BPC-43-2022-08B

REGULATION (EU) NO 528/2012 CONCERNING THE MAKING AVAILABLE ON THE MARKET AND USE OF BIOCIDAL PRODUCTS

Assessment of ACTIVE SUBSTANCES

ASSESSMENT REPORT

FORMIC ACID

Product type 5
"Drinking water"

EC Number : 200-579-1

CAS Number : 64-18-6

Applicant : Formic Acid Task Force (BASF SE, Kemira Oyj)

Contact details of evaluating CA : BELGIUM

Date : 15/10/2022

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1 STATEMENT OF SUBJECT MATTER AND PURPOSE

This assessment report has been established as a result of the evaluation of the active substance **FORMIC ACID** in PT 5 "*Drinking Water*", carried out in the context of the working programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

In accordance with the provisions of Article 7(1) of Commission Regulation (EC) No 1451/2007, Belgium was designated as Evaluator Member State to carry out the assessment on the basis of the submitted dossier.

FORMIC ACID (CAS N° 64-18-6) was notified as an existing active substance by BASF SE and KEMIRA OYJ. This notification was intended to encompass both FORMIC ACID/FA and PERFORMIC ACID/PFA *in situ*-generated (from formic acid and hydrogen peroxide) in which FA was considered the active substance and PFA the representative product.
- In the period 2007 to 2009, the BE eCA received the dossier and numerous updates from the two applicants (BASF SE and Kemira Oyj).
- In March 2015, it was decided according to the CA-March15-Doc.5.1 that the original review programme entry (37) for Formic Acid was to be split in two separate entries for Formic Acid and Performic Acid (generated from formic acid and hydrogen peroxide).
Subsequently, a resubmission of the dossier was necessary, since the original dossier consisted of a tightly interwoven dossier between the now two distinct substances.

In September 2015, a new dossier for Formic Acid was submitted by both applicants, who had now started working together in a Formic Acid Task Force (BASF SE, Kemira Oyj), following numerous updates in the periods 2015 to 2021.

On November 21st 2016 the BE eCA submitted a CLH dossier to ECHA. ECHA provided their accordance check on the CLH report on February 9th 2017, concluding that revisions and clarifications were required.

Before submitting the CAR to ECHA, the applicants were given the opportunity to provide written comments in line with Article 8(1) of Regulation (EU) No 528/2012.

On September 15st 2021, the BE eCA submitted to ECHA a copy of the assessment report containing the conclusions of the assessment, hereafter referred to as the competent authority report (CAR).
By the time of submitting this new CAR, according to the biocides Review Program Regulation/Biocides working procedure, a revised CLH report (addressing hazard classes that should be included to the already existing C&L) is duly submitted.

After ECHA Accordance Check, a peer-review by technical experts from all Member States of the draft CAR is organised by ECHA. The CAR is presented at the Biocidal Products Committee (and its Working Groups meetings) and thereafter amended according to the revisions agreed upon the comments received.

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of **Formic Acid** for PT 5 and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of the assessment report, which is available from the web-site of ECHA shall be taken into account.

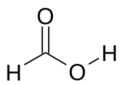
However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

2 ASSESSMENT REPORT

SUMMARY

1 PRESENTATION OF THE ACTIVE SUBSTANCE

1.1 IDENTITY OF THE ACTIVE SUBSTANCE

Main constituent(s)	
ISO name	Formic Acid
IUPAC or EC name	Methanoic Acid
EC number	200-579-1
CAS number	64-18-6
Index number in Annex VI of CLP	607-001-00-0
Minimum purity / content	Min. 99% w/w
Structural formula	

Relevant impurities and additives		
IUPAC name or chemical name or EC name	**Maximum concentration in % (w/w)**	**Index number in Annex VI of CLP**
n.a.	n.a.	n.a.

1.2 INTENDED USES AND EFFECTIVENESS

Use of the active substance	
Product type	**PT2** "Disinfectants and algaecides not intended for direct application to humans or animals" **PT3** "Veterinary hygiene" **PT4** "Food and feed area" **PT5** "Drinking water" **PT6** "Preservatives for products during storage"
Intended use pattern(s)	Formic Acid-based Biocidal products are intended to be used for : – Disinfection of industrial and institutional premises and machinery, kitchen and bathroom surfaces, toilets and sanitary ware in the domestic and institutional environment,

	– Disinfection of waters including bathing and other waters, waste water, and drinking water for both humans and animals. – Disinfection of areas in which animals are housed, kept and transported. – Disinfection of working areas and production surfaces including food preparation and consumption areas. – Preservation of industrial, consumer, household and institutional products.
Users	Industrial, professional and general public - depending on the product.

Effectiveness of the active substance	
Function	Disinfectant Preservative
Organisms to be controlled	To kill microorganisms in general : bacteria (including spore-forming bacteria), yeasts, fungi and viruses
Limitation of efficacy including resistance	– Avoid formulating with, or combining with, ingredients with a strongly alkali pH value : The antimicrobial effectiveness of Formic Acid-based Biocidal products is reduced with increasing system pH and users should take this into account, particularly at pH above 4.5. – Resistance against the mode of action is unlikely to occur, i.e. there is no adaptation to cope with acidic pH values or denaturated proteins, nor is there a mechanism known to exist that a sub-lethal energy supply, due to an incomplete cytochrome C oxidase inhibition, would lead to undesired side-effects or resistance against this inhibitor. – To prevent potential development of resistance or tolerance the use of sub-lethal dosing levels should be avoided. No incidence of resistance to formic acid has been recorded until now.
Mode of action	Two different modes of action are reasonably considered to contribute to the biocidal activity, i.e. acidulant action and corrosion which causes enzyme denaturation and inhibition, cellular structure disruption, and impairment of cellular metabolic pathways. This mode of action is considered to depend on the low pH-value. Secondly, formic acid does inhibit cytochrome C oxidase and thus impairs cellular energy supply. Organisms and tissues with a high energy demand are specifically susceptible.

1.3 CLASSIFICATION AND LABELLING

1.3.1 Classification and labelling for the active substance

Hazard class/ property	Proposed classification
Physical hazards	
Explosives	The active substance is not an explosive
Flammable gases	Not applicable as the active substance is a liquid
Flammable aerosols	Not applicable as the active substance is a liquid
Oxidising gases	Not applicable as the active substance is a liquid
Gases under pressure	Not applicable as the active substance is a liquid
Flammable liquids	Classified as Flam liquid 3 due to the flash point being under 60°C (49°C)
Flammable solids	Not applicable as the active substance is a liquid
Self-reactive substances	The substance is not self-reactive.
Pyrophoric liquids	Not pyrophoric liquid based on auto-ignition temperature and experience in manufacture and handling.
Pyrophoric solids	Not applicable as the active substance is a liquid
Self-heating substances and mixtures	Not applicable
Substances which in contact with water emit flammable gases	Not applicable since formic acid can be diluted in water
Oxidising liquids	Not applicable. Formic acid contains oxygen but is chemically bonded only to carbon and hydrogen.
Oxidising solids	Not applicable as the active substance is a liquid
Organic peroxides	Not applicable as formic acid is not an organic peroxides as it does not contain the bivalent -O-O structure.

Corrosive to metals	Corrosive to steel. Not corrosive to aluminium.
Human health hazards	
Acute toxicity via oral route	Acute Tox. 4, H302 Harmful if swallowed
Acute toxicity via dermal route	Data lacking
Acute toxicity via inhalation route	Acute Tox. 3, H331 Toxic if inhaled EUH071
Skin corrosion/irritation	Skin Corr. 1A, H314
Serious eye damage/eye irritation	Eye Dam. 1, H318 Causes serious eye damage
Respiratory sensitisation	Conclusive but not sufficient for classification
Skin sensitisation	Conclusive but not sufficient for classification
Germ cell mutagenicity	Conclusive but not sufficient for classification
Carcinogenicity	Conclusive but not sufficient for classification
Reproductive toxicity	Conclusive but not sufficient for classification
Specific target organ toxicity-single exposure	Conclusive but not sufficient for classification
Specific target organ toxicity-repeated exposure	Conclusive but not sufficient for classification
Aspiration hazard	Conclusive but not sufficient for classification
Environmental hazards	
Hazardous to the aquatic environment	Conclusive but not sufficient for classification
Hazardous to the ozone layer	Hazard class not assessed

1.3.1.1 *CURRENT CLASSIFICATION AND LABELLING*

Current Classification and Labelling according to Regulation (EC) No 1272/2008							
Classification		**Labelling**					
Hazard Class and Category	**Hazard statements**	**Pictograms**	**Signal word**	**Hazard statements**	**Suppl. Hazard statements**	**Precautionary statements**	**SCLs and M-factors**
Skin Corr. 1A	H314	GHS05	danger	H314	-	(-)	Skin Corr. 1B; H314: 10% ≤ C < 90% Skin Corr. 1A; H314: C ≥ 90% Skin Irrit. 2; H315: 2% ≤ C < 10% Eye Irrit. 2; H319: 2% ≤ C < 10%

1.3.1.2 *PROPOSED CLASSIFICATION AND LABELLING*

Proposed Classification and Labelling according to Regulation (EC) No 1272/2008							
Classification		**Labelling**					
Hazard Class and Category	**Hazard statements**	**Pictograms**	**Signal word**	**Hazard statements**	**Suppl. Hazard statements**	**Precautionary statements**	**SCLs and M-factors**
Corrosive to metal	H290 - May be corrosive to metals	GHS05	warning	May be corrosive to metals	-	P234 P390 P406	-

Flammable liquid – category 3	H226 - Flammable liquid and vapour	GHS02	Warning	Flammable liquid and vapour		P210 P233 P240 P242 P243 P280 P303+P361+P353 P403+P235 P501	
Acute tox. 4 (oral)	H302	GHS07	warning	H302	-	Prevention P264, P270 Disposal P501	
Acute tox. 3 (Inhalation – vapour)	H331	GHS06	danger	H331	EUH071	Prevention P261, P271 Response P304+P340, P311 Storage P403+P233, P405 Disposal P501	
Skin Corr. 1A	H314	GHS05	danger	H314	-	Prevention P280, P260, P264 Response P310, P305+P351+P338, P304+P340, P303+P361+P353, P301+P330+P331, Storage P405 Disposal P501	Skin Corr. 1B; H314: 10% ≤ C < 90% Skin Corr. 1A; H314: C ≥ 90% Skin Irrit. 2; H315: 2% ≤ C < 10%

Eye dam./Irrit. 1	H318	-	-	-	-	Prevention H280 Response P310, P305+P351+P338	Eye dam./Irrit. 1; H318: C ≥ 10% Eye Irrit. 2; H319: 2% ≤ C < 10%

1.3.2 Classification and labelling for the representative product(s)

1.3.2.1 *PROPOSED CLASSIFICATION AND LABELLING*

Proposed Classification and Labelling according to Regulation (EC) No 1272/2008							
FENNOPUR® MH 85							
Classification		**Labelling**					
Hazard Class and Category	**Hazard statements**	**Pictograms**	**Signal word**	**Hazard statements**	**Suppl. Hazard statements**	**Precautionary statements**	**SCLs and M-factors**
Corrosive to metal	H290 - May be corrosive to metals	GHS05	warning	May be corrosive to metals	-	P234 P390 P406	-
Acute tox. 4 (oral)	H302	GHS07	warning	H302	-	Prevention P264, P270 Disposal P501	
Acute tox. 3 (Inhalation – vapour)	H331	GHS06	danger	H331	EUH071	Prevention P261, P271 Response P304+P340, P311 Storage P405 P403+P233 Disposal P501	

Skin Corr. 1B	H314	GHS05	danger	H314	-	Prevention P280, P260, P264 Response P310, P305+P351+P338, P304+P340, P303+P361+P353, P301+P330+P331, Storage P405 Disposal P501	Skin Corr. 1B; H314 if 10% ≤ C < 90%
Eye dam./Irrit. 1	H318	-	-	-	-	Prevention P280 Response P310, P305+P351+P338	Eye dam./Irrit. 1; H318: C ≥ 10%

1.3.2.2 *PACKAGING OF THE BIOCIDAL PRODUCT*

FENNOPUR® MH 85					
Type of packaging	**Size/volume of the packaging**	**Material of the packaging**	**Type and material of closure(s)**	**Intended user (e.g. professional, non-professional)**	**Compatibility of the product with the proposed packaging materials (Yes/No)**
IBC; Drum, Sample bottles	1050 L(IBC), 220 L (Drums) 1L (bottles)	PE (outer container corrosion resistant steel) or brown glass (bottles)	PE	professional	yes

2 SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT

2.1 SUMMARY OF THE ASSESMENT OF EFFECTS ON HUMAN HEALTH

Introductory note:	
The repeated dose toxicity via the oral route of formic acid is assessed with its non-corrosive salts, sodium formate and potassium diformate, in order to achieve sufficiently high dose levels. Neurotoxicity is assessed with methanol. This read across approach is in accordance with Article 6(3) of the EU No. 528/2012 (BPR) following point 1.5(2) under Annex IV: "*common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals and indicates the presence of dangerous properties*". The full read-across justification, which was performed following the Read-Across Assessment Framework developed by ECHA, can be found in Appendix VII.	
Endpoint	**Brief description**
Toxicokinetics	Absorption: rapid, but no quantitative data available Distribution: seemingly a significant proportion of formate distributes in the tissue, but more likely undergoes rapid metabolism and excretion Metabolism: rapid: hepatic first pass effect; oxidation to CO_2; no indication of accumulation Excretion: Rapid elimination via exhalation of CO_2; low urinary excretion of formic acid
Acute toxicity	predominantly determined by formic acid's inherent irritating/corrosive properties. The toxicity values after oral uptake and inhalation in rats suggest formic acid to be acutely harmful. The clinical signs give no evidence of specific systemic adverse effects. Proposed classification: Acute tox 4 (oral) H302 LD_{50} 730 mg/kg bw[1] Acute tox 3 (inhal) H331 LC_{50} 7.4 mg/l
Corrosion and irritation	Formic acid is corrosive to skin and eye. Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive in the EU (12th ATP). Respiratory irritation: we propose to classify formic acid as EUH071, 'corrosive to the respiratory tract', as its corrosive properties determine its toxicity.
Sensitisation	Formic acid is not a skin sensitizer. There is no indication that formic acid would be a respiratory sensitizer.
Repeated dose toxicity	The short-term toxicity of formic acid has not been investigated. The medium-term oral toxicity was studied in the rat and the pig. Oral administration of potassium diformate led to largely reversible local irritation effects in the stomach and histological changes of the stomach and gastrointestinal tract. High doses may produce adverse effects, such

[1] Final LD_{50} will be set by RAC; it is the LD_{50} value from the adopted RAC opinion that will need to be used in biocidal product authorisation.

	as decrease in body weight gain, possibly due to the inherent irritating potential. Rat: $NOAEL_{local}$ < 420 mg formate/kg bw/d $NOAEL_{syst}$ 840 mg/kg bw/d Pig: < 149 mg formate/kg bw/d Medium-term inhalation toxicity was studied in rats and mice exposed to formic acid vapours for 13 weeks. Histological changes were observed in the upper respiratory tract. In addition, a decrease in body weight gain was observed at the highest dose level in mice. Medium-term inhalation toxicity: overall $NOAEC_{local}$ = 60 mg formic acid/m³ $NOAEC_{systemic}$ = 244 mg formic acid/m³ The long-term oral toxicity was studied in the rat and the pig. Oral administration of potassium diformate led to local irritation effects in the stomach, which were confirmed histopathologically. In the high dose animals, body weight (gain) was decreased and there was a lower incidence of pelvic mineralization in the kidney. $NOAEL_{systemic}$ = 280 mg formate/kg bw/d
Genotoxicity	Available data indicate that formic acid has no genotoxic potential.
Carcinogenicity	No data are available on formic acid. A carcinogenicity study on potassium diformate indicates that potassium diformate has no carcinogenic potential.
Reproductive toxicity	No data are available on formic acid. No developmental toxicity and teratogenicity was observed for formate in rats and rabbits. No adverse effects on fertility were observed for formate in rats. No adverse effects on or via lactation are expected for formic acid. Two-generation study, rat: $NOAEL_{parental}$ = 200 mg formate/kg bw/d $NOAEL_{offspring}$ = 670 mg formate/kg bw/d $NOAEL_{reproduction\ parameters}$ = 670 mg formate/kg bw/d Teratogenicity studies, rat, rabbit: $NOAEL_{maternal}$ = 640 mg formate/kg bw/d $NOAEL_{developmental}$ = 640 mg formate/kg bw/d
Neurotoxicity	At moderate doses, no neurotoxic effects are expected for formic acid. When the metabolic capacity to dispose of formate is exceeded, formate accumulation and adverse effects on the optical nerve and photoreceptors can occur. However, these symptoms are considered to be an exclusive sequel of acute methanol intoxication in primates.
Immunotoxicity	There are no indications that Formic Acid has the potential to induce adverse effects involving the immune system.
Disruption of the endocrine system	ED criteria are not met for Human Health

Other effects	Workplace measurements, health records from industry and case reports show that local corrosive effects prevail but systemic effects may result after contact of concentrated formic acid to extended areas of the body surface. Occupational and accidental dermal exposure records report skin corrosion and metabolic acidosis. After oral exposure observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the esophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity, potentially leading to the death of the patient. For inhalation exposure at the threshold limit of 5 ppm or 9.5 mg/m^3 an effect on the blood pH is unlikely.

2.2 REFERENCE VALUES

	Study	**NOAEL/ LOAEL**	**Overall assessment factor**	**Value**
$AEL_{short-term}$	90-day feeding study, potassium diformate, rat	840 mg formate/kg bw/d (2100 mg formate/kg bw/d)	100	8.4 mg formate/kg bw/d
$AEL_{medium-term}$	90-day feeding study, potassium diformate, rat	840 mg formate/kg bw/d (2100 mg formate/kg bw/d)	100	8.4 mg formate/kg bw/d
$AEL_{long-term}$	2-year feeding study, potassium diformate, rat	280 mg formate/ kg bw/d (1400 mg formate/kg bw/d)	100	2.8 mg formate/kg bw/d Rounded to 3 mg formate/kg bw/d[2]
ARfD	not required	/	/	/
ADI	EU SANCO D3/AS D, 2005; JECFA, 2003	/	/	3 mg/kg bw/d
Occupational exposure limit	EU WEL, MAK/TLV (8-hour TWA) IOELV Commission Directive 2006/15/EC	/	/	5 ppm or 9.5 mg/m^3 5 ppm or 9 mg/m^3
$AEC_{resp\ tract\ irrit}$	inhalation, 13 weeks, formic acid, rat/mice	60 mg/m^3	10	6 mg/m^3

2 We refer to TAB entry TOX-4 as the impact of rounding is less than 10%. Please note that for this CAR, the risk characterization has been performed with the non-rounded 2.8 mg formate/kg bw/d value. The decision for rounding the AEL long-term was taken at HH WG I-2022; however it was decided that there was no need to alter the risk characterization of the CAR. For product approval, the rounded 3 mg formate/kg bw/d value should be used.

2.3 RISK CHARACTERISATION

Summary table: scenarios			
Scenario number	**Scenario (e.g. mixing/ loading)**	**Primary or secondary exposure Description of scenario**	**Exposed group (e.g. professionals, non-professionals, bystanders)**
1.	Mixing and loading: charging Formic Acid 85% into animal drinking water systems	1a.primary exposure during mixing and loading by professionals: charging of system	professionals
		1b.application: automated system	
		1c. disposal of containers, cleaning of equipment	
2.	Secondary exposure	Dermal and inhalation exposure to disinfected drinking water for animals	professionals

The risk assessment performed for formic acid, PT5, covers professional mixing and loading i.e. charging Formic Acid 85% into animal drinking water systems via automated pumping, and exposure of professionals to disinfected drinking water for animals.

Charging Formic Acid 85% into animal drinking water systems

There is no concern for professionals charging the biocidal product in animal drinking water systems to disinfect water which will be used as drinking water for animal consumption PT5, when appropriate PPE, RPE and ventilation are applied.

Secondary exposure: dermal and inhalation exposure to treated drinking water

There is no concern for professionals exposed via the dermal and inhalation route to treated drinking water containing low concentrations of Formic Acid (0.17%). There is a concern for professionals exposed to treated drinking water containing higher concentrations of formic acid (5%).

General remark:

The main issue identified is the high vapour pressure of formic acid and the resulting inhalation of formic acid vapours.

These concerns should be dealt with at product authorization level. Possible refinements that can be suggested include improved assessment factors for ventilation, the use of workplace measurements and identification of acceptable RMM per type of application.

Conclusion of risk characterisation for professional user

Scenario, Tier	Relevant reference value[2]	Estimated uptake Syst: mg/kg bw/d Local: mg/m³	Estimated uptake/reference value (%)	Acceptable (yes/no)
Scenario 1: Mixing & loading, 85% FA Tier 1/ no PPE	Systemic effects $AEL_{long-term}$ 2.8 mg/kg bw/d	14.336	512%	No
	Local inhalation vapour AEC 6 mg/m^3	8.1	135	No
Scenario 1: Mixing & loading, 85% FA Tier 2/ coveralls, boots, gloves, face protection, RPE APF 10	Systemic effects $AEL_{long-term}$ 2.8 mg/kg bw/d	0.1458	5.2%	Yes
	Local inhalation vapour AEC 6 mg/m^3	0.81	13.5%	Yes
Scenario 2: exposure to treated drinking water, 0.17% FA Tier 1/ no PPE	Systemic effects $AEL_{long-term}$ 2.8 mg/kg bw/d	0.232	8.3%	Yes
	Local inhalation vapour AEC 6 mg/m^3	Very low to negligible	Very low to negligible	Yes
Scenario 2: exposure to treated drinking water, 0.17% FA Tier 2/ gloves	Systemic effects $AEL_{long-term}$ 2.8 mg/kg bw/d	0.0232	0.8%	Yes
	Local inhalation vapour AEC 6 mg/m^3	Very low to negligible	Very low to negligible.	Yes
Scenario 2: exposure to treated drinking water, 5% FA Tier 1/ no PPE	Systemic effects $AEL_{long-term}$ 2.8 mg/kg bw/d	Up to 8.2	293%	No
	Local inhalation vapour AEC 6 mg/m^3	Up to 10	167%	No
Scenario 2: exposure to treated	Systemic effects $AEL_{long-term}$ 2.8 mg/kg bw/d	Up to 2	71.4%	Yes

drinking water, 5% FA Tier 2/ gloves	Local inhalation vapour AEC 6 mg/m^3	Up to 10	167%	No
0.17% FA dil Scenarios 1+2, tier 1	Systemic effects AEL$_{long-term}$ 2.8 mg/kg bw/d	14.568	520%	No
	Local inhalation vapour AEC 6 mg/m^3	no addition of exposure levels performed; only highest exposure level in air considered relevant		No
0.17% FA dil Scenarios 1+2, tier 2	Systemic effects AEL$_{long-term}$ 2.8 mg/kg bw/d	0.169	6.04%	Yes
	Local inhalation vapour AEC 6 mg/m^3	no addition of exposure levels performed; only highest exposure level in air considered relevant		Yes
5% FA dil Scenarios 1+2, tier 1	Systemic effects AEL$_{long-term}$ 2.8 mg/kg bw/d	22.469	802%	No
	Local inhalation vapour AEC 6 mg/m^3	no addition of exposure levels performed; only highest exposure level in air considered relevant		No
5% FA dil Scenarios 1+2, tier 2	Systemic effects AEL$_{long-term}$ 2.8 mg/kg bw/d	2.129	76.04%	Yes
	Local inhalation vapour AEC 6 mg/m^3	no addition of exposure levels performed; only highest exposure level in air considered relevant		No
Local exposure				
conc	task	classification	Hazard category	Potential exposure route
85%	Mixing & loading	Skin corr 1B EUH071	High	Skin, eye, respiratory tract
	Conclusion on risk: ACCEPTABLE +engineering controls +low frequency +short duration +professionals using PPE/RPE +professionals following instructions for use +good standard of personal hygiene			

5%	Intermittent contact with disinfected water	Skin/eye irrit 2	Low	Skin, eye
	Conclusion on risk: ACCEPTABLE +engineering controls +reversible effect +professionals following instructions for use +experience expected			
0.17%	Intermittent contact with disinfected water	none	None; qualitative RA not triggered	Skin, eye

3 SUMMARY OF THE ENVIRONMENTAL RISK ASSESSMENT

3.1 FATE AND BEHAVIOUR IN THE ENVIRONMENT

Summary table on compartments exposed and assessed		
Compartment	**Exposed (Y/N)**	**Assessed (Y/N)**
Freshwater	Y	Y
Sediment	N	N
Seawater	N	N
Seawater sediment	N	N
STP	Y	Y
Air	N	N
Soil	Y	Y
Groundwater	Y	Y
Biota	N	N

Summary table on relevant physico-chemical and fate and behaviour parameter of the active substance			
	Value	**Unit**	**Remarks**
Molecular weight	46.03	g/mol	
Melting point	8	°C	
Boiling point	100.23	°C	
Vapour pressure (at 12 °C)	2400	Pa	
Water solubility (at 12 °C)	$1.09x10^6$	mg/l	
Log10 Octanol/water partition coefficient	-2.10	---	(pH 7)
Organic carbon/water partition coefficient (Koc)	30	l/kg	(pH 7)
Henry's Law Constant (at 12 °C)	0.101	$Pa/m^3/mol$	
Acid dissociation constant	3.7	---	Predominant species at a pH of 7 is formate, which is reflected in the pH dependent Koc.
Biodegradability	Readily biodegradable		

Summary table on relevant physico-chemical and fate and behaviour parameter of the active substance			
	Value	**Unit**	**Remarks**
DT50 for degradation in soil (12 °C)	1	day	
Half-life for biodegradation in manure	19.9	d	(12 °C)

3.2 EFFECTS ASSESSMENT

Summary table on calculated PNEC values	
Compartment	PNEC
Freshwater	≥ 2 mg/L
STP	> 50 mg/L
Soil	≥ 1.29 mg/kg_{wwt} (≥ 1.47 mg/kg_{dwt})
Groundwater	Not applicable

For groundwater, calculated PECs are compared to the reference value of 0.1 µg/L.

3.3 EXPOSURE ASSESSMENT

PEC values were calculated for all stable types. Only the maximum values are presented in the summary table below.

Summary table on calculated PEC values				
	PEC_{STP}	**PEC_{water}**	**$PEC_{soil,twa}$**	**PEC_{GW}**[1]
	[mg/L]	[mg/L]	[mg/kg_{wwt}]	[µg/L]
Scenario 1a (0.2% dilution) – maximum values	2.37E-01	2.37E-02	4.35E-01	1.121E+02
Scenario 1b (5% dilution) – maximum values	5.91E+00	5.91E-01	1.09E+01	2.803E+03
1 TIER 1: porewater concentration				

3.4 RISK CHARACTERIZATION

PEC/PNEC values were calculated for all stable types. Only the maximum values are presented in the summary table below.

Summary table on calculated PEC/PNEC values (TIER 1)			
	$PEC/PNEC_{STP}$	**$PEC/PNEC_{water}$**	**$PEC/PNEC_{soil}$**
Scenario 1a (0.2% dilution) – maximum values	< 4.74E-03	≤ 1.18E-02	≤3.37E-01
Scenario 1b (5% dilution) – maximum values	< 1.18E-01	≤ 2.96E-01	≤8.45E+00

The risks for all environmental compartments were considered to be acceptable for scenario 1a. For scenario 1b, however the risks for the soil compartment are concluded to be unacceptable for emissions directed to the manure.

Groundwater concentrations for both scenarios are below the threshold of 0.1 µg/L after refinement of the exposure calculation.

Conclusion:

The risks for the environment are acceptable for scenario 1a. For scenario 1b however, an unacceptable risk cannot be excluded for the soil compartment for emissions directed to the manure.

4 ASSESSMENT OF EXCLUSION, SUBSTITUTION CRITERIA AND POP

Conclusion on exclusion criteria	The exclusion criteria in BPR Article 5(1)a-c are not met.
Conclusion on CMR	Formic acid is not classified and does not meet the criteria to be classified as CMR
Conclusion on ED assessment	Formic acid does not have endocrine disrupting activities.
Conclusion on PBT and vP/vB criteria	Formic acid is not a PBT/vPvB substance.

Conclusion on substitution criteria	The substitution criteria in BPR Article 10(1)a-f are not met.

Conclusion on LRTAP/POP assessment	Formic acid does not meet the criteria for being a POP or LRTAP.

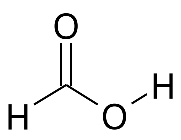
PART A : ASSESSMENT OF INTRINSIC PROPERTIES AND EFFECTS OF THE ACTIVE SUBSTANCE

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

Summary table on substance identity	
Common name (ISO name, synonyms)	Formic Acid
Chemical name (EC name, CA name, IUPAC name	Methanoic Acid
EC number	200-579-1
CAS number	64-18-6
other CAS numbers (e.g. deleted, related, preferred, alternate)	/
Molecular formula	CH_2O_2
SMILES notation	C(=O)O
Molar mass	46.025 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not relevant
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant
Degree of purity (%)	Min. 99% w/w

Structural formula



Origin of the natural active substance or precursor(s) of the active substance
Please refer to BASF Confidential Annex.

Method of manufacture

Please refer to BASF Confidential Annex.

1.2 COMPOSITION OF THE SUBSTANCE (REFERENCE SPECIFICATIONS)

Main constituent(s)			
Constituent (chemical name)	**Typical concentration (%(w/w))**	**Concentration range (%(w/w))**	**Remarks / Discussion**
Formic Acid	**Please refer to BASF Confidential Annex.**		

Impurities			
Constituent (chemical name)	**Typical concentration (%(w/w))**	**Concentration range (%(w/w))**	**Remarks / Discussion**
Please refer to BASF Confidential Annex.			

Additives				
Constituent (chemical name)	**Function**	**Typical concentration (%(w/w))**	**Concentration range (%(w/w))**	**Remarks / Discussion**
Please refer to BASF Confidential Annex.				

1.3 PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Aggregate state at 20°C and 101.3 kPa (99.4% (w/w))	The substance is a clear and colorless liquid which is homogeneous at 20 °C and 101.3 kPa.	Organoleptic	/	Study no. 07L00084, [redacted] (2007)
Physical state (appearance) at 20°C and 101.3 kPa (99.4% (w/w))	Liquid	Organoleptic	/	Study no. 07L00084, [redacted] (2007)
Colour at 20°C and 101.3 kPa (99.4% (w/w))	Colourless	Organoleptic	/	Study no. 07L00084, [redacted] (2007)
Odour at 20°C and 101.3 kPa 1. 99-100% 2. 85%	Pungent	Organoleptic	/	BASF AG (2007) BPD ID B3_04 [redacted] (2007a)
Melting / freezing point (99.4% (w/w))	8 °C	OECD 102	No decomposition observed	[redacted] (2018) 20181112_07L00084 Amendment01 Final Report BPD_ID_A3_01.pdf
Boiling point at (99.4% (w/w))	100.23 °C	OECD 103	Obtained by interpolation	Study no. 07L00084, [redacted] (2007)
Relative density (99.4% (w/w))	D_4^{20} = 1.2195	OECD 109	/	Study no. 07L00084, [redacted] (2007)

Acidity/alkalinity	$pH_{85\%\ formic\ acid}$ = -1.6 At 1%: pH = 2.2	German Industrial Standard DIN 19268	Potentiometric measurement	Study no. 07L00172, [redacted] (2007)
	90.9530 ± 0.0663 % acidity	CIPAC MT 191	On 85% formic acid in water sample. Since test item is an acid, only acidity was tested.	Study no 16011907G975, [redacted] (2016a)
	pH = 2.18	CIPAC MT 75	At 24.8 °C On 1% aqueous solution of 85% formic acid sample	Study no 16011907G907, [redacted] (2016c)
	pH = 2.13	CIPAC MT 75.3	At 19.1 °C On 1% aqueous solution of 99% formic acid sample	Study no. S16-06389 [redacted] (2017)
	108.03% (m/m) mean acidity	CIPAC MT 191	On 99% formic acid	Study no. S16-06390 [redacted] (2017)
Vapour pressure (99.4% (w/w))	At 20 °C: 42.71 hPa At 25 °C: 54.96 hPa At 50 °C: 170.7 hPa	OECD 104	Extrapolated from regression-derived equation	Study no. 07L00084, [redacted] (2007)
Henry's law constant	At 20 °C: 0.16 Pa.m^3/mol		Calculation based on measured relative density as a surrogate for water solubility and measured vapour pressure	ECT Oekotoxikologie GmbH (2015)
Surface tension (99.4% (w/w))	At 20 °C: 71.5 mN/m (at 1g/L)	OECD 115	The test item is not surface active	Study no. 07L00084, [redacted] (2007)

Water solubility at 20 °C	Completely miscible Corresponding to 1220 g/L (= D_4^{20})	SOP PCE/006/04 (BASF AG, GKA Analytik, chapter 4: visual method) Based on OECD 105 Deviation: Preparation of saturated solution was not possible and results are not expected to be different since missing part of the test solution for a pure solution is water.	At pH 5 / 7 / 9 At 20.1 ± 0.1 °C Temperature dependence was not investigated due to complete miscibility.	Study no. 02L00109, [redacted] (2002)
Partition coefficient (n-octanol/water) and its pH dependency Surface tension at 20 °C	At pH 5: Log K_{OW} = -1.9 At pH 7: Log K_{OW} = -2.1 At pH 9: Log K_{OW} = -2.3	EC method A.8	At 23 ± 1 °C The purity of the test solution (performed on a 85.3 w/w solution including water as "impurity") is seen as not relevant, and is not expected to influence the outcome	Study no. 02L00109, [redacted] (2002)
Thermal stability and identity of breakdown products (99.4% (w/w))	Decomposition onset temperature: 350 °C Energy release: >150 J/g Auto-ignition temperature: 528 °C (corrected according to EN 14522)	OECD 113 EC method A.15	Combustion products are H_2O and CO_2 At room temperature and during incomplete combustion CO and H_2 may be formed	Study no. SIK-Nr.07/1018, [redacted] (2007)
Reactivity towards container material (99.4% (w/w))	Compatible: - stainless steel, types 1.4306, 1.4307, 1.4311, 1.4404, 1.4541, 1.4571	Based on experience	Formic acid and solutions of formic acid are acidic. Therefore, materials which are not sufficiently resistant towards acids should not be	[redacted] (2007a)

	- plastics: different types of PE like HD-PE; PP (for plugs and caps) Not compatible: - carbon steel, paper, board		used to avoid equipment damage and spoilage of products	
Dissociation constant (99.4% (w/w))	At 20 °C: pK_a = 3.70	OECD 112	/	Study no. 07L00084, [redacted] (2007)
Granulometry	Waived	-	Not applicable, substance is not a powder or granule	-
Viscositiy (capillary viscometer) (99.4% (w/w))	Dynamic viscosity At 20 °C: 1.80 mPa.s At 40 °C: 1.22 mPa.s Kinematic viscosity At 20 °C: 1.47 mm^2/s At 40 °C: 1.02 mm^2/s	OECD 114	/	Study no. 07L00084, [redacted] (2007)
Solubility in organic solvents, including effect of temperature on solubility (99.4% (w/w))	Miscible at ratios: 1:9, 1:1 and 9:1 Miscible at 20 and 30 °C Corresponding to: > 850 g/L N,N-dimethylformamide > 92.9 g/L 1,4-dioxane > 1190 g/L Dichloromethane	SOP PCE/006/04 (BASF AG, GKA Analytik, chapter 4: visual method) Based on OECD 105 Deviation: Preparation of saturated solution was not possible and results are not expected to be different since missing part of the test solution for a pure solution is water.	3 solvents: - N,N-dimethylformamide (Density 0.9445 g/cm^3 at 25°C) - 1,4-dioxane (Density 1.0329 g/cm^3 at 20°C) - Dichloromethane (Density 1.3255 g/cm^3 at 20°C)	Study no. 07L00084, [redacted] (2007)

Stability in organic solvents used in biocidal products and identity of relevant degradation products	Waived	-	Organic solvents not used in the biocidal products	-

1.4 PHYSICAL HAZARDS AND RESPECTIVE CHARACTERISTICS

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Explosives	The substance is not explosive	UN Manual of Tests and Criteria (2010)	The substance has no chemical groups indicating explosive properties	[redacted] (2006)
Flammable gases	Waived	-	Not applicable	-
Flammable aerosols	Waived	-	Not applicable	-
Oxidising gases	Waived	-	Not applicable	-
Gases under pressure	Waived	-	Not applicable	-
Flammable liquids	Flash point = 49.5 °C Is a flammable liquid category 3, as its flash point is ≥ 23 °C and ≤ 60 °C (H226)	EC method A.9	Closed cup; corrected for atmospheric pressure and rounded to units of 0.5 °C	Study no. SIK-Nr.07/1018, [redacted] (2007)
Flammable solids	Waived	-	Not applicable	-

Self-reactive substances and mixture	The substance is not self-reactive	UN Manual of Tests and Criteria (2010)	The substance has no chemical groups indicating explosive or self-reactive properties	-
Pyrophoric liquids	Waived	-	Not a pyrophoric liquid, based on auto-ignition temperature (528 °C) and experience in manufacture and handling	Study no. SIK-Nr.07/1018, [redacted] (2007)
Pyrophoric solids	Waived	-	Not applicable	-
Self-heating substances and mixtures	Waived	-	Not applicable, substance has a melting point of 8 °C	-
Substances and mixtures which in contact with water emit flammable gases	Waived	-	The active substance is a weak acid that, in presence of water, will partially dissociate and provide ions (ion hydronium and formate). This dissociation do not liberate any flammable gas. This is a well known process.	-
Oxidising liquids	The substance is not an oxidising liquid	UN Manual of Tests and Criteria (2010)	The compound contains oxygen but this element is chemically bonded only to carbon and hydrogen The compound does not contain any halogen atoms	[redacted] (2006)
Oxidising solids	Waived	-	Not applicable	-
Organic peroxide	Waived	-	Not applicable	-

Corrosive to metals	Corrosive to steel Not corrosive to aluminium	UN Test C.1 (37.4)	On 99% formic acid	Study no. 16092902G979 [redacted] (2017) Study no 16011907G979 [redacted] (2016b)
	Corrosive to steel Not corrosive to aluminium	UN Test C.1 (37.4)	On 85% formic acid in water sample	Study no 16011907G979 [redacted] (2016b)
	Compatible materials: - stainless steel, types 1.4306, 1.4307, 1.4311, 1.4404, 1.4541, 1.4571 Not compatible: - carbon steel As a conclusion, a classification as Corrosive to metals (H290) is justified.	Based on experience	On 99% formic acid	[redacted] (2007a)
Auto-ignition temperature (liquids and gases)	Auto-ignition temperature: 528 °C (corrected according to EN 14522)	EC method A.15	/	Study no. SIK-Nr.07/1018, [redacted] (2007)
Relative self-ignition temperature for solids	Waived	-	Not applicable	-
Dust explosion hazard	Waived	-	Not applicable	-

1.5 HAZARD IDENTIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Formic acid is a flammable liquid category 3. Further it does not present any other hazard from a physico-chemical point of view with regard to the available information. It presents a high self-ignition temperature, and has no explosive or oxidising properties.

1.6 ANALYTICAL METHODS FOR DETECTION AND IDENTIFICATION

Analytical methods								
Analyte (type of analyte e.g. active substance, metabolite etc.)	**Compartment**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ), Maximum Residue Limits or other limits**	**Reference**
				Fortification range / Number of measurements	**Mean**	**RSD**		
GCMS (column: DB FFAP, 30 m x 0.32 mm (inner diameter), film thickness 0.25 µm, batch: USN526534H, AGILENTInsert) *Electron impact (EI) positive*	-	-	GC-MS analysis of the test item was performed and showed the absence of any other acid or impurity that could interfere with the titration.	-	-	-	-	[redacted] (2017)

CIPAC Method MT 30.5, "Water, Karl Fischer method using pyridine-free reagents", Hydranal-Composite 1, titer 0.8 – 1.2 mg/mL	*Pure 100% Diluted with water 85%*	12 conc R=1.0000 0.118-6.347% w/w water		12 replicates	103%	3.37%	LoQ = 0.122% w/w	Idem

<table>
<tr>
<td>Remark: The enzymatic method of determination of formic acid in aqueous solutions is acknowledged to represent a specific, sensitive, and reliable method, and in Germany it is contained in the official list of methods which are suited to examine foodstuffs.

Photometer (wavelength 334, 340, or 360 nm) to detect formation of NADH</td>
<td>Soil</td>
<td>Linearity is given in the range 0.2 mg formic acid /l sample solution to 200 mg formic acid/l sample (cf. full test description in Section A4.1_01).</td>
<td>Enzyme is highly specific for formic acid. Test may be disturbed by:
Low or high pH outside approx. 7-8
Reducing agents
Colour, turbidity, or protein</td>
<td>25</td>
<td>
<table>
<tr><th>Fortification [mg/kg]</th><th>Concentration, mean [mg/kg soil]</th><th>Recovery [%]</th></tr>
<tr><td>0</td><td>1.59</td><td>n.d.</td></tr>
<tr><td>5</td><td>1.61</td><td>31</td></tr>
<tr><td>10</td><td>9.05</td><td>85</td></tr>
<tr><td>50</td><td>47.8</td><td>93</td></tr>
</table>

<table>
<tr><th>Fortification [mg/kg]</th><th>Concentration, mean [mg/kg soil]</th><th>Rel SD [%]</th></tr>
<tr><td>0</td><td>1.59</td><td>70</td></tr>
<tr><td>5</td><td>1.61</td><td>53</td></tr>
<tr><td>10</td><td>9.05</td><td>3.8</td></tr>
<tr><td>50</td><td>47.8</td><td>4.7</td></tr>
</table>
</td>
<td>LoQ was set at 10 mg/L for soil extracts</td>
<td>[redacted] (2007</td>
</tr>
</table>

<table>
<tr>
<td>Photometer (wavelength 334, 340, or 360 nm) to detect formation of NADH</td>
<td>Water surface</td>
<td>Surface water: given in the range 0.2 to 5 mg/L. R^2= 0.99998 for the regression curve for all measurements
Linearity confirmed in the range 0.2-100 mg/L (Keller and Hartmann, 2013: cf. Section A4.1_03).</td>
<td>None (enzyme specific for formic acid)</td>
<td>(5 measurements at each of the four fortification levels) and blanks</td>
<td>
<table>
<tr><th>Fortification level [mg/L]</th><th>Recovery [%] Drinking water</th><th>Recovery [%] Surface water</th></tr>
<tr><td>0.2</td><td>103</td><td>116</td></tr>
<tr><td>0.5</td><td>91</td><td>n.d.</td></tr>
<tr><td>2</td><td>103</td><td>81</td></tr>
<tr><td>5</td><td>101</td><td>78</td></tr>
</table>
<table>
<tr><th>Fortification level [mg/L]</th><th>Rel SD[%] Drinking water</th><th>Rel SD [%] Surface water</th></tr>
<tr><td>0.2</td><td>17</td><td>7.7</td></tr>
<tr><td>0.5</td><td>2.4</td><td>n.d.</td></tr>
<tr><td>2</td><td>6.6</td><td>1.6</td></tr>
<tr><td>5</td><td>3.7</td><td>1.7</td></tr>
</table>
</td>
<td>LoQ of 0.2 mg/L</td>
<td>[redacted] (2007)</td>
</tr>
</table>

<table>
<tr>
<td>Photometer (wavelength 334, 340, or 360 nm) to detect formation of NADH</td>
<td>Drinking water</td>
<td>Drinking water: given in the range 0.2 to 5 mg/L. R^2= 0.9997 for the regression curve for all measurements
Linearity confirmed in the range 0.2-100 mg/L (Keller and Hartmann, 2013: cf. Section A4.1_03)</td>
<td>None (enzyme specific for formic acid)
Drinking water: precipitation of magnesium phosphate caused turbidity that was removed by filtering the solution.</td>
<td>(5 measurements at each of the four fortification levels)</td>
<td>
<table>
<tr><th>Fortification level [mg/L]</th><th>Recovery [%] Drinking water</th><th>Recovery [%] Surface water</th></tr>
<tr><td>0.2</td><td>103</td><td>116</td></tr>
<tr><td>0.5</td><td>91</td><td>n.d.</td></tr>
<tr><td>2</td><td>103</td><td>81</td></tr>
<tr><td>5</td><td>101</td><td>78</td></tr>
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<table>
<tr><th>Fortification level [mg/L]</th><th>Rel SD[%] Drinking water</th><th>Rel SD [%] Surface water</th></tr>
<tr><td>0.2</td><td>17</td><td>7.7</td></tr>
<tr><td>0.5</td><td>2.4</td><td>n.d.</td></tr>
<tr><td>2</td><td>6.6</td><td>1.6</td></tr>
<tr><td>5</td><td>3.7</td><td>1.7</td></tr>
</table>
</td>
<td>LoQ of 0.2 mg/L</td>
<td>[redacted] (2007)</td>
</tr>
</table>

Ion chromatography *Material and conditions: Ion chromatographer DIONEX DX 120 with conductivity detector and autosampler.*	*Air*	*Formic acid, 1.2 to 47.8 mg/L*	*Methoxyacetic acid cannot be completely separated from formic acid*	Measures were performed at three different concentration (6 replicates by concentration):	Formic acid [mg/m³] / Recovery [%] 0.9 / 95 9.0 / 95 18.0 / 94	Formic acid [mg/m³] / Relative standard deviation [%] 0.9 / 9,7 9.0 / 6,4 18.0 / 3,8	*Absolute limit of quantification: 0.1 µg formic acid. This corresponds to a relative limit of quantification of 0.12 mg/m³ for an air sample volume of 140 L, an absorption volume of 10 mL, and an injection volume of 50 µL*	[redacted] (2007)
Photometer (wavelength 334, 340, or 360 nm) to detect formation of NADH	*animal and human body fluids and tissues*	*Linearity is given in the range 0.2 mg formic acid/l sample solution to 200 mg formic acid/l sample*	*None (enzyme specific for formic acid)*	n.a.	*100% because formic acid is water soluble and the volatility is low. The enzyme reaction is complete under the specified test conditions.*	*Coefficient of variance: 0.48 – 2.40 %*	*Detection limit 0.2 mg/l sample*	[redacted] (2007)

<table>
<tr>
<td>Photometer (wavelength 334, 340, or 360 nm) to detect formation of NADH</td>
<td>food and feedstuffs</td>
<td>Linearity is given in the range 0.2 mg formic acid/l sample solution to 200 mg formic acid/l sample</td>
<td>None (enzyme specific for formic acid)</td>
<td>16</td>
<td>
<table>
<tr><th>Fortification level [mg/L]</th><th>Number of measurements</th><th>Mean concentration [mg/L]</th><th>Rel SD [%]</th></tr>
<tr><td>0</td><td>6</td><td>9.96</td><td>2.5</td></tr>
<tr><td>10</td><td>4</td><td>18.77</td><td>11</td></tr>
<tr><td>50</td><td>5</td><td>62.88</td><td>0.9</td></tr>
</table>
</td>
<td>Detection limit 0.2 mg/l sample</td>
<td>[redacted] (2007)</td>
</tr>
</table>

No data submitted for sediments:

Based on the physico-chemical properties as well as the environmental fate of formic acid, the compartment sediment is of no concern for this substance.

Formic acid

- is readily biodegradable,
- is completely miscible with water,
- has a low potential for adsorption (log Kow -1.9 to -2.3; log Koc < 1.25)
- will predominantly distribute into the compartment water (93.5%), while a negligible fraction will be associated with the sediment (5.9E-05%) according to the Mackay Level I model (BPD ID IIA4.1.1.3_01).

It can be concluded that formic acid will be rapidly removed from the environment due to biodegradability. As it is completely miscible with water and has a low adsorption potential formic acid will not distribute into the compartment sediment. This is supported by the Mackay level I model result, which shows that formic acid will predominantly distribute into the compartment water. Therefore, no analytical method for the detection of formic acid is provided.

2 EFFECTS AGAINST TARGET ORGANISMS

2.1 FUNCTION AND FIELD OF USE ENVISAGED

FUNCTION

Main Group 1 : DISINFECTANTS

- *PT2* "Disinfectants and algaecides not intended for direct application to humans or animals"
- *PT3* "Veterinary hygiene"
- *PT4* "Food and feed area"
- *PT5* "Drinking water"

Main Group 2 : PRESERVATIVES

- *PT6* "Preservatives for products during storage"

With Bactericidal, yeasticidal & fungicidal activity.

To control the spread of microorganisms which may be harmful to human health.

FIELD OF USE ENVISAGED

The Formic Acid-based Biocidal products are wide-spread and have the following aims :

- *PT2 :* Disinfection of industrial and institutional premises and machinery, for Cleaning-In-Place procedures, bathroom surfaces, toilets and sanitary ware in the domestic and institutional environment i.e. walls, toilets and other hard surfaces.
  Products are applied by non-professionals by pouring and wiping; professionals apply the diluted concentrate as cleaning-in-place. Products to be used by professionals are concentrated formulations and by general public RTU formulations.
- *PT3 :* Disinfection of areas in which animals are housed, kept and transported.
  Products to be used for animal house disinfection (by fogging), for disinfection of footwear (by dipping) and for animal's feet and animal transport vehicles disinfection
  Products to be used by professionals (i.e. professional contractors or experienced farm workers)
- *PT4 :* Disinfection of working areas and production surfaces including food preparation and consumption areas.
  Products to be used for hard surface disinfection (by trigger spraying) and for Cleaning-In-Place procedures. Products to be used by professionals.
- *PT5 :* Disinfection of drinking water for animals
  Products to be used by professionals
- *PT6 :* Preservation of industrial, consumer, household and institutional products, washing and cleaning fluids and other detergents, and formulation of detergent end product.

2.2 INTENDED USES

Summary table of intended use(s)	
Product Type	**PT5** Drinking water

Summary table of intended use(s)	
Product description	Formic Acid-based Biocidal products are recommended to control the growth of microorganisms in drinking water for the consumption by animals
Target organisms (including development stage)	Bacteria including *L. pneumophila* Yeasts
Description of use(s)	Formic Acid is commercially available as solutions in water, to be diluted in water before being used.
Mode of action	The biocidal activity of Formic Acid, i.e. acidulant action and corrosion which causes enzyme denaturation and inhibition, cellular structure disruption, and impairment of cellular metabolic pathways. This mode of action is considered to depend on the low pH-value. Secondly, formic acid does inhibit cytochrome C oxidase and thus impairs cellular energy supply. Organisms and tissues with a high energy demand are specifically susceptible : 1. Acidulant: acidification of cytoplasm; 2. Inhibitor for decarboxylases and haemin enzymes such as catalase; 3. Organic acids in general may disrupt the proton-motive force, as well as inhibit substrate transport, energy-yielding processes and macromolecular synthesis. Acidulant action is responsible for formic acid being most effective at lower pH values (below 3.5), but enzyme inhibition and other modes also provide some antimicrobial action at higher pH values. Enzyme inhibition is less significant in the control of fungi; therefore, higher concentrations of formic acid are needed to control fungi. The activity of formic acid against some viruses is presumably explained by the action of acid in denaturing polypeptide chains.
Objects to be protected	Animals The aim of the treatments is to control infectious diseases.
Concentration of active substance in the in-use formulation/product	Representative product (used in efficacy tests): ***FENNOPUR® MH 85*** with 85.9% Formic Acid

Summary table of intended use(s)	
Application rate(s)	The product ***FENNOPUR® MH 85*** is active against *Legionella pneumophila*) in suspension at **0.2%** (pH = 1.85; 0.1718 % FORMIC ACID ⬄ % used for Risk Assessment) at +20°C in 60 min. FOR INFORMATION : The representative product ***FENNOPUR® MH 85*** (with 85.9% Formic Acid) is bactericidal (with the exception of spore-forming bacteria and mycobacteria) and yeasticidal in suspension at +20°C in clean conditions (0.03% BSA) at **5%** (pH = 1.73; 4.29% formic acid) respectively in 5 and 15 min. At +10°C in 30 min, the representative product ***FENNOPUR® MH 85*** has a bactericidal activity at 5%.
Frequency of application	The drinking water is treated on a daily basis.
Season/period for use (where relevant)	Not relevant
Field of use (indoors/outdoors)	Indoor
Category(ies) of user(s)	Professional users only
Instruction for use	The product is intended to be used for animal drinking water disinfection via automated supply systems. The biocidal product is supplied in containers which are opened prior to the addition of the dosing equipment. The drinking water is treated on a daily basis. The product is then automatically dosed into the drinking water supply system at the appropriate concentration and the treated water is subsequently supplied to the feeders within the animal accommodation.

2.3 SUMMARY ON EFFICACY

2.3.1 Efficacy

General overview

Formic acid-based products exert toxic effects on the target organisms.

No efficacy studies have been performed and submitted using only the active substance. Therefore, to review efficacy data available for formic acid, please see information in **Part B** of this CAR.

2.3.2 Mode of action

Different modes of action are reasonably considered to contribute to the biocidal activity of Formic Acid, i.e. acidulant action and corrosion which causes enzyme denaturation and inhibition, cellular structure disruption, and impairment of cellular metabolic pathways.

This mode of action is considered to depend on the low pH-value. Secondly, formic acid does inhibit cytochrome C oxidase and thus impairs cellular energy supply. Organisms and tissues with a high energy demand are specifically susceptible.

1. Acidulant: acidification of cytoplasm;
2. Inhibitor for decarboxylases and haemin enzymes such as catalase;
3. Organic acids in general may disrupt the proton-motive force, as well as inhibit substrate transport, energy-yielding processes and macromolecular synthesis.

Acidulant action is responsible for formic acid being most effective at lower pH values (below 3.5), but enzyme inhibition and other modes also provide some antimicrobial action at higher pH values. Enzyme inhibition is less significant in the control of fungi; therefore, higher concentrations of formic acid are needed to control fungi. The activity of formic acid against some viruses is presumably explained by the action of acid in denaturing polypeptide chains.

2.3.3 Resistance

There is no adaptation to cope with acidic pH values or denaturated proteins, nor is there a mechanism known to exist that a sub-lethal energy supply, due to an incomplete cytochrome C oxidase inhibition, would lead to undesired side-effects or resistance against this inhibitor.

No incidence of resistance to formic acid has been recorded until now.

2.4 CONCLUSION ON EFFICACY

No efficacy studies have been performed and submitted using only the active substance. Therefore, to review efficacy data available for formic acid and to read a conclusion on efficacy, please see information in **Part B** of this CAR.

3 ASSESSMENT OF EFFECTS ON HUMAN HEALTH

3.1 TOXICOKINETICS

In aqueous solution and at neutral pH, formic acid and water-soluble formate salts dissociate and are present as the formate anion in solution. The behaviour of chemical dissociation in water has particularly been investigated with potassium diformate [CAS No. 20642-05-1], which served as test compound in several toxicity studies (DocIIIA6.2_01; FA_BPR_Ann_II_8_8_01: [redacted] 1997). Based on the physico-chemical properties, it is justified to include kinetic and metabolism studies conducted with water-soluble formate salts.

Potassium formate is expected to form the following equilibriums in aqueous solutions:

HCOOH-HCOOK ⇆ HCOOH + HCOOK [equation 1]

HCOOH ⇆ $HCOO^-$ + H+ [equation 2]

HCOOK ⇆ $HCOO^-$ + K+ [equation 3]

Mapping the pH as function of dilution and titer curve allowed to estimate the buffer effect of the diformate system

HCOOH-HCOOK ⇆ HCOOH + HCOOK [equation 1]

and to calculate the concentration profile of diformate, formic acid and formate as function of concentration in aqueous solutions. The same procedure was applied to formic acid.

The calculations indicate that in aqueous solutions

i) at pH <4 and at concentrations >0.1% the equilibrium in equation 1 is in favor of potassium diformate.
ii) at pH of 4 to 5, and at dilution down to 0.001%, most of the formic acid content is released from potassium formate.
iii) further dilution and increase of pH above 5, the concentrations of formic acid and diformate decrease rapidly, leaving only formate left at pH 7 and above. No diformate exists above pH 7.

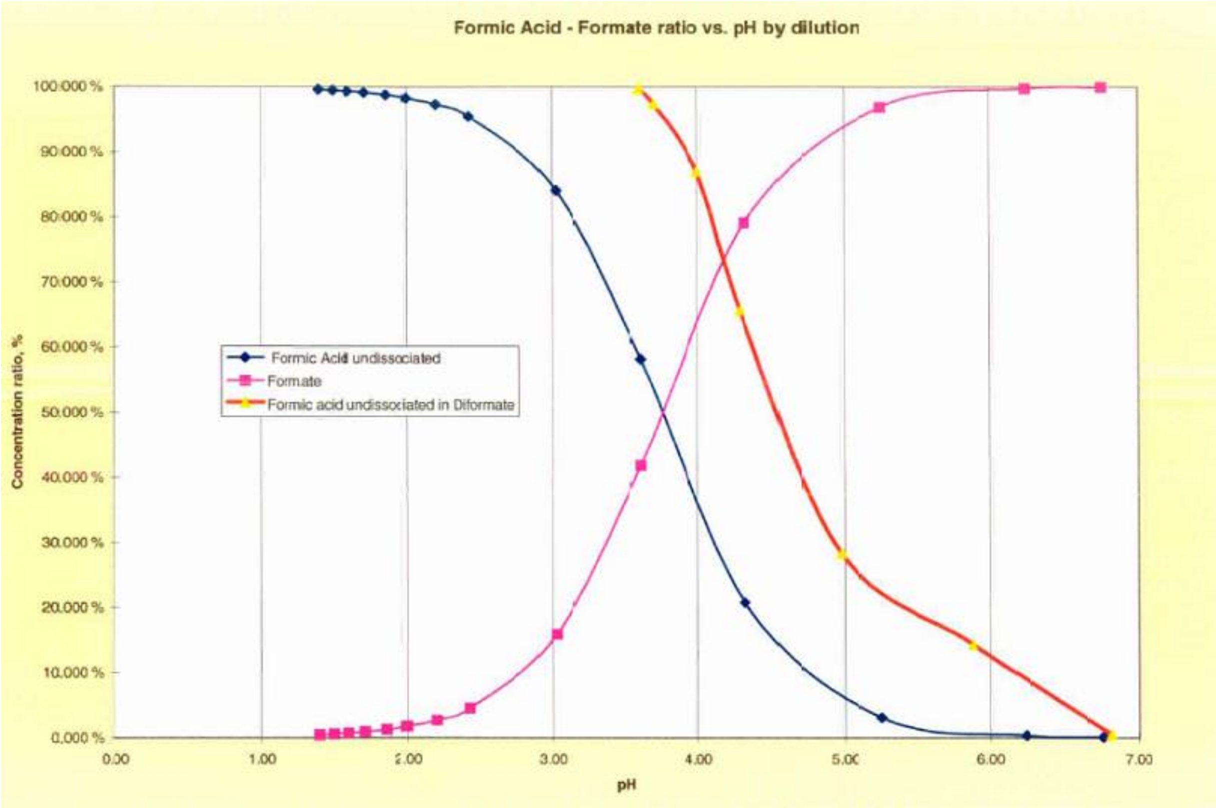

Fig. 3.1 *Formic acid – Formate ratio vs. pH by dilution*

Formic acid occurs naturally in animals and most plants. Formic acid is an inherent ingredient in human food. The content reported for some common foods and beverages: fruits 20 to 40 mg/kg; honey 20 to 2000 mg/kg; wines 1 to 340 mg/kg; roasted coffee 30 to 40 mg/kg; cheese 20 to 200 mg/kg. Formic acid was added intentionally to some foods such as ice cream, soft drinks and fruit drinks as a flavor adjunct. The dietary consumption in adults was estimated to range between 0.4 and 1.2 mg/kg per day (DocIIIA6.2_09; FA_BPR_Ann_II_8_8_08: Boeniger, 1987). JECFA/IPCS (2003, originally published by WHO, 1997; BPD ID A6.15.4_01b, FA_BPR_Ann_II_8_16_1_01) stated that endogenous formate is generally present in human blood at levels of 0.07 – 0.4 mM (3.2 – 18.4 mg/l). Further, formic acid is required for the biosynthesis of purines and pyrimidines in the intermediary metabolism.

Formic acid is considered to be available by all potential exposure routes.

The toxicokinetic properties and the metabolism of formic acid have been investigated after oral, inhalation, intravenous, or intraperitoneal administration, in different species: rat, mouse, dog, monkey, pig, and humans. None of the studies were performed according to regulatory guidelines (some are pre-guideline). Nevertheless, the studies were conducted in accordance with generally accepted scientific principles, techniques and methods, and hence are acceptable for assessment. In addition, PBPK models were developed based on data collected after intravenous and inhalation exposure.

<u>Justification for read-across:</u>

The repeated dose toxicity via the oral route of formic acid is assessed with its non-corrosive salts, sodium formate and potassium diformate, in order to achieve sufficiently high dose levels. Neurotoxicity is assessed with methanol. A read across approach is provided in accordance with Article 6(3) of the EU No. 528/2012 (BPR) following point 1.5(2) under Annex IV: "*common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals and indicates the presence of dangerous properties*". The full read-across justification, which was performed following the Read-Across Assessment Framework developed by ECHA, can be found in Appendix VII.

The read-across justification concludes that the hypothesis that systemic toxicity of formic acid can be established by its salts, sodium formate and potassium diformate, and a closely related substance methanol, as these chemicals have a common breakdown product *in vivo*, is supported by the available information on physicochemical properties and its toxicokinetics.

When making use of this read-across, reference values will be derived for formate and expressed as mg formate/kg bw/d. At physiological pH 7, formic acid and potassium diformate are both exclusively present as formate anion. Therefore, inside the body, the major form present after exposure to either formic acid or potassium diformate is formate. (pKa of FA is 3.70 at 20°C). In water, there is an equilibrium between formic acid and the dissociated acid (HCOOH ↔ H+ & COOH-). Once its corrosive properties have been exerted, only formate is released/available. Therefore, for those HH endpoints where read-across is relevant, the endpoint will be expressed as formate. A conversion is not needed as the difference between formic acid and formate is limited to 1 H+ (MW of formate is 1 less than formic acid).

Toxicokinetics

The toxicokinetic properties of formic acid and sodium formate were studied in **human volunteers** following **oral** ingestion (DocIIIA6.2_07; FA_BPR_Ann_II_8_8_06: Malorny, 1969b). Formate and formic acid were both rapidly absorbed and reached peak plasma levels within 10 to 30 min after ingestion. Resorption of the unprotonated acid started already in the stomach; sodium formate was converted to the unprotonated acid under the pH conditions of the stomach. After ingestion of a single dose of 1000 mg formic acid (12.5 mg/kg bw), the increase in the plasma level of formate was barely distinguishable against a baseline (about 4 mg/l), while a transient 3- to 4-fold increase in formate (20 mg/l plasma) was noted after ingestion of 2000 mg formic acid (26.7 mg/kg bw). Formate was eliminated from the plasma with a half-life time $t_{1/2}$= 45 min. The background urinary formate excretion in humans was approx. 13 mg/24 hours. The average urinary excretion accounted for approx. 2 - 4 % of the administered dose, but was very variable among the individuals. The major part of ~65 - >80 % was excreted within the first 6 hours after ingestion and returned to normal levels at 12 hours after dosing. The blood pH remained unchanged following single formate or formic acid doses that were equivalent to 3000 mg formic acid. Urine volume and pH were increased as long as formate was excreted via urine.

In a human pharmacokinetic study (Hanzlik et al. (2005); FA_BPR_Ann_II_8_8_10) females (n=14) ingested 3900 mg calcium formate (equivalent to 2700 mg formate). The endogenous formate level was approx. 0.024 ± 0.008 mM in this study. Absorption was fast and the mean maximal serum level of 0.50 mM was seen at 60 minutes after dosing.

The toxicokinetic properties from plasma formate concentrations were studied in the **pig** following **oral** ingestion of potassium diformate by [redacted] 1998 (DocIIIA6.2-10; FA_BPR_Ann_II_8_8_09). Potassium diformate dissociated to formate in vivo as expected when it was fed with the diet to pigs. Absorption was rapid; the mean half maximal plasma level of approx. 200 mg formate/l plasma was reached in less than 2 hours, and the mean maximal plasma level C_{max} = 386.4 mg/l was seen 4 to 5 hours after feeding had been started. The values were derived from those 4 pigs which consumed at least 80% of the feed within 40 minutes after it had been offered. Formate was rapidly and completely eliminated. The mean biological half-life was calculated to be $t_{1/2}$ = 2.73 hours, i.e. about 25 % of the amount in blood will be removed per hour (first-order elimination, k_{el} = 0.25 h^{-1}). In 3 pigs, control plasma levels (mean: 1.9 mg/l) were reached within 12 hours; after 24 hours all pigs had normal plasma levels. There was no indication of an accumulation of formate. Only 13.5 % of the high oral dose was found systemically bioavailable. This seemed to be due mainly to the metabolic activity of the liver (hepatic "first-pass effect") and secondly to the urinary elimination. Furthermore, it was assumed that not 100 % of the dose was resorbed, while part of it might also have been subjected to degradation by the gut microflora. A quantitative gastro-intestinal absorption rate could not be derived from this study.

A PBPK model (multicompartment dynamic system) developed by Bouchard et al., 2001 (DocIIIA6.2-03; FA_BPR_Ann_II_8_8_02), described the toxicokinetics of methanol, formaldehyde and formic acid in rats, monkeys, and humans for up to 48 h following **inhalation** exposure to methanol. The volume of distribution of formate of 6.4 to 4.2 l/kg bw suggested that a significant proportion of formate distributes in the tissue, but more likely undergoes rapid metabolism and excretion, thus leading to an apparently high distribution volume. The metabolism rate constant ratio k_{form}/k_{fald} was twice as high in rats as in monkeys (0.53 vs. 0.26). Thus, in monkeys and plausibly in humans, a much larger fraction of formaldehyde is rapidly converted to unobserved forms rather than metabolized to formic acid and further to CO_2. For humans, the simulations showed that after continuous inhalation of 260 mg methanol/m^3 (200 ppm) for 5 days, methanol-related blood and urinary formate levels (0.16 mg/L and 1.5 mg/L, respectively) remained far below reported baseline levels in unexposed subjects (4.9-10.3 and 6.3-13 mg/L, respectively). Furthermore, the model predicted that an 8-hour inhalation of 650 - 2600 mg/m^3 (500 to 2000 ppm) methanol would be required to reach endogenous baseline values of formate.

Additional information on distribution is provided in section 3.6.1 on sub-chronic oral toxicity: systemic bioavailability data were provided in the study by [redacted] (1998; BPD ID A6.4.1_01, FA_BPR_Ann_II_8_9_2_01) notably it was reported that formate plasma levels of approx. 90 to 160 mg /L were regularly found in rats after oral exposure to potassium diformate. In section 3.14 on Further human data, for a case report on suicidal ingestion of Formic Acid, data on post-mortem formate concentrations are available.

Crossing of barriers as blood/brain, blood/testes, blood/placenta, and exposure via the breastmilk: It may be deduced from the physico-chemical properties of formic acid that the possibility of formate to cross the mentioned barriers is low. The substance is highly soluble in water and the logKow is around -2.0. The pKa is 3.70 at 20°C, and therefore formic acid (and the related salt potassium diformate) is almost exclusively present in the ionised form at physiological pH (DocIIIA6.2-01; FA_BPR_Ann_II_8_8_01). It is known that only the unionised form is likely to cross biological membranes, and that substances with a logP of 2-4 would likely cross membranes. The physico-chemical properties of formic acid differ largely, hence it is unlikely that formate would cross biological membranes. This does not preclude the uptake by means of active transport systems. Penetration into (and through) membranes may occur in minor quantities because the small size of the formate molecule. Transfer into breast milk may be given due to the high solubility in water. In this context it should also be mentioned that endogenous formic acid is produced in the intermediary metabolism in humans, and that the C1-fragment is required in the biosynthesis of amino acids and nucleic acids (DocIIIA6.2-09; FA_BPR_Ann_II_8_8_08), i.e. there is a need in the developing fetus. Excess blood formate is rapidly metabolised to background levels in humans, i.e. formate does not accumulate. Finally, there were no adverse effects noted in the testes, the brain, or the development of offspring, in any of the numerous studies requiring repeated dosing. This includes all subchronic and chronic repeated dose studies, carcinogenicity studies, multigeneration reproduction and teratogenicity studies, conducted in several species (rat, mouse, rabbit, pig) with either sodium formate or potassium diformate. Neurotoxicity is known to occur in humans only in the optical nerve following severe methanol intoxication leading to very high blood formate levels over an extended period of time (DocIIIA6.9; FA_BPR_Ann_II_8_13_2_0). Thus, though formate crossing of the blood/brain, blood/testes, blood/placenta barriers, and the exposure via the breast milk cannot be fully excluded, no adverse effects were seen in the parental animals and their progeny of several species following high-level long-term dosing, or dosing during reproduction and development, of either sodium formate or potassium diformate.

Metabolism

The metabolism of formic acid in animals has been extensively documented. Formic acid is an intermediate in normal metabolism. It takes part in the metabolism of one-carbon compounds and its carbon may appear in methyl groups undergoing transmethylation. The metabolic oxidation of formate to CO_2 involves tetrahydrofolate (THF). Formyl-THF synthetase catalyzes the binding of formate to THF to yield 10-formyl-THF. The latter liberates CO_2, and the folate moiety is reduced to THF by Formyl THF dehydrogenase.

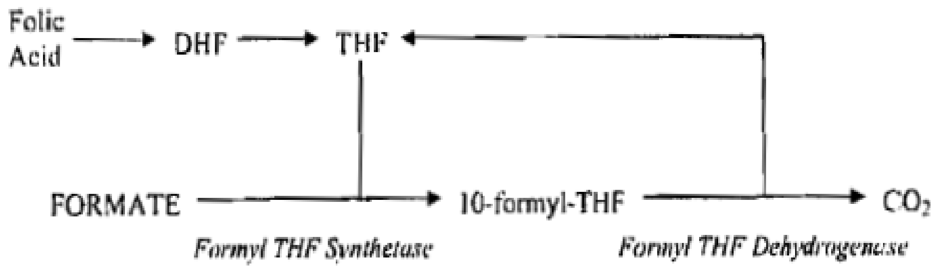

Fig. 3.2 *Oxidation of formate to CO2*

The oxidation rate of formate to CO_2 depends on the hepatic folate pathway, i.e. the levels of folate coenzymes and folate-dependent enzymes. These levels are higher in rodents than in primates, and consequently the rate of formate oxidation to CO_2 is also higher in rodents (DocIIIA6.2_04; FA_BPR_Ann_II_8_8_03: NTP, 2004). In monkeys, the maximum elimination rate of formate is reported to be about 34 mg/kg bw/h, whereas in rats it was about 73 mg/kg bw/h (BPD ID A6.2_12; ; FA_BPR_Ann_II_8_8_13: Kavet & Nauss, 1990). The formate plasma elimination half-life in various species following intravenous infusion (see table 3.1-1) was discussed in a review by Malorny, 1969a (DocIIIA6.2_06; FA_BPR_Ann_II_8_8_05). There is a clear species difference in the extent of formic acid metabolism and elimination rate which is consequently dose-dependent. As humans and primates have reduced capacity for formate oxidation compared with rodents and dogs, humans and primates are more susceptible to formate intoxication.

Formic acid was rapidly oxidised to CO_2 and water by the liver in human volunteers, while a minor part of 2 to 4 % was excreted unchanged into the urine within 24 hours (DocIIIA6.2_07; FA_BPR_Ann_II_8_8_06: Malorny, 1969b). Based on the first-order elimination kinetics (see Table 3.1-1), it is evident that after exposure to one single dose of formic acid or formate salt that was systemically bioavailable, normal blood levels will be reached within 4 to 5 hours post-application in humans.

In the recent single dose human study (FA_BPR_Ann_II_8_8_10: Hanzlik et al., 2005), a mono-exponential decline of serum concentrations with an average half-life of 59 +/- 7 minutes was seen, and baseline levels were reached within 240 minutes after dosing (see figure and legend below).

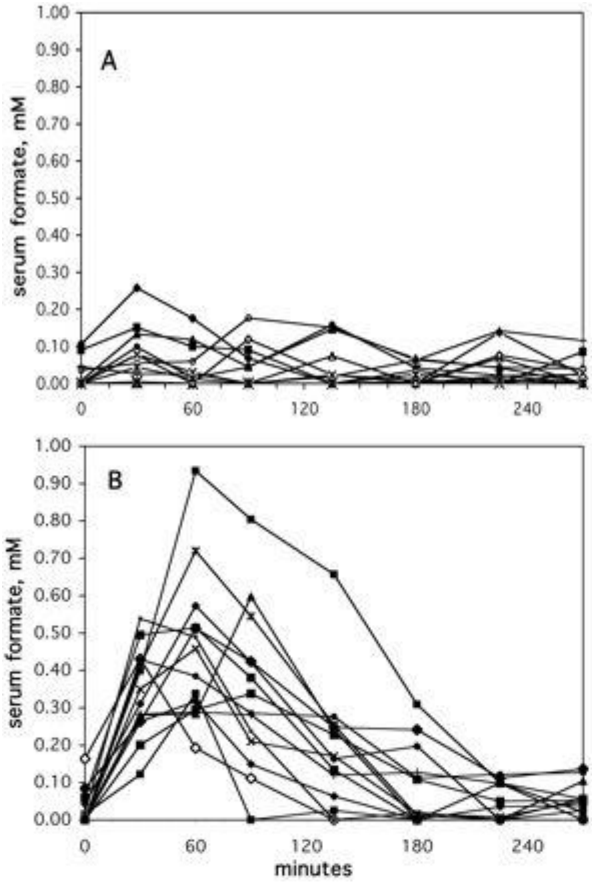

Fig. 3.3 *Plasma formate concentration versus time for 14 adult female human subjects following administration of placebo (A) or calcium diformate (B).*

This finding is in good correlation with the earlier reported human half-life of 45 minutes (Malorny (1969b); BPD ID A6.2_07; FA_BPR_Ann_II_8_8_06).

The disappearance of formate from blood is shown in Table 3.1-1.

Table 3.1-1: First-order elimination half-lives of formate in blood plasma in various species		
Species	**$t_{1/2}$ (min)**	**Source**
Rat	12	BPD ID A6.2_06; FA_BPR_Ann_II_8_8_05: Malorny, 1969a
Guinea pig	22	BPD ID A6.2_06; FA_BPR_Ann_II_8_8_05: Malorny, 1969a
Rabbit	32	BPD ID A6.2_06; FA_BPR_Ann_II_8_8_05: Malorny, 1969a
Monkey	30 - 50	BPD ID A6.2_11; FA_BPR_Ann_II_8_8_12: Clay et al., 1975
Human	45	BPD ID A6.2_07; FA_BPR_Ann_II_8_8_06: Malorny, 1969b
Human	59	FA_BPR_Ann_II_8_8_10: Hanzlik et al., 2005
Cat	67	BPD ID A6.2_06; FA_BPR_Ann_II_8_8_05: Malorny, 1969a
Dog	77	BPD ID A6.2_06; FA_BPR_Ann_II_8_8_05: Malorny, 1969a
Pig	87	BPD ID A6.2_08; FA_BPR_Ann_II_8_8_07: Makar et al., 1990
Pig	164	BPD ID A6.2_10; FA_BPR_Ann_II_8_8_09: [redacted] 1998

The pig shows the most limited metabolic capacities of reported test species (mouse >rat >monkey >human >pig). Formate metabolism in the pig in comparison to the rat was studied by Makar et al. (1990) (DocIIIA6.2_08; FA_BPR_Ann_II_8_8_07). 14C-radiolabeled formate was applied i.p. and determined in blood only, not including urine levels and exhaled CO2. No complete mass balance was provided. The species-specific metabolic capacities of the liver to convert formate were also analysed. The results indicated that the pig has very low levels of folates and low levels of key enzyme in the folate pathway as compared to rodents, monkey and humans. The pig's ability to dispose of formate was found more limited and much slower than that observed in rats or monkeys. It was suggested that the pig may be a suitable model for studying formate metabolism, because accumulation of formate and susceptibility to its toxic effects must be considered.

In humans, formate bioaccumulation is less likely to occur, based on the results of the early and the more recent single dose human studies (e.g. FA_BPR_Ann_II_8_8_10: Hanzlik et al, 2005), and based on the results of a recent repeat dose human study (Altaweel et al., 2009: FA_BPR_Ann_II_8_8_11). No formate accumulation was noted in a 14-day human study (12 females) who ingested 3900 mg calcium formate/day. The baseline serum formate level was 0.539 ± 0.06 mM in this study, maximal serum levels were approx. 0.8 mM (see below; figure and legend from Altaweel et al. (2009); FA_BPR_Ann_II_8_8_11).

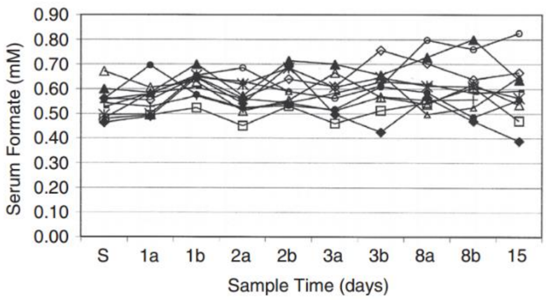

Fig. 3.4 *Serum formate concentrations determined prior to and throughout the 14-day study. The concentrations observed at screening (S) do not vary significantly, either for time groups or for individual subjects, over the course of the study. Observations 1a, 2a, 3a, 8a, and 15 were made prior to the first dose of the day indicated, while observations 1b, 2b, 3b, and 8b were made 40–60 min after ingesting the second 1,300 mg dose of calcium formate on the day indicated. The sample times "a" and "b" correspond, respectively, to the times of trough and peak levels of serum formate following single doses (see Ref. 36). The data show no accumulation of serum formate with repeated administration of 1,300 mg calcium formate three times per day over 14 days.*

Data on maximum blood levels of formate reported after single or repeated dosing of formic acid or formate salt are summarised in Table 3.1-2.

Massive serum formate levels are seen in primates (humans, monkeys) following methanol intoxication (see below). Higher formate serum levels are achievable following oral ingestion, compared to inhalation or dermal absorption. Massive serum formate levels are seen in primates (humans, monkeys) following methanol intoxication, whereas levels remain low in rats (not listed) unless the formic acid oxidase is inhibited by N2O-treatment. Under these conditions, formate levels are comparable to those seen in primates, i.e. the metabolic capacity of the rat was lowered to that of the primates, and under these conditions, the rat is also susceptible to toxic optical neurotoxicity.

Table 3.1-2: Maximum formate blood levels either after dosage of formic acid or formate salt or following methanol poisoning (see also Table 3.1-3)

Species	Substance	Route	Dose [mg/kg bw]	Peak blood level [mg/l]	Reference
Dog	Formic acid or Na formate	i.v. (~10 min)	~54 (as formic acid)	~200	BPD ID A6.2_06; FA_BPR_Ann_II_8_8_05: Malorny, 1969a
Pig	Na formate [CAS No. 141-53-7]	i.p.	~350 (as formic acid)	~470	BPD ID A6.2_08; FA_BPR_Ann_II_8_8_07: Makar et al., 1990
Pig	Potassium diformate [CAS No. 20642-05-1]	oral feed	~700 (as formic acid)	~400	BPD ID A6.2_10; FA_BPR_Ann_II_8_8_09: [redacted] 1998
Human (single cases)	Formic acid or Na formate	oral	~13	4 – 5 (baseline)	BPD ID A6.2_07; FA_BPR_Ann_II_8_8_06: Malorny, 1969b
		oral	~27	20	
		oral	~40	85	
Human (n=14) Single dose	Calcium formate	oral	2700 mg (as formate)	0.50 mM (mean)	FA_BPR_Ann_II_8_8_10: Hanzlik et al., 2005
Human (n=12) 14-day repeated dose	Calcium formate	oral	2700 mg/day (as formate)	0.572 mM (mean)	FA_BPR_Ann_II_8_8_11: Altaweel et al., 2009
Rat, N_2O-pre-treated	Methanol intoxication	oral	4000 mg/kg (methanol)	16 mM	Cited in BPD ID A6.10_01; FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000
Monkeys	Methanol intoxication	oral	Dose not stated (methanol)	11.4 mM	Cited in BPD ID A6.10_01; FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000
Humans	Methanol intoxication	oral	Dose not stated (methanol)	19.3 mM	Cited in BPD ID A6.10_01; FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000

A great deal of knowledge about the metabolism of formic acid has been extensively documented within the investigations into the mechanism of methanol intoxication. Formic acid is one of the main metabolites of methanol. The absorption, distribution and elimination of methanol and formate have successfully been modeled after inhalation exposure to methanol in various species including humans. The model predictions were in good agreement with experimental data in various species, i.e. rat, monkey, and human data, suggesting that the values of the pharmacokinetic constants used in the model are close to real values (DOCIIIA6.2_03; FA_BPR_Ann_II_8_8_02: Bouchard et al., 2001).

