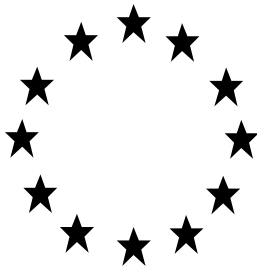
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Citric Acid

Product-type 2
(Disinfectants and algaecides not intended for direct application to humans or animals)

March 2016

Belgium

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1 STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 PROCEDURE FOLLOWED

This assessment report has been established as a result of the evaluation of the active substance ***Citric Acid*** as product-type 2 (Disinfectants and algaecides not intended for direct application to humans or animals) carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

Citric Acid (EC no. 201-069-1/ CAS no. 77-92-9) was initially notified as an existing active substance, by Kimberly-Clark Europe Ltd, hereafter referred to as the applicant, in product-type 1.

After the Working Group on Efficacy meeting in September 2014, two issues were raised: whether an anti-viral tissue placed on the market with the claim 'kills 99,9 % of cold & flu viruses in the tissue' is a biocidal product or a treated article and, if considered a biocidal product, whether it would belong to product-type 1 (human hygiene) or 2 (disinfectants and algaecides not intended for direct application to humans or animals).
A request to the Commission in accordance with Article 3(3) of the BPR was submitted by the Competent Authority (BE) to obtain a legally binding opinion on both issues.
After a discussion at the 60th CA meeting on 21 May 2015, the Commission adopted the decision, that "**an anti-viral tissue impregnated with citric acid and placed on the market with the claim "kills 99.9% of cold & flu viruses in the tissue" shall be considered as a biocidal product** in accordance with Article 3(1)(a) of Regulation (EU) No 528/2012 **and shall fall within product-type 2** as defined in Annex V to that Regulation" (Article 1 of Decision No 2015/1985[2])".

Commission Regulation (EC) No 1451/2007 of 4 December 2007[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

In accordance with the provisions of Article 7(1) of that Regulation, Belgium 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 ***Citric Acid*** as an active substance in Product Type 1 was 30 March 2006, in accordance with Annex V of Regulation (EC) No 1451/2007.

[1] 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] Commission Implementing Decision (EU) 2015/1985 of 4 November 2015 pursuant to Article 3(3) of Regulation (EU) No 528/2012 of the European Parliament and of the Council on an anti-viral tissue impregnated with citric acid.

On 28 February 2006, the Belgian competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 30 June 2006.

On 23 August 2013, the Rapporteur Member State submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

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 Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2 PURPOSE OF THE ASSESSMENT REPORT

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of ***Citric Acid*** for product-type 2 and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

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

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

2 OVERALL SUMMARY AND CONCLUSIONS FOR CITRIC ACID

2.1 PRESENTATION OF THE ACTIVE SUBSTANCE

The evaluation has established that for the active substance notified by Kimberly-Clark Europe Ltd, no substances of concern among the manufacturing impurities were identified.

EPA registered the first citric acid-containing products in the early 1970's. The currently registered products are used as fungicides and bactericides sanitizers, virucides, and algicides. Citric acid is Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration for use in food.

Citric acid is also approved by the Joint FAO/WHO Expert Committee on Food Additives for use in foods without limitation.

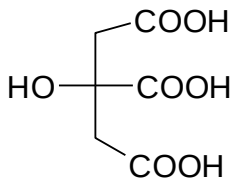
Citric acid occurs naturally in plant and animal tissues and fluids. It may be produced on an industrial scale by mycological fermentation of carbohydrates such

as corn starch and crude sugar solutions (molasses). Strains of mold used include *Aspergillus niger* and *Candida lypolytica*. Citric acid is a well-known intermediate in carbohydrate metabolism (Krebs cycle) and ingested citrate is considered to be completely metabolized.

Citric acid from living organisms is found naturally in soil and water. Citrates leached from rotting vegetation and produced by micro-organisms have been detected at low levels throughout the ecosystem. Citric acid degrades rapidly when in contact with a variety of micro-organisms that are found in soil, natural waters or sewage treatment systems (background concentration in Atlantic coast seawater: 0.025 – 0.145 mg/l; river: 0.040 – 0.2 mg/l; sewage effluent: <0.1 – 1.4 mg/l).

2.1.1 Identity, physico-chemical properties, and intended uses

2.1.1.1. Identity – Characterisation of the Active Substance

CAS-No.	77-92-9
EINECS-No.	201-069-1
Other No. (food additive no.)	E330
IUPAC Name	2-hydroxy-1,2,3-propanetricarboxylic acid
Common name	citric acid
Molecular formula	$C_6H_8O_7$
Structural formula	
Molecular weight	192.13/mol

2.1.1.2 Physico-chemical properties

- Citric acid is a white or colourless crystalline powder and has a low vapour pressure: 1.6 E-10 Pa at +25°C (O'Conner, B, 2006). Therefore, volatilisation is not expected to significantly contribute to the dissipation of citric acid in the environment.

- The compound is soluble in water (65 – 69.9% w/w +10, +20 and +30°C) and ionises at pH 5-9 (O'Conner, B, 2006).

- The Henry's Law Constant is 4.398 E-14 Pa.m³/mol.

- The substance is moderately soluble in organic solvents and is characterised by a partition coefficient n-octanol /water (log P_{ow}) < -3.76 at +21°C (O'Conner, B, 2006).

- The substance is an acid and the pH depends on the concentration of citric acid in the solution:
The pH of solutions of anhydrous citric acid of differing concentrations were measured as part of a water solubility test and were found to be less than 2.
pH of 1.8 for a 5% solution of citric acid (European Chemical Bureau, IUCLID Dataset Citric Acid, 2000).
pH of 2.8 for a 0.1% aqueous solution at +20°C (Occupational Toxicants. 2001 Ed. Greim, H. Vol 16 Wiley VCH, Weinheim).

- The 3 dissociation constants of the carboxylic acid functions are: pK1 = 3.01, pK2 = 4.50, pK3 = 5.87 (O'Conner, B, 2006)

- Citric acid is thermally stable and stable in air up to at least +150°C (O'Conner, B, 2006).

- The active substance is not highly flammable (Tremain, S, 2006) and auto flammability does not occurs at temperatures below melting temperature (Tremain, S, 2006).

- Melting point was measured to +151°C (O'Conner, B, 2006).

- The boiling point is > +171°C and the substance decomposes prior to boiling (O'Conner, B, 2006).

- No explosive properties are expected from the structure of the molecule (Tremain, S, 2006).

- The relative density of citric acid is 1.65 E03 kg/m^3 (O'Conner, B, 2006).

- The substance shows no UV/Vis significant absorbance at 290 nm. The IR, NMR and MS spectra are consistent with the proposed structure.

- Surface tension is 73.6 mN/m for a 1.01g/l solution at +21°C (O'Conner, B, 2006) and the molecule does not show oxidising properties, (Tremain, S, 2006).

Melting point	+151°C
Boiling point	> +171°C Decomposes prior to boiling
Relative density	1.65 E03 kg/m^3
Vapour Pressure	1.6 E-10 Pa at +25°C
Henry's Law Constant	4.398 E-14Pa.m^3/mol
Appearance	white or colourless crystalline powder
UV/Vis	No significant absorbance at 290 nm

IR	Consistent with the proposed structure
NMR	Consistent with the proposed structure
MS	Consistent with the proposed structure
Solubility in water	65 – 69.9% w/w at +10, +20 and +30°C Substance ionises at pH 5-9
pH	Depends on the concentration 0.1% aqueous solution at +20°C : 2.8 5% solution : 1.8 (IUCLID)
Dissociation constant	pK_1 = 3.01 pK2 = 4.50 pK_3 = 5.87
Solubility in organic solvents	Moderately soluble in organic solvents Hexane ≤ 7.84 E-05 g/L Diethyl ether = 7.34 g/L Methanol > 250 g/L
Partition coefficient n-octanol /water	log P_{ow} ≤ -3.76 at +21°C
Thermal stability	Thermally stable and stable in air up to at least +150°C
Flammability	Not highly flammable
Autoflammability	None below melting temperature
Surface tension	73.6 mN/m for a 1.01g/l solution at +21°C
Explosive properties	No explosive properties predicted from the structure
Oxidising properties	No oxidising properties

2.1.1.3 Intended uses and efficacy

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organisms and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

- Field of use envisaged / Function:

In the context of a decision on the approval of ***Citric Acid*** for product-type 2, the only intended use claimed and evaluated in the CAR, is impregnation of facial tissues.
The Applicant Kimberly-Clark Europe Ltd does not require any other use.

