Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report

Benzoic acid

Product-type 03
(Veterinary hygiene)

September 2013

Germany

Benzoic acid (PT 03)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on 27 September 2013

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Principle of evaluation

This assessment report has been established as a result of the evaluation of Benzoic acid as product-type 03 (Veterinary hygiene biocidal products), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market1, with the original view to the possible inclusion of this substance into Annex I or IA to that Directive.

The evaluation has therefore been conducted in the view to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product-type 3 containing Benzoic acid that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that Directive.

1.2. Purpose of the assessment

The aim of the assessment report is to support a decision on the approval of Benzoic acid for product-type 03, and should it be approved, to facilitate the authorisation of individual biocidal products in product-type 3 that contain Benzoic acid. 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.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Regulation (EU) No 528/2012.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report 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 has been granted.

1.3. Procedure followed

This assessment report has been established as a result of the evaluation of Benzoic acid as product-type 03 (Veterinary hygiene biocidal products), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive

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1 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

98/8/EC concerning the placing of biocidal products on the market[2], with a view to the possible inclusion of this substance into Annex I or IA to the Directive.

Benzoic acid (CAS no. 65-85-0) was notified as an existing active substance, by Menno Chemie-Vertrieb GmbH, hereafter referred to as the applicant, in product-type 03.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[3] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, Germany was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for Benzoic acid as an active substance in Product Type 03 was 31.07.2007, in accordance with Annex V of Regulation (EC) No 1451/2007.

On 26.07.2007, German competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 31.01.2008.

On 03.02.2011, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 14.02.2011. The competent authority report included a recommendation for the inclusion of Benzoic acid in Annex I to the Directive for product-type 03.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on 10.03.2011. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 27 September 2013.

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2 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

3 Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

Identity, Physico-chemical Properties and Method of Analysis of Benzoic acid

Benzoic acid is a white, crystalline solid with an odourless to slightly benzaldehyde-like odour. The melting point of Benzoic acid is at 122.4°C and it boils at 249.2°C. The vapour pressure is determined to 0.04 – 0.07 Pa at 20°C. The solubility in water dependence on the pH (2.9g/l at pH 2.94g/l; 5 g/l at pH 5.2; 15 g/l at pH 9), the water solubility increases with a higher pH – value. Additionally the calculated pKa value is 4.19. The Henry Law constant is calculated for the water solubility at pH 2.94 to be 0.0016-0.0029 Pa*m3 * mol-1. Furthermore Benzoic acid has a good solubility in various organic solvents like Acetone (55.60 g/100g), Benzene (12.17 g/100g), Carbon Tetrachloride (4.14 g/100g), Chloroform (15.02 g/100g), Ethanol (58.40 g/100g), Ethylether (40.80 g/100g), Hexane (17°C) (0.94 g/100g), Methanol (23°C) (71.50 g/100g), Toluene (10.60 g/100g). The Log Pow is 1.87 at 20°C for the unionised molecule, moreover it has a surface tension of 60 mN/m at 20°C.

The determination of benzoic acid was done by an external standard isocratic HPLC-method on a reversed stationary phase (Ultrasep ES RP 18) with UV detection of benzoic acid at 245 nm.

Analytical methods for detection and Identification

Relevant residues in food of plant and animal origin and in the environmental compartments arising from the application of benzoic acid as biocidal product are not expected to occur. As benzoic acid is a ubiquitous occurring substance, positive findings in soil and in surface and drinking water cannot be associated with an application of the biocidal product. Furthermore benzoic acid is listed in Annex IV of the new regulation 396/2005/EC for pesticides as an active substance for which no MRLs are required. Therefore, residue analytical methods for the determination of the active substance in food of plant and animal origin for enforcement purposes as well as for soil, drinking and surface water are not required.

Since inhalation exposure at the workplace could occur due to spray application of the b.p. analytical method in air is needed. An analytical method for detection and identification is available for the active substance in air. A validated confirmatory method is presented.

Analytical methods for the determination of benzoic acid in body fluids and tissues were not submitted, because at the time of submission the active substance was not classified as toxic or very toxic. In the RAC Opinion from 25th November 2012 a classification as toxic was proposed. If this proposal is implemented in a corresponding ATP of Regulation (EC) 1272/2008 at the time of product authorisation analytical methods for the determination of the active substance in body fluids and tissues must be submitted.

Identity, Physico-chemical Properties and Method of Analysis of the biocidal product Menno Florades

The product Menno Florades is a soluble concentrate of the active substance benzoic acid. The product is a clear slightly amber liquid with no intense odour. The product has a flash point of 28.5°C, so it has to be classified (labelled) as “flammable” (R10).

Analytical methods for detection and Identification

No residues are expected in soil, air, drinking and surface water, as well as in food and feeding stuffs and in animal and human body fluids and tissues.

No methods for the determination of non-active ingredients were submitted. They were not considered necessary as no relevant residues of non-active ingredients are expected.

2.1.2. Intended Uses and Efficacy

Benzoic acid is a bactericide, fungicide and virucide which is intended to be used in animal premises in order to prevent growth of microorganisms.

The intended use of the biocidal product “Menno Florades” is the treatment of surfaces in animal premises in order to prevent growth of microorganisms. potentially harmful organisms.

The performed tests provide reliable results for basic efficacy assessment. The following results could be derived from the studies:

-The product Menno Florades shows a basic bactericidal effectiveness on samples of the target organisms (Staphylococcus aureus and Pseudomonas aeruginosa) under clean conditions by a 1% solution (corresponds to 0.9 g/L benzoic acid) after a contact time of 60 min.

-The product shows a basic fungicidal effectiveness on samples of the target organisms under clean conditions by a 2% solution (contains 1.8 g/L benzoic acid) againstfor Candida albicans and byafter a 4% solution (contains 3.6 g/L benzoic acid) against Aspergillus brasiliensiscontact time of 60 min.

- The product shows a basic virucidal effectiveness on the model organism for the genus picornavirus Bovine enterovirus Type 1 (Enteric Cytopathogenic Bovine Orphan Virus – ECBO) by a 2% solution (corresponds to 1.8 g/L benzoic acid) at conditions without organic soiling after a contact time of 60 min.

Although the test criteria of DIN EN 1040 and DIN EN 1275 were not fulfilled, the tests are accepted in the frame of Annex I-inclusion of the active substance, because it may be possible that the efficacy achieved is sufficient for the in use situations.

The information provided is only sufficient to show a basic efficacy of benzoic acid. This is accepted in the frame of Annex-I-inclusion. Within the frame of product authorisation, essentially more information has to be provided: To support the full label claim virucidal, bactericidal and fungicidal, further laboratory tests would be necessary. Additionally, further tests in the field of use have to be provided.

At least the tests listed in EN 14885 for the respective field of use or comparable tests have to be provided in the frame of product authorisation. As not for all possible label claims an EN norm exists, further test will then be necessary depending on the specific label claim.

Mode of action

In solution, benzoic acid exists in a pH-dependent equilibrium between the undissociated and dissociated form. Only in its undissociated state, the acid is able to pass the cells membrane. At a relatively low pH, the uncharged acid enters the cell. Inside the cell, the benzoic acid dissociates due to the higher pH. The molecules remain inside the cell, because the resulting ions cannot pass the membrane. The pH inside the cell is lowered and metabolic reactions are inhibited. Further effects are also reported: Decrease of the membrane permeability for amino acids, organic acids, phosphates resulting in uncoupling of both substrate transport and oxidative phosphorylation from the electron transport system. Furthermore, an inhibition of the citric acid cycle is observed.

The intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

Development of resistance

Many publications are available that report about resistance of micro-organisms against benzoic acid, mainly in the context of food spoilage (Davidson, PM and Harrison, MA, 2002; Brul, S and Coote, P, 1999). A number of yeasts are known to be resistant to benzoates. It is suggested that the mechanism by which yeasts develop resistance to weak acidic antimicrobials, including benzoic acids, is related to membrane permeability and the ability of the cells to continuously pump antimicrobials out of the cell. Some micro-organisms on the other hand have innate resistance to benzoates because they metabolize the compounds. These bacteria and moulds degrade benzoic acid through either the ortho or the meta cleavage pathway. Few studies examine the potential for acquired resistance to benzoic acid in yeasts previously exposed to sub-inhibitory concentrations of benzoic acid. Pre-exposure to benzoic acid caused a 1.4 to 2.2 fold increase in MIC. The proposed resistance mechanism was increased cellular efflux (Warth, AD, 1988). There was neither any evidence of indicating increased resistance due to mutation nor any evidence that the resistance was stable. Further, there is little or no evidence in the literature of acquired bacterial resistance to benzoic acid.

Considering the length of time that benzoic acid has been applied to food products as a food additive it would seem, however, that the development of acquired resistance by spoilage and pathogenic micro-organisms is very rare or non-existent.

2.1.3. Classification and Labelling

Benzoic acid is not yet listed in Annex VI of Regulation (EC) No 1272/2008 (2nd ATP; former Annex I of Directive 67/548/EEC (up to 31st ATP)).

Table 1 Proposed classification of Benzoic Acid based on Directive 67/548/EEC

	Classification	Wording
Hazard Symbols, Indications of danger	T* Xi	Toxic Irritant
R-phrases	R48/23* R38 R41	Toxic, Danger of serious damage to health by prolonged exposure through inhalation Irritating to skin Risk of serious damage to eyes

*** According to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

The proposed classification on the basis of toxicological properties regarding R 41 (Risk of serious damage to eyes) is in accordance with the proposal under Directive 91/414 EEC (SANCO/1396/2001-Final, Monograph on Benzoic Acid, EU, 2003). The classification “Xi; R41” is warranted due to non-reversible corneal lesions caused by benzoic acid instilled in rabbits’ eyes.

Based on the positive results in human skin irritation studies and the underlying non-immunogenic irritant and inflammatory mechanism which does not involve sensitisation, the data are regarded sufficient to justify labelling benzoic acid with **R38 resp. H315** in a weight of evidence approach. In comparison to sorbic acid for which classification with R38 was proposed based on the same effect, the reaction provoked by benzoic acid is stronger, of longer duration and higher frequency.

Thus, the data are regarded sufficient to justify classification of benzoic acid “Xi; R38” (Irritant; Irritating to skin).In addition to the proposal by the RMS, classification with T; R48/23 is proposed in the RAC Opinion from 25. November 2012.

The active substance is readily biodegradable and is not considered toxic to aquatic organisms. Consequently, no environmental classification of the active substance benzoic acid is required.

Table 2 Proposed classification of Benzoic Acid based on Regulation (EC) No 1272/2008

	Classification	Wording
Hazard classes, Hazard categories	Skin Irrit. 2, Eye Dam. 1 STOT RE 1	
Hazard statements	H315 H318 H372*	Causes skin irritation Causes serious eye damage Causes damage to lungs through prolonged or repeated inhalative exposure

*** According to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

The proposed classification on the basis of toxicological properties regarding H318 (Causes serious eye damage) is in accordance with the proposal under Directive 91/414 EEC (SANCO/1396/2001-Final, Monograph on Benzoic Acid, EU, 2003). The classification "Eye Dam. 1; H318" is warranted due to non-reversible corneal lesions caused by benzoic acid instilled in rabbits' eyes.

Non-immunogenic contact urticaria (transient intense erythema and oedema, also termed pseudoallergy) is evoked by benzoic acid when applied to human skin of sensitive persons as reported in several studies and case reports or to the ear lobes of guinea pigs. While not proven in a narrow sense, there is mechanistic evidence, that these skin reactions are mediated by release of vasoactive substances. An immunological T-cell mediated mechanism is ruled out, because no sensitisation (induction phase) is required for the reaction. In comparison to sorbic acid for which classification with H315 was proposed based on the same effect, the reaction provoked by benzoic acid is stronger, of longer duration and higher frequency.

Thus, the data are regarded sufficient to justify classification of benzoic acid "Skin Irrit. 2; H315" (Causes skin irritation).In addition to the proposal by the RMS, the RAC Opinion of 25th November 2012 considers that there is evidence for pulmonary toxicity after repeated exposure to benzoic acid dust via inhalation and proposes a classification with STOT RE1 H372 (lungs, inhalation).

The active substance is readily biodegradable and is not considered toxic to aquatic organisms. Consequently, no environmental classification of the active substance benzoic acid is required.

Table 3 Proposed labelling of Benzoic Acid based on Directive 67/548/EEC

	Labelling	Wording
Hazard Symbols, Indications of danger	T*	Toxic
R-phrases	R38 R41 R48/23*	Irritating to skin Risk of serious damage to eyes Toxic, Danger of serious damage to health by prolonged exposure through inhalation
S-phrases	S1/2 S26 S37/39 S 45	Keep locked up and out of the reach of children In case of contact with eyes, rinse immediately with plenty of water and seek medical advice Wear suitable gloves and eye/face protection. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

*** According to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

S26 and S39 are obligatory because of R41. S25 is usually dispensable for substances which are not likely to be used by the general public.

In addition to the proposal by the RMS, classification with T; R48/23 is proposed in the RAC Opinion from 25. November 2012.

The active substance is readily biodegradable and is not considered toxic to aquatic organisms. Consequently, no labelling according to environmental classification of the active substance benzoic acid is required.

Table 4 Proposed labelling of Benzoic Acid based on Regulation (EC) No 1272/2008

	Labelling	Wording
Pictograms	GHS 05 GHS 08*	Danger
Signal Word	Danger	
Hazard statements	H315 H318 H372*	Causes skin irritation Causes serious eye damage Causes damage to lungs through prolonged or repeated inhalative exposure
Suppl. Hazard statements	-	-
Precautionary statements	(P102) P260* P280 P302 + P352 P333 + P313 P305 + P351 + P338 P310 P501	Keep out of reach of children Do not breathe dust Wear protective gloves/eye protection/face protection IF ON SKIN: Wash with plenty of soap and water If skin irritation or rash occurs: Get medical advice/attention IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing Immediately call a POISON CENTER or doctor/physician Dispose of contents/container to...

*** According to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

In addition to the proposal by the RMS, the RAC Opinion of 25th November 2012 considers that there is evidence for pulmonary toxicity after repeated exposure to benzoic acid dust via inhalation and proposes a classification with STOT RE1 H372 (Causes damage to lungs through prolonged or repeated inhalative exposure).

The active substance is readily biodegradable and is not considered toxic to aquatic organisms. Consequently, no labelling according to environmental classification of the active substance benzoic acid is required.

Classification and Labelling of MENNO Florades

Table 5 Proposed classification of MENNO Florades based on Directive 1999/45/EC

	Classification	Wording
Hazard symbols, Indications of danger	Xn Xi	Harmful Irritant
R-phrases	R10 R48/20* R41 R67	Flammable Danger of serious damage to health by prolonged exposure through inhalation. Risk of serious damage to eyes. Vapours may cause drowsiness and dizziness.

*** In adaptation to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

Beside benzoic acid (90 g/l), the biocidal product Menno Florades contains propan-1-ol and propan-2ol. Therefore, the biocidal product has to be classified with R67 (Vapours may cause drowsiness and dizziness) in addition to "Xi; R41" (Irritant; Risk of serious damage to eyes) and – in adaptation of the RAC Opinion – "Xn, R48/20 (Harmful; Danger of serious damage to health by prolonged exposure through inhalation)".

No environmental classification of the model formulation is required.

Table 6 Proposed classification of MENNO Florades based on Regulation (EC) No 1272/2008

	Classification	Wording
Hazard classes, Hazard categories	Flam. Liq. 3 Eye Dam. 1 STOT SE 3 STOT RE 2	
Hazard statements	H226 H318 H336 H373	Flammable liquid and vapour Causes serious eye damage May cause drowsiness or dizziness May cause damage to lungs through prolonged or repeated inhalative exposure

*** In adaptation to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

Beside benzoic acid (90 g/l), the biocidal product Menno Florades contains propan-1-ol and propan-2ol. Therefore, the biocidal product has to be classified "STOT SE 3; H336 (May cause drowsiness or dizziness) in addition to "Eye Dam. 1; H318 (Causes serious eye damage)" and –

in adaptation of the RAC Opinion – "STOT RE 2; H373 (May cause damage to lungs through prolonged or repeated inhalative exposure)".

No environmental classification of the model formulation is required.

Table 7 Proposed labelling of Menno Florades based on Directive 1999/45/EC

	Labelling	Wording
Hazard Symbols, Indications of danger	Xn (Xi)	Harmful (Irritant)
R-phrases	R10 R41 R48/20* R67	Flammable Risk of serious damage to eyes. Harmful, Danger of serious damage to health by prolonged exposure through inhalation. Vapours may cause drowsiness and dizziness.
S-phrases	S2 S13 S16 S24 S26 S39 S46	Keep out of the reach of children Keep away from food, drink and animal feedingstuffs Keep away from sources of ignition - No smoking Avoid contact with skin In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear eye/face protection If swallowed, seek medical advice immediately and show this container or label

*** According to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Remark:

The Safety phrases S26 and S39 are mandatory because of R41 according to Annex VI of Directive 67/548/EEC. S16 is added to the labelling proposal because of R10. S24 is added because of the possible dermal effects by benzoic acid and the results of human health risk assessment. S13 is required as a general hygienic measurement and the fact that the biocidal product is used in food-producing facilities. S2 and S46 are required since the biocidal product is used in areas (farms) where access of person s equivalent to the general public cannot be excluded.