Formate has to be considered as the causative agent for optical neural damage in methanol-intoxicated humans and animals (DOCIIIA6.2_05; FA_BPR_Ann_II_8_8_04: Martin-Amat et al., 1978; DocIIIA6.10_01; FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000). The blood levels of formate that correlated with the emergence of pathological changes were very high: In a review by Eells et al. (2000) the following values after accidental and experimental methanol intoxication were summarised (see fig 3.5 representing Table 2 from Eells et al. (2000)):

TABLE 2. Blood formate, pH and bicarbonate concentrations in methanol-intoxicated rats, monkeys and humans.

Species	Blood Formate (mM)	Blood Bicarbonate (mEq/L)	Blood pH
N_2O - Treated Rats[a]	16.1 ± 0.7	7.7 ± 1.2	6.91 ± 0.06
Monkeys[b]	11.4 ± 1.2	6.5 ± 0.5	7.19 ± 0.02
Humans[c,d]	19.3 ± 4.4	3.2 ± 0.4	6.93 ± 0.02

Note: Methanol-intoxicated rats were exposed to a mixture of N_2O/O_2 (1:1) for 4 hours prior to methanol administration (4 g/kg at zero time followed by 2g/kg at 12-hour intervals) and exposure to the gas mixture was continued throughout the experiment. Blood formate concentrations and blood gas measurements were determined 60 hours after the initial dose of methanol. Each value represents the mean ± SE for 6 rats. Rodent data was compiled from studies by Eells *et al.*, (1996)[a]. The monkey data was compiled from studies by Martin-Amat *et al.*, (1977)[b] and the human data was compiled from studies conducted by McMartin *et al.*, (1980)[c] and Eells *et al.*, (1991)[d].

Fig. 3.5 *Eells et al. (2000) Table 2*

In four monkeys (Rhesus, *Maccaca mulatta*) receiving ~142 mg/kg bw/h of Na formate by i.v. infusion, the (steady-state) blood levels of formate amounted to 540, 950, 1350, and 1530 mg/l after 12, 20, 30 and 34 hours, respectively (DocIIIA6.2_05; FA_BPR_Ann_II_8_8_04: Martin-Amat et al., 1978). After 10 hours, all animals accumulated maximum formate in blood between 10 and 30 mEq/L (460 – 1380 mg/l). Under this extreme dosing regimen, the elimination half-lives had increased considerably up to about 5 hours, evidently due to metabolic overload and saturation [compare the dose of 142 mg/kg bw/h with the maximum metabolic capacity of 34 mg/kg bw/h, see above].

Critical blood concentrations of 8 – 15 mM formate (= 360 – 680 mg/l) maintained over 30 – 40 hours were considered potentially detrimental, producing experimental ocular toxicity in monkeys (DocIIIA6.2_05; FA_BPR_Ann_II_8_8_04: Martin-Amat et al., 1978) and were associated with visual toxicity in acute cases of human methanol intoxication (DocIIIA6.10_01; FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000).

Inhalation exposure to formic acid is supposed to be limited due to the warning of its pungent smell and its respiratory irritation unless through accidental events. 60 mg/m3 is considered to be the 13-weeks NOAEC for histological changes in the nasal region of rats and mice [see 13-week studies on rats and mice, DOCIIIA6.4.3_01/ FA_BPR_Ann_II_8_9_2_03 and

DOCIIIA6.4.3_02/ FA_BPR_Ann_II_8_9_2_04, and section 3.6.4]. As for solid formate, inhalable quantities of solid formate salts are limited.

Assuming 100% absorption, a human body weight of 60 kg, and a high respiration volume of 1.25 m3/h under working conditions (BPD ID A6.12.8_01; FA_BPR_Ann_II_8_12_8_01: NIOSH, 1990), this concentration would correspond to a systemic dose of 610 mg/8 h or ~10.2 mg/kg bw/d or ~1.3 mg/kg bw/h.

Compared with the maximum conversion rate of formate to CO2 in primates (BPD ID A6.2_12; FA_BPR_Ann_II_8_8_13: Kavet & Nauss, 1990), such an exposure level would not result in accumulation of formate.

At the maximum occupational exposure level of 5 ppm (9.5 mg/m^3), the systemic dose would be only 1.6 mg/kg bw/d or 0.2 mg/kg bw/h under these assumptions (BPD ID BPD ID A6.12.8_01; FA_BPR_Ann_II_8_12_8_01: NIOSH, 1990).

Table 3.1-3 Main results from key and supporting study summaries					
Summary table of toxicokinetic studies					
Method Guidelin e, GLP status, Reliabilit y	**Species, Strain, Sex, No/Grou p**	**Test substance, Dose levels Duration of exposure**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
In vitro / Physico-chemical studies on the behaviour of the TS in aqueous solutions. No guideline available	n.a.	Formic acid [CAS No. 64-18-6] Potassium diformate [CAS No. 20642-05-1] Route: not applicable Test procedure: Titration, calculations	At physiological pH 7, formic acid and potassium diformate are both exclusively present as formate anion		[redacted] 1997 BPD ID A6.2_01 FA_BPR_Ann_II_8_8_01
In vivo / No data, pharmaco-logical standards	Dog, not specified, 6/group	Formic acid [CAS No. 64-18-6] and Na formate [CAS No. 141-53-7] Route: i.v. (~10 min) Dose: ~54 mg/kg bw Sampling intervals : 0, 1, 2, 4 hours	<u>Elimination:</u> from blood $t_{1/2}$ = 77 min k_{el} = 0.54 h^{-1} <u>Blood levels:</u> Max. ~200 mg/l, Return to normal after 4 h <u>Baseline blood level</u>: ~7 – 12		Malorny, 1969a BPD ID A6.2_06 FA_BPR_Ann_II_8_8_05

		after dosing: blood pH, formate blood levels	mg/l (but high variance) Blood pH: transient acidosis, severe after formic acid and slight after Na formate, Return to normal after 3 to 4 h		
In vivo / No data, pharmaco -logical standards	Humans m + f 12, 7 and 2-3 per group	Formic acid [CAS No. 64-18-6] and Na formate [CAS No. 141-53-7] Route: oral Formic acid: 0.4% aqueous solution Na formate: in food Single dose Formic acid: 2000mg Na formate: 1.48, 2.96, 4.44 g (equivalent to 1000, 2000, and 3000 mg formic acid = ~13, 27, and 40 mg/kg bw) Sampling: kinetics plasma levels: blood after 5, 120 min; urine after 15 min to 6 h urinary excretion: before, 0-6, 6-12, 12-24 hrs after ingestion blood pH: before, at 15,	Absorption: rapid, maximum in blood after 10 – 30min Bioavailability: at 13 mg/kg bw in blood barely measureable, at ≥27 mg/kg max. 3-4fold increase in blood. Baseline blood level: ~3 – 4 mg/l (2 subjects) and 18 mg/l (1 subject) Max. blood level: 20 - 85 mg/l at 2000 mg Elimination: from blood $t_{1/2}$ = 45 min => k_{el} = 0.92 h^{-1} Clinical signs: transient gastric irritation immediately after the ingestion of 2 g formic acid as 0.4% aqueous solution.		Malorny, 1969b BPD ID A6.2_07 FA_BPR_Ann_II_8_8_06

		30, 45, 60, 75, 90 min after ingestion			
In vivo / no data	Pig (crossbred) n=6 sex not reported *Control animal: Rat Spraque-Dawley male, n=5*	[14]C-Na formate [CAS No. 141-53-7] Route: i.p. Dose: 500 mg/kg bw. (~350 mg formic acid/kg) Blood kinetics and liver folate metabolism (comparison among various species) Sampling intervals: 90, 180, 240, 300 min after dosing	<u>Elimination:</u> from blood $t_{1/2}$ = 87 min k_{el} = 0.48 h^{-1} Max. blood level: ~470 mg/L The pig shows the most limited metabolic capacities of reported test species (mouse >>rat >monkey >human >pig).		Makar et al., 1990 BPD ID A6.2_08 FA_BPR_Ann_II_8_8_07
In vivo / No data, pharmacol. standards	Pig Crossbred (50% Duroc, 25% Yorkshire, 25% Danish Landrace) n=4, female	Potassium diformate [CAS No. 20642-05-1] Route: 6% in oral feed High single dose: 1000 mg/ kg bw (= ~700 mg formic acid/kg bw) Blood sampling: before, 0.5, 1, 1.5, 2, 3, 4, 5, 7, 12, 24 hours after at least 80% of the feed was eaten.	<u>Absorption:</u> rapid with maximum in blood after ~4 h <u>Bioavailability:</u> Mean dose systemically bioavailable (AUC) = 2834.6 mg x h/l = ~13.5 % of the mean dose applied Baseline blood level: ~1.9 mg/l Max. blood level, C_{max} = 386 mg/l <u>Elimination:</u> from blood $t_{1/2}$ = 2.73 h		[redacted] 1998 BPD ID A6.2_10 FA_BPR_Ann_II_8_8_09

		Plasma formate concentrations used for calculation of the biological half-life ($t_{1/2}$), AUC, and C_{max}. Calculations according to a two compartment pharmacokinetic model, absorption and elimination processes considered to follow first-order kinetics.	k_{el} = 0.25 h^{-1} Plasma formate concentrations returned to baseline after ~12 h p.a.		
In vivo / No data, pharmacol. standards	**Human subjects**, females, n=14	Calcium formate [CAS No. 544-17-2] Route: oral Single oral dose, 3900 mg (i.e. 2700 mg formate), split into 6 doses of 650 mg each	Endogenous formate level 0.024 ± 0.008 mM <u>Absorption</u>: maximal serum level (mean: 0.50 mM) @ 60 min after dosing. <u>Elimination</u>: mono-exponential decline of serum concentrations, average half-life 59 +/- 7 min. Baseline levels within 240 minutes post dosing		Hanzlik et al., 2005 FA_BPR_Ann_II_8_8_10
In vivo / No data, pharmacol. standards	**Human subjects**, females, n=12	Calcium formate [CAS No. 544-17-2] Route: oral 14-days study, 3900 mg/day (i.e.	Mean basal serum formate level before study initiation: 0.539 ± 0.06 mM Formate levels only slightly		Altaweel et al., 2009 FA_BPR_Ann_II_8_8_11

		2700 mg formate/day), split into 3 daily doses of 1300 mg each	increased at 40-60 min after dosing: up to 0.8 mM: No formate accumulation: serum formate level on day 15: 0.582 ± 0.091 mM; no significant difference between this value and the basal level before treatment (p=0.268).		

3.1.1 Short summary of the toxicokinetic information

Conclusions:

Formic acid is considered to be available by all potential routes of exposure. Inhalation may be the most relevant route during production and application.

For risk characterisation a value of 100% is used for oral absorption (rapid, but no quantitative data available) and for absorption via inhalation (no data available).

Dietary consumption of formic acid and its salts (estimated 0.4 and 1.2 mg/kg bw/day), inhalation as air contaminant as well as the endogenous turn-over maintain a baseline blood level of about 3 to 18 mg/l in humans; in a more recent study, it was found to be 0.539 mM.

Biotransformation of formate to CO2 in primates is rapid: the first-order elimination half-life in human blood is approx. 45 min, corresponding to an elimination constant of about 0.9 h-1, and the metabolic oxidation rate of formate is reported to be 34 mg/kg bw/h (0.75 mmol/kg bw/h). In human volunteers, a minor part was excreted unchanged into the urine within 24 hours. No accumulation is expected to occur, except at prolonged exposures above the critical capacity limit.

The steady-state blood concentration from a continuous dosage of 10 mg formic acid/kg bw/h that is systemically bioavailable will be of the order of 11 mg/l in humans, while a continuous dose of 30 mg/ kg bw/h, at the borderline of metabolic saturation, is supposed to level off at 33 mg/l (see assumptions and estimation below).

Following inhalation, the experimental NOAEC of 61 mg/m3 in mice, corresponding to a 8-h dose of ~1.3 mg/kg bw/h would remain well below the metabolic capacity limit and result in a transient steady-state of approx. 17 mg/l in blood (in addition to the baseline level).

At the maximum occupational exposure level of 5 ppm (9.5 mg/m3), the systemic dose would be only 0.2 mg/kg bw/h, and the increment expected in blood would be indistinguishable from the endogenous fraction in blood.

Toxic effects are only expected, if the maximum metabolic oxidation rate becomes exhausted [>34 mg/kg bw/d], and thus critical formate blood concentrations are reached. These are reportedly in the range of 8 to 15 mM (= 360 – 680 mg/l).

The estimation below demonstrates that a bioavailable body burden of 1 mg formate/kg bw/h still fails to produce blood increases that are distinguishable from the baseline level, remaining at a factor of 300 to 600 below toxicologically relevant blood levels.

Estimation of a steady-state blood level:

The single-dose data can be used to estimate a blood concentration in equilibrium (steady state):

Assumption: Continuous oral uptake

Exemplary dose [D]: 1, 10, and 30 mg/(kg bw∗h)

Gastro-intestinal bioavailability: 100 %

Elimination constant [k_{el}]: 0.9 h^{-1} (from BPD ID A6.2_07/ FA_BPR_Ann_II_8_8_06)

Distribution volume [V_d]: 1 litre/kg bw*)

*) Note: Reportedly, the distribution volumes for formate range from about 4 to 6 litre/kg bw. But these values appear to be governed mainly by the rapid metabolism and excretion from the circulatory system. However, these processes are already comprised in the elimination constant k_{el}. Hence, a *high* distribution volume in the algorithm would be a bias resulting in underestimating the blood level. Therefore, adopting the conservative assumption of 1 litre/kg bw for the distribution volume of formate appears to be the more appropriate approach.

The steady-state concentration [C_{eq}] is described by the following equation:

$$C_{eq} = \frac{\text{Dose [mg/h]}}{bw * V_d * k_{el}} \text{ mg/l}$$

Table 3.1-4 Predicted steady-state concentration in blood C_{eq} during continuous dosage of Na-formate above baseline level						
	Elimination constant k_{el} [h^{-1}] / distribution volume Vd [L/kg]	**Predicted steady-state concentration in blood C_{eq} during continuous dosage of Na-formate above baseline level (excluding baseline) (assumed absorption rate 100 %)**			**Baseline level in blood [mg/l]**	**Toxicologically relevant level [mg/l]**
		Dose [mg/(kg∗h)]				
		1	**10**	**30**		
Pig	0.25 / 1	4	40	120	~2 1)	No data
Human	0.90 / 1	1.1	11	33	3 – 18 2)	>360 3)

1) from BPD ID A6.2_10/ FA_BPR_Ann_II_8_8_09
2) from BPD ID A6.2_07/ FA_BPR_Ann_II_8_8_06
3) BPD ID A6.10_01/ FA_BPR_Ann_II_8_13_5_01

Dermal absorption

Dermal absorption of formic acid has not been investigated. Due to the corrosive properties of formic acid, no dermal absorption study is requested. In a first tier of risk assessment, a worst case value for dermal absorption of 100% is used for external dermal exposure. Severe metabolic acidosis resulting from dermal contact with formic acid as described in several case reports (see section 3.3 and 3.14), demonstrated rapid dermal absorption through the acid-burned skin.

3.1.2 Values and conclusions used for the risk assessment

Value(s) used in the Risk Assessment – Oral absorption	
Value(s)	100%
Justification for the selected value(s)	Formic acid is rapidly absorbed after oral ingestion by humans (DocIIIA6.2_07; FA_BPR_Ann_II_8_8_06: Malorny, 1969b) Rapid absorption, but no quantitative data available[3]

Value(s) used in the Risk Assessment – Dermal absorption	
Value(s)**	100%
Justification for the selected value(s)	Dermal absorption of formic acid has not been investigated. A dermal absorption of 100% is used for external dermal exposure because rapid dermal absorption was demonstrated following acid skin burns in several case reports.

** the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Value(s) used in the Risk Assessment – Inhalatory absorption	
Value(s)	100%
Justification for the selected value(s)	no data available (assumed 100% resorption)

Conclusion(s) used in the Risk Assessment – Distribution	
Conclusion	No data

[3] Due to animal welfare reasons an oral absorption study was not provided for formic acid as corrosive substance. However, the available toxicokinetic data and data on absorption after accidental or suicidal oral ingestion of the substance by humans indicate rapid and almost quantitative absorption.
Generally, the smaller the molecule the more easily it may be taken up. With a molecular weight of 46.03 g/mol formic acid is very favorable for oral absorption.
Furthermore, formic acid is miscible with water at any ratio which also favors oral absorption since water-soluble substances will readily dissolve into gastrointestinal fluids. Additionally, molecules with a molecular weight lower than 200 may pass through aqueous pores or may be carried through the epithelial barrier by the bulk passage of water.
Together with the observed clinical signs after oral ingestion, it is highly probable that formic acid is orally absorbed to a high extent.
As worst case 100% absorption is assumed.

Justification for the conclusion	no data available; assumed distribution in the aqueous compartment: seemingly a significant proportion of formate distributes in the tissue, but more likely undergoes rapid metabolism and excretion Assumptions presented are based on a PBPK model. The physico-chemical properties of formic acid suggest the likelihood of it crossing blood/brain, blood/testes, and blood/placenta barriers is low. Transfer into breast milk may occur due to high water solubility.

Conclusion(s) used in the Risk Assessment – Metabolism	
Conclusion	Rapid oxidation to CO_2 and H_2O No toxicologically significant metabolites
Justification for the conclusion	maximum elimination rate of formate: Monkey: 34 mg/(kg bw*h) Rat: 73 mg/(kg bw*h)

Conclusion(s) used in Risk Assessment – Elimination	
Conclusion	Rapid elimination from blood plasma No potential for accumulation Rate and extent of excretion: human: 2 to 4%/24h unchanged into the urine, ~65 - >80% thereof excreted within the first 6h.
Justification for the conclusion	Humans: elimination half-life (t1/2) = 45 min corresponding to an elimination constant of about 0.9 h^{-1} Rapid biotransformation of formate to CO_2 in primates Metabolic oxidation rate of formate 34 mg/kg bw/h (monkey). Human volunteers: minor part was excreted unchanged into the urine within 24 hours (see above). No accumulation is expected to occur, except at prolonged exposures above the critical capacity limit.

Species	**$t_{1/2}$ (min)**
Rat	12
Guinea pig	22
Rabbit	32
Monkey	30 - 50
Human	**45**
Cat	67
Dog	77
Pig	87
Minipig	164

3.2 ACUTE TOXICITY

The acute toxic action profile of formic acid is predominantly determined by its inherent irritating/corrosive properties. The toxicity values after oral uptake and inhalation in rats suggest formic acid to be acutely harmful. The clinical signs give no evidence of specific systemic adverse effects.

3.2.1 Acute oral toxicity

Summary table of animal studies on acute oral toxicity						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance Dose levels, Type of administration** *(gavage, in diet, other)*	**Signs of toxicity** *(nature, onset, duration, severity, reversibility)*	**Value LD50**	**Remarks** *(e.g. major deviations)*	**Reference**
OECD 401 GLP: no Rel: 1	Rat Wistar m + f 5/sex/group	Formic acid purity 99% Lot/batch: no data 501, 631, 794, 1000 mg/kg bw gavage	Clinical signs: - observed 30 min after dosing: unkept fur, hunched posture, stagger, aggressiveness, dyspnea, sedation and ataxia, lateral and abdominal position, convulsions, bloody noses, blood in urine. - later: hypothermia, pale limbs, body weight loss. - Symptoms subsided and were absent in all animals but one which showed symptoms until d14.	730 mg/kg bw (m +f) Males: 863 mg/kg bw Females: 618 mg/kg bw		BPD ID A6.1.1_01, FA_BPR_Ann_II_8_7_1_01: [redacted], 1985

Formic acid is of moderate toxicity via the oral route when tested in the rat. Oral LD_{50} = 730 mg/kg bw.

After a single *oral* administration of formic acid in the rat (DocIIIA6.1.1-01, FA_BPR_Ann_II_8_7_1_01: [redacted] 1985), there was a clear dose-response relationship with respect to mortality and decrease in body-weight gain of survivors. The clinical symptoms and pathological organ lesions (hyperemia of the stomach and intestines, congestion in spleens, mottled livers and kidneys, discoloration of kidneys and pancreas) are largely nonspecific and can be explained primarily by the local corrosive character of formic acid, associated secondary systemic effects.

For human data: see section 3.14.

Several case reports report on fatal suicidal ingestion of formic acid (see section 3.14 for a detailed discussion). Due to the corrosivity of formic acid, local effects occur at all dose levels. The amount ingested and the concentration determine the grade and the location of the effects. Therefore, the observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the esophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity. Systemic toxicity was seen after ingestion **of 30 g formic acid** or more. Prognosis is poor after massive oral ingestion (>45 to 200 g formic acid); prognosis is moderate after moderate oral ingestion (approx. 30 to 45 g); lesions, but low mortality, are expected in most cases with low amounts ingested (<30g); persistent lesions due to tissue corrosion must be expected in cases with >10 g formic acid ingested. Tissue destruction of the gastrointestinal tract may result in fatal bleeding, septic shock, or stricture which may require surgical treatment. Reversibility of effects was often seen in cases with low amounts ingested (<10 g formic acid).

Important note: Final LD_{50} will be set by RAC; it is the LD_{50} value from the adopted RAC opinion that will need to be used in biocidal product authorisation.

Value used in the Risk Assessment – Acute oral toxicity	
Value	LD_{50} 730 mg/kg bw[4]
Justification for the selected value	BPD ID A6.1.1_01, FA_BPR_Ann_II_8_7_1_01: [redacted] 1985 Acute oral toxicity of formic acid has been assessed in a study according to OECD 401.

4 Final LD_{50} will be set by RAC; it is the LD_{50} value from the adopted RAC opinion that will need to be used in biocidal product authorisation.

3.2.2 Acute dermal toxicity

Summary table of animal studies on acute dermal toxicity					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, Vehicle, Dose levels, Surface area,**	**Value LD_{50}**	**Remarks** *(e.g. major deviations)*	**Reference**
OECD 402 GLP: yes Rel: 1	Rat Wistar m + f 5/sex/group	Sodium formate [CAS No. 141-53-7] purity 100% Lot/batch: 1292066 2000 mg/kg bw limit test Vehicle: 0.5% CMC 24 hours, semi-occlusive Surface area 40 cm^2 (10% of body surface)	>2000 mg/kg bw No clinical signs, or local, or systemic effects observed. No mortality.	Other test substance: sodium formate	BPD ID A6.1.2_01, FA_BPR_Ann_II_8_7_3_01 [redacted] 2007

No acute *dermal* study has been conducted with formic acid itself because of its corrosive properties. After single dermal exposure of the sodium salt in the rat (DocIIIA6.2.1-01, FA_BPR_Ann_II_8_7_3_01: [redacted] 2007), no local irritation and systemic effects were observed. Dermal LD_{50} of sodium formate >2000 mg/kg bw.

Human case reports on acute 'accidental' dermal (and inhalation) exposure are rather rare. Besides local effects, severe acid skin burns and respiratory tract irritation, patients suffered and recovered rapidly from metabolic acidosis (described in section 3.3 and 3.14).

Value used in the Risk Assessment – Acute dermal toxicity	
Value	No data available on formic acid Supportive data: Sodium formate: LD_{50} >2000 mg/kg bw

Justification for the selected value	According to regulation (EU) 528/2012 Annex II 8.7 acute toxicity studies does not generally need to be conducted if the substance is classified as corrosive to the skin due to animal welfare reasons. Hence, the information on the acute dermal toxicity of the corresponding salt, sodium formate, is only supportive information, as no information on acute dermal toxicity is needed for this substance. BPD ID A6.1.2_01, FA_BPR_Ann_II_8_7_3_01: [redacted] 2007 Acute dermal toxicity of sodium formate has been assessed in a study according to OECD 402.

Data waiving	
Information requirement	Acute dermal toxicity of formic acid
Justification	Corrosive substance

3.2.3 Acute inhalation toxicity

Summary table of animal studies on acute inhalation toxicity					
Method, Guideline, **GLP status, Reliability**	**Species, Strain, Sex, No/group**	**Test substance, form** *(gas, vapour, dust, mist)* **and particle size** *(MMAD)* **Actual and nominal concentration, Type of administration** *(nose only / whole body/ head only)*	**Value LC50**	**Remarks** *(e.g. major deviations)*	**Reference**

Comparable to OECD 403 GLP: no Rel. 2	Rat Sprague-Dawley m+f 10/sex/group	Formic acid purity 98% Lot/batch: no data 2.82, 6.60, 8.08, 10.6, 14.7 mg/l (analytical); 4.03, 8.50, 10.58, 13.40, 17.90 mg/l (nominal) 4 hours whole body vapour	7.4 mg/l (m+f) Males: 7.3 mg/l Females : 7.5 mg/l Clinical signs (in all treated groups): Closed lids, snout swiping, discharge from the nose and eye, corrosion of nose and eyes, salivation, corneal opacity, loss of pain reflex, dyspnea, respiration sounds, flatulence, apathy, hunched posture, unsteady gait Symptoms persisted until d14 after treatment (except for the 2.82 mg/l group: symptom free at d11) Mortality: within 7 days post exposure (inflated lungs, dilated hearts). BW at d7: dose-dependent decrease		BPD ID A6.1.3_01; FA_BPR_Ann_II_8_7_2_01 [redacted] 1980

Formic acid is of moderate toxicity via inhalation when tested in the rat. LC_{50} (4hrs) = 7.4 mg/l = 7400 mg/m³.

Following a 4-hour *inhalation* of formic acid vapours in rats (DocIIIA6.1.3-01; FA_BPR_Ann_II_8_7_2_01: [redacted] 1980), clinical signs indicated corrosive properties of the test substance, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose in some cases. Symptoms persisted until termination 14 days after the rats were exposed to 6.6 mg/l or above. Deaths occurred within 7 days. Inflated lungs and dilated hearts were seen in animals that died; gross pathology revealed no changes in animals sacrificed at termination.

Human case reports on acute ‘accidental‘ inhalation (and dermal) exposure are rather rare. Besides local effects, severe acid skin burns and respiratory tract irritation, patients suffered and recovered rapidly from metabolic acidosis (described in section 3.3 and 3.14).

Note: the applicant has submitted a re-interpretation of the 1980 [redacted] study (FA_BPR_Ann_II_8_7_2_01-new) and concludes to a higher LC_{50} value of 7.85 mg/l. BE cannot accept this re-interpretation. The applicant’s justification for this re-interpretation can be found in the PT5 specific Kemira confidential Annex to the PT5 CAR, along with BE’s clarification for refusal.

Value used in the Risk Assessment – Acute inhalation toxicity	
Value	LC_{50} 7.4 mg/l
Justification for the selected value	DocIIIA6.1.3-01; FA_BPR_Ann_II_8_7_2_01: [redacted] 1980 Acute inhalation toxicity of formic acid has been assessed in a study comparable to OECD 403.

3.2.4 Overall conclusion on acute toxicity

Value used in the Risk Assessment – Acute systemic toxicity	
Value	See below
Justification for the selected value	Appropriate studies are available for determining the LD_{50} oral and LC_{50} inhalation of formic acid. The acute toxic action profile of formic acid is predominantly determined by its inherent irritating/corrosive properties. The toxicity values after oral uptake and inhalation in rats suggest formic acid to be acutely harmful. The clinical signs give no evidence of specific systemic adverse effects.
Classification according to CLP and DSD	Acute toxicity, oral, cat. 4, H302 Acute toxicity, inhalation, cat. 3, H331 Corrosive properties determine the toxicity of formic acid; additional labeling EUH071

Value/conclusion used in the Risk Assessment – Acute local effects	
Value/conclusion	LD_{50} oral 730 mg/kg bw (formic acid)[5] LC_{50} inhalation 7.4 mg/l (formic acid) LD_{50} dermal >2000 mg/kg bw (Na formate)

5 Final LD_{50} will be set by RAC; it is the LD_{50} value from the adopted RAC opinion that will need to be used in biocidal product authorisation.

Justification for the selected value/conclusion	Appropriate studies are available for determining the LD_{50} oral and LC_{50} inhalation of formic acid. Due to the corrosivity of formic acid, local effects occur at all dose levels. Pathological organ lesions recorded after oral administration included hyperemia of the stomach and intestines, congestion in spleens, mottled livers and kidneys, discoloration of kidneys and pancreas. Clinical signs after inhalation, closed lids, snout swiping, discharge from the nose and eye, corrosion of nose and eyes, salivation, corneal opacity, loss of pain reflex, dyspnea, respiration sounds, flatulence, apathy, hunched posture, unsteady gait, indicated the corrosive properties of formic acid, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose. The acute dermal toxicity of formic acid was not tested and not requested because of its corrosive properties.

3.3 IRRITATION AND CORROSION

3.3.1 Skin corrosion and irritation

Summary table of animal studies on skin corrosion/irritation					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, Vehicle,** **Dose levels, Duration of exposure**	**Results** *Average score (24, 48, 72 h), observations and time point of onset, reversibility, other adverse local/systemic effects, histopathological findings*	**Remarks** *(e.g. major deviations)*	**Reference**
n.a. corrosive substance; no *in vivo* testing acc to OECD 404 performed					
OECD 406 Buehler Test GLP: yes Rel. 1	Guinea pig Female 20/group 10 naïve controls	Formic acid purity 85.3% Induction: 7.5% formic acid in water challenge: 2% formic acid in water	Result: not sensitizing Pre-test: Min. irritant conc.: 5%; Max. non-irritant conc. 2%		BPD ID A6.1.5_01; FA_BPR_Ann_II_8_3_01 [redacted] 2002.

Summary table of human data on skin corrosion/irritation				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Case report	Formic acid conc. not known	Route of exposure: dermal 1 male, 35-year-old	Accidental splash from a container on the maxilla, chin, around mouth, thorax Clinical signs: burning pain, scialorrhae, nausea, vomiting Skin: blisters, necrotic areas Systemic: blood pressure 110/60, pulse and breathing regular, blood gases and acido-balance normal, no formic acid detected in blood and urine Result: Skin corrosion Reversible within 8 days	BPD ID A6.12.2_07a ; FA_BPR_Ann_II_8_12_2_07 Malizia et al.,1977
Case report	Formic acid undiluted, conc. not known	Route of exposure: dermal 1 female, 15-year-old	Accidental splash on lower extremities (20% of total body surface) Clinical signs: burns, nausea, vomiting (4 hrs after exposure = start treatment) Skin: depth of burns not determined, became full-thickness. Gross edema on d2 and d3 without fever, ocular damage or pulmonary complications. Burns surgically revived on d16, grafted several times. Major scarring of burned areas persisted. Urine: brownish, hemoglobinuria Blood: pH 7.23, HCO_3 16.7 mmol/l, base deficit 9.5, hemolysis Patient recovered rapidly from metabolic acidosis	BPD ID A6.12.2_08 ; FA_BPR_Ann_II_8_12_2_08 Sigurdsson et al., 1983

			Result: Skin corrosion Mild metabolic acidosis Reversibility: No: severe burns required several grafts, major scarring	
Case report	Formic acid 90%	Route of exposure: dermal 1 female, 3-year-old	Accidental splash on right torso and extremities (35% of total body surface) Clinical signs: severe distress (10 min after exposure = start treatment) Skin: full-thickness second- and third-degree burns. Required several skin grafts during several months Urine: initially dark red, hemoglobinuria resolved within few days without kidney failure Blood: pH 6.85, HCO_3 16.7 mmol/l, base deficit -29.7 on 100% oxygen, bicarbonate 6mEq/l; initial serum formate level 400 µg/ml, hemolysis Patient recovered rapidly from metabolic acidosis. Result: Skin corrosion Metabolic acidosis Reversibility: No: severe burns required several grafts	BPD ID A6.12.2_09 ; FA_BPR_Ann_II_8_12_2_09 Chan et al., 1995

No skin and eye irritation study reports are available on formic acid itself. Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive (according to DSD: C, R 35) in the EU (12th ATP) (see DOC-IIIA6.4.1_e / FA_BPR_Ann_II_8_2_0: Justification and A6.4.1_s/ FA_BPR_Ann_II_8_1_0: Justification).

A Buehler test was made available for assessment of skin sensitization ([redacted] 2002; BPD ID A6.1.5_01; FA_BPR_Ann_II_8_3_01). There was no evidence of a sensitising potential in guinea pigs using the method of Buehler. During the irritation screen performed for this study with formic acid diluted in water, the minimum irritant concentration was found to be 5% formic acid in water; the maximum non-irritant concentration was found to be 2% formic acid in water.

Sodium formate [CAS No. 141-53-7] produced no skin irritation in an acute dermal toxicity test (see section 3.2.2).

Human data: see 3.14 for a detailed discussion.

The corrosive potential of formic acid has been reported on several [redacted] occasions after accidental dermal exposure in humans and documented in case reports. Malizia et al., 1977 (DocIIIA6.12.2-07; FA_BPR_Ann_II_8_12_2_07) reported blisters and necrotic areas on the skin of a man after an accidental exposure from a formic acid splash on the face and thorax. The skin around the acid-burned region was hyperaemic and oedematous. The local skin corrosion was without signs of systemic toxicity. The patient recovered after 8 days.

Sigurdsson et al., 1983 (DocIIIA6.12.2-08; FA_BPR_Ann_II_8_12_2_08) reported an agricultural accident with a girl who's legs were hit by a splash of formic acid. The patient complained of nausea and vomited on arrival at the hospital. The burns turned out to be full-thickness. Gross oedema formed on d2 and d3. The burn was surgically revised and grafted. However, major scarring of the burned area persisted. Apart from the local skin corrosion and scarring, there was absorption of formic acid, which caused metabolic acidosis with hemolysis and hemoglobinuria.

Another accidental splash exposure on the right torso and extremities of a 3-year-old girl was reported by Chan et al., 1995 (DocIIIA6.12.2-08; FA_BPR_Ann_II_8_12_2_09). The patient was in severe distress. The dermal exposure to formic acid caused severe systemic toxicity: severe metabolic acidosis with haemolysis and haemoglobinuria. Only 10 minutes after the accident medical treatment started and further dermal absorption prevented. Nevertheless, the initial serum formate level was 400 µg/ml. Full-thickness second- and third-degree burns affected 35% of the total body surface, and required several grafts and long-term treatment.

Conclusion used in the Risk Assessment – Skin irritation and corrosivity	
Value/conclusion	Formic acid is corrosive to skin
Justification for the value/conclusion	No skin and eye irritation study reports are available on formic acid itself. Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive in the EU (12^{th} ATP) Harmonized classification and SCLs: Skin Corr 1A; H314 Skin Corr. 1B; H314: 10% ≤ C < 90% Skin Corr. 1A; H314: C ≥ 90%

	Skin Irrit. 2; H315: 2% ≤ C < 10%

Data waiving	
Information requirement	Skin irritation study on formic acid
Justification	Formic acid is a corrosive substance

3.3.2 Eye irritation

Conclusion used in Risk Assessment – Eye irritation and corrosivity	
Value/conclusion	Formic acid is corrosive to the eye
Justification for the value/conclusion	No skin and eye irritation study reports are available on formic acid itself. Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive in the EU (12^{th} ATP) Harmonized classification and SCLs: Skin corr 1A, H314 Eye Irrit. 2; H319: 2% ≤ C < 10% Additional proposed classification and SCLs: Eye dam/irrit 1, H318 Eye dam. 1; H318: C ≥ 10%

Data waiving	
Information requirement	Eye irritation study on formic acid
Justification	Formic acid is a corrosive substance

3.3.3 Respiratory tract irritation

Summary table of animal studies on respiratory tract irritation					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance** **Dose levels, Duration of exposure**	**Results** *clinical signs, histopathology, reversibility*	**Remarks** *(e.g. major deviations)*	**Reference**
Alarie (1973), ASTM (1984). GLP: yes Rel. 1	Mouse, Swiss Webster male, 5/group	Formi®LHS Potassium formate (1:2) Purity 99.8% Lot/batch: B0298 Inhalation nebulation, nose-only 267, 568, 622, and 802 mg/m³ (analytical) MMAD: 1.2µm 10 min acclimatisation, 30 min exposure, 20 min recovery	RD50 = 615 mg/m³ [RD50 = 608 mg/m³ (Alarie, 1973) RD50 = 623 mg/m³ (Bos et al., 1992)] ~ weak sensory irritant of the upper respiratory tract Asymptomatic decrease of the breathing rate at exposure time. Max. decrease towards the end. RD50 calculated from the mean of the 7 last measurements (minutes 18 to 30 of exposure). No other changes in behaviour. Breathing rate returned to normal within the recovery period. The tidal volume was not affected by treatment. Necropsy: 1 petechia noted in 1 lung lobe of 1 animal. Similar occasional findings in unexposed animals. No mortality. Reversibility: Yes, within the 20-min recovery period		BPD ID A6.1.6_01; FA_BPR_Ann_II_8_13_2_01 [redacted] (1999)
In accordance with OECD 413	Rat, Fischer 344/N, m + f	Formic acid purity 95%	$NOAEL_{local}$: 30 mg/m³		BPD ID A6.4.3_01; FA_BPR_Ann_II_8_9_2_

GLP: yes Rel. 1	10/sex	0, 15, 30, 61, 122, 244 mg/m^3 (nominal) 6h/d, 5d/wk, 13 weeks Vapour, whole body	LOAEL$_{local}$: 61 mg/m^3 No clinical signs Local effects: nasal irritation, squamous metaplasia of the respiratory epithelium, olfactory degeneration, severity minimal to mild. Respiratory epithelium squamous metaplasia: mg/m^3 0 15 30 61 122 244 male 0 0 0 0 0 9 female 0 0 0 0 0 6 Olfactory epithelium degeneration: minimal to mild mg/m^3 0 15 30 61 122 244 male 0 0 0 1 1 9 female 0 0 0 0 0 5		03 Thompson, 1992
In accordance with OECD 413 GLP: yes Rel. 1	Mice B6C3F$_1$ m + f 10/sex	Formic acid purity 95% 0, 15, 30, 61, 122, 244 mg/m^3 (nominal) 6h/d, 5d/wk, 13 weeks Vapour, whole body	NOAEL$_{local}$: 61 mg/m^3 LOAEL$_{local}$: 122 mg/m^3 No clinical signs Local effects: nasal irritation, olfactory degeneration, severity minimal but dose-related. Olfactory epithelium degeneration: minimal mg/m^3 0 15 30 61 122 244 male 0 0 0 0 0 2 female 0 0 0 0 2 5		BPD ID A6.4.3_01; FA_BPR_Ann_II_8_9_2_04 Thompson, 1992

Summary table of human data on respiratory tract irritation				
Type of data/report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Case report	Formic acid 98%	Route of exposure: inhalation 1 male, 39-year-old	Accidental spray (aerosol) onto the face with concomitant inhalation Clinical signs: facial burns (3% of total body surface), dyspnea Nasopharyngoscopy: mild supraglottic erythema, normal vocal cords Skin: second-degree burns Pulmonary function tests: Vital capacity reduced on d1, recovered largely within 14 days. Complains of dyspnea till d15 Day 1 FVC (L): 3.74 (79% predicted) FEV_1 (L): 2.86 (73% predicted) FEV_1/FVC: 76.38 (92% predicted) FEF $_{25\%-75\%}$ (l/sec): 2.32 (56% predicted) Day 15 FVC (L): 4.35 (92% predicted) FEV_1 (L): 3.62 (92% predicted) FEV_1/FVC: 83.09 (101% predicted) FEF $_{25\%-75\%}$ (l/sec): 3.82 (92% predicted) Reversible Pulmonary dysfunction: Reactive Airway Dysfunction Syndrome Reversible within 15 days	BPD ID A6.12.2_10 ; FA_BPR_Ann_II_8_12_2_10 Yelon et al., 1996

The airway irritating properties were studied by exposing mice to potassium diformate at concentrations of 267, 568, 622, 802 mg/m³ for a single period of 30 minutes (DocIIIA6.1.6-01; FA_BPR_Ann_II_8_13_2_01: [redacted] 1999). Animals were necropsied 7 days after exposure. Inhalation of nebulized potassium diformate solutions irritated the upper airways and caused a decrease of the respiratory rate and post-inspiratory apnoea in a concentration-dependent manner. Treatment-related changes in tidal volume were not observed. The RD_{50} values were obtained with two calculation methods, which were in good agreement. Since the RD_{50} values found at each concentration level did not increase or decrease with increasing concentrations, it was concluded that except sensory irritation other possible toxic actions were absent. No other effects were observed (behaviour, body weight, lung weight, macroscopic and histopathological findings: lungs, nasal cavity). The overall RD_{50} was 615 mg/m³. This study detected clearly the irritating effects caused by potassium diformate, however without any histopathological changes. As such, this data does not allow a conclusion on a relationship between the RD_{50} and the concentration inducing histopathological changes in the respiratory tract.

In addition, in the acute inhalation study in rats (see 3.2. Acute toxicity) clinical signs indicated the corrosive properties of formic acid, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose. Symptoms persisted until termination 14 days after the rats had been exposed to 6600 mg/m³ and above.

Further evidence of respiratory tract irritation is found in the histopathological data of the nasal cavity of the repeated dose inhalation toxicity studies performed with formic acid vapours (13-week inhalation, rat, mouse). See section 3.6. for a more detailed discussion.

Subchronic 13-week inhalation studies with formic acid vapour at concentrations of 0, 15, 30, 61, 122, 244 mg/m³ were conducted in rats and mice (DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_03 and DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_04: Thompson, 1992). Both in the rat and the mouse, the inhalation of formic acid did not result in clinical effects. In the rat, microscopic changes occurred in the respiratory and olfactory epithelium of the nose. Changes on the respiratory epithelium consisted of a minimal squamous metaplasia in which the pseudostratified, ciliated columnar cells were replaced by a flattened, non-ciliated epithelium with approximately 2 to 5 cells in thickness. Squamous metaplasia occurred most often in the respiratory epithelium that lines the most dorsal portion of the dorsal meatus in the nose's anterior section (Level I). In the olfactory epithelium, degenerative changes were minimal to mild and generally limited to the area of the dorsal meatus in the mid-nasal section (Level II). Degeneration was characterised by a loss of the usual orderly arrangement of the pseudostratified layer of nuclei and by a slight reduction on the normal thickness of the olfactory epithelium. There was no necrosis. No evidence was seen of metaplasia of the olfactory epithelium or atrophy of the nerve fibres in the olfactory mucosa. In the mouse, microscopic changes were limited to the degeneration of the olfactory epithelium of the nose. The minimal degeneration occurred in the dorsal portion o f the dorsal meatus in the anterior or mid-nasal section (Levels I and II). Degeneration was characterised by a loss of the usual orderly arrangement of the pseudostratified layer of nuclei and by a slight reduction on the normal thickness of the olfactory epithelium. In conclusion, both in the rat and the mouse the upper respiratory tract was the major target for toxicity. The overall $LOAEC_{local}$ = 122 mg formic acid/m³ and $NOAEC_{local}$ = 60 mg formic acid/m³, based on histological changes in the nasal region in both the rat and the mouse.

<u>Human data</u>

Due to the warning effect of the pungent smell of formic acid, only few human data due to (accidental) inhalation exposure is available. Yelon et al., 1996 (DocIIIA6.12.2-10; FA_BPR_Ann_II_8_12_2_10) reported a case of an inhalation injury as a result of aerosolized formic acid from an accidental spray in the face. Apart from the skin burns, the man complained of dyspnea. Despite the oxygen therapy and nebulised metaproterenol therapy, the patient continued to complain of dyspnea, it even worsened. Pulmonary function tests within the first 12 hours were consistent with mild restrictive disease (FEV_1 of 2.86L, 73% of predicted; normal FEV_1/FVC of 76.38%); the $FEF_{25\%-75\%}$ of 2.32L/sec (56% predicted) was consistent with small airway dysfunction. On day 3, the patient had improvement in dyspnea, but developed a nonproductive cough at the same time. The patient continued to complain of dyspnea on moderate-severe exertion. The patient recovered slowly. As all criteria were met, the patient could be diagnosed with Reactive Airway Dysfunction Syndrome (RADS).

Based on physico-chemical data, animal data and human findings, the corrosive nature of formic acid is found to affect the respiratory tract. We propose additional labelling with EUH071, ‘corrosive to the respiratory tract’, as the corrosive properties determine the toxicity of formic acid (CLP Regulation Annex II, point 1.2.6).

Conclusion used in the Risk Assessment – Respiratory tract irritation	
Conclusion	formic acid is to be classified as EUH071, corrosive to the respiratory tract.
Justification for the conclusion	The corrosive properties of formic acid have been observed to affect the respiratory tract in appropriate studies relating to inhalation toxicity and in a human case report.

3.3.4 Overall conclusion on corrosion and irritation

Conclusion used in the Risk Assessment – Corrosion and irritation	
Value	Formic acid is corrosive to skin and eye, and to the respiratory tract.
Justification for the selected value	No skin and eye irritation study reports are available on formic acid itself. Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive in the EU (12th ATP) The corrosive properties of formic acid were evidenced by numerous human case reports. In addition, based on physico-chemical data, animal data (acute inhalation toxicity, respiratory irritation test, repeated inhalation toxicity) and human findings, formic acid is observed to affect the respiratory tract. For $NOAEC_{local}$ see 13-week inhalation study, rat, mouse; section 3.6.3 below). RD50 = 615 mg potassium diformate/m³.
Classification according to CLP and DSD	Harmonized classification and SCLs: Skin corr 1A, H314 Skin Corr. 1B; H314: 10% ≤ C < 90% Skin Corr. 1A; H314: C ≥ 90% Skin Irrit. 2; H315: 2% ≤ C < 10% Eye Irrit. 2; H319: 2% ≤ C < 10%

	Additional proposed classification and SCLs: Eye dam/irrit 1, H318 Eye dam. 1; H318: C ≥ 10% EUH071

3.4 SENSITISATION

3.4.1 Skin sensitisation

Summary table of animal studies on skin sensitisation

Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, Vehicle, Dose levels, Route of exposure** *(topical/intradermal, if relevant)***, Duration of exposure**	**Results** *(EC3-value or amount of sensitised animals at induction dose)*	**Remarks** *(e.g. major deviations)*	**Reference**
OECD 406 Buehler Test GLP: yes Rel. 1 Inductions, topically on d0, d7, d14; Challenge, topically on d28 Scoring 1 on d29 Scoring 2 on d30 Evaluation according to Magnusson and Kligman: 0=no visible change 1=dicrete or patchy erythema 2= moderate and	Guinea pig Female 20/group 10 naïve controls	Formic acid purity 85.3% Induction: 7.5% formic acid in water challenge: 2% formic acid in water	Result: not sensitizing Scoring after 24h: naïve control: 0/10 formic acid: 0/20 pos. control*: 13/20 Scoring after 48h: naïve control: 0/10 formic acid: 0/20 pos. control*: 14/20 Pre-test: Min. irritant conc.: 5%; Max. non-irritant conc. 2% Observations after induction 1, 2, 3: Discrete to moderate erythema in 20/20 test animals. Mean score 1.65, 1.85,		BPD ID A6.1.5_01; FA_BPR_Ann_II_8_3_01 [redacted] 2002.

<table>
<tr>
<td>confluent erythema
3= intense erythema and swelling</td>
<td></td>
<td></td>
<td>2.45, respectively. Swelling in 10/20, 11/20, 9/20 test animals, respectively.
*Pos control : α-HCA, historic data
24h: 13/20
48h: 14/20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OECD 406
GPMT
GLP: yes
Rel. 1</td>
<td>Guinea pig
Female
20/group
10 naïve controls</td>
<td>Formi®LHS Potassium formate (1:2)

Intradermal induction: 0.5% m/v in purified water and/or adjuvant
Topical induction: 15% m/m in Vaseline
Challenge application: 10 and 5% m/m in vaseline</td>
<td>Result: not sensitizing

<u>Incidences naïve control group:</u>
<table>
<tr><th rowspan="2">Rea-ding time</th><th rowspan="2">Con-centr a-tion</th><th colspan="4">Incidence</th><th rowspan="2">% animals with incide n-ces ≥ 1</th></tr>
<tr><th>0</th><th>1</th><th>2</th><th>≥ 3</th></tr>
<tr><td>24h</td><td>10%</td><td>8</td><td>2</td><td>0</td><td>0</td><td>20%</td></tr>
<tr><td>48h</td><td>10%</td><td>9</td><td>1</td><td>0</td><td>0</td><td>10%</td></tr>
<tr><td>24h</td><td>5%</td><td>10</td><td>0</td><td>0</td><td>0</td><td>0%</td></tr>
<tr><td>48h</td><td>5%</td><td>10</td><td>0</td><td>0</td><td>0</td><td>0%</td></tr>
<tr><td>24h</td><td>0%</td><td>10</td><td>0</td><td>0</td><td>0</td><td>0%</td></tr>
<tr><td>48h</td><td>0%</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0%</td></tr>
</table>
<u>Incidences test group:</u>
<table>
<tr><th>Rea-ding time</th><th>Con-centra-tion</th><th>Incidence</th><th>% animals with incide</th><th>% of animals with reactions[6]</th></tr>
</table>
</td>
<td></td>
<td>Report number: 1516/22-1032, [redacted] 1998
BPD ID A6.1.5_02;
FA_BPR_Ann_II_8_3_03

SIAP (2008)</td>
</tr>
</table>

6 <u>Data interpretation:</u> The incidences of the test animals were compared to the naïve control animals at the same concentration and reading time. If the challenge response of a test animal was less marked or the same as the maximum reaction apparent among naïve control animals at the same concentration and reading time, those animals were not counted as animals with reactions. Furthermore, the percentage of test animals with reactions was reduced by the percentage of test animals with reactions treated with vaseline alone.

								n-ces ≥ 1		
			0	**1**	**2**	**≥ 3**			
			24h	10%	14	6	0	0	30%	0%	

Pre-test:

Min. irritant conc.:

- Intradermal injection: 0.5%
- Topical application: 15%

Max. non-irritant conc: 10%

Observation after intradermal injection:

Well-defined erythema was noted at injection sites with Freund's Complete Adjuvant (FCA) for both test and control animals.

Observation after topical induction:

Slight erythema was apparent in test animals following application of 15% Formi®LHS in Vaseline.

No erythema was apparent at the topical application sites in the control animals.

Positive control: 2-Mercaptobenzo-thiazole (MBTZ), historic control data

			03-04/1997: 6/9 positive, 2/9 inconclusive, 1/9 negative 08-09/1997: 6/10 positive, 2/10 inconclusive, 2/10 negative		

No guinea-pig maximisation test on the active substance, formic acid, was made available by the applicant. Instead, a Buehler test was made available. Nevertheless, the conduct of an additional Maximisation test (GPMT) is scientifically not justified. A negative GPMT result was obtained with potassium diformate, that liberates formate and formic acid in equimolar quantities in aqueous solution. This substance was included in the "Formic acid and formates" category that was treated in the OECD/ICCA-HPV program, and the negative result can be read across to formic acid. The final SIAP (2008) is publicly available at: http://webnet.oecd.org/Hpv/UI/handler.axd?id=81d8d2fe-5244-4699-93ab-c501433db94c. In the concept of skin sensitisation it is generally assumed that protein-hapten conjugates need to be formed by covalent binding in order to be recognised by the immune system. Therefore, a compound which is able to cause contact allergy must have electrophilic properties, either by itself or after metabolic transformation. This concept is generally accepted and provides the mechanistic basis for Structure-activity-relations (SAR) for the skin sensitisation endpoint. Both formic acid and formate lack electrophilic properties, and are, therefore, considered to lack sensitising properties. In fact formic acid is not contained in publicly available structural alert lists, and acknowledged recently available QSAR models (CAESAR, OASIS) predict that formic acid is not a skin sensitizer. The negative result of the Buehler test with formic acid in Guinea pigs fits into the described concept. Additionally, no case reports of skin sensitisation following skin contact of workers or of the general public were retrieved. Case reports of accidental dermal exposure to formic acid also do not indicate that skin sensitisation was seen. The considerations on structure and electrophilicity do not suggest the conduct of a GPMT. Under REACH the conduct of a maximisation test is not allowed because formic acid is corrosive to the skin. The RMS BE accepted the justification given by the applicant.

There was no evidence of a sensitising potential in guinea pigs using the method of Buehler. During the irritation screen with formic acid diluted in water, the minimum irritant concentration was found to be 5% formic acid in water; the maximum non-irritant concentration was found to be 2% formic acid in water. The inductions performed with 7.5% formic acid caused discrete or patchy erythema to intense erythema, swelling and eczematoid skin changes. No sensitisation responses were elicited by formic acid: no visual changes (score=0) were observed in both the naïve control and test animals. In contrast, the positive control (not included, but routinely conducted twice a year in the laboratory) showed a clear sensitising effect, which confirmed the validity of the study.

A GMPT was performed with potassium diformate ([redacted] 1998; BPD ID A6.1.5_02; FA_BPR_Ann_II_8_3_03/SIAP 2008). In the pre-test a topical minimal irritation concentration of 15% and a maximal non-irritant concentration of 10% were established. For the intradermal injection 0.5% with and without Freund's Complete Adjuvant (FCA) were used. Well defined erythema was noted for both test and control animals after intradermal injections with FCA. No erythema was apparent in test animals receiving the test substance without FCA and in control animals receiving purified water alone. During the induction slight erythema was apparent in test animals following topical application of 15% potassium diformate in Vaseline. No erythema was apparent at the topical application sites in the control animals. During the challenge application light erythema was noted in some control and test animals treated with the higher challenge concentration (10%). In addition, four test animals showed slight erythema at the lower challenge application site although two of these animals also had a slight response to application of the vehicle Vaseline. Those two animals were therefore not considered in the assessment of animals with reactions. The reactions had generally resolved by the 48-hour assessment, and it was noted that the dermal reactions seen in the test group animals were no more persistent or marked than those seen among the controls. In conclusion, it can be stated that no evidence of skin sensitising properties of potassium diformate was observed.

In addition, there is no data available (human data e.g. market surveillance data, animal data, open literature) which may be indicative of the potential of formic acid to cause skin sensitisation and sensitisation by inhalation in humans.

Conclusion used in Risk Assessment – Skin sensitisation	
Value/conclusion	Formic acid does not fulfill the criteria of the CLP regulation to be classified as a skin sensitiser
Justification for the value/conclusion	Skin sensitization (Buehler test) by formic acid has been assessed in an OECD 406 study (Buehler test). The results do not trigger a classification as skin sensitizer.

Data waiving	
Information requirement	Local Lymph Node Assay (LLNA),
Justification	LLNA not available as FA is corrosive to skin: Step 2, Point 8.3, Title 1, Annex II of EU 528/2012 indicates in vivo testing (preferably with the LLNA) does not need to be conducted if the substance is classified for corrosivity.

3.4.2 Respiratory sensitisation

Conclusion used in the Risk Assessment – Respiratory sensitisation	
Value/conclusion	There is no indication that formic acid would be a respiratory sensitizer.
Justification for the value/conclusion	No data are available (human data e.g. market surveillance data, animal data, open literature) which may be indicative of the potential of formic acid to cause sensitisation by inhalation in humans. No respiratory sensitisation was seen with formic acid in two subchronic rat and mouse inhalation studies (see 3.6.3, Thompson 1992). Hence, there is no indication that formic acid would be a respiratory sensitizer.

3.4.3 Overall conclusion on sensitisation

Conclusion used in the Risk Assessment – Sensitisation	
Value	Formic acid is not a skin sensitizer. There is no indication that formic acid would be a respiratory sensitizer.
Justification for the selected value	Classification as a sensitizer is not triggered by appropriate tests. Studies in guinea pigs (method of Buehler) showed that there is no evidence that formic acid has a potential to induce skin sensitisation. In addition, there are no data available (human data including market surveillance, animal studies, open literature) that may be indicative of the potential of formic acid to cause skin sensitisation and sensitisation by inhalation in humans.
Classification according to CLP and DSD	none

3.5 SHORT TERM REPEATED DOSE TOXICITY

3.5.1 Short-term oral toxicity

No data are available on short-term oral toxicity.

Value used in the Risk Assessment – Short-term oral toxicity	
Value/conclusion	The short-term toxicity of formic acid has not been investigated.
Justification for the value/conclusion	The additional conduct of a study with repeated administration via the oral, dermal, or inhalation route was not considered to be necessary.

Data waiving	
Information requirement	short-term oral toxicity of formic acid
Justification	According to the Guidance on the BPR VIII Human Health – Part A Information Requirements (ECHA, 2014), no studies are required because subchronic rodent toxicity studies are available for the oral route (rat, potassium diformate). The use of potassium diformate is justified because it is transformed into formic acid (DocIIIA6.2-01; FA_BPR_Ann_II_8_8_01: [redacted] 1997).

3.5.2 Short-term dermal toxicity

No data are available on short-term dermal toxicity.

Value used in the Risk Assessment – Short-term dermal toxicity	
Value/conclusion	The short-term toxicity of formic acid has not been investigated.
Justification for the value/conclusion	The additional conduct of a study with repeated administration via the oral, dermal, or inhalation route was not considered to be necessary.

Data waiving	
Information requirement	short-term dermal toxicity of formic acid
Justification	Dermal repeated dose studies were not conducted for reasons of animal welfare, because formic acid and potassium diformate are both corrosive to the skin. Moreover, only limited repeated exposure is expected because of the corrosivity to the skin.

3.5.3 Short-term inhalation toxicity

No data are available on short-term inhalation toxicity.

Value used in Risk Assessment – Short-term inhalation toxicity	
Value/conclusion	The short-term toxicity of formic acid has not been investigated.
Justification for the value/conclusion	The additional conduct of a study with repeated administration via the oral, dermal, or inhalation route was not considered to be necessary.

Data waiving	
Information requirement	short-term inhalation toxicity of formic acid
Justification	According to the Guidance on the BPR VIII Human Health – Part A Information Requirements (ECHA, 2014), no studies are required because subchronic rodent toxicity studies are available for the inhalation route of exposure (rat and mouse, formic acid).

3.5.4 Overall conclusion on short-term repeated dose toxicity

Value used in the Risk Assessment – Short-term repeated dose systemic toxicity

Value	The short-term toxicity of formic acid has not been investigated.
Justification for the selected value	The additional conduct of a study with repeated administration via the oral, dermal, or inhalation route was not considered to be necessary. According to the Guidance on the BPR VIII Human Health – Part A Information Requirements (ECHA, 2014), no studies are required because subchronic rodent toxicity studies are available for the oral route (rat, potassium diformate) and the inhalation route of exposure (rat and mouse, formic acid). The use of potassium diformate is justified because it is transformed into formic acid (DocIIIA6.2-01: [redacted] 1997). Dermal repeated dose studies were not conducted for reasons of animal welfare, because formic acid and potassium diformate are both corrosive to the skin. Moreover, only limited repeated exposure is expected because of the corrosivity to the skin.
Classification according to CLP and DSD	n.a.

Value/conclusion used in the Risk Assessment – Short-term repeated dose local effects	
Value/conclusion	The short-term toxicity of formic acid has not been investigated.
Justification for the selected value/conclusion	The additional conduct of a study with repeated administration via the oral, dermal, or inhalation route was not considered to be necessary. According to the Guidance on the BPR VIII Human Health – Part A Information Requirements (ECHA, 2014), no studies are required because subchronic rodent toxicity studies are available for the oral route (rat, potassium diformate) and the inhalation route of exposure (rat and mouse, formic acid). The use of potassium diformate is justified because it is transformed into formic acid (DocIIIA6.2-01: [redacted] 1997). Dermal repeated dose studies were not conducted for reasons of animal welfare, because formic acid and potassium diformate are both corrosive to the skin. Moreover, only limited repeated exposure is expected because of the corrosivity to the skin.
Classification according to CLP and DSD	n.a.

3.6 SUB-CHRONIC REPEATED DOSE TOXICITY

3.6.1 Sub-chronic oral toxicity

Summary table of oral sub-chronic animal studies (usually 90-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Route of exposure** *(gavage, in diet, other)*, **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
OECD 408 GLP: yes Rel. 1	Rat, Crl:CDBR m + f 10/sex/group 10/sex/satellite group	$KHCO_2 \bullet H_2CO_2$ [CAS No. 20642-05-1] purity 95% 0, 600, 1200, 3000 mg Formi/kg bw/d (nominal) = 0, 420, 840, 2100 mg formate/kg bw/d Oral, feed 13 wk, 4 wk recovery continuous, 7 d/week	$NOAEL_{Local}$: as formate: <420 mg/kg bw/d $LOAEL_{Local}$: as formate: 420 mg/kg bw/d $NOAEL_{Systemic}$: as formate: 840 mg/kg bw/d $LOAEL_{Systemic}$: as formate:	No clinical signs No active substance related mortality. Local effects: gastric irritation = thickening of the stomach, usually involving the limiting ridge, dose-related increase in severity and incidence of squamous cell hyperplasia in the stomach (m + f) partial reversibility during the treatment-free period Systemic or target organ toxicity: not overt Bw: dose-dependent decrease in bw (males), decrease in bw at high dose (females); in the recovery period, the bw gain was in parallel for the high dose and control group,		BPD ID A6.4.1_01 FA_BPR_Ann_II_8_9_2_01 [redacted] 1998

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>2100
mg/kg bw/d</td>
<td>but no increase in body weight gain compared to the control.

Food intake: only slight but dose-dependent decrease in food consumption (not stat. sign.), in recovery period comparable food intake for all groups.

Haematology at week 13:

Haematology at week 13:
<table>
<tr><th></th><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th></th><th>Low</th><th>Int.</th><th>High</th><th>Low</th><th>Int.</th><th>High</th></tr>
<tr><td>RBC</td><td></td><td></td><td>↑</td><td></td><td></td><td></td></tr>
<tr><td>MCV</td><td></td><td></td><td>↓</td><td></td><td>↓</td><td>↓</td></tr>
<tr><td>MCH</td><td></td><td></td><td>↓</td><td></td><td></td><td>↓</td></tr>
<tr><td>MCHC</td><td></td><td></td><td></td><td></td><td></td><td>↑</td></tr>
<tr><td>Platelet</td><td></td><td></td><td>↑</td><td></td><td></td><td></td></tr>
<tr><td>WBC</td><td></td><td></td><td>↑</td><td></td><td></td><td></td></tr>
</table>

Clinical chemistry at week 13:
<table>
<tr><th></th><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th></th><th>Low</th><th>Int.</th><th>High</th><th>Low</th><th>Int.</th><th>High</th></tr>
<tr><td>AST</td><td></td><td></td><td>↑ (trend)</td><td></td><td></td><td></td></tr>
<tr><td>AP</td><td></td><td></td><td>↑ (trend)</td><td></td><td></td><td></td></tr>
<tr><td>Tot bilir</td><td></td><td></td><td></td><td></td><td></td><td>↓</td></tr>
<tr><td>Tot prot</td><td></td><td></td><td></td><td></td><td></td><td>↓</td></tr>
<tr><td>K</td><td></td><td></td><td></td><td></td><td></td><td>↓</td></tr>
<tr><td>Ca</td><td></td><td></td><td></td><td></td><td></td><td>↓</td></tr>
<tr><td>Creatinine</td><td></td><td></td><td>↓</td><td>↑</td><td>↓</td><td></td></tr>
<tr><td>Urea</td><td></td><td></td><td></td><td></td><td>↑</td><td>↑</td></tr>
<tr><td>Tot Chol</td><td></td><td></td><td></td><td></td><td>↑</td><td>↑</td></tr>
<tr><td>Globulin</td><td></td><td></td><td></td><td></td><td></td><td>↓</td></tr>
<tr><td>A/G ratio</td><td></td><td></td><td></td><td></td><td></td><td>↓</td></tr>
</table>
</td>
<td></td>
<td></td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>Clinical chemistry at week 17:
<table><tr><td></td><td colspan="3">Males</td><td colspan="3">Females</td></tr><tr><td></td><td>Low</td><td>Int.</td><td>High</td><td>Low</td><td>Int.</td><td>High</td></tr><tr><td>AST</td><td></td><td></td><td>↑</td><td></td><td></td><td></td></tr><tr><td>AP</td><td></td><td></td><td>↑</td><td></td><td></td><td></td></tr><tr><td>Glucose</td><td></td><td></td><td>↓</td><td></td><td></td><td>↓</td></tr></table>
all changes considered of no biological relevance, no dose-response and no microscopic changes observed.

Absorption study (high-dose): formate plasma levels morning: 90 µg (f)-160 µg (m) formate/ml
afternoon: < LOD
rapid absorption and metabolism, no accumulation</td><td></td><td></td></tr>
<tr><td>No guideline, but following scientific standards

GLP: yes

Rel. 2</td><td>Pig,
Large White x Landrace hybrid breed

f
6/group</td><td>$KHCO_2 \bullet H_2CO_2$
[CAS No. 20642-05-1]
purity 98.7%

0, 1.2%, 3.0%, 6.0% in the diet

Mating to farrowing:
0, 132, 324, 624 mg/(kg*d)
= 0, 92, 226,</td><td>$NOAEL_{Local}$:
as formate: < 149 mg/kg bw/d

$LOAEL_{Local}$:
as formate: 149 mg/kg bw/d

$NOAEL_{Systemic}$:
as formate:</td><td>No clinical signs

No active substance related mortality.

Local effects: gastric irritation = forestomach gastritis and erosion/ulcer in approx. 30 to 60% of the treated animals.

No systemic or target organ toxicity:</td><td></td><td>BPD ID A6.4.1_02

FA_BPR_Ann_II_8_9_2_02
[redacted] 2004</td></tr>
</table>

		437 mg formate/(kg*d) *Farrowing to weaning:* 0, 213, 513, 1086 mg/(kg*d) = 0, 149, 359, 760 mg formate/(kg*d) Oral, feed 140 days: 114 from service to farrowing, and until day 26 post partum continuous, 7 d/week	760 mg/kg bw/d LOAEL$_{Systemic}$: as formate: >760 mg/kg bw/d	No effect on bw (gain) and food intake. Haematology: Week 15 (Low Int. High) / Weaning (Low Int. High) RBC* dose-dependent trend ↓ Hb* dose-dependent trend ↓ WBC dose-dependent trend ↓ PCV dose-dependent trend ↓ * stat. sign. at week 15 Clinical chemistry: Week 15 (Low Int. High) / Weaning (Low Int. High) AP ↓ K* ↑ ↑ * dose-dependent. Reproduction parameters not affected. Development of piglets not affected at birth and until weaning.		

No human data are available on subchronic oral toxicity.

The 90 day oral toxicity of potassium diformate was studied in rats (DocIIIA6.4.1-01; FA_BPR_Ann_II_8_9_2_01: [redacted] 1998). The formic acid salt, potassium diformate ("Formi"), was used as test material as it allowed to achieve high dose levels of the formate ion with the feed due to less irritating potency than formic acid itself. The systemic bioavailability of the test substance was considerable as reflected in the increased formate plasma levels of approx. 90 to 160 mg formate/l that were regularly found after the nocturnal feed intake of the rats in the high-dose group over the entire feeding period. The formate salt failed to produce any detectable target-organ toxicity. Local irritation effects in the stomach caused a dose-related thickening of the stomach at all dose levels, which was confirmed to be squamous cell hyperplasia. After the 4 week recovery period, the squamous cell hyperplasia in the forestomach subsided and was largely reversible. No overt systemic toxicity was observed: There was a dose-dependent decrease in bw gain in males and a decrease in bw gain in the high dose females. However, the RMS is not convinced that the slight dose-related reduction in feed intake in males is entirely responsible for the significant decrease in bw gain. There was no reduction in feed intake in females. In the recovery period, body weight development in males and females was comparable between the high dose and control groups. In addition, is the observed systemic effect (dose-dependent bw gain decrease in males and bw gain decrease at the highest dose in females) secondary to the corrosive local GI tract effect? Using a precautionary approach the $LOAEL_{systemic}$ according to the RMS is 2100 mg formate/kg bw/d, based on decreased bw gain in males and females. The $NOAEL_{systemic}$ is 840 mg formate/kg bw/d. $LOAEL_{local}$ = 420 mg formate/kg bw/d and $NOAEL_{local}$ < 420 mg formate/kg bw/d, based on histological changes in the stomach.

The pig oral feed study was conducted to assess the safety of potassium diformate at dose levels of up to five times the recommended dose in the reproducing pig and its offspring (DocIIIA6.4.1-02; FA_BPR_Ann_II_8_9_2_02: [redacted] 2004). No guideline was followed, but the test design obeyed scientific standards. The study provided additional toxicity data on a species that has a more limited metabolism capability to dispose of formate than humans. Therefore, the pig appears to be a more appropriate test species than the rat: any symptomatology possibly related to formate in pig will have significance for the extrapolation to human beings. Potassium diformate ("Formi") was used as test material at nominal concentrations of 0%, 1.2%, 3%, and 6% in the feed. Dose levels of 0, 92, 226, and 437 mg formate/kg bw/d were achieved during 114 days of gestation, dose levels of 0, 149, 359, and 760 mg/kg bw/d during lactation until day 26 post-partum. There were no mortalities or clinical signs that were treatment-related. There was no indication of visual problems in any of the animals. Haematology, clinical chemistry, urinalysis, necropsy and histopathology did not indicate any systemic toxicity. At week 15 and weaning time points, there was a trend towards lowered red blood cell counts (RBC), hemoglobin concentration (Hb), white blood cell count, packed cell volume and haemoglobin. Plasma potassium levels were dose-dependently increased at weak 15 and at weaning ($p<0.05$). There was a clear trend in sodium concentration decrease with increasing dose at the Week 15 and weaning time points, and there was also a trend for potassium concentration to increase with dose at the same time points. Likewise, there was a clear trend towards a higher pH with increased dose levels. The increased potassium uptake was considered to be related with the observed effects, rather than with formic acid. Organ weights were not recorded, but the appearance was normal. Histopathology revealed local irritating effects, as evidenced by forestomach gastritis and erosion/ulcer in approx. 30 to 60 % of the treated animals. The reproduction parameters of the pig were not changed by the treatment. The development of the piglets was also unaffected at birth and up to day 26 post-partum. The $NOAEL_{systemic}$ is 760 mg formate/kg bw/d, the highest dose tested, based on the lack of any systemic effects. $LOAEL_{local}$ = 149 mg formate/kg bw/d and $NOAEL_{local}$ < 149 mg formate/kg bw/d, based on histological changes in the stomach.

Value used in Risk Assessment – Sub-chronic oral toxicity	
Value/conclusion	90 day oral toxicity, potassium diformate, rats: $LOAEL_{systemic}$ 2100 mg formate/kg bw/d, $NOAEL_{systemic}$ 840 mg formate/kg bw/d. $LOAEL_{local}$ 420 mg formate/kg bw/d, $NOAEL_{local}$ < 420 mg formate/kg bw/d

	140 day oral oxicity, potassium diformate, pig: $LOAEL_{systemic}$ >760 mg formate/kg bw/d, $NOAEL_{systemic}$ 760 mg formate/kg bw/d, $LOAEL_{local}$ 149 mg formate/kg bw/d, $NOAEL_{local}$ < 149 mg formate/kg bw/d
Justification for the value/conclusion	BPD ID A6.4.1_01, FA_BPR_Ann_II_8_9_2_01: [redacted] 1998 Subchronic oral toxicity of potassium diformate in the rat has been assessed in a study according to OECD 408. $NOAEL_{systemic}$ = 840 mg formate/kg bw/d, based on decreased bw gain at 2100 mg formate/ kg bw/d; $NOAEL_{local}$ < 420 mg formate/kg bw/d, based on histological changes in the stomach. BPD ID A6.4.1_02, FA_BPR_Ann_II_8_9_2_02: [redacted] 2004 Subchronic oral toxicity of potassium diformate in the pig has been assessed in a non-guideline study following scientific standards. $NOAEL_{systemic}$ = 760 mg formate/kg bw/d, the highest dose tested, based on the lack of any systemic effects; $NOAEL_{local}$ < 149 mg formate/kg bw/d, based on histological changes in the stomach.

Data waiving	
Information requirement	Subchronic oral toxicity study on formic acid
Justification	Subchronic toxicity studies are available for the oral route using potassium diformate. The use of potassium diformate is justified because it is transformed into formic acid (DocIIIA6.2-01; FA_BPR_Ann_II_8_8_01: [redacted] 1997).

3.6.2 Sub-chronic dermal toxicity

No data are available on subchronic dermal toxicity.

Value used in Risk Assessment – Sub-chronic dermal toxicity	
Value/conclusion	n.a.
Justification for the value/conclusion	n.a.

Data waiving	
Information requirement	Subchronic dermal toxicity study on formic acid
Justification	Subchronic dermal toxicity studies were not conducted for reasons of animal welfare, because formic acid and potassium diformate are both corrosive to the skin. In addition, formate salts differ in their local effects on skin and presumably also in the absorption characteristics compared to the acid, and therefore subchronic studies using formate were not considered to represent an adequate alternative to formic acid testing. Moreover, only limited repeated exposure is expected because of the corrosivity to the skin and because of the measures taken to prevent skin contact with the corrosive material.

3.6.3 Sub-chronic inhalation toxicity

Summary table of inhalatory sub-chronic animal studies (usually 90-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, form *(gas, vapour, dust, mist)* and particle size (MMAD), Actual and nominal concentration, Type of administration *(nose only / whole body/ head only)*, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks *(e.g. major deviations)***	**Reference**

<table>
<tr>
<td>In accordance with OECD 413
GLP: yes
Rel. 1</td>
<td>Rat,
Fischer 344/N,
m + f
10/sex</td>
<td>Formic acid purity 95%
0, 15, 30, 61, 122, 244 mg/m^3 (nominal)
Vapour, whole body
6h/d, 5d/wk
13 wk</td>
<td>$NOAEL_{Local}$:
30 mg/m^3
$LOAEL_{Local}$:
61 mg/m^3
$NOAEL_{Systemic}$:
244 mg/m^3
(highest dose tested)
$LOAEL_{Systemic}$:
Not achieved</td>
<td>No clinical signs
No active substance related mortality.
Local effects: nasal irritation, squamous metaplasia of the respiratory epithelium, olfactory degeneration, severity minimal to mild.
Respiratory epithelium squamous metaplasia:
<table>
<tr><td>mg/m³</td><td>0</td><td>15</td><td>30</td><td>61</td><td>122</td><td>244</td></tr>
<tr><td>male</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>9</td></tr>
<tr><td>female</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>6</td></tr>
</table>
Olfactory epithelium degeneration: minimal to mild
<table>
<tr><td>mg/m³</td><td>0</td><td>15</td><td>30</td><td>61</td><td>122</td><td>244</td></tr>
<tr><td>male</td><td>0</td><td>0</td><td>0</td><td>1</td><td>1</td><td>9</td></tr>
<tr><td>female</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>5</td></tr>
</table>
No systemic toxic effects:
No effect on body weight (gain) in males and females. Liver weight (abs. and rel.) increased for all treated groups in males, no effects in females. Relative lung weights decreased for all treated males, absolute lung weights only decreased for the 122 and 244 mg/m³ males. Lung weights (abs. and rel.) decreased for all treated groups in females. Decrease in lung weight was without dose-response relationship and histopathological manifestations.
Haematological and clinical chemistry changes were mild and generally unremarkable, and of no biological relevance:</td>
<td></td>
<td>BPD ID A6.4.3_01
FA_BPR_Ann_II_8_9_2_03
Thompson, 1992</td>
</tr>
</table>

				Slight neutropenia in males and females of all exposure levels after week 13: Statistically significant decreases in the number of segmented neutrophils (p<0.01) Slight leukocytosis in males and females at 64 and 128 ppm, in females also at 8 ppm, after 3 days (p<0.01) Slight decreases in urea nitrogen (UN), albumin, globulin, total protein, and creatinine in males and females at day 3 at 64 and 128 ppm, protein parameters only statistically significant for females (p<0.01). A significant decrease in UN also in the female 16- and 32-ppm groups (p<0.01). These changes were attributed to reduced feed intake during the first exposure period according to authors. Increase in sorbitol dehydrogenase in males of all groups exposed to ≥16 ppm after 3 days (p<0.01). No changes for other liver-specific indicators. Increase in alkaline phosphatase in males at 128 ppm after 3 days, while decreases in females at 64 and 128 ppm at the same time point, and again increases in both top-dosed sexes after 13 weeks (p<0.01). Decrease in creatine kinase in males from 16 to 128 ppm after 3 days (p<0.01).		

				Decrease in amylase in females at 64 and 128 ppm after 3 and 23 days. Reproductive parameters: No effects on sperm motility, density or testicular or epidydimal weights, no changes in the length of the oestrous cycle.		
In accordance with OECD 413 GLP: yes Rel. 1	Mice B6C3F1 m + f 10/sex	Formic acid purity 95% 0, 15, 30, 61, 122, 244 mg/m³ (nominal) Vapour, whole body 6h/d, 5d/wk 13 wk	NOAEL_{Local}: 61 mg/m³ LOAEL_{Local}: 122 mg/m³ NOAEL_{Systemic}: 122 mg/m³ LOAEL_{Systemic}: 244 mg/m³	No clinical signs No active substance related mortality. Local effects: nasal irritation, olfactory degeneration, severity minimal but dose-related. Olfactory epithelium degeneration: minimal mg/m³: 0, 15, 30, 61, 122, 244 male: 0, 0, 0, 0, 0, 2 female: 0, 0, 0, 0, 2, 5 Systemic toxic effects: Decrease in body weight gain in males and females at 244 mg/m³ (male terminal bw = 84% of the control, female terminal bw = 80% of the control). Relative liver weight increased for the 61, 122, 244 mg/m³ groups in males, and the 244 mg/m³ group in females. Relative kidney weights were increased in females in the 61, 122, and 244 mg/m³ groups. These changes were without histopathological manifestations. Reproductive parameters: No effects on sperm motility, density or testicular		BPD ID A6.4.3_01; FA_BPR_Ann_II_8_9_2_04 Thompson, 1992

				or epidydimal weights, no changes in the length of the oestrous cycle.		

No human data are available on subchronic inhalation toxicity.

Subchronic 13-week inhalation studies with formic acid vapour at concentrations of 0, 15, 30, 61, 122, 244 mg/m³ were conducted in rats and mice (DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_03 and DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_04: Thompson, 1992).

In the rat, the inhalation of formic acid did not result in clinical effects. All animals survived, and no effect on the body weight was observed. Changes in haematological and clinical chemistry changes measured at 3 time points (day 3, day 23, and at 13 weeks) were few and generally unremarkable. There were no gross lesions noted at necropsy. Absolute liver weights were increased in male rats in all exposure groups and relative liver weights were increased in males exposed to 61, 122, 244 mg/m³ formic acid. Absolute and relative lung weights were decreased in females in all treated groups. In males, relative lung weights were decreased for all treatment groups, absolute lung weights were decreased for the 122 and 244 mg/m³ groups. Microscopic changes occurred in the respiratory and olfactory epithelium of the nose. Changes on the respiratory epithelium consisted of minimal squamous metaplasia in which the pseudostratified, ciliated columnar cells were replaced by a flattened, non-ciliated epithelium of approximately 2 to 5 cells in thickness. Squamous metaplasia occurred most often in the respiratory epithelium that lines the most dorsal portion of the dorsal meatus in the nose’s anterior section (Level I). In the olfactory epithelium, degenerative changes were minimal to mild and generally limited to the area of the dorsal meatus in the mid-nasal section (Level II). Degeneration was characterised by a loss of the usual orderly arrangement of the pseudostratified layer of nuclei and by a slight reduction on the normal thickness of the olfactory epithelium. There was no necrosis. No evidence was seen of metaplasia of the olfactory epithelium or atrophy of the nerve fibres in the olfactory mucosa. There were no effects on measures of sperm motility, density, or testicular or epidydimal weights, and no changes in the length of the estrous cycle. In conclusion, the upper respiratory tract was the major target for toxicity in rats. There was no evidence of systemic toxicity. The $NOAEC_{systemic}$ is 244 mg formic acid/m³, the highest dose tested, based on the lack of any systemic effects. $LOAEC_{local}$ = 61 mg formic acid/m³ and $NOAEC_{local}$ = 30 mg formic acid/m³, based on histological changes in the nasal region.

In the mouse, the inhalation of formic acid did not result in clinical effects. There was no mortality associated with the exposure to formic acid. Body weight gain was decreased for both males and females for the 244 mg/m³ group, and for the females for the 122 mg/m³ group. Relative liver weights were increased in males and females in the 122 and 244 mg/m³ groups and relative kidney weights were increased in females in the 61, 122, and 244 mg/m³ groups. There were no gross lesions noted at necropsy. Microscopic changes were limited to the degeneration of the olfactory epithelium of the nose in mice from the 122 mg/m³ and 244 mg/m³ formic acid groups. The minimal degeneration occurred in the dorsal portion of the dorsal meatus in the anterior or mid-nasal section (Levels I and II). Degeneration was characterised by a loss of the usual orderly arrangement of the pseudostratified layer of nuclei and by a slight reduction on the normal thickness of the olfactory epithelium. Blood analysis (haematology, clinical chemistry, urinalysis) was not documented. There were no effects on the reproductive parameters evaluated. In conclusion, also in the mouse the upper respiratory tract was the major target for toxicity. $LOAEC_{systemic}$ is 244 mg formic acid/m³, $NOAEC_{systemic}$ is 122 mg formic acid/m³, based on the reduced body weight gain observed at 244 mg/m³. $LOAEC_{local}$ = 122 mg formic acid/m³ and $NOAEC_{local}$ = 61 mg formic acid/m³, based on histological changes in the nasal region.