Kleenex®Anti-Viral Facial Tissues impregnated with citric acid are intended to be used by general public.

The tissue is a 3-ply tissue of which the middle layer is impregnated with citric acid (7.5%). Citric Acid is irreversibly bound into the tissue's matrix and would remain in the product throughout its lifecycle.
Citric acid is intended to inactive the viral load within the tissue after it has been used (i.e. when moisture after sneezing, coughing or blowing of the nose into the tissue hits the middle layer) in order to prevent transfer back to the hands, transmittance of the virus from hand to hand contact and transmittance to surfaces with which the tissue comes into contact.

- Organism(s) to be controlled and products, organisms or objects to be protected:

The organisms to be controlled and claimed are Rhinoviruses 1A, Rhinoviruses 2, Respiratory Syncytial Virus (RSV), Influenza A and Influenza B.

The organisms to be protected are Human beings.

- Effects on target organisms – Mode of action:

According to the P. Maris scientific paper (Maris P. 1995 *"Modes of action of disinfectants"* Rev Sci Tech. 1995 Mar; 14(1):47-55), "the elucidation of the exact mechanism of action of a disinfectant against viruses is more difficult than for action against bacteria. Nevertheless, many studies on the susceptibility of viruses to chemical agents demonstrate that the following factors are important in understanding this action: presence of lipids in the viruses and size of the viruses". Furthermore, "many authors observe that the presence of lipid in a virus is uniformly associated with a high degree of susceptibility to all disinfectants".
Influenza virus A and B (genus of the *Orthomyxoviridae* family of viruses) and RSV (virus of the family *Paramyxoviridae*) are lipid-containing viruses and thus more susceptible to disinfectants than non-lipid viruses such as rhinovirus (virus of the family *Picornaviridae*).

The efficacy of acidic disinfectants, such as citric acid, is linked to the concentration of hydrogen (H+) and hydroxyl (OH-) ions and function by destroying the bonds of nucleic acids and precipitating proteins. With regard to viral particles the acids will first destroy or disrupt the capsid proteins and then destroy the nucleic acids with in the capsid.

On bacteria, organic acids act by destroying the bonds of nucleic acids and precipitating proteins. They also change the pH of the micro-organisms environment. As citric acid gives away protons in solution, there is a decrease in the pH of the solution, which directly co-relates with the antimicrobial properties of the biocide agent. The main effect is due to the prevention of absorption of essential nutrients by the microorganisms due to disruption of the protein motive force, which provides energy for active absorption of nutrients. It alters the permeability of cell wall causing damage and hence cell death, especially in gram negative bacteria. It is also capable of chelating metal ions present in the cell wall thereby causing damage.
Please note that activity against bacteria is neither supported by relevant efficacy data nor claimed by the applicant. The mode of action of citric acid against bacteria is mentioned only as information.

- Efficacy studies with the biocidal product *Kleenex®Anti-Viral Facial Tissue*:

To assess and to prove the microbicidal activity of *Kleenex®Anti-Viral Facial Tissues*, the Applicant has submitted 8 documents.

About information on soiling requested by Germany, the Applicant has provided a document (namely document B5.10.2.6 – *Minerath B.* 2003) with details and an argumentation: The soil loading used in the efficacy tests was dependent on the virus tested. For Rhinoviruses and RSV, 2% Fetal Bovine Serum was used. For Influenza virus (A and B), 2.5% Bovine Serum Albumin was used.
In the document, authors mentioned that it's very difficult to make up an unequivocal estimation of the amount of protein present in nasal secretions during a cold in order to determine the relevancy of the soil loading used in the efficacy tests. Nevertheless, taken together the results of the studies indicate that the total protein content of nasal secretions is about 0.3% and suggests that the soil load used in the efficacy tests is appropriate and representative of the amounts encountered in actual use.

Two field test studies to assess the effect of *Kleenex®Anti-Viral Facial Tissues* on viral contamination of the hands and transmission of infection: Even if RMS is of the opinion that these studies are only supportive data (with a reliability factor of 4), the results suggest that the R16 Rhinovirus did not spread, that the transmission from nose to hands and from infected to non-infected volunteers was found to be significantly reduced through the use of treated tissues.

Five efficacy studies were conducted according to USEPA guidance documents and to ASTM Method E 1053-97* (with a log 3 reduction as pass criteria) with modifications selected as simulating the practical conditions appropriate to its

intended use. Furthermore, the studies were conducted in accordance with Good Laboratory Practice Standards. From the IND opinion, efficacy studies conducted according to simulated-use conditions seem to be appropriate if we consider the intended use claimed.
Efficacy tests were not performed according to EU standards. The EN 14885 standard was introduced in 2006 and the EN 14476 standard in 2005 after the date when the application for citric acid had to be submitted. RMS has never asked for efficacy tests performed according to P2/S1 standards, considering that the tests performed were relevant enough to be taken into account for the inclusion procedure.

Samples of 3-ply tissue treated with citric acid (equivalent to 2,54 cm x 2,54 cm square disks) were exposed at room temperature for 15 minutes to different virus solutions : Influenza A virus (causing flu), Influenza B virus (causing flu), Rhinovirus Type 1A virus (leading causes of colds), Rhinovirus Type 2 virus (leading causes of colds) and Respiratory Syncytial Virus-RSV (leading cause of lower respiratory tract infection in children).
Comparison with untreated tissue samples (i.e. the control tissue is exactly the same as the treated tissue with the exception of the inclusion of the citric acid. allowed an evaluation of the magnitude of viable virus reduction achieved.

Log reduction after 15 min contact – on fresh or 60 days-old treated tissues

Virus species	Log reduction on fresh treated tissues	Log reduction on 60 days-old treated tissues
Rhinovirus Type 1A	3,7	3,2
Rhinovirus Type *2*	3,1	3,1
Influenza A	4,4	3,2
Influenza B	4,4	4,3
RSV	5,0	4,4

According to the results, with tissues freshly treated with citric acid, a log 4 reduction is achieved with Influenza virus (A and B) and RSV. As expected, naked viruses (such as Rhinoviruses) are more resistant to disinfectants than enveloped viruses (such as influenza viruses and RSV) and only a log 3 is achieved for Rhinovirus Type 1A and 2. The tests provided do not show sufficient efficacy according to the requirements of EU standards such as EN14476 (i.e. 4 log reduction) for rhinoviruses. But, in the case of influenza viruses and SRV, the requirements are achieved.

Overall conclusion for Efficacy:
Even if the test conditions/requirements are not equivalent to those found in the EU standards, the tests provided showed a basic efficacy, robust enough for the inclusion procedure.
In the context of inclusion, the RMS is thus of a mind to accept/validate the claims about influenza viruses (A and B) and RSV.

Furthermore, RMS do agree with other MS that the 15 min contact time is too long and obviously unrealistic. At the Product Authorization Stage, efficacy tests with realistic shorter contact times must be submitted.
At the Product Authorization Stage, the RMS is also of a mind to ask for efficacy tests performed according to the EN 14476:2013 standard on the product used to impregnate the tissues.

- Development of resistance:

Citric acid is naturally present in almost all forms of life. Consequently, it seems to be very unlikely that organisms can develop resistance to citric acid. Therefore, the development of a management strategy is not considered to be an urgent task.

2.1.1.4 Classification of the Active Substance

- Proposed classification of the active substance according to Regulation EC 1272/2008 CLP:

Classification	**According to Regulation EC 1272/2008 - CLP**
GHS Pictogram(s)	 **GHS07**
Signal word	Warning
Hazard Class and Category Codes	Eye Irrit.2 Skin Irrit.2
Hazard Statement Codes	**H315** (Causes skin irritation) **H319** (Causes serious eye irritation)
Precautionary Statement Codes	**P264** Wash hands thoroughly after handling **P280** Wear protective gloves/protective clothing/eye protection/face protection **P302+P352** IF ON SKIN: wash with plenty of soap and water **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing **P321** Specific treatment (see on this label). **P332+P313** IF SKIN irritation occurs: Get medical advice/attention **P337+P313** IF eye irritation persists: Get medical advice/attention **P362** Take off contaminated clothing and wash before reuse.

Citric acid is potentially irritating to skin and eyes:

- According to a study performed on rabbits (with a 30% solution of citric acid), citric acid is potentially severe irritating to eyes.

Therefore, the classification as Cat. 2 Eye Irritant (H319) seems to be appropriate.

