RISK PROFILE

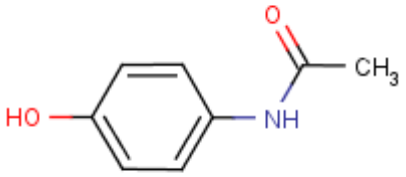
Acetaminophen

CAS No.103-90-2

Date of reporting 14.02.2012

Content of document

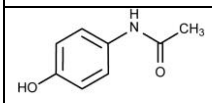
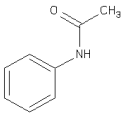
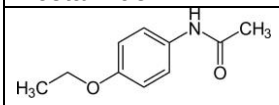
1. Identification of substance

Chemical name (IUPAC):	N-(3-hydroxyphenyl)acetamide
INCI	Acetaminophen
Synonyms	4-Hydroxyacetanilide, N-Acetyl-p-aminophenol, Paracetamol
CAS No.	103-90-2
EINECS No.	203-157-5
Molecular formula	$C_8H_9NO_2$
Chemical structure	
Molecular weight	151.2
Contents (if relevant)	
Physiochemical properties	Appearance: Solid, white crystalline substance Density: 1.3 g/cm^3 Boiling point: 387.8 °C at 760 mmHg Melting point: 169-170°C Flash point: 188.4 °C Log P_{ow}: 0.49 Vapor pressure: 1.43E-06 mmHg at 25°

	Solubility (water): 12.78 g/L pH: 5.5 - 6.5 References: (IPCS [online]; SpecialChem [online]; Granberg et al., 1999).

2. Uses and origin

Uses	➢ **Cosmetic products:** *Functions according to:* o CosIng database (the European Commission database with information on cosmetic substances and ingredients): "Skin conditioner" - Maintains the skin in good condition (CosIng [online]). o Other Acetaminophen finds use also as a H_2O_2 stabilizer (NTP 1993, Lewis RJ 2001), and may therefore, potentially, be present in some of the cosmetic products that contain H_2O_2. *Frequency of use* In a search at Codecheck.info, Acetaminophen showed up as an ingredient in a total of 15 different cosmetic products, whereas none was found at EWG's Skin Deep. • Oxidative (permanent) hair dyes /the is "developer" based on hydrogen peroxide / hair bleachers (13 products) • a shampoo and a hair styling product (2 products) (Codecheck [online]; EWG's Skin Deep [online]). *As H_2O_2 stabilizer* Because of its H_2O_2 stabilizing property it is assumed that Acetaminophen occurs to some extent in cosmetic products wherein H_2O_2 is employed as an ingredient. The cosmetics then concerned would mainly be the oxidative hair coloring products the hair bleaching products and possibly also to some degree the tooth bleaching products. Because of lack of data we in accordance with SCCS guidance apply the default it is present in every oxidative hair coloring / bleaching product currently being placed on the market in Europe. The Codecheck database, mentions 13 hair coloring /hair bleaching products that according to the list of ingredients contain Acetaminophen. The molecule is together with hydrogen peroxide in these products. These 13 products all contain 10 – 25 different ingredients each. The Acetanilide is mostly in the 9^{th} - 8^{th} place in the list of ingredients of the developer- and we judge that the concentration is roughly of the same magnitude as that of two other structurally very similar H_2O_2 stabilizer Acetanilide and Phenacetin

Stabilizer [1]	Number of product in Codecheck containing it together with H_2O_2	Concentration
 Acetaminophen	13	Assumed: 0.4 % in developer
 Acetanilide	2	0.4 % in developer (industry application)
 Phenacetin	1	In developer: 0.26 % ([2]). 0.05 - 0.3 % ([3]) 0.05 (MSDS)

There are about 300 products in the Codecheck database that contains hydrogen peroxide according to the list of ingredients. With few exceptions it goes about oxidative hair coloring products and hair bleaching products. The limited listing of Acetaminophen as concerns these products we assume is due to the fact that most marketers think it not obligatory to declare auxiliary substances in raw material going into cosmetics as ingredients.

Concentrations being applied

According to the distributor of one of the other hair products, acetaminophen is added as a stabilizer and for the skin conditioning effect at concentration up to 0.1 %. At the present, we have no information of the concentrations used in other products.

- **Food and drinking water**

Data not retrieved.