Effects on the respiratory and olfactory epithelium at 13 weeks consisted of squamous metaplasia (minimal, rats) and degeneration (minimal, rats and mice), respectively. Based on the findings in the 13-week studies the overall $NOAEC_{local}$ for microscopic lesions in the rats and mice is considered 60 mg/m³.

Note: The applicant does not agree with the estimated NOAEC for local effects in rats and proposes a local NOAEC in rats of 122 mg formic acid/m³ and a LOAEC of 244 mg formic acid/m³. However, eCA BE is adhering to the $NOAEC_{local, rat}$ of 30 mg formic acid/m³. The applicant's justification for this re-interpretation can be found in the PT5 specific Kemira confidential Annex to the PT5 CAR, along with BE's clarification for refusal.

Value used in Risk Assessment – Sub-chronic inhalation toxicity	
Value/conclusion	13-week inhalation toxicity, formic acid, rat: $LOAEC_{systemic}$ not achieved, $NOAEC_{systemic}$ 244 mg formic acid/m³ $LOAEC_{local}$ 61 mg formic acid/m³, $NOAEC_{local}$ 30 mg formic acid/m³ 13-week inhalation toxicity, formic acid, mouse: $LOAEC_{systemic}$ 244 mg formic acid/m³, $NOAEC_{systemic}$ 122 mg formic acid/m³ $LOAEC_{local}$ 122 mg formic acid/m³, $NOAEC_{local}$ 61 mg formic acid/m³ overall $NOAEC_{local}$ for microscopic lesions in the rats and mice is considered 60 mg/m³
Justification for the value/conclusion	DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_03 ; DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_04: Thompson, 1992 Subchronic inhalation toxicity of formic acid in the rat and mouse has been assessed in a study in accordance with OECD 413. The upper respiratory tract was the major target organ: minimal to mild squamous metaplasia of the respiratory epithelium and minimal degeneration of the olfactory epithelium. In addition, a decrease in body weight gain was observed at the highest dose level in mice. $NOAEC_{systemic}$ = 122 mg formic acid/m³, based on the reduced bodyweight gain observed at 244 mg/m³ in the mouse. The overall $NOAEC_{local}$ = 60 mg formic acid/m³, based on histopathological changes in the nasal region of both rats and mice observed at 122 mg/m³.

3.6.4 Overall conclusion on sub-chronic repeated dose toxicity

Value used in the Risk Assessment – Sub-chronic repeated dose systemic toxicity

Value	medium-term oral toxicity : Rat: $NOAEL_{systemic}$ = 840 mg formate/kg bw/d Pig: $NOAEL_{systemic}$ = 760 mg formate/kg bw/d Medium-term inhalation toxicity: $NOAEC_{systemic}$ = 122 mg formic acid/m³
Justification for the selected value	The medium-term oral toxicity of formic acid, administered as potassium diformate in the feed, was studied in the rat (90 days) and the pig (140 days). Local irritation effects in the stomach caused a dose-related thickening of the stomach at all dose levels, which was confirmed to be squamous cell hyperplasia of the stomach and gastrointestinal tract, and was largely reversible. High doses may produce adverse effects, such as decrease in body weight gain (rat), which might be due to the inherent irritating potential. In the rat, the $NOAEL_{systemic}$ = 840 mg formate/kg bw/d, based on decreased bw gain at 2100 mg formate/ kg bw/d; in the pig, the $NOAEL_{systemic}$ = 760 mg formate/kg bw/d, the highest dose tested, based on the lack of any systemic effects. Medium-term inhalation toxicity was studied in rats and mice exposed to formic acid vapours for 13 weeks. The upper respiratory tract was the major target organ: minimal to mild squamous metaplasia of the respiratory epithelium and minimal degeneration of the olfactory epithelium. In addition, a decrease in body weight gain was observed at the highest dose level in mice. $NOAEC_{systemic}$ = 122 mg formic acid/m³, based on the reduced bodyweight gain observed at 244 mg/m³ in the mouse.
Classification according to CLP and DSD	None

Value/conclusion used in the Risk Assessment – Sub-chronic repeated dose local effects	
Value/conclusion	medium-term oral toxicity : Rat: $NOAEL_{local}$ < 420 mg formate/kg bw/d Pig: < 149 mg formate/kg bw/d Medium-term inhalation toxicity:

	overall $NOAEC_{local}$ = 60 mg formic acid/m³
Justification for the selected value/conclusion	The medium-term oral toxicity of formic acid, administered as potassium diformate in the feed, was studied in the rat (90 days) and the pig (140 days). Local irritation effects in the stomach caused a dose-related thickening of the stomach at all dose levels, which was confirmed to be squamous cell hyperplasia of the stomach and gastrointestinal tract, and was largely reversible. High doses may produce adverse effects, such as decrease in body weight gain (rat), which might be due to the inherent irritating potential. In the rat, the $NOAEL_{local}$ < 420 mg formate/kg bw/d, based on histological changes in the stomach. In the pig, the $NOAEL_{local}$ < 149 mg formate/kg bw/d, based on histological changes in the stomach. Medium-term inhalation toxicity was studied in rats and mice exposed to formic acid vapours for 13 weeks. The upper respiratory tract was the major target organ: minimal to mild squamous metaplasia of the respiratory epithelium and minimal degeneration of the olfactory epithelium. In addition, a decrease in body weight gain was observed at the highest dose level in mice. The overall $NOAEC_{local}$ = 60 mg formic acid/m³, based on histopathological changes in the nasal region of both rats and mice observed at 122 mg/m³.
Classification according to CLP and DSD	None

3.7 LONG-TERM REPEATED DOSE TOXICITY

3.7.1 Long-term oral toxicity

Summary table of oral long-term animal studies						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Route of exposure *(gavage, in diet, other),* Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks *(e.g. major deviations)***	**Reference**
Comparable to 94/40/EEC GLP: yes Rel. 1	Rat, Wistar, m + f main: 50/sex/group interim: 20/sex/group	$KHCO_2 \bullet H_2CO_2$ [CAS No. 20642-05-1] purity 98-99% 0, 50, 400, 2000 mg/(kg*d) = 0, 35, 280, 1400 mg formate/kg bw/d (nominal) Oral, feed continuous, 7 d/week 104 wk (interim kill at 52 wk)	$NOAEL_{Local}$: as formate: 35 mg/kg bw/d $LOAEL_{Local}$: as formate: 280 mg/kg bw/d $NOAEL_{Systemic}$: as formate: 280 mg/kg bw/d $LOAEL_{Systemic}$: as formate: 1400 mg/kg bw/d	<u>52 weeks</u> No clinical signs No active substance related mortality BW (gain): ↓ for high dose m+f Ophthalmoscopy: no effects on the eye Haematology, clinical chemistry, urinalysis: no consistent pattern of variation, no treatment effect Organ weight: no effect Necropsy: thick stomach (high dose) Histopathology: gastric irritation, stomach: foveolar epithelial (*males* grade 1: 11, grade 2: 3 /20 high dose animals vs 0/20 controls; *females* grade 1: 10, grade 2: 1 /20 high dose		BPD ID A6.5_01/ BPD ID A6.7.-02 FA_BPR_Ann_II_8_9_3_01 FA_BPR_Ann_II_8_11_1_02 [redacted] 2002a/b

				animals vs 0/20 controls) and basal cell hyperplasia (*males* grade 1: 10, grade 2: 2 /20 high dose animals vs 0/20 controls; *females* grade 1: 10, grade 2: 2 /20 high dose animals vs 0/20 controls), salivary gland: acinar cell hypertrophy (incidence high dose males 7/20, females 3/20 vs 0/20 controls), kidney: ↓ incidence of pelvic mineralisation (high dose males 0/20vs 6/20 control, high dose females 6/20 vs 14/20 controls) <u>104 weeks</u> No clinical signs No active substance related mortality BW (gain): ↓ for high dose, bw gain: 27% (m), 19% (f) Food intake: ↓ for high dose, 3% (m), 6% (f) over 104 weeks Ophthalmoscopy: no effects on the eye Haematology, clinical chemistry, urinalysis: no consistent pattern of variation, trend to ↓ RBC at pre-terminal investigation Organ weight: no effect Necropsy: nodules, raised focus, and thick stomach (high dose) Histopathology: gastric irritation, stomach: ↑ incidence and severity of basal cell/squamous		

				cell hyperplasia at the lining ridge (mid dose *males* grade 1: 13/39, grade 2: 6/39, high dose males grade 1: 9/43, grade 2: 19/43, grade 3: 14/43 vs 3/42 grade 1 and 1/42 grade 2 controls; mid dose fe*males* grade 1: 11/36, grade 2: 1/36, high dose females grade 1: 7/38, grade 2: 28/38, grade 3: 3/38 vs 4/39 grade 1 controls), foveolar epithelial hyperplasia (high dose *males* grade 1: 17/43, grade 2: 23/43 vs 1/41 grade 1 and 0/42 grade 2 controls; high dose *females* grade 1: 21/38 vs 0/39 grade 1 controls), acanthosis, hyperkeratosis (high dose) salivary gland: acinar cell hypertrophy ((high dose males 17/43 vs 0/42 controls, high dose females 10/38 vs 0/39 controls) duodenum: hypertrophy of the Brunner's glands (high dose males 16/43 vs 0/42 controls, high dose females 8/38 vs 0/39 controls) kidney: ↓ incidence of pelvic mineralisation (high dose males 4/43 vs 28/42 controls, high dose females 20/38 vs 37/39 controls) and papillary mineralisation (high dose females 2/38 vs 8/39 controls)		

94/40/EEC GLP: yes Rel. 1	Mouse, CD, m + f 51/sex	$KHCO_2 \bullet H_2CO_2$ [CAS No. 20642-05-1] purity 98-99%: 0, 50, 400, 2000 mg/kg bw/d = 0, 35, 280, 1400 mg formate/kg bw/d (nominal), Oral, feed, continuous, 7 d/week, 80 wk	$NOAEL_{Local/systemic}$: as formate: 280 mg/kg bw/d $LOAEL_{Local/systemic}$: as formate: 1400 mg/kg bw/d	<u>80 weeks</u> Clinical signs: none related to treatment No active substance related mortality BW (gain): slightly but significantly lower in high-dose males (p<0.05). No difference between control and low and mid dose animals and for all female groups. Food intake: comparable between all groups, although with a very slight increasing trend in the high-dose males. Macroscopic investigations: no effects Haematology: No adverse effects on RBC or WBC Ophthalmoscopy: not examined clinical chemistry, urinalysis: not examined Organ weight: no data Necropsy: some evidence of treatment-related thick stomach in high-dose females, the only macroscopic finding, but not noted in males Pathology: limited signs of chronic irritation in the stomach; otherwise		BPD ID A6.7_02. FA_BPR_Ann_II_8_11_2_01 [redacted] 2002b

unremarkable
Histopathology:

No increase in any tumour type, slight local irritation of the forestomach with increased incidence of hyperplasia of the limiting ridge in high-dose males.

<u>Non-neoplastic observations:</u>
gastric irritation,
Thick stomach seen in some animals, no dose-response relationship in males, little correlation with microscopic findings

Incidence of findings in the stomach:

	males				females			
(mg/kg bw/d)	0	35	280	1400	0	35	280	1400
n	51	51	51	51	51	51	51	51
thick	6	3	7	2	1	2	3	6
raised focus	0	0	0	0	0	2	0	0

Incidence of limiting ridge hyperplasia in the stomach:

	males				females			
(mg/kg bw/d)	0	35	280	1400	0	35	280	1400
n	36	40	36	33	37	34	35	40
grade 1	4	7	6	13	7	5	7	7
grade 2	0	0	0	6	0	0	0	0

increased incidence of grade 1 (minimal) and grade 2 (slight) in high-dose males.

NOAEL = 280 mg formate/kg bw/d

<table>
<tr>
<td></td>
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<td><u>Neoplastic observations:</u>
Increased incidence of primary lung tumours in high-dose males, but not in females: bronchiolo-alveolar adenomas and carcinomas
Bronchiolo-alveolar tumour incidence:
<table>
<tr><td></td><td colspan="4">males</td><td colspan="4">females</td></tr>
<tr><td>(mg/kg bw/d)</td><td>0</td><td>35</td><td>280</td><td>1400</td><td>0</td><td>35</td><td>280</td><td>1400</td></tr>
<tr><td>n</td><td>51</td><td>19</td><td>30</td><td>51</td><td>51</td><td>25</td><td>25</td><td>51</td></tr>
<tr><td>m. carcinoma</td><td>0</td><td>2</td><td>5</td><td>2</td><td>0</td><td>3</td><td>0</td><td>3</td></tr>
<tr><td>b. adenoma</td><td>4</td><td>7</td><td>11</td><td>9</td><td>5</td><td>6</td><td>4</td><td>5</td></tr>
<tr><td>all</td><td>4</td><td>9</td><td>16</td><td>11</td><td>5</td><td>9</td><td>4</td><td>8</td></tr>
</table>
Alveolar epithelial tumour statistics:
numbers of tumour bearing animals and results of test for dose response
<table>
<tr><td></td><td colspan="2">males</td><td colspan="2">females</td><td>dose response</td></tr>
<tr><td>(mg/kg bw/d)</td><td>0</td><td>1400</td><td>0</td><td>1400</td><td>.</td></tr>
<tr><td>fatal</td><td>0</td><td>1</td><td></td><td></td><td>ns (m, f)</td></tr>
<tr><td>non-fatal</td><td>4</td><td>10</td><td>5</td><td>7</td><td>ns</td></tr>
<tr><td>all</td><td>4</td><td>11</td><td></td><td></td><td>0.038*</td></tr>
</table>
* increasing dose response; ns = not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No guideline, but following scientific standards
GLP: no</td>
<td>Pig, crossbred
f
7 control sows, 8 sows in treated groups</td>
<td>$KHCO_2 \bullet H_2CO_2$ [CAS No. 20642-05-1] purity 95%
0, 1.2%, 3.6% in the diet</td>
<td>NOAEL as formate: 301 mg/(kg*d) (highest dose tested)</td>
<td>No signs of maternal toxicity (clinical signs, body weight development) or toxicity to reproduction or development at any dose level.</td>
<td></td>
<td>BPD ID A6.5_02
FA_BPR_Ann_II_8_9_4_0_JNS
[redacted] 2003</td>
</tr>
</table>

Rel. 3		0, 140, and 430 mg/kg bw/d = 0, 98, 301 mg formate/kg bw/d nominal) Oral, feed continuous, 7 d/week >300 days				

No human data are available on long-term oral toxicity.

The chronic oral toxicity of formate was investigated in the rat for up to 52 weeks and the effects on the incidence and morphology of tumours following oral administration of potassium diformate ("Formi") at 0, 50, 400, and 2000 mg/kg bw/d (0, 35, 280, 1400 mg formate/kg bw/d) for 104 weeks (DocIIIA6.5.-01/ FA_BPR_Ann_II_8_9_3_01 and DocIIIA6.7.-02/ FA_BPR_Ann_II_8_11_1_02: [redacted] 2002a/b). The formate salt failed to produce any target-organ toxicity. There were no treatment related clinical signs or mortality. Local irritation effects in the stomach caused thickening of the stomach, which was confirmed histopathologically. At 52 weeks, in the high dose animals foveolar epithelial hyperplasia in the stomach was characterized by an increase in the depth of intensely eosinophilic epithelium on the surface of the fundic mucosa. Basal cell hyperplasia was restricted to the squamous epithelium of the limiting ridge. In addition, there was minor acinar cell hypertrophy in the submaxillary salivary gland of some high dose animals. In the kidney there was a lower incidence of pelvic mineralisation in high dose animals. At 104 weeks, there was an increase in the incidence and severity of basal cell/squamous cell hyperplasia at the limiting ridge in high and intermediate dose animals. In addition to the basal proliferation, there was increased acanthosis and hyperkeratosis. Foveolar epithelial hyperplasia was similar as at 52 weeks. There was acinar cell hypertrophy in the submaxillary salivary gland of high dose animals. Brunner's gland hypertrophy characterized by large acinar cells was observed in the duodenum of high dose animals. In the kidney there was a lower incidence of pelvic mineralization in high dose animals. Body weight and body weight gain was decreased for high dose animals. Ophthalmoscopy showed no effect on the eye. Haematology, clinical chemistry, urinalysis, and organ weight showed no indications for treatment-related effects. In conclusion, there was no evidence of systemic target organ toxicity, including the eyes, due to formate administration. $LOAEL_{systemic/local}$ (52 wk) = 1400 mg formate/kg bw/d, and $NOAEL_{systemic/local}$ (52 wk) = 280 mg formate/kg bw/d, based on reduced bw gain and gastric hyperplasia. $LOAEL_{systemic}$ (2 y) = 1400 mg formate/kg bw/d, and $NOAEL_{systemic}$ (2 y) = 280 mg formate/kg bw/d, based on reduced bw gain. $LOAEL_{local}$ (2 y) = 280 mg formate/kg bw/d, and $NOAEL_{local}$ (2 y) = 35 mg formate/kg bw/d, based on hyperplastic changes in the stomach and gastrointestinal tract.

The effects on the incidence and morphology of tumours was investigated in the **mouse** following oral administration in the feed of potassium diformate (“Formi”) at 0, 50, 400, and 2000 mg/kg bw/d (0, 35, 280, 1400 mg formate/kg bw/d) for 80 weeks (DocIIIA6.7.-02, FA_BPR_Ann_II_8_11_2_01: [redacted] 2002b; see also section 3.9). The animals were examined for mortality, clinical signs of toxicity and body weight. Haematological, but no clinical-chemical parameters were evaluated. The surviving animals were subjected to necropsy, and tissue slices prepared for histopathology. There were no treatment-related clinical signs, morbidity or mortality. Body weight gain was slightly but significantly lower in high-dose males, although with a very slight trend in increased food consumption in the high-dose males. There were no treatment-related effects on the red and white blood cell counts. Local irritation effects in the stomach caused thickening of the stomach but without dose-response relationship in the males, and with little correlation with microscopic findings. There was an increased incidence of limiting ridge hyperplasia in the forestomach of high-dose males. This was characterized by a minor increase of thickness and folding of the squamous epithelium at the limiting ridge, with a slightly more basophilic basal layer. This finding was considered to indicate an adaptive change to minor local irritation by the test substance. Minor limiting ridge hyperplasia was seen in all group including controls. Increased incidences of Grade 1 (minimal) and Grade 2 (slight) were seen in high-dose males. There was no evidence of progression to neoplasia. The spectrum of neoplasia was generally consistent with that expected in mice of this strain. However, there was a higher incidence of primary lung tumours (bronchiolo-alveolar adenomas and carcinomas) in high dose males than in controls. One primary tumour of the stomach was seen in one control female. According to the authors of this study, primary lung tumours are common background tumours in mice of this strain, and the incidence in the high dose males was within the background range of the laboratory. The incidence of the control males was slightly lower than expected, and the incidences across all treated groups showed no dose-related trend. Therefore, the slight background variation seen in high dose males was not considered to be of toxicological relevance, despite the statistical significance. In conclusion, the dietary administration of potassium formate to mice at dose levels up to 1400 mg formate/kg bw/) for 80 weeks was well tolerated without treatment-related clinical effects or mortality. Treatment-related changes were limited to high-dose males and included decreased body weight, (not significant) increased food consumption, and an increased incidence of limiting ridge hyperplasia in the forestomach. The NOAEL for local/systemic toxicity was 280 mg formate/kg bw/d. There was no evidence of a tumorigenic effect in the stomach or any other tissue. The effects observed in this study and the NOAEL and LOAEL values derived from them are supportive of the effects and NOAEL and LOAEL values described in the [redacted] 2002a study on rats.

A chronic pig study on the effects of potassium diformate on ovulation and fertility in breeding sows was made available (DocIIIA6.5.-02, FA_BPR_Ann_II_8_9_4_0_JNS; [redacted] 2003). It focused on effects on fertility and, therefore, did not provide the full range of pathological and histopathological data which would be expected to be contained in guideline studies pertaining to chronic toxicity, reproduction toxicity, or developmental toxicity. However, the study provides additional data because the metabolic capability to dispose of formate is more limited in pigs. The study met generally accepted scientific standards, is well documented and, therefore, acceptable for assessment. In this study, pigs were fed 0, 140, 430 mg potassium diformate/kg bw/d (0, 98, 301 mg formate/kg bw/d) for over 300 days. No treatment-related effects were observed for maternal toxicity (clinical signs, mortality, body weight, feed consumption), nor on ovulation, fertility, gestation parameters, number of live born piglets, piglet viability and weight gain until weaning. $NOAEL_{systemic}$ = 301 mg formate/kg bw/d, based on lack of systemic and local toxicity at the highest dose tested.

Value used in Risk Assessment – Long-term oral toxicity	
Value/conclusion	104-w oral toxicity, potassium formate, rat: $LOAEL_{systemic}$ (2 y) = 1400 mg formate/kg bw/d, $NOAEL_{systemic}$ (2 y) = 280 mg formate/kg bw/d $LOAEL_{local}$ (2 y) = 280 mg formate/kg bw/d, $NOAEL_{local}$ (2 y) = 35 mg formate/kg bw/d >300d oral toxicity, potassium formate, pig: $NOAEL_{systemic}$ = 301 mg formate/kg bw/d
Justification for the value/conclusion	BPD ID A6.5_01, FA_BPR_Ann_II_8_9_3_01: [redacted] 2002a Chronic oral toxicity of potassium formate in the rat has been assessed in a study in comparable to 94/40/EEC. There was no evidence of systemic target organ toxicity, including the eyes, due to formate administration. $LOAEL_{systemic}$ (2 y) = 1400 mg formate/kg bw/d, and $NOAEL_{systemic}$ (2 y) = 280 mg formate/kg bw/d, based on reduced bw gain. $LOAEL_{local}$ (2 y) = 280 mg formate/kg bw/d, and $NOAEL_{local}$ (2 y) = 35 mg formate/kg bw/d, based on hyperplastic changes in the stomach and gastrointestinal tract. BPD ID A6.5.-02, FA_BPR_Ann_II_8_9_4_0_JNS; [redacted] 2003: A chronic pig study on the effects of potassium diformate on ovulation and fertility in breeding sows was made available. No treatment-related effects were observed for maternal toxicity (clinical signs, mortality, body weight, feed consumption), nor on ovulation, fertility, gestation parameters, number of live born piglets, piglet viability and weight gain until weaning. $NOAEL_{systemic}$ = 301 mg formate/kg bw/d, based on lack of systemic and local toxicity at the highest dose tested.

Data waiving	
Information requirement	Chronic oral toxicity study on formic acid
Justification	A chronic toxicity study is available for the oral route using potassium diformate. The use of potassium diformate is justified because it is transformed into formic acid (DocIIIA6.2-01; FA_BPR_Ann_II_8_8_01: [redacted] 1997).

3.7.2 Long-term dermal toxicity

No data are available on long-term dermal toxicity.

Value used in Risk Assessment – Long-term dermal toxicity	
Value/conclusion	n.a.
Justification for the value/conclusion	n.a.

Data waiving	
Information requirement	Long-term dermal toxicity study on formic acid
Justification	Long-term oral toxicity test provides adequate information

3.7.3 Long-term inhalation toxicity

No data are available on long-term inhalation toxicity.

Value used in Risk Assessment – Long-term inhalation toxicity	
Value/conclusion	n.a.
Justification for the value/conclusion	n.a.

Data waiving	
Information requirement	Long-term inhalation toxicity study on formic acid
Justification	Long-term oral toxicity test provides adequate information

3.7.4 Overall conclusion on long-term repeated dose toxicity

Value used in the Risk Assessment – Long-term repeated dose systemic toxicity	
Value	long-term oral toxicity : Rat: $NOAEL_{systemic}$ = 280 mg formate/kg bw/d
Justification for the selected value	The long-term oral toxicity of formic acid, administered as potassium diformate in the feed, was studied in the rat (2-year) and the pig (300 days). In the rat, local irritation effects in the stomach caused thickening of the stomach, which was confirmed histopathologically. There was an increase in the incidence and severity of basal cell/squamous cell hyperplasia, increased acanthosis, hyperkeratosis, foveolar epithelial hyperplasia, acinar cell hypertrophy in the submaxillary salivary gland, Brunner's gland hypertrophy in the duodenum. In the high dose animals, body weight (gain) was decreased and there was a lower incidence of pelvic mineralization in the kidney. $NOAEL_{systemic}$ = 280 mg formate/kg bw/d, based on decreased bw gain at 1400 mg/kg bw/d in the 2-year rat study.
Classification according to CLP and DSD	None

Value/conclusion used in the Risk Assessment – Long-term repeated dose local effects	
Value/conclusion	long-term oral toxicity : Rat: $NOAEL_{local}$ = 35 mg formate/kg bw/d
Justification for the selected value/conclusion	The long-term oral toxicity of formic acid, administered as potassium diformate in the feed, was studied in the rat (2-year) and the pig (300 days). In the rat, local irritation effects in the stomach caused thickening of the stomach, which was confirmed histopathologically. There was an increase in the incidence and severity of basal cell/squamous cell hyperplasia, increased acanthosis, hyperkeratosis, foveolar epithelial hyperplasia, acinar cell hypertrophy in the submaxillary salivary gland, Brunner's gland hypertrophy in the duodenum. In the high dose animals, body weight (gain) was decreased and there was a lower incidence of pelvic mineralization in the kidney. $NOAEL_{local}$ = 35 mg formate/kg bw/d, based on hyperplastic changes in the stomach and gastrointestinal tract at 280 mg/kg bw/d in the 2-year rat study.

Classification according to CLP and DSD	none

3.8 GENOTOXICITY

3.8.1 In vitro

Summary table of in vitro genotoxicity studies					
Method, Guideline,GLP status, Reliability	**Test substance, Doses**	**Relevant information about the study *(e.g. cell type, strains)***	**Results**	**Remarks *(e.g. major deviations)***	**Reference**
Bacterial reverse mutation test Ames, pre-incubation variant, acc.to Haworth et al., Environ. Mutagen. 5(1): 3-142, 1983 GLP: no Rel. 4	Formic acid purity 98% dissolved in water 0, 10, 33, 100, 333, 1000, 3333 µg/plate	*Salmonella typhimurium* TA97, TA98, TA100, TA1535	+S9 : - -S9 : -	**Not considered as key study for concluding on in vitro mutagenicity in bacterial cells** Cytotoxicity at ≥1000 µg/plate (-/+S9) Test conducted with/without S9 from hamster and rat liver Positive controls confirmed the validity of the test Publication Deviations: -missing *E. coli* or TA102 strain; -2-Aminoanthracene as sole positive control (microsomal enzymes not tested) -No pH conditions stated	BPD ID A6.6.1_01 FA_BPR_Ann_II_8_5_1_01 Zeiger et al., 1992

				-individual plate counts are not presented	
Bacterial reverse mutation test Ames, OECD 471 GLP: yes Rel. 1 Standard plate test (SPT) Pre-incubation test (PIT)	Formic acid purity 85% dissolved in water SPT 0, 33, 100, 333, 1000, 2500, 5000 µg/plate PIT 0, 10, 33, 100, 333, 1000, 2500 µg/plate	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 *E. coli* WP2 uvrA	+S9 : - -S9 : -	**Not mutagenic in bacterial cells** SPT: Cytotoxicity at ≥1000 µg/plate PIT: Cytotoxicity at ≥100 µg µg/plate Depending on strain & test conditions Test conducted with/without S9 from rat liver Positive controls confirmed the validity of the test +S9: 2-Aminoanthracene as positive control; S9 batch characterized with benzo(a)pyrene (pur. ≥96%) in TA98 & TA100 No pH conditions stated	BPD ID A6.6.1_02 FA_BPR_Ann_II_8_5_1_02 [redacted] 2022
Mammalian chromosome aberration test, OECD 473 GLP: no data Rel. 2	Formic acid 2M stock solution dissolved in water 270-1380 µg/ml 270, 360, 450, 540, 630 µg/ml (6-14mM), at increased	CHO K1 cells	+S9 : ± -S9 : ±	**Not clastogenic in mammalian cells** Pos. results attributed to low pH (pH 6.1 - 6.4):dose-dependent increased aberration rate. 1st series At initial pH 6.1, without buffering: 12 mM (-S9): 15.9%	BPD ID A6.6.2_01 FA_BPR_Ann_II_8_5_2_01 Morita et al., 1990

	buffer capacity up to 1380 µg/ml (30 mM)			aberrations 10mM (+S9): 20.5% aberrations Toxic concentration 12 – 14 mM (pH ≤ 6.0). 2nd series Effect of neutralization of the medium 12-14 mM: % aberrations initial pH / -S9 / +S9 6.0 / 12 / 33 6.4 / 4 / 2 7.2 / 0 / 3 3rd series Effect of buffer capacity At enhanced buffer, toxic conc. increased to 30 mM. Dose (mM) / initial pH / NaHCO3 34mM / HEPES 30mM 0 / 7.4 / 0.75 / 20 / 6.1 / 0.5 / 25 / 5.8 / 0.5 / 27.5 / 5.7 / 10.5 / 30 / 5.4 / toxic / 0 / 8.5 / / 0 10 / 7.6 / / 0.5 20 / 7.1 / / 0 25 / 6.7 / / 12 30 / 5.9 / / toxic Chromosomal aberrations: chromatid specific: chromatid gaps, breaks, exchanges	

				No positive control included, but positive results at acidic pH levels, demonstrated the sensitivity of the test system Testing program included acetic and lactic acid	
In vitro mammalian cell gene mutation test (HPRT), OECD 476; EEC 2000/32, B.12 GLP: yes Rel. 1	Formic acid 85.3% Water 14.3% 31 – 500 µg/ml *1st experiment* <u>-S9</u>: 0, 31.25, 62.5, 125, 250, 500 µg/ml <u>-S9</u>: 0, 25, 50, 100, 200, 400 µg/ml *2nd experiment* <u>-S9/-S9</u>: 0, 100, 200, 300, 400, 500 µg/ml Vehicle control: culture medium Positive controls: EMS 300 µg/ml (-S9): MCA 10 µg/ml (+S9):	CHO K1 cells	+S9 : - -S9 : -	**Not mutagenic in mammalian cells** There was no increase in the number of mutant colonies with or without metabolic activation compared with the vehicle control. Cytotoxicity: -S9: # colonies and cell density not reduced +S9: # colonies ↓ at 200-300 µg/ml cell density ↓ at 300-400 µg/ml (2nd exp.) 2 experiments, 6 replicates, pH and osmolality measured Mutant frequency (per 10^6 cells), corrected: <u>Vehicle EMS MCA</u> 1st exp –S9 2.96 295.88 1st exp +S9 4.05 242.94 2nd exp –S9 2.88 302.03 2nd exp + S9 3.54 149.02	BPD ID A6.6.3_01 FA_BPR_Ann_II_8_5_3_01 [redacted] 2002

Formic acid was tested together with a high number of chemicals for its potential to induce reverse **mutations** in **bacterial** strain *Salmonella typhimurium* TA97, 98, 100, 1535 at concentrations between 100 and 3333 µg/plate in the presence and absence of metabolic activation (rat, hamster derived), using the pre-incubation variant of the Ames test according to Haworth et al., 1983 (DocIIIA6.6.1-01, FA_BPR_Ann_II_8_5_1_01; Zeiger et al., 1992). Two series of tests were performed. In case the result had been negative or equivocal in the first run, the S9-mix concentration was enhanced from 10 (first test) to 30%. A negative solvent control (water) and appropriate positive controls were carried along. Formic acid did not induce reverse mutations in S. typhimurium at concentrations between 100 and 3333 µg/plate in the presence and absence of metabolic activation (rat and hamster source), where the positive controls led to a clear increase in revertant colonies. Slight cytotoxicity was reported at 3333 µg/plate, in isolated cases at 1000 µg/plate. The authors concluded that formic acid was to be considered not mutagenic in bacterial cells. The following methodological deficiencies were identified for this study: only four strains of bacteria were used; neither *E. coli* WP2 uvrA, *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 were utilized; 2-Aminoanthracene was used as the sole positive control in the presence of S9-mix without further characterization of the S9 batch with a mutagen that requires metabolic activation by microsomal enzymes; pH conditions were not stated, and no individual plate counts were presented. Therefore this study could not be considered as key study for concluding on *in vitro* mutagenicity in bacterial cells.

A recent GLP-compliant study report in line with OECD 471 has been made available (DocIIIA6.6.1-02, FA_BPR_Ann_II_8_5_1_02; [redacted] 2022). Using both the standard plate (SPT) and pre-incubation (PIT) assay variant, formic acid was tested up to a dose of 5000 (SPT) and 2500 µg/plate (PIT), in the presence and absence of metabolic activation (rat derived). Formic acid did not lead to a relevant increase in the number of revertant colonies in the two assay variants, with or without S9 mix. Cytotoxicity was occasionally observed depending on the strain and test conditions at and above 1000 µg/plate (SPT) or at and above 100 µg/plate (PIT).
All required bacterial tester strains were accounted for. The number of revertant colonies in the negative controls, with and without S9 mix, were within the range of the respective historical control data of each tester strain. Suitable positive controls were selected per strain which induced an appropriate mutagenic response, in line with historical control data. As positive control in the presence of metabolic activation, 2-aminoanthracene was used for all tester strains. The S9 batch was characterized with benzo(a)pyrene (pur. ≥96%) in TA98 and TA100 strains. pH conditions were not stated. However, as cytotoxicity was observed mainly at top dose levels, the impact of the pH value on the reliability of the study can be considered minor. Moreover, the selected top dose is in compliance with OECD TG 471. The study can be accepted as a key study. It can be concluded that formic acid is not mutagenic in bacterial cells.

Formic acid was tested for its potential to induce **chromosomal aberrations** in **mammalian** cells, CHO K1 cells (DocIIIA6.6.2-01, FA_BPR_Ann_II_8_5_2_01; Morita et al., 1990). A positive control was missing. The study was focused upon the influence of the pH of the medium, comprising various operations for shifting the pH as desired. Acetic and lactic acid were also tested in this study. In a first series, incubation was carried out in a standard medium without pH regulation. In a second series, the initial pH of the medium was adjusted to pH 6.0 with 14mM or 12 mM formic acid. These media were then neutralised to pH 6.4, and a second group to pH 7.2. In a third series, the effect of an increased buffer capacity was examined with 2 different buffer systems. All experiments were conducted with and without metabolic activation. There was a dose-related response in the chromosomal aberration rate. In the absence of additional buffer the effective doses of formic acid were 10-12 mM. Under the condition of enhanced buffer capacity, the effective doses increased. Depending on the buffer used, aberrant cells were seen at 25 or 27.5 mM and above. But there was no clastogenic activity at 20 or 25 mM formic acid. At 30 mM the formic acid was cytotoxic irrespective of the buffer system. Mainly chromatid-specific lesions (chromatid-type gaps and breaks with/without S9, chromatid exchanges with S9) were induced, also several-fold per cell at the high doses (= lower pH or buffer capacity). This also applied to acetic and lactic acid, both included in the testing programme. It was concluded that formic acid is not itself clastogenic to these cells but that the acidic conditions of the medium were responsible for the chromosome aberrations observed (false –positive responses).

Formic acid was tested for its ability to induce gene **mutations** at the HPRT locus in **mammalian cells**, CHO K1 cells (DocIIIA6.6.3.-01, FA_BPR_Ann_II_8_5_3_01; [redacted] 2002). Two independent experiments were carried out with and without metabolic activation, including a vehicle and appropriate positive controls. The negative controls gave mutant frequencies within the range expected, and the positive controls led to the expected increase in the frequencies of forward mutations. Formic acid did not cause any increase in the mutant frequencies with or without S9-mix compared to the vehicle control. Cytotoxicity was observed in the presence of metabolic activation. Without S9, the number of colonies and cell density were not reduced at 500 µg/ml. Formic acid is not mutagenic in mammalian cells.

Conclusion used in Risk Assessment – Genotoxicity *in vitro*	
Conclusion	*In vitro*, formic acid was not mutagenic in bacterial and mammalian cells.
Justification for the conclusion	BPD ID A6.6.1_02, FA_BPR_Ann_II_8_5_1_02: [redacted] 2022 BPD ID A6.6.2_01, FA_BPR_Ann_II_8_5_2_01 : Morita et al., 1990 BPD ID A6.6.3_01, FA_BPR_Ann_II_8_5_3_01: [redacted] 2002 In vitro genotoxicity of formic acid has been assessed in appropriate studies. There was no increase in the number of mutant colonies observed with or with metabolic activation. Cytotoxicity occurred at/above 1000 µg/plate (Ames-SPT) or at/above 100 µg/plate (Ames-PIT) or 300 µg/ml, respectively. In mammalian CHO cells, formic acid produced a dose-related response in the chromosomal aberration rate at an initial pH 6.1-6.4 without buffering, with an effective dose of 10-12 mM. Under the condition of enhanced buffer capacity, the effective doses increased. Depending on the buffer used, aberrant cells were seen at 25 or 27.5 mM and above. But there was no clastogenic activity at 20 or 25 mM formic acid. At 30 mM the formic acid was cytotoxic irrespective of the buffer system. Mainly chromatid-specific lesions were induced. It was concluded that formic acid is not itself clastogenic to these cells but that the acidic conditions of the medium were responsible for the chromosome aberrations.

3.8.2 In vivo

No in vivo data on genotoxicity are available.

Conclusion used in Risk Assessment – Genotoxicity *in vivo*

Conclusion	n.a.
Justification for the conclusion	n.a.

Data waiving	
Information requirement	In vivo genotoxicity testing for formic acid
Justification	Formic acid gave negative results in the *in vitro* gene mutation study in bacteria, the *in vitro* cytogenicity study in mammalian cells, and *in vitro* gene mutation assay in mammalian cells. Therefore, no *in vivo* genotoxicity studies (bone marrow assay for chromosomal damage or a micronucleus test) are required.

3.8.3 Overall conclusion on genotoxicity

Conclusion used in the Risk Assessment – Genotoxicity	
Conclusion	Formic acid has no genotoxic potential.
Justification for the conclusion	*In vitro*, formic acid was not mutagenic in bacterial and mammalian cells. There was no increase in the number of mutant colonies observed with or with metabolic activation. In mammalian CHO cells, formic acid is not itself clastogenic but the acidic conditions of the medium were responsible for chromosome aberrations. I*n vivo* data are not available and not required. The overall evaluation of the data leads to the conclusion that formic acid has no genotoxic potential itself.
Classification according to CLP and DSD	none

3.9 CARCINOGENICITY

Summary table of carcinogenicity studies in animals						
Method, Guideline, GLP status, Realibility	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Route of exposure, Duration of exposure**	**NOAEL, LOAEL**	**Results *(Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects)***	**Re-marks *(e.g. major devia-tions)***	**Reference**
Comparable to 94/40/EEC GLP: yes Rel. 1	Rat, Wistar, m + f 50/sex	$KHCO_2 \bullet H_2CO_2$ [CAS No. 20642-05-1] purity 98-99%: 0, 50, 400, 2000 mg/kg bw/d = 0, 35, 280, 1400 mg formate/kg bw/d (nominal), Oral, feed, continuous, 7 d/week, 104 wk	$NOAEL_{Local}$: as formate: 35 mg/kg bw/d $LOAEL_{Local}$: as formate: 280 mg/kg bw/d $NOAEL_{Systemic}$: as formate: 280 mg/kg bw/d $LOAEL_{Systemic}$: as formate: 1400 mg/kg bw/d	**No increase in any tumour type, local irritation in the gastro-intestinal tract associated with hyperplasia.** Non-neoplastic observations: gastric irritation, stomach: ↑ incidence and severity of basal cell/squamous cell hyperplasia at the lining ridge (mid dose *males* grade 1: 13/39, grade 2: 6/39, high dose males grade 1: 9/43, grade 2: 19/43, grade 3: 14/43 vs 3/42 grade 1 and 1/42 grade 2 controls; mid dose fe*males* grade 1: 11/36, grade 2: 1/36, high dose females grade 1: 7/38, grade 2: 28/38, grade 3: 3/38 vs 4/39 grade 1 controls), foveolar epithelial hyperplasia (high dose *males* grade 1: 17/43, grade 2: 23/43 vs 1/41 grade 1 and 0/42 grade 2 controls; high dose		BPD ID A6.5_01/ BPD ID A6.7.-02 FA_BPR_Ann_II_8_9_3_01 FA_BPR_Ann_II_8_11_1_02 [redacted] 2002a/b (see also 3.7.1)

				females grade 1: 21/38 vs 0/39 grade 1 controls), acanthosis, hyperkeratosis (high dose) salivary gland: acinar cell hypertrophy ((high dose males 17/43 vs 0/42 controls, high dose females 10/38 vs 0/39 controls) duodenum: hypertrophy of the Brunner's glands (high dose males 16/43 vs 0/42 controls, high dose females 8/38 vs 0/39 controls) kidney: ↓ incidence of pelvic mineralisation (high dose males 4/43 vs 28/42 controls, high dose females 20/38 vs 37/39 controls) and papillary mineralisation (high dose females 2/38 vs 8/39 controls) Neoplastic observations: Reduced incidence of fibroadenoma in the mammary gland of high dose females		
94/40/EEC GLP: yes Rel. 1	Mouse, CD, m + f 51/sex	$KHCO_2 \bullet H_2CO_2$ [CAS No. 20642-05-1] purity 98-99%: 0, 50, 400, 2000 mg/kg bw/d = 0, 35, 280,	$NOAEL_{Local/systemic}$: as formate: 280 mg/kg bw/d $LOAEL_{Local/systemic}$: as formate:	**No increase in any tumour type, slight local irritation of the forestomach with increased incidence of hyperplasia of the limiting ridge in high-dose males.** Non-neoplastic observations: gastric irritation,		BPD ID A6.7_02. FA_BPR_Ann_II_8_11_2_01 [redacted] 2002b

<table>
<tr>
<td></td>
<td></td>
<td>1400 mg formate/kg bw/d (nominal),
Oral, feed,
continuous, 7 d/week,
80 wk</td>
<td>1400 mg/kg bw/d</td>
<td>Thick stomach seen in some animals, no dose-response relationship in males, little correlation with microscopic findings
Incidence of findings in the stomach:
<table>
<tr><td></td><td colspan="4">males</td><td colspan="4">females</td></tr>
<tr><td>(mg/kg bw/d)</td><td>0</td><td>35</td><td>280</td><td>1400</td><td>0</td><td>35</td><td>280</td><td>1400</td></tr>
<tr><td>n</td><td>51</td><td>51</td><td>51</td><td>51</td><td>51</td><td>51</td><td>51</td><td>51</td></tr>
<tr><td>thick</td><td>6</td><td>3</td><td>7</td><td>2</td><td>1</td><td>2</td><td>3</td><td>6</td></tr>
<tr><td>raised focus</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
</table>
Incidence of limiting ridge hyperplasia in the stomach:
<table>
<tr><td></td><td colspan="4">males</td><td colspan="4">females</td></tr>
<tr><td>(mg/kg bw/d)</td><td>0</td><td>35</td><td>280</td><td>1400</td><td>0</td><td>35</td><td>280</td><td>1400</td></tr>
<tr><td>n</td><td>36</td><td>40</td><td>36</td><td>33</td><td>37</td><td>34</td><td>35</td><td>40</td></tr>
<tr><td>grade 1</td><td>4</td><td>7</td><td>6</td><td>13</td><td>7</td><td>5</td><td>7</td><td>7</td></tr>
<tr><td>grade 2</td><td>0</td><td>0</td><td>0</td><td>6</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
increased incidence of grade 1 (minimal) and grade 2 (slight) in high-dose males.
NOAEL = 280 mg formate/kg bw/d

<u>Neoplastic observations:</u>
Increased incidence of primary lung tumours in high-dose males, but not in females: bronchiolo-alveolar adenomas and carcinomas
Bronchiolo-alveolar tumour incidence:
<table>
<tr><td></td><td colspan="4">males</td><td colspan="4">females</td></tr>
<tr><td>(mg/kg bw/d)</td><td>0</td><td>35</td><td>280</td><td>1400</td><td>0</td><td>35</td><td>280</td><td>1400</td></tr>
<tr><td>n</td><td>51</td><td>19</td><td>30</td><td>51</td><td>51</td><td>25</td><td>25</td><td>51</td></tr>
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				m. carcinoma 0 2 5 2 0 3 0 3 b. adenoma 4 7 11 9 5 6 4 5 all 4 9 16 11 5 9 4 8 Alveolar epithelial tumour statistics: numbers of tumour bearing animals and results of test for dose response males / females / dose response (mg/kg bw/d) 0 1400 0 1400 . fatal 0 1 ns (m, f) non-fatal 4 10 5 7 ns all 4 11 0.038* * increasing dose response; ns = not significant		

No human data are available on carcinogenicity.

The carcinogenic potential of formic acid was investigated in rats and mice. The formic acid salt, potassium diformate ("Formi"), was used as test material as it allowed to achieve high dose levels of the formate ion with the feed due to less irritating potency than formic acid itself.

The effects on the incidence and morphology of tumours was investigated in the **rat** following oral administration in the feed of potassium diformate ("Formi") at 0, 50, 400, and 2000 mg/kg bw/d (0, 35, 280, 1400 mg formate/kg bw/d) for 104 weeks (DocIIIA6.5.-01/ FA_BPR_Ann_II_8_9_3_01 and DocIIIA6.7.-02/ FA_BPR_Ann_II_8_11_1_02: [redacted] 2002a/b). Other parameters than non-neoplastic and neoplastic lesions are discussed in detail in section 3.7.1. That the systemic bioavailability of the test substance was considerable was reflected in the increased formate plasma levels of approx. 90 to 160 mg formate/l that were regularly found after the nocturnal feed intake of the rats in the high-dose group over the entire feeding period (see DOC-IIIA6.4.1_01/ FA_BPR_Ann_II_8_9_2_01, section 3.6.1.).

Non-neoplastic treatment-related changes were observed in the stomach, duodenum, salivary gland and kidney. In the stomach of high dose animals, there were treatment-related increased incidences of nodules, raised focus and thick stomach when compared with controls. These correlated with microscopic findings. A decrease in subcutis masses was noted in high-dose females. Compared to controls, findings in the stomach included: (1) increased incidence and severity of basal cell/squamous cell hyperplasia at the limiting ridge in mid and high dose animals. This correlated with the macroscopic findings described above; (2) acanthosis, hyperkeratosis, formation of variably sized and shaped rete pegs and papillae; associated with minor inflammatory cell infiltration in lamina propria and submucoso; (3) foveolar epithelial hyperplasia in high dose animals; (4) mild inflammatory lesions in the glandular stomach of high dose animals. The NOAEL was 35 mg/kg bw/d. Acinar cell hypertrophy of the salivary gland was similar to that observed in the interim-kill animals (52 weeks, see 3.7.1). Brunner´s gland hypertrophy characterised by large acinar cells was noted in the duodenum of high-dose animals. In the kidney, there was a lower incidence of pelvic and papillary mineralisation and of pyelitis in high-dose groups. In females, there was a decrease in acinar hyperplasia in the mammary gland, decrease in neuropathy in the sciatic nerve, cardiomyopathy in the heart and cysts in the ovary. Notably in high-dose males, there was a decrease in hepatocyte vacuolisation and of eosinophilic and basophilic foci.

The spectrum of **neoplasia** was consistent with that expected in rats of this strain. A reduced incidence of fibroadenoma in the mammary gland was noted in the high dose females. There were no tumours of unusual nature or incidence indicative of specific target organ carcinogenicity on the stomach or any other tissue.

The effects on the incidence and morphology of tumours was investigated in the **mouse** following oral administration in the feed of potassium diformate ("Formi") at 0, 50, 400, and 2000 mg/kg bw/d (0, 35, 280, 1400 mg formate/kg bw/d) for 80 weeks (DocIIIA6.7.-02, FA_BPR_Ann_II_8_11_2_01: [redacted] 2002b). The animals were examined for mortality, clinical signs of toxicity and body weight. Haematological, but no clinical-chemical parameters were evaluated. The surviving animals were subjected to necropsy, and tissue slices prepared for histopathology. There were no treatment-related clinical signs, morbidity or mortality. Body weight gain was slightly but significantly lower in high-dose males, although with a very slight trend in increased food consumption in the high-dose males. There were no treatment-related effects on the red and white blood cell counts. Local irritation effects in the stomach caused thickening of the stomach but without dose-response relationship in the males, and with little correlation with microscopic findings. There was an increased incidence of limiting ridge hyperplasia in the forestomach of high-dose males. This was characterized by a minor increase of thickness and folding of the squamous epithelium at the limiting ridge, with a slightly more basophilic basal layer. This finding was considered to indicate an adaptive change to minor local irritation by the test substance. Minor limiting ridge hyperplasia was seen in all group including controls. Increased incidences of Grade 1 (minimal) and Grade 2 (slight) were seen in high-dose males. There was no evidence of progression to neoplasia. The spectrum of neoplasia was generally consistent with that expected in mice of this strain. However, there was a higher incidence of primary lung tumours (bronchiolo-alveolar adenomas and carcinomas) in high dose males than in controls. One primary tumour of the stomach was seen in one control female. According to the authors of this study, primary lung tumours are common background tumours in mice of this strain, and the incidence in the high dose males was within the background range of the laboratory. The incidence of the control males was slightly lower than expected, and the incidences across all treated groups showed no dose-related trend. Therefore, the slight background variation seen in high dose males was not considered to be of toxicological relevance, despite the statistical significance. In conclusion, the dietary administration of potassium formate to mice at dose levels up to 1400 mg formate/kg bw/) for 80 weeks was well tolerated without treatment-related clinical effects or mortality. Treatment-related changes were limited to high-dose males and included decreased body weight, (not significant) increased food consumption, and an increased incidence of limiting ridge hyperplasia in the forestomach. The NOAEL for local/systemic toxicity was 280 mg formate/kg bw/d. There was no evidence of a tumorigenic effect in the stomach or any other tissue.

Conclusion used in Risk Assessment – Carcinogenicity

Value/conclusion	There is no carcinogenic potential in rats and mice fed potassium diformate.
Justification for the value/conclusion	The effects on the incidence and morphology of tumours were investigated in rats and mice following oral administration in the feed of potassium diformate (0, 35, 280, 1400 mg formate/kg bw/d). Gastric irritation was observed in the rat and the mouse. However, non-neoplastic lesions were more pronounced in the rat than the mouse. In the rat, non-neoplastic treatment-related changes were observed in the stomach, duodenum, salivary gland and kidney, in the stomach with a clear correlation with stomach thickening. In the mouse non-neoplastic changes were observed in the stomach, low-grade limiting ridge hyperplasia in the forestomach, but with little correlation with the thickening of the stomach. There was no evidence of progression to neoplasia. NOAEL rat = 35 mg formate/kg bw/d, NOAEL mouse = 280 mg formate/kg bw/d, based on gastric hyperplasia. There was no evidence of a tumorigenic effect in the stomach or any other tissue. However, in the mouse there was a higher incidence of primary lung tumours, bronchiolo-alveolar adenomas and carcinomas, in the 1400 mg formate /kg bw/d males. Although there was a background variation, the incidence of the high dose group was within the historical range for this mouse strain in the test laboratory. This was not considered to be of toxicological relevance. In conclusion, the studies provided evidence that there was no cancerogenic potential in rats and mice fed potassium diformate.
Classification according to CLP and DSD	none

Data waiving	
Information requirement	Carcinogenicity testing of formic acid
Justification	A carcinogenicity study is available using potassium diformate. The use of potassium diformate is justified because it is transformed into formic acid (DocIIIA6.2-01; FA_BPR_Ann_II_8_8_01: [redacted] 1997).

3.10 REPRODUCTIVE TOXICITY

3.10.1 Developmental toxicity

Summary table of animal studies on adverse effects on development						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Duration of exposure**	**NOAELs, LOAELs *(also for maternal effects)***	**Results**	**Remarks *(e.g. major deviations)***	**Reference**
OECD 414 GLP: yes Rel. 1	Rat Wistar female 25/group	sodium formate [CAS 141-53-7] purity >99% 0, 59, 236, 945 mg/kg bw/d = 0, 40, 160, 640 mg formate/kg bw/d Oral, gavage Exposure period day 6–19 p.c.	NO(A)EL teratogenicity embryotoxicity 945 mg/kg bw/d = 640 mg formate/kg bw/d LO(A)EL teratogenicity embryotoxicity >945 mg/kg bw/d = >640 mg formate/kg bw/d	Dams: no maternal systemic toxicity reached Foetuses: no influence on gestation parameters no evidence of teratogenetic or embryotoxic effects *Morphological effects:* - External malformation (anophthalmia of the left eye): 1/213 high dose foetuses in 1/24 litters - Skeletal malformation (misshapen humerus): 1/213 control foetuses in 1/24 litters - External variations: none - Soft tissue variations (dilated renal pelvis with/without dilated ureters): no relation to dosing		BPD ID A6.8.1_01 FA_BPR_Ann_II_8_10_3_01 [redacted] 2005

			NO(A)EL maternal 945 mg/kg bw/d = 640 mg formate/ kg bw/d LO(A)EL maternal >945 mg/kg bw/d = >640 mg formate/ kg bw/d	mg/kgbw 0 40 160 640 % 5.0 3.8 6.1 1.9 tot # 5 4 5 2 - Skeletal variations: broad range in all groups, no relation to dosing		
OECD 414 GLP: yes Rel. 1	Rabbit Himalayan female 25/group	sodium formate [CAS 141-53-7] purity 100% 0; 100; 300; 1000 mg/kg bw/d =0, 68, 203, 677 mg formate/kg bw/d Oral, gavage Exposure period day 6–28 p.i.	NO(A)EL teratogenicity embryotoxicity 1000 mg/kg bw/d = ~670 mg formate/ kg bw/d NO(A)EL maternal 1000 mg/kg bw/d = ~670 mg formate/ kg bw/d	<u>Dams:</u> no maternal systemic toxicity reached <u>Foetuses:</u> no influence on gestation parameters no evidence of teratogenetic or embryotoxic effects *Morphological effects:* - external, soft tissue, skeletal malformations: mg/kgbw 0 68 203 677 litter 24 23 22 23 foetuses 163 169 137 139 foetal incidence 5 4 5 9 litter incidence 5 4 4 9 affected		BPD ID A6.8.1_02 FA_BPR_Ann_II_8_10_1_01 [redacted] 2008a

				foet/litter 3.8 2.6 3.1 6.7 - external, soft tissue, skeletal variations: mg/kgbw 0 68 203 677 litter 24 23 22 23 foetuses 163 169 137 139 foetal incidence 92 116 90 93 litter incidence 24 22 21 22 affected foet/litter 58.0 66.1 67.2 66.6		

No human data are available on adverse effects on development.

The potential teratogenicity of formic acid was studied in rats and rabbits.

In **rats**, teratogenicity was studied at dose levels of 0, 40, 160, 640 mg formate/kg bw/d administered by oral gavage as sodium formate from day 6 to day 19 post coitum (DocIIIA6.8.1.-01, FA_BPR_Ann_II_8_10_3_01; [redacted] 2005). Sodium formate was applied to avoid unspecific maternal toxic effects through the corrosive action of formic acid, while its potential bioavailability was expected to be equal to that of formic acid itself. No maternal toxicity was observed at any dose level. There were no treatment-related clinical signs or mortality observed, nor changes seen for body weight and food consumption in the dams. Intrauterine growth and survival were unaffected up to and including the highest dose level. The type and incidence of malformations and developmental variations did not indicate a treatment-related finding and were considered to be of spontaneous origin. Therefore no developmental toxicity and teratogenicity was observed up to and including the highest dose level tested i.e. 640 mg formate/kg bw/d. $NOAEL_{maternal}$ = 640 mg formate/kg bw/d, $NOAEL_{developmental,\ teratogenicity}$ = 640 mg formate/kg bw/d.

In **rabbits**, teratogenicity was studied at dose levels of 0, 68, 203, 677 mg formate/kg bw/d administered by oral gavage of sodium formate from day 6 to day 28 post insemination (DocIII6.8.1.-02, FA_BPR_Ann_II_8_10_1_01; [redacted] 2008a). No treatment-related effects were observed in the dams concerning mortality, clinical signs, food consumption, (corrected) body weight (gain), uterus weight, and necropsy findings. With regard to reproduction, no dose-related effects were observed including conception rate, mean number of corpora lutea, total implantations, pre-and postimplantation losses, resorption, live foetuses, and foetal sex ratio. Marginally, but not statistically significant lower foetal body weights were observed at the highest dose tested. Examination of the foetuses revealed external, soft tissue and skeletal malformations in all test groups including the control. They did neither show a consistent pattern since a number of morphological structures of different ontogenic origin were affected nor a clear dose-response relationship. Findings appeared at incidences which were generally similar to historical control data. One external (paw hyperflexion), three soft tissue (absent lobus inferior medialis, dilated cerebral ventricle and malpositioned carotid branch), and a broad range of skeletal variations (e.g. incomplete ossifications of different bony structures) occurred in all test groups including the control. There was no relation seen to dosing, and a comparable frequency was seen in the historical control data. Therefore no maternal and developmental toxicity and teratogenicity was observed up to and including the highest dose level tested i.e. 670 mg formate/kg bw/d. $NOAEL_{maternal}$ = 670 mg formate/kg bw/d, $NOAEL_{developmental,\ teratogenicity}$ = 670 mg formate/kg bw/d.

Conclusion used in Risk Assessment – Effects on development	
Value/conclusion	No developmental toxicity and teratogenicity was observed for formate in rats and rabbits. Rats: $NOAEL_{maternal,\ developmental,\ teratogenicity}$ = 640 mg formate/kg bw/d Rabbits: $NOAEL_{maternal,\ developmental,\ teratogenicity}$ = 670 mg formate/kg bw/d
Justification for the value/conclusion	In rats, the type and incidence of malformations and developmental variations did not indicate treatment-related findings. In rabbits, no maternal and developmental toxicity and teratogenicity was observed up to and including the highest dose level tested.

Data waiving	
Information requirement	Adverse effects of formic acid on development
Justification	Sodium formate was applied to avoid unspecific maternal toxic effects through the corrosive action of formic acid.

3.10.2 Fertility

Summary table of animal studies on adverse effects on fertility						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Duration of exposure**	**NOAELs, LOAELs**	**Results**	**Remarks *(e.g. major deviations)***	**Reference**

OECD 416 GLP: yes Rel. 1	Rat Wistar, m/f 25/group	sodium formate [CAS 141-53-7] purity 100% 0, 100, 300, 1000 =0, 68, 203, 677 mg formate/kg bw/d continuous, 7 d/week, exposure period: Before mating: at least 75 days Duration of exposure in general: from beginning of the study until sacrifice of parent F1, F2 generation	$NOAEL_{syst}$ 200 mg formate/kg bw/d For F0 and F1 parental rats $NOAEL_{fertility, reprod\ performance}$ 670 mg formate/kg bw/d For F0 and F1 parental rats $NOAEL_{developmental}$ 670 mg formate/kg bw/d For F1 and F2 progeny	<u>Parental F1 males:</u> ↓ food consumption during 7/15 study weeks (↓ 5-9%) ↓ bw (up to 6%) from week 9 till end of study ↓ bw gain (up to 34%) , average bw gain ↓ 9% <u>F1, F2 generation pups:</u> No adverse effects **not reprotoxic,** **not developmental toxic**		BPD ID A6.8.2_01 FA_BPR_Ann_II_8_10_2_01 [redacted] 2008b

No human data are available on adverse effects on fertility.

Considering the toxicity to fertility of formic acid, a two-generation reproduction toxicity study was conducted in the **rat** at dose levels of 0, 68, 203, 677 mg formate/kg bw/d administered orally in the feed as sodium formate over two parental (F0, F1) generations (DocIIIA6.8.2.-01, FA_BPR_Ann_II_8_10_2_01; [redacted] 2008b). At least 75 days after the beginning of treatment, F0 animals were mated to produce a litter (F1). Mating pairs were of the same dose groups and F1 animals selected for breeding were continued in the same dose group as their parents. Groups selected from F1 pups were to become F1 parental generation, were offered diets containing test substance post weaning, and the breeding program was repeated to produce F2 litter.

No treatment-related clinical signs or mortality were observed. Signs of **systemic toxicity** were observed in the F1 male parental generation at the highest dose. Food consumption and body weight gain were dose-dependently decreased. This resulted in secondary weight changes of brain and liver, but without correlating histopathological findings. Pathological examinations revealed no test-substance-related changes in organ weight, gross lesions, changes in differential ovarian follicle counts or microscopic findings. There were no indications that the **fertility or reproductive performance** of the F0 or F1 parental animals were affected. Estrous cycle data, mating behaviour, conception, gestation, parturition, lactation, weaning, and sperm parameters, sexual organ weights, and gross and histopathological findings of these organs (including differential ovarian follicle counts in the F1 females) were comparable between all test groups and ranged within the historical control data of the test facility. All data recorded during gestation and lactation (embryo/foetal/pup development) gave no indications of any **developmental toxicity** in the F1 and F2 offspring up to the highest dose level. Pup viability, pup body weight, sex ratio, sex maturation were not affected.

In conclusion,

$NOAEL_{systemic}$ = 200 mg formate/kg bw/d for the F0 and F1 parental rats,

based on adverse effects on food consumption and bw gain at 670 mg formate/kg bw/d in the F1 parental males.

$NOAEL_{fertility,\ reproductive\ performance}$ = 670 mg formate/kg bw/d for the F0 and F1 parental rats,

based on the lack of adverse effects at the highest dose.

$NOAEL_{developmental}$ = 670 mg formate/kg bw/d for the F1 and F2 progeny,

based on the lack of adverse effects at the highest dose.

There were no negative findings on reproductive or on developmental parameters. The number and developmental of the pups was normal and comparable to the control. Formate, administered in the feed of rats as sodium formate, was not toxic with regard to reproduction or development.

In addition, there were no effects on fertility observed in the 13-week inhalation studies performed with formic acid vapours (0, 15, 30, 61, 122, 244 mg/m³). For a more detailed discussion, see section 3.6.3: DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_03 and DocIIIA6.4.3-01/ FA_BPR_Ann_II_8_9_2_04: Thompson, 1992. There were no effects on measures of sperm motility, density, or testicular or epidydimal weights, and no changes in the length of the estrous cycle. However, no functional fertility parameters were studied.

The effects of potassium diformate (oral feed for 140 d or 300d) in breeding sows was studied by [redacted] 2004 (DocIIIA6.4.1-02/ FA_BPR_Ann_II_8_9_2_02) and [redacted] 2003 (DocIIIA6.5.-02/ FA_BPR_Ann_II_8_9_4_0_JNS). For a more detailed discussion, see section 3.6.1/3.7.1. The studies focused on effects on fertility and, therefore, did not provide the full range of pathological and histopathological data which would be expected to be contained in guideline studies pertaining to chronic toxicity, reproduction toxicity, or developmental toxicity. However, the study provides additional data because the metabolic capability to dispose of formate is more limited in pigs. No treatment-related effects were observed for maternal toxicity (clinical signs, mortality, body weight, feed consumption), nor on ovulation, fertility, gestation parameters, number of live born piglets, piglet viability and weight gain until weaning up to doses of 301 mg formate/k gbw/d for over 300 days.

Conclusion used in Risk Assessment – Fertility	
Value/conclusion	No adverse effects on fertility were observed for formate in rats. NOAEL $_{\text{parental, syst F0, F1}}$ ~ 200 mg formate/kg bw/d; NOAEL $_{\text{fertility, reprod performance, developmental}}$ ~ 670 mg formate/kg bw/d
Justification for the value/conclusion	There were no negative findings on reproductive or on developmental parameters. The number and development of the pups was normal and comparable to the control. Formate, administered in the feed of rats as sodium formate, was not toxic with regard to reproduction or development. Signs of systemic toxicity were observed in the F1 male parental generation at the highest dose.

Data waiving	
Information requirement	Adverse effects of formic acid on fertility
Justification	Sodium formate was applied to avoid unspecific toxic effects through the corrosive action of formic acid.

3.10.3 Effects on or via lactation

Conclusion used in Risk Assessment – Effects on or via lactation	
Value/conclusion	No adverse effects on or via lactation are expected for formic acid.
Justification for the value/conclusion	Crossing of barriers as blood/brain, blood/testes, blood/placenta, and exposure via the breastmilk: It may be deduced from the physico-chemical properties of formic acid that the possibility of formate to cross the mentioned barriers is low. The substance is highly soluble in water and the logKow is around -2.0. The pKa is 3.70 at 20°C, and therefore formic acid (and the related salt potassium diformate) is almost exclusively present in the ionised form at physiological pH (DocIIIA6.2-01, FA_BPR_Ann_II_8_8_01). It is known that only the unionised form is likely to cross biological membranes, and that substances with a logP of 2-4 would likely cross membranes. The physico-chemical properties of formic acid differ largely, hence it is unlikely that formate would cross biological membranes. This does not preclude the uptake by means of active transport systems. Penetration into (and through) membranes may occur in minor quantities because the small size of the formate molecule. Transfer into breast milk may be given due to the high solubility in water. In this context it should also be mentioned that endogenous formic acid is produced in the intermediary metabolism in humans, and that the C1-fragment is required in the biosynthesis of amino acids and nucleic acids (DocIIIA6.2-09, FA_BPR_Ann_II_8_8_08), i.e. there is a need in the developing fetus. Excess blood formate is rapidly metabolised to background levels in humans, i.e. formate does not accumulate. Finally, there were no adverse effects noted in the testes, the brain, or the development of offspring, in any of the numerous studies requiring repeated dosing. This includes all subchronic and chronic repeated dose studies, carcinogenicity studies, multigeneration reproduction and teratogenicity studies, conducted in several species (rat, mouse, rabbit, pig) with either sodium formate or potassium diformate. Neurotoxicity is known to occur in humans only in the optical nerve following severe methanol intoxication leading to very high blood formate levels over an extended period of time (DocIIIA6.9). Thus, though formate crossing of the blood/brain, blood/testes, blood/placenta barriers, and the exposure via the breast milk cannot be fully excluded, no adverse effects were seen in the parental animals and their progeny of several species following high-level long-term dosing, or dosing during reproduction and development, of either sodium formate or potassium diformate.

3.10.4 Overall conclusion on reproductive toxicity

Conclusion used in the Risk Assessment – Reproductive toxicity	
Value	Two-generation study, rat: $NOAEL_{parental}$ = 200 mg formate/kg bw/d $NOAEL_{offspring}$ = 670 mg formate/kg bw/d $NOAEL_{reproduction\ parameters}$ = 670 mg formate/kg bw/d Teratogenicity studies, rat, rabbit: $NOAEL_{maternal}$ = 640 mg formate/kg bw/d $NOAEL_{developmental}$ = 640 mg formate/kg bw/d
Justification for the selected value	The reproductive toxicity of formic acid was studied in a two-generation study in the rat administered orally in the feed as sodium formate (0, 68, 203, 677 mg formate/kg bw/d). The developmental toxicity of formic acid, administered by gavage as sodium formate, was studied in the rat (0, 40, 160, 640 mg formate/kg bw/d) and the rabbit (0, 68, 203, 677 mg formate/kg bw/d) teratogenicity studies. **The two-generation study** involving oral administration by feed of sodium formate in the rat showed that formate exerts no effect on the different reproduction parameters examined and induces no malformations in the selected dose range. $NOAEL_{parental}$ = 200 mg formate/kg bw/d (based on reduced food consumption and body weight gain in F1 parental males at 670 mg formate/kg bw/d) $NOAEL_{offspring}$ = 670 mg formate/kg bw/d $NOAEL_{reproduction\ parameters}$ = 670 mg formate/kg bw/d **The teratogenicity studies** involving gavage administration of sodium formate in the rat and the rabbit showed that formate exerts no foetotoxic or teratogenic effects. No treatment-related effects were noted on the type and incidence of malformations and developmental variations in the selected dose range.

	$NOAEL_{maternal}$ = 640 mg formate/kg bw/d $NOAEL_{developmental}$ = 640 mg formate/kg bw/d
Classification according to CLP and DSD	none

3.11 NEUROTOXICITY

Summary table of animal studies on neurotoxicity						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks *(e.g. major deviations)***	**Reference**
Mechanistic study GLP: no Rel. 2	Rat Long Evans, males 6/group	Methanol [CAS 67-56-1] purity unknown 4 g methanol/kg bw (20% w/v in saline) by i.p., followed by supplemental doses of 2 g/kg bw at 12-24 hour intervals Pretreatment rats: exposed to a subanaesthetic concentration of nitrous oxide (N_2O/O_2 1:1) Route: i.p.		Nitrous oxide inhibited methionine synthetase in pretreated rats. The hepatic tetrahydrofolate (THF) level and the rate of formate oxidation were reduced to 50% compared to untreated rats (= comparable to the levels observed in monkeys and humans). Methanol intoxication of pre-treated rats resulted in acidosis and blood formate levels which were comparable to those seen in intoxicated monkeys and humans; Blood formate concentrations ranged between 8-15mM for 30-40 hours in the treated rats. Functional tests: Statistically significant changes were seen in both the retinal function (by electroretinogram) and the optical nerve integrity (by flash-evoked cortical potential) at 36 hours after the initial dose until the end of the experiment at 60 hours after initial dosing. Histopathology: The retina of the methanol-intoxicated rats showed diffuse edema and vacuolization at the junction of the inner and outer segments of the		BPD ID A6.10_01 FA_BPR_Ann_II_8_13_5_01 Eells et al., 2000

<table>
<tr><td></td><td></td><td></td><td></td><td>photoreceptor cells, and in the retinal pigmented epithelial cells. Mitochondrial cristae swelling was seen in the retinal pigmented epithelium cells and photoreceptors of intoxicated rats. Ultrastructural changes were much less pronounced in the optical nerve than in the retina</td><td></td><td></td></tr>
<tr><td>No guideline, but following scientific standards
GLP: no
Rel. 2</td><td>Monkey Rhesus males
4/group</td><td>Sodium formate [CAS 141-53-7] purity unknown
Single i.v. 1.25 mmol/kg bw (57.5 mg/kg), followed by continuous infusion of 3.1mEq/kg bw/h = ~140 mg formate/ kg bw/h
Rate of infusion such as to produce blood concentrations similar to those seen in methanol-intoxicated monkeys

Route: i.v.</td><td></td><td>Ocular/optic effects:
Pupillary reflexes were rapidly altered, and in most animals no response to light was observed between 24 and 48 h. Ophthalmology revealed marked optic disc edema (mainly in the prelaminar region, central portion of the proximal part of the optic nerve without significantly reaching to the distal part. The retina including the ganglion-cell layer were completely normal.
Blood pH: maintained between 7.4 and 7.6
Blood formate levels:
<table>
<tr><td>Animal</td><td>Conc. in blood</td><td>Time of infusion</td><td colspan="2">Clinical observations</td></tr>
<tr><td>No.</td><td>mg/l (mEq/l)</td><td>h</td><td>Pupillary reflex</td><td>Fundus changes</td></tr>
<tr><td>1</td><td>1560 (34)</td><td>39</td><td>No response, mydriasis 7 mm</td><td>Moderate optic disc edema with retinal edema</td></tr>
<tr><td>2</td><td>1380 (30)</td><td>50</td><td>No response, mydriasis 8 mm</td><td>Severe optic disc edema</td></tr>
</table></td><td></td><td>BPD ID A6.2_05
FA_BPR_Ann_II_8_13_2_02
Martin-Amat et al., 1978</td></tr>
</table>

				3	920 (20)	41	No response, mydriasis 8 mm	Severe optic disc edema		
				4	550 (12)	25	Normal 3 mm	Moderate optic disc edema		

No regulatory neurotoxicity studies were made available for formic acid.

Formic acid, or formate, is associated with optical nerve and photoreceptor toxicity which is observed in humans and animals following methanol intoxication (DOCIIIA6.2_05, FA_BPR_Ann_II_8_13_2_02: Martin-Amat et al., 1978; DocIIIA6.10_01, FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000). See also Section 3.1.

The lesion may occur under conditions which allow formate to accumulate far above the background level, thus leading to high formate blood concentrations for extended periods of time. The blood levels of formate that correlate with the emergence of pathological changes are high. In a review by Eells et al. (2000) the following values after accidental and experimental methanol intoxication were summarised (see Review, Table 2):

TABLE 2. Blood formate, pH and bicarbonate concentrations in methanol-intoxicated rats, monkeys and humans.

Species	Blood Formate (mM)	Blood Bicarbonate (mEq/L)	Blood pH
N_2O - Treated Rats[a]	16.1 ± 0.7	7.7 ± 1.2	6.91 ± 0.06
Monkeys[b]	11.4 ± 1.2	6.5 ± 0.5	7.19 ± 0.02
Humans[c,d]	19.3 ± 4.4	3.2 ± 0.4	6.93 ± 0.02

Note: Methanol-intoxicated rats were exposed to a mixture of N_2O/O_2 (1:1) for 4 hours prior to methanol administration (4 g/kg at zero time followed by 2g/kg at 12-hour intervals) and exposure to the gas mixture was continued throughout the experiment. Blood formate concentrations and blood gas measurements were determined 60 hours after the initial dose of methanol. Each value represents the mean ± SE for 6 rats. Rodent data was compiled from studies by Eells *et al.*, (1996)[a]. The monkey data was compiled from studies by Martin-Amat *et al.*, (1977)[b] and the human data was compiled from studies conducted by McMartin *et al.*, (1980)[c] and Eells *et al.*, (1991)[d].

Formate accumulated in all non-human primates (Rhesus monkey) 10 hours after an initial i.v. load of 57.5 mg formate/kg bw, followed by a continuous intravenous infusion of another 140 mg formate/kg bw/h. Maximum blood levels in the range 550 to 1560 mg/l were seen at 25 to 50 hours after the infusion had been started. The ophthalmological examinations revealed ocular problems evidenced by the lack of the light reflex, and moderate to severe retinal and optic disk edema. It is noteworthy that the blood pH was not changed by this treatment (BPD ID A6.2_05, FA_BPR_Ann_II_8_13_2_02; Martin-Amat et al., 1978).

Critical blood concentrations of 8 – 15 mM formate (= 360 – 680 mg/l) maintained over 30 – 40 hours were considered potentially detrimental, producing experimental ocular toxicity in monkeys (DocIIIA6.2_05, FA_BPR_Ann_II_8_13_2_02: Martin-Amat et al., 1978) and were associated with visual toxicity in acute cases of human methanol intoxication (DocIIIA6.10_01, FA_BPR_Ann_II_8_13_5_01: Eells et al., 2000).

In a review on methanol toxicity published by the CERHR Expert Panel (DocIIIA6.2_04, FA_BPR_Ann_II_8_8_03; NTP/USA, 2004), the background blood methanol and formate levels in humans have been reported to range between 0.6 and 2 mg methanol/l and between 3.8 and 11.2 mg formate/l. The blood methanol levels were increased in exposed males and females. However, inhalation exposure of 200 ppm methanol for 4 to 6 hours resulted in blood methanol levels of approx. 2 to 8 mg/l but had no influence on the blood formate levels (3.6 to 9.5 mg/l). It was further reported that the rate of formate oxidation in rats exceeds the maximal rate at which methanol is converted to formate: 1.6 versus 0.9 mmol/kg bw/h, respectively, whereas in non-human primates receiving moderately high doses the formate formation can exceed the oxidation of formate: 1.5 versus 0.75 mmol/kg bw/h, respectively.

An estimate of the methanol concentration that saturates the human folate pathway is 11 mM or 210 mg methanol/kg (DocIIIA6.2_04, FA_BPR_Ann_II_8_8_03: NTP/USA, 2004; BPD ID A6.2_12, FA_BPR_Ann_II_8_8_13: Kavet & Nauss, 1990). The latter would be equivalent to approx. 12.5 g methanol for a 60-kg adult.

The metabolic rate of 0.75 mmol formate/(kg bw∗h) in pigtail monkeys is equivalent to approx. 34 mg formate/(kg bw∗h) (DocIIIA6.2_04, FA_BPR_Ann_II_8_8_03: NTP/USA, 2004; BPD ID A6.2_12, FA_BPR_Ann_II_8-8_13: Kavet & Nauss, 1990). A metabolic saturation would occur only at higher intake rates. This finding is in line with the rapid and complete metabolism of formic acid or sodium formate observed in humans receiving 1, 2, or 3 g formic acid equivalents (DOCIIIA6.2_07, FA_BPR_Ann_II_8_8_06; Malorny, 1969b).

The concept that ocular problems are associated with increased formate levels over an extended time period is supported by the findings of a mechanistic study (DocIIIA6.10_01, FA_BPR_Ann_II_8_13_5_01; Eells et al., 2000). Pretreatment of rats with a subanaesthetic concentration of nitrous oxide lowered the rat's folate pool and hence the formate oxidation rate (see review, Table 1), and rendered the rats susceptible to methanol poisoning, as evidenced by blood formate levels of 8 to 15 mM for 30 to 40 hours and functional and morphological changes of the photoreceptor and the optical nerve.

TABLE 1. Hepatic Folate Concentrations, Hepatic Tetrahydrofolate Concentrations and Rates of Formate Oxidation in Rats, N_2O-Treated Rats, Monkeys and Humans.

Species	Total Hepatic Folate (nmole/g)	Hepatic Tetrahydrofolate (nmole/g)	Rate of Formate Oxidation (mg/kg/hr)
Untreated Rats[a]	26.9 ± 3.3	14.2 ± 0.9	69 ± 1.6
N2O-Treated Rats[a]	28.5 ± 1.2	8.5 ± 0.8	34 ± 1.0
Cynomolgus Monkeys[a]	25.5 ± 0.5	8.1 ± 0.2	34 ± 2.0
Humans[b]	15.8 ± 0.8	6.5 ± 0.3	N.D.

Note: Data compiled from studies conducted by Eells *et al.*, (1981, 1982)[a] and Johlin *et al.*, (1987)[b].

Similar blood formate concentrations over these time periods have been shown to produce ocular toxicity in monkeys and are associated with visual toxicity in human methanol intoxication. Blood levels of 10 - 20 mM formate would be equivalent to 450 to 900 mg formate/l, based on the formate approx. molecular weight (approx. 45). Statistically significant changes were seen in both the retinal function (by electroretinogram) and the optical nerve integrity (by flash-evoked cortical potential) at 36 hours after the initial dose until the end of the experiment at 60 hours after initial dosing. The retina of the methanol-intoxicated rats showed diffuse edema and vacuolization at the junction of the inner and outer segments of the photoreceptor cells, and in the retinal pigmented epithelial cells. Mitochondrial cristae swelling was seen in the retinal pigmented epithelium cells and photoreceptors of intoxicated rats. Ultrastructural changes were much less pronounced in the optical nerve than in the retina (DocIIIA6.10_01, FA_BPR_Ann_II_8_13_5_01; Eells et al., 2000).

The common pathophysiological basis of the so-called toxic optical neurotoxicity was recently reviewed by Altiparmak (2013; FA_BPR_Ann_II_8_13_5_03). Formate inhibits the mitochondrial cytochrome oxidase which results in disrupted energy supply and generation of reactive oxygen species (ROS). The prelaminar portion of the optic nerve has a higher number of mitochondria and a high oxygen demand; consequently, this portion is more vulnerable.

Waiver for further studies on neurobehavioral and neuropathological effects of formic acid:

It is known from methanol intoxications that methanol cause selective optical nerve toxicity. This toxicity likely occurs through a direct effect of formic acid (metabolite of methanol in the body). Although no effect on the optical nerve was seen in the toxicological studies with formic acid or its salts, two studies specifically investigating these effects were added in the dossiers to account for the effects of formic acid when formed as an exclusive sequel of acute methanol intoxication.

The 2 animal studies on neurotoxicity provided are limited to investigations of the optical nerve and eye. A further study investigating neurobehavioral and neuropathological effects (in general) after single and repeated exposure is not available. However, neurotoxicity is part of the ADS. Further studies investigating neurobehavioral and neuropathological effects are only necessary if there is an indication, or knowledge from acute or repeated dose studies that the active substance may have neurotoxic properties.

Though the acute oral and inhalation toxicity studies show some behavioural changes, the repeated dose toxicity studies (Thompson '92, [redacted] '98, [redacted] 2002a/b) do not give rise to requesting additional neurotoxicity data as the main effects seen seem to be related mostly to irritation of the GIT and RT.

Human data on neurotoxicity:

In all human volunteer studies where formic acid or formate salts play a role, and in all human case reports, the single observation related to neurotoxicity is that formic acid, or formate, is associated with optical nerve and photoreceptor toxicity, which is frequently noted in humans following methanol intoxication. The aspect is addressed in more detail within the context of the toxico-kinetics and metabolism of formate in Section 3.1.