- According to experimental data (i.e. results of a skin irritation study) and to cosmetic application of citric acid based on its low pH (at concentration higher than 5%), citric acid is also a skin irritant and must be classified as Cat. 2 Skin Irritant (H315).

Explanation about classification will be provided in the CLH dossier for Citric Acid.

Information about the classification of the representative product:

The tissue impregnated with citric acid is considered as the representative product in this dossier.

Placed on the market with the claim "kills 99.9% of cold & flu viruses in the tissue", the tissue impregnated with citric acid has to be considered as a biocidal product.

Based on the presented studies performed with the impregnated tissue with citric acid, it does not need to be classified.

2.2 HAZARD IDENTIFICATION OF THE ACTIVE SUBSTANCE

2.2.1 Summary of the human health effects assessment

Oral intake of the active substance results in absorption and metabolism of the parent compound via the Krebs cycle, which takes place in all cells. Citric acid occurs naturally in many food-stuffs and is often used as a food additive. The average daily intake of the active substance from sources other than the biocidal use can exceed 400 mg/kg/day. Citrates are usually found associated with calcium in the bones (70%) and with the liver, renal cortex and skeletal muscles. Citric acid is mainly excreted in urine as bicarbonate.

The active substance is not harmful by acute oral (LD_{50} = 3000 mg/kg) or dermal (LD_{50} > 2000 mg/kg) exposure. Indications of toxicity in the acute studies are consistent with local irritation effects caused by the active substance.

Citric acid is potentially irritating to skin and eyes:

- According to a study performed on rabbits (with a 30% solution of citric acid), citric acid is potentially severe irritating to eyes. Therefore, the classification as Cat. 2 Eye Irritant (H319) seems to be appropriate.

- According to experimental data (i.e. results of a skin irritation study) and to cosmetic application of citric acid based on its low pH (at concentration higher than 5%), citric acid is also a skin irritant and must be classified as Cat. 2 Skin Irritant (H315).

Explanation about classification will be provided in the CLH dossier for Citric Acid.

There is no publicly available data on sensitisation in animals. There are several studies in humans on potential allergenic reactions to the substance via the oral route, in addition to patch testing of the biocidal product containing the active substance. The results of these human studies indicate that there is no conclusive evidence for allergic effects caused by oral exposure or for contact sensitisation from dermal exposure. The active substance is therefore considered not to be a sensitizer.

There are several reported sub-acute, sub-chronic and chronic oral dietary studies in the rat, rabbit and dog. Toxic effects are indicative of overloading of the metabolic pathways. The lowest NOAEL for repeat oral dose is therefore 1960 mg/kg/day based on the 2-year study in the rat.

There is no data on dermal absorption of the active substance. However, citric acid is used in a wide range of topical medicines and cosmetics. No observations of systemic effects have been noted from this use pattern. A repeat dose study by the dermal route of exposure is also considered to be scientifically unjustified as there have been no indications of systemic toxicity in man from topical use.

According to EFSA guidance, a default value of **25%** (default value for product containing >5% active substance) can be applied for the dermal absorption.

There is no evidence of genotoxic potential of citric acid in *in vitro* or *in vivo* studies conducted in bacteria, mammalian cells and rats. No genotoxic effects have been observed during the long history of exposure via food, cosmetics and medicines.

There is no evidence of carcinogenic potential without inducement using additional test materials when rats were dosed with 5% citric acid in diet (ca. 2000 mg/kg/day).

No evidence of embryotoxic or teratogenic potential was obtained independent of maternal toxicity. The NOEL for teratogenicity is 241 mg/kg/day in the rat and > 425 mg/kg/day in the rabbit. A NOAEL has not been observed for teratogenic effects up to a dose level of 5% citric acid in diet of rats (ca. 2000 mg/kg/day).

There were no effects on the reproductive performance of rats below the level of toxicity in the parent animals. The NOEL for reproductive effects is 600 mg/kg/day. A NOAEL has not been observed for reproductive effects up to a dose level of 5% citric acid in diet of rats (ca. 2000 mg/kg/day).

2.2.2 Determination of toxicological hazard endpoints

Since the different nature of the sources of citric acid, citric acid occurs in food (naturally present and as additive), in cosmetics, and in humans as a metabolite we will not derive and AEL based on NOAEL. But instead we will derive it from food and/or drug regulations.

The active substance is used extensively in the food industry as an additive. A value for ADI has not been determined for this active substance as its toxicity is considered to be very low (Occupational Toxicants. (2001) Ed. Greim, H. Vol 16 Wiley VCH, Weinheim). Besides there is set a lowest dietary limit by EFSA for inclusion into fruit and vegetable juices of 100 mg/kgbw/d considering the limiting factor of irritation in the gastro-intestinal tract. There is also a MRTD (Maximum Recommended Therapeutic Dose) in FDA list (US Food and Drugs Admnisstration) of 100 mg/kgbw/d, this quantity is added to the background level exposure from the diet, without inducing adverse effect and seems to be relevant in this case. So there appears to be a good correlation between this MRTD and the lowest dietary limit set by EFSA for inclusion into fruit and vegetable juices.
So **we will take the MRTD value of 100 mg/kg bw/d*** as a reference value in order to perform the risk characterization for citric acid.

**** Human Health WG - Ad hoc follow-up on Citric Acid***
- Discussion and conclusion about the AEL derivation –
(See Discussion table on Draft CAR on Citric Acid (PT 1) – WGIV2014_TOX_6-3 - Updated draft minutes – 4 November 2014)

Background: In the first draft CAR, no AEL was derived. For the risk characterization, the margin of safety (MOS) approach had been applied. The

estimated exposure levels had been compared to the lowest NOAEL from a 2-year rat study i.e. 1960 mg/kg bw/d. But FR requested to derive the AELs. Therefore, the eCA proposed to derive one AEL from the NOAEL of a 2-year rat study by applying an AF of 100. The AEL would then be 19.6 mg/kg bw/d. During the WG meeting, it was not possible to agree with the eCA proposal of AEL of 19.6 mg/kg bw/d. AEL derivation should rather refer to an existing reference value. In order to perform the risk characterization, an estimation of the exposure is needed and a reference value should therefore be defined. The WG decided to continue the discussion (through e-mail exchanges) in an ad hoc follow-up.

ECHA proposed to take the MRDT value of 100 mg/kg bw/d as a reference value in order to perform the risk characterization for citric acid. Indeed, this quantity is added to the background level exposure from the diet, without inducing adverse effect and seems to be relevant in this case. Furthermore, there appears to be good correlation between this MRTD and the lowest dietary limit set by EFSA for inclusion into fruit and vegetable juices of 100 mg/kg bw/day, considering the limiting factor of irritation in the gastro-intestinal tract.

All the participants came to an agreement to take the MRDT value of 100 mg/kg bw/d as the unique[a] reference value to be used in the risk characterization for citric acid.

[a] For the purpose of transparency, eCA would like to mention that the Applicant was of the opinion to consider an AEL of 440 mg/kg bw/day for infants (0-1 year). In the end, the Applicant does agree to use only one reference value of 100 mg/kg bw/d for adults, children (> 1 year) and infants (0-1 year).

2.2.3 Summary of the environmental fate and effects assessment

Citric acid occurs naturally in all living systems and is used in cells via the Krebs cycle. Environmental background concentrations of < 0.04 – 0.2 mg/l in river surface water and 0.025 – 0.145 mg/l in Atlantic coast seawater have been observed. The active substance is highly water soluble, with a low log P_{ow} (<-3.76) and is inherently and readily biodegradable. It is not predicted to undergo indirect photodegradation in air (t½ = 2.3 days). Organic acids such as citric acid do not undergo hydrolysis, however they ionise in aqueous solution to produce salts with available cations.

In soil citric acid degraded within one to two weeks. Although the active substance has a low log P_{ow} which would indicate that the substance is mobile in soil, the substance also ionises easily at environmental pH. This is shown from the results of the adsorption/desorption study, where the active substance adsorbs to all soils independent of the organic matter content.

On the basis of the acute ecotoxicity studies, the active substance is not harmful to fish (LC_{50} (96h) = 440 mg/l) and sewage sludge micro-organisms (EC_{50} = 370 mg/l), but it is to invertebrates (EC_{50} (48h) = 34 mg/l) and is toxic to algae (EC_{50} (72h) = 1.9 mg/l). However, it should be noted that toxicity is considered to be caused by the initial drop in pH caused by addition of the active substance to water. During the course of the acute study, the effect of the pH was seen to be mitigated as the algae adapted and removal processes (ionisation, degradation and uptake of citric acid by the algae) were initiated.