No labelling according to environmental classification of the model formulation is required.

Additional labelling of the biocidal product:
Due to the pseudoallergic properties of benzoic acid to induct non-immunological contact urticaria the biocidal product Menno Florades has to be labelled with:
Contains benzoic acid. May produce pseudo-allergic reactions.

Table 8 Proposed labelling of Menno Florades based on Regulation (EC) No 1272/2008

	Labelling	Wording
Pictograms	GHS02 GHS05 GHS07 GHS08	
Signal Word	Danger	
Hazard statements	H226 H318 H336 H373	Flammable liquid and vapour Causes serious eye damage May cause drowsiness or dizziness May cause damage to lungs through prolonged or repeated inhalative exposure
Precautionary statements	P102 P210 P241 P243 P271 P280 P301 + P310 P304 + P340 P305 + P351 + P338 P310*) P333 + P313 P403 + P233 P501	Keep out of reach of children Keep away from heat/sparks/open flames/hot surfaces. — No smoking Use explosion-proof electrical/ventilating/ lighting/…/equipment Take precautionary measures against static discharge Use only outdoors or in a well-ventilated area Wear protective gloves/eye protection/face protection IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing Immediately call a POISON CENTER or doctor/physician If skin irritation or rash occurs: Get medical advice/attention Store in a well-ventilated place. Keep container tightly closed Dispose of contents/container to …

***) in combination with P305 + P351 + P338^{+} In adaptation to RAC Opinion from 25th November 2012, in addition to the proposal by the RMS**

Further labelling: **The biocidal product contains two co-formulants in a total amount of 36%, for which no information on inhalation toxicity (e.g. LC50 or equivalent data) are available. Thus, in accordance with Regulation (EC) No 1272/2008 the following additional labelling is required.**

'36 percent of the mixture consist of ingredients of unknown inhalation toxicity.'

Remark:

Precautionary statements are also selected on the whole in accordance with the recommendations given in the Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (IHCP, DG Joint Research Centre, European Commission, 2009).

Additional labelling of the biocidal product:
Due to the pseudoallergic properties of benzoic acid to induct non-immunological contact urticaria the biocidal product Menno Florades has to be labelled with:
Contains benzoic acid. May produce pseudo-allergic reactions.

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification

Benzoic acid and its salts are natural compounds widely spread in the environment. They are generated in plant and animal metabolism and therefore, are constituents in many foodstuffs: up to ca. 40 mg/kg are found in milk products and up to 100 mg/kg in honey (IPCS, 1999; BUA Report, 1993). Benzoic acid and benzoates are used as therapeutic substances in human and veterinary medicine. Because of its antimicrobial activity, benzoic acid is commonly used as preservative in food, cosmetics and pharmaceuticals.

The worldwide industrial production volume is about 700 000 tons per year (OECD SIDS dossier, 2005).

Bridging concept

Although the application for Annex I Inclusion under Directive 98/8/EC is restricted to benzoic acid, benzoates are included in the toxicological evaluation because a considerable part of data was generated with these substances. Particularly sodium benzoate has been used in many experiments because of the low water solubility of benzoic acid at neutral pH. Furthermore, after ingestion of sodium benzoate the acidic pH of the stomach moves the equilibrium to the undissociated benzoic acid molecule (pKa: 4.19). Additionally, for some studies it was not definitely stated whether benzoic acid or benzoates were used. Regarding the great similarity of the toxicological profile (with the exception of irritancy), benzoic acid and sodium benzoate can in general be considered together.

Quality of data

The toxicological evaluation of the a.s. benzoic acid is based on literature which is very heterogeneous. In several studies – especially in short-term and long-term studies - only one or two doses and only few parameters were tested. Results were often insufficiently reported.

As stated in the OECD SIDS dossier, *"several of the toxicological studies on [...] benzoic acid and its salts were carried out some years ago and do not always fulfill for 100% present-day guidelines. However, well-known research groups and/or test laboratories ran the studies according to scientific standards and/or accepted protocols at that time. They did appear to be acceptable studies for evaluation. Also, all were peer-reviewed and published in high quality scientific literature. Most of them have been reviewed and accepted by other fora like FDA, JECFA, and IPCS as acceptable studies. In addition, there is good consistency in the individual data for a substance in the group as well as between members of the group [...]. Therefore, taken as a whole, the available studies give a robust database for hazard assessment and hazard evaluation of these compounds and further studies are not indicated."*

Regarding the overall conclusions on the toxicological properties of benzoic acid/benzoates in this report, they resemble those drawn in other evaluations (see Doc II Table 3-1). The ADI derived in this monograph is in agreement with the ADI of JECFA (1983) and EU (2003, 2005). The FDA accepted benzoic acid as a GRAS (Generally Recognized As Safe) direct food substance in 1972.

Taking into account the natural occurrence of benzoic acid and benzoates in the environment and the long and extensive experience with the use of these substances, e.g. as food preservative and as medication, further testing is not necessary. It is concluded that an exemption from the requirement of toxicological studies for the active ingredient according to current standard test guidelines is justified. No further studies have to be submitted.

2.2.1.2. Effects assessment

Absorption, Distribution, Excretion, and Metabolism

Extensive information regarding the absorption, distribution, metabolism and excretion (ADME) of benzoic acid/sodium benzoate was derived from the published literature covering investigations with very different objectives (e.g. perfusion experiments with different organs, elucidation of basic metabolism principles, special absorption phenomena). In these investigations, a great variety of animal species, including monkey, rat, and rabbit, as well as humans were studied. A comprehensive ADME study based on a current guideline (e.g. EU, OECD or EPA) is not available.

Absorption

After oral ingestion of benzoic acid/sodium benzoate, the gastrointestinal absorption is rapid and virtually complete in humans, rats, dogs, and hamsters. In humans, the peak plasma concentration is reached within 1 to 2 hours. The rapidity of absorption was substantiated by perfusion experiments with colon of the rat. It was also shown that absorption is based on diffusion of the unionized molecule and is dependent on pH.

Excretion

The excretion of benzoic acid/sodium benzoate with urine is rapid and virtually complete in humans, rats, hamsters, and dogs but seems less effective in other species such as ferrets and subhuman primates. Faecal and respiratory excretion appears to be minor routes of elimination. Because of the high rate and extent of elimination in most of the species investigated, no accumulation is to be expected.

Metabolism

Hippuric acid and benzoyl glucuronide are the two main metabolites of benzoic acid/sodium benzoate in mammals. These metabolites result from conjugation reactions of benzoic acid with glycine or glucuronate (Doc II figure 3-1).

From the maximum excretion rate, it was calculated that the elimination capacity via glucuronate and glycine conjugation is approx. 20 g benzoic acid per day in humans.

The maximum rate of biotransformation of benzoic acid to hippuric acid has a mean value of 23.0 mg/kg bw/h which is close to the daily maximum dose of 500 mg/kg bw (21 mg/kg bw/h) recommended for the treatment of hyperammonaemia (see Doc II chapter 3.10: Medical data).

Like in humans, benzoic acid is almost entirely excreted as hippuric acid in rabbits, rats, and pigs, whereas other species such as marmosets and ferrets excrete also considerable quantities of benzoyl glucuronide.

In neonatal and protein-deficient rats, the proportion excreted as hippuric acid appeared to be reduced, approx. 20 % of the urinary radiolabel were identified as benzoyl glucuronide.

In cats, which lack the metabolic pathway of glucuronic acid conjugation, benzoic acid will build up to toxic levels when glycine conjugation to hippuric acid is saturated.

The major sites of conversion of benzoic acid to hippuric acid and benzoyl-glucuronic acid in humans are the liver and the kidneys. While the conjugation rate was greater in the renal cortex than in the liver, the larger mass and strategic anatomical position of the liver were considered to make it quantitatively the more important organ with respect to glycine conjugation. In vitro experiments indicated that after percutaneous absorption of benzoic acid a small amount can also be converted to hippuric acid in the skin.

Dermal Absorption

Because of the immense use of benzoic acid/sodium benzoate as preservative in cosmetics and the suitability of benzoic acid as reference substance, many investigations dealt with the percutaneous absorption in several animal species in vivo, e.g. rat, rhesus monkey, dog, pig, guinea pig and in humans as well as in human and rat skin in vitro.

Overall, the percutaneous absorption in humans accounts for approximately 40 % in vivo (14 – 42.6 %) and 70 % (53 - 99 %) in vitro. However, in the absence of data for the biocidal product and due to the heterogeneous results in human dermal absorption studies, a dermal absorption of 100 % is assumed.

Acute Toxicity including irritancy and skin sensitisation

Benzoic acid is of low toxicity in rat, mouse, rabbit and dog, and of moderate toxicity in cat. The oral LD50 of benzoic acid in the rat is in the range of 2000 to 3040 mg/kg bw, the dermal LD50 is >10000 mg/kg bw and the inhalative LC50 > 1.2 mg/L air x 6 h (dust, highest attainable concentration).

Classification and labelling for acute toxicity according to Directive 67/548/EEC:
Not required
Classification and labelling for acute toxicity according to Regulation (EC) No 1272/2008:
Not required

Benzoic acid is not irritating to the skin (below classification threshold) in standard animal irritation studies but highly irritating to the eyes. The effects observed on the eyes comprised corneal opacity (severe (1/3 animals) and not reversible (2/3 animals), no reaction to light up to d 21 (1/3 animals), non-reversible chemosis (2/3 animals), iridial injection and conjunctival redness as reported in the SCCP report (SCCP/0891/05-Opinion on Benzoic Acid and Sodium Benzoate, EU, 2005). Sodium benzoate is not skin-irritating.

Classification (labelling) for irritation/corrosivity according to Directive 67/548/EEC:
Xi; R41 (Irritant; Risk of serious damage to eyes)
Classification (labelling) for irritation/corrosivity according to Regulation (EC) No 1272/2008:
Eye Dam. 1; H318 (Causes serious eye damage)

No sensitising potential of benzoic acid was observed in a guinea pig maximisation test, in a local lymph node assay, a Buehler test and a mouse ear swelling test.

Non-immunogenic contact urticaria (NICU):

Transient, but nevertheless intense erythema and oedema are evoked by benzoic acid when applied to the ear lobes of guinea pigs and human skin of sensitive persons in various parts of the body (cf. Doc II chapter 3.10 Medical data). While not proven in a narrow sense, some mechanistic evidence was presented, that these skin reactions are mediated by release of vasoactive substances. An immunological T-cell mediated mechanism is ruled out, also because no systemic reaction has been observed in the respective patients and no sensitisation (induction phase) is required for the reaction.

Together with the guinea pig data on non-immunological contact urticaria (NICU), the findings are regarded in the medical surveillance reports (cf. Doc II chapter 3.10 Medical data) sufficient to justify labelling of benzoic acid with R38 (Irritating to the skin) resp. H315 (Causes skin irritation).

Classification (labelling) for sensitisation according to Directive 67/548/EEC:
Not required for sensitisation.
For the induction of NICU: Xi; R38 (Irritant; Irritating to the skin)
Classification (labelling) for sensitisation according to Regulation (EC) No 1272/2008:
Not required for sensitisation.
For the induction of non-immunological contact urticaria (NICU): Skin Irrit. 2; H315 (Causes skin irritation).

Short-term Toxicity

A large number of subacute and subchronic oral toxicity studies with benzoic acid or sodium benzoate have been performed in various mammalian species. However, in general these do not meet current standards with regard to study design and reporting. Many of these studies primarily relied on clinical observations.

Typical signs caused by benzoic acid in the rat were similar to those from acute studies and included ataxia, aggressiveness, tremor, convulsions, reduction of food consumption and bw gain, and mortality. With few exceptions, histopathological evaluation was not performed or included only few organs. A 35-d CNS toxicity study reported regional CNS necrosis from daily doses of 2250 mg/kg in the rat. The kidney weight was increased in some studies. Generally, LOAEL values for the rat were between 1200 and 2250 mg/kg bw/d for subacute and subchronic exposure without strict correlation to exposure time. A reliable NOAEL for derivation of threshold limit values may be based on a multigeneration study. In this study, no changes in bw gain (data supplied only for up to 12/8 weeks for M/F) and histopathology of key organs performed after wk 16 were reported at the top dose of 500 mg/kg bw/d benzoic acid.

Survival at this dose remained unaffected. NOAELs reported in other studies were between 500 and 1360 mg/kg bw/d. Mortalities and CNS effects observed at doses ≥ 1200 mg/kg bw/d are considered to be related to metabolic acidosis after saturation of glycine and glucuronate conjugation pathways. Thus, the threshold dose that leads to metabolic acidosis and its related symptoms is not regarded to deteriorate from subchronic to chronic exposure.

The submitted data (NOAEL/LOAEL = 600/800 mg/kg bw/d, 25-d oral) further supports the conclusion, that dogs are of similar sensitivity to subacute benzoate toxicity as rats and show similar symptoms. In contrast, results by another study suggest that the mouse is less sensitive (NOAEL/LOAEL = 3750/4500 mg/kg bw/d, 10-d oral), but typical adverse effects were similar to that observed in the rat and included tremor/convulsions as well as liver toxicity.

The cat currently represents the most sensitive mammalian species tested. This sensitivity is thought to be related to species-specific deficiencies in benzoate metabolism paired with a cat-typical feeding behaviour. Therefore, the subacute NOAEL/LOAEL derived for cats (200/340 mg/kg bw/d, 15-d feeding) is not considered relevant for human risk assessment.

According to a study summary, the NOAEL for subacute dermal toxicity of benzoic acid in rabbits is 2500 mg/kg bw/d (the highest dose tested) when applied 5 days per week over 3 weeks (OECD SIDS Dossier on Benzoates, 2001).

Inhalation toxicity of benzoic acid was evaluated in one rat study using fine benzoic acid dust with a mean aerodynamic particle diameter of 4.7 µm. Evaluation of survival, body weight and organ weight demonstrated significant systemic toxicity including 2/20 mortalities at the top dose of 1.2 mg/L. A reddish discharge around the nares was observed at doses ≥ 0.25 mg/L. In addition to systemic toxicity, compound-related microscopic lesions consisting of multifocal to generalised inflammatory cell infiltrates and interstitial fibrosis of the lung were observed. This was reported for all groups of benzoic acid treated animals with a concentration-dependent increase in intensity and incidence. It is widely accepted, that particles of low-solubility materials retained in the lower lung are cleared by phagocytic cells, mostly alveolar macrophages. Excessive activation of these cells is linked to the release of ROS (reactive oxygen species) as well as inflammatory and fibrogenic mediators initiating lung remodelling well described for silica pneumoconiosis. The systemic effects observed at higher concentrations differed from those observed after oral exposure at higher concentrations (organ weight decrease, platelet decrease) and are thought to be secondary to local lung toxicity. Because the toxic effects observed in this study are attributed to the physico-chemical properties of these fine low-solubility particles, the study was not considered relevant for the evaluation of human health effects after repeated exposure to fluid benzoic acid formulations used in biocidal applications. In addition, a rough estimate of the inhalation exposure from evaporating surface disinfectants showed that inhalation exposure to benzoic acid vapours is negligible (calculation as proposed by Human Exposure Expert Group (HEEG)). Exposure to benzoic dusts is not expected but any risk would be sufficiently addressed by general exposure limits for dusts, e.g. national OELs such as MAK for fine dust (DFG, 2011). This conclusion was based on the observation that effects after dust inhalation are most likely due to pneumoconiosis and are not substance-specific. A need is not seen to revise the AEL setting and preference is given to derive AELs on the basis of the oral studies.

Classification and labelling for repeated dose toxicity according to Directive 67/548/EEC according to the RAC Opinion:
R48/23 (Toxic: danger of serious damage to health by prolonged exposure through inhalation)
Classification and labelling for repeated dose toxicity according to Regulation (EC) No 1272/2008 according to the RAC Opinion:
STOT RE1; H372 (Causes damage to lungs through prolonged or repeated inhalative exposure)

Genotoxicity

In vitro tests:

While the reverse mutation assays and sister chromosome exchange assays (except one equivocal result) with benzoic acid, sodium benzoate and the metabolite hippuric acid were negative, weak genotoxic effects or equivocal results were observed in most of the chromosome aberration assays in mammalian cell lines with benzoic acid and sodium benzoate.