Conclusion used in Risk Assessment – Neurotoxicity	
Value/conclusion	Classification/labelling of the active substance 'formic acid' for neurotoxicity according to the criteria in Regulation 1272/2008/EC: none
Justification for the value/conclusion	In methanol poisoning the metabolic capacity to dispose of formate is exceeded. The subsequent formate accumulation is characterized by very high blood formate levels in the range of 8 to 20 mM (i.e. approx. 350 to 900 mg/l) for more than 24 hours. Under such conditions, formate was demonstrated to cause functional and morphological changes of the retina and the optical nerve. It is conceivable that the ingestion of large doses of formate salts could have comparable results. The ingestion of large doses of formic acid would also cause high blood formate levels, but the acute effects, i.e. corrosivity and systemic toxicity, would prevail. Smaller doses of formate salts or formic acid are unlikely to saturate the metabolic rate which is 34 mg formate/kg bw/h in non-human primates.

	Overall, lesions of the optical nerve and the photoreceptors are expected to occur only at formate doses, or formate precursor doses, which exceed by far the folate pathway saturation and thus cause high formate levels for an extended period of time. The proper use of biocidal products containing formic acid is unlikely to be associated with exposures that are sufficiently high to exceed the metabolic rate of approx. 34 mg formate/kg bw/h. No further neurotoxicity testing is required because formate accumulation and adverse effects on the optical nerve and photoreceptors are considered to be an exclusive sequel of acute methanol intoxication in primates. Repeated dose toxicity studies do not give rise to requesting additional neurotoxicity data as the main effects seen seem to be related mostly to irritation of the GIT and RT.

3.12 IMMUNOTOXICITY

No data are available on immunotoxicity.

Conclusion used in Risk Assessment – Immunotoxicity	
Conclusion	There are no indications that Formic Acid has the potential to induce adverse effects involving the immune system.
Justification for the conclusion	There is no evidence from skin sensitisation, repeated dose or reproduction toxicity studies, that formic acid may have immunotoxic properties.

Data waiving	
Information requirement	Immunotoxicity study on Formic Acid
Justification	There is no evidence from skin sensitisation, repeated dose or reproduction toxicity studies, that formic acid may have immunotoxic properties. Hence, no specific study is required according to ECHA (2014) Guidance on the Biocidal Products Regulation v 1.1: Volume III: Human health - Part A: Information Requirements.

3.13 DISRUPTION OF THE ENDOCRINE SYSTEM

To assess potential effects on the endocrine system of formic acid the analysis of available information was conducted by implementing the assessment strategy outlined in the "*Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009*" (ECHA/EFSA, 5 June 2018) referred hereafter as the "guidance on ED".

STEP 1 - Gathering of all relevant information

Level 1: existing data and existing or new non-test information

Formic acid is the simplest carboxylic acid. The formate anion is the common metabolite of formic acid and formate salts in aqueous solutions at physiological pH values. Formic acid and its conjugate base, formate, are also naturally occurring in virtually all living organisms as essential endogenous metabolites critical for one-carbon metabolism [Lamarre et al. 2013]. Formate is formed from precursors in the intermediary metabolism and is used as an important constituent of the C1 intermediary metabolism which is required for the biosynthesis of amino acids and nucleic acid bases (purines and pyrimidines). As a critical endogenous metabolite, formate is not assumed to be inherently endocrine active.

Endocrine activity was investigated using in silico methods. None of the endocrine activity related profilers of the OECD QSAR Toolbox V4.1 showed an alert for formic acid. In fact, formic acid was grouped into the category "non-binder, non-cyclic structure". Furthermore, binding to either oestrogen receptor (ER) or androgen receptor (AR) was estimated using in silico models implemented in OASIS TIMES (V2.27.19.13). None of the three models predicted a binding of formic acid to ER (with or without metabolisation of parent compound) and AR (without metabolisation). Please note that formic acid and formate have no structural similarity to intrinsic endocrine active substances (e.g. oestrogen, androgen). Altogether, based on in silico data it is very unlikely that formic acid exerts an endocrine/EATS-specific effect based on an endocrine mode of action.

Level 2: In vitro assays providing data about selected endocrine mechanism(s) /pathways(s)

Formic acid was not tested in any of the listed in vitro receptor binding or transactivation assays. Only some in vitro information is available from other studies (with reliability 3) but not specific of endocrine activity. Therefore they are not considered relevant regarding ED activity.

Level 3 In vivo assays providing data about selected endocrine mechanism(s) /pathway(s)

No information on such in vivo assays is available for formic acid.

Level 4 & 5 In vivo assays providing data on adverse effects on endocrine relevant endpoints

Table 3.1 Summary table of animal data on endocrine disruption*					
Summary table of animal data on endocrine disruption					
Method, Duration of exposure, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	**Species, Strain, Sex, No/group**	**Test substance (including purity), Vehicle, Dose levels,**	**Results**	**Remarks (e.g. major deviations)**	**Reference**
Two-generation reproduction Toxicity Oral OECD 416(2001) GLP Reliability 1	Rat Wistar rats, strain Crl:WI(Han) Male & Female 25 animals/dose group	Sodium formate Purity 100% Doses: 0; 100; 300; 1000 mg/bw sodium formate =0, 68, 203, 677 mg formate/kg bw/d	For EAS-mediated: No effect on : Age at preputial separation, Age at vaginal opening, Anogenital distance, Cervix histopathology, Coagulating gland weight and histopathology, Epididymis histopathology, Estrus cyclicity, Genital abnormalities, Ovary histopathology, Oviduct histopathology, Prostate	NOAEL parental, syst F0, F1 ~ 200 mg formate/kg bw/d NOAEL fertility, reprod performance, developmental 670 mg formate/kg bw/d	BPD ID A6.8.2_01 FA_BPR_Ann_II_8_10_2_01 [redacted] 2008b

			histopathology and weight, Seminal vesicles histopathology and weight, Sperm morphology, motility and number, Testis histopathology and weight, Uterus histopathology and weight, Vagina histopathology and smears, Increase of relative cauda epididymis weight (300) (no effect on absolute weight and no effect in higher dose) Increase of relative ovary weight (300 and 1000) (no effect on absolute weight)		

			For Thyroid-mediated: No effect on Thyroid histopathology and weight. For parameters sensitive to, but not diagnostic of, EATS: No effect on: Adrenals histopathology and weight Pituitary histopathology, Live birth index, Male and Female fertility index, Gestation index and length, Lactation index, Litter size and viability, Number of implantations, Number of live births, Number of ovarian follicles, Post-implantation loss,		

			Pup weight, clinical observation and mortality, Male and female mating index, Sex ratio and Time to mating Increase (20%) of pituitary weight (68 and 677 mg) but no dose-response relationship <u>For general toxicity:</u> Decrease of food consumption, body weight and absolute liver weight at 677 mg		
Subchronic oral toxicity in rodents 13 weeks, Oral OECD 408 GLP	Rat, Crl:CDBR Male & Female 10 animals/sex/dose group	Potassium diformate Purity 95% Doses : 0, 600, 1200, 3000 mg Formi/kg	<u>For EAS-mediated:</u> No effect on: Epididymis histopathology and weight, Macroscopic examination of mammary gland (M & F)	$NOAEL_{Systemic}$: as formate: 840 mg/kg bw/d $LOAEL_{Systemic}$: as formate: 2100 mg/kg bw/d	BPD ID A6.4.1_01 FA_BPR_Ann_II_8_9_2_01 [redacted] 1998

Reliability 1		bw/d (nominal) = 0, 420, 840, 2100 mg formate/kg bw/d	Ovary histopathology, Testis histopathology and weight, Uterus histopathology, Vagina histopathology <u>For Thyroid-mediated:</u> No effect on Thyroid histopathology <u>For parameters sensitive to, but not diagnostic of, EATS:</u> No effect on: Adrenals histopathology and Pituitary histopathology Decrease of adrenals weight (but not dose related and not statistically significant) <u>For general toxicity:</u>		

			Decrease of food consumption and body weight at 600 mg.		
Subchronic inhalation toxicity 13 weeks, Inhalation Similar to OECD 413 GLP Reliability 1	Rat, Fischer 344/N rats Male & Female 10 animals/sex/dose group	Formic acid Purity 95% Dose: 0, 8, 16, 32, 64 and 128 ppm	For EAS-mediated: No effect on: Epididymis histopathology and weight, Estrus cyclicity, Ovary histopathology, Prostate histopathology, Seminal vesicles histopathology, Sperm morphology, motility and numbers, Testis histopathology and weight, Uterus histopathology. For Thyroid-mediated: No effect on Thyroid histopathology For general toxicity:	$NOAEL_{Systemic}$: 244 mg/m^3 (highest dose tested)	BPD ID A6.4.3_01; FA_BPR_Ann_II_8_9_2_03 Thompson, 1992

			No effect		
Subchronic inhalation toxicity 13 weeks, Inhalation Similar to OECD 413 GLP	Mouse, B6C3F1 Male & Female 10 animals/sex/dose group	Formic acid Purity 95% Dose: 0, 8, 16, 32, 64 and 128 ppm	For EAS-mediated: No effect on: Epididymis histopathology and weight, Estrus cyclicity, Ovary histopathology, Prostate histopathology, Seminal vesicles histopathology, Sperm morphology, Testis histopathology, Uterus histopathology. Decrease in sperm motility (32 ppm)compared to controls but within the historical range for controle mice. No dose-response relationship Increase sperm number (up to 33%) dose-	$NOAEL_{Systemic}$: 122 mg/m^3 $LOAEL_{Systemic}$: 244 mg/m^3	**BPD ID A6.4.3_01;** ; FA_BPR_Ann_II_8_9_2_04 Thompson, 1992

			response relationship Increase relative testis weight (128 ppm) (no effect on absolute weight) <u>For Thyroid-mediated:</u> No effect on Thyroid histopathology <u>For general toxicity:</u> Decrease of body weight and absolute liver weight at dose 128 ppm. Increase of absolute liver weight (8.4%) at 32 and 64 ppm but not at 128 ppm (M) and decrease at 64 and 128 ppm (F)		
Combined chronic toxicity and (dietary administration) **oncogenicity study in the rat** 104 weeks, Oral	Rat, Wistar: Crl:HanWist(Glx:BRL)BR Male & Female	Potassium formate Purity: 98% and 99%	<u>For EAS-mediated:</u> No effect on: Epididymis histopathology and weight, Macroscopic examination of	$NOAEL_{Systemic}$: as formate: 280 mg/kg bw/d $LOAEL_{Systemic}$: as formate: 1400 mg/kg bw/d	BPD ID A6.5_01/ BPD ID A6.7.-01 FA_BPR_Ann_II_8_9_3_01 FA_BPR_Ann_II_8_11_1_02 [redacted] 2002a/b

Similar to OECD 451-3 GLP Reliability 1	20 animals/sex/dose group	Doses 0, 50, 400, 2000 mg/kg bw/d = 0, 35, 280, 1400 mg formate/kg bw/d	mammary gland (M & F), Ovary weight, Prostate histopathology, Testis histopathology and weight, Uterus histopathology and Vagina histopathology Decrease of incidence of fibroadenoma on mammary gland. Decrease in Ovary cysts in high dose females. <u>For Thyroid mediated:</u> No effect on Thyroid histopathology <u>For parameters sensitive to, but not diagnostic of, EATS</u> No effect on:		

			Adrenals histopathology and weight Pituitary histopathology For general toxicity: Decrease of food consumption, body weight and incidence of basophilic foci in liver at 1400 mg.		
Prenatal Developmental Toxicity Study Oral, day 6 to 29 post insemination OECD 414(2001) GLP Reliability 1	Rabbit, Himalayan Rabbit Females 25 animals/dose group	Sodium formate, Purity 100% Doses: 0, 100, 300, 1000 mg/kg bw/day	For parameters sensitive to, but not diagnostic of, EATS: No effect on: Fetal mortality and weight, Live fetus, Number of implantations, Pre and Post implantation loss, Placental weight, Resorption and Sex ratio Increase of fetal malformations (dose 1000) but	NO(A)EL teratogenicity embryotoxicity =670 mg formate/ kg bw/d NO(A)EL maternal =670 mg formate/ kg bw/d	BPD ID A6.8.1_02 FA_BPR_Ann_II_8_10_1_01 [redacted] 2008a

			within the historical range. <u>For general toxicity:</u> No effect		
Prenatal Developmental Toxicity Study Oral, day 6 to 20 post coitum OECD 414(2001) GLP Reliability 1	Rat, Wistar: Crl:HanWist(Glx:BRL) Females	Sodium formate Purity >99% Doses: 0, 40, 160, 640 mg formate/(kg bw*d)	<u>For parameters sensitive to, but not diagnostic of, EATS:</u> No effect on: Fetal development, mortality and weight, Conception rate, Live fetus, Placental weight, Number of implantations, Pre and post implantation loss, Resorption and Sex ratio <u>For general toxicity:</u> No effect	NO(A)EL teratogenicity embryotoxicity =640 mg formate/kg bw/d NO(A)EL maternal = 640 mg formate/ kg bw/d	BPD ID A6.8.1_01 **FA_BPR_Ann_II_8_10_3_01** [redacted] 2005
Prenatal Developmental Toxicity Study Oral, 140 days	**Pig,** Large White x Landrace hybrid Female 6 animals/ dose group	**Potassium diformate** purity 98.7% Doses:	**<u>For parameters sensitive to, but not diagnostic of, EATS:</u>** **No effect** on: Reproduction parameters and		BPD ID A4.4.1_02 B [redacted] (2004)

No guideline GLP Reliability 2		0, 157, 384, 753 mg/kg bw/d	development of piglets at birth and until weaning. **For general toxicity:** No effect		

STEP 2 - Assemble and assess lines of evidence for endocrine activity and adversity

	Grouping	Lines of evidence	Species	Exposure, length	Route of exposure	Effect dose	Observed effects (positive or negative)	Assessment of each line of evidence	Assessment of the integrate line of evidence	Modality
Integrated line of evidence for endocrine adversity	EATS-mediated parameter	Thyroid histopathology	Rat	13 weeks	Oral	n.a.	No effect	No evidence of adversity		
				13 weeks	Inhalation					
				132 days	Oral					
				104 weeks	Oral					
			mouse	13 weeks	inhalation					
		Thyroid weight	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Age at preputial separation	rat	132 days	oral	n.a.	No effect	No evidence of adversity		

		Age at vaginal opening	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Anogenital distance	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Cervix histopathology	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Coagulating gland histopathology	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Coagulating gland weight	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Epididymis histopathology	rat	13 weeks	oral	n.a.	No effect	No evidence of adversity		
			mouse	13 weeks	inhalation					
			rat	13 weeks	inhalation					
			rat	132 days	oral					
			rat	104 weeks	oral					
		Epididymis weight	rat	132 days	oral	203 mg (formate)/kg bw/day	Increase of relative cauda epididymis weight Due in part to the	Overall no evidence of adversity.		

							decrease of body weight (No effect on absolute weight). Moreover there is no dose-response relationship.			
			rat	13 weeks	oral	n.a.	No effect			
			mouse	13 weeks	inhalation					
			rat	13 weeks	inhalation					
			rat	104 weeks	oral					
		Estrus cyclicity	mouse	13 weeks	inhalation	n.a.	No effect	No evidence of adversity		
			rat	13 weeks	inhalation					
			rat	132 days	oral					
		Genital abnormalities	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Macroscopic examination of mammary gland	rat	13 weeks	oral	n.a.	No effect	No evidence of adversity		
			rat	104 weeks	oral					

		Mammary gland histopathology	rat	104 weeks	oral	1400 mg(formate)/ kg bw/day	Decreased incidence of fibroadenoma. This is a known secondary effect of low body weight and is described commonly in the literature1	Overall no evidence of adversity.		
		Ovary histopathology	mouse	13 weeks	inhalation	n.a.	No effect	Overall no evidence of adversity.		
			rat	13 weeks	inhalation					
			rat	13 weeks	oral					
			rat	132 days	oral					
			rat	104 weeks	oral	1400 mg(formate)/ kg bw/day	Decrease in cysts in high dose females, related to a lower body weight.			
		Ovary weight	rat	132 days	oral	203 mg (formate)/kg bw/day	Increase relative ovary weight Due in part to the	Overall no evidence of adversity		

							decrease of body weight (No effect on absolute ovary weight). Moreover there is no dose-response relationship.			
			rat	104 weeks	oral	n.a.	No effect			
		Oviduct histopathology	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Prostate histopathology	mouse	13 weeks	inhalation	n.a.	No effect	No evidence of adversity		
			rat	13 weeks	inhalation					
			rat	132 days	oral					
			rat	104 weeks	oral					
		Prostate weight	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Seminal vesicles histopathology	mouse	13 weeks	inhalation	n.a.	No effect	No evidence of adversity		
			rat	13 weeks	inhalation					
			rat	132 days	oral					

		Seminal vesicles weight	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Sperm morphology	mouse	13 weeks	inhalation	n.a.	No effect	No evidence of adversity		
			rat	13 weeks	inhalation					
			rat	132 days	oral					
		Sperm motility	Mouse	13 weeks	inhalation	6 ppm	Decrease of sperm motility with no dose-response relationship. Moreover the values for exposed mice fall well within the historical range for controle mice	Overall no evidence of adversity		
			rat	13 weeks	inhalation	n.a.	No effect			
			rat	132 days	oral					
		Sperm numbers	Mouse	13 weeks	inhalation	32 ppm	Increase of concentration at 32 and 128 ppm	No evidence of adversity		

			rat	13 weeks	inhalation	n.a.	No effect			
			rat	132 days	oral					
		Testis histopathology	rat	13 weeks	oral	n.a.	No effect	No evidence of adversity		
			mouse	13 weeks	inhalation					
			rat	13 weeks	inhalation					
			rat	132 days	oral					
			rat	104 weeks	oral					
		Testis weight	Mouse	13 weeks	inhalation	128 ppm	Increase of the relative testis weight at the higher dose. Related to a lower body weight (No effect on absolute testis weight)	Overall no evidence of adversity.		
			rat	13 weeks	oral	n.a.	No effect			
			rat	13 weeks	inhalation					
			rat	132 days	oral					
			rat	104 weeks	oral					

		Uterus histopathology	rat	13 weeks	oral	n.a.	No effect	No evidence of adversity		
			mouse	13 weeks	inhalation					
			rat	13 weeks	inhalation					
			rat	132 days	oral					
			rat	104 weeks	oral					
		Uterus weight	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Vagina histopathology	rat	13 weeks	oral	n.a.	No effect	No evidence of adversity		
			rat	132 days	oral					
			rat	104 weeks	oral					
		Vaginal smears	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
	Parameter sensitive to, but not diagnostic of EATS	Adrenals histopathology	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
			rat	13 weeks	oral					
			rat	104 weeks	oral					
		Adrenals weight	rat	13 weeks	oral	2100 mg	Decrease of adrenals weight in the highest dose in females. Related to a lower	Overall no evidence of adversity		

							terminal body weight.			
			rat	104 weeks	oral	n.a.	No effect			
			rat	132 days	oral					
		Live birth index	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Birth index	pig	>150 days	oral	n.a.	No effect	No evidence of adversity		
		Male and Female Fertility index	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Fetal development	rat	17 days	oral	n.a.	No effect	Overall no evidence of adversity		
			rabbit	22 days	oral	1000 mg	Increase of fetal malformatio ns at the highest dose but within the historical control range.			
		Fetal mortality	rat	17 days	oral	n.a.	No effect	No evidence of adversity		
			rabbit	22 days	oral					
			pig	>150 days	oral					
		Fetal weight	rat	17 days	oral	n.a.	No effect			

			rabbit	22 days	oral			No evidence of adversity		
		Gestation index	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Conception rate	rat	17 days	oral	n.a.	No effect	No evidence of adversity		
		Gestation length	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Lactation index	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Litter size	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Litter viability	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Live fetus	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
			rat	17 days	oral					
			rabbit	22 days	oral					
		Number of implantations	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
			rat	17 days	oral					
			rabbit	22 days	oral					

		Number of live births	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Number of ovarian follicles	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Pituitary histopathology	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
			rat	13 weeks	oral					
			rat	104 weeks	oral					
		Pituitary weight	rat	132 days	oral	100 & 1000 mg	Increase (20%) of pituitary weight but no dose-response relationship	Overall no evidence of adversity		
		Placental weight	rat	17 days	oral	n.a.	No effect	No evidence of adversity		
			rabbit	22 days	oral					
		Post implantation loss	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
			rat	17 days	oral					
			rabbit	22 days	oral					
		Pre implantation loss	rat	17 days	oral	n.a.	No effect	No evidence of adversity		
			rabbit	22 days	oral	n.a.	No effect			
		Pup development	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Pup mortality	rat	132 days	oral	n.a.	No effect			

			pig	>150 days	oral			No evidence of adversity		
		Male and Female mating index	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
		Resorption	rat	17 days	oral	n.a.	No effect	No evidence of adversity		
			rabbit	22 days	oral					
		Sex ratio	rat	17 days	oral	n.a.	No effect	No evidence of adversity		
			rabbit	22 days	oral					
			rat	132 days	oral					
		Time to mating	rat	132 days	oral	n.a.	No effect	No evidence of adversity		
General toxicity		Body weight	mouse	13 weeks	inhalation	128 ppm	Decrease	Decrease of body weight at high doses only; related to the decrease of food consumption		
			pig	>150 days	oral	n.a.	No effect			
			rabbit	22 days	oral	n.a.	No effect			
			rat	13 weeks	Oral	600 mg	Decrease			
			rat	17 days	oral	n.a.	No effect			
			rat	132 days	oral	1000 mg	Decrease			
			rat	104 weeks	oral	2000 mg	Decrease			
			rat	13 weeks	inhalation	n.a.	No effect			

		Food consumption	pig	>150 days	oral	n.a.	No effect	Decrease of food consumption at high doses only.		
			rabbit	22 days	oral					
			rat	17 days	oral					
			rat	13 weeks	Oral	600 mg	Decrease			
			rat	132 days	oral	1000 mg	Decrease			
			rat	104 weeks	oral	2000 mg	Decrease			
		Liver histopathology	mouse	13 weeks	inhalation	n.a.	No effect	Overall no evidence of liver toxicity, except at high dose in 1 study.		
			pig	>150 days	oral					
			rat	13 weeks	inhalation					
			rat	104 weeks	oral	2000 mg	Increase hepatocyte vacuolisation, eosinophilic and basophilic foci in the liver of high dose males.			
		Liver weight	mouse	13 weeks	inhalation	32 ppm	Absolute liver weight: Increase (8.4%) at 32 and 64 ppm but not at 128 ppm (M) and	Minor effects in liver weight.		

							decrease at 64 and 128 ppm (F)			
			rat	13 weeks	Oral	n.a.	No effect			
			rat	132 days	oral	1000	Decrease (7.5%) Related to the reduced body weight.			
			rat	13 weeks	inhalation	n.a.	No effect			
			rat	104 weeks	oral					
		Kidney histopathology	mouse	13 weeks	inhalation	n.a.	No effect	No evidence of adversity		
			pig	>150 days	oral					
			rat	132 days	oral					
			rat	13 weeks	inhalation					
			rat	104 weeks	oral					
		Kidney weight	mouse	13 weeks	inhalation	64 ppm	Increase of relative kidney weight at 64 ppm (F) and 128 ppm (M&F) Related to the reduced	Minor effects in kidney weight in 2 studies.		

							body weight (no effect on absolute kidney weight)			
			rat	132 days	oral	300 mg	Increase of absolute and relative kidney weight at dose 300 and 1000. (up to 8.1%)			
			rat	13 weeks	oral	n.a.	No effect			
			rat	13 weeks	inhalation					
			rat	104 weeks	oral					
		Brain histopathology	rat	104 weeks	oral	n.a.	No effect	No evidence of adversity		
		Brain weight	rat	132 days	oral	300 mg	Increase of relative brain weight in female F0 (but reduced terminal body weight)	Overall no evidence of adversity		
			rat	104 weeks	oral	n.a.	No effect			
		Mortality	mouse	13 weeks	inhalation	n.a.	No effect	No evidence of		

			pig	>150 days	oral			effect on mortality		
			rabbit	22 days	oral					
			rat	13 weeks	Oral					
			rat	17 days	oral					
			rat	132 days	oral					
			rat	104 weeks	oral					
			rat	13 weeks	inhalation					

[1]Ghanta, N. R. et al (1987): Influence of body weight on the incidence of spontaneous tumours in rats and mice of long term studies. American Journal of Clinical Nutrition 45: 252-260
Roe, J. C. (1987): The problem of pseudocarcingenicity in rodent bioassays.
Banbury Report 25: Nongenotoxic Mechanisms in Carcinogenicity.

STEP 3 - Sufficiency of the dataset

For EAS parameters, according the guidance on ED, a two-generation reproductive toxicity study (OECD TG416, test protocol according to latest version of January 2001) is enough to consider that EAS-mediated adversity has been sufficiently investigated.

A two-generation reproductive toxicity study was performed with sodium formate in 2008 according to OECD TG416 guidelines (2001).

Therefore, **EAS-mediated parameters are considered to be sufficiently investigated.**

Regarding thyroid, the available ED adversity related studies (OECD 416, 414 (two species), 408, 451-3 and 413 (two species)) did not investigate all thyroid parameters, since some of the studies are old and did not recorded mandatory T parameters (T3/T4 and TSH level, HDL/LDL ratio and thyroid weight for 2 key studies are missing).

No effect of formic acid was detected in the investigated parameters (macroscopic aspect, histopathology and weight).

Since no adverse effect on thyroid was recorded in the life time carcinogenicity study or in the others available studies, it was agreed at the 14^{th} ED expert group (4-5 june 2019) to consider that the **data set is sufficient for Thyroid.**

Please also note that further vertebrate testing was not supported because the substance is corrosive to the gastro-intestinal tract at low doses.

STEP 4 - Initial analysis of the evidence

According the available studies, there is no evidence of adversity for either "EATS-mediated" or "sensitive to but not diagnostic of EATS" parameters.

Effects on liver and kidney, were recorded in some studies but they are inconsistent between sex, studies and species and cannot be explained by an endocrine pathway.

According the guidance on ED, page 36, scenario 1a is concluded and therefore **ED criteria are not met for Human Health**.

Conclusion used in Risk Assessment – Endocrine disruption	
Conclusion	ED criteria not met for Human Health
Justification for the conclusion	Scenario 1a : No evidence of EATS-mediated adversity

3.14 FURTHER HUMAN DATA

Summary table of further human data				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Report on workplace exposure	Formic acid	Measurement of formic acid at the workplace	production, filling, processing, laboratory. The mean values and the 95% percentiles were all far below the threshold limit of 5 ppm or 9.5 mg/m^3. The highest	DocIIIA6.12.1-01 FA_BPR_Ann_II_8_12_1_01

		(8-hour time weighed average) 138 workplace measurements	values were seen at the filling station, but still below the threshold, with the mean value of 1.1 mg/m^3, and the 50%, 90% and 95% percentiles at 0.65, 2.7 and 8.2 mg/m^3, respectively.	[redacted] 2006
Health records from industry	Formic acid Concentration not stated; presumably 50-85%	Sex: not reported Age: 25, 20, 34 and 53 years Route of exposure: dermal	Lesions of skin and eye following facial splashes (3 cases) during filling operations and transportation; one case of skin lesions following contact with contaminated wood.	DocIIIA6.12.3-01 FA_BPR_Ann_II_8_12_3_01 [redacted] 1994, 2002
Case report	Formic acid 60%	1 male, 27-year-old Route of exposure: oral	Suicidal ingestion, 45-90 ml (decalcifying agent). Clinical signs: vomiting, abdominal pain Blood: pH 6.86, pCO_2 70.4 mmHg, HCO_3 10.6 mmol/l, base deficit -22 mmol/l, initial serum formate level 370.3 µg/ml, haemolysis Autopsy: ulceration of oesophagus, complete necrosis of gastric mucosa, oedema and necrotic areas in deeper tissue layers of stomach, no perforation, coagulated blood in stomach, necrosis of mucosa duodenum. Post-mortem formate concentrations: 855.4 µg/ml (heart blood) 2712 µg/ml (gastric contents) 1128 µg/ml (hemorrhagic fluid abdominal cavity) 3051 µg/ml (bile) 2664 µg/ml (contents small intestine) 442.7 µg/g (liver) 542.3 µg/g (kidney) Within 30 hours after ingestion: corrosion of the gastro-intestinal tract, metabolic acidosis, haemolysis, massive bleeding, hepatic and renal failure, death.	BPD ID A6.12.2_01 FA_BPR_Ann_II_8_12_2_01 Westphal et al., 2001

Case report	Formic acid 50%	1 female, 39-year-old Route of exposure: oral	Suicidal ingestion, 200 ml (descaling product). Clinical signs: severe retrosternal and epigastric pain, dyspnea, cyanotic appearance, vomiting blood (2 h after ingestion) Blood: pH 6.87, pCO_2 46.1 mm Hg, HCO_3 8.6 mmol/l, base deficit of -26.4 mmol/l, haemolysis (20 min after admission to hospital) Initial serum formate level 348 µg/ml (7.6 mmol/l), elimination $T_{1/2}$ 2.5 hours Urine: red Gastroscopy: severe lesions oesophagus and stomach, superficial burns duodenum Complications: severe gastrointestinal bleeding, pneumonia, acute tubular necrosis, adult respiratory distress syndrome, peritonitis, sepsis Result: Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death: 6 weeks after ingestion	BPD ID A6.12.2_02 FA_BPR_Ann_II_8_12_2_02 Verstraete et al., 1989
Case report	Formic acid conc. not known	30 males 23 females 16 to 46 year-old Route of exposure: oral	Suicidal ingestion, ≥ 10 ml, (rubber workers) Major complications: Gastro-intestinal: facial burns, ulcerations of oral and pharyngeal mucosa, abdominal pain, contractures and keloid formation of affected skin, oesophagus stricture (16/53 cases) requiring reparative surgery Respiratory system: inhalation pneumonitis (45 of 53 patients) with cough dyspnea, cyanosis, could proceed to respiratory infection and failure Vascular hypotension: 17/53 cases	BPD ID A6.12.2_03 FA_BPR_Ann_II_8_12_2_03 Rajan et al., 1985

			Haemolysis, haematuria within few hours of ingestion, rapidly followed by renal failure in severe cases, within a day in less severe cases, in total 20/53 cases Result: Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death: 15/53 patients	
Case report	Formic acid 40-55%	1 male 2 females 35, 56, 66 year-old Route of exposure: oral	Suicidal ingestion, estimated volumes 'one mouthful' to 50-100 ml (descaling product) *35-year-old woman, 40% formic acid, 3 mouthfuls:* massive bleeding, haemolysis, died on d14 after shock and massive haematemesis. Ulcerations throughout oesophagus and stomach, tubular necrosis, early thrombosis of the portal vein *66-year-old woman, 55% formic acid, 55 to 100 ml:* massive bleeding, haemolysis, extensive erosion of oesophagus, stomach, duodenum, died on d5 *56-year-old man, mouthful of 55% formic acid:* died on d11 due to circulatory failure Result: Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death	BPD ID A6.12.2_04 FA_BPR_Ann_II_8_12_2_04 Naik et al., 1980
Case report	Formic acid 44 to 60%	male/female <12 years to adult	Accidental and suicidal ingestion Estimated doses: < 10 g (children) to 200 g (adults)	BPD ID A6.12.2_05

		45 cases Route of exposure: oral	Children: accidental ingestion of low doses (≤ 10 g), reversible oropharyngeal burns in 9 children, no deaths Adults: suicidal ingestion (34/36 cases), accidental ingestion (2/36) 5-30 g: reversible oropharyngeal burns (16); abdominal pain, vomiting, dyspnea, dysphagia (5); hematemesis, pneumonitis, esophageal strictures (2) 30-45 g: intravascular coagulation, acute renal failure, hematemeses, liver impairment, oesophagal strictures 45-200 g: corrosive perforations of the abdominal viscera and gastrointestinal hemorrhage, acute renal failure dose up to 45g: 28/29 patients survived dose 45g-200g: 14/16 patients died Result: Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death	FA_BPR_Ann_II_8_12_2_05 Jefferys and Wiseman, 1980.
Case report	Formic acid 87 to 96%	male/female children 183 cases Route of exposure: oral	Accidental ingestion: only small quantities Vomiting (10/183 children) and visible caustic lesions in mouth and throat (28/183 cases) Result: Reversible burns of oesophagus	BPD ID A6.12.2_06 FA_BPR_Ann_II_8_12_2_06 von Muehlendahl et al., 1978
Case report	Formic acid conc. not known	1 male, 35-year-old Route of exposure: dermal	Accidental splash from a container on the maxilla, chin, around mouth, thorax (occupational) Clinical signs: burning pain, sialorrhoae, nausea, vomiting Skin: blisters, necrotic areas Systemic: blood pressure 110/60, pulse and breathing regular, blood gases and acido-balance normal, no formic acid detected in blood and urine	BPD ID A6.12.2_07a FA_BPR_Ann_II_8_12_2_07 Malizia et al.,1977

			Result: skin corrosion	
Case report	Formic acid undiluted, conc. not known	1 female, 15-year-old Route of exposure: dermal	Accidental splash on lower extremities (20% of total body surface) Clinical signs: burns, nausea, vomiting (4 hrs after exposure = start treatment) Skin: depth of burns not determined, became full-thickness. Gross oedema on d2 and d3 without fever, ocular damage or pulmonary complications. Burns surgically revived on d16, grafted several times. Major scarring of burned areas persisted. Urine: brownish, hemoglobinuria Blood: pH 7.23, HCO_3 16.7 mmol/l, base deficit 9.5, hemolysis Patient recovered rapidly from metabolic acidosis. Result: Skin corrosion Mild metabolic acidosis	BPD ID A6.12.2_08 FA_BPR_Ann_II_8_12_2_08 Sigurdsson et al., 1983
Case report	Formic acid 90%	1 female, 3-year-old Route of exposure: dermal	Accidental splash on right torso and extremities (35% of total body surface) Clinical signs: severe distress (10 min after exposure = start treatment) Skin: full-thickness second- and third-degree burns. Required several skin grafts during several months Urine: initially dark red, hemoglobinuria resolved within few days without kidney failure Blood: pH 6.85, HCO_3 16.7 mmol/l, base deficit -29.7 on 100% oxygen, bicarbonate 6mEq/l; initial serum formate level 400 µg/ml, hemolysis Patient recovered rapidly from metabolic acidosis. Result: Skin corrosion	BPD ID A6.12.2_09 FA_BPR_Ann_II_8_12_2_09 Chan et al., 1995

			Metabolic acidosis	
Case report	Formic acid 98%	1 male, 39-year-old Route of exposure: inhalation	Accidental spray (aerosol) into the face with concomitant inhalation (occupational) Clinical signs: facial burns (3% of total body surface), dyspnea Nasopharyngoscopy: mild supraglottic erythema, normal vocal cords Skin: second-degree burns Pulmonary function tests: Vital capacity reduced on d1, recovered largely within 14 days. Complains of dyspnea till d15 <u>Day 1</u> FVC (L): 3.74 (79% predicted) FEV_1 (L): 2.86 (73% predicted) FEV_1/FVC: 76.38 (92% predicted) FEF $_{25\%-75\%}$ (l/sec): 2.32 (56% predicted) <u>Day 15</u> FVC (L): 4.35 (92% predicted) FEV_1 (L): 3.62 (92% predicted) FEV_1/FVC: 83.09 (101% predicted) FEF $_{25\%-75\%}$ (l/sec): 3.82 (92% predicted) Result: Reversible Pulmonary dysfunction: Reactive Airway Dysfunction Syndrome	BPD ID A6.12.2_10 FA_BPR_Ann_II_8_12_2_10 Yelon et al., 1996
Case report	Fumes from formic acid (85%) and carbon monoxide (concentration not known)	1 male, 22-year-old Route of exposure: inhalation	Suicide by mixing formic acid with concentrated sulphuric acid in a confined space External chemical burns Internal injuries mainly to the respiratory tract. Injury to the oropharyngeal area and trachea, pulmonary edema, and subpleural petechiae. Complete lack of the respiratory epithelium of the trachea, edema of mucosa, and submucosa of the trachea, thrombi, and hemolysis inside	Bakovic M, et al (2015) FA_BPR_Ann_II_8_12_2_11

			the small vessels of the trachea, pulmonary edema, hemolysis, and thrombosis in the lung vessels Death due to CO intoxication; corrosion/irritation of skin, trachea, lungs, stomach due to formic acid fumes.	
Case report	Fumes from formic acid (concentration not reported, amount 950 ml) and carbon monoxide (concentration not known)	1 male, 26-year-old Route of exposure: inhalation	Suicide by mixing formic acid with concentrated sulphuric acid in a confined space. Death. The body showed pronounce bright pink-red lividity. The autopsy was otherwise unremarkable. No further info on formic acid effects.	Lin PT and Dunn (2014) FA_BPR_Ann_II_8_12_2_12
Case report	Fumes from formic acid (98-100%) and carbon monoxide (concentration not known)	1 male, 26-year-old; 1male, 53-year-old, 1 female, 53-year-old Route of exposure: inhalation	Suicide by mixing formic acid with concentrated sulphuric acid in a confined space 26-year-old: death. No autopsy 53-year-old father: coma, hypoxemia, metabolic acidosis, and a carboxyhemoglobin level of 45.8%. Developed acute respiratory distress syndrome. Transient ulceration of vocal cords. 53-year-old mother: dizziness, headache, carboxyhemoglobin level of 23.0% In addition to the toxicities of carbon monoxide, concomitant inhalation of formic acid fumes can cause severe lung injury, which may complicate the management of carbon monoxide poisoning.	Yang CC et al. (2008) FA_BPR_Ann_II_8_12_2_13
Retrospective study	formic acid	302 cases Males and females	Suicide Mean (SD) quantity consumed: 110 (78) mL The most common symptoms noted at presentation were: vomiting (78.5 %)	Dalus D et al. (2013) FA_BPR_Ann_II_8_12_5_01

		Age: 29.7-55, mean age 42.8 years Route of exposure: Oral, dermal, inhalation	abdominal pain (56.3% hematemesis (48.3%) respiratory distress (44 %) haematuria (30.1%) oliguria (24.5%) hypotension (24.5%) melena (22.2%) direct corneal injury (0.007%) Mean (SD) pH of all patients was 7.3 and the bicarbonate concentration was 19.2 (5.1) mEd/L. Leucocytosis was seen in 57.5% of the patients; liver enzymes (GOT, GPT) were elevated above normal values in 62.1% of the patients. The effectivity of medical treatment depends largely on the ingested dose and concentration of FA, the time delay after exposure. Low blood pH and bicarbonate concentration reflect the severity. The mortality rate was 35.4%. Bowel perforation, shock, and tracheoesophageal fistula were associated with 100% mortality. A higher blood pH was less likely to result in mortality. Dysphagia was noted in 154 patients, 98 of whom showed oesophageal stricture on evaluation, requiring repeat endoscopic dilatations after discharge. The prevalence of oesophageal stricture among the 195 patients who survived was 50.2%.	

Medical surveillance on manufacturing plant personnel:

A total of 138 workplace measurements have been conducted during the period 2001-2006, covering all kinds of operations (production, filling, processing, laboratory). All reported results represented 8 hours shift average values (TWA) obtained by personal air sampling. None of the measurements exceeded the threshold limit of 5 ppm or 9.5 mg/m^3 (most well below). To prevent direct skin contact, protective gloves (neoprene or nitrile rubber) are used. According to the applicant workplace exposure is low, due to the appropriate protective measures taken. Consequently, medical surveillance on plant personnel is not required (DocIIIA6.12.1-01: [redacted] 2006).

Four cases of accidental skin and eye contact were seen during 14 years (1989-2002) of operation of BASF's production plant. Lesions of skin and eye were seen following facial splashes (3 cases) during filling operations and transportation, and one case of skin lesions following contact with contaminated wood. As concentrated formic acid is corrosive, the employees underwent First Aid measures and required further medical treatment in hospital. Type and duration of medical treatment were not reported, nor the outcome in the health records (DocIIIA6.12.3-01: [redacted] 1994, 2002).

Clinical cases and poisoning incidents (professional operators and the general population), Expected effects of poisoning, aspects of diagnosis of poisoning, prognosis:

Oral ingestion

There are published cases of accidental ingestion of formic acid, but the incidence is relatively low. The suicidal ingestion (34 of 36 cases, i.e. 94%) clearly prevailed over the accidental ingestion (2 of 36 cases) in adults (DocIIIA6.12.2_05, FA_BPR_Ann_II_8_12_2_05: Jefferys and Wiseman, 1980). Easy access to formic acid was considered to promote the suicidal ingestion of formic acid in the State of Kerala, India, among workers of the rubber industry who used formic acid as a coagulant (DocIIIA6.12.2_03, FA_BPR_Ann_II_8_12_2_03: Rajan et al., 1985).

In children, the accidental ingestion occurs generally at low doses, i.e. **up to 10 g formic acid,** which reportedly caused reversible burns of the pharyngeal tract in 9 children, who all survived (DocIIIA6.12.2_06, FA_BPR_Ann_II_8_12_2_06: von Muehlendahl et al., 1978). The consumption of only small quantities might be related to the pungent smell of formic acid.

The doses are much higher in cases of deliberate ingestion by adults. Doses **up to 45 g** formic acid were survived by 28 of 29 patients. Most of the patients died (14 of 16; 88%) after doses between 45 – 200 g formic acid (DocIIIA6.12.2_05, FA_BPR_Ann_II_8_12_2_05: Jefferys and Wiseman, 1980). In a retrospective study with 302 patients who committed suicide, the estimated mean ingested quantity was 110 mL of formic acid. The mortality rate was 35.4% in this study. The prognosis depended largely on the concentration of formic acid and the amount ingested and the lag time until onset of medical treatment (FA_BPR_Ann_II_8_12_8_02: Dalus et al., 2013).

Due to the corrosivity of formic acid, local effects must be expected at all dose levels. The amount ingested and the concentration determine the grade and the location of the effects. Therefore, the observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the esophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity:

- Nine children accidentally ingested **less than 10 g of formic acid**. They suffered oropharyngeal burns, which were only superficial, and they fully recovered. Two adults accidentally ingested formic acid, whilst 34 deliberately consumed it.

- Consumption, by 23 subjects, of between **5 and 30 g of formic acid** produced no deaths. The majority (16) developed minor superficial oropharyngeal burns only. Five had more severe symptoms including abdominal pain, vomiting, dyspnea and dysphagia, whilst two experienced sustained hematemesis and pneumonitis, and subsequently developed esophageal strictures.
- Ingestion of **30-45 g of formic acid** produced more serious effects. Of the six patients recorded, one died, one had reversible disseminated intravascular coagulation and three had reversible acute renal failure. All suffered hematemesis and had biochemical evidence of liver impairment. Four needed subsequent treatment for esophageal strictures.
- Ingestion of **45 to 200 g of formic acid** was recorded from 16 patients, of whom 14 died; two recovered. Considering the fatalities, the majority (9) died painfully within the first 36 hours from corrosive perforations of the abdominal viscera and from gastrointestinal hemorrhage. The other five developed acute renal failure which contributed to their death (BPD ID A6.12.2_05, FA_BPR_Ann_II_8_12_2_05).
- **Systemic toxicity** was seen after ingestion **of 30 g formic acid** or more.

Prognosis is poor after massive oral ingestion (>45 to 200 g formic acid); prognosis is moderate after moderate oral ingestion (approx. 30 to 45 g); lesions, but low mortality, are expected in most cases with low amounts ingested (<30g); persistent lesions due to tissue corrosion must be expected in cases with >10 g formic acid ingested. Tissue destruction of the gastrointestinal tract may result in fatal bleeding, septic shock, or stricture which may require surgical treatment. Reversibility of effects was often seen in cases with low amounts ingested (<10 g formic acid).

Dermal exposure

Due to the corrosivity of concentrated formic acid, local effects must be expected following contact to the skin and to the eyes.

Prognosis: Local burns heal only slowly. Tissue destruction of the skin may result in scarring.

Systemic effects may result after contact of concentrated formic acid to extended areas of the body surface (DocIIIA6.12.2_07, FA_BPR_Ann_II_8_12_2_07: Malizia et al., 1977; DocIIIA6.12.2_08, FA_BPR_Ann_II_8_12_2_08: Sigurdsson et al., 1983; DocIIIA6.12.2_09, FA_BPR_Ann_II_8_12_2_09: Chan et al., 1995).

Prognosis: Systemic effects were reversible within few days without sequelae in cases where the medical treatment was rapid and strict to counteract the metabolic acidosis.

Inhalation exposure

Due to the warning effect of the pungent smell of formic acid, inhalation exposure is generally low.

As **local effect,** pulmonary dysfunction was observed which was reversible within 14 days in one presumably high-dose case (DocIIIA6.12.2_10, FA_BPR_Ann_II_8_12_2_10: Yelon et al., 1996).

Inhalation of fumes created by mixing formic acid with concentrated sulphuric acid leads to injuries to the respiratory tract from formic acid, and deadly carbon monoxide intoxication (Bakovic et al., 2015; Lin & Dunn, 2014; Yang et al., 2008).

Systemic effects are unlikely to occur. An estimate that was presented in the MAK-justification indicated that the uptake of formic acid at the threshold exposure concentration (MAK-value: 5 ppm i.e. 9.5 mg/m³) equals approx. 0.5% of the metabolic rate observed in non-human primates. It was therefore concluded that an effect on the blood pH is unlikely. Formic acid inhalation concentrations from 30 ppm onwards were regarded as being immediately dangerous to life and health (DocIIIA6.12.8_01: Greim, 2003; NIOSH, 1990).

Aspects of diagnosis: Effective treatment requires an examination which provides adequate poisoning information. The case history provides information on the route of exposure and in some cases on the chemical concentration and amount. Clinical signs (mouth or skin affected) support this. The examination should generally comprise (1) and additionally (2) in cases of inhalation exposure:

(1) Blood pressure, blood count, hemolysis, blood gases, acid-balance, urine. Blood and urine formate concentrations.

(2) Inhalation (additionally): Chest radiograph, Lung function tests

First aid measures, therapeutic regimes

The primary goal must be to restore the metabolic acidosis to counteract the systemic toxicity. Second, the burns must be appropriately treated including the use of antibiotics. Special attention requires internal bleeding, due to local corrosion of the gastrointestinal tract after oral ingestion.

After suicidal exposures the doses are often extremely high, and there is no specific treatment in such cases.

Conclusion on prognosis: The prognosis depends on the exposure (concentration of chemical, amount, route of exposure), the rapid onset of treatment, the proper examination on admission to the hospital, and a strict treatment regimen to counteract systemic and local effects.

The prognosis may be good in cases of low oral, dermal, and inhalation exposure, as the systemic toxicity may be low. The prognosis of severe systemic toxicity is often bad. Tissue corrosion due to local effects heals slowly with scarring in most cases.

Conclusion used in Risk Assessment – Further human data	
Conclusion	Dermal exposure: Due to the corrosivity of concentrated formic acid, local effects must be expected following contact to the skin and to the eyes. Local burns heal only slowly. Tissue destruction of the skin may result in scarring. Systemic

	effects may result after contact of concentrated formic acid to extended areas of the body surface. Occupational and accidental dermal exposure records report skin corrosion and metabolic acidosis. Oral exposure: Due to the corrosivity of formic acid, local effects must be expected at all dose levels. The amount ingested and the concentration determine the grade and the location of the effects. Therefore, the observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the esophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity (Systemic toxicity observed after ingestion of 30 g formic acid or more). Accidental and suicidal oral exposure records report reversible burns of the oesophagus after ingestion of small quantities (up to 10g). Consumption of between 5 and 30 g of formic acid led to minor superficial oropharyngeal burns or more severe symptoms including abdominal pain, vomiting, dyspnea and dysphagia, hematemesis and pneumonitis, and esophageal strictures. Doses up to 45 g formic acid were survived by most patients. The majority of patients died after doses between 45 – 200 g formic acid. Reported symptoms at high doses were corrosion of the gastro-intestinal tract, metabolic acidosis, haemolysis, loss of blood pressure, massive bleeding, hepatic and renal failure, and death. Inhalation exposure: Systemic effects are unlikely to occur. Workplace measurements showed mean values and 95% percentiles far below the threshold limit of 5 ppm or 9.5 mg/m^3. Uptake of formic acid at this threshold exposure concentration equals approx. 0.5% of the metabolic rate observed in non-human primates. Therefore, an effect on the blood pH is unlikely. Formic acid inhalation concentrations from 30 ppm onwards are regarded as being immediately dangerous to life and health. One accidental inhalation exposure record reported reversible Pulmonary dysfunction in the form of Reactive Airway Dysfunction Syndrome. Suicidal inhalation exposure records (mixing of formic acid with concentrated sulphuric acid to form carbon monoxide) report death due to CO intoxication alongside corrosion/irritation of skin, trachea, lungs, stomach due to formic acid fumes.
Justification for the conclusion	Workplace measurements, health records from industry, case reports

Data waiving	
Information requirement	Epidemiological studies on formic acid
Justification	None available

3.15 OTHER DATA

Summary table of other data			
Type of data/ report, Reliability	**Test substance**	**Observations**	**Reference**
Proposed acceptable residue levels	Residue definition: Group formic acid and ethyl formate	ADI 3 mg/kg bw/day	European Commission (2005) BPD ID A6.15.4_01a FA_BPR_Ann_II_8_16_1_01
	Residue definition: Group formic acid and ethyl formate	ADI 3 mg/kg bw/day	JECFA (2003) BPD ID A6.15.4_01b FA_BPR_Ann_II_8_16_1_01
	Formic acid, formate	No MRL set	EFSA (2009, 2014, 2015) FA_BPR_Ann_II_8_16_1_01 FA_BPR_Ann_II_8_16_2_0_JNS FA_BPR_Ann_II_8_16_3_0_JNS

When applied as recommended by the biocidal use patterns, no prolonged continuance of formic acid residues on treated surfaces is expected, owing to the volatility of formic acid and the water solubility of the acid and its salts. After uptake, formic acid and formate is readily and completely metabolised with the consequence that no relevant residue quantities are found in meat, milk, eggs, honey, or other products in addition to naturally occurring trace amounts which result from the fact that formic acid does naturally occur in food and plants. Hence, the formate consumer exposure is not increased through the diet.

As to the animal health, formic acid and formate salts (FORMI™ LHS, ammonium formate and sodium formate) showed a positive effect on the intestinal microflora which is beneficial for the treated animals. Therefore, formic acid and formate salts (FORMI™ LHS and sodium formate) were proposed as feed additives. Formic acid, FORMI™ LHS, and sodium formate are approved feed and drinking water additives, whereas ammonium formate was not approved because of the inevitable presence of formamide, a developmental toxicant, while formate was not considered to be problematic (EFSA, 2009; 2014, 2015; cf. outline further below).

The consumer average daily intake of formic acid with the natural food content was estimated to range between 0.1 to 0.43 mg/kg body weight.

Historically, higher intakes must be considered in those European countries where formic acid, or formate salts, was used as approved food preservative until 1998. A group ADI-value (Acceptable Daily Intake) of 3 mg/kg bw was established by JECFA for formic acid and ethyl formate in 1979 and maintained in 1997, and this value was adopted in the latest synoptic document of the EC updated in 2005.

Following ingestion formic acid distributes rapidly, and it is rapidly metabolised to CO_2. Further, it is required for the biosynthesis of purines and pyrimidines in the intermediary metabolism. In the case of unintentional uptake of residual product, no accumulation is expected as formic acid is rapidly removed from blood in all species that have been investigated.

Formic acid, FORMI™ LHS, and sodium formate are approved feed and drinking water additives, and their use in feed (up to 12,000 ppm for pigs, 10,000 ppm for birds, ruminants, and other species) and drinking water (4,000 ppm) as specified in the Scientific Opinions is considered to be safe for the animals, the consumer, and the environment, whereas users might need protective measures (PPE: skin, eye, respiratory protection) because of the corrosivity of formic acid at concentrations >10%. The EFSA panel (FEEDAP) does not expect relevant residue levels and did not propose a MRL value (EFSA, 2009; 2014, 2015).

Conclusion:

When applied as recommended by the biocidal use patterns, no considerable potential or actual exposure of formic acid to animals and /or humans through diet or other means is expected.

Summary of Scientific EFSA Opinions pertaining to formic acid and its salts			
	EFSA (2009) No. 1315	**EFSA (2014) No. 3827**	**EFSA (2015) No. 4113**
Reference No.	FA_BPR_Ann_II_8_16_1_01 FA_BPR_Ann_II_8_16_2_0_JNS FA_BPR_Ann_II_8_16_3_0_JNS		
Objective	Re-evaluation	Re-authorisation	Authorisation of new use
Legal basis of evaluation	Request from BASF SE to the EU Commission; technical dossier obtained directly from BASF SE	Request from ACIAC-EEIG consortium to the EU Commission; technical dossier obtained directly from the applicant.	Request from FEFANA/HYFAC to the EU Commission; technical dossier obtained directly from the applicant.

Trade name	FORMI™ LHS	Formic acid	Not appropriate
Chemical	Potassium diformate, min. 98%	Formic acid, min 84.5%	Formic acid min. 84.5% Ammonium formate; min 35%(liquid) Sodium formate min 98% (solid); min 15% (liquid)
Formula	(KCOOH*HCOOH)	HCOOH	HCOOH NH_4COOH NaCOOH
Contains	Formic acid, formate	Formic acid	Formic acid, formate salts
Intended use	Feed additive for sows. 0.8 – 1.2% in feed	Feed additive (pigs 1.2%, poultry1%, ruminants 1%; all other species 1%) Drinking water 0.4%	Feed additive Formic acid: all species except pigs; 1% in feed Formic acid: pigs; 1.2 % in feed Ammonium formate: all species except pigs; 1% in feed Ammonium formate: pigs; 1.2 % in feed Sodium formate: all species except pigs; 1% in feed Sodium formate: pigs; 1.2 % in feed
Conclusions of safety evaluation	Safe at a max. dose of 1.2% in feed (12,000 ppm); MoS = 4	Safe doses: up to 1.2% in feed. No MoS identified.	Safe doses: up to 1.2% in feed. No MoS identified. Ammonium formate: unsafe, due to inevitable presence of formamide (developmental toxicant)
Livestock	Well tolerated by sows; no adverse effects up to 1.2% in feed.	Safe doses: Pig: 1.2% Poultry, ruminants: 1% Other species: 1% (extrapolation)	Safe doses: Pig: 1.2% (both formic acid and sodium formate) Poultry, ruminants: 1% (both formic acid and sodium formate)

			Other species: 1% (extrapolation; both formic acid and sodium formate)
user	FORMI LHS is an eye irritant. Requires protection measures.	Safe concentrations > 10% considered to be corrosive to skin and eyes. Volatile liquid. Inhalation exposure and exposure of skin and eyes present a risk for unprotected workers	Formic acid: cf. EFSA (2014) No. 3827 Sodium formate: mildly irritating to the skin. Safe handling ma yrequire PPE. Formic acid, sodium formate, ammonium formate were all considered to be skin sensitizers due to the lack of data (cf. remark 3 in last line)
consumer	Safe. No consumer formate exposure expected, due to rapid and complete metabo-lism in the pig.	Safe. No contribution to consumer exposure, due to rapid turnover and no accumulation	Safe ((both formic acid and sodium formate). No contribution to consumer exposure, due to rapid turnover and no accumulation
environment	Safe, when used as intended	Safe, when used as intended	Safe, when used as intended
microbiology	MIC values for Gram-positive and Gram-negative bacteria in the range 0.2-0.4%. No incidence of resistance to formic acid has been recorded until now.	MIC values not reported	MIC values mentioned but no details reported
Efficacy	Given at 1.2 % in feed	Recommended concentrations inhibit bacterial growth in feedingstuffs, drinking water, and in silage.	
MRLs (max. residue levels)	None definded. No negative effect on meat quality at proposed dose.	None definded. No negative effect on meat quality at proposed dose.	
Remark 1		ACIAC-EEIG consortium liquidated and rights transferred to FEFANA (includes Addcon Nordic SA; BASF	FEFANA/HYFAC members: Kemira Oyj; Perstorp AB; Selko feed Additives; Andres Pintaluba; BASF SE; Anitox Ltd.

		SE; Kemira Oyj Pestorp AB; Selko BV)	
Remark 2			Formic acid: conclusions from previous opinion reiterated.
Remark 3			Formic acid, sodium formate, ammonium formate were all considered to be skin sensitizers due to the lack of data. It should be noted that formic acid was negative in a valid Buehler test, and that potassium formate was also negative in a valid assay. This result can be read across to sodium formate. Apparently, the applicants did not present data on this endpoint.

Conclusion used in Risk Assessment – Other data	
Conclusion	An ADI has previously been set at 3 mg/kg bw/day. No further data on residues on the treated or contaminated food or feedingstuffs including kinetics of disappearance are needed.
Justification for the conclusion	When applied as recommended, neither prolonged remain of formic acid residues in food or feeding stuffs nor significant exposure to animal or human is expected, due to volatilisation, wash-off, and rapid and complete metabolism. The EFSA Feed additive panel (FEEDAP) shares this opinion and concludes the use of feed additives containing formic acid or formate salts is safe for the consumer, the animals, and the environment in three Scientific Opinions.

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4 ENVIRONMENTAL EFFECT ASSESSMENT

In aqueous solution and at neutral pH, formic acid and water-soluble formate salts dissociate and are present as the formate anion in solution. Based on this, it is deemed justified to include studies conducted with water-soluble formate salts in the evaluation of the environmental effects of formic acid.

4.1 FATE AND DISTRIBUTION IN THE ENVIRONMENT

4.1.1 Degradation

4.1.1.1 *ABIOTIC DEGRADATION*

4.1.1.1.1 Hydrolysis

The hydrolytic stability of formic acid at pH 4, 7 and 9 was investigated in a study following OECD 111, covering also Directive 92/69/EEC C.7 and US EPA OPPTS 835.2110.

The test item was dissolved in 50 mL of appropriate buffer solutions to give a final concentration of 400 mg a.i./L. The solutions were incubated at 50 °C and aliquots were taken after certain intervals and analysed in a modular HPLC system with UV/vis detector. After 5 days (120 h) the test was terminated since no hydrolysis was observed at any pH (preliminary test). At test end about 100 % recovery of the parent compound was reached at pH 4, 7, and 9

Conclusion:
Formic acid is considered to be hydrolytically stable, independent of the pH.

Summary table - Hydrolysis							
Method, Guideline, GLP status, Realibility	**pH**	**Temp. [°C]**	**Initial TS concentration, C_0[mol/l]**	**Half-life, DT_{50} [d]**	**Coefficient of correlation, r^2**	**Remarks**	**Reference**
OECD TG 311; Directive 92/69/EEC, C.7; US EPA	4 7 9	49.9 ± 0.5 °C	8.7 mmol/L (400 mg a.s./L)	> 1 year	Not applicable	/	[redacted] (2002) BPD ID A7.1.1.1.1_01 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_1_a*

OPPTS 835.2110 (Hydrolysis as a function of pH); GLP-study; Reliability 1							

Converted to environmentally relevant conditions (pH 7; 12 °C) the DT50 value becomes > 20.7 years (Guidance on BPR: Volume IV Environment Parts B+C (Version 2.0 October 2017), Equation 28).

Value used in Risk Assessment	
Value/conclusion	DT50 > 1 year (pH 4, 7 and 9; 49.9±0.5 °C) DT50 > 20.7 years (pH 7; 12 °C)
Justification for the value/conclusion	According to Guideline OECD 111 a substance is considered hydrolytically stable if, in the preliminary test at 50 °C, less than 10 % of hydrolysis is observed after 5 days. No additional testing is required at this point. Conversion of DT50 value to 12 °C using Equation 28 of the Guidance on BPR: Volume IV Environment Parts B+C (Version 2.0 October 2017), Equation 28.

4.1.1.1.2 Phototransformation in water

No new data was submitted for this endpoint, instead a justification for non-submission based on other available data (literature) was submitted *(Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_1_b).*

Direct photolysis
According to the HSDB database (available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB) formic acid does not absorb at wavelengths > 290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight.

Phototransformation with OH-radicals in water
From the literature (Buxton et al., 1988, BPD ID A7.1.1.1.2_01), a rate constant (k) for the reaction of formic acid and the formate ion with OH-radicals in water were compiled:

pH	Molecule	Rate constant (k) [L/mol*sec]
0.4 – 1.0	Formic acid (HCOOH)	4.4×10^5
7.0 – 13.5	Formate ion ($HCOO^-$)	2.1×10^8

In order to be able to derive half-lives from these data, hydroxyl-radical concentrations in water have to be assumed. This is also derived from literature (Zepp et al., 1987, BPD ID A7.1.1.1.2_02), wherein it is described that for the small lake Greifensee in Switzerland, the average OH-radical concentration over the whole water column (14 m) over the whole year is 3.0×10^{-18} mol/L. From this, a half-life for aquatic photolysis can be calculated for the formate ion, which is the relevant form of formic acid in water, of approximately 35 years (34,89 years).

<u>Phototransformation with NO_3-radicals in water</u>
At pH 5 – 9, the rate coefficients for the aqueous reactions of NO_3 with $HCOO^-$ at 25 °C were experimentally determined to range from $4.7 \pm 0.6 \times 10^7$ to $5.0 \pm 0.4 \times 10^7$ L/mol*sec. With formic acid the rate constant was $3.3 \pm 0.4 \times 10^5$ L/mol.sec at pH 0.5 and 25 °C. The differences in reactivity of the anion $HCOO^-$ compared to HCOOH were explained by the higher reactivity of NO_3 in the charge transfer processes compared to H-atom abstraction (Exner et al., 1994, BPD ID A7.1.1.1.2_03).

<u>Transformation products</u>
Formic acid is a simple C1-molecule which can be degraded chemically to innocuous substances in most environments.

Value used in Risk Assessment	
Value/conclusion	• Direct photolysis: not expected • Photo-oxidation with OH-radicals in water: DT_{50} $HCOO^-$ = 35 years
Justification for the value/conclusion	The information submitted by the applicant was deemed sufficient. Phototransformation will not likely play a role in the degradation of formic acid in the environment.

4.1.1.1.3 Estimated photo-oxidation in air

According to the HSDB database (available online at <u>http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB</u>) formic acid does not absorb at wavelengths > 290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight.

The photo-degradation of formic acid in air was estimated through the modelling program AOP v1.91, included in the EPISUITE program developed by US EPA.

For a 12-hour day, with an OH-radical concentration of 1.5×10^6 OH/cm³, a half-life of 20.6 days or 493.7 hours was estimated.

For a 24-hour day, with an OH-radical concentration of 0.5×10^6 OH/cm³, a half-life of 30.9 days or 740.5 hours was estimated.

Summary table – Photo-oxidation in air					
Model	**Light protection (yes/no)**	**Estimated daily (24h) OH concentration [OH/cm³]**	**Overall OH rate constant [cm³/molecule sec]**	**Half-life [hr]**	**Reference**
AOP v.1.91	/	0.5×10^6	5.2×10^{-13}	740.5	[redacted] (2006) BPD ID A7.3.1_01 *Doc IIIA JOINT: FA_BPR_Ann_II_10_3_1*

Furthermore, according to §2.3.6.3 of the Guidance on the BPR: Volume IV Part B on photochemical reactions in the atmosphere, the pseudo-first order rate constant in air can be calculated using the following:

$$kdeg_{air} = k_{OH} \times OHCONC_{air} \times 24 \times 3600$$

$$\Leftrightarrow kdeg_{air} = 5.2 \cdot 10^{-13} \times 5 \cdot 10^{5} \times 24 \times 3600$$

$$\Leftrightarrow kdeg_{air} = 0.0225 d^{-1}$$

In a monograph on kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds (Atkinson., 1989, BPD ID A7.3.2_01), a unit-weighted average of the rate constants reported in different sources results in a recommended rate constant of 4.5×10^{-13} cm³/mol.sec for formic acid. From this, using the same formula as above, a degradation half-life of 35.7 days or 855.7 hours can be derived.

The latter derived half-life will be used for further risk assessment purposes, since it is more conservative than the half-life estimated through the AOP program.

Value used in Risk Assessment	
Value/conclusion	DT_{50} = 855.7 hours Formic acid is only moderately subjected to photodegradation
Justification for the value/conclusion	The information submitted by the applicant was acceptable.

4.1.1.2 *BIOTIC DEGRADATION*

4.1.1.2.1 Biodegradability (ready/inherent)

Four studies are available on the aerobic biodegradation of formic acid in fresh water. All four tests document on ready biodegradability.

Two identical studies were performed by [redacted] (1988a/b) on formic acid, both using the modified OECD screening test (OECD 301E).

In both tests 20 mg DOC/L of test substance was inoculated with 0.5 ml effluent per litre medium (composition according to OECD). The mixture was aerated in the dark or diffuse light at room temperature (22°C±2 °C). A reference substance (sodium benzoate; 20 mg/l DOC) was tested in parallel. Both tests were performed in duplicate.

In the first test (BPD ID A7.1.1.2.1_01), samples were taken on day 0, 1, 7, 10, 13 and 14, while in the second test (BPD ID A7.1.1.2.1_02) samples were taken daily, to measure the DOC concentrations with an oxygen electrode.

In the first tests, 4 additional controls were run next to the test substance and reference substance: a control without test substance (blank), a control with reference substance, an abiotic control and a toxicity control. In the second test, the abiotic and toxicity control was omitted, which can be seen as a deficiency.

For the first test, 90-100% of the initial formic acid (20 mg/L DOC) was eliminated from water after 14 days. The 10-day window was reached.

For the second test, 99 % of the intial formic acid (20 mg/L DOC) was eliminated from water after 11 days, also reaching the 10-day window.

With these results, both tests indicate that formic acid is readily biodegradable.

The third and fourth ready biodegradability test are both closed bottle tests (OECD 301D) performed with potassium formate, for which the formate ion is representative for formic acid in water.

The oldest test ([redacted] 1992a, BPD ID A7.1.1.2.1_03) was performed according to the principles of GLP.

In this study the test substance and reference substance (sodium benzoate) were tested at respective concentrations of 18 and 3 mg/L. BOD bottles of 250 mL were filled with a standard nutrient medium, the test substance or reference substance and 1 drop/L of activated sewage sludge bacteria. Samples were taken after days 0, 5, 15 and 28 to measure the BOD with an oxygen electrode. Additionally, a blank control, an inoculum control and an inhibition control were run in parallel. The test was performed at 20 °C in a water bath and was performed in duplicate.

92 % of the initial test substance concentration was eliminated from water after 28 days.

Between day 5 (15 % degradation) and day 15 (90 % degradation) more than 60 % degradation related to ThOD was observed. The 14-day window was met.

The second closed bottle test ([redacted] 2000, BPD ID A7.1.1.2.1_04) confirmed the results of the first study, albeit not being GLP. In this study the test substance and reference substance (aniline) were tested at respective concentrations of 20 and 1.95 mg/L. The preparation of the BOD bottles was identical to that in the first test and samples were taken at appropriate intervals (days 0, 2, 5, 7, 9, 12, 14, 16, 22 and 28) to measure the BOD with an oxygen electrode. Additional controls, such as in the first test, were run in parallel.

82 % of the initial test substance concentration was eliminated from water after 28 days.

Between day 2 (10 % degradation) and day 9 (75 % degradation) more than 60 % biodegradation related to ThOD was observed. The 14-day window was met.

Conclusion:
Overall, considering the 4 ready biodegradability tests performed with the active substance, it can be concluded that Formic Acid is readily biodegradable.
Further screening tests on inherent biodegradability are deemed unnecessary (applicant justification *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_2_b)*.

Summary table - biodegradation studies (ready/inherent)											
Method, Guideline, GLP status, Realibility	**Test type [1]**	**Test parameter**	**Inoculum**			**Additional substrate**	**Test sub-stance concentr.**	**Degradation**		**Remarks**	**Reference**
			Type	**Concentration**	**Adaptation**			**Incuba-tion period**	**Degree [%]**		
Modified OECD Screening Test, 79/831/EEC, Annex V, C3;	Ready	DOC	Effluent municipal STP (lab. culture)	0.5 mL (total batch volume: 900 mL)	no	no	Formic acid; 20 mg DOC/L	28 (terminated after day 14)	90-100 10-day window passed		[redacted] 1988a BPD ID A7.1.1.2.1_01 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_2_a_1*

non-GLP study, Reliability 2											
Modified OECD Screening Test, 79/831/EEC, Annex V, C3; non-GLP, Reliability 2	Ready	DOC	Effluent municipal STP (lab. culture)	0.5 mL (total batch volume: 900 mL)	no	no	Formic acid; 20 mg DOC/L	28 (terminated after day 11)	99 10-day window passed		[redacted] 1988b BPD ID A7.1.1.2.1_02 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_2_a_2*
Closed Bottle Test, OECD TG 301D, GLP Reliability 1	Ready	BOD	Activated sewage sludge of municipal STP	1 drop/L	no	Nutrient medium	Potassium formate; 18 mg/L	28 (90% removal after 15 days)	92 14-day window passed		[redacted] 1992a BPD ID A7.1.1.2.1_03 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_2_a_3*
Closed Bottle Test, OECD TG 301D, non-GLP, Reliability 2	Ready	BOD	Activated sludge cultivated on synth. sewage; supplied w. domes. sewage	$6.8*10^5$ CFU/L (hetero-trophic bacteria)	no	Nutrient medium	Potassium formate; 20 mg/L	28 (75% removal after 9 days)	82 14-day window passed		[redacted] 2000 BPD ID A7.1.1.2.1_04 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_1_2_a_4*

			5 d prior to start								
[1] Test on inherent or ready biodegradability according to OECD criteria											

Value used in Risk Assessment	
Value/conclusion	Ready biodegradable (meeting the 10 or 14-day window)
Justification for the value/conclusion	Based on the available studies, formic acid is well within the pass levels of 70 % DOC and 60 % ThOD removal. The 10-day or 14-day window (depending on test-type) is met each time.

4.1.1.3 *RATE AND ROUTE OF DEGRADATION INCLUDING IDENTIFICATION OF METABOLITES AND DEGRADATION PRODUCTS*

4.1.1.3.1 Biological sewage treatment

4.1.1.3.1.1 Aerobic biodegradation

Data waiving	
Information requirement	A justification of non-submission of data was submitted by the applicant (*Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_1_a)*, based on the fact that such a test is not a core data requirement and that submitted studies showed formic acid to be ready biodegradable.
Justification	Justification is accepted.

4.1.1.3.1.2 Anaerobic biodegradation

A study on the acclimation and degradation of petrochemical wastewater components by methane fermentation was submitted for this data point (Chou et al., 1979, BPD ID A7.1.2.1.2_01). The study dates from 1979 and does not follow a known guideline or is performed according to GLP.

Hungate serum bottles were filled with water and displaced with an inert gas mixture of CO_2 and CH_4. A 50 mL inoculum of acetate enriched cultures (1000 mg/L SS, laboratory culture if domestic sludge fed with acetate for years) was injected into the bottle, together with 100 mL of acetate and 25 mg of test substance (formic acid, amongst others).

Gas production was monitored and test substance was injected with a microliter syringe as needed.

For formic acid, the test showed 89 % of substrate removal after a lag time of 4 days. An overall degradation rate of 286 mg/L.day was established.

Summary table - STP anaerobic biodegradation								
			Inoculum			**Degradation**		**Reference**

Method, Guideline, GLP status, Reliability	Test type[1]	Test parameter	Type	Concen-tration	Adaptation	Additional substrate	Test substance concentr.	Incubation period	Degree [%]	Remarks	
No guideline (Hungate serum bottle) Non-GLP Reliability 4	no guideline (anaerobic)	CH_4 evolution	Acetate enriched cultures (lab. cult. domestic sludge)	1000 mg /L SS	no	Acetate	Formic acid; 500-1000 mg/L (renewed)	unknown (up to 30 days)	89		Chou et al., 1979 BPD ID A7.1.2.1.2_01 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_1_b*

[1] Test according to OECD criteria

The BE eCA assigns a reliability of 4 to this test, since the test report contains insufficient details. Therefore the results of this test can only be considered as indicative.

The test did not follow an official guideline and contains insufficient details in order to assess whether it could be compared to one.

The applicant was asked if they could provide further information, but they could not and accepted the reliability of 4 assigned by the BE eCA.

Since the anaerobic biodegradation is not a strict data-requirement, further testing was not deemed necessary.

Value used in Risk Assessment	
Value/conclusion	Indication that anaerobic degradation may be possible
Justification for the value/conclusion	Test report contains insufficient details, does not follow a known guideline and was not performed according to GLP. Since this endpoint is not strictly a data requirement, no new testing is required at this point.

4.1.1.3.1.3 STP simulation test

Data waiving	
Information requirement	A justification of non-submission of data was submitted by the applicant (*Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_1_a)*, based on the fact that such a test is not a core data requirement and that other submitted studies showed formic acid to be ready biodegradable.
Justification	Justification is accepted.

4.1.1.3.2 Biodegradation in freshwater

4.1.1.3.2.1 Aerobic aquatic degradation

Data waiving	
Information requirement	A justification of non-submission of data was submitted by the applicant (*Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_2_a)*, based on the fact that such a test is not a core data requirement and that other submitted studies showed formic acid to be ready biodegradable.
Justification	Justification is accepted.

4.1.1.3.2.2 Water/sediment degradation test

Data waiving	
Information requirement	A justification of non-submission of data was submitted by the applicant (*Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_2_b)*, based on the fact that such a test is not a core data requirement and that other submitted studies showed formic acid to be ready biodegradable.
Justification	Justification is accepted.

4.1.1.3.3 Biodegradation in seawater

4.1.1.3.3.1 Seawater degradation study

One test to assess the biodegradability in seawater was submitted ([redacted] 1994, BPD ID A7.1.1.2.3_01) (*Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_3)*. The test was supposedly performed according to OECD guideline 306 and according to the GLP principles, using potassium formate liquor (i.e. potassium formate 75% in water) as test material.

In a closed bottle test, potassium formate liquor was tested at a concentration of 15 mg/L. Sodium acetate was used as a reference substance. The inoculum was a non-specific mixture of marine microbiota, collected in the field.

The percentage biodegradation was determined by comparing the oxygen depletion value (BOD) with the corresponding Theoretical Oxygen Demand (ThOD), which was calculated as 143 mg O_2/g potassium formate liquor. Samples for oxygen analysis were taken at day 0, 7, 14, 21 and 28.

The test concludes that after 28 days 71.3 % of the initial test substance concentration was eliminated. The 60 % mark was reached between days 0 and 7, with 61.5 % degradation at day 7.

BE eCA is however of the opinion that the test report for this test is severely lacking in details. It is unclear what the exact empirical formula of the test material is to arrive at the calculated ThOD of 143 mg/g. Nor are details on for example the number of repetitions, whether or not a blank control was tested, the reason why a larger concentration than the concentration range suggested in the guideline determinable from the original test report. Merely a statement that the test was performed according to OECD 306 seems insufficiently reliable.

Therefore, BE eCA assigns a reliability 4 to this test, which render its result unusable for further risk assessment purposes.

The applicant was asked if they had any more information on this particular study, but the answer thus far was negative and the applicant accepted the reliability assessment made by BE eCA.

Since this endpoint is not a core data requirement, new testing is not required at this time.

Value used in Risk Assessment	
Value/conclusion	No value from this test is retained for the risk assessment
Justification for the value/conclusion	The test report was deemed too summarily to retain the results as a key value. However, at this point, no further testing is required on the basis that such a data point is not a core data.

4.1.1.3.4 Higher tier degradation studies in water or sediment

No available data.

4.1.1.3.5 Biodegradation during manure storage

A study on the characteristics of volatile fatty acids in stored dairy manure before and after anaerobic digestion (Page et al., 2014, Doc IIIA FA_BPR_Ann_II_10_1_3_4) and a study on changes in swine manure during anaerobic digestion (Iannotti et al., 1979, Doc IIIA FA_BPR_Ann_II_10_1_3_4_Iannotti_1979) are submitted for this data point.

In Page et al. (2014), raw dairy manure and raw dairy manure amended with pre-consumer waste were incubated in reactors without aeration and stirring of the manure; thus simulating storage conditions of manure. Formic acid was not added to the manure samples, but the course of the naturally occurring formic acid was monitored over a period of 100 days at 20 °C. The two types of manure were incubated in duplicate reactors. The reactors were sampled every seven days from the top and the bottom layer. The top layer represents aerobic conditions, while the bottom layer is characterized by anaerobic conditions.

In both manure types the degradation of formic acid could be observed. However, there were also phases were the concentration of formic acid was increasing. These fluctuations can be explained by the degradation of other volatile fatty acids and/or other organic substances, which can lead to the formation of formic acid. Over the last 3 to 5 weeks either formic acid was no longer formed or the degradation activity was equal to the formation rate of formic acid as the observed concentrations were at 0 mg/L.

The study shows that formic acid is degraded under aerobic and anaerobic conditions in manure samples (raw dairy manure and amended dairy manure).Based on the graphical representation of the concentration trends, a DT_{50} for the aerobic top layer of ≤ 7 days and ≤ 10.5 days for the anaerobic bottom layer can be derived for wet manure storage.

Iannotti et al. (1979) investigated changes in swine manure during anaerobic digestion. Swine manure was digested in pilot-size digesters (0.42 m^3) which had been in operation for one year. The loading rate was 3.78 g volatile solids (VS)/L/d. The influent waste was from finishing hogs. The digester temperature was 35 °C. The detention time was 15 days.

The digester was fed swine manure with a total of 4.7±0.6 g/d (= influent). Based on an influent volume of 28.2 L, this results in a concentration of 167 mg/L of formic acid in the swine manure. In the effluent no formic acid was detected which is a removal of 100%. Based on the complete removal of formic acid from the influent and its retention time in the digester, a conservative DT50 of 7.5 days can be deduced.

Summary table – Biodegradation during manure storage								
			Inoculum			**Degradation**		**Reference**

Method, Guideline, GLP status, Reliability	Test type[1]	Test parameter	Type	Concen-tration	Adap-tation	Additional substrate	Test substance concentr.	Incubation period	Degree [%]	Remarks	
No guideline² (reactors without aeration and stirring) Non-GLP Reliability 2	no harmonised guideline available	Concentration of formic acid	Raw dairy manure: R1 & R2 Dairy manure (90.1 %) mixed with blood (5.9%) and trap (4.0%): R3 & R4	N/A	N/A	N/A	Formic acid naturally present in manure samples. R1 & R2: < 850 mg/L R3 & R4: ≤ 27 100 mg/L	98 days (at 20 °C)	100 (measured concentration of 0 mg/L)	N/A	Page et al., 2014 *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_4*
No guideline² (anaerobic pilot-size	no harmonised guideline available	Concentration of formic acid	Swine manure from finishing hogs	N/A	N/A	N/A	Formic acid naturally present in manure samples	22 weeks (at 35 °C)	100	N/A	Iannotti et al., 1979 *Doc IIIA JOINT:* *FA_BPR_Ann_II_10_1_3_4_Iannotti_1979*

digester) Non-GLP Reliability 2							: 167 mg/L				

[1] Test according to OECD criteria

[2] No harmonised guideline available

Page et al. (2014) is selected as key study. Justification on the use of this study as key study is provided in *Doc IIIA JOINT: FA_BPR_Ann_II_10_1_3_4.*

At ENV WG-I-2022, it was agreed that the DT50 of 10.5 days (at 20°C), derived based on cattle manure can be used also for all other animal categories. This DT50 value is derived based on cattle manure (Page et al., 2014) and confirmed for pigs manure (Iannotti et al., 1979). No data is available for poultry manure. However, poultry manure has another consistency compared to cattle and pigs manure and is much dryer. Degradation in such kind of manure tend to be aerobic, in which case the DT50 values are expected to be covered by the DT50 value of 10.5 days (20 °C). Indeed, according to OECD ESD No. 14 (OECD, 2006), DT50 values for degradation in soil can be used as a surrogate for degradation in manure when no other data are available. In the case of poultry manure (aerobic degradation) this would yield a DT50 value of 1 day (see section 4.1.1.3.6 of the CAR).

The swift anaerobic degradation of formic acid in manure is not surprising. Formic acid is the simplest carboxylic acid and is a natural compound occurring at significant concentrations in all environmental compartments (please refer to section 4.3 of the CAR). Several lines of evidence are available to confirm anaerobic degradation. Section 4.1.1.3.1.2 of the CAR (STP anaerobic degradation) contains the study of Chou et al. (1979). Although the publication was rated a reliability of 4, the data indicate that anaerobic degradation of formic acid occurs. In the publication of Page et al. (2014) is stated that methanogens can directly use formic acid. The publication of Héllsten et al. (2005b, see next section), studying aerobic and anaerobic degradation of formate in soil at low temperatures, concludes that *[…] there is a potential for swift aerobic and anaerobic biodegradation of formate in the subsurface of the study site, which is hardly surprising as formate can be utilized by a wide variety of aerobic, facultative, and anaerobic microorganisms*.