- **Medicinal products/applications**

Acetaminophen, also known as paracetamol, is the most widely used analgesic-antipyretic medication in the world. Acetaminophen is available as a registered drug in numerous trade-name preparations for oral, rectal and parenteral use. It is also found in many preparations combined with other drugs (American Academy of Pediatrics, 2001).

- **Other consumer products**

[1] Two other much used stabilizers sodium stannate and tetrasodium pyrophosphate.
[2] http://www.freepatentsonline.com/3607053.pdf
[3] http://osdir.com/patents/Dyeing-textiles/Agent-oxidative-treatment-transparent-gel-form-07534272.html

	Other uses include the manufacture of azo dyes and photographic chemicals (NTP, 1993).
Origin Natural (exo /endo) Synthetic	Acetaminophen is a synthetic compound and is not known to occur naturally.

3. Regulation

Norway	No regulation[4].
EU	No regulation.
Other	No regulation.

4. Relevant toxicity studies

Absorption Skin GI tractus	**Skin** No dermal absorption data is available, and a default value of 100% will therefore be used (SCCS, 2010). **GI tractus** It is estimated that the human oral bioavailability of acetaminophen is 60-100% (Eandi et al., 1984; Norsk Legemiddelhåndbok [online]).
Distribution	Acetaminophen is rapidly and relatively uniformly distributed in the tissues (Gwilt et al., 1963). Binding to plasma proteins is considered to be minimal (Gazzard et al., 1973). Acetaminophen reaches peak plasma levels in 30 to 120 minutes and has a half-life of one to three hours in both humans and experimental animals (Clements et al., 1978).
Metabolism	Acetaminophen is extensively metabolised and only 2-5% of the therapeutic dose is excreted unchanged in the urine (Forrest et al., 1982). The most important site for biotransformation of orally administered acetaminophen is the liver, where the major metabolites are glucuronide and sulphate conjugates. Under normal doses, only a limited amount, 3-10%, of acetaminophen is converted by CYP enzymes, more specifically CYP2E1 and CYP3A4, to the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). This compound is under normal doses rapidly detoxified by conjugation with reduced glutathione, which are further transformed to mercapturic acid conjugates. With high doses of acetaminophen, the glutathione deposits may be depleted, and the glucuronidation and sulfation pathways become saturated (Galinsky et al., 1981). This will in turn lead to an increase of the toxic metabolite NAPQI, which can bind to macromolecules which results in hepatocellular necrosis (Vandenberghe, 1996). The kidney and gut are two other important sites for acetaminophen metabolism (Josting et al., 1976; Mitchell et al., 1977). Acetaminophen causes acute renal tubular necrosis by a similar mechanism as seen in the liver (Mitchell et al., 1977). In the intestine, the glucuronide conjugate can be hydrolysed to the parent compound which thereby can go through enterohepatic circulation (Grafström et al., 1979).

[4] The Norwegian medicinal products agency considers acetaminophen a medicinal remedy. Because of that up till 2008 topical products containing the substance were considered medicines – meaning a topical product containing it were automatically classified a medicine. This regime has since been lifted.