In vivo tests:

All the in vivo genotoxicity tests were negative at somatic or germ cell level.

The essentially negative results obtained in two carcinogenicity studies in rats and mice (see Doc II chapter 3.7) for sodium benzoate, notwithstanding some limitations, give further reassurance. On this basis, it is very unlikely that benzoic acid would interfere with chromosomes in vivo. This evaluation is in line with the judgement of the Scientific Commitee on Food of the EU (Opinion of the Scientific Committee on Food on Benzoic acid and its Salts, SCF/CS/ ADD/CONS/48 Final, 2002).

Classification and labelling for genotoxicity according to Directive 67/548/EEC:
Not required
Classification and labelling for genotoxicity according to Regulation (EC) No 1272/2008:
Not required

Chronic Toxicity/ Carcinogenicity

Chronic toxicity

Four studies that aimed to assess the chronic toxicity of benzoic acid in rat and mice were submitted. Of these, only two rat studies are suitable for risk assessment, although these two studies do neither meet current EU nor OECD standards for chronic toxicity testing. Both did not go beyond assessment of survival and clinical signs. Gross and histopathology in one study was performed after subchronic exposure and body weight was reported for an initial 12/8 wks (M/F) only. In this study, the top dose of 10,000 ppm, corresponding to approx. 500 mg/kg bw/d, did neither reduce lifetime survival nor produced overt clinical symptoms of benzoic acid poisoning. Feeding of 15,000 ppm (~750 mg/kg bw/d) benzoic acid over 18 months increased mortality and reduced body weight and body weight gain in comparison to control rats. Data obtained at later time points and haematological, biochemical or histopathological reports were not available for this study. In summary, it may be concluded that a dose of 500 mg/kg bw/d, as identified as safe in rodents for subchronic exposure, did neither affect survival nor produced clinical signs of benzoic acid poisoning when exposure time was extended. However, the available chronic toxicity data is not suitable to establish a NOAEL for target organ (liver, kidneys, brain) toxicity.

Mortalities observed at 750 mg/kg bw/d in one study and in subacute/subchronic studies at 1200/1500 mg/kg bw/d are considered to be related to metabolic acidosis after saturation of glycine and glucuronic acid conjugation pathways. This effect was also observed in acute studies and human case reports when high doses of benzoic acid/benzoate were administered repeatedly within 10-24 h. Thus, this effect is not regarded to aggravate from subacute/subchronic to chronic exposure.

Carcinogenicity

Carcinogenicity of sodium benzoate was assessed in one 2-year study in rats and one lifetime study in mice. Neither of these meets current EU or OECD requirements for carcinogenicity testing or data reporting and analysis. In the rat study, an unspecified number of interim sacrifices was performed and terminal sacrifices started at month 18, reducing the effective exposure time. This may provide one possible explanation for the low incidence of tumors reported for all treatment groups which were substantially below historical control data cited by the authors. Nevertheless, direct comparison of rats treated with up to 20000 ppm with untreated controls did not indicate carcinogenicity under these conditions. When sodium benzoate was added to the drinking water of mice at the same concentration of 20000 ppm - which according to consumption data provided in the report should correspond to 3000 mg/kg bw/d – no increase in the lifetime tumor incidence, clinical abnormalities or histopathological changes were observed.

Carcinogenicity studies in rat and mice did not provide concern for a potential oncogenicity of benzoate when given with the diet or the drinking water at high dosages. The essentially negative results obtained in the in vitro and in vivo genotoxicity tests give further reassurance that benzoic acid is not a human carcinogen.

Classification and labelling for carcinogenicity according to Directive 67/548/EEC:
Not required
Classification and labelling for carcinogenicity according to Regulation (EC) No 1272/2008:
Not required

Reproduction Toxicity

Developmental Toxicity

Embryotoxicity and teratogenicity of benzoic acid when administered at a single dose of 510 mg/kg bw/d on day 9 of gestation to 7 pregnant rats were evaluated. Under these experimental conditions, there were no indications for embryotoxic or teratogenic activity of benzoic acid. Interestingly, it was noted that high doses of benzoic acid may increase the teratogenicity of other substances, presumably via toxicokinetic interactions by delaying the elimination of these. Nevertheless, this study can not be regarded suitable as the basis for assessment of developmental toxicity (single dose on day 9 only, low no. of animals).

In a developmental neurotoxicity study, sodium benzoate was administered to rats at a similar top dose of 500 mg/kg bw/d sodium benzoate from day 5 of gestation through lactation and after weaning. Mortality and bw of parental animals, mortality of embryos and fetuses as well as survival, activity and bw development of offspring remained unaffected. No teratogenicity was reported, but this endpoint was not addressed specifically.

A more comprehensive teratogenicity study with higher doses of sodium benzoate in rats was reported in another study. No increase in offspring variations and malformations was observed up to doses of ~1330 mg/kg bw/d (corr. to ~1130 mg/kg bw/d benzoic acid) administered with the food during the whole gestational period. However, a slight reduction (5 %) in offspring survival was noted at this dose level. Higher doses led to reduced maternal survival, maternal bw loss, reduction in the number and weight of viable fetuses, reduced perinatal survival and a more than tenfold increase in skeletal and soft tissue malformations. A NOAEL of 1130 mg/kg bw/d benzoic acid equivalents for maternal and developmental effects and a more conservative NOAEL of 600 mg/kg bw/d for other effects on offspring is concluded.

Earlier developmental toxicity studies with sodium benzoate in other species including mouse, hamster and rabbit showed that the highest selected doses of 175 mg/kg bw/d administered from gestational day 6 to 15 in mice, 300 mg/kg bw/d given from day 6 to 10 of pregnant hamsters, and 250 mg/kg bw/d from day 6 to 18 of gestation in rabbits were insufficient to cause detectable maternal toxicity, fetotoxicity or teratogenicity, supporting the conclusions made above (Food and Drug Research Labs., Inc., 1972).

Reproduction Toxicity

Reproductive toxicity was assessed in one non-guideline 3-generation study performed in rats with 0, 0.5 and 1% benzoic acid added to the diet, corresponding to approximate doses of 0, 250 and 500 mg/kg bw/d. These failed to produce detectable toxic effects on parental and offspring generations or reproductive capacity. Another study reported a slight reduction in offspring survival of 5 % and a decrease in lactation rate at the higher dose of 1000 mg/kg bw/d in Wistar rat.

Overall, there is currently no indication for developmental or reproductive toxicity of benzoic acid in rats at or below the NOAEL of 500 mg/kg bw/d for subchronic toxicity.

Classification and labelling for reproduction toxicity according to Directive 67/548/EEC:
Not required.
Classification and labelling for reproduction toxicity according to Regulation (EC) No 1272/2008:
Not required

Neurotoxicity

Subacute (delayed) neurotoxicty and CNS toxicity was assessed in juvenile rats. Benzoic acid was added to the diet for up to 35 days at 0, 1.1, and 3 %, corresponding to approximate doses of 0, 825, and 2250 mg/kg bw/d. At day 4, clinical observation showed signs of neurotoxicity in most animals of the top dose group including ataxia, tremor, excitation, aggressive behaviour and tonoclonic convulsions. 50 % of the animals receiving 2250 mg/kg bw/d died or were sacrificed between day 1 and day 5. For a total of 8 top dose animals surviving day 5, treatment was discontinued and sacrifice was performed on day 24-35. Histological evaluation of the brain showed prominent pathological changes in 2/5 animals treated for 3 days, 18/18 animals treated for 5 days and 13/15 animals with 3 wk of recovery following the 5 days of exposure. These changes included preferentially ischaemic necrosis of ganglial cells in the stratum granulosum of the fascia dentata and the cortex of the lobus piriformis. No histopathology of the brain or clinical abnormality was noted in any of the animals of the low dose group receiving approx. 825 mg/kg bw/d over 7, 14, or 35 days.

Acute neuroexcitation by benzoic acid was studied mechanistically in rats at a dose of approx. 500 mg/kg bw administered intravenously by infusion over 60 min. At this dose, neither change in the somatosensory evoked potential (SEP) nor SEP oscillations in the frequency band of 30-120 Hz were observed. Other endpoints were not reported.

In another developmental neurotoxicity study the effects of sodium benzoate were evaluated on activity and behavior in neonatal and juvenile rats. Treatment with 0, 0.1, 0.5, and 1.0 % benzoate in the diet commenced on day 5 of gestation of the parental animals and continued through lactation and after weaning. Offspring activity was measured every 3 days preweaning and continuously thereafter. Observations were comparable for all treatment groups. On day 9, 15, and 21, one animal per litter was sacrificed for measurement of brain region weight and serotonin, dopamine and noradrenaline levels. The remaining 5 animals per litter were subjected to the same analysis on day 45. There were no treatment-related changes in weight or neurotransmitter content for any of 5 analysed brain regions. Consequently, the NOAEL for developmental neurotoxicity in rats was considered as 1 % in the diet, corresponding to approx. 500 mg/kg bw/d.

Overall, neurotoxicity observed in benzoic acid intoxications seems to be secondary to metabolic changes (acidosis, acyl-CoA and ATP depletion). In addition, subacute exposure to lethal concentrations was associated with non-reversible histopathologic changes of the brain. However, no evidence for neurofunctional abnormalities or histopathological alterations of the CNS were reported following subacute and subchronic exposure to doses up to approx. 500 mg/kg bw/d.

Classification and labelling for neurotoxicity according to Directive 67/548/EEC:
Not required
Classification and labelling for neurotoxicity according to Regulation (EC) No 1272/2008:
Not required

Further Studies

Not required, not submitted

Medical Data

Direct observations in healthy individuals (oral exposure)

Several studies from the 19th and the beginning of the 20th century regarding the oral exposure of humans to benzoic acid or sodium benzoate are described. However, owing to the low number of individuals exposed, the validity of these studies is limited. No adverse effects were reported after a single oral dose of 10.000 mg benzoic acid or up to 1000 mg/d over a period of up to 90 days. In another study no abnormalities were found in hematology, urine composition, nitrogen balance, or well-being of six men given 300-400 mg/d in the diet for up to 62 days. In another study with volunteers given 1000 mg/d for 5 days and subsequently increasing the dose in increments of 500 mg/d every 5 days to 2500 mg/d, signs of discomfort (nausea, headache, weakness, burning and irritation of oesophagus) were reported.

Medical observations

Sodium benzoate is used in the treatment of patients with urea cycle enzymopathies (i.e., hyperammonaemia due to inborn defects of urea synthesis) in order to facilitate an alternative pathway of nitrogen excretion. The therapeutic dose for maintenance of low blood ammonia levels, which might be given over several years, is 125-500 mg/kg bw/d for neonates, children and adults. Clinical signs of toxicity at the maintenance dose of 125-500 mg/kg bw/d are rare and comprise headache, nausea and vomiting. In hyperammonaemia crises and in neonates bolus doses up to 1750 mg/kg bw/d sodium benzoate are reported with some fatalities that might be due to metabolic acidosis. The adverse effects described for benzoic acid overdoses are similar to those observed in salicylate poisoning. Intoxication by both substances is thought to occur via a similar mechanism (inhibition of mitochondrial respiration after saturation of the glycine and glucuronate conjugation): mild symptoms comprise lethargy, nausea/vomiting, tinnitus, dizziness and burning in mouth, throat and oesophagus, moderate symptoms include hyperpnea, tachypnea, restlessness, loss of coordination while severe symptoms include coma/convulsions, pulmonary oedema, and encephalopathy.

In nine patients on penicillin treatment given 12.000 mg benzoic acid divided into eight doses over 5 days in eight subjects and over 14 days in one subject, no adverse effects on blood urea nitrogen or creatinine clearance were reported.

Other authors compiled 1879 27 case reports of patients with acute rheumatic arthritis which were treated with 4 to 25 g/d benzoic acid without adverse effects.

Epidemiologic studies (exposure estimates)

The Concise International Chemical Assessment Document No. 26 (Benzoic Acid and Sodium Benzoate, IPCS, 2000) reports intake data of benzoates based on an assessment of JECFA in 1999 including information provided by Australia, China, Finland, France, Japan, New Zealand, Spain, United Kingdom, and the USA. Soft drinks and soya sauce contributed most to the benzoate intake. The national mean intake was 0.18 mg/kg bw/d in Japan and 2.3 mg/kg bw/d in the USA. High consumers of benzoates have an estimated daily intake of 7.3 mg/kg bw/d in the USA and 14 mg/kg bw/d in China.

Non-immune immediate contact reactions (NIICR) and non-immunogenic contact urticaria (NICU)

Benzoic acid and sodium benzoate are not irritating to the skin (below classification threshold) in standard animal irritation studies (cf. Doc. II table 3-5). However, skin effects have frequently been reported for humans (cf. Doc II table 3-15 for selected publications).

Benzoic acid and its salts are capable of causing non-immune immediate contact reactions (NIICR) and non immunogenic contact urticaria (NICU), also known as pseudoallergy.

Per definition, non-immunologic immediate contact reactions are considered irritant reactions in contrast to immunogenic (allergic) contact reactions. NIICR of the skin are dose-dependent inflammatory reactions that occur within a short time of contact with the eliciting substance and do not require previous sensitisation. Susceptibility of the exposed individuals may vary widely. Contact reactions may involve development of erythema, oedema or appearance of wheals.

In an investigation with unselected volunteers (200), double-blind skin tests were run with benzoic acid. Benzoic acid was applied in chambers onto the skin for 20 min and assessed 30 min after the initiation of the application. In this study, a considerable proportion of volunteers (73.5 %) reacted to benzoic acid at 125 mM (ca. 1.5 % dilution) with erythema, while 12.5 % developed oedema at this test concentration. At 500 mM (ca. 6 % dilution), 78.5 % reacted with erythema and 18 % with oedema. The mean erythema severity scores (applying a grading of 0-8) were 1.81 at 125 mM and 2.12 at 500 mM, respectively, while the oedema scores after 30 min were 0.16 at 125 mM and 0.22 at 500 mM.

1976 a new method was investigated. The chamber-scarification test for skin irritancy, as an alternative for the conventional patch test. Benzoic acid was applied once daily for 3 days in chambers on scarified and unscarified skin on the forearm of 5-10 healthy volunteers and rated 24 h after the last exposure. The irritant threshold concentration of benzoic acid on unscarified skin was 30 %, on scarified skin 7.5 %. Applying a five-point grading system of 0-4, a moderate response (score between 1.5-2.4) was observed at 7.5 % on scarified skin. A marked response, leading to erosions, was observed at 15 % (score between 2.5-4).

Regarding skin testing of benzoates, closed patch tests in patients with an atopic predisposition, asthma or urticaria have been reported (1955: 4 % positive reactions1987 (0.7 %)1993 (0.2 %), among others). The vehicle used for dissolving benzoic acid or sodium benzoate is considered to be of great influence on the outcome of the test. A large amount of positive oral provocation tests with benzoates including skin reactions are also provided in a comprehensive literature (1982 (11 %), 1985 (18 %), 1991 (14 %), among others).

Further characterisation of benzoic acid skin effects

In a human maximisation test, benzoic acid and related compounds did not show any sensitisation potential in volunteers. Investigations from 1980 indicated that NIICRs due to benzoates are not mediated by histamine. The reactions may be mediated by other vasoactive substances. An alteration in arachidonic acid metabolism or in abundance of eicosanoids has been proposed. In particular, prostaglandin D2 (PGD2) has been suspected to act as a mediator of nonimmune contact reactions, as it has been shown to be dose-dependently released in human skin after application of eliciting substances such as benzoic acid. In addition, the NIICR has been reported to be inhibited by oral or topical application of non-steroidal anti-inflammatory drugs that lead to inhibition of prostaglandin synthesis. Ultraviolet irradiation appears to reduce and infra-red irradiation to increase the NIICRs induced by benzoic acid.

Based on the positive results in human skin irritation studies and the underlying non-immunogenic irritant and inflammatory mechanism which does not involve sensitisation, the data are regarded sufficient to justify labelling benzoic acid with R38 resp. H315 in a weight of evidence approach.

Classification (labelling) for skin irritation according to Directive 67/548/EEC:

Xi; R38 (Irritant; Irritating to skin)
Classification (labelling) for skin irritation according to Regulation (EC) No 1272/2008:
Skin Irrit. 2; H315 (Causes skin irritation)

Summary & Conclusion

The NOAEL of 500 mg/kg bw/d based on neurotoxic and hepatotoxic effects and mortalities observed in rats following subacute and subchronic exposure to 1200-1500 mg/kg bw/d as well as the maternal toxicity and the reduced 8-wk offspring survival in a teratogenicity study at 1000 mg/kg bw/d are the relevant starting points for the derivation of systemic reference doses. In humans, the effects described in medical case reports (LOAEL: 125-500 mg/kg bw/d) are similar. In the absence of appropriate acute studies, the NOAEL of 500 mg/kg bw/d is used for a conservative derivation of an Acute Acceptable Exposure Level.