Value used in Risk Assessment	
Value/conclusion	DT_{50} for biodegradation in manure: ≤ 10.5 days (20 °C) DT_{50} for biodegradation in manure: ≤ 19.9 days (12 °C)
Justification for the value/conclusion	Value derived from the graphical representation of concentration trends of formic acid in manure at anaerobic conditions (bottom of reactor). Value agreed at ENV WG-I-2022.

4.1.1.3.6 Biotic degradation in soil

According to the BPR, all tests on fate and behaviour are not part of the core data set. Requirements for such tests only come into play when there is exposure to soil.

For this dossier, the applicant waived all data referred to by BPR Annex II point 10.2. Since no direct exposure to soil is expected from the intended uses of formic acid in PTs 2, 3, 4, 5 and 6, and since formic acid is readily biodegradable, this waiving is accepted.

The applicant submitted nevertheless 3 open literature studies providing indication of rapid biodegradation of formic acid in soil.

- Lissner et al., 2014: Doc IIIA FA_BPR_Ann_II_10_2_a ;
- Hellstén et al., 2005a: Doc IIIA FA_BPR_Ann_II_10_2_b ;
- Hellstén et al., 2005b: Doc IIIA FA_BPR_Ann_II_10_2_c ;
- Glanville et al., 2012 : Doc IIIA FA_BPR_Ann_II_10_2_d

Lissner et al. (2014) is a lysimeter experiment following the degradation of potassium formate executed in Norway. Formate is added to all of the lysimeters together with propylene glycol (PG) as part of a deicing solution in a ratio of 70 g/m² formate and 350 g/m² PG. Due to the presence of PG and the uncertainty to what extend this interferes with the natural fate and behaviour of formate in soil, this study is assigned a reliability of 3.

In Hellstén et al. (2005a), potassium formate was applied to the soil surface of a lysimeter in Finland. Application took place five times (0,68 kg/m² per application) during winter on the snow cover of a lysimeter. The lysimeters were composed of well-graded sand and gravel. The mean formate concentration entering the soil was calculated at 2730 mg/L. The percolated water was collected at 12 dates and analyzed for formate, CO_2, TOC, COD, and other parameters.

The objective of this study was to examine the migration and degradation of potassium formate in the unsaturated zone of a lysimeter in a sandy aquifer in real winter and spring conditions.

The study concluded that formate was effectively removed in a sandy lysimeter after a cold winter period. The disappearance of formate was accompanied by the formation of carbon dioxide and bicarbonate in the percolating water indicating biodegradation of formate.

Hellstén et al. (2005b) investigated the degradability of sodium and potassium formate in soil under aerobic and anaerobic conditions in a set of microcosm experiments using radiolabeled sodium formate. Formate was shown to degrade under aerobic and anaerobic conditions from soil samples (top and subsurface). Given the differences in organic matter content, soil samples at different depths could be considered as different soil types. Based on the graphical representation of the degradation data, a degradation half-life (DT_{50}) of < 1 day could be derived for all soil samples at temperatures of + 1 and +6 °C.

Glanville et al. (2012) investigated the overall relationship between laboratory-field and inter-annual field studies for mineralization of low molecular weight substrates in soil solution. Soil samples were spiked with 14C-labelled compounds, formic acid being one of the substances. The soil samples were taken from freely draining agricultural grassland from a hyper-oceanic climatic region in North Wales (UK) at a soil depth of 10 cm. Sampling was done in 2009 and 2010. The half-life of formic acid was determined under lab and field conditions to be ≤ 1 day. This value was read from the graphs of the paper.

Summary table – Aerobic biodegradation in soil – laboratory study											
Method, Guideline, GLP status, Reliability	**Test type[1]**	**Test parameter**	**Test system**				**Test substance concentr.**	**Incubation period**	**Degradation DT50**	**Remarks**	**Reference**
			Soil origin	Soil type	pH	OM %					
No guideline (microcosm experiments using radiolabeled sodium formate), Non-GLP, Reliability 2	Aerobic mineralisation in soil (no guideline, public literature data)	$^{14}CO_2$ (% of added ^{14}C-formate)	Kauriansalmi study site, Finland. Soil samples taken at various depths.	sandy and gravelly deposits with occasional thin layers of silt	not specified	0.43 (70-80 cm); 5.4 (5-15 cm); 0.70 (50-60 cm); 0.3	Concentration: 100 000 DPM of 14C-formate (Radio-labelled sodium formate (^{14}C): 56 mCi/mmol; Source: Sigma)	up to 45 days	< 1 day for all soil samples at +1 and +6 °C	tested at low temperatures and for various soil depths; two replicates and one blank per sample	Hellstén et al., 2005b *Doc IIIA JOINT : FA_BPR_Ann_II_10_2_c*

						3 (100-110 cm)					
No guideline (microcosm experiments using radiolabeled formic acid), Non-GLP, Reliability 2	Aerobic mineralisation in soil (no guideline, public literature data)	$^{14}CO_2$	Abergwyngregyn, Gwynedd, North Wales (53°14'N, 4°1'W)	sandy clay loam (rhizosphere soil)	4.77-5.35	7.37-7.97	Formic acid, ^{14}C-labelled (Source: Sigma-Aldrich Company Ltd., UK): < 10 nM formic acid	168 h	< 1 day (20 °C)	Experiments were performed in triplicate and in two subsequent years (2009 and 2010).	Glanville et al., 2021 *Doc IIIA JOINT :* *FA_BPR_Ann_II_10_2_d*
[1] Test according to OECD criteria											

Summary table – Field dissipation studies										
Method, Guideline, GLP status, Reliability	**Site**	**Application rate**	**Surface**	**Soil type**	**Soil tex-ture**	**Test duration**	**Degra-dation DT_{50}**	**Degra-dation DT_{90}**	**Remarks**	**Reference**
No guideline (lysimeter experiment with potassium formate),	Oslo airport, Norway	70 g/m² potassium formate	not specified	Soil 1	silty and sandy deposits with low clay	2 years	not determined	not determined	Potassium formate was applied as part of a deicing solution with	Lissner et al., 2014 *Doc IIIA JOINT :* *FA_BPR_Ann_II_10_2_a*

Non-GLP, Reliability 3					content				polypropylene glycol.	
No guideline (lysimeter experiment with potassium formate), Non-GLP, Reliability 2	Southwestern Finland (Oripää lysimeter station, 60°55′ N, 22°44′ E)	Total potassium formate loading: 3.4 kg/m² Substance applied by sprinkler irrigation over surface of one of the snow-covered lysimeter in five stages (0.68 kg/m² per application) between 19 Dec. 2001 and 04 March 2002	Surface covered with local vegetation	Soil 2	well-graded sand and gravel	7 months	not determined	not determined	Experiment conducted in cold climate conditions.	Hellstén et al., 2005a *Doc IIIA Joint : FA_BPR_Ann_II_10_2_b*
No guideline (polypropylene cylinders (6.1 cm² soil surface) placed 2 cm deep in soil),	Abergwyngregyn, Gwynedd, North Wales (53°14′N, 4°1′W)	450 µL soil solution spiked with 50 µL ^{14}C-formic acid (< 10 nM	The vegetation at the site consists of perennia	Soil 3 (freely draining agricultural grassland from a	sandy clay loam	168 h	< 1 day (13.8-17 °C)	not determined	Experiments were performed in triplicate and in two subsequent	Glanville et al., 2021 *Doc IIIA JOINT : FA_BPR_Ann_II_10_2_d*

Non-GLP, Reliability 2		formic acid)	l rye grass (Lolium perenne L.) and white clover (Trifolium repens L.) and is subject to intensive sheep grazing (>5 ewe ha^{-1}) and receives regular fertilizer addition (120 kg N ha^{-1} y^{-1})	hyper-oceanic climatic region)					years (2009 and 2010).	

Based on the overall evidence available in public literature, it can be concluded that formic acid is expected to rapidly biodegrade in soil, even in sub-optimal conditions (low temperatures), and a DT50 for biodegradation in soil of < 1 day can be derived from the available data. Furthermore, it should be noted that in both Hellstén et al. (2005b) and Glanville et al. (2012), mineralisation was measured, meaning that the DT50 for biodegradation might be even more rapid.

Formic acid is the simplest carboxylic acid and is a natural compound occurring at significant concentrations in all environmental compartments (please refer to section 4.3 of the CAR), and can be utilized by a wide variety of aerobic, facultative, and anaerobic microorganisms (Hellstén et al. (2005b)).

None of the studies fulfil all conditions of the Guidance on the BPR: Volume IV Part A (version 1.2 May 2018), section 1.2 paragraph 12 specifying the conditions for public literature data to be considered as key studies. However, given the fact that:

- Hellstén et al. (2005b) and Glanville et al. (2012) use radiolabeled test material from a well-defined source for which a high purity can be assumed;
- the reference specification of formic acid doesn't contain relevant impurities;
- Hellstén et al. (2005b) investigated biodegradation in different soil layers with different organic matter contents, which could be considered as different soil types;

it was agreed at ENV WG-I-2022 to consider Hellstén et al. (2005b) and Glanville et al. (2012) as key studies and to use a DT50 value for soil of 1 day at 12 °C for the exposure assessment.

Value used in Risk Assessment	
Value/conclusion	DT50 value for soil of 1 day at 12 °C
Justification for the value/conclusion	Value agreed at ENV WG-I-2022.

4.1.2 Distribution

4.1.2.1 *ADSORPTION ONTO/DESORPTION FROM SOILS*

The adsorption coefficient (Koc) on soil and sewage sludge of formic acid was investigated in a HPLC screening test following OECD 121. The method of analysis was a modular HPLC system with UV/VIS detector under isocratic conditions ([redacted] 2002, BPD ID A7.1.1.1.1_01) *(Doc IIIA JOINT: FA_BPR_Ann_II_10_1_2)*.

Ten reference compounds were used for the calibration graph. Small amounts were dissolved in 30 vol% acetonitrile (ultrasonic treatment) and the flasks were made up to volume with water. The dead time (t_0) of the HPLC system was measured with formamide. Measurements of the retention times of the reference substances and of formic acid were performed in duplicate at 23 °C.

As formic acid is an ionisable substance with a pKa of 3.70 (Dolich 2007, BPD ID A3_01), two tests were performed with both non-ionised and ionised forms in appropriate buffer solutions (pH 4 and 10). The test item was dissolved in water/acetonitrile (9:1, v/v).

In the test run with the non-ionised formic acid (acidic conditions) the mean retention time (2.1 min) was shorter than the lower limit of the reference interval (acetanilide, 3.5 min) and shorter than the dead time established with formamide (2.2 min). Normally, the OECD test guideline indicates that if the log Koc of the test substance falls outside the calibration interval, the test should be repeated using more appropriate reference substances. However, in this case, the retention time of formic acid is also below the dead time, determined by using a substance (formamide) that does not react with the column, and thus does not have a tendency to adsorb. Knowing this, it can be concluded that formic acid also does not have a tendency to adsorb. For risk assessment purposes, the log Koc could be set to be smaller than that of the lower limit of the reference interval, being 1.25 for acetanilide.

In the test run with the ionised molecule under basic conditions (formate ion) there were no results on retention time at the end of the test, meaning that its retention time is longer than the upper limit of the reference interval (methiocarb, 9.1 min). In this case, the log Koc of formate is higher than 3.10. Sorption of the ionised form of formic acid is thus stronger than that of the non-ionised form, and the log Koc of formic acid of therefore depends on the pH.

It should be noted that the HPLC screening method is not suitable for the estimation of the Koc of formic acid. OECD Test Guideline No. 121 "Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)" states that the method may not work for moderate organic acids and that only log Koc values ranging from 1.5 to 5.0 can be determined. As both forms of formic acid, the protonated as well as the unprotonated, are not in the time range of the calibrated substances, no further conclusions can be derived.

In addition to this HPLC-method provided by the applicant, BE eCA used the screening programme EPI Suite 4.1 to estimate the Koc based on the structure of formic acid. KOCWIN v2.00, a subprogram included into EPI Suite to estimate the Koc, uses two different models to make an estimation. On the one hand, the Sabljic molecular connectivity method (MCI), estimates a Koc for formic acid of 1 L/kg (log Koc = 0). On the other hand, the program calculates the Koc based on the log Kow. When using the programs default log Kow of -0.54 (experimental database), a Koc of 0.7195 L/kg is calculated (log Koc = -0.143). The applicant also submitted a study in which a log Kow is experimentally derived ([redacted] 2002, BPD ID A7.1.1.1.1_01). When using this log Kow of -2.1 (pH 7), the program calculated a Koc of 0.09866 L/kg (log Koc = -1.00586).

However, given the pKa 3.70 for formic acid, the environmental relevant species is not formic acid but the formate ion. Franco et al. (2009) developed a method to estimate the Koc of monovalent organic acids and bases. The regression considers pH-dependent speciation and species-specific partition coefficients, calculated from the dissociation constant (pKa) and the octanol–water partition coefficient of the neutral molecule (log P_n). The pH-dependent estimation of Koc is provided by the following equation:

$$K_{OC} = \frac{10^{0.54 \cdot \log P_n + 0.11}}{1 + 10^{(pH_{soil} - 0.6 - pK_a)}} + \frac{10^{0.11 \cdot \log P_{ion} + 1.54}}{1 + 10^{(pK_a - pH_{soil} + 0.6)}}$$

where pK_a is the dissociation constant; log P_n the octanol-water partition coefficient of the neutral molecule; and pH_{soil} the pH of the soil.

(note: the equation contains a typo error in the second term: log P_{ion} should be log P_n)

No pH_{soil} is defined in Table 3 (Definition of the standard environmental characteristics) of the Guidance on BPR Volume IV Parts B+C (v2.0 October 2017). Therefore a neutral pH of 7 is assumed.

Provided a pK_a of 3.7, a log P_n of -0.54 (derived from the EPI Suite experimental database, see above)[7] and a pH_{soil} of 7, a Koc of 30 (log Koc of 1.48) is yielded.

Conclusion:
The HPLC-method to estimate the Koc for formic acid resulted in an indication that the log Koc for formic acid will be below 1.25 and may vary with pH. The results obtained with KOCWIN, a programme to estimate the Koc, was also in line with the results obtained from the HPLC-method.
A theoretical log Koc of 0 (Koc = 1 L/kg) was estimated for formic acid.

[7] A note regarding the log Kow used in the model of Franco et al.: log Pn in the model is the octanol–water partition coefficient of the neutral molecule, which is estimated to be -0.54 based on the EPI Suite experimental database. The experimentally derived log Kow of -2.1 is determined at a pH of 7, and can therefore not be used in the model because, given a pKa of 3.7, at that pH the predominant species is the ionized molecule (formate).

However, for risk assessment purposes, the environmental relevant species is not formic acid but formate. The method of Franco et al. (2009) was used to estimate a pH-dependent Koc and yielded a slightly higher log Koc of 1.48 to be used for risk assessment purposes assuming a soil with a neutral pH of 7.

Value used in Risk Assessment	
Value/conclusion	log Koc = 1.48 (for a soil with a neutral pH of 7)
Justification for the value/conclusion	Based on the method of Franco et al. (2009) and in line with the results obtained through the HPLC-method and calculations through EPI Suite, this theoretical value is deemed acceptable and no further tests in soil are required at this point.

4.1.2.2 *HIGHER TIER SOIL ADSORPTION STUDIES*

No available data.

4.1.3 Bioaccumulation

4.1.3.1 *MEASURED AQUATIC BIOCONCENTRATION*

Data waiving	
Information requirement	No experimental value is available. The applicant did not submit a justification for non-submission, however the BPR Annex II states that experimental determination may not be necessary if it can be demonstrated on the basis of physico-chemical properties (e.g. log Kow < 3) or other evidence that the substance has a low potential for bioconcentration. This statement is repeated in the Guidance on BPR: Volume IV. Part A, Chapter II: Requirement for Active Substances, §9.1. This exemption of submission of experimental data is the case for formic acid, since the experimental log Kow is well below the cut-off value of 3 (log Kow = -2.10, pH7).
Justification	The applicant did not submit a justification, but based on the guidance/legislation quoted above, no further justification from the applicant is required.

4.1.3.2 *ESTIMATED AQUATIC BIOCONCENTRATION*

To estimate the accumulation of formic acid in aquatic organisms, the applicant submitted an estimation using BCFWIN v.2.17 ([redacted] 2007, BPD ID A7.4.2_01), which is an estimation program included in EPA's EPISUITE. Using this model, the bioconcentration of formic acid in aquatic organisms is estimated based on the experimental log Kow of -2.1 (derived for pH 7 or mean for measured log Kow at pH 5, 7 and 9) ([redacted] 2002, BPD ID A7.1.1.1.1_01). Since the log Kow is below 1, the program assigns a default log BCF of 0.5 (BCF = 3.162 L/kg_{wwt}) and does not calculate a specific BCF for formic acid. However, this value indicates that formic acid is not expected to bioaccumulate in aquatic organisms, which is in accordance with the hydrophilic nature of formic acid, as well as with the log Kow being smaller than 3.

Additionally, BE eCA also calculated the BCF from the log Kow, according to the linear relationship developed by Veith et al. for substances with a log Kow between 2 and 6; and which is included in the Guidance Volume IV part B as equation 74:

$$logBCF_{fish} = 0.85 \times \log Kow - 0.70$$

With this equation a log BCF of -2.48 is calculated (BCF = 0.00327 L/kg_{wwt}).

Summary table – Estimated aquatic bioconcentration					
Basis for estimation	**Log Kow (measured)**	**Estimated BCF for fish (freshwater) [L/kg$_{wwt}$]**	**Estimated BCF for fish eating bird/predator**	**Remarks**	**Reference**
BCFWIN v2.17 (reproduced in BCFBAF v3.01)	-2.1	3.162	/	since log Kow is below 1, the program reverts to a default log BCF of 0.5 (BCF = 3.162)	[redacted] 2007 BPD ID A7.4.2_01 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_4_1*
BPR guidance Volume IV, Part B, eq.74	-2.1	0.00327	/	/	/

Value used in Risk Assessment	
Value/conclusion	The different estimated methods concur that formic acid will have a low potential to bioaccumulate, which is in line with the hydrophilic nature of formic acid and its log Kow being below 3.
Justification for the value/conclusion	/

4.1.3.3 *MEASURED TERRESTRIAL BIOCONCENTRATION*

Data waiving	
Information requirement	No experimental value is available and the applicant submitted a justification for non-submission (*Doc IIIA JOINT: FA_BPR_Ann_II_9_6*), stating the low log Kow (-2.1) as indication of formic acid's low potential to bioaccumulate.
Justification	Justification is acceptable and no experimental test is required.

4.1.3.4 *ESTIMATED TERRESTRIAL BIOCONCENTRATION*

The applicant did not submit an estimation for the terrestrial bioconcentration. BE eCA made its own calculations based on the available guidance.

According to the BPR Guidance Volume IV, Part B; bioconcentration can be described as a hydrophobic partitioning between the pore water and the phases inside the organism. It can be modelled according to the equation described by Jager (1998):

$$BCF_{earthworm} = \frac{(0.84 + 0.012K_{ow})}{RHO_{earthworm}}$$

The log K_{ow} for formic acid was experimentally determined as -2.1, giving a K_{ow} of 0.0079 L/kg. $RHO_{earthworm}$ is set by default on a value of 1 kg_{wwt}/L.
This gives a $BCF_{earthworm}$ of 0.84 L/kg_{wwt}, which indeed indicates a low potential of formic acid for bioaccumulation.

Value used in Risk Assessment	
Value/conclusion	Using the equation proposed in the BPR guidance, a $BCF_{earthworm}$ of 0.84 L/kg_{wwt} is determined
Justification for the value/conclusion	/

4.1.4 Monitoring data

No available data.

4.2 EFFECTS ON ENVIRONMENTAL ORGANISMS

4.2.1 Atmosphere

The vapour pressure of 42.71 hPa (20 °C; [redacted] BPD ID A3_01) and the Henry's Law Constant of 0.16 Pa.m³/mol (20 °C; ECT Oekotoxicologie GmbH; BPD ID A3_11) indicate low to moderate potential for volatilization and evaporation from water and wet surfaces. The potential of formic acid to be degraded by photo-oxidation in air is moderate with an estimated half-life of 855.7 hours (cfr. §4.1.1.1.3. above).

Besides the anthropogenic sources of emission, formic acid and formate are naturally occurring molecules with normal ("background") concentrations in the range of < 0.3 – 35 µg/m³. Concentration levels are dependent upon location and season (Doc IIIA JOINT: FA_BPR_Ann_II_10_3_2).

No effects on the ozone layer or relevant contribution to global warming and acidification are expected.

4.2.2 Sewage treatment plant (STP)

Two tests on the inhibitory effect of formic acid on microbial activity were submitted.

- The inhibition of oxygen consumption in activated sludge due to formic acid was evaluated in a test conducted according to ISO/DIS 8192 Part B, which is similar to OECD 209 ([redacted] 1988c, BPD ID A7.4.1.4_01).

  The highest concentration tested was 988 mg/L and the test concludes that the EC_{20} is greater than this concentration.

  However, BE eCA is of the opinion that this test cannot be used for the further risk assessment, since reliability cannot be assigned (value of 4) due to a severe lack in details in the original test report.

- A second study on the inhibitory effect of formic acid on the respiration rate of aerobic activated sludge, taken from a sewage treatment plant treating predominantly domestic sewage, was submitted by the applicant after the previous study was deemed lacking. The test ([redacted] 2016, BPR ID A9.1.5_01) was performed over a contact period of 3 hours in a static test system, according to OECD 209 and following GLP.

  Three replicates of each nominal test-concentration of 5, 15.8, 50, 158 and 500 mg/L were tested in parallel with six control replicates and four different concentrations of the reference item 3,5-dichlorophenol. Additionally, the same test-concentrations were repeated with the addition of N-allylthiourea to distinguish between total, heterotrophic and nitrification-related respiration.

  The results of the statistical analysis of the respiration data collected, showed no considerable concentration-related inhibition of total, heterotrophic or nitrification-related respiration by formic acid. No EC_x values could therefore be determined at concentrations ≤500 mg/L following this test.

- The effects of formic acid on the growth of *Pseudomonas putida* was studied in a test performed according to DIN 38412 part 8 ([redacted] 1991, BPD ID A7.4.1.4_02).

  Formic acid was tested in Penicillin flasks of 10 mL at nominal concentrations of 0, 7.81, 15.63, 31.25, 62.5, 125, 250, 500 and 1000 mg/L. Four parallel repeats per test concentration were run, including an un-inoculated sample. After an incubation time of 17 hours, the extinction was measured at 436 nm. No analytical monitoring to confirm the nominal test concentrations was performed. The pH was measured in the un-inoculated samples at test start and end, and in the inoculated samples at test end.

  The lowest concentration revealing an inhibition is 31.25 mg/L, with an inhibition of 1.86 %. An inhibition of over 99% compared to the control is observed in the test concentrations of 62.5 mg/L and up. This inhibition can be partly due to the acidic pH, but is not confirmed with a test run at neutralised concentrations.

  Statistical analysis calculates an EC_{10} of 33.9 mg/L, an EC_{50} of 46.7 mg/L and an EC_{90} of 59.5 mg/L.

Summary table – inhibition of microbial activity										
Method, Guideline, GLP status, Reliability	**Test material**	**Species/ Inoculum**	**Endpoint**	**Exposure**		**Results**			**Remarks**	**Reference**
				Design	**Duration**	**EC_{10} [mg/L]**	**EC_{50} [mg/L]**	**EC_{90} [mg/L]**		
ISO/DIS 8192 Part B No GLP Reliability 4	FORMIC ACID	activated sludge	oxygen consumption	respiration inhibition	30 min	EC_{20} = >988	/	/	only single concentration no analytical verification abstract report	[redacted] 1988c BPD ID A7.4.1.4_01 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_5_1_a*
OECD 209 GLP Reliability 1	FORMIC ACID	activated sludge	oxygen consumption	respiration inhibition	3 h	>500	>500	>500	nominal concentrations, adjusted for pH with NaOH	[redacted] 2016 BPR ID 9.1.5_01 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_5_01_final_28Mar2017*

DIN 38412 part 8 no GLP reliability 2	FORMIC ACID	*Pseudomonas putida*	optical cell density at 436 nm	growth inhibition	17 h	33.9	46.7	59.5	no measured concentration No pH adjusted concentrations	[redacted] 1991 BPD ID A7.4.1.4_02 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_5_2*

Value used in Risk Assessment	
Value/conclusion	Formic acid: EC_{10} > 500 mg/L
Justification for the value/conclusion	Based on available results, the short-term test is preferred, in accordance with the retention time in a STP. The EC_{10} value was determined at concentrations >500 mg/L. The 17h test is considered less relevant, since it uses glucose as a substrate.

4.2.3 Aquatic compartment

In aqueous solution and at neutral pH, formic acid and water-soluble formate salts dissociate and are present as the formate anion in solution. The behaviour of chemical dissociation in water has particularly been investigated with potassium diformate (CAS No. 20642-05-1), which served as test compound in several toxicity studies. Based on these physico-chemical properties, it is justified to include kinetic and metabolism studies conducted with water-soluble formate salts in these considerations. In order to provide data for the ecotoxicity of formic acid without effects due to the low pH which is induced by formic acid, study results for ammonium formate and potassium formate were considered. As fish and aquatic invertebrates are sensitive towards ammonium dissolved in water, the results derived from testing with ammonium formate should not be used alone. On the other hand, no effects are expected due to the potassium ion (K^+) contained in potassium formate.

4.2.3.1 *FRESHWATER COMPARTMENT*

4.2.3.1.1 Acute toxicity (freshwater)

4.2.3.1.1.1 Fish

Three acute toxicity tests to fish in freshwater were submitted, one using the test substance formic acid and two other using formate salts, meaning that in water the fish are mainly exposed to the formate anion.

- The acute toxicity of formic acid to the golden orfe (*Leuciscus idus L.*, golden variety) was studied following the German Industrial Standard DIN 38412, Part 15 ([redacted] 1989, BPD ID A7.4.1.1_01).

  The test system was a static system without any analytical monitoring of the test substance concentration. The nominal test concentrations of 0, 10, 21.5, 46.4 and 100 mg/L were tested using 10 fish for each concentration. An additional concentration of 100 mg/L was tested where the pH was neutralised using NaOH, in order to assess the effect of the low pH on the toxicity. The test water was reconstituted water according to the aforementioned guideline.

  The fish were checked for symptoms and mortality after 1, 4, 24, 48, 72 and 96 hours. At these times also other parameters, such as temperature, dissolved oxygen and pH were analysed.

  No mortality was reported for the control group and at test concentrations ranging from 10 and 46.4 mg/L and in the pH adjusted test concentration of 100 mg/L. In the non-pH adjusted 100 mg/L test concentration, 100 % mortality was reached after 1 hour.

  When analysing the measured pH throughout the study, it is noted that the pH in the 100 mg/L test concentration was 3.3, which was probably a factor for the high mortality, since no mortality was reported at the same test concentration with neutralised pH.

  However, it should be mentioned that in the 46.4 mg/L test concentration, pH was initially also quite low (4.3), but quickly rose to a neutral 7.2 at the end of the test. This seems to be an indication that the test substance concentration was not maintained throughout the test and since no analytical monitoring was performed, this can be seen as a major deviation. Therefore BE eCA is of the opinion that the results from this test are not reliable and cannot be used in the further risk assessment.

The applicant was asked to comment on BE's assessment to attribute a reliability of 3 to this test. In their reply they make reference to the acute toxicity test discussed in the next bullet point below. In this test, also performed under static conditions, analytical monitoring showed that the test item concentration remained within the allowed variation. According to the applicant, if it is the case for that static test, it will also be the case for this static test.

BE understands that this perhaps may be some sort of indication, also when considering that the substance is hydrolytically stable (cfr. BPD ID A7.1.1.1.1_01) and the ready biodegradation tests (cfr. BPD ID A7.1.1.2.1_01 and BPD ID A7.1.1.2.1_02) show little degradation in the first couple of days. However, this does not answer the question of the rising pH and without conclusive proof of stability of the test substance, uncertainty remains. Therefore, BE is not inclined to change their assessment of the reliability. Therefore this test remains at reliability 3.

- In a first test, using ammonium formate as test material, the acute toxicity effects on zebrafish (*Danio rerio*) were studied according to OECD 203 ([redacted] 2005, BPD ID A7.4.1.1_02). In a 96 h static test design, 10 fish each were exposed to nominal test concentrations of 0, 45, 90, 180, 360 and 720 mg/L. Samples for chemical analysis via ion chromatography were taken at test start and test end from all test vessels. Mean recovery values were higher than 80 % of the nominal concentrations, therefore the effect concentrations are based on these nominal concentrations.

  Mortality, behavioural abnormalities, temperature, pH and dissolved oxygen were checked for each concentration after 24, 48, 72 and 96 hours. The test conditions - temperature, pH and dissolved oxygen – remained within acceptable limits throughout the test. No mortality was reported in the control group or in the test concentrations up to 90 mg/L. After 96h the lowest test concentration where all fish had died was 180 mg/L. The 96h LC_{50} was determined using the geometric mean of the LC_0 and LC_{100} resulting in a value of 127.28 mg/L.

- A second test using a formate salt, this time potassium formate, was also conducted according to OECD 203 ([redacted] 1992e, BPD ID A7.4.1.1_03) using rainbow trout (*Oncorhynchus mykiss*). The test design was a semi-static one, with daily renewal of the test medium to ensure that test concentrations were maintained. However, no analytical monitoring was performed to corroborate this.

  Ten fish per nominal test concentration of 0, 1000, 1800, 3200, 5600 and 10000 mg/L was used. Mortality was checked after 3, 6, 24, 48, 72 and 96 hours. Temperature, pH and dissolved oxygen were measured at test start and end, and remained within the acceptable limits. No mortality was reported for the control group or in the test concentrations up to 1800 mg/L. After 96h, the lowest test concentration were all fish had died was 5600 mg/L. The 96h LC_{50} was determined using the method of Thompson & Weil (1952, moving-average interpolation) and resulted in a value of 3500 mg/L.

4.2.3.1.1.2 Invertebrates (daphnia magna)

Three acute toxicity tests on the aquatic invertebrate *Daphnia magna* were submitted, one using formic acid as test substance, while the other two used formate salts, meaning that in water the test animals are mainly exposed to the formate anion.

- The acute toxicity of formic acid to *Daphnia magna* was studied in a test performed according to Directive 79/831/EEC, C.2 ([redacted] 1988, BPD ID A7.4.1.2_01).

  The test species were exposed during 48-hours in a static test system without any analytical monitoring of the test concentration. Nominal test concentrations of 0, 0.781, 1.56, 3.12, 6.25, 12.5, 25, 50 and 100 mg/L were tested using 20 animals per concentration. Purified water was used as test medium, in which sulphuric acid was used to reduce the buffering capacity of the carbonic acid system and deionized water was added to reduce the total hardness.

  At the beginning and after 3, 6, 24 and 48 hours, the swimming inability of the Daphnia was checked. Oxygen and pH measurements were performed at test initiation and after 48 hours.

  The immobility in the control group was within the validity criterion (< 10 % immobility). In the two highest concentrations, 50 and 100 mg/L, immobility already reached 100% after 6 and 3 hours respectively. At these concentrations, pH was below 5 at the start of the experiment. No pH adjusted concentrations were tested to distinguish between the effect due to low pH and toxicity. In the test concentration of 25 mg/L, 10 % immobility was reached after 48 hours. The 48h EC_{50} was calculated using the moving average method, resulting in a value of 32.19 mg/L. However, it must be kept in mind that it is unclear if this concentration causes mortality due to toxicity of the test substance or due to a decrease in the pH of the test medium.

- The acute toxicity of ammonium formate to aquatic invertebrates (*Daphnia magna*) was studied in a GLP-study according to OECD 202 ([redacted] 2005, BPD ID A7.4.1.2_02).

  In this 48-hour, static test, the test organisms were exposed to nominal concentrations of 0, 45, 90, 180, 360 and 720 mg/L. The *Daphnia* were checked for immobility at test start and after 24 and 48 hours. Oxygen content, pH and test item concentrations were determined at the start and end of the test. These parameters were within the acceptable ranges, leading to the use of nominal values for determining the toxicity values.

  After 48 hours, no immobilisation was observed in the control and lowest test concentrations up to 90 mg/L, while 100 % immobility was reached in the highest tested concentration of 720 mg/L. The 48h EC_{50} was determined using the ToxRat software (v2.09) and yielded a value of 365 mg/L.

- A second study, testing the acute toxicity of the formate ion to *Daphnia magna* was done using potassium formate as a test substance. The test was conducted according to OECD 202, conform GLP ([redacted] 1992, BPD ID A7.4.1.2_03).

  In this 48-hour static test, *Daphnia* were exposed to nominal concentrations of 0, 10, 18, 32, 56, 100, 180, 320, 560 and 1000 mg/L. Oxygen content and pH were measured at test initiation and after 48 hours, and remained within the acceptable intervals. No analytical monitoring of the test concentration was done, on request by the test sponsor. The applicant was asked why this was requested, but no explanation could be given. The test sponsor probably assumed the test concentration could be maintained for the exposure duration of 48 hours.

After 0, 24 and 48 hours, the test species were checked for mobility. At test end, immobilisation in the control group was within the acceptable range. The highest test concentration where no immobilisation was observed after 48 hours was 56 mg/L. No 100 % immobilisation was reached in any of the tested concentrations. The 48h EC_{50} was determined using the moving average method, resulting in a value of 540 mg/L

4.2.3.1.1.3 Algae

4.2.3.1.1.3.1 Green algae

Three growth inhibition studies on green algae were submitted, one using formic acid as test substance, while the others used a formate salt, meaning that in water the test animals are mainly exposed to the formate anion.

- The inhibitory effect of formic acid on cell multiplication of the unicellular green algae *Desmodesmus subspicatus* was studied in a test performed according to German Industrial Standard DIN 38412, part 9 ([redacted] 1988, BPD ID A7.4.1.3_01).

  Algal exposition was performed in test tubes of 10 mL with flat bottom. The initial cell density of *Desmodesmus subspicatus* was 10^4 cells/mL, which is higher than what is recommended according to OECD 201. The algae were exposed to nominal concentrations of 0, 0.781, 1.56, 3.125, 6.25, 12.5, 25 and 50 mg/L. No analytical monitoring of the test concentrations were done, but pH was measured in the uninoculated test concentrations at test start and after 96h and in the inoculated concentrations after 96h. Fluorescence measurements were performed after 0, 24, 48, 72 and 96 hours.

  An inhibitory effect on the algal growth rate of 3 % was seen starting at the test concentration of 12.5 mg/L and 100 % inhibition was reached at the 50 mg/L test concentration, the highest concentration tested. The inhibition observed at the higher test concentrations might also be due to the low pH (4.9 in inoculated sample after 96h) and since no neutralized concentrations were tested it is not possible to distinguish between effect due to the pH or due to toxicity. After statistical analysis of the results through ToxRatPro, it is concluded that the E_rC_{50} is 30.21 mg/L, the E_bC_{50} is 26.92 mg/L, the E_rC_{10} is 24.52 mg/L, the E_bC_{10} is 17.71 mg/L and the NOE_rC is 6.25 mg/L.

- The inhibitory effect of ammonium formate on the growth of the unicellular green algae *Pseudokirchneriella subpacitata* was studied a 72h test performed according to OECD 201 ([redacted] 2005, BPD ID A7.4.1.3_02).

  Algal exposures were performed in 250 mL flasks containing 100 mL test solutions at the nominal test concentrations of 0, 76.8, 192, 480,1200 and 3000 mg/L. The initial cell density was 10^4 cells/mL and cell number determinations were performed after 24, 48 and 72 hours. Test item concentrations and pH were determined at the start and end of the test. These parameters were within the acceptable ranges, leading to the use of nominal values for determining the toxicity values. The test results were statistically analysed using the software ToxRat. NOEC was determined by the Welch t-test.

  An inhibitory effect of algal growth of 3.4 % was already seen in the lowest test concentration of 76.8 mg/L. At the highest concentration (3000 mg/L) growth inhibition reached 39.8 %. Inhibition of biomass integral showed a 12.6 % inhibition at 76.8 mg/L, while at 3000 mg/L an inhibition of biomass of 85.4 % was reached. Statistical analysis revealed a 72h E_rC_{50} of 1240 mg/L, a 72h NOE_rC of less than 76.8 mg/L and a 72h E_bC_{50} of 320 mg/L.

- A limit test on the inhibitory effect of potassium formate on the growth of the unicellular green algae *Scenedesmus subspicatus*, now known under the name *Desmodesmus subspicatus*, was performed according to OECD 201 ([redacted] BPD ID A7.4.1.3_03).

  Only a single concentration was tested, namely 1000 mg/L, and compared with the untreated control to determine effect. Algal exposure was performed in 250 mL flasks containing 100 mL test solution. The initial cell density was 9.2 x 10^4 cells/mL. Measurements of fluorescence were performed at 0, 24, 48 and 72 hours. The nominal test concentration was not analytically verified, on request by the test sponsor. The applicant was asked for comment, but could not elaborate on the reasoning. The pH was measured at test initiation and end; and remained within the acceptable range.

  The test concentration of 1000 mg/L had an inhibitory effect of 10 % on the algal growth rate (24-48 h), but an increase of 19 % in biomass was reported compared to the control. Since only one test concentration was tested, no EC_{50} can be determined and it can only be stated that it will be higher than the concentration that was tested.

4.2.3.1.1.3.2 Cyanobacteria or diatoms

According to the Guidance on the Biocidal Product Regulation, Volume IV Part A, on information requirements, tests on the effect on growth rate of cyanobacteria or diatoms are required for phytotoxic and/or antimicrobial substances and should preferably be studied in a fresh water species.

The applicant did not submit a test on a freshwater species, but submitted a justification for non-submission (cfr. Doc IIIA JOINT: FA_BPR_ANN_II_9_1_3_JNS_21Sep2016). Therein they argument that an additional study will not provide additional information to address the risk to algae. This justification for non-submission was deemed acceptable.

Summary table - acute aquatic toxicity										
Method, Guideline, GLP status, Reliability	**Test material**	**Species**	**Endpoint**	**Exposure**		**Results**			**Remarks**	**Reference**
				Design	**Duration**	**$L(E)C_0$ [mg/L]**	**$L(E)C_{50}$ [mg/L]**	**$L(E)C_{100}$ [mg/L]**		
Fish										

DIN 38412, GLP-study, Reliability 3	FORMIC ACID	*Leuciscus idus*	mortality	static	96h	46^{n}	67.82^{g}	100^{n}	no measured concentrations, only nominal	[redacted] 1989 BPD ID A7.4.1.1_01 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_1_1*
OECD 203 GLP-study, Reliability 1	Ammonium formate	*Danio rerio*	mortality	static	96h	90^{n}	127.28^{g}	180^{n}	mean measured concentrations at test start and test end were >80 % of the nominal concentrations	[redacted] 2005 BPD ID A7.4.1.1_02 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_1_2*
OECD 203 GLP-study Reliability 2	Potassium formate	*Oncorhynchus mykiss*	mortality	semi-static	96h	1800^{n}	3500^{t}	5600^{n}	semi-static conditions with daily renewal	[redacted] 1992e BPD ID A7.4.1.1_03 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_1_3*
Invertebrates										
79/831/EEC, C.2 no GLP Reliability 2	FORMIC ACID	*Daphnia magna*	immobility	static	48h	25^{n}	32.19^{t}	50^{n}	no measured concentration No pH adjusted concentrations	[redacted] 1988 BPD ID A7.4.1.2_01 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_2_1_1*
OECD 202 GLP study Reliability 1	Ammonium formate	*Daphnia magna*	immobility	static	48h	90^{n}	365	720^{n}	mean measured concentrations at test start and	[redacted] 2005 BPD ID A7.4.1.2_02

									test end were >80 % of the nominal concentrations	*Doc IIIA JOINT: FA_BPR_Ann_II_9_1_2_1_2*
OECD 202 GLP study Reliability 2	Potassium formate	*Daphnia magna*	immobility	static	48h	56^{n}	540^{t}	>1000 (no 100% reached at highest test concentration)	no measured concentrations at request of test sponsor	[redacted] 1992 BPD ID A7.4.1.2_03 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_2_1_3*
Algae (growth inhibition)						**NOE$_{r}$C/E$_{r}$C$_{10}$**	**E$_{b}$C$_{50}$[1]**	**E$_{r}$C$_{50}$[2]**		
DIN 38412, part 9 no GLP Reliability 2	FORMIC ACID	*Desmodesmus subspicatus*	growth inhibition	static	72h	NOEC = 6.25^{n} ErC10 = 24.52 EbC10 = 17.71	26.92^{n}	30.21^{n}	no measured concentrations No pH adjusted concentrations	[redacted] 1988 BPD ID A7.4.1.3_01 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_3_1_1*
OECD 201 GLP study Reliability 1	Ammonium formate	*Pseudokirchneriella subcapitata*	growth inhibition	static	72h	<76.8^{n}	320^{n}	1240^{n}	mean measured concentrations at test start and test end were >80 % of the nominal concentrations	[redacted] 2005 BPD ID A7.4.1.3_02 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_3_1_2*
OECD 201 GLP study	Potassium formate	*Desmodesmus subspicatus*	growth inhibition limit test	static	72h	≥1000^{n}	>1000^{n}	>1000^{n}	no measured concentrations at	[redacted] 1992 BPD ID A7.4.1.3_03

Reliability 2									request of test sponsor	*Doc IIIA JOINT: FA_BPR_Ann_II_9_1_3_1_3*
[n] (based on) nominal concentrations [g] geometric mean of LC_0 and LC_{100} [t] using Thompson & Weil method (moving-average interpolation) [l] using a linear model [1] calculated from the area under the growth curve [2] calculated from growth rate										

Conclusion on acute toxicity (freshwater)

- FORMIC ACID:

  An aquatic acute toxicity test on formic acid was submitted for each trophic level. However, the test submitted for fish was deemed unreliable (3). The growth inhibition test on algae and the test on *Daphnia magna* can be of some value, but it must be born in mind that the endpoints derived in these studies are nominal values and that no distinction can be made between the effect due to acidity and effect due to the intrinsic toxicity of formic acid.

- AMMONIUM FORMATE:

  An aquatic acute toxicity test using ammonium formate as a test substance was submitted for each of the three required trophic levels. All three tests were assessed with a reliability of 1. The resulting $L(E)C_{50}$'s between the three trophic levels are each in the same order of magnitude, with the 96h LC_{50} of 127.28 mg/L for fish being the smallest recorded value.

- POTASSIUM FORMATE:

  Aquatic acute toxicity tests using potassium formate are available for each of the three required trophic levels and are all considered reliable (2).

Value used in Risk Assessment	
Value/conclusion	• 96h LC_{50} fish = 3500 mg/L • 48h EC_{50} daphnia = 540 mg/L

	• 72h E_rC_{50} algae > 1000 mg/L 72h NOE_rC algae = 1000 mg/L Even though the order of magnitude of the endpoints derived from the studies submitted on the three tropic levels is not so different between the species, Daphnia are considered the more sensitive species with the lowest reported EC_{50} of 540 mg/L
Justification for the value/conclusion	Studies conducted with formate salts are considered acceptable to assess the toxicity of formic acid without the effects due to the low pH. Since fish, aquatic invertebrates and algae are known to be sensitive towards ammonium dissolved in water, the results derived from testing with potassium formate are considered more relevant, since no effects are expected due to the potassium ion (K^+).

4.2.3.1.2 Chronic toxicity (freshwater)

No chronic toxicity tests were submitted for fish or other aquatic plants. Based on the results obtained in the acute toxicity tests, it was concluded by the applicant that *Daphnia* were the most sensitive of the three trophic levels, and they therefore submitted a chronic tests using *Daphnia magna*.

- The chronic effect of formic acid on the reproduction of *Daphnia magna* was tested in a study performed according to OECD 211 ([redacted] 2007, BPD ID A7.4.3.4_03).

  Nominal test concentrations of 0, 1.0, 3.2, 10, 32 and 100 mg/L were tested. Because the pH of the two highest test concentrations was below the suitable range, these test concentrations were neutralized using NaOH. The actual concentrations were verified and remained within the acceptable range, so that results are based on the nominal concentrations.

  Final results on statistical evaluations of the parameters reproduction, length and weight indicate that no effects were observed up to the highest concentrations of 100 mg/L. The corresponding NOEC is > 100 mg/L.

Summary table - chronic aquatic toxicity								
Method, Guideline, GLP status, Reliability	**Test material**	**Species**	**Endpoint/ type of test**	**Exposure**		**Results**	**Remarks**	**Reference**
				Design	**Duration**	**LOEC/NOEC/EC_{10} [mg/L]**		

Fish								
No test submitted								
Invertebrates								
OECD 211 GLP-study Reliability 1	FORMIC ACID	*Daphnia magna*	reproduction, length, weight	semi-static (renewal every 2-3 days)	21d	>100	pH was neutralized in the concentrations indicating a too low pH mean measured concentrations at test start and test end were >80 % of the nominal concentrations	[redacted] 2007 BPD ID A7.4.3.4_03 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_6_2_a*
Other aquatic plants								
No additional studies were submitted (cfr. acute toxicity tests on algae)								

Value used in Risk Assessment	
Value/conclusion	21d NOEC aquatic invertebrates ≥ 100 mg/L
Justification for the value/conclusion	See test results (with reliability 1) above.

4.2.3.2 *SEDIMENT COMPARTMENT*

4.2.3.2.1 Acute toxicity (freshwater sediment)

Data waiving	
Information requirement	None
Justification	

4.2.3.2.2 Chronic toxicity (freshwater sediment)

Data waiving	
Information requirement	None
Justification	

4.2.3.3 *MARINE COMPARTMENT*

4.2.3.3.1 Acute toxicity (seawater)

4.2.3.3.1.1 Fish

In the environment, formic acid will mostly be present in its formate form. To test the effect of the formate anion on marine fish species, one study was submitted.

- An acute toxicity test, was performed with synthetic seawater, using potassium formate as the test material and juvenile turbot (*Scophthalmus maximus*) as test species. The test was conducted according to Guidelines of the UK Ministry of Agriculture, Fisheries and Food ([redacted] 1992d, BPD ID A7.4.1.1_04), using a semi static test design, with daily renewal of the test medium. However, no analytical monitoring was performed to confirm that the test concentrations were indeed maintained throughout the test.

  Ten fish each were exposed to the nominal test concentrations of 0, 320, 560, 1000, 1800 and 3200 mg/L. Temperature, pH and dissolved oxygen were checked at test start and after 24, 48, 72 and 96 hours, and the results show that these parameters remained within the acceptable limits. Test concentrations were checked for mortality after 3, 6, 24, 48, 72 and 96 hours. No mortality was reported in the control group or in test concentrations up to 1000 mg/L. After 96 h, the lowest test concentration that had a 100 % mortality rate was 3200 mg/L. The 96h LC_{50} was determined using a linear model and resulted in a value of 1720 mg/L.

4.2.3.3.1.2 Invertebrates (other species)

In addition to the acute toxicity tests on *Daphnia magna*, the applicant submitted two supplementary studies on the acute toxicity effect of the formate ion on two marine invertebrate species.

- The acute toxicity of potassium formate to brown shrimp (*Crangon crangon*) was studied in a 96-hour semi-static test following Guidelines of the Ministry of Agriculture, Fisheries and Food, UK ([redacted] 1992c, BPD ID A7.4.1.2_04).

  Twenty shrimp each were exposed to nominal test concentrations of 0, 1000, 1800, 3200, 5600 and 10000 mg/L. Synthetic seawater was used as a test medium. No chemical analysis was carried out. Temperature, oxygen content and pH were measured at test start and after 24, 48, 72 and 96 hours, and remained within the acceptable ranges.

  The test species were checked for moulting and mortality after 3, 6, 24, 48, 72 and 96 hours. No mortality was reported in the control group and in the test concentrations up to 1000 mg/L. After only 3 hours, all test species had died in the highest concentration of 1000 mg/L. After 96h all shrimp in the test concentration of 1800 mg/L and up had died. The 96h LC_{50} was calculated according to a quadratic model and yielded the value of 1308 mg/L.

- The acute toxicity of potassium formate liquor (i.e. potassium formate 75% in water) to the marine copepod *Acartia tonsa* was studied in a 48-hour static test according to a guideline proposal to ISO TC147/SC5/WG2 ([redacted] 1994, BPD ID A7.4.1.2_05).

Twenty copepods each were exposed to nominal test concentrations of 0, 56, 100, 320, 560 and 1000 mg/L. Natural seawater was used as a test medium. No chemical analysis was carried out. Temperature, salinity, oxygen content and pH were measured at test start and end in the control group and in the group testing 1000 mg/L. Based on these measurements, these parameters remained within the acceptable range.

The test species was checked for mortality after 24 and 48 hours. Mortality in the control group was within the acceptable limits. After 48 hours, no or insignificant mortality occurred in test concentrations up to 320 mg/L. In the 560 mg/L concentration 20 % and in the 1000 mg/L concentration 65 % of the animals had died after 48 hours. The 48h LC_{50} was graphically estimated as 531 mg/L.

4.2.3.3.1.3 Algae (diatoms)

The effect of the formate ion on the growth of marine diatoms was demonstrated by the submission of one test.

- The inhibitory effect of potassium formate liquor (i.e. potassium formate 75% in water) on cell multiplication of the marine diatom *Skeletonema costatum* was studied according to ISO/DIS 10253 ([redacted] 1994, BPD ID A7.4.1.3_04).

  Exponentially growing algae were exposed to nominal concentrations of 0, 56, 100, 320, 560, and 1000 mg/l; using 250 mL flasks containing 200 mL of the test medium. Natural seawater was used as in preparing the culture medium and the initial cell density of the *Skeletonema costatum* was 10^4 cells/mL. No analytical monitoring of the test substance concentrations was performed throughout the test. The pH was measured at the start and end of test and the results show that this parameter remained within the acceptable range.

  Cell density measurements were performed after 24, 48 and 72 hours. The EC_{50} values were estimated using a logarithm linear or logarithm-probit plot of concentration and percent growth inhibition. At the highest tested concentration, 6 % inhibition of the growth rate and 20 % inhibition of the biomass integral was calculated after 72 hours. The 72-hour EC_{50} could therefore only be estimated as being larger than 1000 mg/L.

Summary table - acute aquatic toxicity										
Method, Guideline, GLP status, Reliability	**Test material**	**Species**	**Endpoint**	**Exposure**		**Results**			**Remarks**	**Reference**
				Design	**Duration**	**$L(E)C_0$ [mg/L]**	**$L(E)C_{50}$ [mg/L]**	**$L(E)C_{100}$ [mg/L]**		
Fish										
UK Ministry of Agriculture,	Potassium formate	Scophthalmus maximus	mortality	semi-static, marine	96h	1000^n	1720^l	3200^n	marine species	[redacted] 1992d BPD ID A7.4.1.1_04

Ficheries and Food guideline GLP study Reliability 2									semi-static conditions with daily renewal	*Doc IIIA JOINT: FA_BPR_Ann_II_9_1_1_4*
Invertebrates										
Guidelines of the Ministry of Agriculture, Fisheries and Food, UK GLP study Reliability 2	Potassium formate	*Crangon crangon*	mortality	semi-static marine	96h	1000^{n}	1308	1800	marine species no measured concentrations	[redacted] 1992c BPD ID A7.4.1.2_04 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_2_2_1*
ISO TC147/SC5/WG2 GLP study Reliability 2	Potassium formate liquor	*Acartia tonsa*	mortality	static marine	48h	320^{n}	531	>1000 (no 100% reached at highest test concentration)	marine species no measured concentrations	[redacted] 1994 BPD ID A7.4.1.2_05 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_2_2_2*
Algae (growth inhibition)						**NOE_rC/E_rC_{10}**	**E_bC_{50}[1]**	**E_rC_{50}[2]**		
ISO/DIS 10253 (draft 1991) GLP study Reliability 2	Potassium formate liquor	*Skeletonema costatum*	growth inhibition	static marine	72h	Not reported	>1000^{n}	>1000^{n}	marine species no measured concentrations	[redacted] 1994 BPD ID A7.4.1.3_04 *Doc IIIA JOINT: FA_BPR_Ann_II_9_1_3_2*

^{n} (based on) nominal concentrations
^{g} geometric mean of LC_0 and LC_{100}
^{t} using Thompson & Weil method (moving-average interpolation)
^{l} using a linear model
[1] calculated from the area under the growth curve
[2] calculated from growth rate

Value used in Risk Assessment	
Value/conclusion	• 96h LC_{50} fish = 1720 mg/L • 48h EC_{50} invertebrates = 531 mg/L • 72h E_rC_{50} algae > 1000 mg/L Just as with the studies in fresh water, the order of magnitude of the toxicity values derived from the studies submitted on the three tropic levels is not so different between the species, Daphnia are considered the more sensitive species with the lowest reported marine EC_{50} of 531 mg/L
Justification for the value/conclusion	Studies conducted with formate salts are considered acceptable to assess the toxicity of formic acid without the effects due to the low pH. No effect on the test species is expected due to the potassium ion (K^+).

4.2.3.3.2 Chronic toxicity (seawater)

Data waiving	
Information requirement	None
Justification	

4.2.3.4 *SEA SEDIMENT COMPARTMENT*

4.2.3.4.1 Acute toxicity (sea sediment)

Data waiving	
Information requirement	None
Justification	

4.2.3.4.2 Chronic toxicity (sea sediment)

Data waiving	
Information requirement	None
Justification	

4.2.3.5 *HIGHER TIER STUDIES ON AQUATIC ORGANISMS*

Nonesuch studies for formic acid or the formate ion were submitted or required at this point.

4.2.4 Terrestrial compartment

Formic acid is soluble in water and has a low adsorption potential (log Koc = 1.48). In soil formic acid will be mobile and present in the pore and ground water. The compound is however readily biodegradable and no long-term exposure of soil organisms to formic acid in soil is expected.

No specific results of ecotoxicity tests on terrestrial organisms are available for the risk assessment.

Data waiving	
Information requirement	No specific information submitted, but not required.
Justification	Equilibrium partitioning method will be used in the risk assessment.

4.2.5 Groundwater

No data on groundwater was submitted.

4.2.6 Birds and mammals

No studies on birds were submitted.
The available literature data show a low intrinsic toxicity of formic acid or formate to birds (*Doc IIIA JOINT: FA_BPR_Ann_II_9_4_1*), with a reported LD_{50} ≥ 111 mg/kg_{bw} for wild-trapped redwinged blackbirds and no adverse effects on body weight, feed utilisation or liveability up to 1.0$\%_{w/w}$ Formic Acid and 1.45 % calcium formate in the diets of male broilers.

For oral studies on mammals, please see paragraphs 3.6.1 and 3.7.1 above.

Summary table –toxicity to birds and mammals									
Method, Guideline, GLP status, Reliability	**Species**	**Endpoint**	**Exposure**		**Results [mg a.i./kg bw or feed]**			**Remarks**	**Reference**
			Design	**Duration**	**LD/LC_{50}**	**LOEL/ LOEC**	**NOEL/ NOEC**		
Birds									
No test submitted									
Mammals									
OECD 408 GLP: yes Rel. 1	Rat (≥ 6 weeks)	sub-chronic repeated oral toxicity Systemic values	OECD 408	90 days	/	2100	840	study with potassium diformate as test substance	[redacted] 1998 BPD ID A6.4.1_01 *Doc IIIA JOINT: FA_BPR_Ann_II _8_9_2_01*
Comparable to 94/40/EEC GLP: yes Rel. 1	Rat (≥ 6 weeks)	long-term repeated oral toxicity Systemic values	Comparable to 94/40/EEC	104 weeks	/	1400	280		[redacted] 2002a BPD ID A6.5_01 *Doc IIIA JOINT: FA_BPR_Ann_II _8_11_1_02*

Value used in Risk Assessment

Value/conclusion	$NOAEL_{bird}$ = no value available $NOAEL_{mammal,\ oral\_chr}$ = 280 mg/kg_{bw}.day
Justification for the value/conclusion	Data on the avian toxicity of formic acid is not required. Data on the toxicity of formic acid on mammals was submitted for the human health part (see §3.6.1 and 3.7.1 on sub-chronic and long-term toxicity)

4.2.7 Primary and secondary poisoning

4.2.7.1 *PRIMARY POISONING*

Data waiving	
Information requirement	None
Justification	/

4.2.7.2 *SECONDARY POISONING*

Data waiving	
Information requirement	No
Justification	Formic acid is not expected to bioaccumulate based on the experimentally derived log Kow of -2.1 (23 °C, pH7) and the calculated BCF (see §4.1.3 above). Therefore, secondary poisoning of formic acid in either the aquatic or terrestrial food chain is considered not relevant.

4.3 ENDOCRINE DISRUPTING PROPERTIES

No specific vertebrate tests to assess the endocrine disrupting (ED) properties of formic acid/formate for other non-target organisms were submitted by the applicant.

The 'Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009' (ECHA/EFSA, 7 June 2018)[8] states:

There may be cases in which due to the knowledge on the physico-chemical and (eco)toxicological properties of the substance an ED assessment does not appear scientifically necessary or testing for this purpose not technically possible (BP Regulation, Annex IV or PPP Regulation, Annex, Point 1.5).

The Annex IV, section 1.2 of the BPR states:

There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or does not have a particular dangerous property, while the information from each single source alone is considered insufficient to support this notion. […] Where consideration of all the available data provides sufficient weight of evidence for the presence or absence of a particular dangerous property:

— further testing on vertebrates for that property shall not be undertaken,

— further testing not involving vertebrates may be omitted.

The following discussion focusses on a weight of evidence based argumentation to determine whether an ED assessment for formic acid and its salts, and the subsequent vertebrate testing appear scientifically necessary.

Formic acid is the simplest carboxylic acid. The formate anion is the common metabolite of formic acid and formate salts in aqueous solutions at physiological and environmental pH values. The water soluble formic acid and formate salts rapidly dissociate in aqueous solutions (fresh and salt water, body fluids) to formate and a cation (H^+ or Na^+, K^+, NH_4^+, etc.). Formic acid and formate are both readily biodegradable in freshwater, producing only water and CO_2. Formate is also biodegradable in seawater (Please refer to 4.1 Fate and distribution in the environment). Formic acid has no potential for bioaccumulation (indeed log Kow is - 2.1 at pH 7 and BCF calculated value is 3.2).

Formic acid is a natural compound occurring at significant concentrations in all environmental compartments. Formic acid has been identified as a major contributor to acidic rain in remote environments [Galloway *et al.* 1982; Chameides and Davis, 1983]. Known major sources of formic acid in the atmosphere include fossil fuel and biofuel combustion [Kawamura and Kaplan, 1985], biomass burning [Andreae and Merlet, 2001], plants [Gabriel *et al.* 1999] and photochemical oxidation of volatile organic precursors [Neeb *et al.* 1997]. Stavrakou *et al.* (2012)

[8] Referred to as 'Guidance on ED'.

showed that 90% of the formic acid produced is biogenic in origin, and largely sourced from tropical and boreal forests. The authors suggest that terpenoids – volatile organic compounds released by plants – are the predominant precursors.

In soil, low molecular-weight organic acids (including formic acid) are commonly present and are constantly released from root exudates and decayed plant litter, and through microbial organic matter decomposition. Takata *et al*. (2011) reported measured formic acid concentrations in soil ranging from 0.088 to 0.217 mg/kg_{dwt} on arable land and from 0.072 to 0.444 mg/kg_{dwt} in an adjacent oak forest. In a soil incubation experiment with poorly-drained soil conducted by Tete *et al.* (2015), formate concentrations in soil up to 0.18 mg/kg_{dwt} (at field capacity) and 1.89 mg/kg_{dwt} (in waterlogged soil) were observed. Van Hees *et al.* (2008) determined formate concentrations in the soil solution in different horizons of two coniferous forest soils. The authors observed the highest concentrations in the top soil (O1 horizon), ranging from 0.152 mg/L (3.3 µM, mean of 6 values) at Heden, Sweden to 0.354 mg/L (7.7 µM, mean of 6 values) at Nyänget, Sweden. Formic acid has a rapid turn-over in soil. Half-lives in soil under aerobic conditions of ≤1 day were observed in studies conducted by Glanville *et al.* (2012) and Hellstén *et al.* (2005b).

Formic acid is also reported to be present in manure (up to 1415 mg kg dry matter in fresh dairy manure) [Baziramakenga and Simard, 1998; Spoelstra, 1979; Iannotti *et al.*, 1979] and surface water (up to 155 µg/L) [Murtaugh and Bunch, 1965; Hama and Handa, 1981].

Besides their presence in the environment, formic acid and its conjugate base, formate, are also naturally occurring in virtually all living organisms as essential endogenous metabolites critical for one-carbon metabolism [Lamarre *et al.* 2013]. Formate is formed from precursors in the intermediary metabolism and is used as an important constituent of the C1 intermediary metabolism which is required for the biosynthesis of amino acids and nucleic acid bases (purines and pyrimidines). As a critical endogenous metabolite, formate is not assumed to be inherently endocrine active.

Endocrine activity was investigated using *in silico* methods. None of the endocrine activity related profilers of the OECD QSAR Toolbox V4.1 showed an alert for formic acid. In fact, formic acid was grouped into the category "non-binder, non-cyclic structure". Furthermore, binding to either oestrogen receptor (ER) or androgen receptor (AR) was estimated using in silico models implemented in OASIS TIMES (V2.27.19.13). None of the three models predicted a binding of formic acid to ER (with or without metabolisation of parent compound) and AR (without metabolisation). Please note that formic acid and formate have no structural similarity to intrinsic endocrine active substances (e.g. oestrogen, androgen). Altogether, based on *in silico* data it is very unlikely that formic acid exerts an endocrine/EATS-specific effect based on an endocrine mode of action.

In the mammalian dataset, no pattern related adverse effects in endocrine-sensitive organs or endpoints was identified in the available OECD Level 4 & 5 *in vivo* toxicity studies. Based on that mammalian dataset, it is concluded that formic acid does not meet the endocrine disruptor criteria for humans regarding E,A, S and T modalities (see §**Erreur ! Source du renvoi introuvable.**).

The Guidance on ED states that due to the high level of conservation of the endocrine system and receptor homology across the vertebrates, as well as the key enzymes involved, the mammalian data may also be relevant for other vertebrates.

Considering all above mentioned arguments, it was agreed by the Biocides Environment Working Group Meeting IV-2019 (ENV WG-IV-2019) that no further vertebrate testing is needed to conclude on the endocrine disruptor criteria for other non-target organisms. Based on the evaluation of available data in a weight-of-evidence based approach, it is concluded that formic acid does not meet the endocrine disruptor criteria for non-target organisms regarding E,A, S and T modalities.

Value used in Risk Assessment	
Value/conclusion	Formic acid does not meet the endocrine disruptor criteria for both human health and non-target organisms.
Justification for the value/conclusion	Conclusion agreed by the ENV WG-IV-2019 based on the evaluation of available data in a weight-of-evidence based approach.

4.4 DERIVATION OF PNECS

Compartment	PNEC	Remarks/Justification
Freshwater	$PNEC_{freshwater}$: ≥ 2 mg/L	Organism: *Daphnia magna* Endpoint: 21d NOEC ≥ 100 mg/L Assessment factor: 50 Extrapolation method: assessment factor Justification: The three taxonomic groups (fish, invertebrates, algae) are covered in short term data, of which Daphnia is considered as the most sensitive. A long-term NOEC for Daphnia is also available, and consequently the NOEC derived from the algal growth inhibition test is considered as an additional long-term study. An assessment factor of 50 is thus justified.
Freshwater sediment	$PNEC_{sediment}$: ≥ 2.87 mg/kg_{wwt} (converts to ≥ 13.2 mg/kg_{dwt})	Extrapolation method: Equilibrium partitioning method Justification: No specific data available or required Note: Since also the $PEC_{sediment}$ is calculated from the $PEC_{freshwater}$ using this method, the risk assessment and PEC/PNEC-ratio for the freshwater compartment are considered to cover the sediment compartment as well.
Saltwater	$PNEC_{seawater}$: > 0.2 mg/L	Organism: Daphnia magna Endpoint: 21d NOEC > 100 mg/L Assessment factor: 500 Extrapolation method: assessment factor Justification: short term data for the basic three taxonomic groups (fish, invertebrates, algae) are available for both freshwater and saltwater species. No difference in sensitivity between the aquatic species in both media was observed. Long-term effect data (NOEC/EC_{10}) are available for two trophic levels (algae and crustaceans) covering the

Compartment	PNEC	Remarks/Justification
		most sensitive trophic level (= crustaceans). Therefore, the use of an assessment factor of 500 is justified.
Saltwater sediment	$PNEC_{marine\text{-}sediment}$: ≥ 0.143 mg/$kg_{wwt}$	Extrapolation method: Equilibrium partitioning method Justification: No specific data available or required Note: Since also the $PEC_{marine\text{-}sediment}$ is calculated from the $PEC_{seawater}$ using this method, the risk assessment and PEC/PNEC-ratio for the marine compartment are considered to cover the sediment compartment as well.
Soil	$PNEC_{soil}$: ≥ 1.29 mg/kg_{wwt} (converts to ≥ 1.47 mg/kg_{dwt})	Extrapolation method: Equilibrium partitioning method Justification: No specific data available or required Note: The LOQ of the analytical method for soil established in the APCP section of this CAR is above the PNEC value for the soil compartment. Although not ideal, this is not a problem in the present case: the PNECsoil is determined using the equilibrium partitioning method (and not based on measured test concentrations), and the risk assessment is based on calculated PEC values.
Groundwater	Not applicable	General drinking water limit: 0.0001 mg/L
Air	Not determined	Not relevant
STP	$PNEC_{STP}$: > 50 mg/L	Organism: activated sludge Endpoint: 3h EC_{10} > 500 mg/L Assessment factor: 10 Extrapolation method: assessment factor Justification: EC_{10} derived from OECD209
Secondary poisoning birds	Not determined	No available data, but not considered relevant since no accumulation is expected

Compartment	PNEC	Remarks/Justification
Secondary poisoning mammals	Not relevant	Risk assessment for secondary poisoning is not considered necessary, since no accumulation is expected.

5 ASSESSMENT OF EXCLUSION CRITERIA, SUBSTITUTION CRITERIA AND POP

5.1 EXCLUSION CRITERIA

5.1.1 Assessment of CMR properties

Criteria (BPR Article 5[1])	**Assessment**
Active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, carcinogen category 1A or 1B	Formic acid is not classified and does not meet the criteria to be classified as Carc. Cat. 1A or 1B.
Active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, mutagen category 1A or 1B	Formic acid is not classified and does not meet the criteria to be classified as Muta. Cat. 1A or 1B.
Active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, toxic for reproduction category 1A or 1B	Formic acid is not classified and does not meet the criteria to be classified as Repr. Cat. 1A or 1B.

Conclusion on CMR properties	The exclusion criteria in BPR Article 5(1)a-c are not met.

5.1.2 Assessment of endocrine disrupting properties

Criteria (BPR Article 5)	**Assessment**
Active substances which, on the basis of the criteria specified pursuant to the first subparagraph of paragraph 3 are considered as having endocrine-disrupting properties that may cause adverse effects in humans and to the environment.	The endocrine disrupting properties are assessed in accordance with the scientific criteria set out in COMMISSION DELEGATED REGULATION (EU) 2017/2100. Formic acid is not considered as having endocrine-disrupting properties that may cause adverse effects in humans and to the environment.

Conclusion on ED properties	The exclusion criteria in BPR Article 5(1)d are not met.

5.1.3 PBT Assessment (following Annex XIII to Regulation (EC) No 1907/2006)

5.1.3.1 *ASSESSMENT OF PERSISTENCE*

5.1.3.1.1 Screening

The available data on degradation reveal that formic acid should be considered readily biodegradable.

5.1.3.2 *ASSESSMENT*

P Criteria	Assessment
T1/2 > 60 days in seawater, or	no experimental data
T1/2 > 40 days in fresh- or estuarine water, or	no experimental data
T1/2 > 180 days in seawater sediment, or	no experimental data
T1/2 > 120 days in freshwater- or estuarine sediment, or	no experimental data
T1/2 <= 120 days in soil.	no experimental data

vP Criteria	Assessment
T1/2 > 60 days in sea-, fresh- or estuarine water water, or	no experimental data
T1/2 > 180 days in seawater-, freshwater- or estuarine sediment, or	no experimental data
T1/2 > 180 days in soil.	no experimental data

Conclusion on P / vP properties	Based on degradation data, formic acid is considered readily biodegradable. Therefore formic acid is considered not P or vP

5.1.3.3 *ASSESSMENT OF BIOACCUMULATION*

5.1.3.3.1 Screening

The log octanol-water partitioning coefficient (Log K_{ow}) for formic acid was determined at -2.10 (23 °C, pH7). Formic acid is considered hydrophilic in nature.

5.1.3.3.2 Assessment

B Criteria	**Assessment**
BCF > 2000	no experimental data

vB Criteria	**Assessment**
BCF > 5000	no experimental data

Conclusion on B / vB properties	The log K_{ow} for formic acid is well below the screening criterion of 4.5 for bioaccumulation. Therefore formic acid is not considered B or vB.

5.1.3.4 *ASSESSMENT OF TOXICITY*

5.1.3.4.1 Screening

The lowest available short term toxicity value for formic acid is the 48h EC_{50} for daphnia equal to 540 mg/L, which is well above the screening threshold for short-term aquatic toxicity of 0.01 mg/L.

The lowest chronic endpoint is a 21d NOEC for daphnia of 100 mg/L.

5.1.3.4.2 Assessment

T Criteria	Assessment
NOEC/EC10 (long-term) < 0.01 mg/L for freshwater or seawater organisms, or	The lowest chronic endpoint is a 21d NOEC for daphnia of 100 mg/L, which is well above the criterium.
substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) according to the CLP Regulation, or	Formic acid does not meet the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) according to the CLP Regulation.
there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to the CLP Regulation.	For formic acid there is no other evidence of chronic toxicity, as the substance does not meet the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to the CLP Regulation.

Conclusion on T properties	Based on the available data, formic acid is considered not T

5.1.3.5 *SUMMARY AND OVERALL CONCLUSIONS ON PBT OR VPVB PROPERTIES*

5.1.3.5.1 Summary

- Formic acid is ready biodegradable
- Formic acid is hydrophilic and has no potential to bio-accumulate
- Formic acid is not classified for toxicity

5.1.3.5.2 Overall conclusion:

Based on the assessment described in the subsections above the submission substance is not a PBT / vPvB substance.

5.2 SUBSTITUTION CRITERIA

[Include an assessment if the active substance meets any of the following conditions:]

Substitution criteria (BPR, Article 10)	Assessment
One of the exclusion criteria listed in Article 5(1) is met but AS may be approved in accordance with Article 5(2)	For formic acid, the exclusion criteria in BPR Article 5(1)a-c are not met.
The criteria to be classified, in accordance with Regulation (EC) No 1272/2008, as a respiratory sensitiser is met	For formic acid, the criteria to be classified, in accordance with Regulation (EC) No 1272/2008, as a respiratory sensitiser are not met.
The acceptable daily intake, acute reference dose or acceptable operator exposure level, as appropriate, is significantly lower than those of the majority of approved active substances for the same product-type and use scenario	For formic acid, acceptable daily intake, acute reference dose or acceptable operator exposure level, as appropriate, are not significantly lower than those of the majority of approved active substances for the same product-type and use scenario
Two of the criteria for being PBT in accordance with Annex XIII to Regulation (EC) No 1907/2006 are met	No
There are reasons for concern linked to the nature of the critical effects which, in combination with the use patterns, amount to use that could still cause concern, such as high potential of risk to groundwater, even with very restrictive risk management measures	No
The AS contains a significant proportion of non-active isomers or impurities.	No

Conclusion on substitution criteria	The substitution criteria in BPR Article 10(1)a-f are not met.

5.3 ASSESSMENT OF LONG-RANGE ENVIRONMENTAL TRANSPORTATION AND IMPACT ON ENVIRONMENTAL COMPARTMENTS

Criteria	Assessment
The active substance or a degradation product is a persistent organic pollutant (POP) listed in Annex I of EC 850/2004	No
Assessment of long-range transport potential (LRTAP): • Vapour pressure <1000 Pa and • half-life in air > 2 days or • Monitoring data in remote area showing that the substance is found in remote regions or • Result of multi media modelling	No
The active substance or a degradation product is vP/vB or T?	No

Conclusion on LRTAP/POP asessment	Formic acid does not meet the criteria for being a POP or LRTAP.

PART B : EXPOSURE ASSESSMENT AND EFFECTS OF THE ACTIVE SUBSTANCE IN THE BIOCIDAL PRODUCT(S)

6 GENERAL PRODUCT INFORMATION

6.1 IDENTIFICATION OF THE PRODUCT

Name(s) of the product	
Trade name(s) or proposed Trade name(s)	***FENNOPUR® MH 85***
Manufacturer's development code and number of the product	Not applicable
Fromulation type	Water based concentrate / water soluble concentrate (SL)

6.2 COMPLETE QUALITATIVE AND QUANTITATIVE COMPOSITION OF THE BIOCIDAL PRODUCT

Active substance(s)					
ISO or Trivial name	**IUPAC name or other accepted chemical name**	**EC number**	**CAS number**	**Composition / all constituents (upper and lower concentration limit in % (w/w))**	**Concentration in the product in % (w/w)**
Formic Acid	Methanoic Acid	200-579-1	64-18-6	Minimum 99% w/w purity (BASF)	85% w/w (pure)

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6.3 PHYSICAL, CHEMICAL AND TECHNICAL PROPERTIES

Table 6.3.1: Fennopur MH85				
Property	**Result**	**Test method applied or description in case of deviation**	**Remarks / Discussion / Justification for waiving**	**References**
Physical state at 20°C and 101.3 kPa (85%)	Liquid	Organoleptic	The biocidal product contains 85 % active substance with no other ingredients than water. These properties are expected to be similar as for the active substance	Study no. 07L00084, [redacted] (2007)
Colour at 20°C and 101.3 kPa (85%)	Colourless	Organoleptic		
Odour at 20°C and 101.3 kPa (85%)	Pungent	Organoleptic		
Acidity / alkalinity (85%)	$pH_{85\% \text{ formic acid}}$ = -1.6 At 1%: pH = 2.2	German Industrial Standard DIN 19268	Potentiometric measurement	Study no. 07L00172, [redacted] (2007)
	90.9530 ± 0.0663 % acidity	CIPAC MT 191	On 85% formic acid in water sample. Since test item is an acid, only acidity was tested.	Study no 16011907G975 [redacted] (2016a)
	pH = 2.18	CIPAC MT 75	At 24.8 °C On 1% aqueous solution of 85% formic acid sample	Study no 16011907G907 [redacted] (2016c)
Relative density (85%)	D_4^{20} = 1.1969	OECD 109	/	Study no. 16011907G912, [redacted] (2016d)
Storage stability, stability and shelf-life				

Accelerated storage	The test item is chemically and visually stable when stored in HDPE containers at 54±2 °C for two weeks.	CIPAC MT 46.3-	**/**	Study no. 16011907G978 [redacted] (2016)
Long term storage at ambient temperature (85%)	Shelf life of > 24 months	Storage conditions: translucent HDPE bottles 250 mL; temperature: 20± 2 °C °C	The recovery rate of formic acid was 102.8 % after two years storage. The active ingredient was stated as stable after the storage of the test item at 20 ± 2 °C (except of 3 h above 22 °C with maximum temperature 22.5 °C) for 24 months.	Study no. 16011907G001 [redacted] (2020)
Low temperature stability (liquids)	Waived	/	According to the label of the product, Formic Acid 85% is not to be stored below 0 °C	Kemira (2016)
Effects on content of the active substance				
Light	Waived	/	FA does not absorb at wavelengths > 290 nm; therefore, it is not expected to be susceptible to direct photolysis by sunlight (HSDB, 2006).	HSDB (2006; BPD ID A7.1.1.1.2_04
Temperature and humidity	Waived	-	Boiling point = 107.3 °C Formic Acid 99% shows no signs of decomposition up to the boiling point Therefore the product can be considered stable at high temp. Humidity is irrelevant since the product is an aqueous solution.	Study no. 02L00109, [redacted] (2002) Study no. 07L00084, [redacted] (2007)
Reactivity towards container material	Corrosive to steel.	Corrosive properties UN test 37.4 C1	/	Study no. 16011907G979

	Not corrosive to aluminium.			[redacted] (2016b)
Technical characteristics				
Wettability	Waived	-	Not applicable	-
Suspensibility, spontaneity and dispersion stability	Waived	-	Not applicable	-
Wet sieve analysis and dry sieve test	Waived	-	Not applicable	-
Emulsifiability, reemulsifiability and emulsion stability	Waived	-	Not applicable, **Fennopur MH85** is not an emulsion	-
Disintergration time	Waived	-	Not applicable	-
Particle size distribution, content of dust / fines, attrition, friability	Waived	-	Not applicable	-
Persistent foaming	**Fennopur MH85** is a non-foaming liquid solution	CIPAC MT 47	No foam was observed in the course of the test.	Study no. 16011907G968 [redacted] (2016f)
Flowability, pourability, dustability	Waived	-	Not applicable	-
Burning rate – smoke generators	Waived	-	Not applicable	-

Burning completeness – smoke generators	Waived	-	Not applicable	-
Composition of smoke – smoke generators	Waived	-	Not applicable	-
Spraying pattern - aerosols	Waived	-	Not applicable	-
Other technical characteristics	Waived	-	Not applicable	-
Physical and chemical compatibility with other products including other biocidal products with which its ues is to be authorised				
Physical compatibility	Waived	-	Not applicable, **Fennopur MH85** is not intended to be used in combination with other products	-
Chemical compatibility	Waived	-		-
Degree of dissolution and dilution stability	Waived	-	As the active substance is highly soluble in water, no issue with stability in water is expected.	-
Surface tension	At 20 °C: 72.38 mN/m	OECD 115	The biocidal product is not surface active.	[redacted] (2016f)
Viscosity	Dynamic viscosity At 20 °C: 1.80 mPa.s At 40 °C: 1.22 mPa.s Kinematic viscosity At 20 °C: 1.47 mm^2/s	OECD 114	For more concentrated (99.4 %) formic acid	Study no. 16011907G984 [redacted] (2016h)

	At 40 °C: 1.02 mm^2/s			
	Dynamic viscosity: At 20 °C: 1.705 mPa.s At 40 °C: 1.174 mPa.s	/	/	Study no. 16011907G984 [redacted] (2016h)
	Dynamic viscosity At 20 °C: 1.71 mPa.s At 40 °C: 1.18 mPa.s Kinematic viscosity At 20 °C: 1.42 mm^2/s At 40 °C: 0.99 mm^2/s	Expert judgement	Estimation for product **Protectol® FM 85** with 85 % formic acid	/
Physical hazards and characteristics				
Explosives (85%)	The substance is not explosive	UN Manual of Tests and Criteria (2010)	The substance has no chemical groups indicating explosive properties	[redacted] (2006)
Flammable gases	Waived	-	Not applicable	-
Flammable aerosols	Waived	-	Not applicable	-
Oxidising gases	Waived	-	Not applicable	-
Gases under pressure	Waived	-	Not applicable	-
Flammable liquids	Not a flammable liquid Flash point = 67.3 °C Classified as Flammable Liquid 3 (H226)	EU Method A.9, OPPTS 830.6315, UN Manual Test Methods 32.4 (Pensky-Martens closed cup)	/	Study no. 16011907G964, [redacted] (2016e)

Flammable solids	Waived	-	Not applicable	-
Self-reactive substances and mixtures (85%)	The substance is not self-reactive	UN Manual of Tests and Criteria (2010)	The substance has no chemical groups indicating explosive or self-reactive properties	
Pyrophoric liquids	Waived	-	Not a pyrophoric liquid, based on auto-ignition temperature (528 °C for 99.4 % formic acid) and experience in manufacture and handling	Study no. SIK-Nr.07/1018, [redacted] (2007)
Pyrophoric solids	Waived	-	Not applicable	-
Substances and mixtures which in contact with water emit flammable gases	Waived	-	Not applicable	-
Oxidising liquids (85%)	The substance is not an oxidising liquid	UN Manual of Tests and Criteria (2010)	The compound contains oxygen but this element is chemically bonded only to carbon and hydrogen The compound does not contain any halogen atoms	[redacted] (2006)
Oxidising solids	Waived	-	Not applicable	-
Organic peroxides	Waived	-	Not applicable	-
Corrosive to metals	Corrosive to steel Not corrosive to aluminium	UN Test C.1 (37.4)	On 85% formic acid in water sample	Study no 16011907G979 [redacted] (2016b)

	Classified as Corrosive to Metal (H290)			
	Compatible materials: - stainless steel, types 1.4306, 1.4307, 1.4311, 1.4404, 1.4541, 1.4571 Not compatible: - carbon steel Classified as Corrosive to Metal (H290)	Based on experience	On 99% formic acid	[redacted] (2007a)
Auto-ignition temperature of products (liquid and gas)	Auto-ignition temperature: 528 °C (corrected according to EN 14522)	EC method A.15	Result for solution with 99.4 % formic acid. The only other ingredient of **Fennopur MH85** is water (15%)	Study no. SIK-Nr.07/1018, [redacted] (2007)
Relative self-igniton temperature of solids	Waived	-	Not applicable	-
Dust explosion hazard	Waived	-	Not applicable	-

6.4 HAZARD IDENTIFICATION FOR PHYSICAL AND CHEMICAL PROPERTIES

The product **FENNOPUR® MH 85** as manufactured is a colourless liquid with a pungent smell. The relative density of the product is 1.195 at 20 °C. The product has a long term stability of 24 months. The surface tension is 72.38 nN/m and the viscosity 1.705 mPa.s. Physical and chemical compatibility with other products are not relevant.