Excretion	Urinary excretion is the predominant pathway of elimination for all acetaminophen metabolites. However, excretion in the bile is of importance for the glucuronid and glutathione conjugates (Hjelle et al., 1984).
Local toxic effects Irritation Sensitivity	Acetaminophen is not expected to produce skin or eye irritation and does not have any significant sensitization potential (Gregg et al., 1994).
Systemic toxic effects:	Most of the information on the effects of acute exposure of acetaminophen is from cases of intentional oral overdosing; death is usually attributed to liver failure. There is no available information on inhalation or dermal exposure. The systemic toxic effects of acetaminophen exposure have been reviewed by the National Toxicology Program (NTP, 1993).
Acute and repeated doses	The toxic dose of acetaminophen is highly variable. Higher doses than the recommended maximum dose lead to increasing risk of toxicity, especially hepatotoxicity. In adults, single doses above 10 g or 200 mg/kg bw, whichever is lower, has a reasonable likelihood of causing toxicity (Dart et al., 2006). A toxic dose of acetaminophen in high risk patients, such as chronic heavy alcohol abusers and patients with impaired kidney or liver function is generally considered to be 75 mg/kg (NPIS, 1998).
Mutagenicity /genotoxicity	Acetaminophen is not mutagenic either in bacteria or in mammalian cells. Acetaminophen has been shown to increase the frequency of chromosomal damage in mammalian cell lines, isolated human lymphocytes and experimental animals (Rannug et al., 1995). This might imply that acetaminophen is in fact genotoxic; however, the results are inconclusive (IARC, 1999).
Carcinogenicity	IARC have evaluated the carcinogenicity of acetaminophen and have concluded with the following: There is *inadequate evidence* in humans and experimental animals for the carcinogenicity of acetaminophen. Acetaminophen is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1999). The National Toxicology Program assessed the toxicity and carcinogenicity of oral exposure to acetaminophen in rats and mice. They conducted a 14 day, 13 week and a two year study. Based on the two year study they concluded that there was no evidence of carcinogenic activity of acetaminophen in male F344/N rats that received 600, 3,000, or 6,000 ppm. There was equivocal evidence of carcinogenic activity of acetaminophen in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was no evidence of carcinogenic activity of acetaminophen in male and female $B6C3F_1$ mice that received 600, 3,000, or 6,000 ppm. The average amount of acetaminophen consumed per mouse per day was approximately 90, 450 or 1000 mg/kg bw for low-, mid-, high-dose males and 110, 600 or 1200 mg/kg bw for low-, mid-, high-dose females (NTP, 1993).
Reproductive toxicity/ Teratogenicity	There is evidence that overdoses of acetaminophen during pregnancy increases the risk for adverse reproductive outcomes (e.g. spontaneous abortions, a variety of malformations, fetal distress and hepatic and renal toxicity in infants) (Friedman et al., 1994).
Other effects	Allergic reactions to acetaminophen administered orally are rare. However, some cases of anaphylactic reactions after intake of acetaminophen have been reported (Gowrinath et al., 2004; Bachmeyer et al., 2002).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	**The NOAEL and NOEL values are based on data obtained from clinical trials.** A toxic dose of acetaminophen in high risk patients is generally considered to be 75 mg/kg bw (NPIS, 1998). LOAEL = 75 mg/kg bw **NOAEL**: LOAEL/3 [5] = 75 mg/kg bw/3 = 25 mg/kg bw 25 mg/kg bw is equal to a total dose of 1500 mg acetaminophen for a person weighing 60 kg. Based on the existing literature, Gibb and co-workers (2008) concluded that the lowest effective plasma concentration was likely to be 5 mg/L for fever and 10 mg/L for pain (Gibb et al., 2008). Volume of distribution for acetaminophen is 0.9L/kg (Forrest et al., 1982). This means that with a blood plasma concentration of 5mg/L, the total amount of acetaminophen in the body is 4.5 mg/kg (see annex for calculation). As ingredients used in cosmetic products should not exert a systemic pharmacological effect, it is appropriate to use the lowest identified effect dose level as LOEL in risk assessment of these bioactive compounds. Removal of pain and lowering of fever might reduce the body's alert mechanism and have an impact on the defence mechanisms. LOEL: 4.5 mg/kg bw/day A NOEL value can be obtained by dividing LOEL by 3 [1]: **NOEL =** LOEL/3 = 4.5 mg/kg bw/day / 3 = 1.5 mg/kg bw/day

[5] When making use of the Lowest Observed (Adverse) Effect Level (LO(A)EL) instead of the NO(A)EL, the SCCS usually takes into consideration an additional factor of 3 in the calculation of the MoS. Scientific Committee on Consumer Safety, The SCCS'S notes of guidance for the testing of cosmetic ingredients and their safety evaluation, the 7th revision, p 54.