By setting a default assessment factor of 100, an

Acute Acceptable Exposure Level (AELacute) of 5 mg/kg bw/d, and a

Medium-term Acceptable Exposure Level (AELmedium-term) of 5 mg/kg bw/d

are proposed for acute and repeated, medium-term exposure to benzoic acid.

Adverse toxic effects of benzoic acid were usually observed after repeated bolus doses within a short time. This can be explained by metabolic interference following saturation of the conjugation pathways and/or depletion of glycine/glucuronate. Thus, it appears unlikely that prolongation of exposure from subchronic to chronic aggravates benzoic acid toxicity. In addition, no additional target organs or adverse effects were reported after chronic exposure, neither in animals nor in humans from the use as food additive or therapeutic drug. Therefore, a NOAEL of 500 mg/kg bw/d is considered as the relevant basis for setting a systemic reference dose for long-term exposure to benzoic acid.

By setting a default assessment factor of 100, a

Long-term Acceptable Exposure Level (AELlong-term) of 5 mg/kg bw/d

is proposed for chronic exposure towards benzoic acid.

AELs for local effects are not required as toxic effects after dermal application are covered by the systemic AELs.

Considering the intended use as PT 3, consumer exposure to benzoic acid residues in food or feed items via biocidal products will be much lower compared to consumer exposure to benzoic acid occurring as natural food ingredient and from use as registered food additive and authorised feeding stuff additive. Therefore, the derivation of an **Acceptable Daily Intake (ADI)** is considered not necessary in the context of biocidal use. For the use as a Plant Protection Product an **ADI of 5 mg/kg bw** was derived by JECFA (1983) and EU (2002, 2005), based on the NOAEL of 500 mg/kg bw/d from subacute/subchronic and teratogenicity studies and an assessment factor of 100.

According to an EU guidance document (Doc. 7199/VI/99; EU, 2001) and a publication[4] , an ARfD is not allocated because of low acute oral toxicity of benzoic acid and the cut off value at 5 mg/kg bw[5] .

Summarising the study results and all considerations above, benzoic acid requires classification (labelling) according to Directive 67/548/EEC as follows:
Xi; R38 - 41
According to Regulation (EC) No 1272/2008 benzoic acid requires classification (labelling) as follows:
Skin Irrit. 2; H315 and Eye Dam. 1; H318

2.2.1.3. Exposure assessment

Exposure of Professionals

The active substance benzoic acid is produced outside the EU, the biocidal product Menno Florades is manufactured within the EU.

The following scenarios are covered by the exposure assessment in this report:

- Spraying in animal housings (scenario 1)
- Secondary exposure to Benzoic Acid (scenario 2)
- Combined for both scenarios: Primary and secondary Exposure of farmer

The biocidal product Menno Florades is diluted and applied to hard (man made) surfaces in stables, barns, animal keeping areas for pigs with a low pressure (1 - 3 bar) hand-held sprayer. The spraying device produces a foam to allow a prolonged impact and slowed drying. Prior to application, the biocidal product solution with a concentration of 9 % (90 g/l) active substance in the product concentrate is diluted to 0.1 - 0.4 % (1 - 4 g/l) a.s. in the application solution.

Due to the low vapour pressure of the active substance inhalation exposure to vapour during the mixing & loading phase and the post-application phase is assessed as negligible. Aerosol formation is expected during the spraying in animal housings. The application of foam might reduce the inhalation exposure since the formation of aerosols is reduced. However in the TNsG Human Exposure no model is available to assess such a case and no measurement data are provided by the participant. Therefore the foam application is assessed using a spray model.

To estimate the inhalation exposure to aerosols the value of 104 mg/m3 (50th percentile) is chosen from Model 1 (Spraying) of the TNsG Human Exposure to Biocidal Products (Part 2, pp. 143-145). Taking into account the diluted concentration of at most 0.4 % active substance in the spraying solution and the spraying duration of 120 min per day the inhalation exposure is

4 Solecki et al., 2005. Fd Chem Toxicol 43(11):1569-1593
5 "A value of 5 mg/kg bw is proposed as a conservative value to cover all eventualities for agricultural pesticides, based on practical considerations on consumption and maximum residue levels in foods. An ARfD cut off at 5 mg/kg bw would equate to a NOAEL of 500 mg/kg bw/d in an animal study, when default uncertainty factors are applied."

estimated to be 0.104 mg a.s/m3 (8 h time-weighted average TWA). It is not possible to quantify the exposure reducing effect of the foam, but it is assumed that the use of Spraying Model 1 might overestimate the inhalation exposure.

Dermal exposure to the concentrated biocidal product (90 g/l a.s.) during the mixing phase is possible. In addition, during the application phase dermal exposure to 0.4 % a.s. spray solution is possible. The dermal exposure during the mixing & loading phase and during the application phase is assessed by suitable models of the TNsG Human Exposure to Biocidal Products (Part 2). The dermal exposure during the post-application phase is estimated by in analogy to Marquart et al (2006). The resulting potential dermal exposure for all phases is 131.9 mg a.s./person/day.

A secondary exposure to benzoic acid after the use of Menno Florades cannot be excluded (scenario 2). After the use of Menno Florades the exposure by inhalation is assessed as negligible. A potential dermal exposure to benzoic acid is reasonable for dermal contact to treated surfaces and is calculated to be 30.2 mg a.s./person/day.

For the case that the same farmer applies the biocidal product (scenario 1) and is also secondarily exposed (scenario 2) to the product, the calculated inhalation exposure and dermal exposure are combined for both scenarios. In summary, for inhalation exposure a value of 0.11 mg a.s./m3 is assumed. The resulting dermal exposure is 162.12 mg a.s..

Exposure of Non-Professionals

Primary Exposure

The biocidal product Menno Florades is foreseen for professional use only. Thus, non-professional primary exposure is not expected.

Secondary Exposure

Secondary exposure of the general public is considered low since this group has, in general, no access to animal facilities, in which the biocidal product is applied. However, with drift values from EUROPOEM II, which were determined for plant protection products acute exposure has been assessed for the unrealistic (worst) case, in which they get closer to such an area. The worst case exposure estimates are below the systemic AEL (in maximum 65% of AELacute). Thus, it is concluded that secondary exposure of non-professionals to benzoic acid by application of the biocidal product (Product Type 3) is acceptable in relation to human health. However, since local irritating effects of the biocidal product even if diluted cannot be excluded for unprotected persons, access of the general public to treated areas or building has to be avoided.

Exposure via Residues in Food

Considering the intended use consumer exposure to benzoic acid residues in food or feed items via biocidal products will be much lower compared to consumer exposure to benzoic acid occurring as natural food ingredient and from use as registered food additive and authorised feeding stuff additive.

2.2.1.4. Risk characterisation

Risk Assessment for Professionals

The risk characterisation is performed with the AEL approach. In this approach total internal body burden is compared to the AEL of 5 mg/kg/d (based on a NOAEL of 500 mg/kg bw/d from the teratogenicity, subacute and subchronic studies in rats and setting a default assessment factor of 100). Because the frequency of exposure does not significantly influence systemic effects of benzoic acid acute, medium and long-term AELs are identical.

The total internal dose is calculated with absorption values of 100% for inhalation and dermal uptake. The potential exposure is nearly completely triggered by dermal exposure and results in a total internal body burden of about 2.2 mg/kg/d for application of MENNO Florades.

Overall, against the background of a decision criterion of 1 for the exposure-to-AEL ratio there is no concern for application of the biocidal product MENNO Florades. Additionally no concern is expressed, if a combined calculation of scenario 1 (spraying in animal housings) and scenario 2 (secondary exposure to benzoic acid) will be done. Based on this analysis, there is no need for further refinement of this risk assessment.

It is essential to recognize that this conclusion only applies to the active substance in the biocidal product. However, it should be kept in mind that due to the pseudoallergic properties of benzoic acid to induct non-immunological contact urticaria the assigned risk reduction measures (see below) have to be applied. From the point of view of occupational safety and health there is no risk-related reason for conditioning the requested annex I inclusion for benzoic acid.

Safety Measures for Professionals

Users of the biocidal product are expected to be farmers (unspecialised professionals; use by professional pest control operators cannot be excluded). Application of the liquid biocidal product (dummy) consists of loading the low-pressure hand-held sprayer (thereby, diluting the concentrate), and treating (foam / spray) of the surfaces to be disinfected in animal facilities (PT 3).

Safety measures to be recommended are - if exposure cannot be excluded by engineering and / or organisational measures - safety goggles with side-shields, protective gloves and a coverall (type 4, EN 14605) because of classification as Xi; R 38-41 and possible pseudo-allergic properties (non-immunogenic contact urticaria (NICU) as erythema and oedema).

As this product is applied as foam, respiratory protection measures are not necessary in general but they should be considered during product authorisation, in particular as - according to RAC-

"Opinion proposing harmonised classification and labeling at EU level of Benzoic Acid" (http://echa.europa.eu/documents/10162/bc977357-37b3-495d-b7a9-62a2c8913fcf) - benzoic acid shall be classified as "T, R 48/23" (Toxic: danger of serious damage to health by prolonged exposure through inhalation). Depending on the concentration of the a.s., resp. the classification and labeling of the biocidal product, respiratory protection measures shall be taken into account to avoid or, at least, minimize exposure to benzoic acid. Concerning PPE against spray mist (aerosols), particle filter would be sufficient, but the authorizing CA should insist on engineering and/or organisational measures (e.g. separation of product and user).

Furthermore when handling the product Menno Florades containing 90 g/l benzoic acid, measures should be taken to prevent a fire as this product is a flammable mixture.

Risk Assessment for Non-Professionals

Secondary exposure of the general public to benzoic acid from Menno Florades is considered acceptable with respect to human health. Primary exposure by non-professional use is not intended.

Safety Measures for Non-Professionals

No specific safety measures are required for the general public and the non-professional user since the biocidal product is restricted to professional use. However, these use restrictions have to be ensured by the applicant. Furthermore it has to be clearly indicated in the label of use that other persons than professional operators and other bystanders involved in the application of the biocidal product have to be absent during application. Furthermore the biocidal product has to be labelled with S2/P102 to protect children and the general public against unintended exposure.

Measures to protect animals and companion pets

The biocidal product has to be labelled with S13 to protect animals against unintended exposure via feeding stuff.

2.2.2. Environmental Risk Assessment

The environmental risk characterisation is based on the concept of releases of active substance to the environment taking into account all relevant life cycle stages. The estimation of predicted environmental concentration (PEC) for the "dummy product" as well as the derivation of predicted no effect concentrations (PNECs) for different environmental compartments was performed according to the EU Technical Guidance Document (TGD) on Risk Assessment (2003) and to the Environmental Emission Scenarios for PT 3 (SCC, February 2009).

2.2.2.1. Fate and distribution in the environment

Biodegradation

Based on a weight of evidence approach, considering a test on ready biodegradability according to OECD 301 C ("MITI-I test"), the averaged results of 128 tests performed according to either OECD 301 B, or OECD 301 D, or OECD 301 E, and the fact that sodium salt of benzoic acid is one of the recommended reference compounds proposed in the OECD 301 test guideline, the a.s. benzoic acid was regarded as “readily biodegradable within the 10-day window”.

Further studies on biodegradability in soil, water/sediment or sewage treatment plants were not deemed to be necessary.

Anaerobic biodegradation

An anaerobic biodegradation test was submitted by the applicant as a product type specific (product type 3) data requirement caused by releases of benzoic acid into manure storage facilities. The result shows that more than 75% of theoretical gas production is achieved within 60 days of incubation, which means that complete anaerobic biodegradation, can be assumed for benzoic acid.

Abiotic Degradation

Benzoic acid as an aromatic monocarbon acid possesses no hydrolysable functional groups. For this reason, hydrolysis under environmental conditions is not expected. In real life samples the microbial population will rapidly degrade benzoic acid and compared with biodegradation processes, hydrolysis in surface waters will not be relevant. In conclusion, benzoic acid is stable in pure and sterile water.

Benzoic acid has two absorption bands at wavelength of 228 nm and 274 nm. Thus, a direct photodegradation does not occur for benzoic acid as chemicals with UV/absorption maximum of < 290 nm cannot undergo direct photolysis in sunlight. Nevertheless, in studies with added catalysers and high energy input photodegradation of benzoic acid was observed. Photodecomposition of benzoic acid in these systems depends on temperature and pH of the medium. Benzoic acid was shown to be an end-product of photodecomposition of other organic compound, e.g. DDA (2,2-bis-(p-chlorophenyl) acetic acid.

In air benzoic acid will be degraded by indirect photodegradation, the half-life was calculated to 12.9 d, which corresponds to a value of 18.6 d for the chemical lifetime in the troposphere.

Distribution and Mobility

Based on log Pow, the log Koc was estimated to 1.4 by application of QSAR models (Sabljic and Güsten in EU TGD on Risk Assessment (2003), Part III, Chapter 4.3, Table 4) and calculations based on the generally accepted model PCKOCWIN v1.66. The value was used for classification of benzoic acid as substance with high mobility in soil and for the environmental exposure assessment.

The Koc value for benzoic acid is dependent on pH variation and solubility. Due to the changes of solubility of chemical substances with variation of pH, several QSAR models allow prediction of Koc values depending on pH. The Koc values for benzoic acid in dependence on environmentally relevant pH-values were estimated applying the model ACD/AdsorptionCoefficient 8.02. The predicted Koc for the benzoic acid decreases slightly with pH-value, i.e. from the non-ionised molecule to the gradually ionised molecule. A calculation of Koc was not possible using the model ACD for the completely ionised benzoate. Nevertheless and in conclusion, benzoic acid is expected to exhibit only a weak adsorption in soils and sediments and is regarded to be a highly mobile substance in soil at environmentally relevant pH values.

The mobility of benzoic acid depends on further soil properties. Lower Fe-contents in several soils may have contributed to weaker bonding and greater mobility of benzoic acid in those soils. Lower Al- and Fe-contents decrease the retention of benzoate anions to positively charged surfaces of Fe- and Al-oxides. Removal of organic matter increased the mobility of benzoic acid in all soils.

In conclusion, benzoic acid mobility was positively correlated with soil pH, and negatively correlated with Al- and Fe-contents.

Bioaccumulation and Secondary Poisoning

Based on the physicochemical properties an approximate estimation of the bioconcentration factors (BCFs) can be calculated according to TGD (EC 2003). Applying the experimentally derived log KOW of 1.87, results in a BCFFish of 7.75 L/kg ww and a BCFEarthworm of 1.73 L/kg ww. Hence, the aquatic and terrestrial bioaccumulation potential of benzoic acid can be assumed as low.

In consequence of the log KOW < 3 and the low estimated BCF values, experimental studies are not required. Furthermore, no other indicators point to an intrinsic potential for bioconcentration.

With regard to the low estimated BCF values in aquatic and terrestrial indicator species, benzoic acid is not expected to accumulate in the environment. The risk of secondary poisoning is therefore assumed to be negligible via ingestion of contaminated food by birds or mammals.

2.2.2.2. Effects assessment

Aquatic Compartment including sediment

Short- and long-term tests with fish, daphnids and green algae are available for benzoic acid. The acute effect values for the three trophic levels were all above 100 mg/L. The lowest valid effect value of 25 mg/L was obtained in a long-term test with Daphnia magna. Applying an assessment factor of 10 resulted in a PNECwater of 2.5 mg/L.

No test with benthic organisms is available. As benzoic acid is not expected to partition to the sediment compartment, the effects assessment for the sediment is covered by the effects assessment for the surface water. Nevertheless, a PNECsediment is derived from the PNECwater using the equilibrium partitioning method according to the EU TGD (2003). With a ksusp-water of 1.589 and a RHOsusp of 1150 kg/m^3, a PNECsediment of 3.4 mg/kg ww is derived.

Inhibition of microbial activity (STP)

In a test on the respiration inhibition of activated sludge conducted according to OECD 209 guideline, the EC50 was calculated to be >1000 mg a.s./L nominal. For the risk assessment an EC50 value of 1000 mg/L will be used as a worst case.

Since chemicals may cause adverse effects on microbial activity in STPs it is necessary to derive a PNECmicroorganisms, STP. The PNECmicroorganisms, STP is used for the calculation of the PEC/PNEC ratio concerning microbial activity in STPs. Considering an assessment factor of 100 to the EC50 of the respiration inhibition test a PNECmicroorganisms, STP of 10 mg/L was derived.

Terrestrial Compartment

No tests with terrestrial organisms are available for benzoic acid. According to the TNsG on data requirement, tests with terrestrial organisms need to be performed for this product type, as exposure to the terrestrial compartment via manure occurs from the use in stables. The applicant justified the non-submission of terrestrial studies with the low exposure of the terrestrial compartment. As a first step, the PNECsoil was derived from the PNECwater using the equilibrium partitioning method according to the EU TGD on Risk Assessment (2003). With a ksoil-water of 1.026 and a RHOsoil of 1700 kg/m^3, a PNECsoil of 1.5 mg/kg ww is derived from the PNECwater.