6.5 ANALYTICAL METHODS FOR DETECTION AND IDENTIFICATION

Please note that only Formic acid and the formate ion are analysed in the monitoring table presented below

Analytical methods for monitoring									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	**Mean**	**RSD**		
Depending on extra data request for a.s. (formic acid)	UV absorption *(334, 340 or 365 nm)*	7	r2= 0.99981	none	0.2 to 5 mg/L			0.2 mg/L	[redacted] (2013)

Analytical methods for soil									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	**Mean**	**RSD**		
a.s. (formic acid)	UV absorption after stochiometric , enzyme-catalyzed reduction of NAD+ to NADH by formic acid Formic acid (formate) is	5- 50 mg/kg (25 number of measurements)	r2= 0.99981 *Linearity is given in the range 0.2 mg formic acid /l sample solution to 200 mg formic*	The method is specific for formic acid. Acetic acid, propionic acid, oxalic acid and L-ascorbic acid do not influence the determination. Formaldehyde	Fortification range 5-50 mg/kg	RR 5 mg/L: 31% RR 10 mg/kg: 85% RR 50 mg/kg: 93%	4.7 (at 50 mg/kg)	10 mg/kg	[redacted] (2013)

	quantitatively oxidized to bicarbonate by nicotinamide adenine dinucleotide (NAD) in the presence of formate dehydrogenase (FDH). FDH Formate + NAD^+ + H_2O ⟶ bicarbonate + NADH + H^+ The amount of NADH formed is stoichiometric to the amount of formic acid. The increase in NADH is measured by means of its light absorbance at 334, 340 or 365 nm. The molar extinction coefficient is		*acid/l sample*	reduces the reaction rate but does not influence the specificity of the method.”					

	large at 340 nm [ϵ= 6.3 L/(mmol x c)], i.e. the method is most sensitive at this wavelength. The extinction coefficient allows to calculate the formate concentration from the absorbance difference at the start and at the end of the reaction, which is a common method in biochemical laboratories. *Photometric measurements provide the basis for the majority of quantitative methods in biochemistry and are related to the amount of*								

	light absorbed. The temperature range should be 20-25°C, the pH value at approx. 7.5. The specificity of the method is based on the specificity of the enzyme for its substrate (known as "key-lock principle").								

Analytical methods for air									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	**Mean**	**RSD**		
Depending on extra data request for *a.s.formic acid*	Ion Chromatography *Material and conditions: Ion chromatographer DIONEX DX 120 with conductivity detector and autosampler. Pre-column:*	6 (per concentration)	*Formic acid, 1.2 to 47.8 mg/L*.	Specificity depends on the column and eluant chosen, and also on the	*94%-95%*	*95% RR for 0.9mg/m3*	*9.7% for 0.9 mg/m3 fortification level*	*Absolute: 0.1µg; relative: 0.12 mg/m3 formic acid for a 140 l air sample, 10 ml absoption volume and*	[redacted] 2007

	Micro-Guard Cation H-Cartridge (Bio-Rad, Munich). Column: Aminex HPx-87H (Bio-Rad). Suppresor: AMMS-ICE II P/N 037107 (Dionex). Suppressor solution: Tetrabutyl ammonium hydroxide, 5 mM. Eluent: hydrochloric acid 0.15 mM. Flow rate 0.6 mL/min. Flow rate suppressor: 1 mL/min Injection volume: 50 µL. Temperature: room temperature.			separation condition.				*50 µl injection volume*	

Analytical methods for water									
Analyte (type of analyte e.g. active	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	**Mean**	**RSD**		

<table>
<tr><th>substance)</th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></tr>
<tr>
<td>Active substance formic acid</td>
<td>UV absorption after stochiometric , enzyme-catalyzed reduction of NAD+ to NADH by formic acid
Formic acid (formate) is quantitatively oxidized to bicarbonate by nicotinamide adenine dinucleotide (NAD) in the presence of formate dehydrogenase (FDH).

FDH
Formate + NAD^+ + H_2O ⟶ bicarbonate + NADH +</td>
<td>Drinking water: 20 (5 measurements at each of the four fortification levels) and blanks
Surface water: 15 (5 measurements at each of the three fortification levels) and blanks</td>
<td>given in the range 0.2 to 5 mg/L. R^2= 0.9997 for the regression curve for all measurements given in the range 0.2 to 5 mg/L. R^2= 0.99998 for the regression curve for all measurements</td>
<td>(enzyme specific for formic acid)</td>
<td>0.2 to 5 mg/L</td>
<td><table>
<tr><th>Fortification level [mg/L]</th><th>Recovery [%] Drinking water</th><th>Recovery [%] Surface water</th></tr>
<tr><td>0.2</td><td>103</td><td>100</td></tr>
<tr><td>0.5</td><td>91</td><td>n.d.</td></tr>
<tr><td>2</td><td>103</td><td>81</td></tr>
<tr><td>5</td><td>101</td><td>78</td></tr>
</table></td>
<td><table>
<tr><th>Fortification level [mg/L]</th><th>Rel SD[%] Drinking water</th><th>Rel SD [%] Surface water</th></tr>
<tr><td>0.2</td><td>17</td><td>7.7</td></tr>
<tr><td>0.5</td><td>2.4</td><td>n.d.</td></tr>
<tr><td>2</td><td>6.6</td><td>1.6</td></tr>
<tr><td>5</td><td>3.7</td><td>1.7</td></tr>
</table></td>
<td>0.2 mg/L in drinking water
and surface water</td>
<td>[redacted]
(2013)</td>
</tr>
</table>

	H^+ The amount of NADH formed is stoichiometric to the amount of formic acid. The increase in NADH is measured by means of its light absorbance at 334, 340 or 365 nm. The molar extinction coefficient is large at 340 nm [ϵ= 6.3 L/(mmol x c)], i.e. the method is most sensitive at this wavelength. The extinction coefficient allows to calculate								

	the formate concentration from the absorbance difference at the start and at the end of the reaction, which is a common method in biochemical laboratories. *Photometric measurements provide the basis for the majority of quantitative methods in biochemistry and are related to the amount of light absorbed. The temperature range should be 20-25°C, the pH value at*								

	approx. 7.5. The specificity of the method is based on the specificity of the enzyme for its substrate (known as "key-lock principle").								

Analytical methods for animal and human body fluids and tisues									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	**Mean**	**RSD**		
Active substance formic acid	UV absorption *Formic acid (formate) is quantitatively oxidized to bicarbonate by nicotinamideadenine dinucleotide (NAD)*	n.a.	Linearity is given in the range 0.2 mg formic acid/l sample solution to	yes	0.2 mg/L to 200 mg/L	100%	0.48-2.40%	0.2 mg/L	Anonymous (2007) UV test for the determination of Formic Acid in foodstuffs and other materials,

	in the presence of formate dehydrogenase (FDH). *FDH* *Formate + NAD^+ + H_2O ⟶ bicarbonate + NADH + H^+* *The amount of NADH formed is stoichiometric to the amount of formic acid. The increase in NADH is measured by means of its light absorbance at 334, 340 or 365 nm. NADH and NADPH absorb in the long-wave UV-range with a maximum at 340 nm, whilst the oxidized forms (NAD and NADP) do not show any absorption at this wavelength (see Figure 3). Therefore, any reaction in which either NAD(P) is reduced or NAD(P)H is oxidized may be*		200 mg formic acid/l sample solution (cf. full test description in Section A4.1_01).						Roche commercial test combination, R-Biopharm, Cat. No. 10 979732 035

	measured by recording the change in absorption in this wave length range.								

Analytical methods for monitoring of active substances and residues in food and feeding stuff									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	**Mean**	**RSD**		
Active substance formic acid	UV absorption Formic acid (formate) is quantitatively oxidized to bicarbonate by nicotinamideadenine dinucleotide (NAD) in the presence of formate dehydrogenase (FDH). FDH Formate + NAD^+ + H_2O $\longrightarrow$ bicarbonate + NADH + H^+ The amount of NADH formed is stoichiometric to the	16	Linearity is given in the range 0.2 mg formic acid/l sample solution to 200 mg formic acid/l sample	Specific to formic acid	0 to 50 mg/L	recovery 92% at fortification level 10 mg/L and 101% at fortification level 50 mg/L	11% at 10 mg/L and 0.9 % at 50 mg/L	0.2 mg/L	[redacted] (2013)

	amount of formic acid. The increase in NADH is measured by means of its light absorbance at 334, 340 or 365 nm. The molar extinction coefficient is large at 340 nm [ϵ= 6.3 L/(mmol x c)], i.e. the method is most sensitive at this wavelength. The extinction coefficient allows to calculate the formate concentration from the absorbance difference at the start and at the end of the reaction, which is a common method in biochemical laboratories. Photometric measurements provide the basis for the majority of quantitative methods in biochemistry and are related to the amount of light absorbed								

Additional remarks:

According to the guidance on residue analysis in soil “The LOQ must be below the PNEC water if technically possible”. In the present case it was not technically possible to achieve an LOQ below 5 mg/L.

For drinking water it is suggested that the stringent limit and corresponding analytical LOQ of 0.1µg/L for bioicides should not be relevant for formic acid. Formic acid is a naturally occurring substance, which is expected to be present in drinking water from many other, also natural sources other than only via biocide use

Methods analysis for body fluids: Body fluids was not validated as according to the guidance such method is not necessary for substances that are not toxic or very toxic (systemic toxicity)

7 EFFICACY

Products containing FORMIC ACID are intended to be used as broad spectrum drinking water disinfectants (**PT5**) for the consumption by animals against bacteria (including spore-forming bacteria), yeasts, fungi and viruses.

The product is intended to be used for animal drinking water disinfection via automated supply systems. The biocidal product is supplied in containers which are opened prior to the addition of the dosing equipment. The drinking water is treated on a daily basis.

The product is then automatically dosed into the drinking water supply system at the appropriate concentration and the treated water is subsequently supplied to the feeders within the animal accommodation.

In the context of a decision on the approval of FORMIC ACID for PT5 uses, in order to assess the microbicidal activity of FORMIC ACID-based products, the Applicants have submitted 13 documents :

- Among them, 4 documents are scientific papers with reliability 3-4. Due to lack of critical information or to data so succinctly reported, these documents are not robust enough to state efficacious concentrations usable to perform the risk assessment. Information from these documents is not taken into account and is not reported into the table below.

- Among the remaining documents, we could find :

- Three reports from efficacy tests performed according to EN standards (EN 1657, EN 14349, EN 13697), with reliability 3 due to lack of some raw data (in validation test results for N_v, A, B and C values : only one V_c value reported). Then, these results are not taken into account and are not reported into the table below.

- Six reports from efficacy tests more recently performed according to EN standards (EN 1276, EN 1650, EN 1656, EN14349, EN 13697, EN 13623) under GLP conditions :
These 6 efficacy tests are summarised into the table below.
The results from the efficacy tests performed according to EN phase 2/Step 1 standards (suspension tests – i.e. EN 1276, EN 1650, EN 1656 and EN 13623) are taken into account to support and PT5 claims to state efficacious concentrations (for PT5 intended uses) usable to perform the risk assessment.
The results from the efficacy tests performed according to EN phase 2/Step 2 standards (surface tests – i.e. EN 13697 and EN14349) are reported for information. As the Applicant took the trouble to perform such tests, the RMS is of the opinion to keep them in this CAR.

7.1 EFFICACY

<table>
<tr><th colspan="8">Experimental data on the efficacy of the biocidal product against target organism(s)</th></tr>
<tr><th>Function</th><th>Field of use envisaged</th><th>Test substance</th><th>Test organism(s)</th><th>Test method</th><th>Test system /concentrations applied / exposure time</th><th>Test results: effects</th><th>Reference</th></tr>
<tr>
<td>Bactericide
PT5</td>
<td>Disinfection of Drinking Water for the consumption by animals</td>
<td>FENNOPUR® MH 85 85,9% Formic Acid
(Certificate of analysis provided within the efficacy test report)

pH = 1.73 at 5% dilution</td>
<td>Enterococcus hirae
E.coli
Pseudomonas aeruginosa
Staphylococcus aureus</td>
<td>EN 1276</td>
<td><u>Test concentrations :</u>
5% (pH = 1.73) - 1% (pH = 2.21) - 0,2% (pH = 2.73)

<u>Contact time :</u>
5 min

<u>Test T°C :</u>
+20°C ±1°C

<u>I.S. :</u> 0.03% BSA (Clean)</td>
<td><table>
<tr><td colspan="4">Product : FENNOPUR® MH 85
Contact time : 5 min
Interfering substance : 0.03% BSA (clean)
Test temperature : +20°C ±+1°C</td></tr>
<tr><th>Test Concentration (%)
Test Strain</th><th>5.00</th><th>1.00</th><th>0.20</th></tr>
<tr><td>S. aureus</td><td>5.46</td><td>4.09</td><td>4.09</td></tr>
<tr><td>P. aeruginosa</td><td>5.14</td><td>5.14</td><td>3.77</td></tr>
<tr><td>E. coli</td><td>5.10</td><td>5.10</td><td>3.73</td></tr>
<tr><td>E. hirae</td><td>5.14</td><td>3.77</td><td>3.77</td></tr>
</table>
At +20°C, in suspension under CLEAN conditions (0.30% BSA), the test-product FENNOPUR® MH 85 is bactericidal in 5 min at 5% (4.295% FORMIC ACID)</td>
<td>Doc. IV
KT-BPR-6.7_01
“[redacted] (2016a)”

“Suspension bactericidal effectiveness on FENNOPUR MH85 in clean conditions”

Considered as supportive information, since tests not usable to demonstrate efficacy due to too high concentrations.</td>
</tr>
<tr>
<td>Bactericide
PT5</td>
<td>Disinfection of Drinking Water for the</td>
<td>FENNOPUR® MH 85 85,9% Formic Acid</td>
<td>Enterococcus hirae
Proteus vulgaris
Pseudomonas aeruginosa</td>
<td>EN 1656</td>
<td><u>Test concentrations :</u>
5% (pH = 1.73) - 1% (pH = 2.22) -</td>
<td>Product : FENNOPUR® MH 85
Contact time : 30 min
Interfering substance : 0.3% BSA (clean)
Test temperature : +10°C ±+1°C</td>
<td>Doc. IV
KT-BPR-6.7_05</td>
</tr>
</table>

	consumption by animals		*Staphylococcus aureus*		0,2% (pH = 2.74) *Contact time :* 30 min *Test T°C :* +10°C ±1°C *I.S. :* 0.3% BSA (simulating low-level soiling)	**Test Concentration (%) / Test Strain** – **5.00** / **1.00** / **0.20**: ***S. aureus***: 5.34 / 5.03 / 3.97 ***P. aeruginosa***: 5.27 / 5.27 / 4.16 ***Proteus vulgaris***: 5.39 / 5.39 / 4.75 ***E. hirae***: 5.52 / 4.15 / 4.15 At +10°C, in suspension under CLEAN conditions (0.30% BSA), the test-product ***FENNOPUR® MH 85*** is bactericidal in 30 min at 5% (4.295% FORMIC ACID)	"[redacted] (2016e)" "Suspension bactericidal effectiveness for veterinary area on ***FENNOPUR MH85***" Considered as **supportive information**, since tests not usable to demonstrate efficacy due to too high concentrations.
Bactericide PT5	Disinfection of Drinking Water for the consumption by animals	***FENNOPUR® MH 85*** 85,9% Formic Acid (Certificate of analysis provided within the efficacy test report)	*Legionella pneumophila*	EN 13623	*Test concentrations :* 5% - 1% - 0,2% *Contact time :* 60 min *Test T°C :* +20°C ±1°C *I.S. :* 0.0005% yeast extract	**Product : *FENNOPUR® MH 85*** **Contact time :** 60 min **Interfering substance :** 0.0005% yeast extract **Test temperature :** +20°C ±+1°C **Test Concentration (%) / Test Strain** – **5.00** / **1.00** / **0.20**: *Legionella pneumophila*: 5.52 / 5.52 / 5.52 At +20°C, in suspension under CLEAN conditions (0.30% BSA), the test-product ***FENNOPUR® MH 85*** is active against *Legionella pneumophila* in 60 min at +20°C at 0.2% (0.1718% FORMIC ACID).	Doc. IV KT-BPR-6.7_02 "[redacted] (2016b)" "Suspension bactericidal effectiveness against *Legionella* on ***FENNOPUR MH85***" **Key study R.1**

<table>
<tr>
<td>Yeasticidal
PT5</td>
<td>Disinfection of Drinking Water for the consumption by animals</td>
<td>FENNOPUR® MH 85 85,9% Formic Acid

(Certificate of analysis provided within the efficacy test report)

pH = 1.73 at 5% dilution</td>
<td>Candida albicans</td>
<td>EN 1650</td>
<td><u>Test concentrations :</u>
5% (pH = 1.73) - 1% (pH = 2.21) - 0,2% (pH = 2.74)

<u>Contact time :</u>
15 min

<u>Test T°C :</u>
+20°C ±1°C

<u>I.S. :</u> 0.03% BSA (Clean)</td>
<td>
<table>
<tr><td colspan="4">Product : FENNOPUR® MH 85
Contact time : 15 min
Interfering substance : 0.03% BSA (clean)
Test temperature : +20°C ±+1°C</td></tr>
<tr><td>Test Concentration (%)
Test Strain</td><td>5.00</td><td>1.00</td><td>0.20</td></tr>
<tr><td>Candida albicans</td><td>4.17</td><td>2.80</td><td>2.80</td></tr>
</table>

At +20°C, in suspension under CLEAN conditions (0.30% BSA), the test-product FENNOPUR® MH 85 is yeasticidal in 15 min at 5% (4.295% FORMIC ACID)</td>
<td>Doc. IV
KT-BPR-6.7_03
“[redacted] (2016c)”

“Suspension yeasticidal effectiveness on FENNOPUR MH85 in clean conditions”

Considered as supportive information, since tests not usable to demonstrate efficacy due to too high concentrations.</td>
</tr>
<tr>
<td>Bactericide
PT5</td>
<td>Disinfection of Drinking Water for the consumption by animals</td>
<td>FENNOPUR® MH 85 85,9% Formic Acid
(Certificate of analysis provided within the efficacy test report)</td>
<td>Enterococcus hirae
E.coli
Pseudomonas aeruginosa
Staphylococcus aureus</td>
<td>EN 13697</td>
<td><u>Test concentrations :</u>
5% (pH = 1.74) - 1% (pH = 2.21) - 0,2% (pH = 2.74)

<u>Contact time :</u>
5 min

<u>Test T°C :</u>
+20°C ±1°C</td>
<td>
<table>
<tr><td colspan="4">Product : FENNOPUR® MH 85
Contact time : 5 min
Interfering substance : 0.03% BSA (clean)
Test temperature : +20°C ±+1°C</td></tr>
<tr><td>Test Concentration (%)
Test Strain</td><td>5.00</td><td>1.00</td><td>0.20</td></tr>
<tr><td>S. aureus</td><td>6.42</td><td>3.13</td><td>1.00</td></tr>
<tr><td>P. aeruginosa</td><td>6.46</td><td>6.82</td><td>2.92</td></tr>
<tr><td>E. coli</td><td>6.53</td><td>6.53</td><td>3.29</td></tr>
<tr><td>E. hirae</td><td>6.32</td><td>1.33</td><td>0.90</td></tr>
</table>

At +20°C, on hard/non-porous surfaces under CLEAN conditions (0.30% BSA),</td>
<td>Doc. IV
KT-BPR-6.7_04
“[redacted] (2016d)”

“Surface bactericidal effectiveness on FENNOPUR MH85 in clean conditions”</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><u>I.S. :</u> 0.03% BSA (Clean)</td>
<td>the test-product FENNOPUR® MH 85 is bactericidal in 5 min at 5% (4.295% FORMIC ACID)</td>
<td>Considered as supportive information, since test not relevant for PT5.</td>
</tr>
<tr>
<td>Bactericide
PT5</td>
<td>Disinfection of Drinking Water for the consumption by animals</td>
<td>FENNOPUR® MH 85 85,9% Formic Acid

(Certificate of analysis provided within the efficacy test report)</td>
<td>Enterococcus hirae
Proteus vulgaris
Pseudomonas aeruginosa
Staphylococcus aureus</td>
<td>EN 14349</td>
<td><u>Test concentrations :</u>
5% (pH = 1.72) - 1% (pH = 2.01) - 0,2% (pH = 2.72)

<u>Contact time :</u>
30 min

<u>Test T°C :</u>
+10°C ±1°C

<u>I.S. :</u> 0.3% BSA (simulating low-level soiling)</td>
<td>
<table>
<tr><td colspan="4">Product : FENNOPUR® MH 85 Contact time : 30 min
Interfering substance : 0.3% BSA (clean)
Test temperature : +10°C ±+1°C</td></tr>
<tr><td>Test Concentration (%)
Test Strain</td><td>5.00</td><td>1.00</td><td>0.20</td></tr>
<tr><td>S. aureus</td><td>4.44</td><td>4.44</td><td>1.07</td></tr>
<tr><td>P. aeruginosa</td><td>4.33</td><td>4.33</td><td>0.96</td></tr>
<tr><td>Proteus vulgaris</td><td>4.19</td><td>4.19</td><td>2.77</td></tr>
<tr><td>E. hirae</td><td>4.25</td><td>1.40</td><td>0.88</td></tr>
</table>

At +10°C, on hard/non-porous surfaces under CLEAN conditions (0.30% BSA), the test-product FENNOPUR® MH 85 is bactericidal in 30 min at 5% (4.295% FORMIC ACID)</td>
<td>Doc. IV
KT-BPR-6.7_06
“[redacted] (2016f)”

“Surface bactericidal activity for the veterinary area on FENNOPUR MH85”

Considered as supportive information, since test not relevant for PT5.</td>
</tr>
</table>

According to the section #4.2.2.1 (p.28) of the BPR guidance (Vol. II - Parts B+C – 2018), an extensive data package and evaluation is not required at this approval stage.

1) The APP has provided several efficacy tests, however EN 1276, EN 1656 and EN 1650 test results should be considered only as supportive information since these tests are not usable to demonstrate efficacy due to too high concentrations :
Indeed, as already observed for other Active Substances used for drinking water disinfection, the 5% effective dose validated from basic P2S1 tests (EN standards) seems to be unrealistically high for products dosed continuously in water. In addition, according to the ECHA EFF guidance, a product for animal water disinfection should be at least proven effective against bacteria via adapted P2S1 (with "clean" DOC soiling) and SIM/field tests.

For information ONLY, these tests showed that the product ***FENNOPUR® MH 85*** is bactericidal in suspension at 5% (4.295% FORMIC ACID) at +20°C in clean conditions (0.03% BSA) in 5 min according to the EN 1276 standard and at +10°C in clean conditions (0.3% BSA) in 30 min according to the EN 1656 standard. Furthermore, the product ***FENNOPUR® MH 85*** is yeasticidal in suspension at 5 % (4.295% FORMIC ACID) at +20°C in clean conditions (0.03% BSA) in 15 min according to the EN 1650 standard.

Furthermore, the EN 13697 and EN 14349 test results should also be considered only as supportive information since these tests are not relevant for PT5.

2) Taking into account the results of the EN 13623 efficacy test provided by the Applicant, the product ***FENNOPUR® MH 85*** is active against *Legionella pneumophila* in suspension at 0.2% (0.1718% FORMIC ACID) at +20°C in 60 min contact time.
Via this test, innate efficacy is duly demonstrated and is compatible with the 0.4% FA value proposed as upper limit for animals in the EFSA document (published in 2015) "*Scientific Opinion on the safety and efficacy of formic acid, ammonium formate and sodium formate as feed hygiene agents for all animal species*".
As the consequence, the effective concentration validated through the EN 13623 efficacy test has been considered as acceptable to be used for the Risk Assessment.

7.2 MODE OF ACTION

The biocidal activity of Formic Acid, i.e. acidulant action and corrosion which causes enzyme denaturation and inhibition, cellular structure disruption, and impairment of cellular metabolic pathways.

This mode of action is considered to depend on the low pH-value. Secondly, formic acid does inhibit cytochrome C oxidase and thus impairs cellular energy supply. Organisms and tissues with a high energy demand are specifically susceptible :

1. Acidulant : acidification of cytoplasm;
2. Inhibitor for decarboxylases and haemin enzymes such as catalase;
3. Organic acids in general may disrupt the proton-motive force, as well as inhibit substrate transport, energy-yielding processes and macromolecular synthesis.

Acidulant action is responsible for formic acid being most effective at lower pH values (below 3.5), but enzyme inhibition and other modes also provide some antimicrobial action at higher pH values. Enzyme inhibition is less significant in the control of fungi; therefore, higher concentrations of formic acid are needed to control fungi. The activity of formic acid against some viruses is presumably explained by the action of acid in denaturing polypeptide chains.

7.3 RESISTANCE

There is no adaptation to cope with acidic pH values or denaturated proteins, nor is there a mechanism known to exist that a sub-lethal energy supply, due to an incomplete cytochrome C oxidase inhibition, would lead to undesired side-effects or resistance against this inhibitor.

No incidence of resistance to formic acid has been recorded until now.

7.4 CONCLUSION ON EFFICACY

In conclusion, the data submitted are sufficient to demonstrate a very good efficacy of FORMIC ACID in suspension against bacteria (with the exception of spore-forming bacteria) and yeasts for **PT5** intended uses, are therefore sufficient for the inclusion.

The data submitted are robust enough to state efficacious concentrations usable to perform the risk assessment :

The product ***FENNOPUR® MH 85*** (based on 85,9% Formic Acid), intended to be used for animal drinking water disinfection, is active *Legionella pneumophila*) in suspension at 0.2% (pH = 1.85; 0.1718 % FORMIC ACID) at +20°C in 60 min according to the EN 13623 standard.

At the Product Authorisation Stage, additional efficacy tests (i.e. simulated-uses tests) may be needed according to the requirements mentioned in the PT5 draft section of the Eff-guidance, in revision by the time this CAR was written.

8 HUMAN EXPOSURE ASSESSMENT

Default values and exposure models were taken from the document 'Biocides Human Health Exposure Methodology' and Recommendation no. 6 of the BPC Ad hoc Working Group on Human Exposure (from this point forward referred to as 'Recommendation 6'), unless otherwise stated.

Intended uses

The biocidal product may be used to disinfect water which will be used as drinking water for animal consumption. The product is automatically dosed into the drinking water supply system to the animal accommodation on either a continuous or intermittent basis.

The information pertaining to the intended product concentrations and the users is summarized below. Detailed descriptions are contained in the relevant sections on exposure (8.3 – 8.9).

Table 8.1 Identification of the product type

Product type	**Field of use envisaged**	**Users**	**Maximum concentration at which a.s. will be used**
PT 5	Disinfection of drinking water for animal consumption	Professionals	2000 mg/L (0.2 %) as FENNOPUR® MH 85 or Formic Acid 85% 1700 mg/L as formic acid Note that at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 efficacy was proven for its bactericidal and yeasticidal properties.* Efficacy against *Legionella pneumophila* was shown at 0.2% FENNOPUR® MH 85 (0.17 % FORMIC ACID) RA will take into consideration both 5% and 0.17% FA in drinking water.

*The World Health Organisation Guidelines for Drinking Water Quality, First Addendum to the Fourth Edition (WHO, 2017) do not set a guideline limit for concentrations of formic acid or formate in drinking water. The maximum percentage of Formic Acid which is considered safe in animal water is 0.4% (EFSA, 2014; FA_BPR_Ann_II_8_16_02).

8.1 IDENTIFICATION OF MAIN PATHS OF HUMAN EXPOSURE TOWARDS ACTIVE SUBSTANCE FROM ITS USE IN BIOCIDAL PRODUCT

Summary table: relevant paths of human exposure							
Exposure path	**Primary (direct) exposure**			**Secondary (indirect) exposure**			
	Industrial use	**Professional use**	**Non-professional use**	**Industrial use**	**Professional use**	**General public**	**Via food**
Inhalation	n.a.	Yes	n.a.	n.a.	Yes	no	no
Dermal	n.a.	Yes	n.a.	n.a.	yes	no	no
Oral	n.a.	No	n.a.	n.a.	no	no	negligible

The assessment of exposure towards formic acid as active substance in drinking water disinfectants is based on information provided by the applicant. Possible gaps are bridged by the Rapporteur using reasonable assumptions. For lack of measurement data, exposure models are applied.

For Product Type 5, the biocidal product is handled and used only in automated supply systems. Clean waste water is recirculated back through the water supply system. Fouled water will be disposed of in manure/slurry storage.

The biocidal product is supplied in 30, 200 or 1000 L containers which are opened prior to the addition of the dosing equipment. The product is then automatically dosed into the drinking water supply system at the appropriate concentration and the treated water is subsequently supplied to the feeders within the animal accommodation.

Professionals will be exposed daily to the biocidal product during changing of the product containers and from contact with treated drinking water. The main routes of exposure for professional users will be the dermal and inhalation routes. Operators should wear PPE (overall, gloves, boots and glasses) as the biocidal product is labelled as corrosive.

Indirect exposure to the public may occur from eating products from animals exposed via drinking treated water; however this exposure may be considered minimal.

8.2 LIST OF SCENARIOS

Summary table: scenarios			
Scenario number	**Scenario (e.g. mixing/ loading)**	**Primary or secondary exposure Description of scenario**	**Exposed group (e.g. professionals, non-professionals, bystanders)**
1.	Mixing and loading: charging Formic Acid 85% into animal drinking water systems	1a.primary exposure during mixing and loading by professionals: charging of system	professionals
		1b.application: automated system	
		1c. disposal of containers, cleaning of equipment	
2.	Secondary exposure	Dermal and inhalation exposure to disinfected drinking water for animals	professionals

Use pattern

For Product Type 5, the biocidal product is handled and used only in automated supply systems. In principle, workers do not directly handle the biocidal product.

Application

The biocidal product is supplied in 30, 200 or 1000 L containers which are opened prior to the addition of the dosing equipment. The product is then automatically dosed into the drinking water supply system at the appropriate concentration and the treated water is subsequently supplied to the feeders within the animal accommodation.

Clean waste water is recirculated back through the water supply system. Fouled water will be disposed of in manure/slurry storage. Professionals will be exposed to the biocidal product during changing of the product containers. Dermal and inhalation contact with disinfected drinking water is also considered. The biocidal product is stored in closed 30, 200 or 1000 L containers, which are opened prior to placing the applicator into the container. Empty containers are recycled after use without cleaning.

The maximum duration of exposure to the neat product during changing of containers is 10 minutes every day. Exposure to treated water will be intermittent during the farmer’s working day.

The main routes of exposure for professional users will be the dermal and inhalation routes. Operators should wear PPE (overall, gloves, boots, and goggles) as the biocidal product is labelled as corrosive. In addition, farm workers have to comply with various regulations to prevent the spread of various infections and diseases amongst different animal populations. These include the use of protective equipment, cleaning routines and good hygiene practices that will reduce worker exposure.

Mixing and loading model 7 (corrected), page 142 of the 2002 part 2 version of the Technical Notes for Guidance on Human Exposure to Biocidal Products has been used as the most appropriate scenario for application of a liquid to a system (Mixing and loading Model 7 for pouring and pumping liquids).

Dermal contact with disinfected water has been assessed according to HEEG Opinion 16 (Biocidal products: model for dipping of hands/forearms in a diluted solution). For exposure via inhalation, as no harmonized scenario for exposure to treated drinking water is available, a preliminary risk assessment has been added (appendix II) using a ConsexpoWeb evaporation scenario.

The applicant suggests treatment of drinking water for animal consumption with formic acid concentrations of 0.17%. Note that at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 efficacy was proven for its bactericidal and yeasticidal properties; efficacy against *Legionella pneumophila* was shown at 0.17% FA. Therefore the risk assessment will take into consideration both 5% and 0.17% FA in drinking water.

8.3 INDUSTRIAL EXPOSURE

This section has not been evaluated by the CA-BE because the production/formulation process of the active substance is outside the scope of the Biocidal Products Regulation (EU) No 528/2012.

For the formulation of the biocidal product the liquid raw materials are formic acid and ammonia. Formic acid and ammonia come from plants via tanks, from where it is fed to the production process. The production plant is controlled using a validated process control system. All of the process controllers who are working with the Formic Acid 85% process should be educated properly to their tasks.

The only source of exposure to industrial workers at the industrial plant is likely to be from the quality control sampling stage. However, exposure estimates for industrial workers during these stages have not been calculated as they are already addressed by other legislation. Therefore, in accordance with the Commission Document agreed at the 22nd CA meeting in September 2006, detailed information on exposure associated with the manufacturing process is not required for biocidal product risk assessment.

The transfer of the precursors into the product production tank and the manufacture of the biocidal product is an automated system. Therefore, inhalation and dermal exposure could only occur during quality control sampling stages. Nevertheless, workers are required to wear full PPE (PVC gloves, goggles, boots, coverall).

8.4 *PROFESSIONAL EXPOSURE*

The biocidal product, Formic Acid 85% or ***FENNOPUR® MH 85***, available for professional operators is a concentrated product containing 85% formic acid to be further diluted to the recommended use concentration of 0.2% (or 0.17% pure formic acid) in drinking water intended for animal consumption. Professionals use products on a prolonged basis and are exposed daily via mixing and loading, and intermittently to disinfected water.

General default values:

parameter	***Default value***
Body weight adult (prof/consumer)	60 kg
Respiration rate adult	1.25 m^3/h
Oral absorption	100%
Dermal absorption	100%
Inhalation absorption	100%

PRIMARY EXPOSURE

8.4.1 Scenario 1: Mixing and loading: charging Formic Acid 85% into animal drinking water systems

Disinfection solution applied via automated pumping; automatic circulation of the disinfection solution to automated supply systems.

This scenario involves the following subscenarios:

1a. Charging (mixing and loading) by professionals to the drinking water system

1b. application of the in use solution: automated process

1c. disposal of containers, cleaning of equipment

For this exposure assessment, the daily disinfection of drinking water for 1 stable of broiler chickens was assumed.

Description of Scenario 1a		
Task, exposure model and parameters: *1a. Charging (mixing and loading) by professionals to the drinking water system* Automated loading and dilution of containers. Transfer, filling and emptying liquids. Concentration of a.s. in biocidal product: 85% Density of product: ca. 1200 g/L(1) Frequency: once daily Application duration: 5 min (2) Duration of exposure: 10 min (2) Ventilation rate: 10/h (3) Room volume: 24 m^3 (3) Release area: 100 cm^2 (3) Amount of biocidal product handled: 15 kg (0.17% FA in-use dilution) or 350 kg (5% BP in in-use dilution) (4) Exposed worker: professional Protective equipment: coveralls, gloves, boots and face protection, half mask vapour filter (6) Model: Mixing and loading model 7 for pouring and pumping liquids (corrected) (dermal only), page 142 of the 2002 part 2 version of TNsG; inhalation of vapour: ConsexpoWeb (v 1.0.6), evaporation, area of release constant		
	Parameters[1]	**Value**
Tier 1	Indicative dermal exposure (without gloves)	101 mg/min
Tier 2	Dermal exposure (inside gloves)	1.01 mg/min
	Protection factor respirator	90%

(1) Relative density 1.195 @ 20°C

(2) exposure duration: M&L model 7 TNsG 2002 ; application duration : it is assumed that the Formic Acid 85% container is open only during half of the exposure time. Also, the M&L phase is considered similar to the M&L for hoof bath disinfection (scenario 12 of Recomm. 6, v3).

(3) ventilation rate, room volume and release area: values proposed in scenario 12 of Recomm. 6, v3 (hoof bath disinfection, mixing and loading of volatile compounds) were used.

(4) amount of BP handled:

0.17% FA in-use dilution: 20000 broiler chickens/stable x 0.25L/d = 5000L water to be treated. Final concentration in water: 0.2% of BP or a dilution of 1/425 or approx. 12L BP in 5000L water. Density of BP = 1200 g/L so approx. 15 kg BP is handled to disinfect 5000L water.

5% FA in-use dilution: 20000 broiler chickens/stable x 0.25L/d = 5000L water to be treated. Final concentration in water: 5% of BP or a dilution of 1/17 or approx. 295L BP in 5000L water. Density of BP = 1200 g/L so approx. 350 kg BP is handled to disinfect 5000L water.

(6) See applicant's SDS for 85% FA, section 8 Exposure controls/personal protection

<u>Calculations for Scenario 1a</u>

*At the time of writing, only for in-use concentrations of >5% **FENNOPUR® MH 85** (85.9% FA) efficacy was proven for its bactericidal and yeasticidal properties. Efficacy against Legionella pneumophila was shown at 0.17% FA. The RA will take into consideration both 5% and 0.17% FA in drinking water.*

Model: Mixing and loading model 7 (corrected), pouring and pumping liquids

For this model, the amount of concentrate handled does not affect the outcome.

Tier 1:

85% FA, dermal exposure:

10 min * 101 mg/min * 0.85 /60 kg = 14.308 mg/kg bw per shift

Tier 2:

85% FA, dermal exposure:

10 min * 1.01 mg/min * 0.85 /60 kg = 0.143 mg/kg bw per shift

Model: ConsexpoWeb, evaporation, area of release constant

Exposure to vapour:

For full ConsExpo reports see Appendix II

The amount of concentrate handled does not affect the concentration of FA in air during M&L.

Inhalation

Tier 1:

	no RPE, 85% FA
Mean event concentration	8.1 mg/m³
Peak concentration (TWA 15 min)	8.1 mg/m³
Year average concentration	5.6×10^{-2} mg/m³

External event dose	2.8 x 10^{-2} mg/kg bw
Internal event dose	2.8 x 10^{-2} mg/kg bw
Internal year average dose	2.8 x 10^{-2} mg/kg bw/day

Tier 2:

	RPE, 85% FA
Mean event concentration	8.1 mg/m³
(Taking into account the protection factor for half mask , estimated inhalation exposure will be 10 times lower)	0.81 mg/m³
Peak concentration (TWA 15 min)	
Year average concentration	5.6 x 10^{-2} mg/m³
External event dose	2.8 x 10^{-2} mg/kg bw
Internal event dose	2.8 x 10^{-3} mg/kg bw
Internal year average dose	2.8 x 10^{-3} mg/kg bw/day

Description of Scenario 1b
Tasks, exposure models and parameters: *<u>1b. application: automated process</u>* application of the in use solution: automated process; liquids dispersed by system Concentration of a.s. in treated water: 0.17% / 5% Density of product: ca. 1000 g/L[(1)] Frequency: daily Duration of exposure: N.A. Application rate: N.A., automated process Exposed worker: professional Protective equipment: N.A., automated process Model: N.A., automated process Therefore no calculations are provided for scenario 1b application.

[(1)] aqueous solution

Description of Scenario 1c
Tasks, exposure models and parameters: *<u>1c. disposal of containers, cleaning of equipment</u>* Disposal of emptied containers,cleaning of equipment: no exposure is assumed during this task. Empty containers are recycled after use without cleaning. Concentration of a.s. in biocidal product: 85% Density of product: ca. 1200 g/L Frequency: daily Duration of exposure: N.A. Exposed worker: professional Protective equipment: coveralls, boots, gloves and face protection Model: not relevant: no additional exposure is assumed; no calculations are provided for scenario 1c.

<u>Further information and considerations on scenario 1</u>

Exposure is assumed only during the mixing and loading phase.

Personal Protective Equipment (PPE) incorporating coveralls, boots, gloves and face protection is assumed during Mixing & Loading and will significantly reduce exposure via the dermal route. As a tier 2, the indicative dermal exposure values of M&L model 7 incorporate exposure inside gloves. Despite the short exposure time considered for M&L, the use of RPE was considered due to the acridity of the formic acid fumes released. For Tier 2 risk characterisation the inhalation exposure will be reduced (10x) in line with the BHHEM guide for use of a half mask with vapour filter. A ventilation rate of 10/h was used; we refer to the value proposed in scenario 12 of Recomm. 6, v3 (hoof bath disinfection, mixing and loading of volatile compounds).

No handling of the biocidal product takes place during the actual BP application. Also, during disposal of emptied containers, no exposure is assumed.

In order to take into account the volatility of formic acid, exposure to vapour during mixing and loading was calculated with the ConsExpo – exposure to vapour – evaporation scenario. Refinements for this exposure estimate can be used at product authorisation. In any case, exposure to vapour should be reduced by ventilation and other appropriate risk mitigation measures.

For a graphic representation of the Formic Acid air concentration during mixing and loading, see Appendix II graph II.1.

(Semi-)quantitative assessment for oral, dermal and inhalation routes

Results table exposure to PT5 mixing and loading						
Exposure subscenario	**Tier/PPE**	**Estimated inhalation uptake (mg/kg bw/d)**	**Estimated dermal uptake (mg/kg bw/d)**	**Estimated total uptake (mg/kg bw/d)**	**Local dermal exposure (conc., %)**	**Local inhalation exposure (mg/m3)**
1a M&L 85%	1/none	2.8×10^{-2}	14.308	14.336	85	8.1
	2/ coveralls, boots, gloves and face protection; RPE APF10	2.8×10^{-3}	0.143	0.1458	85	0.81
1b application	N.A.	-	-	-	-	-
1c Cleaning & disposal	N.A.	-	-	-	-	-

Qualitative local assessment for dermal route

As formic acid is corrosive at or above a 10% dilution, a qualitative risk characterisation is needed for local dermal exposure. This RC is triggered for those BP classified for local effects. In BP where formic acid is present at concentrations that do not trigger classification of the product according to the CLP criteria, RC for local effects is not required.

The concentrate (85% FA) for PT5 professional use is classified as corrosive to the skin, cat. 1B. This classification triggers a qualitative local assessment for the dermal route. We refer to section 12.4.2 for relevant RMM end PPE and the conclusion on the acceptability of the risk.

SECONDARY EXPOSURE

8.4.2 Scenario 2: dermal and inhalation exposure to treated drinking water

Professionals will be exposed daily to the biocidal product via dermal contact with treated drinking water. It is assumed that only the hands are exposed. Dermal contact with disinfected water has been assessed according to HEEG Opinion 16 (Biocidal products: model for dipping of hands/forearms in a diluted solution).

Inhalation exposure to disinfected water is also possible. For instance, in a chicken housing, a farmer could be exposed to formic acid evaporating from the drinking system. However, the inhalation could be considered as very low to negligible for the following reasons:

-the ventilation rate in chicken housing is relatively high during large parts of the year;

-the Formic Acid in disinfected water is strongly diluted *NOTE: provided that at product authorisation level, the efficacy of the BP can be shown at lower concentrations in drinking water*;

-the product is intended for automated supply systems;

-the area from which Formic Acid can evaporate in these automated supply systems is limited.

Therefore we conclude that there is no need to take a scenario for inhalation of Formic Acid into consideration for secondary exposure.

However, we did perform a preliminary risk assessment for this type of exposure. As there is no harmonized scenario available, we refer to appendix II for details and results. This scenario is to be considered worst-case and giving only an indication of maximum exposure.

Dermal exposure:

Description of Scenario 2		
Scenario: secondary exposure, professional, dermal contact with disinfected water Dipping hands in treated water Exposed worker: professional Frequency: daily Hand contact surface area: 820 cm^2 (palms + backs)(1) Layer thickness: 0.01 cm(2) Dermal absorption: 100% Concentration of a.s.: 0.17% - 5% FA		
	Parameters[1]	Value
Tier 1	No gloves, penetration factor	100%
Tier 2[2]	with gloves, penetration factor	10%

(1) Recommendation 14, Default human factor values for use in exposure assessments for biocidal products
(2) HEEG Opinion 16, Biocidal products: model for dipping of hands/forearms in a diluted solution

Calculations for Scenario 2, dermal exposure

Dermal exposure is possible via dipping of hands in water treated for animal consumption.

ECHA's 'Manual of Instructions to eCAs for evaluating active substances used in disinfectants' proposes to use generic exposure models to calculate secondary exposure. We will be using the 'film thickness' approach as described in this manual. We opt to use a layer thickness of 0.01 cm for exposure of the palms of both hands.

According to Recommendation 14 on 'Default human factor values for use in exposure assessments for biocidal products', the total surface of an adult's hands is 820 cm^2. Using a layer thickness of 0.01 cm, dermal exposure to the biocidal product would amount to 8.2 ml or, assuming a density of 1g/ml, 8.2 g. Considering the 60 kg default body weight for adults, a dermal absorption of 100% and an in-use concentration of 0.17% formic acid, dermal exposure to the a.s. is 0.232 mg/kg bw/d when no gloves are worn. Wearing gloves would result in a dermal exposure of 0.0232 mg/kg bw/d.

Tier 1, no gloves:

8200 mg x 0.0017 x 1/60kg bw = 0.232 mg/kg bw/d

Tier 2, gloves:

8200 mg x 0.0017 x 1 x 0.1/60kg bw = 0.0232 mg/kg bw/d

Considering the 60 kg default body weight for adults, a dermal absorption of 100% and an in-use concentration of 5% formic acid, dermal exposure to the a.s. is 6.833 mg/kg bw/d when no gloves are worn. Wearing gloves would result in a dermal exposure of 0.683 mg/kg bw/d.

Tier 1, no gloves:

8200 mg x 0.05 x 1/60kg bw = 6.833 mg/kg bw/d

Tier 2, gloves:

8200 mg x 0.05 x 1 x 0.1/60kg bw = 0.683 mg/kg bw/d

Inhalation exposure:

Can be considered as very low to negligible*, but no validated scenario is available. For a preliminary risk assessment for this type of exposure, see appendix II.

**NOTE: provided that at product authorisation level, the efficacy of the BP can be shown at lower concentrations in drinking water*

(Semi-)quantitative assessment for oral, dermal and inhalation routes

Results table exposure to PT5 contact with disinfected water							
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated oral uptake**	**Estimated total uptake (mg/kg bw/d)**	**Local dermal exposure (conc., %)**	**Local inhalation exposure (mg/m3)**
Scenario 2, 0.17%	1/ none	Very low to negligible	0.232 mg/kg bw/d	N.A.	0.232 mg/kg bw/d	0.17%	Very low to negligible
	2/ gloves	Very low to negligible	0.0232 mg/kg bw/d	N.A.	0.0232 mg/kg bw/d	0.17%	Very low to negligible
Scenario 2, 5%	1/ none	Preliminary RA: up to 1.3 mg/kg bw/d @ low ventilation	6.833 mg/kg bw/d	N.A.	Up to 8.2 mg/kg bw/d	5%	Preliminary RA: up to 10 mg/m^3 @ low ventilation
	2/ gloves	Preliminary RA: up to 1.3 mg/kg bw/d @ low ventilation	0.683 mg/kg bw/d	N.A.	Up to 2 mg/kg bw/d	5%	Preliminary RA: up to 10 mg/m^3 @ low ventilation

Qualitative local assessment for dermal route

At 0.17% FA, the in-use dilution does not trigger a qualitative local risk assessment. At 5% FA, the in-use dilution is irritant to skin and eye and does trigger a qualitative local risk assessment. We refer to section 12.4.2 for relevant RMM end PPE and the conclusion on the acceptability of the risk.

8.4.3 Summary tables: systemic and local exposure from professional uses

Summary table: PT5 systemic exposure from professional uses			
Tier/PPE	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated total uptake**
Scenario 1, mixing and loading			
1/none	2.8×10^{-2} mg/kg bw/d	14.308 mg/kg bw/d	14.336 mg/kg bw/d
2/ coveralls, boots, gloves and face protection; RPE APF10	2.8×10^{-3} mg/kg bw/d	0.143 mg/kg bw/d	0.1458 mg/kg bw/d
Scenario 2, exposure to treated drinking water			
1/ 0.17% dil, PPE none	Very low to negligible	0.232 mg/kg bw/d	0.232 mg/kg bw/d
2/ 0.17% dil, gloves	Very low to negligible	0.0232 mg/kg bw/d	0.0232 mg/kg bw/d
1/ 5% dil, PPE none	Preliminary RA: up to 1.3 mg/kg bw/d @ low ventilation	6.833 mg/kg bw/d	Up to 8.2 mg/kg bw/d
2/ 5% dil, gloves	Preliminary RA: up to 1.3 mg/kg bw/d @ low ventilation	0.683 mg/kg bw/d	Up to 2 mg/kg bw/d

Summary table: PT5 local exposure from professional uses		
Tier/PPE	**Local inhalation exposure**	**Local dermal exposure**
Scenario 1, mixing and loading		
1/none	8.1 mg/m^3	85%
2/ coveralls, boots, gloves and face protection; RPE APF10	0.81 mg/m^3	85%
Scenario 2, exposure to treated drinking water		
1/0.17% dil, PPE none	Very low to negligible	0.17%
2/ 0.17% dil, gloves	Very low to negligible	0.17%
1/5% dil, PPE none	Preliminary RA: up to 10 mg/m^3 @ low ventilation	5%
2/ 5% dil, gloves	Preliminary RA: up to 10 mg/m^3 @ low ventilation	5%

8.4.4 Combined scenarios

A possible scenario combination for professionals is that the same worker connects the biocide to the automated water supply system and comes into contact with disinfected water.

For local exposure, no addition of exposure levels is performed; only the highest exposure level in air is considered relevant.

Summary table: combined systemic exposure from professional uses			
Scenarios combined	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated total uptake**
0.17% FA dil Scenarios 1+2, tier 1	2.8 x 10^{-2} mg/kg bw/d	14.540 mg/kg bw/d	14.568 mg/kg bw/d
0.17% FA dil Scenarios 1+2, tier 2	2.8 x 10^{-3} mg/kg bw/d	0.1662 mg/kg bw/d	0.169 mg/kg bw/d
5% FA dil Scenarios 1+2, tier 1	1.328 mg/kg bw/d	21.141 mg/kg bw/d	22.469 mg/kg bw/d
5% FA dil Scenarios 1+2, tier 2	1.303 mg/kg bw/d	0.826 mg/kg bw/d	2.129 mg/kg bw/d

8.5 NON-PROFESSIONAL EXPOSURE

No non-professional use of the biocidal product is foreseen.

8.6 SECONDARY EXPOSURE OF THE GENERAL PUBLIC EXCLUDING DIETARY EXPOSURE

As the biocidal product is intended for professional use and in professional premises only, there is no potential for secondary exposure of the general public.

8.7 DIETARY EXPOSURE

Livestock will be exposed to biocidal products containing formic acid, used for disinfection of drinking water. Possible routes of exposure are oral exposure and inhalation of formic acid vapours from air. Dermal contact with disinfected water is possible but will be a minor exposure route. The question arises whether these residues can enter the food chain.

Formic acid occurs naturally in animals and most plants, and is an inherent ingredient in human food. It is an intermediate in normal metabolism. Its toxicokinetic properties and its metabolism have been investigated in rat, dog, monkey, pig and humans. Formic acid and formate salts are rapidly absorbed, converted and eliminated. There is no indication for accumulation of formate. The possibility for crossing of barriers such as exposure via breastmilk is low.

Formic acid, and two of the formate salts, are approved feed additives in the EU at concentrations up to 1.2% (pigs) and 1.0% in all other species including ruminants and poultry. Approved drinking water concentration for food producing animals is 0.4%. The EFSA Panel concluded that this use would not increase the human formic acid exposure through the consumption of products obtained from the treated animals (EFSA, 2009, FA_BPR_Ann_II_8_16_01; EFSA, 2014; FA_BPR_Ann_II_8_16_02; EFSA, 2015, FA_BPR_Ann_II_8_16_03). The use and risks of feed and drinking water additives containing formic acid and formate salts did not indicate the need for any further studies.

For formic acid currently default MRLs of 0.01 mg/kg apply according to Art.18(1)(b) Reg 396/2005.

Due to its rapid turnover and unlikely accumulation, an estimation of exposure of humans to formic acid residues through diet as a consequence of animal exposure to treated drinking water is not considered here.

It is proposed that assessment of dietary risk for humans and livestock be undertaken at biocidal product authorisation.

For a tentative approach to the 'Guidance on the BPR V III HH-Assessment & Evaluation, Section 6: Guidance On Estimating Livestock Exposure to Active Substances used in Biocidal Products, see Appendix II.

In this tentative approach, it is assumed that the concentration of formic acid required to fulfil the efficacy claims made by the applicant, is below 0.4% (notably 0.17% as suggested by the applicant). However, at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 (85.9% FA) efficacy was proven for its bactericidal and yeasticidal properties; efficacy against *Legionella pneumophila* was shown at 0.17% FA. At product authorization level, the actual efficacious dose of the BP could determine whether dietary exposure needs to be assessed.

8.7.1 Information of non-biocidal use of the active substance

Summary table of other (non-biocidal) uses			
	Sector of use1	**Intended use**	**Reference value(s) 2**
1.	industry	Industrial manufacture of polymers, resins	
2.	industry/professional workers	Polymer processing	
3.	industry/professional workers	(Industrial) use as processing aid	
4.	industry/professional workers	Industrial use in laboratories	
5.	industry	Use as an intermediate	
6.	industry	Uses in coatings	
7.	Industry/professional workers	Use in cleaning agents	
8.	Animal nutrition	Feed hygiene agent	Maximum proposed dose[3]: pigs: 12000 mg/kg All other animal species 10000 mg formic acid equivalents/kg complete feed

[1] *e.g. plant protection products, veterinary use, food or feed additives*
[2] *e.g. MRLs. Use footnotes for references.*
[3] *(EFSA, 2009, FA_BPR_Ann_II_8_16_01; EFSA, 2014; FA_BPR_Ann_II_8_16_02; EFSA, 2015, FA_BPR_Ann_II_8_16_03)*

8.7.2 Estimating Livestock Exposure to Active Substances used in Biocidal Products

It is proposed that assessment of dietary risk for humans and livestock be undertaken at biocidal product authorisation for reasons stated above.

For a tentative approach to the 'Guidance on the BPR V III HH-Assessment & Evaluation, Section 6: Guidance On Estimating Livestock Exposure to Active Substances used in Biocidal Products, see Appendix II.

8.7.3 Estimating transfer of biocidal active substances into foods as a result of professional and/or industrial application(s)

Note that at the time of writing, THE ARTFood 'Guidance on Estimating Transfer of Biocidal Active Substances into Foods – Professional Uses' was still in draft form. For this reason, and backed by EFSA's conclusion that below a drinking water concentration of 0.4%, formic acid will not increase the human exposure through the consumption of products obtained from treated animals, the risks related to transfer of formic acid into foods as a result of this PT5 use have not been assessed here.

8.7.4 Estimating transfer of biocidal active substances into foods as a result of non-professional use

Not applicable; the active substance is not intended for non-professional use.

8.8 EXPOSURE ASSOCIATED WITH PRODUCTION, FORMULATION AND DISPOSAL OF THE BIOCIDAL PRODUCT

Please refer to section 8.3 on industrial exposure; disposal of the biocidal product is mentioned for each scenario in section 8.4 on professional exposure.

9 ENVIRONMENTAL EXPOSURE ASSESSMENT

The representative product Formic Acid 85% / FENNOPUR® MH 85 is intended to be used to control the growth of microorganisms in drinking water for the consumption by animals. The drinking water is treated on a daily basis. No waiting period is required. The product is automatically dosed into the drinking water supply system at the appropriate concentration and the treated water is subsequently supplied to the feeders within the animal accommodation.

According to the information provided by the applicant, the overall concentration of formic acid in the treated water is meant to be 1700 mg/L (0.2% of representative product containing 85.9 wt% formic acid). According to the EFSA Panel on Additives and Products or Substances used in Animal Feed[9] no adverse effects are to be anticipated when formic acid is used at the maximum proposed dose in feed for pigs (12 000 mg formic acid/kg complete feed), poultry or ruminants (10 000 mg formic acid/kg complete feed). These conclusions are extrapolated to other animal species at a maximum dose of 10 000 mg formic acid/kg complete feed. When used as a preservative in water for drinking, the proposed maximum content is 4 000 mg/L water, except for ruminants, for which the dose should be calculated based on the daily ration. Formic acid at the recommended concentrations inhibits bacterial growth in feedingstuffs and water for drinking, and is recognised as an efficacious silage additive. However, considering the available basic efficacy data submitted for this dossier, a use concentration for formic acid of 43000 mg/L (5% of representative product containing 85.9 wt% formic acid) should be used for the exposure calculations. It should be noted however that the available efficacy data show activity against *Legionella pneumophila* at the proposed use concentration of 0.2% of representative product.

Therefore, two scenarios will be considered:

- Scenario 1a representing the minimum exposure using a use concentration of 0.2% of the representative product as proposed by the applicant; and
- Scenario 1b representing the maximum exposure using a use concentration of 5% of the representative product as derived from the basic efficacy data set.

No specific emission scenario for disinfection of animal drinking water is described in the ESD for PT 5 (2003)[10] which considers only disinfection of water for human consumption. However, the 'Manual of instructions to eCAs for evaluating active substances used in disinfectants' (ECHA, 2017) provides a way forward:

> *Regarding disinfection of animal drinking water, the assessment can be done according to the ESD for PT3. The parameter animal drinking water consumption was discussed in the Dietary Risk Assessment Working Group (DRAWG) but a final document has not yet been adopted (the guidance will be published by the end of 2017 as an Annex to Guidance on the Biocidal Products Regulation (BPR)*

9 EFSA(2014) Scientific Opinion on the safety and efficacy of formic acid when used as a technological additive for all animal species. EFSA Journal 2014; 12 (10): 3827

10 Emission Scenario Document on Drinking Water Disinfectants (UBA, 2003)

Volume III Human Health - Assessment & Evaluation (Parts B+C)). These values can be found on the BFR website in the Excel spreadsheet "BfR calculator for estimating external exposure of livestock animals to biocidal active substance".

By default, an emission factor to manure/slurry of e.g. 0.9 can be assumed (i.e. no metabolism in the animal), including also spillages during mixing/loading. A refinement would be possible if metabolism data are available. For very reactive and/or oxidative active substances, a qualitative assessment might be sufficient as no active substance might reach the environment.

Considering this way forward, the applied scenarios below are based on the animal housing scenario of the ESD for PT 3 (2011)[11] and the Addendum for including degradation in soil[12]. Data for drinking water intake is taken from the Guidance on BPR Volume III Parts B+C Version 4.0 (2017), Appendix 6-1 (Table 52: Animal Size and Physiology). All stable types of the PT3 animal housing scenario will be taken into account, except ducks and geese since no data on drinking water intake is available for those animals.

Formic acid is metabolised by the animal body. Half-lives in pigs range from 87 min (Makar et al., 1990) to 164 min ([redacted] 1998). Based on data from publications on humans and rats, Hanzlik et al., 2005 conclude that oxidation to CO_2 is the primary means of eliminating formate that is not utilized biosynthetically. Exhalation of CO_2 accounts for up to 80% of administered doses of formate. Up to 10% of the administered doses is used for endogenous metabolic incorporation into tissue components. The urinary excretion of formate accounts for around 2 to 7 % of the administered dose (in humans and rats). No data on ruminants are available but respected their more complex gastrointestinal system it is assumed that the excreted fraction of formate/formic acid is even lower. Taking into account these ADME-data, an emission factor to the manure/slurry of 0.1 is considered as a realistic worst-case value. Please refer to §**Erreur ! Source du renvoi introuvable.** for further details concerning the ADME-data.

At the AHEE-5 meeting, a spillage fraction of 0.2 for cows and pigs, and of 0.145 for poultry was agreed. So for dairy cows as an example, 20% of the active ingredient is spilled and from the remaining 80% taken up by the animal, 10% is excreted. This results in a total released fraction of 0.28 for cows and pigs, and 0.23 for poultry. Releases are predominantly directed to the manure. Nevertheless, in accordance with TAB entry ENV 229, it is considered that the fraction directed to the STP equals the fraction directed to the manure ('Fmanure = Fstp').

General information	
Assessed PT	PT 5
Assessed scenarios	Scenario 1a: Disinfection of drinking water for the consumption by animals (min) Scenario 1b: Disinfection of drinking water for the consumption by animals (max)

[11] Emission Scenario Document for Product Type 3: Veterinary hygiene biocidal products (JRC Scientific and Technical Reports, 2011)
[12] Addendum to OECD Emission Scenario Document for Insecticides for Stables and Manure Storage Systems (Agreed at the Environment Working Group on November 26, 2015)

ESD(s) used	Manual of instructions to eCAs for evaluating active substances used in disinfectants (ECHA, 2017) Emission Scenario Document for Product Type 3: Veterinary hygiene biocidal products (JRC Scientific and Technical Reports, 2011) Addendum to OECD Emission Scenario Document for Insecticides for Stables and Manure Storage Systems (Agreed at the Environment Working Group on November 26, 2015)
Approach	Average consumption
Distribution in the environment	Calculated based on the ECHA Guidance on the Biocidal Products Regulation, Volume IV Environment – Assessment and Evaluation, Parts B+C (2017)
Groundwater simulation	FOCUS PEARL v4.4.4. (see §13.7 'Aggregated exposure')
Confidential Annexes	No
Lifce cycle steps assessed	Production: No Formulation: No Use: Yes Service life: No
Remarks	Data for drinking water intake is taken from the Guidance on BPR Volume III Parts B+C Version 4.0 (2017), Appendix 6-1 (Table 52: Animal Size and Physiology).

Biocidal product specific data
The applicant provided two addenda to the biocidal active substance registration dossier aiming at assessing the fate of formic acid in soil and manure in order to refine the exposure calculations. The addenda ('Formic acid: Fate and degradability – Soil and Manure' (August 20, 2019) and 'Formic acid: Degradability in Manure' (September 07, 2020)) give an overview of the data found in the public literature on degradability and fate of formic acid in soil and manure. In addition to the mentioned addenda, also Doc IIIA robust study summaries of open literature data were submitted for the degradability and fate of formic acid in soil and manure. Reference is made to sections 4.1.1.3.5 and 4.1.1.3.6 of Part A of the present CAR. The addenda and the evaluation by the eCA are included in Doc IIIB 10.2.

Following ENV WG-I-2022, a DT_{50} value for soil of 1 day (12 °C; please refer to section 4.1.1.3.6) and a DT_{50} value of ≤ 10.5 days (20 °C; please refer to section 4.1.1.3.5) are agreed. At the time of writing (April 2022), no agreed environmental relevant temperature exists for the manure. For this specific case, from a precautionary principle, it was agreed at ENV WG-I-2022 to reconvert the DT_{50} value for manure to a temperature of 12 °C as a first tier.

9.1 EMISSION ESTIMATION

9.1.1 Scenario 1a: Disinfection of drinking water for the consumption by animals (min)

The emission scenario for PT3 animal housing was adapted to be used for evaluating the emissions resulting from the disinfection of drinking water for the consumption by animals. Only the “Set values” are stated in the table below. Detailed calculation sheets are provided in Appendix III.

Taking into account TABv2 entry ENV60, only nitrogen immission standards are considered.

For degradation in the manure storage tank, a DT50-value of 10.5 days is assumed. The amount of active ingredient in manure/slurry after the relevant number of biocide applications for the manure application to grassland (Qai_{grass}) is calculated as follow:

$$Qai_{grass} = \sum_{t=1\,d}^{Tgr-int} Qai_{manure} * e^{-kdeg_{manure}*t}$$

with:

- t: number of days in the manure/slurry storage [d];
- Tgr-int: land application interval for grassland (=manure storage time) [d];
- Qai_{manure}: amount of active ingredient in manure/slurry after one application [kg];
- $kdeg_{manure}$: rate constant for degradation in manure [d^{-1}].

Similarly, the amount of active ingredient in manure/slurry after the relevant number of biocide applications for the manure application to arable land (Qai_{arab}) is calculated as follow:

$$Qai_{arab} = \sum_{t=1\,d}^{Tar-int} Qai_{manure} * e^{-kdeg_{manure}*t}$$

with:

- t: number of days in the manure/slurry storage [d];
- Tar-int: land application interval for arable land (=manure storage time) [d];
- Qai_{manure}: amount of active ingredient in manure/slurry after one application [kg];
- $kdeg_{manure}$: rate constant for degradation in manure [d^{-1}].

For Tgr-int and Tar-int, the default values of respectively 53 days and 212 days are used.

Input parameters for calculating the local emission			
Input	**Value**	**Unit**	**Remarks**
Content of active ingredient in formulation	1.718	g/L	(0.2% biocidal product)
Dilution factor (for preparation of the working solution from the formulation (product))	1	-	
Fraction of active ingredient released (Fslurry/manure)	0.28	-	for cows and pigs (0.23 for poultry)
Half-life for biodegradation in soil	1	d	at 12°C
Half-life for biodegradation in manure	19.9	d	at 12°C

The resulting emissions to the relevant compartments are detailed below. Emission to air is considered negligible.

Resulting local emission to relevant environmental compartments			
	Soil (one year) [mg/kg wwt]		**STP [kg/d]**
	Grassland, degradation PIECgrs4-N_degr	**Arable land PIECars-N**	
1 Dairy cows	3.659E+00	1.085E+00	5.532E+00
2 Beef cattle	1.871E+00	5.550E-01	3.007E+00
3 Veal calves	9.053E+00	2.686E+00	7.697E-01
4 Sows, in individual pens	2.276E+00	6.752E-01	9.525E-01

5 Sows in groups	2.276E+00	6.752E-01	9.525E-01
6 Fattening pigs	3.543E+00	1.051E+00	1.924E+00
7 Laying hens in battery cages without treatment	1.096E+00	3.252E-01	2.074E+00
8 Laying hens in battery cages with aeration (belt drying)	1.223E+00	3.629E-01	2.074E+00
9 Laying hens in battery cages with forced drying (deep pit, high-rise)	1.223E+00	3.629E-01	2.074E+00
10 Laying hens in compact battery cages	1.223E+00	3.629E-01	2.074E+00
11 Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.295E+00	3.842E-01	9.879E-01
12 Broilers in free range with litter floor	1.419E+00	4.211E-01	1.976E+00
13 Laying hens in free range with grating floor (aviary system)	1.295E+00	3.842E-01	1.976E+00
14 Parent broilers in free range with grating floor	7.430E-01	2.204E-01	6.915E-01
15 Parent broilers in rearing with grating floor	1.616E+00	4.795E-01	8.891E-01
16 Turkeys in free range with litter floor	1.837E+00	5.451E-01	3.951E+00
17 Ducks in free range with litter floor	2.424E+00	7.192E-01	2.964E+00
18 Geese in free range with litter floor	2.756E+00	8.177E-01	5.927E+00

9.1.2 Scenario 1b: Disinfection of drinking water for the consumption by animals (max)

The emission scenario for PT3 animal housing was adapted to be used for evaluating the emissions resulting from the disinfection of drinking water for the consumption by animals. Only the “Set values” are stated in the table below. Detailed calculation sheets are provided in Appendix III.

Taking into account TABv2 entry ENV60, only nitrogen immission standards are considered.

For degradation in the manure storage tank, a DT50-value of 10.5 days is assumed. The amount of active ingredient in manure/slurry after the relevant number of biocide applications for the manure application to grassland (Qai_{grass}) is calculated as follow:

$$Qai_{grass} = \sum_{t=1\,d}^{Tgr-int} Qai_{manure} * e^{-kdeg_{manure}*t}$$

with:

- t: number of days in the manure/slurry storage [d];
- Tgr-int: land application interval for grassland (=manure storage time) [d];
- Qai_{manure}: amount of active ingredient in manure/slurry after one application [kg];
- $kdeg_{manure}$: rate constant for degradation in manure [d^{-1}].

Similarly, the amount of active ingredient in manure/slurry after the relevant number of biocide applications for the manure application to arable land (Qai_{arab}) is calculated as follow:

$$Qai_{arab} = \sum_{t=1\,d}^{Tar-int} Qai_{manure} * e^{-kdeg_{manure}*t}$$

with:

- t: number of days in the manure/slurry storage [d];
- Tar-int: land application interval for arable land (=manure storage time) [d];
- Qai_{manure}: amount of active ingredient in manure/slurry after one application [kg];
- $kdeg_{manure}$: rate constant for degradation in manure [d^{-1}].

For Tgr-int and Tar-int, the default values of respectively 53 days and 212 days are used.

Input parameters for calculating the local emission			
Input	**Value**	**Unit**	**Remarks**
Content of active ingredient in formulation	42.95	g/L	(5% biocidal product)
Dilution factor (for preparation of the working solution from the formulation (product))	1	-	
Fraction of active ingredient released (Fslurry/manure)	0.28	-	for cows and pigs (0.23 for poultry)

Half-life for biodegradation in soil	1	d	at 12°C
Half-life for biodegradation in manure	19.9	d	at 12°C

The resulting emissions to the relevant compartments are detailed below. Emission to air is considered negligible.

Resulting local emission to relevant environmental compartments			
	Soil (one year) [mg/kg wwt]		**STP [kg/d]**
	Grassland, degradation PIECgrs4-N_degr	**Arable land PIECars-N**	
1 Dairy cows	9.147E+01	2.714E+01	1.383E+02
2 Beef cattle	4.677E+01	1.387E+01	7.516E+01
3 Veal calves	2.263E+02	6.715E+01	1.924E+01
4 Sows, in individual pens	5.690E+01	1.688E+01	2.381E+01
5 Sows in groups	5.690E+01	1.688E+01	2.381E+01
6 Fattening pigs	8.858E+01	2.628E+01	4.810E+01
7 Laying hens in battery cages without treatment	2.740E+01	8.130E+00	5.186E+01
8 Laying hens in battery cages with aeration (belt drying)	3.058E+01	9.073E+00	5.186E+01
9 Laying hens in battery cages with forced drying (deep pit, high-rise)	3.058E+01	9.073E+00	5.186E+01
10 Laying hens in compact battery cages	3.058E+01	9.073E+00	5.186E+01
11 Laying hens in free range with litter floor (partly litter floor, partly slatted)	3.237E+01	9.604E+00	2.470E+01
12 Broilers in free range with litter floor	3.548E+01	1.053E+01	4.939E+01
13 Laying hens in free range with grating floor (aviary system)	3.237E+01	9.604E+00	4.939E+01
14 Parent broilers in free range with grating floor	1.858E+01	5.511E+00	1.729E+01
15 Parent broilers in rearing with grating floor	4.040E+01	1.199E+01	2.223E+01

16 Turkeys in free range with litter floor	4.594E+01	1.363E+01	9.879E+01
17 Ducks in free range with litter floor	6.061E+01	1.798E+01	7.409E+01
18 Geese in free range with litter floor	6.891E+01	2.044E+01	1.482E+02

9.2 FATE AND DISTRIBUTION IN EXPOSED ENVIRONMENTAL COMPARTMENTS

Identification of relevant receiving compartments based on the exposure pathway									
	Fresh-water	**Sediment**	**Sea-water**	**Seawater sediment**	**STP**	**Air**	**Soil**	**Ground-water**	**Other**
Scenario 1 (a & b)	+	(-)	-	-	++	(+)	++	+	(-)

++ *Compartment directly exposed*
- *Compartment not exposed*
+ *Compartment indirectly exposed*
( ) *Compartment potentially exposed [but unlikely to be a significant concern due to hazard data and / or scale of exposure]*

Input parameters (only set values) for calculating the fate and distribution in the environment			
Input	**Value**	**Unit**	**Remarks**
Molecular weight	46.03	g/mol	
Melting point	8	°C	
Boiling point	100.23	°C	
Vapour pressure (at 12 °C)	2400	Pa	
Water solubility (at 12 °C)	$1.09x10^{6}$	mg/l	
Log10 Octanol/water partition coefficient	-2.10	---	(pH 7)
Organic carbon/water partition coefficient (Koc)	30	l/kg	(pH 7)
Henry’s Law Constant (at 12 °C)	0.101	Pa/m3/mol	
Acid dissociation constant	3.7	---	Predominant species at a pH of 7 is formate, which is reflected in the pH dependent Koc.

Biodegradability	Ready biodegradable		

Calculated fate and distribution in the STP		
Compartment	**Percentage [%]**	**Remarks**
	All scenarios	
Air	0.04222	Calculated with SimpleTreat 4.0[13]
Water	7.991	
Sludge	0.27946	
Degraded in STP	91.69	

Notes to take into account when performing fate and distribution calculations at product authorisation stage:

- For the calculations of the PECsoil, an 'overall removal rate constant' should be considered, taking degradation in soil, leaching and volatilisation into account (Guidance on the BPR Vol IV, Part B+C, Equation 56 (v. 10/19)). In the CAR, only the rate constant for degradation in soil (kdeg_soil) is used (which result in worst-case PECsoil values).
- The calculation for PEC surface water (via run-off) should also consider the sorption onto suspended matter, see TAB (v.2021) ENV 11. The PEC values presented in the CAR represent the worst-case.
- In the calculation of the P(I)ECsoil_10years, Tgr-int_no_manure should be 365d (instead of 206d) according to the revision of AHEE Recom WG V 2015 discussed at WG ENV I 2018. However, this change will not have a significant effect on the PEC values for a rapidly degrading substance as formic acid.

The calculation routines for degradation in manure should be performed following the 'quantity average' approach as presented in Addendum 'Addition of calculation routines to incorporate degradation in manure', section 4.3.

[13] In accordance with TAB entry ENV 9, the concentration of suspended solids (Css) in the effluent is changed manually to 30 mg/L (0.03 kg/m³).

9.3 CALCULATED PEC VALUES

PECs for soil are calculated for grassland and arable land after 10 years of consecutive land application based on nitrogen immission standards and taking into account biodegradation. The PECs for soil are time weighted averaged over a period of 30 days since the $PNEC_{soil}$ is derived by equilibrium partitioning from the $PNEC_{aquatic}$ for chronic exposure.

Emissions to the manure (predominant emission route) and to the STP are considered independently. For the manure route, the PEC_{GW} (Tier 1) and PEC_{water} are calculated based on the maximum PEC_{soil} for each respective stable type. For the STP route, PEC values are only calculated for the worst-case stable type with regards to emissions to the STP (i.c. geese in free range with litter floor).

Summary table on calculated PEC values – manure route					
	Stable type	**$PEC_{soil\_grass,degr,twa}$**	**$PEC_{soil\_arab,degr,twa}$**	**PEC_{GW}[1]**	**PEC_{water}**
		[mg/kg_{wwt}]	[mg/kg_{wwt}]	[mg/L]	[mg/L]
Scenario 1a (0.2%)	Dairy cows	1.76E-01	5.22E-02	4.532E-02	4.53E-03
	Beef cattle	9.00E-02	2.67E-02	2.317E-02	2.32E-03
	Veal calves	4.35E-01	1.29E-01	1.121E-01	1.12E-02
	Sows, in individual pens	1.09E-01	3.25E-02	2.819E-02	2.82E-03
	Sows in groups	1.09E-01	3.25E-02	2.819E-02	2.82E-03
	Fattening pigs	1.70E-01	5.06E-02	4.389E-02	4.39E-03
	Laying hens in battery cages without treatment	5.27E-02	1.56E-02	1.358E-02	1.36E-03
	Laying hens in battery cages with aeration (belt drying)	5.88E-02	1.75E-02	1.515E-02	1.52E-03
	Laying hens in battery cages with forced drying (deep pit, high-rise)	5.88E-02	1.75E-02	1.515E-02	1.52E-03

	Laying hens in compact battery cages	5.88E-02	1.75E-02	1.515E-02	1.52E-03
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	6.23E-02	1.85E-02	1.604E-02	1.60E-03
	Broilers in free range with litter floor	6.83E-02	2.03E-02	1.758E-02	1.76E-03
	Laying hens in free range with grating floor (aviary system)	6.23E-02	1.85E-02	1.604E-02	1.60E-03
	Parent broilers in free range with grating floor	3.57E-02	1.06E-02	9.203E-03	9.20E-04
	Parent broilers in rearing with grating floor	7.77E-02	2.31E-02	2.002E-02	2.00E-03
	Turkeys in free range with litter floor	8.84E-02	2.62E-02	2.276E-02	2.28E-03
	Ducks in free range with litter floor	1.17E-01	3.46E-02	3.003E-02	3.00E-03
	Geese in free range with litter floor	1.33E-01	3.93E-02	3.414E-02	3.41E-03
Scenario 1b (5%)	Dairy cows	4.40E+00	1.30E+00	1.133E+00	1.13E-01
	Beef cattle	2.25E+00	6.67E-01	5.793E-01	5.79E-02
	Veal calves	1.09E+01	3.23E+00	2.803E+00	2.80E-01
	Sows, in individual pens	2.74E+00	8.12E-01	7.048E-01	7.05E-02
	Sows in groups	2.74E+00	8.12E-01	7.048E-01	7.05E-02

	Fattening pigs	4.26E+00	1.26E+00	1.097E+00	1.10E-01
	Laying hens in battery cages without treatment	1.32E+00	3.91E-01	3.394E-01	3.39E-02
	Laying hens in battery cages with aeration (belt drying)	1.47E+00	4.36E-01	3.788E-01	3.79E-02
	Laying hens in battery cages with forced drying (deep pit, high-rise)	1.47E+00	4.36E-01	3.788E-01	3.79E-02
	Laying hens in compact battery cages	1.47E+00	4.36E-01	3.788E-01	3.79E-02
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.56E+00	4.62E-01	4.010E-01	4.01E-02
	Broilers in free range with litter floor	1.71E+00	5.06E-01	4.395E-01	4.40E-02
	Laying hens in free range with grating floor (aviary system)	1.56E+00	4.62E-01	4.010E-01	4.01E-02
	Parent broilers in free range with grating floor	8.93E-01	2.65E-01	2.301E-01	2.30E-02
	Parent broilers in rearing with grating floor	1.94E+00	5.76E-01	5.005E-01	5.00E-02
	Turkeys in free range with litter floor	2.21E+00	6.55E-01	5.690E-01	5.69E-02
	Ducks in free range with litter floor	2.91E+00	8.65E-01	7.507E-01	7.51E-02
	Geese in free range with litter floor	3.31E+00	9.83E-01	8.535E-01	8.54E-02
1 TIER 1: porewater concentration					

The calculated porewater concentrations (PEC_{GW}) exceed the threshold of 0.1 µg/L (1.00E-04 mg/L). Further refinement using FOCUS PEARL to model more realistic groundwater concentrations instead of porewater concentrations is presented in section 13.7 of this CAR (Aggregated exposure).

Summary table on calculated PEC values – STP route (geese in free range with litter floor)								
	PEC_{STP}	**PEC_{water}**	**PEC_{sed}***	**$PEC_{seawater}$**	**PEC_{seased}**	**$PEC_{soil,twa}$****	**PEC_{GW}*****	**PEC_{air}**
	[mg/L]	[mg/L]	[mg/kg_{dwt}]	[mg/L]	[mg/kg_{wwt}]	[mg/kg_{wwt}]	[µg/L]	[mg/m^3]
Scenario 1a (0.2 %)	2.37E-01	2.37E-02	see PEC_{water}*	n/a	n/a	1.67E-03	3.79E-01	n/a
Scenario 1b (5 %)	5.91E+00	5.91E-01	see PEC_{water}*	n/a	n/a	4.17E-02	9.47	n/a

* Since the PNEC sediment was calculated according to the equilibrium partitioning method, the risk assessment for freshwater covers that for the sediment.

** The $PNEC_{soil}$ is derived by equilibrium partitioning from a $PNEC_{aquatic}$ for chronic exposure which justifies the use the time weighted average PEC_{soil}. The PEC_{soil} presented in this table are the PECgrs_10_degr-N_twa.

*** The values for PEC_{GW} presented in this table are the TIER1 porewater concentrations.

The calculated porewater concentrations (PEC_{GW}) exceed the threshold of 0.1 µg/L (1.00E-04 mg/L). Further refinement using FOCUS PEARL to model more realistic groundwater concentrations instead of porewater concentrations is presented in section 13.7 of this CAR (Aggregated exposure).

9.4 PRIMARY AND SECONDARY POISONING

9.4.1 Primary poisoning

Not relevant.

9.4.2 Secondary poisoning

Formic acid is not expected to bioaccumulate based on the experimentally derived log Kow of -2.1 (23 °C, pH7) and the calculated BCF (see §4.1.3 above). Therefore, secondary poisoning of formic acid in either the aquatic or terrestrial food chain is considered not relevant.