2.2.4 Determination of PNECs

PNEC for aquatic organisms

Conventionally, the PNEC is derived from the lowest NOEC out of a set of three long-term single-species toxicity tests, by applying an assessment factor of 10. However, there is no long-term study for citric acid. Only acute studies are available. Therefore, on the basis of the acute toxicity data against fish, invertebrates and algae, it is possible to derive a PNEC for aquatic organisms from the lowest L/EC_{50} value and applying an assessment factor of 1000 for freshwater (TGD part II, chapter 3, Table 16, p.101). From the studies identified, the lowest EC_{50} is from the algae inhibition study, with an E_rC_{50} (72h) of 2.0 mg/l. The PNEC for freshwater organisms is thus equal to 2.0×10^{-3} mg/l.

PNEC for STP micro-organisms

According to the TGD on Risk Assessment (part II, chapter 3, Table 17, p.109), the PNEC for micro-organisms in a STP is derived by applying an assessment factor of 100 to the EC_{50}, or by applying an assessment factor of 10 to the NOEC, and selecting the lowest value as the PNEC. The EC_{50} for STP micro-organisms is 370 mg/l and the NOEC was reported to be 180 mg/l. The lowest value is

obtained by applying an assessment factor of 100 to the EC_{50}. The resulting PNEC for STP micro-organisms is thus equal to 3.7 mg/l.

PNEC for terrestrial organisms

No study was available on terrestrial organisms. Therefore, PNEC for terrestrial organisms ($PNEC_{soil}$) was estimated by the equilibrium partitioning method using $PNEC_{water}$ in the equation n° 72 of TGD, part II, chapter 3, p. 117. The resulting $PNEC_{soil}$ is equal to 2.55×10^{-4} mg/kg_{wwt}.

PNEC for sediment organisms

In the absence of any ecotoxicological data for sediment-dwelling organisms, but with measured data to predict the $PEC_{fresh/marine,sediment}$, the $PNEC_{fresh/marine,sediment}$ may provisionally be calculated using the equilibrium partitioning method. This method uses the $PNEC_{fresh/saltwater}$ for aquatic organisms and the fresh/marine suspended matter-water partitioning coefficient (TGD, part II, chapter 3, equation 70 and equation 88, p. 113 and p. 153). The resulting $PNEC_{sediment}$ for fresh and saltwater are equal to 1.59×10^{-3} and 1.59×10^{-4} mg/kg_{wwt}, respectively.

PNEC for secondary poisoning of birds and mammals

Citric acid naturally occurs in all organisms and there is a mechanism for elimination of the substance via the Kreb's cycle. The active substance is highly water soluble, with a low log P_{ow} (<-3.76) and is inherently and readily biodegradable. A very low BCF value of 1.277×10^{-4} have been determined based on its Log Pow (-3.76). There is therefore negligible concern for bioaccumulation of the active substance. In addition, only a minor fraction of the released citric acid will adsorb to organic matter where it will not persist and will rapidly be biodegraded. Therefore the molecule is not considered as highly adsorptive. Furthermore, the active substance is not classified as toxic to mammalian and therefore no potential to cause any toxic effects if accumulated in higher organisms is foreseen.

In view of these considerations, calculations of PNECs for secondary poisoning for birds and mammals were not considered relevant.

Summary of PNEC values

Compartments		PNECs values
PNEC for aquatic organisms	freshwater	2.0×10^{-3} mg/l
PNEC for STP micro-organisms		3.7 mg/l
PNEC for soil organisms		2.06×10^{-2} mg/kg_{wwt}
PNEC for sediment dwelling-organisms	Freshwater sediment	2.66×10^{-2} mg/kg_{wwt}
	Saltwater sediment	2.66×10^{-3} mg/kg_{wwt}

2.2.5 PBT and POP assessment

Regarding its physico-chemical properties and its degradation pathways, citric acid cannot be regarded, according to TGD (part II, chapter 3, Table 30, p. 164), as a PBT substance.

Persistence criteria (P, vP): citric acid is readily biodegradable.

Bioaccumulation criteria (B, vB): citric acid has a BCF< 2000, bioaccumulation criteria is thus not fulfilled.

Toxicity criteria (T): citric acid is not a CMR (carcinogenic, mutagenic, repro-toxic) substance nor an endocrine disrupting substance. Therefore, T criteria are not fulfilled.

Citric acid does not meet any of the criteria for Persistent, Bioaccumulative and Toxic (PBT) substances or the very Persistent, very Bioaccumulative (vPvB) category.

2.2.6 Assessment of endocrine disruptor properties

No indication or data for Citric acid are available that indicate potential endocrine disruptive properties.

2.3 ASSESSMENT OF USE IN APPLICATION PRODUCT TYPE 02

The biocidal product is a facial tissue for consumer use after contraction of coughs, colds and influenza.

Composition of the biocidal product (Kleenex®Anti-Viral Facial Tissues) and of the formula used to impregnate the tissues is regarded as commercially sensitive.

2.3.1 Critical end point(s) for the formulation

Neat citric acid is potentially irritating to skin and eyes:

- According to a study performed on rabbits (with a 30% solution of citric acid), citric acid is potentially severe irritating to eyes.

- According to experimental data (i.e. results of a skin irritation study) and to cosmetic application of citric acid based on its low pH (at concentration higher than 5%), citric acid is also a skin irritant.

The concentration of citric acid in the FACT formulation used to impregnate the tissues and in the impregnated tissues (confidential information) may cause irritation to skin and eyes.

Concentrated Sodium Lauryl Sulphate is also classified as an irritant.

Animal and human studies on the biocidal product (impregnated tissues) have shown that it may only produce mild irritation effects in a small number of users. The impregnated tissue is specifically aimed at the control of coughs and flu virus.

Other uses such as make-up removal may induce some mild irritation effects. However, the possible misuses constitute a similar risk of exposure compared to the normal use, since the worst case values have been considered for the calculation of the exposure during the use of the product.

The MRTD value of 100 mg/kg bw/d is taken as a reference value in order to perform the risk characterization for citric acid. (see section 2.2.2)

2.3.2 Risk identification for human health

2.3.2.1 Professional exposure

Not relevant.

2.3.2.2 Non-Professional i.e. Consumer Exposure

The human health risk assessment is performed on the basis of treated tissues.

There are no available studies on absorption of citric acid. So, based on the worst exposure case scenario, consumers using the biocidal product, i.e. the tissue, will be potentially exposed by the oral and inhalation routes to 100% of the active substance in each tissue And by dermal route to 25% of active substance according to EFSA guidance, (default value for product containing >5% active substance).

Summary of consumer exposure assessment:

A reverse reference scenario and a normal exposure assessment was performed.

For the reverse reference scenario it is considered that the consumer will be in contact with the complete surface of the tissue.

Reverse reference scenario:

	max. # tissues per day
Infants	24
Toddler	36
Child	86
Adult	359

For every category of the population the maximum amount of tissues will normally never be exceeded. Using 24 tissues or more a day seems exaggerated for infants, nevertheless a normal exposure assessment was carried out.

For the normal exposure assessment it was assumed as worst case for the acute scenario a use of 15 tissues/day and for the chronic scenario a use of 4 tissues every day of the year.

PT	Category of population	Exposure scenario	Dermal Estimated internal exposure [mg/kg bw(/day)]	Oral Estimated internal exposure [mg/kg bw(/day)]	Total Estimated internal exposure [mg/kg bw(/day)]	AEL	MOE
PT 2	Adult	acute : use of 15 tissues a day	6.3	-	6.3	based on MRTD 100 mg/kgbw/d	1598
		chronic : use of 4 tissues every day	1.7	-	1.7		5992
	Children	acute : use of 15 tissues a day	8.2	-	8.2		1220
		chronic : use of 4 tissues every day	2.2	-	2.2		4573
	Toddler	acute : use of 15 tissues a day	5.2	21.1	26.3		380
		chronic : use of 4 tissues every day	1.4	5.6	7.0		1424
	Infant	acute : use of 15 tissues a day	4.8	19.1	23.9		418
		chronic : use of 4 tissues every day	1.3	5.1	6.4		1569

There is no concern for every category of the population, since the MOE is higher than 100.

Secondary exposure may also occur via disposal of the used tissues. However, this exposure will be minimal in comparison to exposure to citric acid from other sources, such as food.