Atmosphere

Benzoic acid is not considered to be used as fumigant. The vapour pressure of benzoic acid is 4 x 10-2 to 7 x 10-2 Pa at 20°C. The Henry's constant is 4.6 x 10-3 to 2.2 x 10-2 Pa □ m3 mol-1 at 20°C. According to a classification scheme after LYMAN et al. (1983) the Henry's law constant indicates moderate volatility from water. The half-life and chemical lifetime of benzoic acid in the troposphere were estimated to 12.9 and 18.6 days, respectively. Thus, benzoic acid has a potential for long-range environmental transport regarding the half-life in air (ref. to Annex D of the Stockholm Convention on Persistent Organic Pollutants (17th May 2004): "… a chemical that migrates significantly through the air, its half-life in air should be greater than two days …"). On the other hand, according to the EU TGD on Risk Assessment (2003) effects on stratospheric ozone and acidification are not expected because benzoic acid does not contain halogens, nitrogen or sulphur substituent. The potential for global warming can not be characterised because there is no information available in the absorption spectrum in the range from 800 to 1200 nm.

2.2.2.3. PBT assessment

The PBT assessment for benzoic acid was performed according to the guidance given in the TGD on risk assessment (2003) as described in part II, chapter 4.4 as well as following the new REACH legislation.

P criterion: Half life > 40 d in freshwater or > 120 d in freshwater sediment or

> 120 d in soil (according to the new REACH legislation)

vP criterion: Half life > 60 d in freshwater or > 180 d in freshwater sediment or

> 180 d in soil (according to the new REACH legislation)

According to ready biodegradability tests, benzoic acid is considered to be readily biodegradable. Generally, it is assumed that a chemical giving a positive result in a test of this type will rapidly biodegrade in the environment. On the basis of this assumption, the P criterion as well as the vP criterion is not fulfilled.

B criterion: BCF > 2000 L/kg

vB criterion: BCF > 5000 L/kg

For benzoic acid with a log Kow less than three, the calculated bioconcentration factor for fish is 7.75 L/kg ww and for earthworm 1.73L/kg ww. Therefore, the B criterion as well as the vB criterion is not fulfilled.

T criterion: Long-term NOEC for freshwater organism < 0.01 mg/L or CMR or endocrine disrupting effects

The lowest long-term NOEC of 25 mg/L for Daphnia magna is clearly above the trigger value. There is no hint for CMR or endocrine disrupting effects. Therefore, the T criterion is not fulfilled.

Conclusion: The active substance benzoic acid is neither PBT - nor vP/vB – candidate.

2.2.2.4. Exposure assessment

For the assessment of the representative biocidal product (b.p.) MENNO Florades, which is a dummy product for evaluation according to Directive 98/8/EC, the following life cycle stages are selected as relevant:

- production of a.s.
- formulation of b.p.
- product use as 0.36 % w/w aqueous solution applied exclusively indoors in stables, barns, animal keeping areas for pigs (PT 3).

An environmental exposure assessment is not performed for the life cycle stage “production” as the a.s. is produced outside the EU. In case of the life cycle stage “formulation”, the argumentation of the applicant is followed that production of the b.p. in closed systems does not require any further environmental exposure assessment. No exposure estimation is performed for further ingredients of the dummy b.p. During national authorisation of b.p. containing benzoic acid as a.s. a re-evaluation of all ingredients in the final product will be required.

Benzoic acid is notified for Annex I inclusion in PT 3 and 4. In this assessment report, the use in PT 3 is considered: as animal hygiene biocidal product (disinfection of pig barns). – The environmental exposure estimation is based on the EU TGD (2003) and the draft ESD for PT 3 (SCC, February 2009). The releases of b.p. MENNO Florades to the environment are assessed by applying emission models to soil after manure applications on grassland and arable land followed by emission models to groundwater and to surface water.

Cumulative Exposure Assessment

According to Article 10(1) of the BPD substances shall be included in Annex I, IA and IB also taking into account, where relevant, cumulation effects from the use of biocidal products containing the same active substances. This refers to environmental risk assessment of an active substance contained in different products of the same Product Type (PT) or of different PTs. The b.p. MENNO Florades is used as 0.36 % w/w aqueous solution indoors in stables, barns, animal keeping areas for pigs (PT 3) as well as in farm feedstuff storage areas adjacent to barns and stables (PT 4). Every intended use of Menno Florades can take place at the same time. Due to the same entry pathways, summing up the local PECs of PT3 and PT4 is the most adequate way to assess the cumulative PEC (PEClocal_cum) based on the information provided by the applicant. Consequently, beside the product type specific calculations for the intended uses in PT3 the risk characterisation in this assessment report is taking into account the cumulative exposure estimation from PT3 and PT4 as well. If more information will become available the assessment could be refined.

2.2.2.5. Risk characterisation

The environmental risk characterisation is based on the concept of releases of active substance to the environment taking into account all relevant life cycle stages. Details on the emission scenarios and PEC estimation for different application areas and environmental compartments are described in the documents Doc II, chapter 8.3. The derivation of predicted no effect concentrations (PNECs) for different environmental compartments is described in detail in Doc II, chapter 4. The PEC/PNEC ratios related to the scenarios for nitrogen immission standards (170 kg. ha-1. yr-1) represent the highest values and are considered as worst case.

Aquatic Compartment including Sediment

Due to the specific applications of the product by professional operators, indoors in empty pig barns/facilities (PT 3) a release via a municipal sewage treatment plant and/or surface water is not relevant. The risk assessment for the aquatic compartment comprises the application of contaminated manure to grassland / arable land and the subsequent translocation of benzoic acid to groundwater and surface water (run off). All the estimated PEC/PNEC values for surface water as well as for sediment were found to be below the trigger value of 1. At a first tier approach the intended use of Menno Florades as a disinfectant of animal housings (pig barns) indicates no unacceptable risk for the aquatic compartment by benzoic acid.

Terrestrial Compartment including Groundwater

In view of the intended use of Menno Florades for disinfection of empty pig barns / facilities a direct exposure to the soil compartment does not occur. The releases of b.p. are due to manure application on grassland / arable land and afterwards to the groundwater. The calculated PEC/PNEC values for soil indicate no risk to this compartment whereas for groundwater the quality standard for pesticides and biocidal products according to Directive 2006/118/EC for drinking water is exceeded. At a second tier PECgroundwater calculation applying FOCUS PEARL (version 3.3.3) was performed, which considers potential mobility of benzoic acid in soils and the leaching behaviour to groundwater. It could be demonstrated that the average concentration of benzoic acid closest to the 80th percentile is < 0.0001 µg.L-1 and thus the predicted concentrations in groundwater are significantly below the threshold criteria of

0.1µg.L-1 for all agricultural scenarios. Therefore, no risk to groundwater after application of MENNO Florades containing benzoic acid is indicated.

Atmosphere

Due to the intended use of the b.p. for product type 3 which is limited to indoor application and on basis of the available substance information the environmental risk of benzoic acid for the atmosphere can be assumed as low.

Cumulative Risk Assessment

As the main entry pathways into the environment are equal for all applications (via slurry application to agricultural land) a combination of exposures to benzoic acid for all environmental compartments affected are possible and realistic as well as feasible in technical terms. The cumulative exposure assessment was conducted by summing up the PEClocal values of product types 3 and 4 on basis of the worst case consumption approach. The cumulative PEC/PNEC ratios indicate no unacceptable risk to the environmental compartments surface water, sediment and soil. As the results for all PECcum_gw calculations correspond to a value of < 0.0001 µg.L-1 from the higher tier approach, the quality standard for pesticides and biocides of 0.1µg.L-1 is not exceeded in any case. It is concluded that no risk to groundwater from application of b.p. is indicated.

Overall Conclusion to the Environment

Considering the intended use of the biocidal product Menno Florades it is concluded that the application of benzoic acid for disinfection of pig barns / facilities poses no unacceptable risk to the environment. The environmental risk was assessed only for use in pig housing where any emissions are discharged in slurry. Additional assessment at product authorisation will be required if other animal housing units (and different emission pathways to environmental compartments) are envisaged for application of the biocidal products. For the assessment of the representative b.p. MENNO Florades which is a "dummy product" for evaluation according to Directive 98/8/EC, no further action is required at the moment. As no exposure estimation for further ingredients of the dummy b.p. is performed, during national product authorisation of b.p. containing benzoic acid as a.s., a re-evaluation of all ingredients in the final product will be required.

2.2.3. List of endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

3. PROPOSED DECISION

3.1. Background to the proposed decision

As benzoic acid is an ubiquitously occuring substance, it is not possible to identify if residues arising in food of plant and animal origin and in the environmental compartments (soil, drinking and surface water) arise as a result of the use of biocidal products containing benzoic acid. Furthermore benzoic acid is listed in Annex IV of the new regulation 396/2005/EC for pesticides as an active substance for which no MRLs are required. Therefore, residue analytical methods for the determination of the active substance in food of plant and animal origin for enforcement purposes as well as for soil, drinking and surface water are not required. Since secondary exposure of the general public is low, analytical methods for the determination of benzoic acid in air are not necessary, but since inhalation exposure at the workplace could occur due to spray application of the b.p. analytical method in air is needed and available for the active substance. Analytical methods for the determination of benzoic acid in body fluids and tissues were not submitted, because at the time of submission the active substance was not classified as toxic or very toxic. In the RAC Opinion from 25th November 2012 a classification as toxic was proposed. If this proposal is implemented in a corresponding ATP of Regulation (EC) 1272/2008 at the time of product authorisation analytical methods for the determination of the active substance in body fluids and tissues must be submitted.

The effects on human health have been assessed, in accordance with the provisions of Article 10(1) of Directive 98/8/EC, for the uses proposed by the applicant. Benzoic acid is of low toxicity in rat, mouse, rabbit and dog, and of moderate toxicity in cat. According to the RAC opinion of 25th November 2012 “there is evidence for pulmonary toxicity after repeated exposure to benzoic acid dust via inhalation”, leading to a classification as toxic. With regard to acute local effects, benzoic acid is not irritating to the skin (below classification threshold) in animal studies but highly irritating to the eyes. No sensitising potential of benzoic acid was observed in a guinea pig maximisation test, in a local lymph node assay, a Buehler test and a mouse ear swelling test. A non-immunogenic contact urticaria (NICU) (as erythema and oedema) was evoked by benzoic acid when applied to the ear lobes of guinea pigs and human skin of sensitive persons in various parts of the body. The evaluation of the active substance has indicated that benzoic acid has no carcinogenic and no genotoxic potential. No substance-related fertility or developmental impairment was noted in the reproduction toxicity studies.

Acceptable exposure levels for acute, medium- and long-term exposure could be derived for benzoic acid. Benzoic acid and its salts are natural compounds widely spread in the environment. They are generated in plant and animal metabolism and therefore, are constituents in many foodstuffs: up to ca. 40 mg/kg are found in milk products and up to 100 mg/kg in honey. Benzoic acid and benzoates are used as therapeutic substances in human and veterinary medicine. Because of its antimicrobial activity, benzoic acid is commonly used as preservative in food, cosmetics and pharmaceuticals.

Therefore, no risk to human health could be anticipated for the active substance used in biocidal products. All studies required by Directive 98/8/EC are available or statements for non submission have been accepted.

Summarising the study results and all considerations above, benzoic acid requires classification (labelling) according to Directive 67/548/EEC as follows:

Xi; R38 - 41 (proposed by the RMS)
T; R48/23 (according to RAC Opinion)
According to Regulation (EC) No 1272/2008 benzoic acid requires classification (labelling) as follows:
Skin Irrit. 2; H315 and Eye Dam. 1; H318 (proposed by RMS)
STOT RE 1; H372 (according to RAC Opinion)

The biocidal product Menno Florades is foreseen for professional use only. Thus, non-professional primary exposure is not expected. Secondary exposure of the general public to benzoic acid from Menno Florades is considered acceptable with respect to human health. Considering the intended use consumer exposure to benzoic acid residues in food or feed items via biocidal products will be much lower compared to consumer exposure to benzoic acid occurring as natural food ingredient and from use as registered food additive and authorised feeding stuff additive.

The biocidal product Menno Florades contains 90g/L benzoic acid and other ingredients.

According to Directive 1999/45/EC the following classification is proposed:
R10 (Flammable),
Xi; R41 (Irritant; Risk of serious damage to eyes)
R67 (Vapours may cause drowsiness and dizziness) and
T, R48/230 (based on the RAC proposal).

The corresponding classification based on Regulation (EC) No 1272/2008 is:
Flam. Liq. 3; H226 (Flammable liquid and vapour)
Eye Dam. 1; H318 (Causes serious eye damage)
STOT SE 3; H336 (May cause drowsiness or dizziness)
STOT RE 2, H373 (based on the RAC proposal).

Considering the intended use of the biocidal product Menno Florades it is concluded that the application of benzoic acid for disinfection of pig barns / facilities poses no unacceptable risk to the environment. The environmental risk was assessed only for use in pig housing where any emissions are discharged in slurry. Additional assessment at product authorisation will be required if other animal housing units (and different emission pathways to environmental compartments) are envisaged for application of the biocidal products. For the assessment of the representative b.p. MENNO Florades which is a “dummy product” for evaluation according to Directive 98/8/EC, no further action is required at the moment.

The active substance benzoic acid is neither PBT - nor vP/vB – candidate as neither the P, B or T criteria are fulfilled.

Benzoic acid is not considered as having endocrine-disrupting properties in the sense of Article 5(3), second and third subparagraphs.

3.2. Proposed decision

The overall conclusion from the evaluation of benzoic acid for use in Product Type 3 (veterinary hygiene biocidal products), is that it may be possible to issue authorisations of products containing benzoic acid in accordance with the conditions laid down in Article 5(1) b), c) and d) of Dir. 98/8/EC.

It is therefore proposed to approve benzoic acid as an active substance for use in product-type 3 (veterinary hygiene), subject to the following specific conditions:

- The active substance Benzoic acid, as manufactured, shall have a minimum purity of 99 %.

- The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.

- Authorisations are also subject to the following particular condition:

    - For industrial or professional users, safe operational procedures and appropriate organizational measures shall be established. Where exposure cannot be reduced to an acceptable level by other means, products shall be used with appropriate personal protective equipment.
    - For products that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council or Regulation (EC) No 396/2005 of the European Parliament and of the Council shall be verified, and any appropriate risk mitigation measures shall be taken to ensure that the applicable MRLs are not exceeded.

3.3. Elements to be taken into account when authorising products

The information provided is only sufficient to show a basic efficacy of benzoic acid. This is accepted in the frame of the approval. In the frame of product authorisation, essentially more information has to be provided: To support the full label claim virucidal, bactericidal and fungicidal, further laboratory tests would be necessary. Additionally, further tests in the field of use have to be provided.

Considering the intended use of the biocidal product it should be mentioned that the environmental risk was assessed only for use in pig housing where any emissions are discharged in slurry. Additional assessment at product authorisation will be required if other animal housing units or application scenarios (and different emission pathways to environmental compartments) are envisaged for application of the biocidal products.

Analytical methods for the determination of benzoic acid in body fluids and tissues were not submitted, because at the time of submission the active substance was not classified as toxic or very toxic. In the RAC Opinion from 25th November 2012 a classification as toxic was proposed. If this proposal is implemented in an corresponding ATP of Regulation (EC) 1272/2008 at the time of product authorisation analytical methods for the determination of the active substance in body fluids and tissues must be submitted.

Even those biocidal products only intended for professional use must carry appropriate labelling to protect the general public.

Only the use of disinfection of pig housing has been assessed for the representative product. Other uses require further assessment at product authorisation stage.

3.4. Requirement for further information

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions, and permit the proposal for the approval of benzoic acid in accordance with Article 9 of Regulation (EU) No 528/2012.

3.5. Updating this Assessment Report

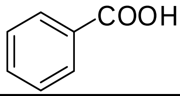
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information submitted in relation with Regulation (EU) No 528/2012. Such adaptations will be examined and finalised in connection with any amendment of the conditions for the approval of Benzoic acid.