10 ASSESSMENT OF EFFECTS ON HUMAN HEALTH FOR THE PRODUCT

10.1 PRODUCT(S)

The toxicological properties of the product may be derived from the properties of the active substance and other components of the product. Information on the toxicity of the active substance is presented in Part A, Section 3. There are no compounds of concern in the formulated product that adversely affect the conclusions of the risk assessment for the active substance in the product , therefore limited further assessment is needed.

10.2 DERMAL ABSORPTION

Since the biocidal product FENNOPUR® MH 85 , containing 85.9% formic acid with no other ingredients than water , and formic acid itself are classified as corrosive it is expected that the irritation potential would be sufficient to prevent use of the solution without taking precautions to prevent dermal exposure and so minimising the potential for absorption.

Furthermore, the corrosive nature of formic acid would also corrode the skin sample used in the test, thereby producing meaningless absorption results.

Severe metabolic acidosis resulting from dermal contact with formic acid from biocidal products as described in several case reports (see section 3.3.1 and 3.14), demonstrated rapid dermal absorption through the acid-burned skin.

Therefore, a dermal absorption study using the biocidal product FENNOPUR® MH 85 is scientifically unjustified.

Value(s) used in the Risk Assessment – Dermal absorption	
Value(s)*	In a first tier of risk assessment, a worst case value for dermal absorption of 100% is used for external dermal exposure.
Justification for the selected value(s)	Severe metabolic acidosis resulting from dermal contact with formic acid from biocidal products as described in several case reports, demonstrated rapid dermal absorption through the acid-burned skin. Due to the corrosive properties the dermal absorption of formic acid was not tested. Dermal absorption is known to occur from incidental exposure to large quantities of concentrated formic acid which led to systemic toxicity (section 3.3.1 and 3.14).

Data waiving	
Information requirement	Dermal absorption of the biocidal product 'FENNOPUR® MH 85 ' containing 85.9% formic acid has not been investigated.
Justification	Due to the corrosive properties of the biocidal product and formic acid, no dermal absorption study is requested.

10.3 ACUTE TOXICITY

The acute toxic action profile of formic acid is predominantly determined by its inherent irritating/corrosive properties. The toxicity values after oral uptake and inhalation in rats suggest formic acid to be acutely harmful. The clinical signs give no evidence of specific systemic adverse effects.

The biocidal product, FENNOPUR® MH 85 , contains the active substance to 85.9% with no other ingredient than water. The marketed products are to be further diluted by end users with water during the application. The intended concentrations of the market products and the concentrations during the use as PT5 products are summarized as follows:

Product Type	**Formic acid concentration [%]**		**Remarks**
	Market product	**Ready-for-use solution**	
5	85%	0.17%	Professional, disinfection of animal drinking water

It is evident from the above that FENNOPUR® MH 85 (85% formic acid) must be considered as the worst case.

Acute effects are likely to be caused by formic acid as the major component of the product. The acute oral and inhalation toxicity of formic acid has been characterised as described in section 3.2 and is applicable to that of the biocidal product.

10.3.1 Overall conclusion on acute toxicity

Value used in the Risk Assessment – Acute toxicity

Value(s)	LD_{50} oral 730 mg/kg bw[14] LC_{50} inhalation 7.4 mg/l
Justification for the selected value	Appropriate studies are available for determining the LD_{50} oral and LC_{50} inhalation of formic acid. See sections 3.2.1 and 3.2.3.
Classification for the product according to CLP and DSD	Acute toxicity, oral, cat. 4, H302 Acute toxicity, inhalation, cat. 3, H331 Corrosive properties determine the toxicity of formic acid; additional labelling EUH071

Data waiving	
Information requirement	Acute toxicity of FENNOPUR® MH 85
Justification	Since both formic acid and the biocidal product are classified as corrosive, additional acute toxicity testing with the biocidal product is scientifically unjustified and is not in the interests of animal welfare.

[14] Final LD_{50} will be set by RAC; it is the LD_{50} value from the adopted RAC opinion that will need to be used in biocidal product authorisation.

10.4 CORROSION AND IRRITATION

No skin and eye irritation study reports on formic acid and the biocidal product, FENNOPUR® MH 85 , are available.

Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive (C, R 35) in the EU (12th ATP to Directive 67/548/EEC).

According to Directive EU CLP 1272/2008, Formic Acid is to be classified as skin corrosive 1A and with the following concentration limits:

Skin Corr. 1B; H314: 10% ≤ C < 90%

Skin Corr. 1A; H314: C ≥ 90%

Skin Irrit. 2; H315: 2% ≤ C < 10%

Eye Irrit. 2; H319: 2% ≤ C < 10%

In addition, the corrosive potential of formic acid and formulations containing formic acid has been reported on several occasions after accidental dermal exposure in humans and documented in case reports. For a more comprehensive discussion see section 3.3.1.

We propose additional labelling with EUH071, 'corrosive to the respiratory tract'. See section 3.3.3 for further details. This classification is transferred to FENNOPUR® MH 85 .

10.4.1 Skin corrosion and irritation

No data on the biocidal product are available.

10.4.2 Serious eye damage and eye irritation

No data on the biocidal product are available.

10.4.3 Respiratory tract irritation

No data on the biocidal product are available.

10.4.4 Overall conclusion on corrosion and irritation

Conclusion used in the Risk Assessment – Corrosion and irritation	
Value(s) or Conclusion(s)	Formic acid and FENNOPUR® MH 85 are corrosive to skin Formic acid and FENNOPUR® MH 85 are corrosive to the respiratory tract
Justification for the selected value/ conclusion	See justification below
Classification of the product according to CLP and DSD	Skin Corr. 1B; H314 EUH071

Data waiving	
Information requirement	No skin and eye irritation study reports on formic acid and the biocidal product, FENNOPUR® MH 85 , are available.
Justification	Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive (C, R 35) in the EU (12^{th} ATP to Directive 67/548/EEC) with the following concentration limits: C ≥ 90 % C, R35 corresponds to Skin Corr. 1A; H314

	10 % ≤ C < 90 % C, R34 Skin Corr. 1B; H314 2 % ≤ C < 10 % Xi, R36/38 Skin Irrit. 2; H315: 2% ≤ C < 10% Eye Irrit. 2; H319: 2% ≤ C < 10% EUH071: the corrosive properties determine the toxicity of formic acid (CLP Regulation Annex II, point 1.2.6).

10.5 SENSITISATION

10.5.1 Skin sensitisation

There was no evidence of a sensitising potential for formic acid (technical, purity 85.3%) in guinea pigs using the method of Buehler according the OECD test guideline 406 (see section 3.3.3). In addition, there is no data available (human data including market surveillance data, animal data, open literature) which may be indicative of the potential of formic acid to cause skin sensitisation and sensitisation by inhalation in humans.

The biocidal product, FENNOPUR® MH 85 , is comprised of 85.9% formic acid and water as only other ingredient. Skin sensitisation of the biocidal product would therefore likely to be caused by formic acid.

The biocidal product is not expected to be a sensitiser. Therefore, the request for a skin sensitisation study with the product would be scientifically unjustified and not in the interests of animal welfare.

Conclusion used in Risk Assessment – Skin sensitisation	
Value/conclusion	Formic acid and FENNOPUR® MH 85 do not fulfill the criteria of the CLP regulation to be classified as a skin sensitiser
Justification for the value/conclusion	Skin sensitization (Buehler test) by formic acid (85.3%) has been assessed in an OECD 406 study (Buehler test). The results do not trigger a classification as skin sensitizer.

Classification of the product according to CLP and DSD	none

10.5.2 Respiratory sensitisation

No data on the biocidal product are available.

Conclusion used in the Risk Assessment – Respiratory sensitisation	
Value/conclusion	There is no indication that formic acid or FENNOPUR® MH 85 would be respiratory sensitizers.
Justification for the value/conclusion	No data are available (human data e.g. market surveillance data, animal data, open literature) which may be indicative of the potential of formic acid to cause sensitisation by inhalation in humans. No respiratory sensitisation was seen with formic acid in two subchronic rat and mouse inhalation studies (see section 3.6.3, Thompson 1992). Hence, there is no indication that formic acid would be a respiratory sensitizer.
Classification of the product according to CLP and DSD	none

10.5.3 Overall conclusion on sensitisation

Conclusion used in the Risk Assessment – Sensitisation	
Conclusion(s)	Formic acid and FENNOPUR® MH 85 are not skin sensitizers. There is no indication that formic acid or FENNOPUR® MH 85 would be respiratory sensitizers.
Justification for the conclusion(s)	Classification as a sensitizer is not triggered by appropriate tests. Studies in guinea pigs (method of Buehler) showed that there is no evidence that formic acid has a potential to induce skin sensitisation. In addition, there are no data available (human data including market surveillance, animal studies, open literature) that may be indicative of the potential of formic acid to cause skin sensitisation and sensitisation by inhalation in humans.

Classification of the product according to CLP and DSD	none

Data waiving	
Information requirement	Skin sensitisation study on FENNOPUR® MH 85
Justification	The biocidal product is not expected to be a sensitiser. Therefore, the request for a skin sensitisation study with the product would be scientifically unjustified and not in the interests of animal welfare.

10.6 OTHER

As far as known, there are no further inherent properties of the active substance and non-active substances (water) the classification of which has to be adopted to the biocidal product according to Regulation 1272/2008/EC.

11 ENVIRONMENTAL EFFECTS ASSESSMENT FOR THE PRODUCT

The ecotoxicological properties of the product may be derived from the properties of the active substance and other components of the product. Information on the ecotoxicity of the active substance is presented in Part A, Section 4.2. There are no compounds of concern in the formulated products that adversely affect the conclusions of the risk assessment for the active substance in the product , therefore no further assessment is needed.

11.1 ATMOSPHERE

No studies submitted.

11.2 STP

No studies submitted.

11.3 AQUATIC COMPARTMENT

No studies submitted.

11.4 TERRESTRIAL COMPARTMENT

No studies submitted.

11.5 PRIMARY AND SECONDARY POISONING

No studies submitted.

PART C : RISK CHARACTERISATION OF THE BIOCIDAL PRODUCT(S)

12 RISK CHARACTERISATION FOR HUMAN HEALTH

12.1 CRITICAL ENDPOINTS

The primary endpoint for formic acid is its corrosiveness. Formic acid is severely irritating and corrosive to the eyes, skin, and mucous membranes (gastrointestinal and respiratory tract) and may cause permanent damage. Due to the corrosivity of formic acid, local effects must be expected at all dose levels. Corrosive intoxication might mediate systemic injury as metabolic acidosis, intravascular hemolysis, and renal failure. Systemic adverse effects such as decrease in body weight gain (rat, mice), might be due to the inherent irritating potential. Formic acid is associated with optical nerve and photoreceptor toxicity which is observed in humans and monkeys following methanol intoxication.

Systemic toxicity of formic acid can be established by its salts, sodium formate and potassium diformate, and a closely related substance methanol, as these chemicals have a common breakdown product *in vivo.* Please see section 3.1 on Toxicokinetics for a justification of the read-across applied.

Reference values will be derived for formate and expressed as mg formate/kg bw/d. A conversion is not needed as the difference between formic acid and formate is limited to 1 H+ (MW of formate is 1 less than formic acid).

12.1.1 Systemic effects

Species	Route	Study duration	Test substance	Dose setting (mg/kg bw/d)	Critical effect	LO(A)EL and NO(A)EL (mg/kg bw/d)	References
Rat	Oral	Acute	Formic acid	501, 631, 794, 1000 gavage	Clinical signs and organ lesions indicated corrosive properties of the test substance - Local effect	LD50 = 730 mg/kg bw[15]	BPD ID A6.1.1_01 FA_BPR_Ann_II _8_7_1_01 [redacted] 1985

[15] Final LD_{50} will be set by RAC; it is the LD_{50} value from the adopted RAC opinion that will need to be used in biocidal product authorisation.

					on of the gastro-intestinal tract		
N.R.	Dermal	Acute	Formic acid	-	-	No data, corrosivity	
Rat	Inhalation	Acute	Formic acid	2.82, 6.60, 8.08, 10.6, 14.7 mg/L vapour	Clinical signs indicated corrosive properties of the test substance, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose - Local effect on the respiratory tract	LC50 = 7.4 mg/L	BPD ID A6.1.3_01 FA_BPR_Ann II _8_7_2_01 [redacted] 1980
Rat	Oral	Teratogenicity study	Sodium formate	0, 40, 160, 640 mg formate /kg bw/d	Systemic: no maternal systemic toxicity reached No evidence of teratogenetic or embryotoxic effects	as formate: LOAELsystemic >= 640 NOAELsystemic = 640 (highest concentration tested)	BPD ID A6.8.1_01 FA_BPR_Ann_II_8_10_3_01 [redacted] 2005
Rat	Oral	Subchronic 90 day feeding study	Potassium diformate	0, 420, 840, 2100 mg formate /kg bw/d	Systemic: reduced bw gain Local: gastric irritation, hyperplastic changes in the stomach	as formate: LOAELsystemic = 2100 (highest concentration tested) [redacted] LOAELlocal = 420 NOAELlocal < 420	BPD ID A6.4.1_01 FA_BPR_Ann_II_8_9_2_01 [redacted] 1998

Rat	Oral	Chronic 2-year feeding study	Potassium diformate	0, 35, 280, 1400 mg formate /kg bw/d	Systemic: reduced bw gain Local: gastric irritation, hyperplastic changes in the stomach and gastrointestinal tract	as formate: LOAELsystemic = 1400 (highest concentration tested) [redacted] LOAELlocal = 280 NOAELlocal = 35	BPD ID A6.5_01 FA_BPR_Ann_II_8_9_3_01 [redacted] 2002a
Rat	Oral	2-generation study	Sodium formate	0, 68, 203, 677 mg formate /kg bw/d	Systemic: decreased food consumption, decreased bw gain in F1 parental males No findings on reproduction and development	as formate: LOAELsystemic = 670 (highest concentration tested) NOAELsystemic = 200	BPD ID A6.8.2_01 [redacted] 2008b FA_BPR_Ann_II_8_10_2_01
Rat	Inhalation	Subchronic 90-day inhalation study	Formic acid	0, 15, 30, 61, 122, 244 mg/m3 Vapour, whole body	Systemic: no evidence of systemic toxicity Local: nasal irritation, histopathological changes in nasal region	LOAELsystemic > 244 mg/m³ NOAELsystemic = 244 mg/m³ (highest dose tested) LOAELlocal = 61 mg/m³ NOAELlocal = 30 mg/m³	BPD ID A6.4.3_01 FA_BPR_Ann_II_8_9_2_03 Thompson, 1992
Mouse	Oral	Carcinogenicity study: 80-week feeding study	Potassium diformate	0, 35, 280, 1400 mg formate	Systemic: reduced bw gain	as formate: LOAELsystemicl = 1400	BPD ID A6.7_02. FA_BPR_Ann_II_8_11_2_01 [redacted] 2002b

				/kg bw/d	Local: gastric irritation, hyperplastic changes in the forestomach	(highest concentration tested) NOAELsystemicl = 280 LOAELlocal = 1400 (highest concentration tested) NOAELlocal = 280	
Mouse	Inhalation	Subchronic 90-day inhalation study	Formic acid	0, 15, 30, 61, 122, 244 mg/m3	Systemic: decreased bw gain Local: nasal irritation, histopathological changes in nasal region	LOAELsystemic = 244 mg/m³ (highest dose tested) NOAELsystemic = 122 mg/m³ LOAELlocal = 122 mg/m³ NOAELlocal = 61 mg/m³	BPD ID A6.4.3_01; FA_BPR_Ann_II_8_9_2_04 Thompson, 1992
Rabbit	Oral	Teratogenicity study	Sodium formate	0, 68, 203, 677 mg formate /kg bw/d	Systemic: no maternal systemic toxicity reached No evidence of terato-genetic or embryotoxic effects	as formate: as formate: LOAELsystemic >= 670 NOAELsystemic = 670 (highest concentration tested)	BPD ID A6.8.1_02 [redacted] 2008 FA_BPR_AnnII_8_10_1_01
Pig	Oral	Subchronic 140-day feed study	Potassium diformate	0, 149, 359, 760 mg formate /(kg bw/d	No signs of maternal systemic toxicity or toxicity to reproduction or	as formate: LOAELsystemic, > 760	BPD ID A6.4_02 FA_BPR_Ann_II_8_9_2_02 [redacted] 2004

					development at any dose level. Local: gastric effects - forestomach gastritis and erosion/ulcer	NOAELsystemic = 760 (highest concentration tested) LOAELlocal = 149 NOAELlocal < 149	
Pig	Oral	Subchronic > 300-day feed study	Potassium diformate	0, 98, 301 mg formate /kg bw/d	No signs of maternal systemic toxicity or toxicity to reproduction or development at any dose level.	as formate: LOAELsystemic, local > 300 NOAELsystemic, local = 300 (highest concentration tested)	BPD ID A6.5_02 FA_BPR_Ann_II_8_9_4_0_JNS [redacted] 2003

12.1.2 Local effects

Route	Effect	Study	Classification	Hazard category[1]
Dermal	corrosive	n.a.	Skin corr 1A	Very high
Respiratory	corrosive	[redacted] (1980) BPD ID A6.1.3_01 FA_BPR_Ann_II_8_7_2_01	EUH071	
		BPD ID A6.4.3_01 FA_BPR_Ann_II_8_9_2_03 Thompson, 1992 (see 12.1.1)		
		BPD ID A6.4.3_01; FA_BPR_Ann_II_8_9_2_04 Thompson, 1992 (see 12.1.1)		
oral	irritating to the gastrointestinal tract (mouth, oesophagus, forestomach)	[redacted] (1998), BPD ID A6.4.1_01; FA_BPR_Ann_II_8_9_2_01 [redacted] (2002a). BPD ID A6.5_01; FA_BPR_Ann_II_8_9_3_01		

		[redacted] (2002b), BPD ID A6.7_02, FA_BPR_Ann_II_8_11_2_01 [redacted] (2004), BPD ID A6.4.1_02; FA_BPR_Ann_II_8_9_2_02 High concentration intake – case reports, a.o. Westphal et al (2001), BPD ID A6.12.2_01, FA_BPR_Ann_II_8_12_2_01		

[1] According to the guidance "Risk characterisation for local effects including sensitisation" – reference to be updated when the guidance is integrated into ECHA guidance.

12.1.3 Absorption

Route	Study	Test substance	Concentration of test substance	Applicability (concentration ranges)	Value
Oral	None, corrosive	/	/	/	Rapid, no quantitative data Assumed 100%
Dermal	None, corrosive	/	/	/	Assumed 100%
Inhalation	None, corrosive	/	/	/	Assumed 100%

12.2 REFERENCE VALUES

12.2.1 Uncertainties and assessment factors

AELshort-term		
Uncertainty	**AF**	**Justification**
Interspecies variability	10	Default AF in the absence of substance-specific data
Intraspecies variability	10	Default AF in the absence of substance-specific data
Route to route extrapolation	1	No indication for route-specific differences in systemic toxicity
Time duration extrapolation	1	no additional extrapolation factor for duration is considered for the calculation of the acute AEL from the repeated 90-day oral toxicity study

NOAEL to LOAEL extrapolation	/	
Dose response	/	
Severity of key health effects	/	reduced bw gain at 2100 mg formate/kg bw/d
Overall AF	100	(n.a.)

AELmedium-term		
Uncertainty	**AF**	**Justification**
Interspecies variability	10	Default AF in the absence of substance-specific data
Intraspecies variability	10	Default AF in the absence of substance-specific data
Route to route extrapolation	1	No indication for route-specific differences in systemic toxicity
Time duration extrapolation	1	Study duration subchronic
NOAEL to LOAEL extrapolation	/	
Dose response	/	
Severity of key health effects	/	reduced bw gain at 2100 mg formate/kg bw/d
Overall AF	100	(n.a.)

AELlong-term		
Uncertainty	**AF**	**Justification**
Interspecies variability	10	Default AF in the absence of substance-specific data
Intraspecies variability	10	Default AF in the absence of substance-specific data
Route to route extrapolation	1	No indication for route-specific differences in systemic toxicity
Time duration extrapolation	1	Study duration chronic
NOAEL to LOAEL extrapolation	/	
Dose response	/	
Severity of key health effects	/	reduced bw gain at 1400 mg formate/kg bw/d
Overall AF	100	(n.a.)

AECrespiratory tract irritation		
Uncertainty	**AF**	**Justification**
Interspecies variability	1	local effects, no toxicokinetic default assessment and toxicodynamic default assessment factor needed because of the similarity in local effects among rodents and humans: effects on the respiratory and olfactory epithelium, squamous metaplasia and degeneration, there is no evidence that humans should be more sensitive than rodents
Intraspecies variability	10	Default AF in the absence of substance-specific data
Route to route extrapolation	1	Subchronic inhalation studies
Time duration extrapolation	/	
NOAEL to LOAEL extrapolation	/	
Dose response	/	
Severity of key health effects	/	Local effects: squamous metaplasia and degeneration of the respiratory and olfactory epithelia
Overall AF	10	(n.a.)

12.2.2 AEL setting

Due to its inherent properties (acidic pH, corrosive substance, volatile) it is most likely that formic acid will induce local effects at a lower dose than systemic effects.

Therefore, it seems to be reasonable to do the risk characterisation starting from systemic AELs and local AECs.

In addition, other international AEL are available:

ADI (residues in food, feed) = 3 mg/kg bw/d (EU SANCO D3/AS D, 2005; JECFA, 2003)[16]

Occupational Exposure Limit: EU WEL, MAK/TLV = 5 ppm or 9.5 mg/m³ (8-hour TWA)); IOELV = 5 ppm or 9 mg/m³ (Commission directive 2006/15/EC).

An ARfD was not derived and not required.

The available data (medium term exposure) does not permit to characterize a significant systemic effect in the context of the reduction in body weight, in fact there is no obvious link between the irritant effects (NOAEL: 840 mg/kg) induced by the substance at a high dose, i.e. 2100 mg/kg (LOAEL), and the individual weight loss (decreased food consumption in males but not in females). Finally, in the recovery period, body weight development in males and females was comparable between the high dose and control groups. Therefore the derivation of ArfD value does not seem relevant.

Systemic AEL

[16] No detailed information can be provided on how the ADI was derived. Despite this, the ADI can be taken up in the CAR because it is in line with the derived $AEL_{long\text{-}term}$.

Systemic toxicity is secondary to local irritant effects. The critical systemic endpoint of formate in the toxicological studies was identified as reduced body weight gain. The NOAELs have been derived from the studies in the most sensitive species showing these effects: the rat and mouse. It is suggested to consider this systemic effect in the risk assessment.

Additional note:

Next to the $NOAEL_{systemic}$ used to derive AELs as reported below, the following NOAEL and LOAEL for local effects are also available:

Species	Route	Study duration	Test substance	Dose setting (mg/kg bw/d)	Critical effect	LO(A)EL and NO(A)EL (mg/kg bw/d)	References
Rat	Oral	Subchronic 90 day feeding study	Potassium diformate	0, 420, 840, 2100 mg formate/kg bw/d	Local: gastric irritation, hyperplastic changes in the stomach	as formate: LOAELlocal = 420 NOAELlocal < 420	BPD ID A6.4.1_01 FA_BPR_Ann_II_8_9_2_01 [redacted] 1998
Rat	Oral	Chronic 2-year feeding study	Potassium diformate	0, 35, 280, 1400 mg formate/kg bw/d	Local: gastric irritation, hyperplastic changes in the stomach and gastrointestinal tract	as formate: LOAELlocal = 280 NOAELlocal = 35	BPD ID A6.5_01 FA_BPR_Ann_II_8_9_3_01 [redacted] 2002a
Mouse	Oral	Carcinogenicity study: 80-week feeding study	Potassium diformate	0, 35, 280, 1400 mg formate/kg bw/d	Local: gastric irritation, hyperplastic changes in the forestomach	as formate: LOAELlocal = 1400 (highest concentration tested) NOAELlocal = 280	BPD ID A6.7_02. FA_BPR_Ann_II_8_11_2_01 [redacted] 2002b
Pig	Oral	Subchronic 140-day feed study	Potassium diformate	0, 149, 359, 760 mg formate/(kg bw/d	Local: gastric effects - forestomach gastritis and erosion/ulcer	as formate: LOAELlocal = 149 NOAELlocal < 149	BPD ID A6.4.1_02 FA_BPR_Ann_II_8_9_2_02 [redacted] 2004
Pig	Oral	Subchronic > 300-day feed study	Potassium diformate	0, 98, 301 mg formate/kg bw/d	No signs of maternal systemic toxicity or toxicity to reproduction or development at any dose level.	as formate: LOAEL, local > 300 NOAEL, local = 300 (highest concentration tested)	BPD ID A6.5_02 FA_BPR_Ann_II_8_9_4_0_JNS [redacted] 2003

For setting of appropriate Reference Values for oral exposures, it is necessary to differentiate between systemic toxicity (decrease in bw) and local effects (irritation on the gastrointestinal tract); Reference Values should be set based on the most sensitive endpoint in the most sensitive species. The most sensitive endpoint is the irritation on the gastrointestinal tract.

However, in the case of Formic Acid, due to its corrosivity, local effects must be expected at all dose levels, and a qualitative RC would be the appropriate approach, assuming that the effects leading to classification will also occur in repeated exposure and at lower concentrations/area doses, and the effects will be managed by means of CLP, RMM's and PPE.

Derived reference values based on systemic effects are lower than those based on local effects, considering the applied assessment factors. Hence the local effects are covered by the reference values for systemic effects; we will apply the AEL of systemic effects for the quantitative risk assessment.

Acute and Medium-term AEL

Although human exposure is mainly dermal and by inhalation, the PODs are based on oral studies.

The teratogenicity study performed with sodium formate in the rat cannot be used to derive a systemic NOAEL as no maternal systemic toxicity was reached. No other short-term toxicity studies are available.

A medium-term 90-day oral toxicity study performed with potassium diformate in the rat revealed a NOAEL oral, 90-days, rat = 840 mg formate/kg bw/d (based on decreased bw gain at 2100 mg formate/kg bw/d).

Two medium-term 90-day inhalation studies performed with formic acid itself in the rat and mouse are available. In the rat, no systemic effects were observed up to the highest concentration tested 244 mg/m³. In the mouse, a NOAEC of 122 mg/m³ was determined based on the reduced bw gain observed at 244 mg/m³. When taking into account: Minute Volume mouse = 0.041 L/min, BW mouse = 0.030 kg, inhalation = 360 min, then 122 mg/m³ corresponds with a systemic dose of ~60 mg/kg bw/d. However, the RMS is convinced that the systemic NOAELs derived from the inhalation studies are not suitable for the determination of systemic AEL's. The systemic effects seen in the mouse study were most probably secondary to the local effects of respiratory irritation induced by formic acid exposure ($NOAEL_{local}$ = 64 mg/m³, based on histopathological changes in the nasal region). In these studies formic acid itself and not the salts were used. In the oral studies the less corrosive formate salts were used to reveal systemic effects not secondary to the corrosive effects.

In conclusion, for the derivation of the acute and medium-term AEL, the NOAEL of the oral 90-day study in the rat performed with potassium formate was used.

POD acute and medium-term: NOAEL formate, oral, 90-day feeding study, potassium diformate, rat = 840 mg formate/kg bw/d

Oral absorption: 100%

AF: 10 x 10 (no additional extrapolation factor for duration is considered for the calculation of the acute AEL from the repeated 90-day oral toxicity study)

Acute and Medium-term $AEL_{systemic}$ = 8.4 mg formate/kg bw/d

Long-term AEL

Long-term toxicity studies are available for the rat and mouse.

The 2-year rat study and 80-week mouse study performed with potassium diformate both revealed a NOAEL oral, long-term = 280 mg formate/kg bw/d (based on decreased bw gain at 1400 mg formate/kg bw/d)

POD: NOAEL formate, oral, 2-year feeding study, potassium diformate, rat = 280 mg formate/kg bw/d

Oral absorption: 100%

AF: 10 x 10

Long-term $AEL_{systemic}$ = 2.8 mg formate/kg bw/d rounded to 3 mg formate/kg bw/d[17]

This value corresponds to the ADI.

A $NOAEL_{systemic}$ of 200 mg/kg bw/d is also available (Two-Generation Reproduction Toxicity Study, Rat, oral, feed). However, it can be justified not to derive the $AEL_{long\ term}$ from this study.

Comparing the results of the 2-generation study ([redacted] 2008b) and the combined chronic toxicity and carcinogenicity study, the results of both studies suggest that formate and its salts exhibit only very minor systemic effects. In both studies animals of the high dose show reduced body weights, body weight gains and food consumption. Unfortunately, the selected doses differed slightly in both studies. The mid dose of the chronic study corresponded to 280 mg/kg bw/d and the mid dose of the 2-generation study corresponded to 203 mg/kg bw/d.

	2-generation study		Chronic study	
	Formate [mg/kg bw/d]	Decrease in BW gain [%]	Formate [mg/kg bw/d]	Decrease in BW gain [%]
Low dose	68	-	35	-
Mid dose	203	-	280	-
High dose	677	m: 8.8	1400	m: 27, f: 19

The 2-generation study is a feeding study using sodium formate as test material. No systemic effects including effects on body weight were observed in the first parental generation. However, mean body weights of the high-dose parental F1 males (1000 mg/kg bw/d) of the 2-generation study were statistically significantly decreased during study weeks 9-15 (up to 5.7%). The mean body weight gain of the high-dose F1 males was statistically significantly decreased on several occasions during the study (up to 33.6%). If calculated for the entire treatment period (weeks 0-15) the high-dose F1 males gained about 8.8% less weight than the control males.

It has to be noted that the route of administration was orally via feed. As well as the body weight gain, the food consumption of male animals of the high dose was also reduced in a similar manner (in average about 9% decreased). Thus, the decrease in body weight gain and the reduced food consumption in high dose parental F1 males correlate and could be indicative

[17] We refer to TAB entry TOX-4 as the impact of rounding is less than 10%. Please note that for this CAR, the risk characterization has been performed with the non-rounded 2.8 mg formate/kg bw/d value. The decision for rounding the AEL long-term was taken at HH WG I-2022; however it was decided that there was no need to alter the risk characterization of the CAR. For product approval, the rounded 3 mg formate/kg bw/d value should be used.

of a palatability problem of the highest dose (acerbity of the test substance) since the decrease in body weight gain was not seen in the presence of normal food consumption.

The combined chronic toxicity/carcinogenicity study in the rat ([redacted] 2002a) was performed via oral administration using potassium formate (1:2) as test material.

In this study, lower body weight and body weight gain than for the controls was seen in the high dose animals together with a minor decrease in food consumption. However, the variation in food consumption was of insufficient magnitude to account for the lower body weight gain. The average decrease in body weight gain accounted in males 27% and in females 19% in this study (104 weeks).

Comparing the results of both studies shows that systemically available formate exhibits only very minor toxicological effects at high doses. Systemic effects other than decreased food consumption, body weight and body weight gain were not observed.

The effects on body weight gain found in the parental F1 animals of the 2-generation toxicity study were, when calculated over the entire treatment period, lower than 10% and could be correlated with the decreased food consumption which may be a hint of palatability problems of the high dose group. Additionally, it should be noted that this minor effect was limited to parental F1 males and was not observed in other generations (e.g. P0).

The effects observed in the chronic feeding study with potassium formate (1:2) were, although also only minor, more pronounced, and not limited to males.

Hence, the minor difference in the established NO(A)ELs of both studies can only be attributed to the minor difference in dose setting. The mid dose, which was the highest dose showing no systemic effects corresponded to 280 mg/kg bw/d formate in the chronic and to 203 mg/kg bw/d formate in the 2-generation study.

In conclusion, the use of the systemic NO(A)EL of 280 mg/kg bw/d formate for derivation of the $AEL_{long\text{-}term}$ is justified by the longer treatment period of the chronic study, the more pronounced systemic effects observed in the chronic study and the minor or negligible difference of established NO(A)Els which can be attributed to the slightly different dose setting of both studies.

Local AECs

Formic acid is classified as corrosive. Formic acid is severely irritating and corrosive to the eyes, skin, and mucous membranes (gastrointestinal and respiratory tract) and may cause permanent damage. Due to the corrosivity of formic acid, local effects must be expected at all dose levels.

Inhalation AEC respiratory tract irritation

A quantitative risk characterisation can be performed as repeated dose 13-week inhalation studies are available performed with formic acid in the rat and mouse. An external reference value (AEC) has been derived for the local effect of respiratory tract irritation:

POD: NOAEC formic acid, inhalation, 13 weeks, rat/mice = 60 mg/m³

AF: 10 x 1

-default assessment factor intraspecies: 10;

-interspecies: assessment factor of 1, please see justification below.

-formic acid causes mainly local effects,

-no toxicokinetic default assessment and toxicodynamic default assessment factor are considered to be required because of the similarity in local effects among rodents and humans: effects on the respiratory and olfactory epithelium, squamous metaplasia and degeneration, there is no evidence that humans should be more sensitive than rodents)

Since there are currently no validated animal tests that deal specifically with respiratory tract irritation, an interspecies assessment factor of >1 could be called for in order to cover this additional uncertainty. However, during HH WGI2022 it was decided that an interspecies AF of 1 is acceptable and that a total assessment factor of 10 is sufficient, mainly due to the fact that FA is likely to be a case of direct/pH-driven chemical action on tissue/cell membranes.

The effect of FA is highly likely a simple destruction of membranes due to the physico-chemical properties (e.g. pH) of the chemical concerned as opposed to a mechanism involving local metabolism (e. g. reactive metabolite). If tissue metabolism is involved, which could lead to the formation of different metabolites at different rates in different species, interspecies dynamic differences on how these metabolites interact with specific targets should be considered.

However, Formic acid is a volatile and strongly corrosive organic acid which is in mammals rapidly metabolized to CO_2 and H_2O. It can be concluded that no toxicologically significant or reactive metabolites are formed and that local irritation due to corrosivity is the most sensitive response and leading health effect. Thus, the mechanism of respiratory irritation is direct pH-reactivity and no further kinetic considerations apply. Furthermore, in terms of toxicodynamic, it can be assumed that rats and humans will respond to the insult in the same way since no significant differences in buffer capacity of cells in respiratory tract against strong acids are expected.

For the following reasons an additional safety factor seems not to be necessary:

- NOAEC derived from validated and reliable subchronic inhalation studies in two species (rat, mice)
- Mechanism of respiratory tract irritation is direct pH-reactivity
- Rodents are obligate nasal breathers with a more complex nasal passage and therefore the upper respiratory tract may be more sensitive than in humans

AEC respiratory tract irritation = 6 mg/m³

(EU workplace exposure limit = 5ppm (9.5 mg/m³), 8-hour time weighted average; IOELV = 5 ppm or 9 mg/m³ (Commission directive 2006/15/EC))

Dermal AEC

Repeated dose dermal studies are not available, and consequently the basis for setting an AEC is lacking.

Therefore a qualitative RC will be performed assuming that the effects leading to classification will also occur in repeated exposure and at lower concentrations/area doses, and the effects will be managed by means of CLP, RMM’s and PPE.

AECdermal <2% formic acid: does not need classification

Oral AEC

No oral AEC will be derived because all repeated dose oral studies were performed with the salts, potassium diformate or sodium formate, because of their less irritating potency.

It is known from published human data (Malorny, 1969b; DocIIIA6.2-07; section 3.1), that immediately after the drinking of 2 g formic acid as 0.4% aqueous solution transient gastric irritation was observed.

12.2.3 Reference values to be used in Risk Characterisation

Reference	Study	NOAEL (LOAEL)	AF	Correction for oral absorption	Value
$AEL_{short-term}$	Subchronic 90 day feeding study, rat	as formate: 840 mg/kg bw/d (2100 mg/kg bw/d)	100	1	8.4 mg/kg bw/d
$AEL_{medium-term}$	Subchronic 90 day feeding study, rat	as formate: 840 mg/kg bw/d (2100 mg/kg bw/d)	100	1	8.4 mg/kg bw/d
$AEL_{long-term}$	Chronic 2-year feeding study, rat	as formate: 280 mg/kg bw/d (1400 mg/kg bw/d)	100	1	2.8 mg/kg bw/d rounded to 3 mg/kg bw/d[18]
ARfD	not required				
ADI	EU SANCO D3/AS D, 2005; JECFA, 2003				3 mg/kg bw/d
Occupational exposure limit		EU WEL, MAK/TLV (8-hour TWA) IOELV (Commission Directive 2006/15/EC)			5 ppm or 9.5 mg/m³ 5 ppm or 9 mg/m³

18 We refer to TAB entry TOX-4 as the impact of rounding is less than 10%. Please note that for this CAR, the risk characterization has been performed with the non-rounded 2.8 mg formate/kg bw/d value. The decision for rounding the AEL long-term was taken at HH WG I-2022; however it was decided that there was no need to alter the risk characterization of the CAR. For product approval, the rounded 3 mg formate/kg bw/d value should be used.

$AEC_{respiratory\ tract\ irritation}$	Subchronic 13w inhalation study, rat/mice	Rat: 30 mg/m³ (61 mg/m³) Mice: 61 mg/m³ (122 mg/m³) Overall NOAEC formic acid, inhalation, 13 weeks, rat/mice = 60 mg/m³	10	n.a.	6 mg/m³

12.2.4 Maximum residue limits or equivalent

MRLs or other relevant reference values	Reference	Relevant commodities	Value
default MRL	Art.18(1)(b) Reg 396/2005	all	0.01 mg/kg

12.3 INDUSTRIAL USES

This section has not been evaluated by the CA-BE because the production/formulation process of the active substance is outside the scope of the Biocidal Products Regulation (EU) No 528/2012. As such, exposure estimates for industrial workers during these stages have not been calculated as they are already addressed by other legislation.

Formic acid is severely irritating and corrosive to the eyes, skin, and mucous membranes (gastrointestinal and respiratory tract) and may cause permanent damage. The effect must be managed by means of classification (CLP), Risk Management Measures (RMM's), and Personal Protective Equipment (PPE). The production processes are technically controlled. Workers in industry should be fully trained and protected.

The industry worker exposure during production, filling and mixing processes is routinely determined. The results of 138 measurements made during 2001-2006 indicate that the formic acid concentrations in the air at the workplace did not exceed the threshold limit value of 9.5 mg/m^3 (5 ppm; AOEL) at any of the workplaces which cover all types of operations at the production plant.

Conclusion: There is no concern for industrial workers in the production and formulation of the active substance and the biocidal product.

12.4 PROFESSIONAL USES

The biocidal product may be used to disinfect water which will be used as drinking water for animal consumption. The product is automatically dosed into the drinking water supply system to the animal accommodation on either a continuous or intermittent basis.

Professionals will be exposed daily to the biocidal product during changing of the product containers and from contact with treated drinking water. The main routes of exposure for professional users will be the dermal and inhalation routes. Operators must wear PPE (coveralls, gloves, boots and face protection) as the biocidal product is labelled as corrosive. The use of RPE is compulsory for handling the concentrate.

The applicant suggests an in-use dilution of 0.2% FENNOPUR® MH 85 (0.17% FA) for disinfection of animal drinking water. Note that at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 efficacy was proven for its bactericidal and yeasticidal properties; efficacy against *Legionella pneumophila* was shown at 0.17% FA. eCA BE took into consideration both 5% and 0.17% FA in drinking water for the risk assessment.

12.4.1 Systemic effects

Task/ Scenario	**Tier/PPE**	**Systemic NOAEL mg/kg bw/d**	**AEL mg/kg bw/d**	**Estimated uptake mg/kg bw/d**	**Estimated uptake/ AEL (%)**	**Acceptable (yes/no)**
Scenario 1, Mixing & loading, 85% FA	1/none	280	2.8	14.336	512	No
	2/ coveralls, boots, gloves and face protection; RPE APF10	280	2.8	0.1458	5.2	Yes
Scenario 2, exposure to treated drinking water, 0.17% FA	1/none	280	2.8	0.232	8.3	Yes
	2/ gloves	280	2.8	0.0232	0.8	Yes
Scenario 2, exposure to treated drinking water, 5% FA	1/none	280	2.8	Up to 8.2	293	No
	2/ gloves	280	2.8	Up to 2	71.4	Yes

12.4.1.1 *COMBINED SCENARIOS*

A possible scenario combination for professionals is that the same worker connects the biocide to the automated water supply system and comes into contact with disinfected water.

For local exposure, no addition of exposure levels is performed; only the highest exposure level in air is considered relevant.

Scenarios combined	**Tier/PPE**	**Systemic NOAEL** mg/kg bw/d	**AEL** mg/kg bw/d	**Estimated uptake** mg/kg bw/d	**Estimated uptake/ AEL** (%)	**Acceptable** (yes/no)
0.17% FA dil Scenarios 1+2, tier 1	Tier 1/ none	280	2.8	14.568	520	No
0.17% FA dil Scenarios 1+2, tier 2	Sc 1 coveralls, boots, gloves and face protection; RPE APF10 /Sc 2 gloves	280	2.8	0.169	6.04	Yes
5% FA dil Scenarios 1+2, tier 1	Tier 1/ none	280	2.8	22.469	802	No
5% FA dil Scenarios 1+2, tier 2	Sc 1 coveralls, boots, gloves and face protection; RPE APF10 /Sc 2 gloves	280	2.8	2.129	76.04	Yes

12.4.2 Local effects

As a local AEC for respiratory tract irritation is available, a quantitative risk characterisation can be performed.

Task/ Scenario	**Tier/PPE**	**NOAEC** mg/m³	**AEC** mg/m³	**Estimated inhalation exposure** mg/m³	**Estimated exposure / AEC** (%)	**Acceptable** (yes/no)
	1/none	60	6			

Scenario 1, Mixing & loading, 85% FA				8.1 (ConsExpo vapour)	135	No
	2/ coveralls, boots, gloves and face protection; RPE APF10	60	6			
				0.81 (ConsExpo vapour)	13.5	Yes
Scenario 2, exposure to treated drinking water, 0.17% FA	1/none	60	6	Very low to negligible	N.A.	Yes
	2/ gloves	60	6	Very low to negligible	N.A.	Yes
Scenario 2, exposure to treated drinking water, 5% FA	1/none	60	6	up to 10 mg/m^3	167	No
	2/ gloves	60	6	up to 10 mg/m^3	167	No

As formic acid is corrosive at or above a 10% dilution, a qualitative risk characterization is needed for local dermal and inhalation exposure. This RC is triggered for those BP classified for local effects. In BP where formic acid is present at concentrations that do not trigger classification of the product according to the CLP criteria, RC for local effects is not required.

For use in PT5, the following concentrations are either marketed or made by dilution of a concentrate:

concentration	PT	task	Classification with regard to corrosivity	Hazard category	Exposure foreseen
concentrate					
85%	5	Mixing and loading	Skin corr 1B EUH071	high	Yes, skin, RT
In-use dilution					
5% (supports efficacy claims)	5	Treated drinking water	Skin/eye irrit 2	low	Yes, skin, RT

					eye (accidental)
0.17% (recommended by applicant)	5	Treated drinking water	None	None	Yes, skin, RT eye (accidental)

Professional user – concentrate – M&L										
Hazard			Exposure							Risk
Hazard Category	Effects in terms of C&L	Additional relevant hazard information	PT	Who is exposed?	Tasks, uses, processes	Potential exposure route	Frequency and duration of potential exposure	Potential degree of exposure	Relevant RMM&PPE	Conclusion on risk
High	Skin corr. 1B (H314)	$pH_{85\%\ formic\ acid}$ = -1.6 $pH_{concentrate}$ TBD EUH071	5	Professionals/experienced farmers	Charging (M&L) to the drinking water system	Skin Eye RT	10 minutes per day, daily	85% Splashes, hand to eye transfer vapour	**<u>Product integrated RMM</u>** <u>Labelling</u> • Labelling according to CLP • Instructions for use and storage • Labelling for general safety and hygiene measures (see below) <u>Formulation</u> • Product formulation which reduces e.g. splashes <u>Packaging</u> • Packaging reducing risk for eye exposure by splashes **<u>Trained personnel</u>** • Experienced farmers • Containment as appropriate • Good standard of general ventilation • Regular cleaning of equipment and work area	**ACCEPTABLE** +engineering controls +low frequency +short duration +professionals using PPE +professionals following instructions for use +good standard of personal hygiene +professional bystander is expected to use the same set of PPE as the professional user

									• Avoidance of contact with contaminated tools and objects • Training for staff on good practice • Good standard of personal hygiene **<u>PPE</u>** **Respiratory protection:** RPE APF10 half mask vapour filter The professional bystander needs to observe the same set of PPE as the worker. **Hand protection:** chemical-resistant gloves **Eye protection:** Safety goggles **Skin and body protection:** Chemical resistant apron & clothing, boots **<u>General safety and hygiene measures</u>** Avoid contact with skin, eyes and clothing. Wash hands before breaks and immediately after handling the product.	

									Remove and wash contaminated clothing and gloves, including the inside, before re-use	

Professional user – dilution - contact with treated drinking water										
Hazard			**Exposure**							**Risk**
Hazard Category	**Effects in terms of C&L**	**Additional relevant hazard information**	**PT**	**Who is exposed?**	**Tasks, uses, processes**	**Potential exposure route**	**Frequency and duration of potential exposure**	**Potential degree of exposure**	**Relevant RMM&PPE**	**Conclusion on risk**
Low	5% formic acid: Skin irrit 2 (H315) Eye irrit 2 (H319)	pH TBD (product evaluation)	5	Experienced farmers	Intermittent contact with disinfected water	Skin, eye RT	Daily, intermittent short contact	5% FA Splashes, hand to eye transfer vapour	**<u>RMM</u>** • Experienced farmers respecting general safety and hygiene measures (see below) • Good standard of general ventilation • Training for staff on good practice • Good standard of personal hygiene **<u>PPE</u>** **Hand protection:** chemical-resistant gloves **body protection:** coveralls **eye protection:** safety goggles	**ACCEPTABLE** +engineering controls +reversible effect +professionals following instructions for use +experience expected

									General safety and hygiene measures Avoid contact with skin, eyes and clothing. Wash hands before breaks and immediately after handling the product. Remove and wash contaminated clothing and gloves, including the inside, before re-use	

12.4.3 Conclusion

Charging Formic Acid 85% into animal drinking water systems

Prolonged skin contact with the product is unlikely under practical conditions of use due to its corrosive effects. In practice, primary dermal and inhalation exposure of the professional operator will be reduced by the effects of exposure reduction measures (automatic dosing system) and the use of PPE.

Without personal protective equipment (PPE) professionals may be exposed to corrosive effects on the skin from spills and on mucous membranes from exposure to formic acid vapours. However, professionals are trained to handle the product and must use PPE and RPE as advised on the label (coveralls, boots, gloves and face protection, half mask with vapour filter) to prevent exposure to skin, eyes and respiratory tract. With proper use of such PPE, exposure is reduced and risk of adverse effects is minimised. Thus, with the assumption that the obligatory PPE is used, the total internal dose is below the long-term AEL for formic acid.

Formic acid is a volatile substance (vapour pressure >0.01 Pa at 20°C). The inhalation exposure to formic acid vapours is above the local $AEC_{respiratory\ tract\ irritation}$ for formic acid when mixing and loading is performed without the protection of RPE. During typical M&L activities, the operators are exposed for only short periods of time (10 mins). The $AEC_{respiratory\ tract\ irritation}$ is based on 6 hour inhalation exposure. By using a half mask with vapour filter, exposure to FA vapours during M&L is reduced sufficiently to levels far below the $AEC_{respiratory\ tract\ irritation.}$ In any case, premises where these concentrates are used should be well-ventilated both during and after mixing and loading.

In case of spillage, the onset of odour and irritant symptoms associated with formic acid exposure would be expected shortly after the exposure begins. Fortunately formic acid has good warning properties. To date, the OEL of 5 ppm (9.5 mg/m³) agrees with the $AEC_{respiratory\ tract\ irritation}$ of 6 mg/m³ as estimated by the RMS. Higher exposure to formic acid can result in the development of prolonged adverse effects, such as RADS.

Conclusion: There is no concern for professionals charging the biocidal product in animal drinking water systems to disinfect water which will be used as drinking water for animal consumption PT5, when appropriate PPE, RPE and ventilation are applied.

Secondary exposure: dermal and inhalation exposure to treated drinking water

The applicant suggests an in-use dilution of 0.2% FENNOPUR® MH 85 (0.17% FA) for disinfection of animal drinking water. Note that at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 efficacy was proven for its bactericidal and yeasticidal properties; efficacy against *Legionella pneumophila* was shown at 0.17% FA. eCA BE took into consideration both 5% and 0.17% FA in drinking water for the risk assessment.

Professionals will be exposed daily to the biocidal product via dermal contact with treated drinking water. Hand exposure only was considered. Calculations show that when the in-use dilution is low (0.17% FA), the internal dose is below the long-term AEL for formic acid, even when no gloves are worn. Secondary inhalation exposure was considered very low to negligible.

When the in-use dilution is high (5% FA), the internal dose is above the long-term AEL for formic acid when no gloves are worn. Applying gloves as PPE would reduce the systemic exposure to FA sufficiently. However, our preliminary assessment indicates that local inhalation exposure would in worst case exceed the $AEC_{respiratory\ tract\ irritation}$; use of higher FA concentrations for disinfection of animal drinking water is to be avoided. In any case, at these FA concentrations, palatability could be considered questionable.

Conclusion: There is no concern for professionals exposed to treated drinking water containing 0.17% Formic Acid. There is a concern for professionals exposed to treated drinking water containing 5% Formic Acid. This concern is due to both dermal and inhalation exposure to formic acid.

Combined scenarios

A possible scenario combination for professionals is that the same worker connects the biocide to the automated water supply system and comes into contact with disinfected water.

For this scenario combination also, with the assumption that the obligatory PPE (and RPE for M&L) is used, the total internal dose is below the long-term AEL for formic acid.

When low concentrations of formic acid are used in drinking water, exposure to disinfected water contributes only in a minor way to the inhalation exposure to formic acid vapours as exposure via this route is considered very low to negligible. Here, inhalation exposure results are derived from mixing and loading only. As stated above, this exposure is above the local $AEC_{respiratory\ tract\ irritation}$

for formic acid. However, during typical M&L activities, the operators are exposed for only short periods of time (10 mins). The $AEC_{respiratory\ tract\ irritation}$ is based on 6 hour inhalation exposure. Using a half mask with vapour filter would reduce the inhalation exposure sufficiently to levels far below the $AEC_{respiratory\ tract\ irritation}$. In any case, premises where formic acid concentrates are used, should be well-ventilated both during and after mixing and loading.

At higher in-use dilutions and conditions of low ventilation however, exposure to disinfected water could contribute significantly to the inhalation exposure to formic acid vapours. Local inhalation exposure would in worst case exceed The $AEC_{respiratory\ tract\ irritation}$; use of higher FA concentrations for disinfection of animal drinking water is to be avoided.

General conclusion: There is no concern for professionals charging the biocidal product in animal drinking water systems to disinfect water which will be used as drinking water for animal consumption PT5, when appropriate PPE, RPE and ventilation are applied. There is no concern for professionals exposed via the dermal and inhalation route to treated drinking water containing low concentrations of Formic Acid (0.17%). There is a concern for professionals exposed to treated drinking water containing higher concentrations of formic acid (5%). This concern is due to both dermal and inhalation exposure to formic acid. Use of higher FA concentrations for disinfection of animal drinking water is to be avoided.

General remark:

The main issue identified is the high vapour pressure of formic acid and the resulting inhalation of formic acid vapours.

However, eCA BE is convinced that these concerns should be dealt with at product authorization level. Possible refinements that can be suggested include improved assessment factors for ventilation, the use of workplace measurements and identification of acceptable RMM per type of application.

12.5 NON-PROFESSIONAL USERS

Non-professional use of the biocidal product is not foreseen.

12.6 SECONDARY (INDIRECT) EXPOSURE AS A RESULT OF USE

As the biocidal product is intended for professional use and in professional premises only, there is no potential for secondary exposure of the general public.

12.7 INDIRECT EXPOSURE VIA FOOD

Dietary exposure to formic acid is considered unlikely and has not been assessed here (see section 8.7).

BE eCA is of the opinion that there is no concern for indirect exposure to the general public from food. Toxicokinetic studies referred to in section 3.1 show that formic acid is fully metabolised in the animal leaving no residues in the animal products. In addition, formic acid is used as a food preservative and has been granted GRAS status (Generally Regarded As Safe) by the US FDA regulatory authority[19]. Therefore, the indirect exposure to the general public from eating animal products can be considered negligible.

Conclusion: Therefore, there is no concern for the general public from the consumption of potentially contaminated animal products as a result of the use of the biocidal product to disinfect water which will be used as drinking water for animal consumption PT5.

However, at product authorisation, the need for an assessment of dietary exposure should be reviewed.

Note:

For a tentative approach to the 'Guidance on the BPR V III HH-Assessment & Evaluation, Section 6: Guidance On Estimating Livestock Exposure to Active Substances used in Biocidal Products, see Appendix II.

In this tentative approach, it is assumed that the concentration of formic acid required to fulfil the efficacy claims made by the applicant, is below 0.4% (notably 0.17% as suggested by the applicant). However, at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 (85.9% FA) efficacy was proven for its bactericidal and yeasticidal properties; efficacy

[19] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=186.1316&SearchTerm=formic%20acid

against *Legionella pneumophila* was shown at 0.17% FA. At product authorization level, the actual efficacious dose of the BP could determine whether dietary exposure needs to be assessed.

12.8 PRODUCTION / FORMULATION OF ACTIVE SUBSTANCE

Please refer to section 12.3 on industrial exposure.

In accordance with the Commission Document agreed at the 22nd CA meeting in September 2006, detailed information on exposure associated with the manufacturing process is not required for biocidal product risk assessment.

13 RISK CHARACTERISATION FOR THE ENVIRONMENT

The risks to the environment resulting from the use of formic acid as a PT5 biocide are summarised in the paragraphs below.

The product, Formic Acid 85% / Fennopur MH 85, is intended to be used for disinfection of animal drinking water under PT5.

Direct emissions are to the manure/slurry storage followed by indirect emissions to soil, groundwater and surface water.

13.1 ATMOSPHERE

The vapour pressure of 42.71 hPa (20 °C; [redacted] 2007; BPD ID A3_01) and the Henry's Law Constant of 0.16 Pa.m³/mol (20 °C; ECT Oekotoxikologie GmbH; BPD ID A3_11) indicate low to moderate potential for volatilization and evaporation from water and wet surfaces.

Conclusion:

The atmosphere is not considered a compartment of concern.

13.2 SEWAGE TREATMENT PLANT (STP)

Summary table on calculated PEC/PNEC values – manure route	
	$PEC/PNEC_{STP}$
Scenario 1a (0.2%)	N/A
Scenario 1b (5%)	N/A

Summary table on calculated PEC/PNEC values – STP route (Geese in free range with litter floor)	
	$PEC/PNEC_{STP}$
Scenario 1a (0.2%)	< 4.74E-03
Scenario 1b (5%)	< 1.18E-01

The $PEC/PNEC_{stp}$ are all below 1.

Conclusion:

The risks for the STP are acceptable.

13.3 AQUATIC COMPARTMENT

Summary table on calculated PEC/PNEC$_{water}$ values – manure route		
	Stable type	**PEC/PNEC$_{water}$**
Scenario 1a (0.2%)	Dairy cows	≤ 2.27E-03
	Beef cattle	≤ 1.16E-03
	Veal calves	≤ 5.60E-03
	Sows, in individual pens	≤ 1.41E-03
	Sows in groups	≤ 1.41E-03
	Fattening pigs	≤ 2.20E-03
	Laying hens in battery cages without treatment	≤ 6.80E-04
	Laying hens in battery cages with aeration (belt drying)	≤ 7.60E-04
	Laying hens in battery cages with forced drying (deep pit, high-rise)	≤ 7.60E-04
	Laying hens in compact battery cages	≤ 7.60E-04
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	≤ 8.00E-04
	Broilers in free range with litter floor	≤ 8.80E-04
	Laying hens in free range with grating floor (aviary system)	≤ 8.00E-04
	Parent broilers in free range with grating floor	≤ 4.60E-04
	Parent broilers in rearing with grating floor	≤ 1.00E-03
	Turkeys in free range with litter floor	≤ 1.14E-03
	Ducks in free range with litter floor	≤ 1.50E-03
	Geese in free range with litter floor	≤ 1.71E-03
Scenario 1b (5%)	Dairy cows	≤ 5.65E-02
	Beef cattle	≤ 2.90E-02
	Veal calves	≤ 1.40E-01
	Sows, in individual pens	≤ 3.53E-02
	Sows in groups	≤ 3.53E-02
	Fattening pigs	≤ 5.50E-02
	Laying hens in battery cages without treatment	≤ 1.70E-02
	Laying hens in battery cages with aeration (belt drying)	≤ 1.90E-02
	Laying hens in battery cages with forced drying (deep pit, high-rise)	≤ 1.90E-02
	Laying hens in compact battery cages	≤ 1.90E-02
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	≤ 2.01E-02
	Broilers in free range with litter floor	≤ 2.20E-02

	Laying hens in free range with grating floor (aviary system)	≤ 2.01E-02
	Parent broilers in free range with grating floor	≤ 1.15E-02
	Parent broilers in rearing with grating floor	≤ 2.50E-02
	Turkeys in free range with litter floor	≤ 2.85E-02
	Ducks in free range with litter floor	≤ 3.76E-02
	Geese in free range with litter floor	≤ 4.27E-02

Summary table on calculated PEC/PNEC values – STP route (Geese in free range with litter floor)	
	$PEC/PNEC_{water}$
Scenario 1a (0.2%)	≤ 1.18E-02
Scenario 1b (5%)	≤ 2.96E-01

All the $PEC/PNEC_{water}$ ratio are below 1 for both the manure route and the STP route.

Conclusion:

The risk for freshwater is considered acceptable.

13.4 TERRESTRIAL COMPARTMENT

Summary table on calculated $PEC/PNEC_{soil}$ values – manure route			
	Stable type	**Grassland**	**Arable land**
		$PEC/PNEC_{soil}$	**$PEC/PNEC_{soil}$**
Scenario 1a (0.2%)	Dairy cows	≤1.36E-01	≤4.05E-02
	Beef cattle	≤6.98E-02	≤2.07E-02
	Veal calves	≤3.37E-01	≤1.00E-01
	Sows, in individual pens	≤8.45E-02	≤2.52E-02
	Sows in groups	≤8.45E-02	≤2.52E-02
	Fattening pigs	≤1.32E-01	≤3.92E-02
	Laying hens in battery cages without treatment	≤4.09E-02	≤1.21E-02
	Laying hens in battery cages with aeration (belt drying)	≤4.56E-02	≤1.36E-02
	Laying hens in battery cages with forced drying (deep pit, high-rise)	≤4.56E-02	≤1.36E-02
	Laying hens in compact battery cages	≤4.56E-02	≤1.36E-02
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	≤4.83E-02	≤1.43E-02

	Broilers in free range with litter floor	≤5.29E-02	≤1.57E-02
	Laying hens in free range with grating floor (aviary system)	≤4.83E-02	≤1.43E-02
	Parent broilers in free range with grating floor	≤2.77E-02	≤8.22E-03
	Parent broilers in rearing with grating floor	≤6.02E-02	≤1.79E-02
	Turkeys in free range with litter floor	≤6.85E-02	≤2.03E-02
	Ducks in free range with litter floor	≤9.07E-02	≤2.68E-02
	Geese in free range with litter floor	≤1.03E-01	≤3.05E-02
Scenario 1b (5%)	Dairy cows	≤3.41E+00	≤1.01E+00
	Beef cattle	≤1.74E+00	≤5.17E-01
	Veal calves	≤8.45E+00	≤2.50E+00
	Sows, in individual pens	≤2.12E+00	≤6.29E-01
	Sows in groups	≤2.12E+00	≤6.29E-01
	Fattening pigs	≤3.30E+00	≤9.77E-01
	Laying hens in battery cages without treatment	≤1.02E+00	≤3.03E-01
	Laying hens in battery cages with aeration (belt drying)	≤1.14E+00	≤3.38E-01
	Laying hens in battery cages with forced drying (deep pit, high-rise)	≤1.14E+00	≤3.38E-01
	Laying hens in compact battery cages	≤1.14E+00	≤3.38E-01
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	≤1.21E+00	≤3.58E-01
	Broilers in free range with litter floor	≤1.33E+00	≤3.92E-01
	Laying hens in free range with grating floor (aviary system)	≤1.21E+00	≤3.58E-01
	Parent broilers in free range with grating floor	≤6.92E-01	≤2.05E-01
	Parent broilers in rearing with grating floor	≤1.50E+00	≤4.47E-01
	Turkeys in free range with litter floor	≤1.71E+00	≤5.08E-01
	Ducks in free range with litter floor	≤2.26E+00	≤6.71E-01
	Geese in free range with litter floor	≤2.57E+00	≤7.62E-01

Summary table on calculated PEC/PNEC values – STP route (Geese in free range with litter floor)	
	$PEC/PNEC_{soil}$
Scenario 1a (0.2%)	≤ 1.14E-03
Scenario 1b (5%)	≤ 2.84E-02

For scenario 1a, disinfection of animal drinking water at a biocidal product use concentration of 0.2%, all PEC/PNEC$_{soil}$ ratios are below 1, for both the manure route as the STP route.

For scenario 1b, disinfection of animal drinking water at a biocidal product use concentration of 5%, still some PEC/PNEC$_{soil}$ ratios for the manure route are higher than 1 (especially for application of manure on grassland), indicating unacceptable risks. Note that scenario 1b uses a concentration (43 000 mg/L) that is 10x higher than the proposed maximum content of formic acid when used as a preservative in water for drinking (4 000 mg/L) by EFSA. Therefore, scenario 1b could be considered as unrealistic worst-case.

Conclusion:

For scenario 1a, disinfection of animal drinking water at a biocidal product use concentration of 0.2%, the risk for the soil compartment is considered to be acceptable.

Based on the available data, the risk for the soil compartment for scenario 1b, disinfection of animal drinking water at a biocidal product use concentration of 5%, is evaluated as unacceptable for emissions to the manure.

13.5 GROUNDWATER

The PEC$_{groundwater}$ values are compared to the allowed maximum concentration of 0.1 µg/L (98/8/EC, Annex VI, art. 82).

Calculated PEC$_{GW}$ values – manure route		
	Stable type	**PEC$_{GW}$ [µg/L]**
Scenario 1a (0.2%)	Dairy cows	4.53E+01
	Beef cattle	2.32E+01
	Veal calves	1.12E+02
	Sows, in individual pens	2.82E+01
	Sows in groups	2.82E+01
	Fattening pigs	4.39E+01
	Laying hens in battery cages without treatment	1.36E+01
	Laying hens in battery cages with aeration (belt drying)	1.52E+01
	Laying hens in battery cages with forced drying (deep pit, high-rise)	1.52E+01
	Laying hens in compact battery cages	1.52E+01
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.60E+01
	Broilers in free range with litter floor	1.76E+01
	Laying hens in free range with grating floor (aviary system)	1.60E+01
	Parent broilers in free range with grating floor	9.20E+00
	Parent broilers in rearing with grating floor	2.00E+01

	Turkeys in free range with litter floor	2.28E+01
	Ducks in free range with litter floor	3.00E+01
	Geese in free range with litter floor	3.41E+01
Scenario 1b (5%)	Dairy cows	1.13E+03
	Beef cattle	5.79E+02
	Veal calves	2.80E+03
	Sows, in individual pens	7.05E+02
	Sows in groups	7.05E+02
	Fattening pigs	1.10E+03
	Laying hens in battery cages without treatment	3.39E+02
	Laying hens in battery cages with aeration (belt drying)	3.79E+02
	Laying hens in battery cages with forced drying (deep pit, high-rise)	3.79E+02
	Laying hens in compact battery cages	3.79E+02
	Laying hens in free range with litter floor (partly litter floor, partly slatted)	4.01E+02
	Broilers in free range with litter floor	4.40E+02
	Laying hens in free range with grating floor (aviary system)	4.01E+02
	Parent broilers in free range with grating floor	2.30E+02
	Parent broilers in rearing with grating floor	5.01E+02
	Turkeys in free range with litter floor	5.69E+02
	Ducks in free range with litter floor	7.51E+02
	Geese in free range with litter floor	8.54E+02

Calculated PEC_{GW} values – STP route (Geese in free range with litter floor)	
	PEC_{GW} [µg/L]
Scenario 1a (0.2%)	3.79E-01
Scenario 1b (5%)	9.47

The calculated porewater concentrations (as an estimate for the groundwater concentration) are above the threshold value of 0.1 µg/L. To obtain more realistic groundwater concentrations, the modelling software FOCUS PEARL v.4.4.4. is used to simulate leaching to groundwater.

FOCUS PEARL calculations are presented in §13.7 (Aggregated exposure) and show that the modelled groundwater concentrations are likely to be below the threshold value of 0.1 µg/L for both scenarios.

Conclusion:

The risks for the groundwater compartment are acceptable.

13.6 PRIMARY AND SECONDARY POISONING

13.6.1 Primary poisoning

Not considered relevant.

13.6.2 Secondary poisoning

Conclusion:

Not considered relevant.

13.7 AGGREGATED EXPOSURE (COMBINED FOR RELEVANT EMMISSION SOURCES)

Formic acid is intended to be used as an active substance for biocidal products in a wide variety of product types: PT2, PT3, PT4, PT5 and PT6. An aggregated exposure assessment is conducted by summing up all release streams for which an overlap in time and space is to be expected.

Two main release routes separated in time and/or space are considered:

1. STP route: PT2, PT4, PT6;
2. Manure route: PT3 (Footwear, Animal feet), PT5.

For the STP route, it is considered that the emissions of PT2, PT4 and PT6 are redirected to the same STP. For the manure route, it is considered that the representative products for the respective PT3 and PT5 uses are used on the same farm. In the following paragraphs, the aggregated exposure of those two main release routes is elaborated. Releases to the air compartment are considered not relevant.

Note that in section §9 for the PT3 scenarios (Footwear and Animal feet), emissions were doubled: the same emission was considered to be directed to both the manure storage and the STP (total fraction emitted >1). To avoid double emissions, it is for the aggregated exposure calculation considered that all emissions from disinfection of footwear and animal feet are directed to the manure storage.

Disinfection of animal housing by means of fogging (PT3, scenario 3) is not included in the aggregated exposure exercise for the following reasons:

- According to the ESD for PT3, fogging is only carried out in exceptional cases.
- The aggregated exposure exercise considers a dairy cows farm (see below, §13.7.2.1) whereas the fogging scenario considers a veal calves farm. No overlap in time and space is thus to be expected.
- The emissions of the fogging scenario are 1 or 2 orders of magnitude lower as compared to the other ‘manure’ scenarios.

13.7.1 STP route

Not relevant for PT3.

13.7.2 Manure route

13.7.2.1 *EMISSION ESTIMATION*

It is considered that the representative products for PT3 (Footwear, Animal feet) and PT5 (Animal drinking water) are applied on the same farm and that the emission streams are collected in the same manure/slurry storage pit. For PT5 only scenario 1a (disinfection of animal drinking water at a use concentration of the representative biocidal product of 0.2 %) is considered since this concentration is in line with the EFSA recommendations.

The sum of emissions for the aggregated exposure of the manure route is based on the concentration of the biocide (active ingredient) in soil (mg/kg) in the case of an immission standard for nitrogen and land application on grassland (PIECgrs-N_i1,i2,i3,i4) and arable land (PIECars-N_i1,i2,i3,i4) respectively.

The PT3 scenario 'Disinfection of animal feet' is only elaborated for dairy cows. Therefore, a dairy cows farm is considered to calculate the aggregated emissions. The emissions are summarised in the table below.

Summary of aggregated emissions for the manure route			
	PIECgrs4-N_degr [mg/kg_wwt]	**PIECarab-N [mg/kg_wwt]**	**Remarks**
PT3 – Footwear	0.33	0.10	dairy cows
PT3 – Animal feet	5.25	1.53	dairy cows
PT5 – Animal drinking water (scenario 1a – 0.2% b.p.)	3.66	1.09	dairy cows
SUM	**9.24**	**2.72**	**aggregated emission**

13.7.2.2 *FATE AND DISTRIBUTION IN EXPOSED ENVIRONMENTAL COMPARTMENTS*

Identification of relevant receiving compartments based on the exposure pathway									
	Fresh-water	**Sediment**	**Sea-water**	**Seawater sediment**	**STP**	**Air**	**Soil**	**Ground-water**	**Other**
Manure route	+	(-)	-	-	-	(+)	++	+	(-)

++ *Compartment directly exposed*
- *Compartment not exposed*
+ *Compartment indirectly exposed*
( ) *Compartment potentially exposed [but unlikely to be a significant concern due to hazard data and / or scale of exposure]*

Input parameters (only set values) for calculating the fate and distribution in the environment			
Input	**Value**	**Unit**	**Remarks**
Molecular weight	46.03	g/mol	
Melting point	8	°C	
Boiling point	100.23	°C	
Vapour pressure (at 12 °C)	2400	Pa	
Water solubility (at 12 °C)	1.09×10^{6}	mg/l	
Log10 Octanol/water partition coefficient	-2.10	---	(pH 7)
Organic carbon/water partition coefficient (Koc)	30	l/kg	(pH 7)
Henry's Law Constant (at 12 °C)	0.101	Pa/m3/mol	
Acid dissociation constant	3.7	---	Predominant species at a pH of 7 is formate, which is reflected in the pH dependent Koc.
Biodegradability	Ready biodegradable		
DT50 for degradation in soil (12 °C)	1	day	

13.7.2.3 *CALCULATED AGGREGATED ΣPEC VALUES*

The maximum ΣPEC values per compartment are presented in the table below.

Summary table on calculated ΣPEC values					
	ΣPEC_{STP}	**ΣPEC_{water}**	**ΣPEC_{sed}[1]**	**$\Sigma PEC_{soil,twa}$[2]**	**ΣPEC_{GW}**
	[mg/L]	[mg/L]	[mg/kg_{wwt}]	[mg/kg_{wwt}]	[µg/L]
Manure route	N/A	1.145E-02	see ΣPEC_{water}[1]	4.444E-01	1.145E+02
1 Since the PNEC sediment was calculated according to the equilibrium partitioning method, the risk assessment for freshwater covers that for the sediment. 2 Initial concentration after sludge application considering the average time for the terrestrial ecosystem. The $PNEC_{soil}$ is derived by equilibrium partitioning from a $PNEC_{aquatic}$ for chronic exposure.					

13.7.2.3.1 Manure route: refinement of the exposure calculation

The calculation of the groundwater concentration is further refined using FOCUS PEARL v.4.4.4. to simulate leaching to groundwater, taking into consideration the specific parameters and formulas indicated according to the TAB v2.

In the table below, the FOCUS PEARL input parameters for Formic Acid are summarised.

PEARL input parameters for substance Formic Acid			
Parameter	**Value**	**Unit**	**Remarks**
GENERAL			
Molecular weight	46.03	g/mol	
Vapour Pressure	2400	Pa	at 12°C
Water solubility	$1.00x10^6$	mg/l	maximum allowed value
Freundlich sorption			
Kom	17.4	L/kg	pH 7, 20°C (Kom = Koc/1.724)
Freundlich sorption exponent (1/n)	1	[-]	TAB v2, ENV 22 (conservative value)
Transformation			
Half-life	1	d	
Molar activation energy	54	kJ/mol	TAB v2, ENV 23
Crop			
Coefficient for uptake by plant	0	[-]	TAB v2, ENV 23

Simulation was run for both grassland (alfalfa) and arable land (maize) (cfr. TAB v2, ENV 165).
In the case of alfalfa, the scenario considers 4 manure/slurry applications per year on fixed dates 1st of March, 23rd of April, 15th of June and 7th of August (considering 53 days between application) and 5 cm incorporation depth. In the case of maize, one manure/slurry application per year 20 days before crop emergence and 20 cm incorporation depth is considered.

The application rate of the active substance *Appl_rate* [kg/ha] at one specific application date as necessary input parameter in FOCUS groundwater models is calculated on basis of the aggregated predicted initial environmental concentrations (∑PIEC).

The application rate for the grassland scenario is calculated by:

$$Appl\_rate_{grass} = \sum PIEC_{grs} \times RHO_{soil\_wet} \times DEPTH_{grassland} \times 10^{-2} = \sum PIEC_{grs} \times 0.85$$

With:

$Appl\_rate_{grs}$ = concentration of active ingredient in grassland soil after 1 manure slurry application based on the nitrogen immission standard for grassland [kg/ha]
$\sum PIEC_{grs}$ = aggregated concentration of the active ingredient in grassland soil after 1 manure/slurry application based on the nitrogen immission standard for grassland [mg/kg] according to OECD ESD PT 18 No.14 (2006)
RHO_{soil_wet} = wet bulk soil density = 1,700 kg/m³
$DEPTH_{grassland}$ = mixing depth with soil for grassland = 0.05 m

The application rate for the arable land scenario is calculated by:

$$Appl\_rate_{ar\_maize} = \sum PIEC_{ars} \times RHO_{soil\_wet} \times DEPTH_{arableland} \times 10^{-2} = \sum PIEC_{ars} \times 3.4$$

$Appl\_rate_{ar\_maize}$ = initial concentration of the active substance in soil of arable land after 1 manure/slurry application based on the nitrogen immission standard for arable land [kg/ha]
$\sum PIEC_{ars}$ = initial aggregated concentration of the active substance in soil of arable land after 1 manure/slurry application based on the nitrogen immission standard for arable land [mg/kg] according to OECD ESD PT 18 No.14 (2006) and to the Addendum (Nov.2015)
RHO_{soil_wet} = wet bulk soil density = 1,700 kg/m³
$DEPTH_{arable\ land}$ = mixing depth with soil for arable land = 0.2 m

PEARL input parameters for Application Schemes				
Parameter	**Value**		**Unit**	**Remarks**
	Grassland	**Arable Land**		
Crop	Alfalfa	Maize	[-]	
Application type	incorporation	incorporation	[-]	
Date(s)	01 March, 23 April, 15 June, 07 August	20 days before emergence		TAB v2, ENV 165
Mixing depth	0.05	0.2	m	
∑PIEC	9.24	2.72	mg/kg_{wwt}	
Dosage (Appl_rate)	**7.85**	**9.25**	kg/ha	

PEARL was then run for the nine available locations for each application scheme. Repeat interval for years was set to 1. The resulting groundwater concentrations closest to the 80th percentile are presented below.

PEARL groundwater assessment [µg/L]		
Location	**Grassland**	**Arable Land**
Chateaudun	0.000000	0.000000
Hamburg	0.000000	0.000000
Jokioinen	0.000000	N/A
Kremsmuenster	0.000000	0.000000
Okehampton	0.000000	0.000000
Piacenza	0.000004	0.000000
Porto	0.000000	0.000000
Sevilla	0.000000	0.000000
Thiva	0.000000	0.000000

All modelled groundwater concentrations are below the threshold value of 0.1 µg/L.

13.7.2.4 *AGGREGATED RISK CHARACTERISATION*

The calculated aggregated ΣPEC/PNEC values for the manure route are summarised in the table below.

Summary table on calculated aggregated ΣPEC/PNEC values for the manure route					
	$\Sigma PEC/PNEC_{STP}$	**$\Sigma PEC/PNEC_{water}$**	**$\Sigma PEC/PNEC_{sed}$[1]**	**$\Sigma PEC/PNEC_{soil,twa}$**	**ΣPEC_{GW}[2]**
Manure route	N/A	5.73E-03	see $\Sigma PEC/PNEC_{water}$[1]	3.45E-01	1.15E+02
1 Since the PNEC sediment was calculated according to the equilibrium partitioning method, the risk assessment for freshwater covers that for the sediment. 2 Tier 1 porewater concentration					

The groundwater concentrations are below the threshold of 0.1 µg/L after refinement of the PEC calculations using FOCUS PEARL.

13.8 SUMMARY OF THE RISK ASSESSMENT FOR THE ENVIRONMENT

Summary table on environmental risk assessment					
	STP	**Fresh water**	**Sediment**	**Soil**	**Groundwater**
Scenario 1a (0.2% biocidal product)	acceptable	acceptable	acceptable	acceptable	acceptable (FOCUS PEARL)
Scenario 1b (5% biocidal product)	acceptable	acceptable	acceptable	**not acceptable**[20]	acceptable (FOCUS PEARL)
Aggregated exposure (manure route)	N/A	acceptable	acceptable	acceptable	acceptable (FOCUS PEARL)

<u>Conclusion:</u>

The risks for the environment are acceptable for scenario 1a. For scenario 1b however, an unacceptable risk cannot be excluded for the soil compartment.

The risks for the environment from the aggregated exposure of biocidal products containing formic acid are acceptable.

[20] Acceptable for emissions to the STP, but not for emissions to the manure which is the predominant emission route.

14 RISK CHARACTERISATION FOR THE PHYSICO-CHEMICAL PROPERTIES

Formic acid is thermally stable up to 350 °C at which combustion starts. It is a flammable liquid (flash point in closed cup: 49.5 °C) with a high auto-ignition temperature of 528 °C. Thermal breakdown and combustion products are carbon monoxide and water/hydrogen. Pure formic acid is not corrosive to metals, while FA85% is corrosive to steel, but not corrosive to aluminium (UN test 37.4 C1). Formic acid is not explosive and has no oxidizing properties.

15 MEASURES TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

Professional users need to be trained and instructed on the proper use of the formic acid, its handling, storage, disposal, the selection and use of protective equipment, and First Aid measures. Safety Data Sheets (SDS) should be supplied.

Consumer products should be labelled with the same or similar information. The labels should transfer the information contained in the SDS into the consumer’s language, taking into account the concentration of formic acid.

Human exposure:

Formic acid is corrosive for skin and eye at concentrations from 10% onwards. Concentrations from 2% onwards are skin and eye irritants. Personal protection should be applied, as recommended by classification and labelling, and as established through the risk assessment. See the relevant sections in the CAR for details.

If an unacceptable risk is identified for non-professional users due to exposure to the biocidal product triggering local effects, appropriate product integrated risk mitigation measures, like packaging and/or formulation controls, or other engineering controls shall be applied.

Due to the high volatility and corrosiveness of formic acid, care should be taken when there is potential for exposure via the inhalation route for professionals, non-professionals and bystanders. For the professional user and bystander appropriate RPE are required when handling high formic acid concentrations. The professional and non-professional end user should apply ventilation-related risk mitigation measures to protect himself and possible bystanders; see the relevant sections in the CAR for details. Ventilation-related RMM should be defined at product authorization level, especially if the risk assessment cannot be refined in other ways (e.g. by performing actual measurements of FA concentrations in air).

At product level, the risk assessment should take into account the in-use dilutions for which efficacy is supported by sufficient testing. Effects of other parameters on the risk assessment, such as the necessary contact time of the mixture, should also be taken into account.

Exposure through the dietary route and livestock exposure: due to its rapid turnover and unlikely accumulation, an estimation of exposure of humans to formic acid residues through diet, and exposure of livestock to FA were not considered. However, it is proposed that the need for assessment of dietary risk for humans and livestock be evaluated at biocidal product authorisation.

Environmental precautions:

Do not empty into drains.