2.3.3 RISK IDENTIFICATION FOR THE ENVIRONMENT

2.3.3.1 Fate and distribution in the environment

Aquatic compartment:

Citric acid occurs naturally in all living systems and is used in cells via the Krebs cycle. Environmental background concentrations of < 0.04 – 0.2 mg/l in river

surface water and 0.025 – 0.145 mg/l in Atlantic coast seawater have been observed (Khomenco *et al.*, 1969; Shannon *et al.*, 1977; Creac'h, 1955). The active substance is highly water soluble (O'Connor and Mullee, 2006), with a low log Pow and is inherently and readily biodegradable (Gerike and Fischer, 1979). Organic acids such as citric acid do not undergo hydrolysis ($t_{1/2}$ >1 year), however they ionise in aqueous solution to produce salts with available cations (O'Connor and Mullee, 2006).

Atmospheric compartment:

Based on its vapour pressure (1.6×10^{-10} Pa at +25°C), and its Henry's constant (4.398 E-14Pa.m³/mol, QSAR estimation), volatilisation of citric acid is considered to be negligible. Moreover, indirect photodegradation in air is rapid, t½ = 2.3 days (Meylan and Howard, Epiwin, SRC).

Terrestrial compartment:

In soil citric acid degraded within one to two weeks (Miles Laboratories, Inc., Pfizer, Inc., and Proctor and Gamble Co., 1977; Brynhildsen and Rosswall, 1995). Although the active substance has a low log P_{ow} and is highly water soluble which would indicate that the substance is mobile in soil, the substance also ionises easily at environmental pH and so adsorbs strongly to soil irrespective of the organic matter content.

Non compartment specific effects relevant to the food chain (secondary poisoning)

The active substance is a naturally occurring substance, which has high water solubility, is inherently and readily biodegradable and has a low Log Pow (< -3.76). The active substance naturally occurs in all organisms and there is a mechanism for elimination of the substance via the Kreb's cycle. There is therefore negligible concern for bioaccumulation from the active substance.

2.3.3.2 Predicted Environmental Concentrations

Predicted Environmental Concentrations are calculated only for the active substance citric acid.

There is no release of the active substance to the environment from processing and packaging (taking place outside E.U.).

The main disposal method of the biocidal product (impregnated tissues) used by the consumer will be via domestic wastes.
Tissue and active substance stored in landfill will degrade rapidly prior to any potential release via leaching to the landfill soil and groundwater. Those minor leaching to landfill soils are not expected to reach grassland and agricultural soils. However, agricultural and grassland soils might be exposed via sewage sludge. Releases into the environment could take place via the sewer system (e.g. when tissues are disposed of via toilet) or directly (e.g. if tissue falling down a pocket). All tissue waste containing the active substance is sent for disposal by incineration. Normally, there will be no additional exposure via the environment from disposal as citric acid is naturally occurring in the environment**,** therefore additional concentrations of citric acid from this source will be negligible against the background concentration.
In addition, it should be noted that calculated PECs using EUSES 2.1.1 and presented in Doc IIA are below the monitored background concentrations for fresh and seawater by, respectively a factor 1000 and 100.

PEC in aquatic compartment (STP, surface water, groundwater and sediment):

- **STP**

PEC_{STP} represents the worst-case concentration the micro-organisms in the sewage treatment plant are exposed to. For freshwater, PEC_{STP} is equal to 1.63×10^{-3}mg/l.

- **Surface water**

The use of the biocidal product do not allow direct exposure to surface water, only indirect exposure via an effluent of the sewage treatment plant can occur. The annual average local PEC in fresh/salt water resulted in 1.63×10^{-4} mg/l and 1.35×10^{-4} mg/l, respectively.

- **Sediment**

The concentration of citric acid in freshly deposited sediment is taken as the PEC for sediment. Therefore, the properties of suspended matter are used. PEC in fresh/salt water sediment resulted in 2.16×10^{-3} mg/kgwwt and 1.79×10^{-3} mg/kgwwt, respectively.

- **Groundwater**

The concentration in groundwater is calculated for indirect exposure of humans through drinking water. $PEC_{groundwater}$ under agricultural soil is equal 5.80×10^{-5} mg/l.

PEC in soil

The main disposal method of the biocidal product used by the consumer will be to landfill. The active substance is readily biodegradable and is naturally occurring in the environment, therefore additional concentrations of citric acid from this source will be negligible against the background concentration.

Tissue and active substance stored in landfill will degrade rapidly prior to any potential release via leaching to landfill soil and groundwater. However, agricultural and grassland soils might be exposed via sewage sludge. In the case of citric acid, the fraction of the emission directed to sludge by STP calculated with EUSES 2.1.1 represents 5.05%.

The resulting local PEC_{soil} are summarised in the table below:

Parameters	PECs values (mg/kgwwt)
Local PEC in agricultural soil averaged over 30 days	1.82×10^{-3}
Local PEC in agricultural soil averaged over 180 days	5.97×10^{-4}
Local PEC in grassland averaged over 180 days	2.37×10^{-4}

PEC in air

Based on its vapour pressure (1.6×10^{-10} Pa at 25°C) and the Henry's constant (4.398 E-14Pa.m³/mol), citric acid is not volatile and is fixed within the biocidal product. It will not be released to air from processing, packaging or use. Calculations of the chemical lifetime in the troposphere (document II-A section 4.1.1.1.3) resulted in a half-life of 2.3 days. According to these results, citric acid is rapidly degraded by photochemical processes and no accumulation of citric acid in the air is to be expected. The calculation of PEC_{air} is therefore of no relevance.
Therefore, the annual average PEC in air is equal to zero:
PEC_{air} = 0 mg/m³

Non-compartment specific exposure relevant to the food chain (secondary poisoning)

Citric acid naturally occurs in all organisms and there is a mechanism for elimination of the substance via the Kreb's cycle. The active substance is highly water soluble, with a low log P~~ow~~ (<-3.76) and is inherently and readily biodegradable. A very low BCF value of 1.277 x 10^{-4} has been determined based on its Log P_{ow} (-3.76). There is therefore negligible concern for bioaccumulation of the active substance. In addition, only a minor fraction of the released citric acid will adsorb to organic matter where it will not persist and will rapidly be biodegraded. Therefore the molecule is not considered as highly adsorptive. Furthermore, the active substance is not classified as toxic to mammalian and therefore no potential to cause any toxic effects if accumulated in higher organisms is foreseen.

In view of these considerations, calculations of PNECs for secondary poisoning for birds and mammals were not considered relevant.

Summary of PEC values

Compartments		PECs values
PEC $STP_{freshwater}$		1.63×10^{-3} mg/l
$PEC_{freshwater}$		1.63×10^{-4} mg/l
$PEC_{seawater}$		1.35×10^{-4} mg/l
$PEC_{freshwater,}$sediment		2.16×10^{-3} mg/kgwwt
$PEC_{seawater,}$sediment		1.79×10^{-3} mg/kgwwt
$PEC_{groundwater}$		5.80×10^{-5} mg/l
PEC_{soil}	$PEC_{agric.}$ soil (30 d)	1.82×10^{-3} mg/kgwwt
	$PEC_{agric.}$ soil (180 d)	5.97×10^{-4} mg/kgwwt
	$PEC_{grassland}$ (180 d)	2.37×10^{-4} mg/kgwwt
PEC_{air}		0 mg/m³

2.4 RISK CHARACTERISATION

2.4.1 Human Health

Local effects are predominant for citric acid and systemic effects appear to be secondary toxicity.
The biocidal product is not classified for local effects and no direct exposure to the a.s. is foreseen, therefore a LRA is not necessary.

2.4.1.1 Professional users

Not relevant

2.4.1.2 Overall assessment of the risk for the use of the active substance in biocidal products

There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

2.4.1.3 Indirect Exposure as a result of use of the active substance in Biocidal Product

Primary exposure during service life (Exposure to general public during the use of the tissue):

Consumers will be exposed to the active substance via the dermal and inhalation routes during the use of the impregnated tissue. The systemic dose has been calculated for a child using the product as 15.89 mg/kg/day.

The Margin of Safety is calculated by comparison of the worst-case NOAEL against the predicted exposure. The Margin of Safety is therefore 123.

The active substance presents no potential for concern for human health effects from the biocidal product use scenario.

Secondary exposure (Exposure via emissions due to disposal):

Secondary exposure may occur via disposal of the used tissues. However, this exposure will be minimal in comparison to exposure to citric acid from other sources, such as food.