Appendix I: List of endpoints

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Common Name)	Benzoic acid
Product-type	03 (Veterinary hygiene biocidal products)

Identity

Chemical name (IUPAC)	Benzoic acid
Chemical name (CA)	Benzoic acid
CAS No	65-85-0
EC No	200-618-2
Other substance No.	CIPAC: 622
Minimum purity of the active substance as manufactured (g/kg or g/l)	990 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	none
Molecular formula	C7H6O2
Molecular mass	122.12
Structural formula	

Physical and chemical properties

Melting point (state purity)	122.4°C (> 99%)
Boiling point (state purity)	249.2°C (> 99%)
Temperature of decomposition	Decarboxylation above 370 °C
Appearance (state purity)	white odourless crystalline solid (99%)
Relative density (state purity)	d204 = 1.321 (> 99%)
Surface tension	60.0 mN/m (> 99%, T = 20°C, 1g/L)
Vapour pressure (in Pa, state temperature)	0.04 – 0.07 Pa at 20°C (> 99%)
Henry's law constant (Pa m^3 mol^{-1})	0.0016-0.0029 Pa*m3 * mol-1 (> 99%)
Solubility in water (g/l or mg/l, state temperature)	pH 5.2: 5 g/l (> 99%, T = 20°C) pH 9: 15g/l (> 99%, T = 20°C) pH 2.94: 2.9g/l (> 99%, T = 20°C)
Solubility in organic solvents (in g/l or mg/l, state temperature)	Acetone 55.60 g/100g Benzene 12.17 g/100g Carbon-tetrachloride 4.14 g/100g Chloroform 15.02 g/100g Ethanol 58.40 g/100g Ethyl ether 40.80 g/100g Hexane (17°C) 0.94 g/100g Methanol (23°C) 71.50 g/100g Toluene 10.60 g/100g
Stability in organic solvents used in biocidal products including relevant breakdown products	Benzoic acid is stable in organic solvents.
Partition coefficient (log P_{OW}) (state temperature)	log pow = 1.87 at 20°C (unionised molecule)
Hydrolytic stability (DT_{50}) (state pH and temperature)	no hydrolysis
Dissociation constant	Ka= 6.339 *10-5 at 25°C (> 99%)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	pH 2; λ=230 nm ; pH 4; λ=228 nm ;
Photostability (DT_{50}) (aqueous, sunlight, state pH)	pH 7; λ=224 nm ; pH 9; λ=224 nm
Quantum yield of direct phototransformation in water at Σ > 290 nm	--
Flammability	Not flammable
Explosive properties	Not explosive

Classification and proposed labelling of the active substance

with regard to physical/chemical data	No classification is required
with regard to toxicological data	Xi, T R38, R41, R48/23* S1/S2; S26, S37/39; S45
with regard to fate and behaviour data	No classification is required
with regard to ecotoxicological data	No classification is required

*** According to RAC opinion from 25th November 2012, in addition to the proposal by the RMS**

Classification and proposed labelling of the active substance based on Regulation (EC) No 1272/2008

with regard to physical/chemical data	No classification is required
with regard to toxicological data	Skin Irrit. 2, Eye Dam. 1, STOT RE 1 H315, H318, H372* (P102), P260*, P280, P302 + P352, P333 + P313, P305 + P351 + P338, P310, P501
with regard to fate and behaviour data	No classification is required
with regard to ecotoxicological data	No classification is required

*** According to RAC opinion from 25th November 2012, in addition to the proposal by the RMS**

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	Determination of benzoic acid by an external standard isocratic HPLC-method on a reversed stationary phase (Ultrasep ES RP 18) with UV detection of benzoic acid at 245 nm.
Impurities in technical active substance (principle of method)	Benzoic acid does not contain toxicological, ecotoxicological or environmental relevant impurities in quantities above 10 g/kg. Methods for identification and determination of impurities are described in the pharmacopoeias for pharmaceutical grade and in the EC directive 96/77 for food grade benzoic acid.

Analytical methods for residues

Soil (principle of method and LOQ)	Not applicable, no relevant residues expected
Air (principle of method and LOQ)	Ion chromatography-UV LOQ: 0.1 mg/m³
Water (principle of method and LOQ)	LC-UV (245 nm) LOQ: 0.75 mg/L method for surface water only; no relevant residues expected
Body fluids and tissues (principle of method and LOQ)	To be submitted at product authorisation depending on entry in ATP of Regulation (EC) 1272/2008.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not applicable, no relevant residues expected
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not applicable, no relevant residues expected

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Rapid: peak plasma concentration within 1-2 h, nearly complete: excretion >80 % based on urinary excretion, human data
Rate and extent of dermal absorption for the active substance:	100 % default value
Rate and extent of dermal absorption for the representative product(s)[6]:	100 % (default value in the absence of data for the biocidal product)
Distribution:	Widely distributed, highest residues (up to 0.3 %) in skin and fat
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	Excretion in man and rat: 80-100 % within 24 h, nearly completely urinary
Toxicologically significant metabolite(s)	Toxicity of metabolites (hippuric acid and benzoyl glucuronide) not assessed

Acute toxicity

Rat LD_{50} oral	> 2000 mg/kg bw (2000-3040 mg/kg bw)
Rat LD_{50} dermal	> 5000 mg/kg bw
Rat LC_{50} inhalation	> 1.2 mg/L air (6 h exposure; first exposure day during a subacute inhalation study, highest attainable concentration)
Skin irritation	Not irritating in animal tests (cf. medical data section)
Eye irritation	Severely irritating **R41 (H318)**
Skin sensitisation (test method used and result)	Not sensitising (M+K, Buehler, LLNA)

Repeated dose toxicity

Species/ target / critical effect	Rat (oral): CNS (tremor, convulsions, necrosis), liver (liver enzymes, histopathology) Rat (inhalative): Systemic: mortality, liver, kidney Pulmonary: inflammation, fibrosis **R48/23** **(H372)***

6 Please consider Q5 on *Derivation of dermal absorption values* of section 4.1.1 of the Manual of Technical Agreements (MOTA) version 5.

*** According to RAC opinion from 25th November 2012, in addition to the proposal by the RMS**

	Dog (oral): CNS (ataxia, tremor, convulsions, death)
Lowest relevant oral NOAEL / LOAEL	Medium-term NOAEL: Rat (teratogenicity, subacute, subchronic): 500 mg/kg bw/d Long-term NOAEL: Rat (all subchronic and carcinogenicity data): 500 mg/kg bw/d
Lowest relevant dermal NOAEL / LOAEL	Rabbit (3-wk): 2500 mg/kg bw/d (highest dose tested)
Lowest relevant inhalation NOAEL / LOAEL	Route-to-route extrapolation (oral to inhalative): Rat (subacute, subchronic): 500 mg/kg bw/d

Genotoxicity	No evidence for genotoxic potential

Carcinogenicity

Species/type of tumour	No increase in tumour rate observed
lowest dose with tumours	N/A

Reproductive toxicity

Species/ Reproduction target / critical effect	Rat: Parental and Offspring: No systemic toxic effects observed Reproductive: No reproductive toxic effects observed
Lowest relevant reproductive NOAEL / LOAEL	500 mg/kg bw/d (highest dose tested)
Species/Developmental target / critical effect	Rat: Maternal: Decreased survival, decreased food consumption, bw, lactation rate; Developmental: Decreased fetal viability, abnormalities/malformations; Offspring: Reduced postnatal survival

Developmental toxicity

Lowest relevant developmental NOAEL / LOAEL	1130 mg/kg bw/d

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect*	Subacute: Rat: CNS necrosis
Lowest relevant developmental NOAEL / LOAEL.	35-d rat: 825 mg/kg bw/d

* Neurotoxicity is presumably secondary to metabolic interference

Other toxicological studies

....	Not required, not submitted

Medical data

Case reports	Oral: - Sodium benzoate is therapeutically used, e.g. in the treatment of hyperammonaemia, at doses between 125-500 mg/kg bw/d - No sensitisation potential of benzoic acid and benzoates in a maximisation test developed for man - Causes non-immunogenic contact urticaria in susceptible individuals **R38 (H315)**

Summary	Value	Study	Safety factor
Non-professional user			
ADI* (acceptable daily intake, external long-term reference dose)	5 mg/kg bw	Rat, subchronic, carcinogenicity studies	100
AEL_{acute}	5 mg/kg bw	Rat, subacute, subchronic, reproductive and developmental studies	100
ARfD** (acute reference dose)	Not allocated, not necessary		
Professional user			
Reference value for inhalation (proposed OEL)	Not determined		
Reference value for dermal absorption concerning the active substance:	Not determined		

* Derived by JECFA (1983) and EU (2002, 2005) for the use of benzoic acid as a Plant Protection Product
** According to an EU guidance document (Doc. 7199/VI/99; EU, 2001) an ARfD is not allocated

Acceptable exposure scenarios (including method of calculation)

Professional users

Production of active substance:	Not assessed by the rapporteur under the requirements of the BPD
Formulation of biocidal product	Not assessed by the rapporteur under the requirements of the BPD

Intended uses	Liquid with 0.4 % active substance
Spraying in animal housings	
Mixing & Loading:	
Opening retail pack and mixing and diluting product to a concentration of 0.4 % a.s.	
Form of exposure: liquid (90 g/l active substance)	
Duration: 5 min	
Frequency: 3 times a year (farmer), regular basis	
(pest control operator)	
Model (inhalation): Expert judgement	
Model (dermal): Model 1 (Spraying), TNsG HE Part 2	
Application:	Potential inhalation exposure (all phases): 0.104 mg/m³ Potential dermal exposure (all phases): 131.9 mg a.s./person/day
Spraying in animal housing (spray pressure 1-3 bar)	
Form of exposure: aerosol (0.4 % active substance)	
Duration: 120 min	
Frequency: 3 times a year (farmers), regular basis (pest control operator)	
Model (inhalation and dermal): Model 1 (Spraying), TNsG HE Part 2	
Post-application:	
Unblocking spray nozzle and cleaning	
Form of exposure: liquid (0.4 % active substance)	
Duration: 5 min	
Frequency: 3 times a year (farmer), regular basis (pest control operator)	
Model (inhalation): expert judgement	
Model (dermal): Marquart et. al. (2006)	
Secondary exposure	Working in animal housing after spraying
Form of exposure: dust containing active substance (inhalation), active substance on wall surfaces (dermal)	Potential inhalation exposure: Negligible Potential dermal exposure: 30.2 mg a.s./person/day
Model (inhalation): expert judgement	
Model (dermal): expert judgement	
Non-professional users	
Indirect exposure as a result of use	Exposure of bystanders, unrealistic worst case (65% of AELacute).

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)	no hydrolysis due to no hydrolysable functional groups
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	not applicable, no absorption maximum > 290 nm
Readily biodegradable (yes/no)	yes
Biodegradation in seawater	No data
Non-extractable residues	No data
Distribution in water / sediment systems (active substance)	No data
Distribution in water / sediment systems (metabolites)	No data

Route and rate of degradation in soil

Mineralization (aerobic)	No data
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (20°C, aerobic): 0.3 days DT_{50lab} (12°C, aerobic): 0.57 days
	DT_{90lab} (20°C, aerobic):No data
	DT_{50lab} (10°C, aerobic):No data
	DT_{50lab} (20°C, anaerobic): No data
	degradation in the saturated zone: No data
Field studies (state location, range or median with number of measurements)	DT_{50f}: No data DT_{90f}: No data
Anaerobic degradation	Completely biodegradable
Soil photolysis	---
Non-extractable residues	No data
Relevant metabolites - name and/or code, % of applied active ingredient (range and maximum)	No data
Soil accumulation and plateau concentration	No data

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc}	log Koc = 1.4 (application of QSAR models)
pH dependence (yes / no) (if yes type of dependence)	yes (benzoic acid mobility was positively correlated with soil pH)

Fate and behaviour in air

Direct photolysis in air	---
Quantum yield of direct photolysis	---
Photo-oxidative degradation in air	half-life $\tau_{½}$ = 12.9 d, chemical lifetime in the troposphere = 18.6 d
Volatilization	---

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)

Species	Time-scale	Endpoint	Toxicity
Fish			
Oncorhynchus mykiss	96 h	Mortality	LC50 > 120 mg/L (nominal concentration confirmed by analytical monitoring)
Oncorhynchus mykiss	28 d	Mortality, Growth	NOEC = 92.4 mg/L (mean measured concentration)
Invertebrates			
Daphnia magna	48 h	Immobilisation	EC50 > 120 mg/L (nominal concentration confirmed by analytical monitoring)
Daphnia magna	21 d	Reproduction	NOEC = 25 mg/L (nominal concentration confirmed by analytical monitoring)
Algae			
Desmodesmus subspicatus	72 h	Growth inhibition	ErC50 ≥ 1000 mg/L NOErC ≥ 1000 mg/L (nominal concentration confirmed by analytical monitoring)
Microorganisms			
Activated sludge (municipal sewage treatment plant)	3 h (static)	respiration inhibition	EC50 ≥ 1000 mg a.s./L (nominal)

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	---
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)	Calculated BCFfish = 7.75 L/kg ww Calculated BCFearthworm = 1.73 L/kg ww
Depuration time(DT_{50}) (DT_{90})	---
Level of metabolites (%) in organisms accounting for > 10 % of residues	---

Chapter 6: Other End Points

Residues

Considering the intended use as PT3, consumer exposure to benzoic acid residues in food or feed items via biocidal products will be low compared to consumer exposure to benzoic acid occurring as natural food ingredient and from use as registered food additive and authorised feeding stuff additive.

Appendix II: List of Intended Uses

Summary of intended uses

Benzoic acid is a bactericide, fungicide and virucide which is intended to be used in animal premises in order to prevent growth of microorganisms.

Object and/or situation	Member State or Country	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Re marks:
(a)			(c)	Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
Bactericide	EU	dummy: MENNO Florades	Harmful bacteria	SL	9%	Watering or spraying with foam	2	6 months	0.9	0.4	0.36	
Fungicide	EU	Dummy MENNO Florades	Harmful fungi	SL	9%	Watering or spraying with foam	2	6 months	3.6	0.4	1.44	
Virucide	EU	dummy: MENNO Florades	Harmful viruses	SL	9%	Watering or spraying with foam	2	6 months	1.8	0.4	0.72	

(a) e.g. biting and suckling insects, fungi, molds; (b) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(c) GCPF Codes - GIFAP Technical Monograph No 2, 1989 ISBN 3-8263-3152-4); (d) All abbreviations used must be explained

(e) g/kg or g/l;(f) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench;

(g) Kind, e.g. overall, broadcast, aerial spraying, row, bait, crack and crevice equipment used must be indicated;

(h) Indicate the minimum and maximum number of application possible under practical conditions of use;

(i) Remarks may include: Extent of use/economic importance/restrictions

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. For studies marked Yes(i) data protection is claimed under Article 12.1(c) (i), for studies marked Yes(ii) data protection is claimed under Article 12.1(c) (ii). These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

References which have been marked (*) in the tables are considered to be KEY STUDIES.