PART D : APPENDICES

APPENDIX I: LIST OF ENDPOINTS

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Formic Acid
Product-type	2, 3, 4, 5, 6

Identity	
Chemical name (IUPAC)	Formic Acid
Chemical name (CA)	Formic Acid
CAS No	64-18-6
EC No	200-579-1
Other substance No.	
Minimum purity of the active substance as manufactured (g/kg or g/l)	99%
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Not applicable
Molecular formula	CH_2O_2
Molecular mass	46.025
Structural formula	HCOOH

Physical and chemical properties	
Melting point (state purity)	8°C
Boiling point (state purity)	100.23
Thermal stability / Temperature of decomposition	350°C
Appearance (state purity)	Liquid (20°C)
Relative density (state purity)	D_4^{20} = 1.2195
Surface tension (state temperature and concentration of the test solution)	At 20 °C: 71.5 mN/m

Vapour pressure (in Pa, state temperature)	At 20 °C: 42.71 hPa At 25 °C: 54.96 hPa At 50 °C: 170.7 hPa
Henry's law constant (Pa m^3 mol^{-1})	At 20 °C: 0.16 Pa.m^3/mol
Solubility in water (g/l or mg/l, state temperature)	Completely miscible Corresponding to 1220 g/L (= D_4^{20}) At pH 5 / 7 / 9 At 20.1 ± 0.1 °C
Solubility in organic solvents (in g/l or mg/l, state temperature)	Miscible at ratios: 1:9, 1:1 and 9:1 Miscible at 20 and 30 °C Corresponding to: > 850 g/L N,N-dimethylformamide > 929 g/L 1,4-dioxane > 1190 g/L Dichloromethane
Stability in organic solvents used in biocidal products including relevant breakdown products	Waived, since no organic solvent is used in the biocidal product.
Partition coefficient (log P_{OW}) (state temperature)	At pH 5: Log K_{OW} = -1.9 At pH 7: Log K_{OW} = -2.1 At pH 9: Log K_{OW} = -2.3
Dissociation constant	At 20 °C: pK_a = 3.70
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	n.a.
Flammability or flash point	49.5°C
Explosive properties	The substance is not explosive.
Oxidising properties	The substance is not an oxidising liquid
Auto-ignition or relative self ignition temperature	528°C

Classification and proposed labelling

with regard to physical hazards	H290 H226

with regard to human health hazards	H302 H331 H314 H318 EUH071
with regard to environmental hazards	

Chapter 2: Methods of Analysis

Analytical methods for the active substance	
Technical active substance (principle of method)	Titration with sodium hydroxide Confirmatory method: GC-MS chromatography
Impurities in technical active substance (principle of method)	Determination of Water by Karl-Fischer titration

Analytical methods for residues	
Soil (principle of method and LOQ)	UV absorption after stochiometric , enzyme-catalyzed reduction of NAD+ to NADH by formic acid Formic acid (formate) is quantitatively oxidized to bicarbonate by nicotinamide adenine dinucleotide (NAD) in the presence of formate dehydrogenase (FDH). $\text{Formate} + NAD^{+} + H_2O \xrightarrow{FDH} \text{bicarbonate} + NADH + H^{+}$ The amount of NADH formed is stoichiometric to the amount of formic acid. The increase in NADH is measured by means of its light absorbance at 334, 340 or 365 nm 10 mg/kg
Air (principle of method and LOQ)	Ion chromatography; LOQ = 0.1 µg
Water (principle of method and LOQ)	UV absorption after enzymatic reaction; LOQ = 0.2 mg/L in drinking water; LOQ = 0.2 mg/L in surface water
Body fluids and tissues (principle of method and LOQ)	0.2 mg/L
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	UV absorption after enzymatic reaction; LOQ = 0.2 mg/L

Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	UV absorption after enzymatic reaction; LOQ = 0.2 mg/L

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals	
Rate and extent of oral absorption:	Rapid, no quantitative data Assumed 100%
Rate and extent of dermal absorption*:	Corrosive Assumed 100%
Rate and extent of inhalation absorption:	Corrosive Assumed 100%
Distribution:	Significant, no quantitative data
Potential for accumulation:	no indication of accumulation
Rate and extent of excretion:	Rapid elimination via exhalation of CO_2; low urinary excretion of formic acid
Toxicologically significant metabolite(s)	none

* the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Acute toxicity	
Rat LD_{50} oral	730 mg/kg bw[21] Classification as Acute tox cat. 4 (oral) is warranted; H302.
Rat LD_{50} dermal	No data for Formic Acid Sodium formate: LD_{50} >2000 mg/kg bw
Rat LC_{50} inhalation	7.4 mg/l Classification as Acute tox cat. 3 (inhalation) is warranted; H331.

Skin corrosion/irritation	Formic Acid is classified as Skin Corr 1A, H314 (harmonised classification) Formic acid solutions ≥ 2% are considered skin irritants

21 RAC agreed in June 2022 on the classification and labelling for formic acid according to Regulation (EC) No 1272/2008 : H302 (& H331) duly confirmed. LD_{50} values from the adopted RAC opinion that will need to be used in biocidal product authorisation.

Eye irritation	Formic Acid is classified as Skin Corr 1A, H314 (harmonised classification), covering also eye damage/irritation effects Formic acid solutions ≥ 2% are considered eye irritants

Respiratory tract irritation	Classification as EUH071 'corrosive to the respiratory tract' is warranted as the substance is classified for inhalation toxicity with corrosivity as the mechanism of toxicity.

Skin sensitisation (test method used and result)	No classification for skin sensitization warranted (Buehler test: no sensitising properties shown)

Respiratory sensitisation (test method used and result)	There is no indication that formic acid would be a respiratory sensitizer.

Repeated dose toxicity

Short term

Species / target / critical effect	No data available on short-term toxicity Covered by subchronic toxicity studies
Relevant oral NOAEL / LOAEL	No oral repeated dose study available
Relevant dermal NOAEL / LOAEL	No dermal repeated dose study available
Relevant inhalation NOAEL / LOAEL	No inhalation repeated dose study available

Subchronic

Species/ target / critical effect	Rat, pig (oral), rat, mouse (inhal) local: histological changes in stomach (rat, pig) and upper respiratory tract (rat, mouse) syst: decreased body weight gain (rat, oral & mouse, inhalation)
Relevant oral NOAEL / LOAEL	As formate: Rat $LOAEL_{syst}$ 2100 mg/kg bw/d $NOAEL_{syst}$ 840 mg/kg bw/d $LOAEL_{local}$ 420 mg/kg bw/d $NOAEL_{local}$ <420 mg/kg bw/d Pig $LOAEL_{syst}$ >760 mg/kg bw/d $NOAEL_{syst}$ 760 mg/kg bw/d $LOAEL_{local}$ 149 mg/kg bw/d $NOAEL_{local}$ <149 mg/kg bw/d
Relevant dermal NOAEL / LOAEL	No dermal repeated dose study available

Relevant inhalation NOAEL / LOAEL	Rat LOAEC$_{syst}$ not achieved NOAEC$_{syst}$ 244 mg/m^3 LOAEC$_{local}$ 61 mg/m^3 NOAEC$_{local}$ 30 mg/m^3 Mouse LOAEC$_{syst}$ 244 mg/m^3 NOAEC$_{syst}$ 122 mg/m^3 LOAEC$_{local}$ 122 mg/m^3 NOAEC$_{local}$ 61 mg/m^3 overall NOAEC$_{local}$ 60 mg/m^3 (histopathological changes in nasal region of rats and mice at 122 mg/m^3)
Long term	
Species/ target / critical effect	Rat, pig (oral) local: histological changes in stomach & GI (rat) syst: decreased body weight gain (rat)
Relevant oral NOAEL / LOAEL	As formate: Rat LOAEL$_{syst}$ 1400 mg/kg bw/d NOAEL$_{syst}$ 280 mg/kg bw/d LOAEL$_{local}$ 280 mg/kg bw/d NOAEL$_{local}$ 35 mg/kg bw/d Pig NOAEL$_{syst}$ 301 mg/kg bw/d
Relevant dermal NOAEL / LOAEL	No dermal repeated dose study available
Relevant inhalation NOAEL / LOAEL	No inhalation repeated dose study available

Genotoxicity	Formic acid gave negative results in the *in vitro* gene mutation study in bacteria, the *in vitro* cytogenicity study in mammalian cells, and *in vitro* gene mutation assay in mammalian cells. Chromosome aberrations were observed; it was concluded that formic acid is not itself clastogenic but that the acidic conditions of the medium were responsible for the chromosome aberrations. No *in vivo* genotoxicity studies are warranted. Formic acid has no genotoxic potential.

Carcinogenicity

Species/type of tumour	Rat, mouse: no evidence of a tumorigenic effect in the stomach or any other tissue was found. Mouse: a higher incidence of primary lung tumours, bronchiolo-alveolar adenomas and carcinomas was not of toxicological relevance.
Relevant NOAEL/LOAEL	As formate: Rat $LOAEL_{local}$ 280 mg/kg bw/d $NOAEL_{local}$ 35 mg/kg bw/d $LOAEL_{syst}$ 1400 mg/kg bw/d $NOAEL_{syst}$ 280 mg/kg bw/d Mouse $LOAEL_{local/syst}$ 1400 mg/kg bw/d $NOAEL_{local/syst}$ 280 mg/kg bw/d

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	Rat, rabbit Formate: no developmental toxicity and teratogenicity observed
Relevant maternal NOAEL	As formate: Rat NOAEL 640 mg/kg bw/d Rabbit NOAEL 670 mg/kg bw/d
Relevant developmental NOAEL	As formate: Rat NOAEL 640 mg/kg bw/d Rabbit NOAEL 670 mg/kg bw/d

Fertility

Species/critical effect	Rat Formate: no adverse effects on fertility observed
Relevant parental NOAEL	As formate: NOAEL 200 mg/kg bw/d
Relevant offspring NOAEL	As formate: NOAEL 670 mg/kg bw/d
Relevant fertility NOAEL	As formate: NOAEL 670 mg/kg bw/d

Neurotoxicity

Species/ target/critical effect	Formic acid is associated with optical nerve and photoreceptor toxicity at high doses. However, adverse effects on the optical nerve and photoreceptors are considered to be an exclusive sequel of acute methanol intoxication in primates. Classification of formic acid as neurotoxic is not warranted.

Developmental Neurotoxicity

Species/ target/critical effect	No evidence of a neurotoxic effect is found in developmental toxicity studies.

Immunotoxicity

Species/ target/critical effect	No immunotoxicity studies available There is no evidence from skin sensitisation, repeated dose or reproduction toxicity studies, that formic acid may have immunotoxic properties.

Developmental Immunotoxicity

Species/ target/critical effect	No developmental immunotoxicity studies available

Other toxicological studies

None available

Medical/human data

Human data are available from health records from industry and from clinical case reports (accidental or suicidal).

Oral exposure

Due to the corrosivity of formic acid, local effects must be expected at all dose levels. The amount ingested and the concentration determine the grade and the location of the effects. Therefore, the observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the esophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity (Systemic toxicity observed after ingestion of 30 g formic acid or more).

Accidental and suicidal oral exposure records report reversible burns of the oesophagus after ingestion of small quantities (up to 10 g). Consumption of between 5 and 30 g of formic acid led to minor superficial oropharyngeal burns or more severe symptoms including abdominal pain, vomiting, dyspnoea and dysphagia, hematemesis and pneumonitis, and oesophageal strictures. Doses up to 45 g formic acid were survived by most patients. The majority of patients died after doses between 45 – 200 g formic acid. Reported symptoms at high doses were corrosion of the gastro-intestinal tract, metabolic acidosis, haemolysis, loss of blood pressure, massive bleeding, hepatic and renal failure, and death.

Dermal exposure

Due to the corrosivity of concentrated formic acid, local effects must be expected following contact to the skin and to the eyes. Local burns heal only slowly. Tissue destruction of the skin may result in scarring. Systemic effects may result after contact of concentrated formic acid to extended areas of the body surface. Occupational and accidental dermal exposure records report skin corrosion and metabolic acidosis.

Inhalation

Systemic effects are unlikely to occur. Workplace measurements showed mean values and 95% percentiles far below the threshold limit of 5 ppm or 9.5 mg/m^3. Uptake of formic acid at this threshold exposure concentration equals approx. 0.5% of the metabolic rate observed in non-human primates. Therefore, an effect on the blood pH is unlikely. Formic acid inhalation concentrations from 30 ppm onwards are regarded as being immediately dangerous to life and health.

One accidental inhalation exposure record reported reversible Pulmonary dysfunction in the form of Reactive Airway Dysfunction Syndrome. Suicidal inhalation exposure records (mixing of formic acid with concentrated sulphuric acid to form carbon monoxide) report death due to CO intoxication alongside corrosion/irritation of skin, trachea, lungs, stomach due to formic acid fumes.

Summary

	Value	Study	Safety factor
$AEL_{short-term}$	8.4 mg/kg bw/d	Subchronic 90 day feeding study, rat	100
$AEL_{medium-term}$	8.4 mg/kg bw/d	Subchronic 90 day feeding study, rat	100

$AEL_{long-term}$	2.8 mg/kg bw/d rounded to 3 mg/kg bw/d[22]	Chronic 2-year feeding study, rat	100
ADI[23]	3 mg/kg bw/d	EU SANCO D3/AS D, 2005; JECFA, 2003	
ARfD	Not required		
Occupational exposure limit	5 ppm or 9.5 mg/m³ 5 ppm or 9 mg/m³	EU WEL, MAK/TLV (8-hour TWA) IOELV (Commission Directive 2006/15/EC)	
$AEC_{resp\ tract\ irrit}$	6 mg/m³	Subchronic 13w inhalation study, rat/mice	10

MRLs

Relevant commodities	default MRL acc to Art.18(1)(b) Reg 396/2005

Reference value for groundwater

According to BPR Annex VI, point 68	N/A

Dermal absorption

Study (*in vitro/vivo*), species tested	None, corrosive substance
Formulation (formulation type and including concentration(s) tested, vehicle)	N.A.
Dermal absorption values used in risk assessment	100%

Acceptable exposure scenarios (including method of calculation)

Formulation of biocidal product	Not evaluated
Intended uses	Professional uses: disinfection of animal drinking water / automated systems
Industrial users	Not evaluated

22 We refer to TAB entry TOX-4 as the impact of rounding is less than 10%. Please note that for this CAR, the risk characterization has been performed with the non-rounded 2.8 mg formate/kg bw/d value. The decision for rounding the AEL long-term was taken at HH WG I-2022; however it was decided that there was no need to alter the risk characterization of the CAR. For product approval, the rounded 3 mg formate/kg bw/d value should be used.

23 If residues in food or feed.

Professional users	**Mixing and loading: charging Formic Acid 85% into animal drinking water systems:** Loading, post-application: PPE: chemical-resistant gloves, eye/face protection, coveralls, boots; M&L: appropriate RPE RMM: sufficient ventilation Models used: Dermal exposure: Mixing and loading model 7 for pouring and pumping liquids (corrected) Inhalation of vapours: ConsexpoWeb evaporation, area of release constant **Secondary exposure to disinfected drinking water for animals:** Acceptable at low %FA RMM: sufficient ventilation Models used: HEEG Opinion 16, model for dipping of hands/forearms in a diluted solution Inhalation of vapours: ConsexpoWeb evaporation, area of release constant
Non professional users	Not evaluated
General public	Not evaluated
Exposure via residue in food	Dietary exposure to formic acid from the representative uses is considered unlikely. At product authorisation, the need for an assessment of dietary exposure should be reviewed.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water	
Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	DT50 > 1 year (pH 4, 7 and 9; 49.9±0.5 °C) DT50 > 20.7 years (pH 7; 12 °C)
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	• Direct photolysis: not expected • Photo-oxidation with OH-radicals in water: DT50 HCOO- = 35 years
Readily biodegradable (yes/no)	Yes
Inherent biodegradable (yes/no)	-
Biodegradation in freshwater	-

Biodegradation in seawater	-
Non-extractable residues	-
Distribution in water / sediment systems (active substance)	-
Distribution in water / sediment systems (metabolites)	-

Route and rate of degradation in soil

Mineralization (aerobic)	-
Laboratory studies (range or median, with number of measurements, with regression coefficient)	-
DT_{50lab} (20°C, aerobic):	-
DT_{90lab} (20°C, aerobic):	-
DT_{50lab} (10°C, aerobic):	-
DT_{50lab} (20°C, anaerobic):	-
degradation in the saturated zone:	-
Field studies (state location, range or median with number of measurements)	Open literature data suggest DT_{50}-values in the range of 1 day for biodegradation of formic acid in soil, even at low temperatures.
DT_{50f}:	1 day (12 °C)
DT_{90f}:	-
Anaerobic degradation	Indication that anaerobic degradation may be possible.
Soil photolysis	-
Non-extractable residues	-
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	-
Soil accumulation and plateau concentration	Not relevant due to rapid degradation in soil.

Biodegradation during manure storage

Biodegradation during manure storage	DT_{50} ≤ 10.5 days (20 °C) DT_{50} ≤ 19.9 days (12 °C)

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	The Koc for formic acid is pH dependent, with an increasing Koc at increasing pH levels. For risk assessment purposes at a pH of 7, a Koc value of 30 L/kg (log Koc of 1.48) is used.

Fate and behaviour in air

Direct photolysis in air	-
Quantum yield of direct photolysis	-
Photo-oxidative degradation in air	Latitude: - Season: - DT_{50} = 855.7 hours
Volatilization	-

Reference value for groundwater

According to BPR Annex VI, point 68	0.1 µg/L

Monitoring data, if available

Soil (indicate location and type of study)	-
Surface water (indicate location and type of study)	-
Ground water (indicate location and type of study)	-
Air (indicate location and type of study)	-

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group) : FRESHWATER

Species	Time-scale	Endpoint	Toxicity
Fish			
Oncorhynchus mykiss	96 h	LC_{50}	3500 mg/L
Invertebrates			
Daphnia magna	48 h	EC_{50}	540 mg/L
Daphnia magna	21 d	NOEC	100 mg/L
Algae			
Desmodesmus subspicatus	72 h	E_rC_{50}	> 1000 mg/L
	72 h	NOE_rC	1000 mg/L
Microorganisms			
Activated sludge	3 h	EC_{50}	> 500 mg/L

Toxicity data for aquatic species (most sensitive species of each group) : SEAWATER

Species	Time-scale	Endpoint	Toxicity
Fish			

Scophthalmus maximus	96 h	LC_{50}	1720 mg/L
Invertebrates			
Acartia tonsa	48 h	EC_{50}	531 mg/L
Algae			
Skeletonema costatum	72 h	E_rC_{50}	> 1000 mg/L

Effects on earthworms or other soil non-target organisms	
Acute toxicity to	-
Reproductive toxicity to	-

Effects on soil micro-organisms	
Nitrogen mineralization	-
Carbon mineralization	-

Effects on terrestrial vertebrates	
Acute toxicity to mammals	$NOAEL_{mammal, oral\_chr}$ = 280 mg/kg_{bw}.day
Acute toxicity to birds	-
Dietary toxicity to birds	-
Reproductive toxicity to birds	-

Effects on honeybees	
Acute oral toxicity	-
Acute contact toxicity	-

Effects on other beneficial arthropods	
Acute oral toxicity	-
Acute contact toxicity	-
Acute toxicity to	-

Bioconcentration	
Bioconcentration factor (BCF)	• Estimated BCFfish = 0.00327 L/kg_{wwt} • Estimated BCFearthworm = 0.84 L/kg_{wwt}
Depration time (DT_{50})	-
Depration time (DT_{90})	-

Level of metabolites (%) in organisms accounting for > 10 % of residues	-

Chapter 6: Other End Points

APPENDIX II: HUMAN EXPOSURE CALCULATIONS

Scenario 1, exposure to vapour during mixing & loading of Formic Acid 85% for disinfection of drinking water for animal consumption

Substance	
Name	Formic Acid
Molecular weight	46 g/mol
K_{OW}	-2.1 10Log
Product	
Name	**Formic Acid 85%**
Weight fraction substance	85 %
Population	
Name	Professionals
Body weight	60 kg
Frequency	once per day for professionals
Description	Mixing & Loading: Charging Formic Acid 85% into animal drinking water systems

Exposure model	Exposure to vapour - Evaporation
Exposure duration	10 minute
Product is substance in pure form	no
Molecular weight matrix	18 g/mol
The product is used in dilution	no
Amount of solution used	15000 g / 350000g
Weight fraction substance	85 %
Room volume	24 m³
Ventilation rate	10 per hour
Inhalation rate	1.25 m³/hr
Application temperature	20 °C
Vapour pressure	4.27E+03 Pa
Molecular weight	46 g/mol
Mass transfer coefficient	10 m/hr
Release area mode	constant
Release area	100 cm²
Application duration	5 minute
Absorption model	Fixed fraction
Absorption fraction	1 / 0.025

Results

The amount of concentrate handled does not affect the concentration of FA in air during M&L.

Inhalation tier 1

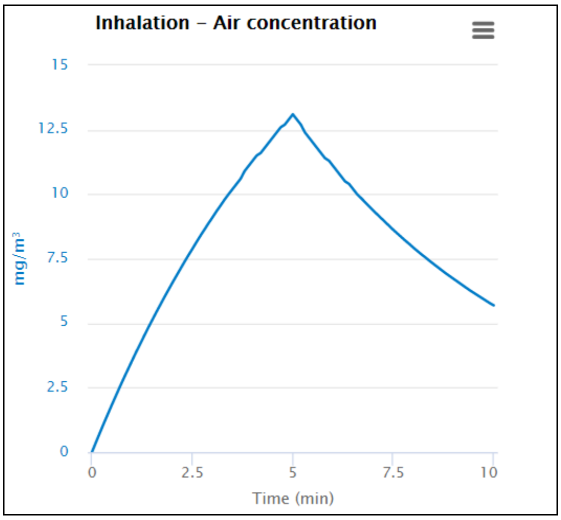
	No RPE, 85% FA
Mean event concentration	8.1 mg/m³
Peak concentration (TWA 15 min)	8.1 mg/m³
Mean concentration on day of exposure	5.6×10^{-2} mg/m³
Year average concentration	5.6×10^{-2} mg/m³
External event dose	2.8×10^{-2} mg/kg bw
External dose on day of exposure	2.8×10^{-2} mg/kg bw
Internal event dose	2.8×10^{-2} mg/kg bw
Internal dose on day of exposure	2.8×10^{-2} mg/kg bw/day
Internal year average dose	2.8×10^{-2} mg/kg bw/day

Inhalation tier 2

	RPE, 85% FA
Mean event concentration	8.1 mg/m³
(Taking into account the protection factor for half mask with vapour filter, estimated inhalation exposure will be 10 times lower)	0.81 mg/m³
Peak concentration (TWA 15 min)	8.1 mg/m³
Mean concentration on day of exposure	5.6×10^{-2} mg/m³
Year average concentration	5.6×10^{-2} mg/m³
External event dose	2.8×10^{-2} mg/kg bw
External dose on day of exposure	2.8×10^{-2} mg/kg bw
Internal event dose	7.0×10^{-4} mg/kg bw
Internal dose on day of exposure	7.0×10^{-4} mg/kg bw/day
Internal year average dose	7.0×10^{-4} mg/kg bw/day

Graph II.1 Formic Acid air concentration during mixing and loading for disinfection of drinking water for animal consumption

	0.17% FA fin or 5% FA fin

85% FA, +/- RPE	

pt5 ML.xlsx

Excel table:

Scenario 2, preliminary scenario for exposure to vapour during contact with disinfected drinking water

Assumptions:

The following is to be considered a preliminary and conservative estimate for inhalation of FA vapour with an automated poultry drinking system dispensing FA-treated drinking water as a source. It is included in the HE annex to the PT5 CAR as it is not a harmonized model/scenario.

This estimate of exposure to formic acid vapours is for a farmer present during 6h in a standard broiler housing of 4170 m^3 containing 20000 broiler chickens. The automated water supply system presented here consists of water nipples connected to a central water supply via piping, including a drip cup of 8 by 8 cm per nipple. Each nipple provides drinking water for 10 chickens; therefore 2000 nipple/drip cup units are foreseen. The total surface of water from which formic acid can evaporate is 12.8 m^2 (64 cm^2 x 2000). Assuming that the fill height of each drip cup is 1 cm, the total volume of water available for evaporation is 128L. Ventilation rates for chicken housings are 4.3/h min in winter and up to 30.2/h in summer (BPR HH Guidance Part B+C, table 53).

Substance		
Name	Formic Acid	
Molecular weight	46 g/mol	
K_{OW}	-2.1 10Log	
Product		
Name	**FA dilution 0.17 %**	**FA dilution 5 %**

Weight fraction substance	0.17 %	5%
Population		
Name	Professionals	
Body weight	60 kg	
Frequency	Once/d	
Description	Evaporation from drinking water system	

Exposure model	Exposure to vapour - Evaporation	
Exposure duration	360 minute	
Product is substance in pure form	no	
Molecular weight matrix	18 g/mol	
The product is used in dilution	no	
Amount of solution used	1.28E+05 g	
Weight fraction substance	0.17 %	5%
Room volume	4170 m³	
Ventilation rate	4.3 per hour / 30.2 per hour	
Inhalation rate	1.25 m³/hr	
Application temperature	20 °C	
Vapour pressure	4.27E+03 Pa	
Molecular weight	46 g/mol	
Mass transfer coefficient	10 m/hr	
Release area mode	Constant	
Release area	12.8 m²	
Application duration	360 minute	
Absorption model	Fixed fraction	
Absorption fraction	1	

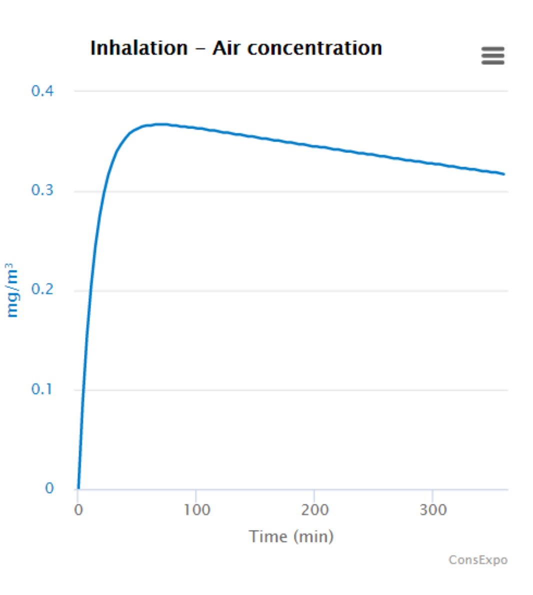
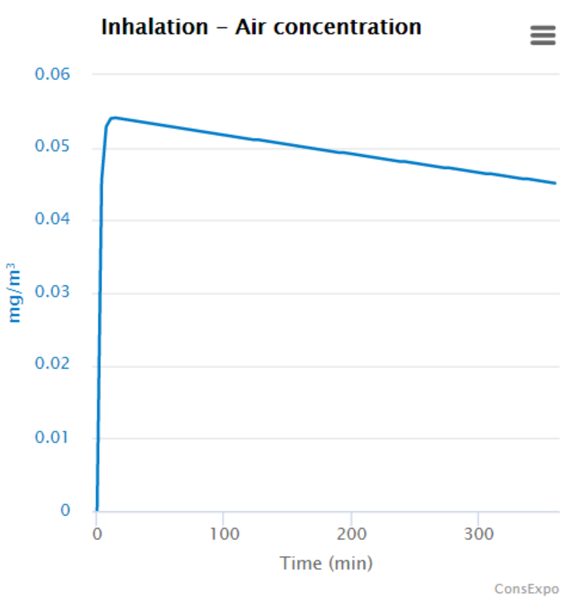
Results

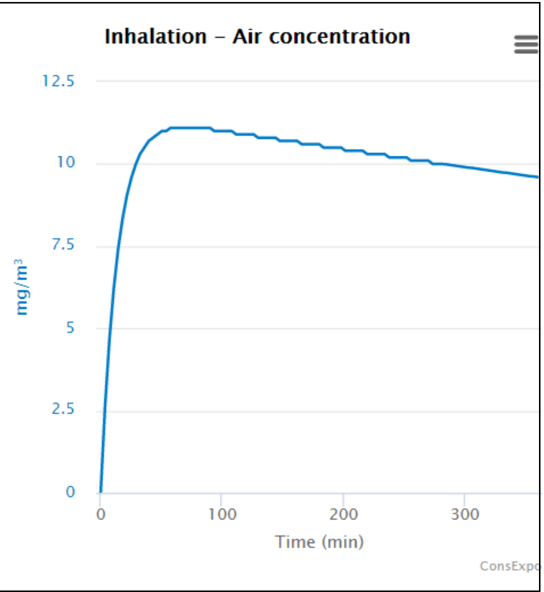
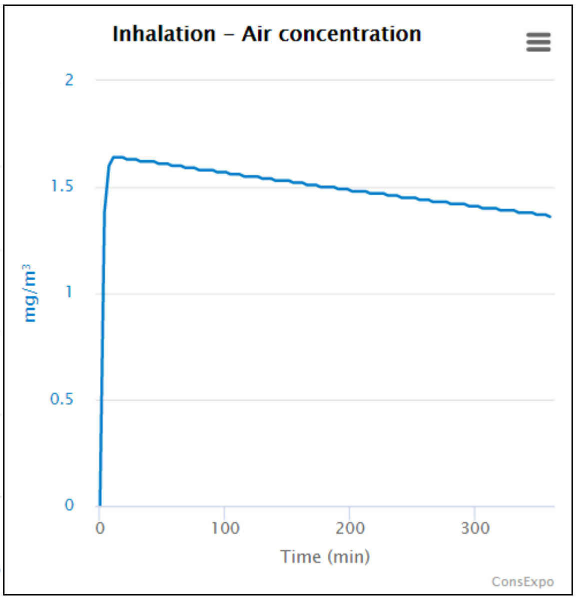
Inhalation

	0.17%, 4.3/h	**0.17%, 30.2/h**
Mean event concentration	3.3×10^{-1} mg/m³	4.9×10^{-2} mg/m³
Peak concentration (TWA 15 min)	3.6×10^{-1} mg/m³	5.1×10^{-2} mg/m³
Mean concentration on day of exposure	8.3×10^{-2} mg/m³	1.2×10^{-2} mg/m³
Year average concentration	8.3×10^{-2} mg/m³	1.2×10^{-2} mg/m³
External event dose	4.2×10^{-2} mg/kg bw	6.1×10^{-3} mg/kg bw
External dose on day of exposure	4.2×10^{-2} mg/kg bw	6.1×10^{-3} mg/kg bw
Internal event dose	4.2×10^{-2} mg/kg bw	6.1×10^{-3} mg/kg bw
Internal dose on day of exposure	4.2×10^{-2} mg/kg bw/day	6.1×10^{-3} mg/kg bw/day
Internal year average dose	4.2×10^{-2} mg/kg bw/day	6.1×10^{-3} mg/kg bw/day

	5%, 4.3/h	**5%, 30.2/h**
Mean event concentration	1.0 x 10^{1} mg/m^3	1.5 mg/m^3
Peak concentration (TWA 15 min)	1.1 x 10^{1} mg/m^3	1.5 mg/m^3
Mean concentration on day of exposure	2.5 mg/m^3	3.7 × 10^{-1} mg/m^3
Year average concentration	2.5 mg/m^3	3.7 × 10^{-1} mg/m^3
External event dose	1.3 mg/kg bw	1.9 × 10^{-1} mg/kg bw
External dose on day of exposure	1.3 mg/kg bw	1.9 × 10^{-1} mg/kg bw
Internal event dose	1.3 mg/kg bw	1.9 × 10^{-1} mg/kg bw
Internal dose on day of exposure	1.3 mg/kg bw/day	1.9 × 10^{-1} mg/kg bw/day
Internal year average dose	1.3 mg/kg bw/day	1.9 × 10^{-1} mg/kg bw/day

Graph II.2 Formic Acid air concentration in animal housing from disinfected drinking water

	Ventilation rate 4.3/h	**Ventilation rate 30.2/h**
0.17 % in-use dilution		

5 % in-use dilution		

Excel table: pt5 inhal drinking water.xlsx

Tentative approach to 'Guidance on the BPR V III HH-Assessment & Evaluation, Section 6: Guidance On Estimating Livestock Exposure to Active Substances used in Biocidal Products'

eCA BE proposes that the assessment of dietary risk for humans and livestock resulting from use of formic acid in PT5 biocidal products be undertaken at biocidal product authorisation. However, a preliminary estimate of this dietary risk is presented here.

<u>Exposure as a consequence of drinking disinfected drinking water:</u>

Concentration of formic acid in disinfected drinking water: 0.17%

The trigger value of 0.004 mg a.s./kg bw/d is exceeded for oral exposure due to intake of treated drinking water, as illustrated below.

However, considering that the maximum percentage of Formic Acid which is considered safe in animal water is 0.4% (EFSA, 2009, FA_BPR_Ann_II_8_16_01; EFSA, 2014; FA_BPR_Ann_II_8_16_02; EFSA, 2015, FA_BPR_Ann_II_8_16_03), and the prescribed concentration of formic acid in drinking water for this biocidal product is only 0.17%, then it could be disputed whether the default trigger value for a Tier II assessment is applicable here.

Animal species	Bw (kg)	Water consumption (L/d)	F.A. in water (mg/d) at 0.17% dilution	Total FA intake (mg/kg bw/d)	Max F.A. in water (mg/d) at 0.4% dilution	Max allowed FA intake (mg/kg bw/d)
Broiler chicken	1.7	0.25	425	250	1000	588
Beef cattle	500	50	85000	170	200000	400
Dairy cattle	650	115	195500	301	460000	708
pigs	100	10	17000	170	40000	400
Laying hens	1.9	0.25	425	224	1000	526

In this tentative approach, it is assumed that the concentration of formic acid required to fulfil the efficacy claims made by the applicant, is below 0.4% (notably 0.17% as suggested by the applicant). However, at the time of writing, only for in-use concentrations of >5% FENNOPUR® MH 85 (85.9% FA) efficacy was proven for its bactericidal and yeasticidal properties; efficacy against *Legionella pneumophila* was shown at 0.17% FA. At product authorization level, the actual efficacious dose of the BP could determine whether dietary exposure needs to be assessed.

APPENDIX III: ENVIRONMENTAL EMISSION (AND EXPOSURE) CALCULATIONS

This appendix contains the following documents :

- Emission estimation and PEC calculation manure route – scenario 1a;
- Emission estimation and PEC calculation manure route – scenario 1b;
- PEC calculation STP route – scenario 1a ;
- PEC calculation STP route – scenario 1b ;
- PEC calculations aggregated exposure – manure route.

PT5_Drinking water_Animal housi PT5_Drinking water_Animal housi PEC_aq_Drinking water_Animal-housi PEC_aq_Drinking water_Animal-housi PEC_aggregated_revApril2022.xlsm

APPENDIX IV: LIST OF TERMS AND ABBREVIATIONS

Not relevant

APPENDIX V: OVERALL REFERENCE LIST

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner
[redacted]	1994	Annex II.1 - 8.12.3 / BPD ID A6.12.3_01a	Werksärztlicher Dienst, Department of Occupational Medicine, Unveröffentlichte Mitteilung. BASF, Internal information, -. non-GLP / Unpublished	Yes	BASF SE (LoA: Kemira / Taminco)
[redacted]	2002	Annex II.1 - 8.12.3 / BPD ID A6.12.3_01b	Werksärztlicher Dienst, Department of Occupational Medicine, Unveröffentlichte Mitteilung. BASF, Internal information, -. non-GLP / Unpublished	Yes	BASF SE (LoA: Kemira / Taminco)
Altaweel MM et al.	2009	Annex II.1 - 8.8 / FA_BPR_Ann_II_8_8_11	Ocular and Systemic Safety Evaluation of Calcium Formate as a Dietary Supplement. JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS Volume 25, Number 3, 223-230, -. - / Published	No	Public
Altiparmak UE	2013	Annex II.1 - 8.13.2 / FA_BPR_Ann_II_8_13_5_01	Toxic optic neuropathies. Curr Opin Ophthalmol, 24:534–539, -. - / Published	No	Public
Andreae, M. O. & Merlet, P.	2001	CAR (ED) / -	Emission of trace gases and aerosols from biomass burning. Global Biogeochem. Cy. 15, 955–966 , -. - / Published	No	Public
Anonymous	1990	Annex II.1 - 8.12.8 / BPD ID A6.12.8_01b	NIOSH Pocket Guide to Hazardous Chemicals. U.S. Departm. of Health and Human Services. Washington, D.C., USA, -. - / Published	No	Public
Anonymous	2007	Annex II.1 - 5.1, 5.2, 5.3 / BPD ID A4.1_01	UV test for the determination of Formic Acid in foodstuffs and other materials. R-Biopharm, Cat. No. 10 979732 035. - / Published	No	Public
Anonymous	2019	Annex II.1 – 10.1 / 190910 FA_Addendum_Water_final sent to BE 2019-09-10	Formic acid: Degradation kinetics in water, Addendum to the biocidal active substance registration dossier of formic acid according to biocidal products regulation (EU) No 528/2012. FATF, September10_ 2019. non-GLP / Unpublished	Yes	FATF

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner
Anonymous	2019	Annex II.1 – 10.1, 10.2 / FA_Addendum_Soil_Deg_2019-08-20	Formic acid: Fate and degradability, Soil and Manure, Addendum to the biocidal active substance registration dossier of formic acid according to biocidal products regulation (EU) No 528/2012. FATF, August20_ 2019. non-GLP / Unpublished	Yes	FATF
Anonymous	2020	Annex II.1 – 10.1 / FA_Addendum_Manure_Deg_2020-09-07	Formic Acid: Degradability in Manure; Addendum to the biocidal active substance registration dossier of formic acid according to biocidal products regulation (EU) No 528/2012. FATF, September07_2020. Non-GLP / Unpublished	Yes	FATF
Anonymous	2020	Annex II.1 – 8.9.2 / 20200904_BASF_FA_Inhalation MAK	Compilation on public information on the MAK value of formic acid; FATF, September04_2020. non-GLP / Unpublished	Yes	FATF
Anonymous	2021	Annex II.1 – 8 / 20210117_ FA_BASF_ToxicityEndpoints	Formic acid: Toxicity Endpoints (LC_{50} acute inhalation, NOAEC local effects in 90-days rat; Addendum to the biocidal active substance registration dossier of formic acid according to biocidal products regulation (EU) No 528/2012. FATF, January17_2021. Non-GLP / Unpublished	Yes	FATF
Anonymous	2021	Addendum: use of public data as key data / 20210225 FA_Justification_Public data as key info_deg soil manure	Formic acid: Use of information from public literature as key studies: Degradation in soil, Degradation in manure; Addendum to the biocidal active substance registration dossier of formic acid according to biocidal products regulation (EU) No 528/2012. BASF SE and Kemira OYJ, February25_2021. Non-GLP / Unpublished	Yes	BASF SE, Kemira OYJ
Anonymus	2021	Addendum: Parameter justification / 20210117_FA_BASF_Justification HHRA Parameters	Formic Acid: Human Health Risk Assessment, Justifications for parameter adaptations; Addendum to the biocidal active substance registration dossier of formic acid according to biocidal products regulation (EU) No 528/2012. BASF SE, January17_2021. Non-GLP / Unpublished	Yes	BASF SE
Atkinson R	1989	Annex II.1 - 10.3.2 / BPD ID A7.3.2_01	Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. J. Phys. Chem. Ref. Data, Monograph No. 1, -. - / Published	No	Public

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner
Bakovic M et al.	2015	Annex II.1 - 8.12.2 / FA_BPR_Ann_II_8_12_2_11.pdf	Suicidal chemistry: combined intoxication with carbon monoxide and formic acid. Int J Legal Med; published online; DOI 10.1007/s00414-015-1208-0, -. - / Published	No	Public
Baziramakenga R and Simard RR	1998	Annex II.1 – 10.1 / -	Low molecular weight aliphatic acid contents of composted manures. J. Environ. Qual. 27, 557-561., -. - / Published	No	Public
[redacted]	2007	Annex II.1 - 3.11, 4.6, 4.17.1; [BASF: III-B 3.4] , Annex III.1 - 4.17.1 / BPD ID A3_02	Evaluation of physical and chemical properties according to Directive 67/548/EC Annex V. BASF AG, GCT/S-L511. Laboratory study code SIK-Nr. 07/1018. GLP / Unpublished	Yes	FATF
Boeniger MF	1987	Annex II.1 - 8.8 / BPD ID A6.2_09	Formate in urine as a biological indicator of formaldehyde exposure: a review . Am. Ind. Hyg. Assoc. J. 48(11), 900-908, -. - / Published	No	Public
Bouchard M, Brunet RC, Droz P-O, Carrier G	2001	Annex II.1 - 8.8 / BPD ID A6.2_03	A biologically based dynamic model for predicting the disposition of methanol and its metabolites in animals and humans . Toxicol. Sci. 64, 169-184, -. - / Published	No	Public
[redacted]	2016	Annex III.1 - 3.4.1.1 / KT_BPR_Ann3_13	Determination of the accelerated storage of Formic acid 85% (also known under the tradename Fennopur MH85) . Laus GmbH, Kirrweiler, Germany, 16011907G978. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2020	Annex III.1 - 3.4.1.2 / KT_BPR_Ann3_15	Determination of the storage stability of Formic acid 85% (also known under the tradename Fennopur MH85) at room temperature. Laus GmbH, Kirrweiler, Germany, 16011907G001. GLP / Unpublished	Yes	Kemira / Taminco
Buxton GV, Greenstock CL, Helman WP, Ross AB	1988	Annex II.1 - 10.1.1.1.b / BPD ID A7.1.1.1.2_01	Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxy radicals (.OH/.O-) in aqueous solution. J. Phys. Chem Data 17(2), 513-882, -. - / Published	No	Public
[redacted]	2016f	Annex III.1 - 6.7 / BPR-6.7-06	Surface bactericidal effectiveness for veterinary area on Fennopur MH85.. Eurofins Biolab S.r.l, Vimodrone, Italy, S-2016-00244 AM. GLP / Unpublished	Yes	Kemira / Taminco

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner
[redacted]	2016d	Annex III.1 - 6.7 / BPR-6.7-04	Surface Bactericidal Effectiveness on Fennopur MH85 in Clean Conditions.. Eurofins Biolab S.r.l, Vimodrone, Italy, S-2016-00242 AM. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016b	Annex III.1 - 6.7 / BPR-6.7-02	Suspension Bactericidal Effectiveness against Legionella on Fennopur MH85.. Eurofins Biolab S.r.l, Vimodrone, Italy, S-2016-00240 AM. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016e	Annex III.1 - 6.7 / BPR-6.7-05	Suspension bactericidal Effectiveness for veterinary area on Fennopur MH85.. Eurofins Biolab S.r.l, Vimodrone, Italy, S-2016-00243 AM. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016a	Annex III.1 - 6.7 / BPR-6.7-01	Suspension Bactericidal Effectiveness on Fennopur MH85 in Clean Conditions.. Eurofins Biolab S.r.l, Vimodrone, Italy, S-2016-00239 AM. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016c	Annex III.1 - 6.7 / BPR-6.7-03	Suspension Yeasticidal Effectiveness on Fennopur MH85 in Clean Conditions.. Eurofins Biolab S.r.l, Vimodrone, Italy, S-2016-00241 AM. GLP / Unpublished	Yes	Kemira / Taminco
Chameides, W. L. & Davis, D. D.	1983	Annex II.1 – 10.1 / -	Aqueous-phase source of formic acid in clouds. Nature 304, 427–429, -. - / Published	No	Public
Chan TC, Williams SR, and Clark RF	1995	Annex II.1 - 8.12.2 / BPD ID A6.12.2_09	Formic acid skin burns resulting in systemic toxicity.. Annals of Emerg. Medicine 26, 383-386, -. - / Published	No	Public
Chou WL, Speece RE, Siddiqi RH	1979	Annex II.1 - 10.1.3.1.b, Annex II.1 - 10.1.5 / BPD ID A.7.1.2.1.2_01	Acclimation and degradation of petrochemical wastewater components by methane fermentation. Biotechnol. Bioeng. Symp 8. 391-414, -. - / Published	No	Public
Clay KL, Murphy RC, Watkins D	1975	Annex II.1 - 8.8 / BPD ID A6.2_11	Experimental methanol toxicity in the primate: Analysis of metabolic acidosis. Toxicol. Appl. Pharmacol.34, 49-61, -. - / Published	No	Public
[redacted]	1994	Annex II.1 - 9.1.3.2, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.3_04	The growth inhibition to Skeletonema costatum of potassium formate liquor. Binnie Environmental Ltd. , ENV340/109410.OUL. GLP / Unpublished	Yes	FATF

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[redacted]	1994	Annex II.1 - 9.1.2, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2 / BPD ID A7.4.1.2_05	The toxicity to Acartia tonsa of potassium formate liquor. Binnie Environmental Ltd., ENV341/109410.OUL. GLP / Unpublished	Yes	FATF
Dalus D et al.	2013	Annex II.1 - 8.12.8 / FA_BPR_Ann_II_8_12_8_03.pdf	FORMIC ACID POISONING IN A TERTIARY CARE CENTER IN SOUTH INDIA: A 2-YEAR RETROSPECTIVE ANALYSIS OF CLINICAL PROFILE AND PREDICTORS OF MORTALITY. The Journal of Emergency Medicine, Vol. 44, No. 2, pp. 373–380, -. - / Published	No	Public
[redacted]	1998	Annex II.1 - 8.3_03 / BPD ID A6.1.5_02/ FA_BPR_Ann_II_8_3_03	Formi-LHS – Skin sensitisation Study in the Guinea Pig. [redacted], Report No. 1516/22-1032, January 1998 / unpublished.	Yes	BASF (LoA Kemira)
[redacted]	2007	Annex II.1 - 3.2, 3.4, 3.5, 3.7, 3.1.2, 3.1.3, 3.6, 3.8, 3.13, 3.15, 3.16, 9.1.2 / BPD ID A3_01	Spectroscopic characterization and determination of physico-chemical properties of "Formic acid". BASF AG, GKA Competence Center Analytics, 07L00084. GLP / Unpublished	Yes	FATF
[redacted]	2018	Annex II.1 - 3.2 / 20181112_07L00084 Amendment01 Final Report BPD_ID_A3_01	1st Amendment to final report 'Spectroscopic characterization and determination of physico-chemical properties of "Formic acid"'. BASF SE, November12_2018, GKA Competence Center Analytics, Ludwigshafen Study No. 07L00084. GLP / Unpublished	Yes	FATF
[redacted]	1992	Annex II.1 - 9.1.2, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.2_03	The acute toxicity of potassium formate to Daphnia magna. Huntington Research Centre Ltd. (HRC) (sponsored by KSEPL, Rijswijk, NL), SLL 237(f)/920574. GLP / Unpublished	Yes	FATF
[redacted]	1992a	Annex II.1 - 10.1.1.2.a, Annex II.1 - 10.1.1.2.b, Annex II.1 - 10.1.3.1.a, Annex II.1 - 10.1.3.2.a, Annex II.1 - 10.1.3.2.b, Annex II.1 - 10.1.5, Annex II.1 - 10.2.1, Annex II.1 - 10.2.8, Annex II.1 - 10.2.4, Annex II.1 - 10.2.6, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex II.1 - 9.6 / BPD ID A7.1.1.2.1_03	Assessment of ready biodegradability of potassium formate (Closed Bottle Test). Huntington Research Centre Ltd. (HRC) (sponsored by KSEPL, Rijswijk, NL), SLL 237(a)/920737. GLP / Unpublished	Yes	FATF

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[redacted]	1992b	Annex II.1 - 9.1.3.1, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.3_03	Potassium formate – the algistatic activity . Huntington Research Centre Ltd. (HRC) (sponsored by KSEPL, Rijswijk, NL), SLL 237(f)/920647. GLP / Unpublished	Yes	FATF
[redacted]	1992c	Annex II.1 - 9.1.2, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.2_04	The acute toxicity of potassium formate to brown shrimp (Crangon crangon). Huntington Research Centre Ltd. (HRC) (sponsored by KSEPL, Rijswijk, NL), SLL 217(d)/911712. GLP / Unpublished	Yes	FATF
[redacted]	1992d	Annex II.1 - 9.1.1, Annex II.1 - 9.1.6, Annex II.1 - 9.1.6.1, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.1_04	The acute toxicity of potassium formate to juvenile turbot (Scophthalmus maximus).. [redacted] (sponsored by KSEPL, Rijswijk, NL), SLL 217(h)/920037. GLP / Unpublished	Yes	FATF
[redacted]	1992e	Annex II.1 - 9.1.1, Annex II.1 - 9.1.6, Annex II.1 - 9.1.6.1, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex II.1 - 10.1.3.3 / BPD ID A7.4.1.1_03	The acute toxicity of potassium formate to rainbow trout (Oncorhynchus mykiss). [redacted] (sponsored by KSEPL, Rijswijk, NL), SLL 217(I)/911691. GLP / Unpublished	Yes	FATF
[redacted]	1994	Annex II.1 - 10.1.3.3 / BPD ID A7.1.1.2.3_01	The biodegradability in seawater of potassium formate liquor. Binnie Environmental Ltd. (sponsored by OSCA UK Ltd.), ENV342/109410.OUL. GLP / Unpublished	Yes	FATF
[redacted]	2002	Annex II.1 - 3.2, Annex II.1 - 3.4, Annex II.1 - 3.5, Annex II.1 - 3.7, Annex II.1 - 3.9, Annex II.1 - 3.10, Annex II.1 - 10.1.1.1.a, Annex II.1 - 10.1.4, Annex II.1 - 10.2.4, Annex II.1 - 10.2.6, Annex II.1 - 9.1.7, Annex II.1 - 9.1.7, Annex II.1 - 9.6 / BPD ID A7.1.1.1.1_01	Physico-chemical properties of "Ameisensäure". BASF AG, GKA Analytik, 02L00109. GLP / Unpublished	Yes	FATF
ECT Oekotoxikologie GmbH	2015	Annex II.1 - 3.7.1 / BPD ID A3_11	Henry's Law Constant calculated from water solubility and vapour pressure. ECT Oekotoxikologie GmbH, Flörsheim, Germany, -. non-GLP / Unpublished	Yes	FATF

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Eells JT, Henry MM, Lewandowski MF, Seme MT and Murray TG	2000	Annex II.1 - 8.7 / BPD ID A6.10_01	Development and characterization of a rodent model of methanol of methanol-induced retinal and optical nerve toxicity. Neuro Tox 21, 321-330, -. - / Published	No	Public
EFSA	2009	Annex II.1 - 8.16, Annex III.1 - 7 / FA_BPR_Ann_II_8_16_01	Scientific Opinion on the safety and efficacy of Formi™ LHS (potassium diformate) as a feed additive for sows. EFSA Journal 2009; 7 (9): 1315, --. non-GLP / Published	No	Public
EFSA	2014	Annex II.1 - 8.16, Annex III.1 - 7 / FA_BPR_Ann_II_8_16_02, EFSA_FormicAcid_2014	Scientific Opinion on the safety and efficacy of formic acid when used as a technological additive for all animal species. EFSA Journal 12 (10): 3827, --. non-GLP / Published	No	Public
EFSA	2015	Annex II.1 - 8.16 / FA_BPR_Ann_II_8_16_03	Scientific Opinion on the safety and efficacy of formic acid, ammonium formate and sodium formate as feed hygiene agents for all animal species. EFSA Journal 13 (5): 4113, -. - / Published	No	Public
[redacted]	2016	Annex II.1 - 9.1.5 / FA_BPR_Ann_II_9_1_5_01	A study on the respiration inhibition of activated sludge according to OECD Guideline for testing of chemicals No. 209. ECT Oekotoxikologie GmbH, Flörsheim/Main, Germany, 16EM1XA. GLP / Unpublished	Yes	FATF
[redacted]	2006	Annex II.1 - 8.12.1 / BPD ID A6.12_01	Workplace exposure of Formic acid. BASF AG, -. non-GLP / Unpublished	Yes	FATF
[redacted]	2002	Annex II.1 - 8.5.3 / BPD ID A6.6.3_01	In vitro gene mutation test with formic acid in CHO cells (HPRT locus assay) . BASF AG, Project No. 50M0102/024017, 27 June 2002. GLP / Unpublished	Yes	FATF
European Commission	2005	Annex II.1 - 8.16.1 / BPD ID A6.15.4_01a	Provisional list of monomers and additives notified to European commission as substances which may be used in the manufacture of plastics or coatings intended to come into contact with foodstuffs. European Commission, Synoptic Docum. (2005.07.25). - / Published	No	Public

Author(s)	**Year**	**Section No / Reference No**	**Title. Source (where different from company) Company, Report No.**	**Data Protection Claimed (Yes/No)**	**Owner**
Exner M, Herrmann H, Zellner R	1994	Annex II.1 - 10.1.1.1.b / BPD ID A7.1.1.1.2_03	Rate constants for the reactions of the NO3 radical with HCOOH/HCOO- and CH3COOH/CH3COO- in aqueous solution between 278 and 328 K. J. Atmos Chem. 18, 359 - 378, -. - / Published	No	Public
Franco A, Fu W, Trapp S.	2009	Annex II.1 – 10.1.2 / 100000_Franco, A._Environ. Toxic_2009	Influence of the soil pH on the sorption of ionizable chemicals: modeling advances. Environ Toxicol Chem 28: 458-464, -. - / Published	No	Public
Gabriel R., Schäfer, L., Gerlach, C., Rausch, T. & Kesselmeier, J.	1999	CAR (ED) / -	Factors controlling the emissions of volatile organic acids from leaves of Quercus ilex L. (Holm oak). Atmos. Environ. 33, 1347–1355, -. - / Published	No	Public
Galloway, J. N., Likens, G. E., Keene, W. C. & Miller, J. M.	1982	CAR (ED) / -	The composition of precipitation in remote areas of the world. J. Geophys. Res. 87, 8771–8786, -. - / Published	No	Public
[redacted]	2007	Annex II.1 - 8.7.3 / BPD ID A6.1.2_01	Natriumformiat (Sodium formate). Acute dermal toxicity study in rats. [redacted], 11A0123/031083. GLP / Unpublished	Yes	FATF
[redacted]	2002	Annex II.1 - 8.3 / -	Formic acid - Buehler test in Guinea pigs. [redacted], 32H0102/022005. non-GLP / Unpublished	Yes	FATF
GESTIS	2006	Annex II.1 - 3.11, 4.6 / BPD ID A3_05	Database (Gefahrstoffinformationssystem der gewerblichen Berufsgenossenschaften). TOXNET, -. - / Published	No	Public
Glanville H, Rousk J, Golyshin P, and Jones DL	2012	Annex II.1 – 10.2 / -	Mineralization of low molecular weight carbon substrates in soil solution under laboratory and field conditions. Soil Biology & Biochemistry 48, 88-95., -. - / Published	No	Public
[redacted]	1998	Annex II.1 - 8.8 / BPD ID A6.2_10	Formi LHS. Pharmacokinetics after oral dosing in pigs. [redacted], report No. 25280. GLP / Unpublished	Yes	FATF

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[redacted]	2006	Annex II.1 - 4.1, 4.13 / BPD ID A3_03	Expert judgement on oxidising and explosive properties of formic acid. [redacted], GCT/S-L511. non-GLP / Unpublished	Yes	FATF
Greim H	2003	Annex II.1 - 8.12.8 / BPD ID A6.12.8_01a	Formic Acid. Occupational Toxicants Vol. 19, 169-180, -. - / Published	No	Public
Hama T, Handa N	1981	Annex II.1 – 10.1 / -	[English title not available]. Rikusiugaku Zasshi 42: 8-19, -. - / Published	No	Public
Hanzlik RP et al.	2005	Annex II.1 - 8.8 / FA_BPR_Ann_II_8_8_10.pdf	ABSORPTION AND ELIMINATION OF FORMATE FOLLOWING ORAL ADMINISTRATION OF CALCIUM FORMATE IN FEMALE HUMAN SUBJECTS. DMD 33:282–286, -. - / Published	No	Public
[redacted]	2004	Annex II.1 - 8.9.1, _8.9.2, _8.9.3, ED-Assessment / BPD ID A6.4.1_02	Formi LHS: Target species safety study in the farrowing pig. Covance Laboratories Ltd., North Yorkshire/UK, 1516/034-D6154. GLP / Unpublished	Yes	FATF
Hellstén PP, Kivimäki AL, Miettinen IT, Mäkinen RP, Salminen JM, Nystém TH	2005a	Annex II.1 – 10.1 / -	Degradation of potassium formate in the unsaturated zone of a sandy aquifer.. Journal of Environmental Quality 34(5), 1665-1671., -. - / Published	No	Public
Hellstén PP, Salminen JM, Jørgensen KS, Nystén TH	2005b	Annex II.1 – 10.1 / -	Use of potassium formate in road winter deicing can reduce groundwater deterioration. Environ Sci Technol 39, 5095-5100, -. - / Published	No	Public
[redacted]	2016a	Annex III.1 - 3.2 / KT_BPR_Ann3_5	Determination of the acidity/alcalinity of Formic acid 85% (also known under the tradename Fennopur MH85) according to CIPAC, MT 191. Laus GmbH, Kirrweiler, Germany, 16011907G975. GLP / Unpublished	Yes	Kemira / Taminco (LoA: BASF SE)
[redacted]	2016b	Annex III.1 - 3.4.2.3 / KT_BPR_Ann3_8	Determination of the corrosion of metals by Formic acid 85% (also known under the tradename Fennopur MH85) following method 37.4 C.1 of the UN Handbook. Laus GmbH, Kirrweiler, Germany, 16011907G979. GLP / Unpublished	Yes	Kemira / Taminco (LoA: BASF SE)

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[redacted]	2016c	Annex III.1 - 3.2 / KT_BPR_Ann3_12	Determination of the pH-value of Formic acid 85% (also known under the tradename Fennopur MH85) according to CIPAC, MT 75. Laus GmbH, Kirrweiler, Germany, 16011907G907. GLP / Unpublished	Yes	Kemira / Taminco (LoA: BASF SE)
[redacted]	2016d	Annex III.1 - 3.3 / KT_BPR_Ann3_10	Determination of the density of Formic acid 85% (also known under the tradename Fennopur MH85) according to OECD 109 resp. EU A.3. Laus GmbH, Kirrweiler, Germany, 16011907G912. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016e	Annex III.1 - 4.6 / KT_BPR_Ann3_11	Determination of the flash point of Formic acid 85% (also known under the tradename Fennopur MH85) according to EU Method A.9, OPPTS 830.6315 and UN Manual Test Methods 32.4. Laus GmbH, Kirrweiler, Germany, 16011907G964. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016f	Annex III.1 - 3.5.7 / KT_BPR_Ann3_9	Determination of the persistent foaming of Formic acid 85% (also known under the tradename Fennopur MH85) according to CIPAC, MT 47. Laus GmbH, Kirrweiler, Germany, 16011907G968. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016g	Annex III.1 - 3.5.7 & 3.8 / KT_BPR_Ann3_6	Determination of the surface tension of an aqueous solution of Formic acid 85% (also known under the tradename Fennopur MH85) according to OECD 115 resp. EU A.5. Laus GmbH, Kirrweiler, Germany, 16011907G960. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	2016h	Annex III.1 - 3.9 / KT_BPR_Ann3_7	Determination of viscosity of Formic acid 85% (also known under the tradename Fennopur MH85) according to OECD 114 / DIN 53015CIPAC, MT 75. Laus GmbH, Kirrweiler, Germany, 16011907G984. GLP / Unpublished	Yes	Kemira / Taminco
[redacted]	1997	Annex II.1 - 8.8 / BPD ID A6.2_01	The chemical behavior of Potassium Diformate in water solutions. Comparison with Formic Acid.. Hydro Research Centre Porsgrunn, Norway, 97B_AO5.SAM. non-GLP / Unpublished	Yes	FATF

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HSDB	2006	Annex II.1 - 10.1.1.1.b, Annex II.1 - 10.3.2, ED-Assessment / BPD ID A7.1.1.1.2_04	Database extract. TOXNET, -. - / Published	No	Public
Iannotti EL, Porter JH, Fischer JR, and Sievers M	1997	Annex II.1 – 10.2 / -	Changes in swine manure during anaerobic digestion. In: Developments in industrial microbiology. Vol. 20: Proceedings of the 35th general meeting of the Society for Industrial Microbiology held at Houston , Texas: August 14-18, 1978. Arlington, VA, USA. Chapter 49, pp. 519-529, -. - / Published	No	Public
Jager T	1998	Annex II.1 – 9.6 / FA_BPR_Ann_II_9_6	Mechanistic approach for estimating bioconcentration of organic chemicals in earthworms (Oligochaeta). Environmental Toxicology and Chemistry 17(10), 2080-2090. Cited in ECHA (2017). Guidance on Biocidal Products Regulation: Volume IV Environment - Assessment and Evaluation (Parts B+C). DoI 10.2823/033935.	No	Public
[redacted]	1988	Annex II.1 - 9.1.2, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex III.1- 9.1 / BPD ID A7.4.1.2_01	Determination of the acute toxicity of formic acid to the waterflea Daphnia magna Straus. BASF AG, Department of Ecology, 1/0290/2/88-0290/88. non-GLP / Unpublished	Yes	FATF
JECFA	2003	Annex II.1 - 8.16.1 / BPD ID A6.15.4_01b	Formic acid. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. JECFA, -. - / Published	No	Public
Jefferys DB and Wiseman HM	1980	Annex II.1 - 8.12.2 / BPD ID A6.12.2_05	Formic acid poisoning. Postgrad. Med. J. 56, 761-763, -. - / Published	No	Public
[redacted]	2012	Annex III.1 - 3.4.1.2 / BPR ID Ann 3_3	Stability data of Kemira formic acid. Kemira Chemicals Oy, Date: 03.01.2012. non-GLP / Unpublished	Yes	Kemira / Taminco

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[redacted]	2000	Annex II.1 - 10.1.1.2.a, Annex II.1 - 10.1.1.2.b, Annex II.1 - 10.1.3.1.a, Annex II.1 - 10.1.3.2.a, Annex II.1 - 10.1.3.2.b, Annex II.1 - 10.1.5, Annex II.1 - 10.2.1, Annex II.1 - 10.2.8, Annex II.1 - 10.2.4, Annex II.1 - 10.2.6, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex II.1 - 9.6 / BPD ID A7.1.1.2.1_04	Biodegradability of potassium formate in water tested with OECD 310D (Closed Bottle Test). [redacted] (sponsored by Norsk Hydro ASA, Porsgrunn, Norway), B387/1. non-GLP / Unpublished	Yes	FATF
[redacted]	2022	Annex II.1 - 8.5.1_02 / BPD ID A6.6.1_02 / FA_BPR_Ann_II_8_5_1_02	Salmonella typhimurium / Escherichia coli reverse mutation assay. BASF SE. 40M0247/14M172	Yes	FATF
Kavet R and Nauss KM	1990	Annex II.1 - 8.8 / BPD ID A6.2_12	The toxicity of inhaled methanol vapors . Crit. Rev. Toxicol. 21, 21-50, -. - / Published	No	Public
Kawamura, K., Ng., L. L. & Kaplan, I. R.	1985	CAR (ED) / -	Determination of organic acids (C1-C10) in the atmosphere, motor exhausts and engine oils.. Environ. Sci. Tech. 19, 1082–1086, -. - / Published	No	Public
[redacted]	2013	Annex II.1 - 5.1, _5.2, _5.3 / BPD ID A4.1_03	Validation of an enzymatic method for the determination of formic acid.. Institute Dr. Appelt, Mannheim, Germany, No. 001. non-GLP / Unpublished	Yes	FATF
[redacted]	1989	Annex II.1 - 9.1.1, Annex II.1 - 9.1.6, Annex II.1 - 9.1.6.1, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 , Annex III.1- 9.1 / BPD ID A7.4.1.1_01	Report on the study of the acute toxicity to golden orfe (Leuciscus idus L., golden variety) (in German). [redacted], 10F0218/885243. non-GLP / Unpublished	Yes	FATF
[redacted]	2003	Annex II.1 - 8.9.4, ED-Assessment / BPD ID A6.5_02	Effect of pre-mating administration of Formi LHS on ovulation/fertility of breeding sows. [redacted], Project No. 818 545M (F-446). non-GLP / Unpublished	Yes	BASF SE (LoA: Kemira / Taminco)
[redacted]	2017	Annex II.1 - 4.16 / KT_BPR_Ann2_13	Determination of the corrosion of metals by Formic acid 99% following method 37.4 C.1 of the UN Handbook. Laus GmbH, Kirrweiler, Germany, 16092902G979. - / Unpublished	Yes	FATF

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Lamarre et al.	2013	CAR (ED) / -	Formate: essential metabolite, a biomarker or more?. Clin Chem Lab Med 51(3):571-578, -. - / Published	No	Public
Lin PT and Dunn WA	2014	Annex II.1 - 8.12.2 / FA_BPR_Ann_II_8_12_2_12.pdf	Suicidal carbon monoxide poisoning by combining formic acid and sulfuric acid with a confined space. J Forensic Sci, January 2014, Vol. 59, No. 1, -. - / Published	No	Public
Lissner H, Wehrer M, Jartun M, Totsche KU	2014	Annex II.1 – 10.2 / -	Degradation of deicing chemicals affects the natural redox system in airfield soils.. Environ Sci Pollut Res 21, 9036-9053. , -. - / Published	No	Public
Makar AB, Tephly TR, Sahin G, Osweiler G	1990	Annex II.1 - 8.8 / BPD ID A6.2_08	Formate metabolism in young swine. Toxicol. Appl. Pharmacol. 105, 315-320, -. - / Published	No	Public
Malizia E, Reale C, Pietropaoli P, and De Ritis GC	1977	Annex II.1 - 8.12.2, Annex II.1 - 8.12.2 / BPD ID A6.12.2_07a	Formic acid intoxications. Acta Pharm. Toxi.,S41342-347, -. - / Published	No	Public
Malorny G	1969a	Annex II.1 - 8.8, Annex II.1 - 8.7, ED-Assessment / BPD ID A6.2_06	Die akute und chronische Toxizität der Ameisensäure und ihrer Formiate. Z. Ernährungs-wiss. 9, 332-339, -. - / Published	No	Public
Malorny G	1969b	Annex II.1 - 8.8, Annex II.1 - 8.13.2 / BPD ID A6.2_07	Stoffwechselversuche mit Natrium-formiat und Ameisensäure beim Menschen. Z. Ernährungs-wiss. 9, 340-348, -. - / Published	No	Public
Martin-Amat G, McMartin, KE, Hayreh SS, Hayreh MS, Tephly TR	1978	Annex II.1 - 8.8, Annex II.1 - 8.13.2 / BPD ID A6.2_05	Methanol poisoning: Ocular toxicity produced by formate. . Toxicol. Appl. Pharmacol., 45, 201-208, -. - / Published	No	Public
[redacted]	2006	Annex II.1 - 10.3.2, Annex II.1 - 10.3.1 / BPD ID A7.3.1_01	Formic acid, EPI Suite v.3.12 calculations. BASF AG, Department of Product Safety, -. non-GLP / Unpublished	Yes	FATF
Morita T, Takeda K, and Okumura K	1990	Annex II.1 - 8.5.2 / BPD ID A6.6.2_01	Evaluation of clastogenicity of formic acid, acetic acid and lactic acid on cultured mammalian cells. Mut Res 240, 195-202, -. - / Published	No	Public

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner
[redacted]	1999	Annex II.1 - 8.4, _8.1, _8.2 / BPD ID A6.1.6_01	A sensory irritation study with Formi@ LHS in male mice.. [redacted] V98.1244. GLP / Unpublished	Yes	FATF
[redacted]	2007	Annex II.1 - 5.2.2, Annex II.1 - 5.2.2 / BPD ID A4.1_02	Method for the determination of formic acid in the air.. BASF AG, -. non-GLP / Unpublished	Yes	FATF
[redacted]	1985	Annex II.1 - 8.7.1 / BPD ID A6.1.1_01	Akute orale Toxizität von Ameisensäure 99 % für Ratten. [redacted], Report No. 0359. non-GLP / Unpublished	Yes	FATF
Murtaugh JJ, Bunch RL	1965	Annex II.1 – 10.1 / -	Acidic Components of Sewage Effluents and River Water. J Water Pollut Control Fed 37: 410-5, -. - / Published	No	Public
Naik RB, Stephens WP, Wilson DJ, Walker A, and Lee HA	1980	Annex II.1 - 8.12.2 / BPD ID A6.12.2_04	Ingestion of formic acid-containing agents – report of three fatal cases. Postgrad. Med. J. 56, 451-456, -. - / Published	No	Public
Neeb, P., Sauer, F., Horie, O. & Moortgat, G. R.	1997	CAR (ED) / -	Formation of hydroxymethyl hydroperoxide and formic acid in alkene ozonolysis in the presence of water vapor. Atmos. Environ. 31, 1417–1423, -. - / Published	No	Public
[redacted]	2007a	Annex II.1 - 3.1.4, 3.12 / BPD ID A3_06	Expert Judgement: Formic acid 99-100 % - materials compatibility and odor. BASF AG, E-CZS/PC. non-GLP / Unpublished	Yes	FATF
NTP-CERHR expert panel	2004	Annex II.1 - 8.8, Annex II.1 - 8.13.2 / BPD ID A6.2_04	NTP-CERHR expert panel report on the reproductive and developmental toxicity of methanol. U.S. DHHS, NTP; Reprod. Toxicol. 18: 303-390, -. - / Published	No	Public
OECD	2007	Annex II.1 - 9.1 / BPD ID IIA4.2.1_01	SIDS Initial Assessment Report on the Ammonia Category. OECD, Paris, -. - / Published	Yes	FATF
Page LH, Ni JQ, Heber AJ, Mosier NS, Liu X, Joo HS, Ndegwa PM, Harrrison JH	2014	Annex II.1 – 10.2 / 2014_Page LH et al_manure_anaerobic digestion	Characteristics of volatile fatty acids in stored dairy manure before and after anaerobic digestion. Biosystems Engineering 118: 16-28, -. - / Published	No	Public

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No.	Data Protection Claimed (Yes/No)	Owner
[redacted]	1988a	Annex II.1 - 10.1.1.2.a, Annex II.1 - 10.1.1.2.b, Annex II.1 - 10.1.3.1.a, Annex II.1 - 10.1.3.2.a, Annex II.1 - 10.1.3.2.b, Annex II.1 - 10.1.5, Annex II.1 - 10.2.1, Annex II.1 - 10.2.8, Annex II.1 - 10.2.4, Annex II.1 - 10.2.6, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex II.1 - 9.6 / BPD ID A7.1.1.2.1_01	Report on the determination of the biological degradability of formic acid in the Modified OECD Screening Test. BASF AG, Lab. of Environm. Analytics & Ecology, 0048/88. non-GLP / Unpublished	Yes	FATF
[redacted]	1988b	Annex II.1 - 10.1.1.2.a, Annex II.1 - 10.1.1.2.b, Annex II.1 - 10.1.3.1.a, Annex II.1 - 10.1.3.2.a, Annex II.1 - 10.1.3.2.b, Annex II.1 - 10.1.5, Annex II.1 - 10.2.1, Annex II.1 - 10.2.8, Annex II.1 - 10.2.4, Annex II.1 - 10.2.6, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex II.1 - 9.6 / BPD ID A7.1.1.2.1_02	Report on the determination of the biological degradability of formic acid in the Modified OECD Screening Test. BASF AG, Lab. of Environm. Analytics & Ecology, 52/0048/88. non-GLP / Unpublished	Yes	FATF
[redacted]	1988c	Annex II.1 - 9.1.5, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.4_01	Report on the Determination of the Respiration Activity of Activated Sludge by Formic Acid in the Short-Term Respiration Inhibition Test. BASF AG, Lab. of Environm. Analytics & Ecology, 01.0048/88. non-GLP / Unpublished	Yes	FATF
Rajan N, Rahim R, and Krishna Kumar S	1985	Annex II.1 - 8.12.2 / BPD ID A6.12.2_03	Formic acid poisoning with suicidal intent: a report of 53 cases. Postgrad. Med. J. 61, 35-36, -. - / Published	No	Public
[redacted]	1998	Annex II.1 - 8.9.1, _8.9.2, _8.9.3, ED-Assessment / BPD ID A6.4.1_01	Formi LHS: 13 week oral (dietary administration) toxicity study in the rat with a 4 week treatment-free period. [redacted], 1516/6-D6154. non-GLP / Unpublished	Yes	FATF
[redacted]	2007	Annex II.1 - 3.3 / BPD ID B3_01b	Physico-chemical properties of "Ameisensäure 85%". BASF AG, GKA Competence Center Analytics, 07L00172. GLP / Unpublished	Yes	BASF SE (LoA: Kemira / Taminco)

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[redacted]	2008a	Annex II.1 - 8.10.1, ED-Assessment / BPD ID A6.8.1_02	Natriumformiat (sodium formate) - Prenatal developmental toxicity study in Himalayan rabbits. Oral administration (Gavage).[redacted], 40R0123/03089. GLP / Unpublished	Yes	FATF
[redacted]	2008b	Annex II.1 - 8.10.2, ED-Assessment / BPD ID A6.8.2_01	Natriumformiat (Sodium formate). Two-Generation Reproduction Toxicity Study in Wistar Rats. Administration via the Diet. [redacted], 70R0123/03091. GLP / Unpublished	Yes	FATF
[redacted]	2005	Annex II.1 - 8.10.3, ED-Assessment / BPD ID A6.8.1_01	Sodium formate - Prenatal developmental toxicity study in Wistar rats. [redacted] 30R0123/03036. GLP / Unpublished	Yes	American Chemistry Council/USA
[redacted]	1988	Annex II.1 - 9.1.3.1 , Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3 / BPD ID A7.4.1.3_01	Algal growth inhibition test. BASF AG, Department of Ecology, 2/0290/88. non-GLP / Unpublished	Yes	FATF
Sigurdsson J, Björnsson A, and Gudmundsson ST	1983	Annex II.1 - 8.12.2 / BPD ID A6.12.2_08	Formic acid burn - local and systemic effects. . Burns 9, 358-361, -. - / Published	No	Public
[redacted]	2017a	Annex II.1 - 3.3 / BASF_BPR_Ann2_1	Acidity or Alkalinity of Protectol FM 99. Eurofins, Niefern-Öschelbronn, EAS Study Code S16-06390. GLP / Unpublished	Yes	BASF SE (LoA: Kemira / Taminco)
[redacted]	2017b	Annex II.1 - 3.3 / BASF_BPR_Ann2_2	pH of Protectol FM 99 (aqueous dilution). Eurofins, Niefern-Öschelbronn, EAS Study Code S16-06389. GLP / Unpublished	Yes	BASF SE (LoA: Kemira / Taminco)
Spoelstra SF	1979	Annex II.1 – 10.2 / -	Volatile fatty acids in anaerobically stored piggery wastes. Neth. J. agric. Sci. 27, 60-66., -. - / Published	No	Public

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Stavrakou, T., Muller, J. F., Peeters, J., Razavi, A., Clarisse, L., Clerbaux, C., Coheur, P., Hurtmans, D., De Maziere, M., Vigouroux, C., Deutscher, N., Griffith, D., Jones, N. & Paton-Walsh, C.	2012	CAR (ED) / -	Satellite evidence for a large source of formic acid from boreal and tropical forests. Nature Geoscience, 5 (1), 26-30, -. - / Published	No	Public
Takata Y, Tani M, Kato T, and Koike M	2011	Annex II.1 – 10.2 / -	Effects of land use and long-term organic matter application on low-molecular-weight organic acids in an Andisol. J. Soil Sci. Manage. 2(10), 292-298, -. - / Published	No	Public
Tete E, Viaud V, and Walter C	2015	Annex II.1 – 10.2 / -	Organic carbon and nitrogen mineralization in a poorly-drained mineral soil under transient waterlogged conditions: an incubation experiment.. European Journal of Soil Science, 66, 427-437., -. - / Published	No	Public
Thompson M	1992	Annex II.1 - 8.9.1, _8.9.2, _8.9.3 / BPD ID A6.4.3_01	NTP Technical Report on Toxicity Studies of Formic Acid. administered by inhalation to F344/N rats and B6C3F1 mice. US Department of Health and Human Services . NTP US DHHS, Toxicity Report Series No: 19, NIH Publ. No: 92-3342, July 1992. - / Published	No	Public
[redacted]	1991	Annex II.1 - 9.1.5, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex III.1- 9.1 / BPD ID A7.4.1.4_02	Bacterial Growth Inhibition Test. [redacted], 9/0290/88. non-GLP / Unpublished	Yes	FATF
Van Hees PAW, Johansson E, and Jones DL	2008	Annex II.1 – 10.2 / -	Dynamics of simple carbon compounds in two forest soils as revealed by soil solution concentrations and biodegradation kinetics.. Plant Soil 310, 11-23., -. - / Published	No	Public

Author(s)	**Year**	**Section No / Reference No**	**Title. Source (where different from company) Company, Report No.**	**Data Protection Claimed (Yes/No)**	**Owner**
Verstraete AG, Vogelaers DP, van den Bogaerde JF, Colardyn FA, Ackerman CM and Buylaert WA	1989	Annex II.1 - 8.12.2 / BPD ID A6.12.2_02	Formic acid poisoning: Case report and in vitro study of the haemolytic activity. Am J Emerg Med 7, 286-290, -. - / Published	No	Public
von Muehlendahl KE, Oberdisse U and Krienke EG	1978	Annex II.1 - 8.12.2 / BPD ID A6.12.2_06	Local injuries by accidental ingestion of corrosive substances by children. Arch Toxicol 39, 299-314, -. - / Published	No	Public
[redacted]	2007	Annex II.1 - 9.1.4.1, Annex II.1 - 9.1.7, Annex II.1 - 9.1.7, Annex II.1 - 9.6, Annex III.1- 10.2 / BPD ID A7.4.2_01	Formic acid, BCFWIN v.2.17 calculations. ECT Oekotoxikologie GmbH, Flörsheim, Germany, -. non-GLP / Unpublished	Yes	FATF
[redacted]	2005	Annex II.1 - 9.1.1, Annex II.1 - 9.1.6, Annex II.1 - 9.1.6.1, Annex II.1 - 9.2.1; Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex III.1- 9.1 / BPD ID A7.4.1.1_02	Acute toxicity of ammonium formate to zebra fish (Danio rerio). [redacted], KEM-001/4-11. GLP / Unpublished	Yes	FATF
[redacted]	2005	Annex II.1 - 9.1.2, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex III.1- 9.1 / BPD ID A7.4.1.2_02	Effect of ammonium formate on the immobilization of Daphnia magna. Fraunhofer-IME, KEM-001/4-20. GLP / Unpublished	Yes	FATF
[redacted]	2005	Annex II.1 - 9.1.3.1, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, Annex III.1- 9.1 / BPD ID FA. A7.4.1.3_02	Effect of ammonium formate on the growth of Pseudokirchneriella subcapitata. Fraunhofer-IME, KEM-001/4-30. GLP / Unpublished	Yes	FATF
Westphal F, Rochholz G, Ritz-Timme S, Bilzer N, Schütz HW, Kaatsch HJ	2001	Annex II.1 - 8.12.2 / BPD ID A6.12.2_01	Fatal intoxication with a decalcifying agent containing formic acid. Int. J. Legal Med. 114, 181-185, -. - / Published	No	Public

Author(s)	**Year**	**Section No / Reference No**	**Title. Source (where different from company) Company, Report No.**	**Data Protection Claimed (Yes/No)**	**Owner**
[redacted]	2002a	Annex II.1 - 8.9.1, _8.9.2, _8.9.3, Annex II.1 - 8.11.1, ED-Assessment / BPD ID A6.5_01	Formi LHS. Combined chronic toxicity and 104 week oral (dietary administration) oncogenicity study in the rat. [redacted], 1516/30-D6154. GLP / Unpublished	Yes	FATF
[redacted]	2002b	Annex II.1 - 8.11.2, ED-Assessment / BPD ID A6.7_02	Formi LHS. 80 week oral (dietary administration) oncogenicity study in the mouse. [redacted], 1516/33-D6154. GLP / Unpublished	Yes	FATF
Yang CC et al.	2008	Annex II.1 - 8.12.2 / FA_BPR_Ann_II_8_12_2_13.pdf	Formic acid: A rare but deadly source of carbon monoxide poisoning. Clinical Toxicology, 46:4, 287-289, -. - / Published	No	Public
Yelon JA, Simpson RL, and Gudjonsson O	1996	Annex II.1 - 8.12.2 / BPD ID A6.12.2_10	Formic acid inhalation injury: a case report.. J. Burn Care Rehab. 17, 241-242., -. - / Published	No	Public
Zeiger E, Anderson B, Haworth S, Lawlor T, and Mortelmans K	1992	Annex II.1 - 8.5.1 / BPD ID A6.6.1_01	Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Molec. Mutagen. 19, Suppl 21, 2-141, -. - / Published	No	Public
[redacted]	1980	Annex II.1 - 8.7.2 / BPD ID A6.1.3_01	Bestimmung der akuten Inhalationstoxizität LC50 von Ameisensäure als Dampf bei 4-stündiger Exposition an Sprague-Dawley Ratten. [redacted], August 21, 1980, 16 pages Report No. 78/651. non-GLP / Unpublished	Yes	FATF
[redacted]	1980	Annex II.1 - 8.7.2 / BPD ID A6.1.3_01EN	*Complete translation of BPD ID A6.1.3_01 into English (Date of translation: Aug 16, 2007).* Acute inhalation toxicity LC50 of formic acid as vapor after 4-hour exposure in Sprague-Dawley rats. [redacted], Report No. 78/651; 16 pages, Non-GLP / Unpublished	Yes	FATF
Zepp RG, Hoigné J, Bader H	1987	Annex II.1 - 10.1.1.1.b / BPD ID A7.1.1.1.2_02	Nitrate-induced photooxidation of trace organic chemicals in water. Environ. Sci. Technol 21, 443-450, -. - / Published	No	Public

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[redacted]	2007	Annex II.1 - 9.1.6, Annex II.1 - 9.1.6.1, Annex II.1 - 9.1.6.2.a, Annex II.1 - 9.2.1, Annex II.1 - 9.2.2, Annex II.1 - 9.2.3, ED-Assessment, Annex III.1- 9.1 / BPD ID A7.4.3.4_03	Final Report: Formic acid – Determination of the chronic effect on the reproduction of the water flea Daphnia magna STRAUS.. BASF AG, Experimental Toxicology and Ecology, 51E0274/073100. GLP / Unpublished	Yes	FATF

APPENDIX VI: CONFIDENTIAL INFORMATION

Please see separate document

APPENDIX VII: HUMAN HEALTH – READ-ACROSS JUSTIFICATION

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