2.4.1.4 Combined exposure

It is not possible the predict the additional exposure effect of use of the active substance in this biocidal product type as citric acid is a naturally occurring substance found in food, the environment and the body used. It is also used as a food additive and in cosmetics and medicines. There are no concentration limits set for exposure via other sources of exposure.

2.4.2 Environment

There is no release of the active substance to the aqueous environment from processing and packaging of the biocidal product. All paper wastes containing the active substance are sent for disposal by incineration. A quantitative risk characterisation is therefore not applicable for this stage of the active substance lifecycle.

There will be minimal release of the active substance from the biocidal product to the environment. In general the tissue will be disposed of by domestic wastes. The active substance is readily biodegradable and is naturally occurring in the environment, therefore additional concentrations of citric acid from this source will be negligible against the background concentration. Tissue sent to landfill will degrade rapidly prior to any potential release via leaching from the landfill site to soil and groundwater. Citric acid has high water solubility, is readily biodegradable and has a low log P_{ow}. The active substance naturally occurs in all organisms and there is a mechanism for elimination of the substance via the Kreb's cycle. There is therefore no concern for bioaccumulation from the active substance.

To allow quantitative risk assessment for the environment after Citric acid use in the Kleenex anti-viral facial tissue, the PEC values are compared to the respective PNEC values for the different compartments.

Risk Characterisation Ratios (PEC/PNEC) for the different compartments of the environment are summarised in the table below:

Compartment		**RCR = PEC / PNEC**
STP	freshwater	4.41×10^{-4}
Surface water	freshwater	0.082
	saltwater	0.675
Sediment	freshwater	0.081
	saltwater	0.0673
Soil		8.88×10^{-2}
Air		0

Any quantitatively relevant contamination of soil or water is minimised in view of the intended use of the biocidal product as a facial tissue. Moreover, regarding Table 5 above, **the use of citric acid in Kleenex anti-viral facial tissue will not pose any unacceptable risk to the environment.**

There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

2.4.3 Physico-chemical properties

There are no concerns for potential physico-chemical effects of the active substance and biocidal product.

CONCLUSION

The risk characterisation shows that there is no concern for use of the active substance, citric acid, in the proposed biocidal use (Kleenex anti-viral facial tissue) to either man or the environment.

2.5 OVERALL CONCLUSION

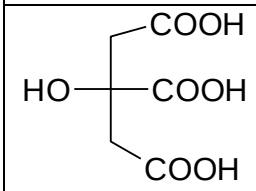
The outcome of the assessment for citric acid in product-type 2 is specified in the BPC opinion following discussions at the 14th meeting of the Biocidal Products Committee (BPC). The BPC opinion is available on the ECHA website.

APPENDIX I : LIST OF END POINTS

CHAPTER 1: IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND PROPOSED CLASSIFICATION AND LABELLING

Active substance (ISO Common Name)	Citric acid
Function (*e.g.* fungicide)	Anti-viral
Rapporteur Member State	Belgium

Identity (Annex IIA, point II.)

Chemical name (IUPAC)	2-hydroxy-1,2,3-propanetricarboxylic acid
Chemical name (CA)	Citric acid
CAS No	77-92-9
EC No	EINECS No: 201-069-1
Minimum purity of the active substance as manufactured (g/kg or g/l)	995g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (% w/w)	No impurities *Please refer to document "confidential information" for additional information.*
Molecular formula	$C_6H_8O_7$
Molecular mass	192.13 g/mol
Structural formula	

Physical and chemical properties (Annex IIA, point III., unless otherwise indicated)

Freezing point (state purity)	+151°C (99,5%)
Boiling point (state purity)	> 171°C Decomposes prior to boiling (99,5%)
Appearance (state purity)	white or colourless crystalline powder
Specific gravity	1.65 10^3 kg/m^3 (at +20°C)
Surface tension	73.6 mN/m for a 1.01g/l solution at +21°C
Vapour pressure (in Pa, state	1.6 E-10 Pa at +25°C

temperature)	
Henry's law constant	4.398 10^{-14} Pa.m^3/mole
Solubility in water (g/l or mg/l, state temperature)	65 – 69.9% w/w +10, +20 and +30°C (pH 5-9 – citric acid ionises at pH 5-9)
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	Hexane ≤ 7.84 E-05 g/L Diethyl ether = 7.34 g/L Methanol > 250 g/L
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	No organic solvent used, therefore testing of organic solvents is not applicable.
Partition coefficient (log P_{OW})	≤ -3.76 at +21°C (at pH 5-9 – citric acid ionises at pH 5-9)
Storage stability (DT_{50}) (state pH and temperature) (point VII.7.6.2.1)	Thermally stable and stable in air up to at least 150°C. Stable at room temperature for 60 days (Stability at 6 months and 12 months to be provided) (US EPA test method)
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	pK_1 = 3.01, pK2 = 4.50, pK_3 = 5.87
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	No significant absorbance at 290 nm
Photostability (DT_{50}) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	Half-life in water = 73 years Direct phototransformation in water: does not absorb at > 290 nm under acidic, neutral and basic conditions. half-life in air = 2.3 days
Flammability	Not highly flammable Looking at the *Tremain S.* study, in the preliminary screening test, the test material did not propagate combustion over the 200 mm.
Explosive properties	No explosive properties predicted from the structure

Classification and proposed labelling (Annex IIA, point IX.)

with regard to physical/chemical data	None
with regard to toxicological data	Eye Irrit. 2 - H319 Skin Irrit. 2 - H315
with regard to fate and behaviour data	None
with regard to ecotoxicological data	None

CHAPTER 2: METHODS OF ANALYSIS

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	Analysis of active substance (5-batches) in accordance with methods specified under Council Directive 91/414/EC. Active ingredient content is determined by HPLC
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1) * The dossier was written before the new Regulation (EC) no. 1107/2009 on crop protection chemicals came into force.	Analysis of active substance (5-batches) in accordance with methods specified under Council Directive 91/414/EC*. - Active ingredient content is determined by HPLC - Water content is determined by Karl Fischer titration - Inorganic residues are determined by gravimetric analysis (dry ashing) - Oxalate is determined by HPLC - Heavy metal content is determined by ICP-ES

Analytical methods for residues

Soil (principle of method and LOQ) (Annex IIA, point 4.2)	Not applicable*
Air (principle of method and LOQ) (Annex IIA, point 4.2)	Not applicable*
Water (principle of method and LOQ) (Annex IIA, point 4.2)	Not applicable*
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	Not applicable*
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not applicable*
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not applicable*

* Justification:

- Analytical methods in soil are not justified for the active substance as the active substance is rapidly removed from the soil compartment. Release to the soil compartment from consumer use of the product will be negligible compared to the naturally occurring concentration of citric acid and release form other sources such as food and cosmetics.

- Analytical methods in air are not necessary as the active substance has a low vapour pressure (7.3E-07 Pa) and is unlikely to be present in air. Furthermore the active is fixed in the product so there is no release to air during processing, packaging and use.

- Environmental background concentrations of < 0.04 – 0.2 mg/l in river surface water and 0.025 – 0.145 mg/l in Atlantic coast seawater (referenced in IUCLID 2000 dataset) have been observed in addition to the use of citric acid in food, cosmetics and medicines which will be released to the aqueous environment. This means it is not possible to determine the concentration of citric acid in water from use of the product.

- Citric acid is naturally occurring in all living systems and is utilised in the cells via the Kreb’s cycle. It is therefore impossible to detect citric acid in animal and human body fluids and tissue which has come from the use of the product.