Active substance

No. A1 - Identity of the Active substance

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A2.6/01	Williams A E	1978	Benzoic acid Encyclopaedia of Chemical Technology. 3. Ed. Not GLP, published	N	-
A2.6/02	Maki T, Takeda K	2002	Benzoic Acid and Derivates in Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Vol. 5, Wiley-VCH, Weinheim, 59-72 The text is identical with the electronic release of the Encyclopedia (7th ed. 2005) Not GLP, published	N	-
A2.8/01	Anonymous	1996	Benzoic acid EC directive 96/77 1996L0077-EN-23.06.2001-003.001 page 5 and 6 Not GLP, published	N	-
A2.8/02	Anonymous	2002	Benzoic acid Ph. Eur. 4. Ausgabe; Page 1271-1272 Not GLP, published	N	-

No. A3 Phys. Chem

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A3.1.1/01	Williams AE	1978	Benzoic acid Encyclopaedia of Chemical Technology. 3. Ed. Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A3.1.1/02	Maki T, Takeda K	2002	Benzoic Acid and Derivates in Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Vol. 5, Wiley-VCH, Weinheim, 59-72 The text is identical with the electronic release of the Encyclopedia (7th ed. 2005) Not GLP, published	N	-
A3.1.2/01	Williams AE	1978	See A3.1.1/01	N	-
A3.1.2/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.1.3/01	Anonymous	1972	Food ingredients: benzoic acid and sodium benzoate, GRAS (Generally Recognized As Safe) National Technic. Information Service (NTIS) U.S. FDA Washington D.C. Not GLP, published	N	-
A3.1.3/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.2	Anonymous	1981	Vapour pressure curve OECD Guideline for Testing of Chemicals: Laboratory Intercomparison Testing Programmes 1981, Page 4 Not GLP, published	N	-
A3.2.1		2007a	Calculation of the Henry's law constant of benzoic acid. Not GLP, unpublished	Y (Exist/First)	MEN
A3.3		2007b	Description of the physical state, colour and odour of both the purified active substance and active substance as manufactured. Not GLP, unpublished	Y (Exist/First)	MEN
A3.4.1/01	Anonymous	1966	UV/VIS Spectrum Benzoic acid Sadtler / Standard spectra Not GLP, published	N	-
A3.4.1/02		2007a	UV/VIS - Spectra Not GLP, unpublished	Y (Exist/First)	MEN
A3.4.2/01	Anonymous	1962	IR Spectrum Benzoic acid Sadtler / Standard spectra Not GLP, published	N	-
A3.4.2/02		2007b	IR - Spectrum Not GLP, unpublished	Y (Exist/First)	MEN
A3.4.3/01	Anonymous	-	NMR Spectrum Benzoic acid Sadtler / Standard spectra Not GLP, published	N	-
A3.4.3/02		2007c	^{1}H-NMR - Spectrum Not GLP, unpublished	Y (Exist/First)	MEN
A3.4.3/03		2007d	^{13}C-NMR - Spectrum Not GLP, unpublished	Y (Exist/First)	MEN
A3.4.4/01	Anonymous	2006	MS Spectrum Benzoic acid NIST Chemistry WebBook / Standard spectra Not GLP, published	N	-
A3.4.4/02		2007e	Mass - Spectrum Not GLP, unpublished	Y (Exist/First)	MEN

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A3.5		1998	Determination of the Water Solubility of Benzoic Acid at pH 5.2 and pH 9.0 Report No. CC98B05, 21.08.1998 Not GLP, unpublished	Y (Exist/First)	MEN
A3.6/01	Williams AE	1978	See A3.1.1/01	N	-
A3.6/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.7/01	Williams AE	1978	See A3.1.1/01	N	-
A3.7/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.9/01	Freitag D, Ballhorn L, Geyer H, Korte F	1985	Environmental hazard profile of organic chemicals Chemosphere, Vol. 14, No.10, pp 1589-1616, 1985 Not GLP, published	N	-
A3.9/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.10	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.11/01	Williams AE	1978	See A3.1.1/01	N	-
A3.11/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.11/03		2008a	Determination of the Flammability of Benzoic Acid unpublished report no. 40821187 GLP, unpublished	Y (Exist/First)	MEN
A3.12/01	Williams AE	1978	See A3.1.1/01	N	-
A3.12/02	Maki T, Takeda K	2002	See A3.1.1/02	N	-
A3.13		2008b	Determination of the Surface Tension of Benzoic Acid unpublished report no. 40821184 GLP, unpublished	Y (Exist/First)	MEN

No. A4 Analytical Methods

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A4.1		2004	Validation of an Analytical Method for the Determination of Benzoic Acid in aqueous Samples unpublished report no. 21953101 GLP, unpublished	Y (Exist/First)	MEN
A4.2.01/01	Baziramakenga R, Simard RR, Leroux GD	1995	Determination of organic acids in soil extracts by ion chromatography Soil Biol. Biochem. 27 (1995), No. 3, pp.349-356 Not GLP, published	N	-
A4.2.01/02	Jalal MAF, Read DJ	1983	The organic acid composition of Calluna heathland soil with special reference to phyto- and fungitoxicity Plant and Soil 70 (1983), pp. 273-286 Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A4.2.02		2009	Method validation – Determination of benzoic acid in air unpublished report no. VB-09TSAA002-1, November 06, 2009	Y	MEN
A4.2.03		2004	See A4.1	N	-

No. A6 Toxicological and Metabolic studies

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6		2012	RAC Opinion proposing harmonised classification and labelling at EU level of Benzoic acid, 25th November 2012 Not GLP, published	No	-
A6.1.1		1979	Report no. 9348 (unpublished report, 1979)	N	-
A6.1.1/01*		1954	Sorbic acid as a fungistatic agent for foods. I. Harmlessness of sorbic acid as a dietary component. Not GLP, published	N	-
A6.1.1/02		1984	Studies on the toxicity of oxaprozin (1) - Acute toxicity of oxaprozin, its metabolites and contaminants Not GLP, published	N	-
A6.1.1/03*		1973	Benzoic acid Data sheet no. 28-4/73 Not GLP, published	N	-
A6.1.1/04		1995	Benzoic acid / sodium benzoate Not GLP, published	N	-
A6.1.1/05		2003	Review report for the inclusion of benzoic acid in Annex I of Directive 91/414/EEC, Not GLP, published	N	-
A6.1.1/06		1972	Experimental benzoic acid poisoning in the cat Not GLP, published	N	-
A6.1.1/07		1958	Pharmacodynamie. - Sur la toxicite des acides phtaliques Not GLP, published	N	-
A6.1.1/08		1923	Aromatische Säuren at: Handbuch der experimentellen Pharmakologie, Not GLP, published	N	-
A6.1.1/09		1962	Aromatic carboxy acids (benzene) Not GLP, published	N	-
A6.1.1/10		1942	The toxicity of benzoic acid for white rats Not GLP, published	N	-
A6.1.1/11*		1965	Experimental materials contributive to hygienic characterizationof combined effects produced by some chemical food preservants. Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.1.1/12		1973	Comparison of the acute toxicity, distribution, fate and some pharmacologic properties of the non - bezenoid aromatic compound azuloic acid with those of benzoic and naphthoic acids Not GLP, published	N	-
A6.1.1/13		1913	Zur Kenntnis der Wirkungen der Benzoesäure und ihres Natriumsalzes auf den tierischen Organismus; Not GLP, published	N	-
A6.1.1/14		1948	Further experience with the range finding test in the industrial toxicology laboratory. Not GLP, published	N	-
A6.1.2/01		1977	Report to RIFM, 22 August 1977 Not GLP, published	N	-
A6.1.2/02		1979	Benzoic acid Not GLP, published	N	-
A6.1.3*		1981	Four Week Subacute Inhalation Toxicity Study of Benzoic Acid in Rats Report No. 163-676 Not GLP, published	N	-
A6.1.3* A6.1.4		1974	Report no. 163-282 (unpublished report, 1974)	N	-
A6.1.4.01/01		1988	Irritation effects of residual products derived from poly (2-hydroxyethyl methacrylate) gels Not GLP, published	N	-
A6.1.4.01/02		1977	(unpublished report), cited in A6.1.4.01/06 Not GLP, published	N	-
A6.1.4.01/03*		1973	Benzoic acid Not GLP, published	N	-
A6.1.4.01/04*		1988a	(unpublished report), study no. 0847/1083 Not GLP, published	N	-
A6.1.4.01/05		1989	(unpublished report), study no. 014658 Not GLP, published	N	-
A6.1.4.01/06		2000	Concise international chemical assessment document No 26 Benzoic Acid and Sodium Benzoate Not GLP, published	N	-
A6.1.4.02/01		no date	(unpublished report), Not GLP, published	N	-
A6.1.4.02/02*		1973	Benzoic acid Not GLP, published	N	-
A6.1.4.02/03*		1988b	(unpublished report), study no. 0847/1084 Not GLP, published	N	-
A6.1.4.02/04		1986	Not GLP, published	N	-
A6.1.5/01*		1992	Examination of the local lymph node assay for use in contact sensitization risk assessment Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.1.5/02*		1986	Development and validation of an alternative dermal sensitization test: The mouse ear swelling test (MEST) Not GLP, published	N	-
A6.1.5/03		1984	An animal model for nonimmunologic contact urticaria Not GLP, published	N	-
A6.2.01/01*		1991	Dose-dependent pharmacokinetics of benzoic acid following oral administration of sodium benzoate to humans Not GLP, published	N	-
A6.2.01/02		1993	Application of 13C-labeling and nuclear magnetic resonance spectroscopy to pharmacokinetic research: measurement of metabolic rate of benzoic acid to hippuric acid in the rat Not GLP, published	N	-
A6.2.01/03		1970	The fate of benzoic acid in various species Not GLP, published	N	-
A6.2.01/04		1991	Urinary excretion of hippuric acid after administration of sodium benzoate (biological monitoring 1) Not GLP, published	N	-
A6.2.01/05		1980	Some pathways of xenobiotic metabolism in the adult and neonatal marmoset (Callithrix jacchus) Not GLP, published	N	-
A6.2.01/06		1982	Some observations on the urinary excretion of glycine conjugates by laboratory animals Not GLP, published	N	-
A6.2.01/07		1956	Über das Schicksal von C14- Benzoesäure und C14-p-Chlorbenzoesäure im Organismus Not GLP, published	N	-
A6.2.01/08		1931	The conjugation of benzoic acid in man Not GLP, published	N	-
A6.2.01/09		1957	The chemical estimation of acyl glucuronides and its application to studies on the metabolism of benzoate and salicylate in man Not GLP, published	N	-
A6.2.01/10		1959	Absorption of drugs from the rat colon Not GLP, published	N	-
A6.2.01/11		1993	Conjugation of benzoic acid with glycine in human liver and kidney: A study on the interindividual variability Not GLP, published	N	-
A6.2.01/12		1980	The metabolic fate of (14C) benzoic acid in protein-energy deficient rats Not GLP, published	N	-
A6.2.02/01		1983	In vivo correlation between stratum corneum reservoir function and percutaneous absorption Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.2.02/02		1980	The guinea-pig: an animal model for human skin absorption of hydrocortisone, testosterone and benzoic acid Not GLP, published	N	-
A6.2.02/03		1990	In vivo percutaneous absorption of chemicals: A multiple dose study in rhesus monkeys Not GLP, published	N	-
A6.2.02/04		1989	Percutaneous absorption and excretion of xenobiotics after topical and intravenous administration to pigs Not GLP, published	N	-
A6.2.02/05*		1970	Absorption of some organic compounds through the skin in man Not GLP, published	N	-
A6.2.02/06		1978	Animal Moedls of Percutaneous Penertration: Comparison between Mexiacan Hairless Dogs and Man Not GLP, published	N	-
A6.2.02/07		1990	Diseased skin models in the hairless guinea pig: in vivo percutaneous absorption Not GLP, published	N	-
A6.2.02/08		1990	In vitro skin absorption and metabolism of benzoic acid, p-aminobenzoic acid, and benzocaine in the hairless guinea pig Not GLP, published	N	-
A6.2.02/09		1990	Percutaneous absorption of benzoic acid across human skin. I: in vitro experiments and mathematical modeling Not GLP, published	N	-
A6.2.02/10*		1989	The effect of aging on percutaneous absorption in man Not GLP, published	N	-
A6.2.02/11*		2004	In vitro predictions of skin absorption of caffeine, testosterone, and benzoic acid: a multi-centre comparison study Not GLP, published	N	-
A6.2.02/12*		1976	Relationship of topical dose and percutaneous absorption in rhesus monkey and man Not GLP, published	N	-
A6.3.1/01*		1967	Physiologische und morphologische Veränderungen an Ratten nach peroraler Verabreichung von Benzoesäure Not GLP, published	N	-
A6.3.1/02		2003	Review report for the inclusion of benzoic acid in Annex I of Directive 91/414/EEC, Not GLP, published	N	-
A6.3.1/03		1972	Experimental benzoic acid poisoning in the cat Not GLP, published	N	-
A6.3.1/04*		1993	Short-term effect of sodium benzoate in F344 rats and B6C3F1 mice Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.3.1/05		1929	Benzoylated amino acids in the animal organism. IV: A method for the investigation of the origin of glycine Not GLP, published	N	-
A6.3.1/06		1942	Report of a study on the toxicity of several food preserving agents Not GLP, published	N	-
A6.3.1/07*		1960	Die Verträglichkeit der Benzoesäure im chronischen Fütterungsversuch Not GLP, published	N	-
A6.3.1/08		1948	Further experience with the range finding test in the industrial toxicology laboratory. Not GLP, published	N	-
A6.3.1/09		1980	Report of carcinogenesis bioassay of sodium benzoate in rats: Absence of carcinogenicity of sodium benzoate in rats Not GLP, published	N	-
A6.3.1/10		2000	Concise international chemical assessment document No 26 Benzoic Acid and Sodium Benzoate Not GLP, published	N	-
A6.3.2		2001	Benzoates, Review Report Not GLP, published	N	-
A6.3.2*		1981	Project no. 163-675 (unpublished report, 1981)	N	-
A6.3.3*		1981	Four Week Subacute Inhalation Toxicity Study of Benzoic Acid in Rats International Research and Development Not GLP, published	N	-
A6.4*		1954	Sorbic acid as a fungistatic agent for foods. I. Harmlessness of sorbic acid as a dietary component. Not GLP, published	N	-
A6.5/01*		1960	Die Verträglichkeit der Benzoesäure im chronischen Fütterungsversuch Not GLP, published	N	-
A6.5/02		2003	Review report for the inclusion of benzoic acid in Annex I of Directive 91/414/EEC, Not GLP, published	N	-
A6.5/03		1960	Zur Verträglichkeit der Benzoesäure (abstract) Not GLP, published	N	-
A6.5/04		1970	Toxicological evaluation of some combinations of food preservatives Not GLP, published	N	-
A6.6.1		1989	The DNA-damaging activity of natural and synthetic food additives	N	-
A6.6.1		1976	Mutagenic activity of styrene oxide (1,2-epoxyethylbenzene), a presumed styrene metabolite.	N	-
A6.6.1		1989	DNA repair tests on food additives. Environ. Mol.	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.6.1		1991	Bacterial mutagenicity testing of 49 food ingredients gives very few positive results.	N	-
A6.6.1		1980	Mutagenicity produced by aqueous chlorination of organic compounds.	N	-
A6.6.1		1982	Genetic toxicology of phthalimide-type fungicides.	N	-
A6.6.1		1991	Performance of 133 compounds in the lambda prophage induction endpoint of the microscreen assay and a comparison with S. typhimurium mutagenicity and rodent carcinogenicity assays.	N	-
A6.6.1		1983	Biological activity of benzylating N-nitroso compounds. Models of activated N-nitrosomethyl benzylamine.	N	-
A6.6.1		1988	Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environmental and	N	-
A6.6.1/01*		1975	Detection of carcinogens as mutagens in the salmonella/microsome test: Assay of 300 chemicals Not GLP, published	N	-
A6.6.1/02		1978	The bacterial mutation test; Appendix II to article of Purchase et al Not GLP, published	N	-
A6.6.1/03		1977	Investigation of mutagenic effects of products of ozonation reactions in water Not GLP, published	N	-
A6.6.1/04		1984	Primary mutagenicity screening of food additives currently used in Japan Not GLP, published	N	-
A6.6.2		1978	The bacterial mutation test. Appendix II to article of Purchase et al., at	N	-
A6.6.2		1980	Chromosome aberration tests with chinese hamster cells in vitro with and without metabolic activation – a comparative study on mutagens and carcinogens.	N	-
A6.6.2		1990	A comparison of SCE test in human lymphocytes and Vicia faba: A hopefull technique using plants to detect mutagens and carcinogens.	N	-
A6.6.2.01/01*		1980	Epstein-barr virus-transformed human lymphoblastoid cells for study of sister chromatid exchange and their evaluation as a test system Not GLP, published	N	-
A6.6.2.01/02		1980	Inhibitors of poly (adeosine diphosphate ribose) polymerase induced sister chromatid exchanges. Not GLP, published	N	-
A6.6.2.01/03		1988	In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke-A study of structure-activity relationships Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.6.2.02/01*		1988	Data Book of Chromosomal aberration test in vitro Not GLP, published	N	-
A6.6.2.02/02		1975	Investigation of the mutagenic activity of drug preparations and food additives in a culture of human lymphocytes Not GLP, published	N	-
A6.6.3		1987	SOS-inducing activity of chemical carcinogens and mutagens in salmonella typhimurium TA Not GLP, published	N	-
A6.6.4*		1974	FDA, Washington D.C.	N	-
A6.6.4/01		1980	Results of recent studies on the relevance of various short-term screening tests in Japan; The predictive value of short-term screening tests in carcinogenicity evaluation Not GLP, published	N	-
A6.6.4/02		2001	Benzoates, Review Report Not GLP, published	N	-
A6.7/01		1980	Report of carcinogenesis bioassay of sodium benzoate in rats: Absence of carcinogenicity of sodium benzoate in rats Not GLP, published	N	-
A6.7/02*		1984	Short communications; Lack of tumorigenicity of sodium benzoate in mice Not GLP, published	N	-
A6.7/03		1985	Improved detection of carcinogens by degranulation of microsomes prepared at low g force by glutathione Not GLP, published	N	-
A6.7/04		1989	Antitumor effect of hippurate. An experimental study using various mouse tumor strains Not GLP, published	N	-
A6.8.1/01		1971	Studies on metabolism and identification of the causative agent in aspirin teratogenesis in rats Not GLP, publisheds	N	-
A6.8.1/02		1995	Benzoic acid / sodium benzoate GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance Not GLP, published	N	-
A6.8.1/03		1985	The effect of chronic sodium benzoate consumption on brain monamines and spontaneous activity in rats Not GLP, published	N	-
A6.8.1/04*		1978	Studies on effects of sodium benzoate on fetuses and offspring of Wistar rats Not GLP, published	N	-
A6.8.1/05		1980	Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo Not GLP, published	N	-
A6.8.2*		1960	Die Verträglichkeit der Benzoesäure im chronischen Fütterungsversuch Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.9		1989	Similarities of toluene and o-cresol neuroexcitation in rats Not GLP, published	N	-
A6.12.1		2001	Benzoates, Review Report Not GLP, published	N	-
A6.12.2/01		1972	Food ingredients: benzoic acid and sodium benzoate, GRAS (Generally Recognized As Safe) Not GLP, published	N	-
A6.12.2/02		1924	Ricerche sulla sintesi ippurica nell organismo umano Not GLP, published	N	-
A6.12.2/03*		1909	Physiologische Wirkungen der Benzoesäure und des benzoesauren Natron. VII. Zusammenfassung der Resultate Not GLP, published	N	-
A6.12.2/04		1925	The effect of sodium benzoate ingestion upon the composition of the blood and urine with especial reference to the possible synthesis of glycine in the body Not GLP, published	N	-
A6.12.2/05		1908	Influence of benzoic acid and benzoates on digestion and health. Bulletin 84, Pt. IV, Bureau of Not GLP, published	N	-
A6.12.3		2007	Survival after treatment with phenyacetate and benzoate for urea-cycle disorders.	N	-
A6.12.3		2000	Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia.	N	-
A6.12.3/01		1981	Therapy of urea cycle enzymopathies: Three case studies Not GLP, published	N	-
A6.12.3/02		1996	Urea cycle disorders: Diagnosis, pathophysiology and therapy Not GLP, published	N	-
A6.12.3/03		1998	Alternative pathway therapy for urea cycle disorders Not GLP, published	N	-
A6.12.3/04		1983	Disposition of sodium benzoate in Existborn infants with hyperammonemia Not GLP, published	N	-
A6.12.3/05		1931	The conjugation of benzoic acid in man Not GLP, published	N	-
A6.12.3/06		1879	Über die Wirkung der Benzoesäure bei der rheumatischen Polyarthritis Not GLP, published	N	-
A6.12.3/07		1983	Effect of long-term administration of sodium benzoate to a patient with partial ornithine carbamoyl transferase deficiency Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.12.3/08		1948	The effect of benzoic acid and caronamide on blood penicillin levels and on renal function Not GLP, published	N	-
A6.12.4		2000	Concise international chemical assessment document No 26 Benzoic Acid and Sodium Benzoate Not GLP, published	N	-
A6.12.6/01		1955	Studies on allergic sensitization to certain topical therapeutic agents Not GLP, published	N	-
A6.12.6/02		1996	Studies on non-immune immediate contact reactions in an unselected population Not GLP, published	N	-
A6.12.6/03		1993	Patch test reaction to a preliminary preservative series Not GLP, published	N	-
A6.12.6/04		1987	Cosmetic intolerance Not GLP, published	N	-
A6.12.6/05		1985	Value of oral provocation tests to aspirin and food additives in the routine investigation of asthma and chronic urticaria Not GLP, published	N	-
A6.12.6/06		1980	Non-immunologic contact urticaria Not GLP, published	N	-
A6.12.6/07		1993	Alcohol vehicles in tests for non-immunologic immediate contact reactions Not GLP, published	N	-
A6.12.6/08		1989	Systemic effect of ultraviolet irradiation on non-immunologic immediate contact reactions to benzoic acid and methyl nicotinate Not GLP, published	N	-
A6.12.6/09		1989a	Effects of infra-red and neodymium yttrium aluminium garnet laser irradiation on non-immunologic immediate contact reactions to benzoic acid and methyl nicotinate Not GLP, published	N	-
A6.12.6/10		1989b	Immediate contact reactions to benzoic acid and the sodium salt of pyrrolidone carboxylic acid Not GLP, published	N	-
A6.12.6/11		1977	Contact sensitization to benzoyl peroxide Not GLP, published	N	-
A6.12.6/12		1982	Allergie aux Coservateurs Not GLP, published	N	-
A6.12.6/13		1976	A follow-up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzoates and azo dyes Not GLP, published	N	-
A6.12.6/14		1991	Release of mediators from human gastric mucosa and blood in adverse reactions to benzoate. Not GLP, published	N	-
A6.12.6/15		1976	Challenge test battery in chronic urticaria Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A6.12.6/16		1989	Effect of the vehicle on non-immunologic immediate contact reactions Not GLP, published	N	-
A6.12.6/17		1987	The prevalence of reaction to food additives in a survey population Not GLP, published	N	-

