week, ad libitum Food intake was recorded.	
3.4.4	Oestrus cycle	Not reported	
3.4.5	Sperm parameters	Not reported	
3.4.6	Offspring	number of pups, live births, birth weight and weight gain	
3.4.7	Organ weights P and F1	Not reported	
3.4.8	Histopathology P and F1	Not reported	
3.4.9	Histopathology F1 not selected for mating, F2		

Section A6.8.2 Annex Point IIA6.8.2		Multigeneration Reproduction Toxicity Study Oral, rat	
3.5	**Further remarks**	Volume of milk secretion in P analysis of fatty acids in milk of P	
		4 RESULTS AND DISCUSSION	
4.1	**Effects**		
4.1.1	Parent males	No effects	
4.1.2	Parent females	Milk secretion showed no difference in mothers because of the diets. Although 85% of the dietary fatty acids were C_8 and C_{10} in the MCT group, these constituted only 24% of the milk fat fatty acids. In contrast the fatty acids in the milk secreted by the oleo acid group were similar to those contained in the dietary fat. Level of fat in milk of animals received MCT was slightly lower with more medium chain fatty acids (C_8 and C_{10}) than in rats receiving oleo oil.	
4.1.3	F1 males	Findings in average birth weight and number of pubs per litter were similar in all 3 diets Wight gain during weaning was lower on the low fat diet than on the MCT or oleo oil diet. Mortality during lactation period was 6% (MCT), 7% (oleo oil) and 2% (low fat diet) respectively	
4.1.4	F1 females	Findings in average birth weight and number of pubs per litter were similar in all 3 diets Mortality during lactation period was 6% (MCT), 7% (oleo oil) and 2% (low fat diet) respectively Milk secretion in F1 mothers was low when fed on MCT diet for 2 generations.	
4.1.5	F2 males	Number of pubs per litter and birth weights were similar for all subgroups Highest weight gain at weaning (21 days) were found in the groups on the oleo oil diet except for the slightly low value in that group which had previously received the low-fat diet. Intermediate weaning weights were found in the groups receiving the MCT diet, and lowest weaning weights were found in groups receiving the low-fat diet. Mortality in groups receiving MCT was 22% for subgroup previously on MCT, 20% for subgroup previously on low-fat diet and 6% for subgroup previously on oleo oil diet. Mortality was 7% or less on other 6 subgroups. No difference in subsequent growth of all animals shown.	X
4.1.6	F2 females	Number of pubs per litter and birth weights were similar for all subgroups Highest weight gain at weaning (21 days) were found in the groups on the oleo oil diet except for the slightly low value in that group which had previously received the low-fat diet. Intermediate weaning weights were found in the groups receiving the MCT diet, and lowest weaning weights were found in groups receiving the low-fat diet. Mortality in groups receiving MCT was 22% for subgroup previously on MCT, 20% for subgroup previously on low-fat diet and 6% for subgroup previously on oleo oil diet. Mortality was 7% or less on other 6 subgroups. No difference in subsequent growth of all animals shown.	X
4.2	**Other**	-	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	non-guideline study, groups of male and female rats were fed with MCT or other fat diets started 3 weeks before mating. F1 was fed with diet of mothers after weaning. At 12 weeks of age each F1 group was divided into 3	

Section A6.8.2 Annex Point IIA6.8.2		Multigeneration Reproduction Toxicity Study Oral, rat	
		subgroups. One subgroup was continued on the same diet whereas the two other subgroups were switched to the diets containing one of the other two fats. After 3weeks the F1 females were mated. Number of pups, live births, birth weight, mortality during lactation and weight gain was recorded. Also volume of milk secretion (P and F1 mothers) and analysis of fatty acids in milk of P mothers were examined.	
5.2	**Results and discussion**	. Feeding of MCT in 1st generation does not implicate any adverse effects either in fertility of the parents or in health of the pubs. Feeding MCT in high concentrations over 2 generations resulted in low milk secretion in F1 mothers which suggested that this factor may have affected weight gain and mortality of the pubs. Still lowest weaning weights in pubs were found in groups receiving the low-fat diet which indicates that reasonable fat content in the diet is required for a healthy pub development. This indicates that mortality and low weight gain in pubs of MCT-fed mothers (F1) is not the result of an adverse effect to MCT but rather results in the lack of high chain fatty acids (partly essential fatty acids) which are difficult or not possible to be synthesised by the body.	
5.3	**Conclusion**	Decanoic acid (35 % in MCT) did not show any adverse effects either in fertility of the parents or in health of the pubs under the described conditions. The described effects in F1 mothers and their pubs are rather caused by the lack of high chain fatty acids which partly have to be supplied with the food especially in lactation animals to enrich the milk sufficiently since the body is not able to synthesise them in decent amount. Therefore the effects in the pubs are caused by deficiency disease rather than by excessive MCT supply followed by adverse effects.	
5.3.1	LO(A)EL		
5.3.1.1	Parent males	n.a.	
5.3.1.2	Parent females	n.a.	
5.3.1.3	F1 males	n.a.	
5.3.1.4	F1 females, F2 male, female	n.a.	
5.3.2	NO(A)EL		
5.3.2.1	Parent males, females F1 males, females F2 males, females	NOAEL decanoic acid ≥ 5.1 g/kg bw/day	X
5.3.3	Reliability	2 This study was performed not according to a guideline study for regulatory purposes. Nevertheless the goal of the study to evaluate the nutritional properties of medium-chain triglycerides (MCT) including any effects on the normal growth or development of offspring make this study suitable to judge the possible effects of decanoic acid during a multigeneration exposure.	
		Decanoic acid occurs is nature and is part of the human diet, it occurs as free acid in 147 individual food items (Gubler 2006; IIC/02) and as triglyceride, which is completely absorbed after ingestion and metabolised (see DOC IIA)to free decanoic acid in the liver. In practice, human intake from both sources has to be considered as systemic. In the next paragraphs the consumption is discussed in some detail.	X