CHAPTER 3: IMPACT ON HUMAN HEALTH

Absorption, distribution, metabolism and excretion in mammals (Annex IIA, point 6.2)

Rate and extent of oral absorption:	No available studies Expected to be orally absorbed up to rate of 100%.
Rate and extent of dermal absorption:	No available studies. Expected to be dermally absorbed up to rate of 25%. (default value for product containing >5% active substance according to EFSA guidance)
Distribution:	Taken up by the cells for use in Krebs cycle, distributed extracellularly and stored in the bones (approximately 70% of citrate in body is bond to bones)
Potential for accumulation:	No
Rate and extent of excretion:	Citric acid is mainly excreted via the liver and kidneys after complete metabolic conversion to bicarbonate. Citric acid is always excreted in urine independent of additional citric acid exposure to the body from either food, cosmetics/medicines or other identified uses. The excretion in the urine is affected by numerous factors. For example, metabolic alkalosis, or high concentrations of citrate or bicarbonate in the plasma result in drastic increases in citrate excretion in the urine. Acidosis reduces urinary excretion.
Toxicologically significant metabolite	None. Rapidly oxidised to carbon dioxide and water in the citric acid (Krebs) cycle in the cells of all the organs of the body. In addition, citric acid is used in the synthesis of fatty acids and amino acids and in gluconeogenesis

Acute toxicity (Annex IIA, point 6.1)

Rat LD_{50} oral	3000 mg/kg bw.
Rat LD_{50} dermal	> 2000 mg/kg
Rat LC_{50} inhalation	No study available
Skin irritation	Irritating based on pH
Eye irritation	Highly irritating
Skin sensitization (test method used and result)	Not sensitising. Human patch test (174/197 subjects elicited no response)

Repeated dose toxicity (Annex IIA, point 6.3)

Species/ target / critical effect	Rat/ oral,6 weeks/no mortality, body weight reduction and weight of brain and thymus. Rat/oral,60 days/ decreased weight gain and haemocrit. Dog/ oral,112-130 days/no adverse dose-related effects observed. Mouse/oral,14 months/ decreased bodyweights and survival Rabbit/oral,150 days/ No adverse dose-related effects observed Rat/oral, 2 years/reduction in body weight, possibly due to reduction in food consumption Rat/ oral, lifetime, plus 3 successive generations/no significant effects
Lowest relevant oral NOAEL / LOAEL	1960 mg/kg/day
Lowest relevant dermal NOAEL / LOAEL	None available
Lowest relevant inhalation NOAEL / LOAEL	None available

Genotoxicity (Annex IIA, point 6.6)	The active substance is not mutagenic *in vitro* with and without metabolic activation. The active substance is not clastogenic *in vitro* without metabolic activation. Citric acid did not induce mutagenic potential in two *in vivo* studies (rat bone marrow and rat dominant lethal assay)

Carcinogenicity (Annex IIA, point 6.4)

Species/type of tumour	Rat/ Citric acid does not induce a

	carcinogenic effect or any signs of toxicity at the dose level tested
lowest dose with tumours	Not applicable

Reproductive toxicity (Annex IIA, point 6.8)

Species/ Reproduction target / critical effect	Rat/oral, 1-gen study, in-utero to 200 days after birth/ F1 males decrease in bodyweight, wet weights of fibula and tibia, haemocrit and haemoglobin levels Rat/oral, 2-gen/ no adverse effects observed
Lowest relevant reproductive NOAEL / LOAEL	5 % citric acid in diet
Species/Developmental target / critical effect	Rat/oral, 1-gen study, in-utero to 200 days after birth/ F1 males decrease in bodyweight, wet weights of fibula and tibia, haemocrit and haemoglobin levels Rat/6-15 day of gestation/no adverse effects Mouse/oral, pre-,during and post-mating/no adverse teratogenic effects Rabbit/oral, 6-18 days of pregnancy/no effects
Lowest relevant developmental NOAEL / LOAEL	5% citric acid in diet

Neurotoxicity / Delayed neurotoxicity (Annex IIIA, point VI.1)

Species/ target/critical effect	No data necessary. Data waiver in place.
Lowest relevant developmental NOAEL / LOAEL.	

Other toxicological studies (Annex IIIA, VI/XI)

Not applicable

Medical data (Annex IIA, point 6.9)

Not applicable

Summary (Annex IIA, point 6.10)

	Value	**Study**	**Safety factor**
ADI (if residues in food or feed)	Not specified		

AEL	MRTD value of 100 mg/kgbw/d is used instead	MRTD (Maximum Recommended Therapeutic Dose) of FDA list (US Food and Drugs Admnistration)	n.a.
Drinking water limit	Not specified		
ARfD (acute reference dose)	Not specified		

Acceptable exposure scenarios (including method of calculation)

Professional users	There is no professional use
Non-professional users	Consumers using the biocidal product, i.e. the tissue, will be potentially exposed by the dermal and inhalation routes to 100% of the active substance in each tissue. Each consumer on average uses 326 tissues per year. Therefore, based on the worst case scenario, the consumer will be exposed to 87 g of the active substance per year. The worst-case scenario is for use of the tissue by children, therefore the systemic dose is based upon a child (weight = 15 kg). The systemic dose is therefore 15.89 mg/kg/day. Lowest MoE for adults : 1598 Lowest MoE for children : 1220 Lowest MoE for toddlers: 380 Lowest MoE for infants : 418
Indirect exposure as a result of use	Secondary exposure may occur via disposal of the used tissues. However, this exposure will be minimal in comparison to exposure to citric acid from other sources, such as food.

CHAPTER 4: FATE AND BEHAVIOUR IN THE ENVIRONMENT

Route and rate of degradation in water (Annex IIA, point 7.6, IIIA, point XII.2.1, 2.2)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	DT_{50} > 1 year, +25°C, pH 4,7 and 9
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Half-life 72.9 years. Indirect Photolysis: t½ = 2.3 days
Readily biodegradable (yes/no)	Yes
Biodegradation in seawater	Not applicable
Non-extractable residues	Not applicable
Distribution in water / sediment systems (active substance)	The active substance is highly water soluble and has a low P_{ow}. However, studies on absorption/desorption to soil show high K_{oc}. The substance ionises in the terrestrial environment which will cause it to strongly adhere to soil or sediment. Background concentrations of < 0.04 – 0.2 mg/l in river surface water and 0.025 – 0.145 mg/l in Atlantic coast seawater.
Distribution in water / sediment systems (metabolites)	The active substance is readily biodegradable.

Route and rate of degradation in soil (Annex IIIA, point VII.4, XII.1.1, XII.1.4; Annex VI, para. 85)

Mineralization (aerobic)	Studies on absorption/desorption to soil show high K_{oc}. The substance ionises in the terrestrial environment which will cause it to strongly adhere to soil, where it will be rapidly biodegraded.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	No studies available
Field studies (state location, range or median with number of measurements)	No studies available
Anaerobic degradation	No studies available
Soil photolysis	No studies available
Non-extractable residues	No studies available
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	No studies available
Soil accumulation and plateau concentration	In a radio-labelled study, there was substantial disappearance from soil in seven days.

Adsorption/desorption (Annex IIA, point XII.7.7; Annex IIIA, point XII.1.2)

Ka , Kd

Ka_{oc} , Kd_{oc}

pH dependence (yes / no)

(if yes type of dependence)

Soil type	K_d	Log K_{oc}	
OECD soil type 2	8.97	2.67	
OECD soil type 3	14.1	2.64	
OECD soil type 4	10.9	2.56	
OECD soil type 5	22.9	3.18	
OECD soil type 7	8.68	1.88	

Fate and behaviour in air (Annex IIIA, point VII.3, VII.5)

Direct photolysis in air	No data available Indirect: t½ = 2.3 days
Quantum yield of direct photolysis	No data available
Photo-oxidative degradation in air	DT_{50} t½ = 2.3 days
Volatilization	No data available. However, a very low vapour pressure would suggest that this would be low.

Monitoring data, if available (Annex VI, para. 44)

Soil (indicate location and type of study)	No data available
Surface water (indicate location and type of study)	Background concentrations of < 0.04 – 0.2 mg/l in river surface water and 0.025 – 0.145 mg/l in Atlantic coast seawater.
Ground water (indicate location and type of study)	No data available
Air (indicate location and type of study)	No data available

CHAPTER 5: EFFECTS ON NON-TARGET SPECIES

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Species	Time-scale	Endpoint	Toxicity
Fish			
Rainbow trout	96h	LC_{50}	>100 mg/l
Invertebrates			
Daphnia magna	48hr	EC_{50}	34 mg/l
Algae			
Scenedesmus subspicatus	72hr	EC_{b50} EC_{r50}	1.9 mg/l 2.0 mg/l
Microorganisms			

Activated sewage sludge	3h	EC_{50}	370 mg/l

Effects on earthworms or other soil non-target organisms

Acute toxicity to (Annex IIIA, point XIII.3.2)	No data
Reproductive toxicity to (Annex IIIA, point XIII.3.2)	No data

Effects on soil micro-organisms (Annex IIA, point 7.4)

Nitrogen mineralization	No data
Carbon mineralization	/

Effects on terrestrial vertebrates

Acute toxicity to mammals (Annex IIIA, point XIII.3.3)	No data
Acute toxicity to birds (Annex IIIA, point XIII.1.1)	No data
Dietary toxicity to birds (Annex IIIA, point XIII.1.2)	No data
Reproductive toxicity to birds (Annex IIIA, point XIII.1.3)	No data

Effects on honeybees (Annex IIIA, point XIII.3.1)

Acute oral toxicity	No data
Acute contact toxicity	No data

Effects on other beneficial arthropods (Annex IIIA, point XIII.3.1)

Acute oral toxicity	No data
Acute contact toxicity	No data
Acute toxicity to	No data

Bioconcentration (Annex IIA, point 7.5)

Bioconcentration factor (BCF)	BCF estimated from Log P_{ow} to be 1.27×10^{-4}
Depuration time (DT_{50}) (DT_{90})	Not available
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not available

Chapter 6: Other End Points

APPENDIX II: LIST OF INTENDED USES

Object and/or situation	Member State or Country	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks
				Type	Conc. of a.s.	Method Kind	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	(m)
Active against viruses – PT2	All	*Kleenex*® *Anti-Viral Tissues*	Respiratory Syncytial Virus (RSV), Influenza A and Influenza B	Facial tissues	7.5% w/w*	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

* Please find in the confidential part of the dossier, explanation on what the dose in the tissue is.