Exposure cosmetic products	**Systemic exposure dose (SED) for acetaminophen in humans:** • ***Shampoo*** Calculated relative daily exposure (mg/kg bw/day) : 1.51[6] Dermal absorption, default value, SCCS: 100% = 1 Concentration in product: 0.1% = 0.001 [7] Calculation of SED: 1.51 mg/kg bw/day x 1 x 0.001 = **0.0015 mg/kg bw/day** • ***Hair styling product*** Calculated relative daily exposure (mg/kg bw/day) : 5,74 [2] Dermal absorption, default value, SCCS: 100% = 1 Maximum concentration in product: 0.1% = 0.001 Calculation of SED: 5.74 mg/kg bw/day x 1 x 0.001 = **0.0057 mg/kg bw/day** • ***Oxidative hair dyes***[8] Amount applied (default): 20 mg/cm^2 Scalp surface area: 580 cm^2 Retention factor: 0.1 Concentration on scalp after mixture: 0.2% = 0.002 [9] Body weight: 60 kg Total amount: 20 mg/cm^2 x 580 cm^2 = 11,600 mg Daily exposure to the product: (11,600 mg/60 kg) x 0.1 = 19 mg/kg bw/day Calculation of SED: 19 mg/kg bw/day x 1 x 0.002 = **0.038 mg/kg bw/day** **Overall SED**: 0.0015 + 0.0057 + 0.038 = **0.045 mg/kg bw/day**
Margin of Safety (MoS)	NOEL: 1.5 mg/kg bw ***MoS for acetaminophen in shampoo:*** SED: 0.0015 mg/kg bw/day MoS: 1.5/ 0.0015 = 1000 ***MoS for acetaminophen in hair styling products:*** SED: 0.00574 mg/kg bw/day MoS: 1.5/0.00574 = 260 ***MoS for acetaminophen in oxidative hair dyes:***

[6] Estimated daily exposure levels for different cosmetic product types according to Colipa data [SCCNFP/0321/02; Hall et al. 2007, 2011].
[7] Note: the used concentration is for illustrative purposes, as the exact concentration in product is unknown.
[8] Note: it has not been taking into consideration that hair dyes are used only once per month. For simplicity the SCCS use the premise the product is used on a daily basis.
[9] Note: the exact concentration in the products is unknown. However, other compounds used as H_2O_2 stabilizer, such as acetanilide, are present in concentrations of 0.2 % in the final product.

	SED: 0.038 mg/kg bw/day 1.5/0.038 = 39 ***MoS for overall exposure for acetaminophen from cosmetic products:*** Total SED: 0.045 mg/kg bw/day MoS: 1.5/0.045 = 33

6. Other sources of exposure than cosmetic products

Food stuffs	Data not retrieved
Pharmaceuticals	In many countries, including Norway, acetaminophen is available without prescription. The conventional oral dose for adults is 500 - 1000 mg. Dosing may be repeated every 4 hour as necessary, but the total daily dose should not exceed 3 gram. For 3-7 years old children the recommended dose is 250 mg three times a day, and for 7-12 years old children, 500 mg three times a day (Norsk Legemiddelhåndbok [online]) Acetaminophen is also available for administration by rectal and intravenous routes, although the latter is not widely used.
Other sources	***Occupational exposure*** Occupational exposure may occur during production of acetaminophen and during its use as an analgesic and antipyretic, chemical intermediate or stabilizer (IARC, 1999). The permissible exposure limit (PEL) for acetaminophen has been set to 10mg/m^3 within an eight hour period (Gregg et al., 1994).
Adverse side effects - from uses other than cosmetics	**Maternal intake and increased risk of cryptorchidism, asthma and allergic reactions** The maternal intake of acetaminophen for more than 4 weeks during pregnancy, especially during the first and second trimesters was associated with a moderate increase in the occurrence of cryptorchidism (Jensen et al., 2010). A possible associated between the use of acetaminophen under pregnancy and the risk of developing asthma and allergic reactions later in life has been implicated (Garcia-Marcos et al., 2011; Eyers et al., 2011; Etminan et al., 2009). These findings are important because more than 50 % of pregnant women in the western world are using pain relieving drugs, with the majority using acetaminophen (Werler et al., 2005). **Self-inflicted injury:** Acetaminophen is one of the most frequently used drugs in intentional overdoses (Gunnell et al., 2000). **Interactions with other compounds/pharmaceuticals:** Acetaminophen has several interactions with other compounds and pharmaceuticals. Those which increase the biotransformation of acetaminophen to a toxic metabolite are isoniazid (an antituburculosis medication) and chronic use of alcohol. Simultaneously intake of acetaminophen and warfarin (an anticoagulant), increase the effect of warfarin. Metoclopramide (an antiemetic and gastroprokinetic agent), increases the absorption of acetaminophen (Felleskatalogen [online]).