Section A6.8.2 Multigeneration Reproduction Toxicity Study

Annex Point IIA6.8.2 **Oral, rat**

Human dietary intake of decanoic acid is much higher from fat consumption. Spychinger (2003; IIB/02) reports that the average consumption of coconut oil in Germany is 1 kg per person. Based on analytical data from the German organisation DGF (Deutsche Gesellschaft für Fettwissenschaft; IIB/03) coconut fat contains between 5.0 – 8.0 % decanoic acid; taking an average of 6.5 % this translates to an average daily consumption of 178 mg/day per person.

5.3.4 Deficiencies -

	Evaluation by Competent Authorities
Date	June 2009
Materials and Methods	**3.3.5 Concentration and 3.3.9 Controls** See table from publication below. The publication does not indicate the uptake of MCT in terms of g/kg bw day, it does not indicate food consumption, weight of the animals or age. Therefore uptake of decanoic acid and octanoic acid in terms of g/kg bw day can only be estimated based on default assumptions. The diet contains 18.5% MCT, 35% of MCT is decanoic acid and 51% of MCT is octanoic acid (tables 1 and 4 in publication). Assuming a default food conversion factor between 0.1 and 0.05 (see e.g. Leeuwen et Vermeire 2007, p 342) the sum of decanoic acid and octanoic acid exposure via the diet results between 8 and 16 g/kg bw day. **3.4.1. Clinical signs** Mortalities were reported **3.4.2. Body weight gain** was recorded at 4, 8, 47 weeks within the growth studies reported in the publication was recorded for F1 and F2 generation at day of birth, then on days 6, 12,18,21,29, 63, 105
Results and discussion	**4.1.5 and 4.1.6 - F2 males and females** Determination of the amount of milk secreted by the mothers of each subgroup suggested that this factor may have affected weight gain and mortality.
Conclusion	Neither Decanoic acid nor Octanoic acid show adverse reproductive toxic effects in this study. NO(A)EL ≥ 8 g/kg bw day based on the sum of Octanoic acid and Decanoic acid doses for a common NOAEL (read across, see point 3.3.5 above).
Reliability	2 (agree with applicant – sufficient for evaluation within a weight of evidence evaluation) The estimates for human exposure to Decanoic and Octanoic acid as natural food content are summarized in Doc II-A 3.1
Acceptability	Acceptable within a weight of evidence evaluation
Remarks	The study summary was submitted by the Fatty acid consortium for Octanoic acid and Decanoic acid. Since the reported study is public literature the RMS added this study summary to the CAR for Nonanoic acid.

Table A6_8_2-1. Fatty acid composition obtained from lactating rats receiving MCT or oleo oil-containing diet

	Milk fat [%]	Fatty acids **[%]** in milk fat / fatty acid no. of carbon atoms											
		8	10	12	14	16	18	16:1	18:1	18:2	18:3	20:4	other
MCT	8.2	6.5	16.8	10.3	11.5	29.9	4.7	0.9	11.7	6.5	0.3	0.3	0.4
Oleo oil	9.8	2.2	5.8	4.4	6.6	20.8	9.4	2.4	86.7	8.0	0.9	0.4	2.8

Composition of diet and dietary fat:

Table I of publication:

Composition of Diets

	Diet 1–6 40% Fat calories	Diet 7 Low fat
	%	%
Fat[a]	21.0	2.5
Casein (ANRC 91.4% protein)	26.2	26.2
Amidex[b]	44.5	63.0
Nonnutritrive fiber	4.0	4.0
Mineral mixture[c]	4.0	4.0
Vitamin mixture[d]	0.35	0.35

Table IV of publication:

	Fatty acids, %											
	C_8	C_{10}	C_{12}	C_{14}	C_{16}	$C_{16:1}$	C_{18}	$C_{18:1}$	$C_{18:2}$	$C_{18:3}$	$C_{20:4}$	Other
Dietary Fat												
MCT[a]	51.0	35.0	2.0		0.9			1.4	9.0			0.7
Oleo oil[a]				2.9	22.1	4.8	13.4	43.2	12.5			1.1
Butter fat[a]	1.9	3.3	2.9	8.1	22.8	3.8	10.5	23.3	13.3			10.1
Coconut oil[a]	8.1	7.2	36.8	17.2	10.0		2.4	7.2	11.0			0.1
Corn oil					13.4		1.4	26.2	57.8			1.2
Safflower oil					6.7		1.9	10.0	80.8	0.2		0.4

Table VIII of publication

TABLE VIII

Birth Weight and Body Weights of Rats Born and Nursed by Mothers Receiving MCT, Oleo Oil, and Low-Fat Diets

Dietary fat[a]		Pups per litter	Day: Birth	Day: 6	Day: 12	Day: 18	Day: 21	Day: 49	Day: 63	Day: 105
			Male and Female				Male			
			Weight, g per rat				Weight, g per rat			
F_1 Generation										
MCT		9.0	6.4	13	21	34	45	181		309
Oleo oil		9.1	6.1	14	24	34	47	186		326
Low fat		9.6	6.4	13	22	29	39	165		286
F_2 Generation										
MCT	MCT	9.2	6.5	12	23	35	45		261	
Oleo oil	MCT	7.0	6.7	12	23	36	45		242	
Low fat	MCT	9.4	6.6	12	23	36	43		243	
MCT	Oleo oil	9.4	6.8	13	25	39	49		249	
Oleo oil	Oleo oil	9.2	6.3	12	24	39	47		244	
Low fat	Oleo oil	10.5	6.0	11	23	35	43		248	
MCT	Low fat	10.8	6.2	11	21	31	36		244	
Oleo oil	Low fat	8.8	6.4	12	25	36	39		245	
Low fat	Low fat	9.3	6.5	12	23	32	38		243	

[a] All diets contained 2.5% safflower oil.

Table IX of publication

TABLE IX

Milk Secreted by F_0 and F_1 Generation Lactating Rats Receiving MCT, Oleo Oil, and Low-Fat Diets[a]

Dietary fat[b]		Day 3	6	9	12	15	18	21	Total
		g milk							
F_0 Generation									
MCT		3.3	4.7	5.0	5.5	7.1	7.3	7.3	40.2
Oleo oil		4.3	6.5	4.5	5.3	6.5	6.0	6.0	41.2
Low fat		4.5	5.6	6.3	6.2	5.4	6.7	8.4	43.1
F_1 Generation									
MCT	MCT	1.7	0.8	4.0	2.3	4.0	5.2	6.3	24.3
Oleo oil	MCT	1.3	2.0	2.8	4.3	6.2	9.0	8.8	34.4
Low fat	MCT	2.4	3.9	5.0	5.0	6.7	8.7	5.5	37.2
MCT	Oleo oil	2.2	3.6	6.2	7.0	6.6	10.2	9.2	45.0
Oleo oil	Oleo oil	1.5	2.2	4.8	5.8	6.3	10.8	9.8	41.2
Low fat	Oleo oil	2.2	4.8	7.5	8.7	8.3	8.3	10.0	49.8
MCT	Low fat	1.8	6.5	5.3	4.0	7.5	11.2	10.0	46.3
Oleo oil	Low fat	2.0	4.2	5.2	4.4	7.6	9.6	8.0	41.0
Low fat	Low fat	1.6	3.9	4.4	5.3	6.6	7.7	9.1	38.6

[a] Milk secretion was estimated as the increase in weight of each litter during a one-hour lactation period; the mother was removed from the litter for six hours beforehand.
[b] All diets contained 2.5% safflower oil.

Section 6.8.2
Annex Point IIA6.8.2

Multigeneration reproduction toxicity study

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	No study was considered necessary due to the maternal and developmental non-toxicity of Pelargonic Acid in the rat (see point 6.8.1.1).	
Undertaking of intended data submission [ ]	----	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant's version. A teratology screening test in rats is available (see document III A 6.8.1.1) See also the justification for non-submission document III A 6.4, 6.5. and 6.7.
Conclusion	The justification for non submission is acceptable taking into consideration also the arguments provided in document III A 6.5 and 6.7.
Remarks	

Section 6.15.x **Annex Point** **IIA6.15.1/2/3/4/5/6**	**Food and feedingstuffs**

		Official use only
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	As the active substance Pelargonic Acid is not used in preparations for use where food for human consumption is prepared, consumed or stored, or where feedingstuff for livestock is prepared, consumed or stored, the tests and results in accordance with paragraphs A6.15.1-6.15.5 are not required.	
Undertaking of intended data submission [ ]	----	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	September 2007
Evaluation of applicant's justification	Agree with applicant's version.
Conclusion	The justification is acceptable.
Remarks	