** key studies*

No. A7 Ecotoxicological Profile including Environmental Fate and Behaviour

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A7.1.1.1.1*		2008a	Statement concerning Hydrolysis as a function of pH and identification of breakdown products Not GLP, unpublished	Y (Exist/First)	MEN
A7.1.1.1.1*	Lyman, W.J., William, F.R. and Rosenblatt, D.H.	1990	Handbook of chemical property estimation methods; Am. Chem. Soc., Washington D.C., p. 7-4, table 7.1	N	-
A7.1.1.1.2/01 *	Deng Y et al.	2003	Separation and identification of photodegradation products of benzoic acid by capillary zone electrophoresis, Elsevier Journal of Chromatography A, 1013, 191-201 Not GLP, published	N	-
A7.1.1.1.2/02 *	Ogata Y, Tomizawa K, Yamashita Y	1979	Photoinduced Oxidation of Benzoic Acid with Aqueous Hydrogen Peroxide, J.C.S. Perkin II, 9/775, 616-619 Not GLP, published	N	-
A7.1.1.1.2/03 *	Oussi Det et al.	1998	Photodegradation of benzoic acid in aqueous solutions, Environmental Technology, 19, 995-960 Not GLP, published	N	-
A7.1.1.1.2/04 *	Ware GW, Crosby DG, Giles JW	1980	Photodecomposition of DDA, Arch. Environm. Contam. Toxicol. Vol. 9, pp 135 – 146 Not GLP, published	N	-
A7.1.1.2.1/01 *		2008b	Gutachten zur biologischen Abbaubarkeit von Natriumbenzoat in Standard-Abbautestverfahren gemäß OECD Richtlinien, Not GLP, published	Y (Exist/First)	MEN
A7.1.1.2.1/02	NITE	1979	National Institute of Technology and Evaluation (NITE) Biodegradation and Bioconcentration of Existing Chemical substances under the Chemical Substances Control Law Information on the chemical published in the Official Bulletin of Economy, Trade and Industry (Former Title: The Official Bulletin of the Ministry of International Trade and Industry) published 1979/12/20 Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A7.1.2.1.2/01 *	Shelton DR, Tiedje JM	1984	General Method for Determining Anaerobic Biodegradation Potential, Departments of Crop and Soil Sciences and Microbiology and Public Health, Michigan State University, East Lansing, Michigan, USA Applied and Environmental Microbiology, Apr. 1984, 850-857 Not GLP, published	N	-
A7.1.2.1.2/02	Healy JB, Young LY	1979	Anaerobic Biodegradation of Eleven Aromatic Compounds to Methane, Environmental Engineering and Science, Departments of Civil Engineering, Stanford University, Stanford, California, USA Applied and Environmental Microbiology, Apr. 1984, 850-857 Not GLP, published	N	-
A7.1.2.1.2/03	Elder JE, Kelly D	1994	The bacterial degradation of benzoic acid and benzenoid compounds under anaerobic conditions: unifying trends and new perspectives, Departments Molecular Biology and Biotechnolgy, University of Sheffield, of Sheffield, UK FEMS Microbiology Reviews 13, 441-468 Not GLP, published	N	-
A7.1.3*		2008b	Statement concerning Adsorption/desorption Screening Test Not GLP, unpublished	Y (Exist/First)	MEN
A7.2.1*	Verschueren K	2001	Handbook of Environmental Data on Organic Chemicals, 4th ed., Vol 1, 2001, Wiley & Sons, 286-287 Not GLP, published	N	-
A7.2.1*	Verschueren K	2009	Handbook of Environmental Data on Organic Chemicals, 5th ed., 2009, Wiley & Sons, Vol 1, 382-386, Vol 4, 4157 Not GLP, published	N	-
A7.2.1	Van Beelen, P., and Peijnenburg, W. J. G. M	1989	De Afbraak van Organische Stoffen in het Grondwater“ RIVM, rep. No. 718604002, The Netherlands,	N	-
A7.2.1*	Ward, Thomas E.	1984	Characterizing the aerobic and anaeobic microbial activities in surface and subsurface Soils	N	-
A7.2.1*	Alexander M, Lustigman BK	1966	Effect of chemical structure on microbial degradation of substituted benzenes J. Agr. Food Chem., 14, 410-413	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A7.2.3*	Stolpe NB et al.	1993	Mobility of Aniline, Benzoic Acid and Toluene in Four Soils and Correlation with Soil Properties, Department of Agronomy, Department of Biochemistry, University of Nebraska-Lincoln, Lincoln, Nebraska, USA Environmental Pollution 81, 287-295 Not GLP, published	N	-
A7.4.1.1/01*		1998a	Acute Toxicity Test on the Rainbow Trout (Oncorhynchus mykiss), Semi static Test Procedure. Test Substance: Benzoic Acid. Study No. NA 98 9408/3GLP, unpublished	Y (Exist/First)	MEN
A7.4.1.1/02*	Ewell WS, Gorsuch JW, Kringle RO, Robillard KA, Spiegel RC	1986	Simultaneous evaluation of the acute effects of chemicals on seven aquatic species; Environmental Toxicology and Chemistry, Vol. 5, pp.831-840 Not GLP, published	N	-
A7.4.1.1/03*	McKee, JE Wolf HW	1963	Water Quality Criteria, 2nd edition The Resources Agency of California State Water Resources Control board; Publication No. 3-4 Not GLP, published	N	-
A7.4.1.2/01*		1998b	Acute Immobilisation Test on Daphnia magna (Semi static Test Procedure). Test Substance: Benzoic Acid., Study No. NA 98 9408/2GLP, unpublished	Y (Exist/First)	MEN
A7.4.1.2/02*	Kamaya Y, Fukaya Y, Suzuki K	2005	Acute Toxicity of benzoic acid to the crustacean *Daphnia magna* Chemosphere 59 (2005), 255-261 Not GLP, published	N	-
A7.4.1.2/03*	Bringmann G, Kühn R	1977	Befunde der Schadwirkung wassergefährdender Stoffe gegen *Daphnia magna;* Zeitschrift für Wasser- und Abwasserforschung, 10. Jahrgang, Nr. 5/77 Not GLP, published	N	-
A7.4.1.3/01*		2008a	Study on the 'toxicity towards algae' of Benzoic Acid according to OECD-Test Guideline 201 (Algae, Growth Inhibition Test) Version dated 23-Mar-2006 Study No. IF-08/01196420GLP, unpublished	Y (Exist/First)	MEN
A7.4.1.3/02*		1998c	Determination of the growth inhibition on Pseudokirchneriella subcapitata (former name: Ankistrodesmus bibraianus). Test Substance: Benzoic AcidStudy No. NA 98 9408/1GLP, unpublished	Y (Exist/First)	MEN
A7.4.1.3/03*	Stratton GW, Corke CT	1982	Toxicity of the insecticide Permethrin and some degradation products towards algae and cyanobacteria Environmental Pollution (Series A) 29, page 71-80 Not GLP, published	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A7.4.1.3/04*	Verschueren K	2001	Handbook of Environmental Data on Organic Chemicals, 4th ed., Vol 1, 2001, Wiley & Sons, page286-287 Not GLP, published	N	-
A7.4.1.4/01*	Klečka GM, Landi LP, Bodner KM	1985	Evaluation of the OECD Activated Sludge, Respiration Inhibition Test Chemosphere 14, 9, 12139-12511 Not GLP, published	N	-
A7.4.1.4/02*	Bringmann G, Kühn R	1980	Comparison of the Toxicity Thresholds of Water Pollutants to Bacteria, Algae, and Protozoa in the Cell Multiplication Inhibition Test. Institute for Water, Soil and Air Hygiene, Federal Health Office, Berlin, Germany Water Research, 14, 231-241 Not GLP, published	N	-
A7.4.1.4*	Anonymous, OECD-SIDS	2001	Benzoates, Review Report OECD SIDS Not GLP, published	N	-
A7.4.3.1*		2004a	Toxicity of Benzoic Acid to Rainbow Trout (*Oncorhynchus mykiss)* in a Prolonged Semi Static Test over 28 Days report no. 21951231 GLP, unpublished	Y (Exist/First)	MEN
A7.4.3.4*		2004b	Influence of Benzoic Acid to *Daphnia magna* in a Reproduction Test report no. 22561221 no report no. GLP, unpublished	Y (Exist/First)	MEN

** key studies*

Biocidal Product

No. B3 Phys. Chem.

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
B3.1		2007c	Description of the physical state, colour and odour of the biocidal product. Not GLP, unpublished	Y (Exist/First)	MEN
B3.4/01		1994	Report – Determination of the Flash Point - Method: DIN 51755 Not GLP, unpublished	Y (Exist/First)	MEN
B3.4/02		2000	Determination of the Auto-Ignition Temperature (Liquids and Gases) of MENNO Florades according to EC Council Directive 92/69/EEC, Part. A.15 GLP, unpublished	Y (Exist/First)	MEN
B3.5		2008c	Determination of the Acidity or Alkalinity of MENNO Florades unpublished report no. 43961349 GLP, unpublished	Y (Exist/First)	MEN
B3.6		2008d	Determination of the Relative Density of MENNO Florades unpublished report no. 43962182 GLP, unpublished	Y (Exist/First)	MEN
B3.7/01		1996b	MENNO Florades Batch No. 9507 Prüfung der Lagerstabilität bei 54 °C (+/-2) für 14 Tage Not GLP, unpublished	Y (Exist/First)	MEN
B3.7/02		1996c	MENNO Florades Batch No. 9507 Test on Storage Stability at 0 °C (+/-1) over 7 days Not GLP, unpublished	Y (Exist/First)	MEN
B3.7/03		2005	Shelf Life Following Storage at Ambient Temperature over 65 resp. 68 months with MENNO Florades report no. CC05D04 Not GLP, unpublished	Y (Exist/First)	MEN
B3.10		2000	Determination of the Surface Tension of MENNO Florades in Aqueous Solution report no. IF-100/22588-00 GLP, unpublished	Y (Exist/First)	MEN
B3.11		2008e	Determination of the Viscosity of MENNO Florades unpublished report no. 43963196 GLP, unpublished	Y (Exist/First)	MEN

No. B4 Analytical Methods

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
B4.1		2008	Validation of an Analytical Method for the Determination of Benzoic Acid in Formulation unpublished report no. 43964101 GLP, unpublished	Y (Exist/First)	MEN

No. B5 Effectiveness

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
B5.10.2/01		2007a	Test report number 071245-1 according to DIN EN 1040 (march 2006) - Quantitative suspension test for the evaluation of basic bactericidal activity of chemical disinfectants and antiseptics – Test method and requirements (phase 1) report no. 071245-1, April 24, 2007 Not GLP, unpublished	Y (Exist/First)	MEN
B5.10.2/02		2007b	Test report number 071245-2 following prEN 1275 (may 2005) - Quantitative suspension test for the evaluation of basic fungicidal activity of chemical disinfectants and antiseptics – Test method and requirements (phase 1) report no. 071245-12, April 24, 2007 Not GLP, unpublished	Y (Exist/First)	MEN
B5.10.2/03		2007	Test report prEN 14675 , Virucidal Activity (optional conditions) Not GLP, unpublished	Y (Exist/First)	MEN
B5.10.2/04		2011	Test report number 0717245-2 and 1135004 following prEN 1275:2005 and DIN EN 1275:2006. Quantitative suspension test for the evaluation of basic fungicidal or yeasticidal activity of chemical disinfectants and antiseptics– Test method and requirements (phase 1) report no 0717245-2 and 1135004, September 02, 2011		

No. B6 Toxicological studies

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
B6.1.1*		1994a	Acute oral toxicity test of “MENNO FLORADES“ in rats report no. 10-04-0859/00-94 GLP, unpublished	Y (Exist/First)	MEN
B6.1.2*		1994b	Acute dermal toxicity test of “MENNO FLORADES“ in rats report no.10-04-08560/00-94 GLP, unpublished	Y (Exist/First)	MEN
B6.2/01*		1994c	Acute dermal irritation/corrosion test of “MENNO FLORADES“ in rabbits report no. 10-03-0862/00-94 GLP, unpublished	Y (Exist/First)	MEN
B6.2/02*		1994d	Acute eye irritation / corrosion test of “MENNO FLORADES“ in rabbits report no.10-03-0861/00-94 GLP, unpublished	Y (Exist/First)	MEN
B6.3*		2003	Maximisation sensitisation test according to Magnusson & Kligman of "VP-FL/5" (commercial name MENNO Florades) in the Guinea pig report no. 10-5-0202-02 GLP, unpublished	Y (Exist/First)	MEN

* key studies