7. Assessment

Acetaminophen is a widely used non-prescription pain reliever. In cosmetics, acetaminophen is used only to a limited extent. The toxic effects of acetaminophen occur at doses far larger than those used in cosmetics. However, there are some aspects that need to be considered when assessing the safety of acetaminophen in cosmetics:

i) Anaphylactic reactions are possibly life threatening, and have been reported after oral medicinal use of acetaminophen. However, in light of the widespread use of this drug, it seems to be a very rare side-effect, and will probably represent a negligible risk at the low exposure doses from cosmetics.
ii) Acetaminophen is commonly used and the recommended daily drug dose has the potential to cause unwanted effects. Any additional contribution from cosmetics to the total exposure of acetaminophen might increase the risk of side-effects.

It is desirable to keep the exposure of acetaminophen from cosmetics at a level which do not or only to a minimum, causes or increases the risk for unwanted effects. Thus, we chose to use the lowest effective plasma concentration dose divided by three as a NOEL value. We have estimated the margin of safety (MoS) for three different cosmetic product categories that contain acetaminophen: i) oxidative and permanent hair dyes, ii) shampoo, and iii) hair styling product. Since the NOEL is based on human data, a MoS of 10 is sufficient as a safety margin.

MoS for overall exposure for acetaminophen from cosmetic products: 33

The overall systemic exposure dose from cosmetics based on our calculation is 0.045 mg/kg bw/day, which yields a MoS above the minimum requirement of 10. The overall systemic dose is low in comparison to the doses of acetaminophen used as a pharmaceutical (50 mg/kg bw/day (3000 mg/60 kg)). The exposure of acetaminophen from cosmetics and pharmaceuticals combined (3002 mg/day (50.045 mg/kg bw/day x 60 kg)), does not yield a toxic dose. We consider that the exposure of acetaminophen from cosmetics at the specified concentrations do not or only to a minimum increase the risk of side-effects.

8. Conclusion

We consider that acetaminophen is safe for use in cosmetics at specified concentrations. We propose the following usage limits for acetaminophen in cosmetic products:

Oxidative hair dyes (on scull after mixing):	0.2 %
Shampoo:	0.1 %
Leave-on hair styling product:	0.1 %

9. References

Articles and documents:

American Academy of Pediatrics. Committee on Drugs. Acetaminophen toxicity in children. Pediatrics. 2001 Oct;108(4):1020-4.

Bachmeyer C, Vermeulen C, Habki R, Blay F, Leynadier F. Acetaminophen (paracetamol)-induced anaphylactic shock. South Med J. 2002 Jul;95(7):759-60.

Clements JA, Heading RC, Nimmo WS, Prescott LF. Kinetics of acetaminophen absorption and gastric emptying in man. Clin Pharmacol Ther. 1978 Oct;24(4):420-31.

Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, Caravati EM, Wax PM, Keyes DC, Woolf AD, Scharman EJ, Booze LL, Troutman WG; American Association of Poison Control Centers. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila). 2006;44(1):1-18.

Eandi M, Viano I, Ricci Gamalero S. Absolute bioavailability of paracetamol after oral or rectal administration in healthy volunteers. Arzneimittelforschung. 1984;34(8):903-7.

Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. Chest. 2009 Nov;136(5):1316-23.

Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. Clin Exp Allergy. 2011 Apr;41(4):482-9.

Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet. 1982 Mar-Apr;7(2):93-107.

Friedman JM, Polifka JE. Teratogenic Effects of drugs: A resource for clinicians. TERIS, Baltimore, The Johns Hopkins University Press, 1994.

Galinsky RE, Levy G. Dose- and time-dependent elimination of acetaminophen in rats: pharmacokinetic implications of cosubstrate depletion. J Pharmacol Exp Ther. 1981 Oct;219(1):14-20.

Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V. Early exposure to acetaminophen and allergic disorders. Curr Opin Allergy Clin Immunol. 2011 Jun;11(3):162-73.

Gazzard BG, Ford-Hutchinson AW, Smith MJ, Williams R. The binding of paracetamol to plasma proteins of man and pig. J Pharm Pharmacol. 1973 Dec;25(12):964-7.

Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child. 2008 Mar;93(3):241-7.

Gowrinath K, Balachandran C. Anaphylactic reaction due to paracetamol. J Indian Med Assoc. 2004 Apr;102(4):223, 226.

Grafström R, Ormstad K, Moldéus P, Orrenius S. Paracetamol metabolism in the isolated perfused rat liver with further metabolism of a biliary paracetamol conjugate by the small intestine. Biochem Pharmacol. 1979 Dec 15;28(24):3573-9.