APPENDIX III: LIST OF STUDIES

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

Author(s)	Section No / Reference No	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Unpublished	Data Protection Claimed (Yes/ No)	Owner
A Wiley-Interscience Publication	Supporting information for the active substance	1993	: Chlorocarbons and Chlorohydrocarbons to Combustion Technology, Encyclopedia of Chemical Technology, Fourth Edition, Vol. 6	N	
Abbott T.R.	A6.2(10)	1983	: Changes in serum calcium fractions and citrate concentrations during massive blood transfusions and cardiopulmonary bypass, British Journal of Anaesthesia, Vol. 55, p 753-759, 1983	N	
Anbar M. and Neta P.	A7.3.1	1967	A Compilation of Specific Bimolecular Rate Constants for the Reactions of Hydrated Electrons, Hydrogen Atoms and Hydroxyl Radicals with Inorganic and Organic Compounds in Aqueous Solution	N	
Anderson B.G.	Supporting information for Section 7.4.1.2	1944	: The Toxicity Thresholds of Various Substances Found in Industrial Wastes as Determined by the Use of Daphnia magna, Sewage Works J., Vol. 16, No. 6, p 1156-1165, 1944	N	
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Baxter, K.A	B5.10.2(3)	2002	: Virucidal Efficacy of Facial Tissue for Treated and Untreated Tissue Against Influenza A, ATCC VR-1469, Hill Top Research Inc, 02-120048-106, (Un)	N	
Baxter, K.A	B5.10.2(5)	2002	: Virucidal Efficacy of Facial Tissue for Treated and Untreated Tissue Against Respiratory Syncytial Virus, ATCC VR-26, Hill Top Research Inc, 02-120091-106, (Un)	N	
Baxter, K.A	B5.10.2(4)	2002	: Virucidal Efficacy of Facial Tissue for Treated and Untreated Tissue Against	N	

			Influenza B, CDC ID# 2001701156, Hill Top Research Inc, 02-120088-106, (Un)		
Baxter, K.A	B5.10.2(1)	2002	: Virucidal Efficacy of Facial Tissue for Treated and Untreated Tissue Against Rhinovirus IA, ATCC VR-1364, Hill Top Research Inc, 02-120089-106, (Un)	N	
Baxter, K.A	B5.10.2(2)	2002	: Virucidal Efficacy of Facial Tissue for Treated and Untreated Tissue Against Rhinovirus 2, ATCC VR-482, Hill Top Research Inc, 02-120090-106, (Un)	N	
Barros M.J et al	A6.12.2(3)	1990	: Importance of Inspiratory Flow Rate in the Cough Response to Citric Acid Inhalation in Normal Subjects, Clinical Science, 78 (5), p 521-525, 1990	N	
Baruch S.B. et al	A6.2(13)	1975	: Renal Metabolism of Citrate, Medical Clinics of North America, Vol. 59, No. 3, p 569-582, 1975	N	
BIBRA	Supporting information for the active substance	1993	: Toxicity Profile: Citric ac id and its common salts, BIBRA Information Services Ltd., BIBRA	N	
Bonting S.L., Jansen B.C.	A6.5(2), A6.8.2(1)	1956	: The effect of a prolonged intake of phosphoric acid and citric acid in rats, Voeding, 17: 137-148	N	
Bringmann G. and Kuhn R.	Supporting information for Section 7.4.1.4	1980	: Comparison of the Toxicity Thresholds of Water Pollutants to Bacteria, Algae and Protozoa in the Cell Multiplication Inhibition Test, Water Research, Vol. 14, No. 3, p 231-241, 1980	N	
Bringmann G. and Kuhn R.	A7.4.1.2(2)	1982	: Results of toxic action of water pollutants on Daphnia magna strauss treated by an improved standardised procedure, Z. Wasser Abwasser Forsch, 15:1-6	N	
Brynhildsen L. and Rosswall Th.	Doc II B 3.3.3	1997	EFFECTS OF METALS ON THE MICROBIAL MINERALIZATION OF ORGANIC ACIDS Department of Water and Environmental Studies, Link¨oping University, S-581 83 Link¨oping, Sweden (Received 13 February, 1995; accepted 3 December, 1995) Water, Air, and Soil Pollution 94: 45–57, 1997.	N	
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Creach P.	Doc II B 3.3.3	1955	C.R. Acad. Sci. Paris 240, 2551-2553	N	
Daubert T.E. and Danner R.P.	A3.1.1(2)	1995	: Thermodynamic Properties of Pure Chemicals, Data Compliant, 1995, Taylor & Francis	N	
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Denlinger J.K	A6.2(4)	1976	: Hypocalcaemia during rapid blood transfusion in anaesthetised man, British Journal of Anaesthesia, Volume 48, p 995-1000, 1976	N	
Dick, E.C.	B5.10.2(7)	1986	: Interruption of Transmission of Rhinovirus Colds among Human Volunteers Using Virucidal Paper Handkerchiefs, , , (Un)	N	
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Dzik W.H et al	A6.2(1)	1988	: Citrate toxicity during massive blood transfusion, Transfusion Medicine Reviews, Vol. 2, No. 2, pp 76-94, 1988	N	
EPA	Supporting information for the active substance	1992	: Citric Acid, EPA Reregistration Eligibility Document (RED), 33756	N	
EPA	Supporting information for the active substance	2004	: Citrate Esters; Exemption from the Requirement of a Tolerance, Federal Register, September 29, 2004 (vol. 69, No. 188, p 58066-58071)	N	
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Greim, H	Document II	2001	: Citric acid and its alkali metal salts. Occupational Toxicants. Critical evaluation for MAK Values and Classification of Carcinogens., Wiley-VCH Verlag GmbH, Weinheim.,	N	Greim, H
Grant W.M.	Supporting information for the active substance	1986	: Toxicology of the Eye, Charles C Thomas, Publisher, Third Edition	N	
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Hayden, G.F.	B5.10.2(8)	1985	: The Effect of Placebo and Virucidal Paper Handkerchiefs on Viral Contamination of the Hand and Transmission of Experimental Rhinovirus Infection, Kimberly Clark, , (Un)	N	
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Jaffe	Supporting information for the active substance	1995	Jaffe toxicol. Ind. Health 11(5): 543	N	
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OECD	A3.2.1, A3.3/A6.1.1(2)/A6.1.1(3)/A6.7/A6.8.1(1)/A6.8.1(3)/A7.1.1.2.1/A7.1.1.2.2(1)/A7.2.1/A7.4.2	2001	: Citric acid: CAS No. 77-92-9 OECD ICCA HPV programme (SIDS dossier) , OECD UNEP Publications,	N	
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Simpson D.P.	A6.2(12)	1983	: Citrate Excretion: a Window on Renal Metabolism, Am. J. Physiol., 244 (Renal Electrolyte Physiol. 13): F223-F234, 1983	N	
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Various	Supporting information for the active substance	2004	: The Citric Acid Cycle, http://people.unt.edu, Internet	N	
Various	B7.3	2006	: Information on Sodium Lauryl Sulphate, Internet search,	N	
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Youchen Z. and Zhiqiang C.	Supporting information for the active substance	1987	: Teratogenic Effect of Citric Acid in Rats, Acta Academiae Medicinae Shanghai, Vol. 14, No. 3, p 195-198, 1987	N	