Granberg RA and Rasmuson ÅC. Solubility of Paracetamol in Pure Solvents. *J. Chem. Eng. Data*, 1999, *44* (6), pp 1391–1395.

Gregg N, Rajan B, Wright A, and White J. Paracetamol: Criteria document for an occupational exposure limit. Health and Safety Executive, HSE Books, Sudbury, United Kingdom, 1994.

Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav. 2000 Winter;30(4):313-26.

Gwilt JR, Robertson A, Goldman L, Blanchard AW. The absorption characteristics of paracetamol tablets in man. J Pharm Pharmacol. 1963 Jul;15:445-53.

Hjelle JJ, Klaassen CD. Glucuronidation and biliary excretion of acetaminophen in rats. J Pharmacol Exp Ther. 1984 Feb;228(2):407-13.

Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, Henriksen TB, Olsen J. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology. 2010 Nov;21(6):779-85.

IARC (International Agency for Research on Cancer). Paracetamol. In: IARC Monographs on the evaluation of carcinogenic risks to humans, vol. 73. Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. Summary of data reported and evaluation. Lyon: 1999.

Josting D, Winne D, Bock KW. Glucuronidation of paracetamol, morphine and 1-naphthol in the rat intestinal loop. Biochem Pharmacol. 1976 Mar 1;25(5):613-6.

Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 14th Edition. John Wiley & Sons, Inc. New York, NY 2001., p. 10

Mitchell JR, McMurtry RJ, Statham CN, Nelson SD. Molecular basis for several drug-induced nephropathies. Am J Med. 1977 Apr;62(4):518-26.

NPIS. Management of acute paracetamol poisoning, Guidelines agreed by the UK National Poisons Information Service. London, 1998.

NTP (National Toxicology Program). NTP Toxicology and Carcinogenesis Studies of Acetaminophen (CAS No. 103-90-2) in F344 Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 1993 Jan;394:1-274.

Rannug U, Holme JA, Hongslo JK, Srám R. International Commission for Protection against Environmental Mutagens and Carcinogens. An evaluation of the genetic toxicity of paracetamol. Mutat Res. 1995 Mar;327(1-2):179-200.

SCCS (Scientific Committee on Consumer Safety). The SCCS's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 7th revision. 2010.

Vandenberghe, J. Hepatotoxicology: Mechanisms of liver toxicity and methodological aspects. In Toxicology, Principles and Applications (R. J. M. Niesink, de J. Vries, and M. A. Hollinger, Eds.), chapter 23, 702–723, 1996. CRC Press, Inc., Boca Raton, FL.

Wang M, Shu B, Bai WX, Liu J, Yao J, Pan WN, Pan YY. A 4-week oral toxicity study of an antiviral drug combination consisting of arbidol and acetaminophen in rats. Drug Chem Toxicol. 2010 Jul;33(3):244-53.

Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 1):771-7.

Online

Codecheck © 2011. Available at: http://www.codecheck.info/ (accessed 5th September 2011).

CosIng, European Commission, Health and Consumers, Cosmetics. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/) (accessed 5th September 2011).

EWG's Skin Deep © Cosmetic Safety Database. Environmental Working group. Available at: http://www.ewg.org/skindeep/ (accessed 27th October 2011).

Felleskatalogen. Available at: http://213.225.88.53/felleskatalogen/show.do?filename=/content/interaksjons-register/N02BE01.html&printable=1&frameset=0&href=1&highlight=0&thin=0 (accessed 12th September 2011).

IPCS. International Programme on Chemical Safety. Available at: http://www.inchem.org/documents/pims/pharm/pim396.htm (accessed 12th September 2011).

Norsk Legemiddelhåndbok, Paracetamol. Available at: http://www.legemiddelhandboka.no/xml/) (accessed 19th September 2011).

SpecialChem website. Available at: http://www.specialchem4cosmetics.com/services/inci/ingredient.aspx?id=179 (accessed 12th September 2011).

10. Annexes

Calculation of the lower therapeutic dose:

Lowest drug blood plasma concentration that yield a therapeutic effect: 5 mg/L
V_D: 0.9 L/kg

V_D = Total amount of drug in the body / Drug blood plasma concentration

Total amount of drug in the body = V_D x Drug blood plasma concentration
= 0.9 L/kg x 5 mg/L
= **4.5 mg/kg**