

## RISK PROFILE

# Acetanilide

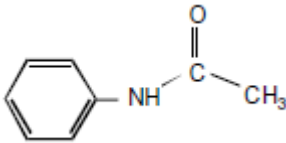
CAS No. 103-84-4

Date of reporting 26.05.2011

### Content of document

1. Identification of substance	Page 1
2. Uses and origin	Page 2
3. Regulation	Page 5
4. Relevant toxicity studies	Page 5
5. Exposure estimates and critical NOAEL/NOEL	Page 7
6. Other sources of exposure than cosmetic products	Page 8
7. Assessment	Page 11
8. Conclusion	Page 12
9. References	Page 13
10. Annexes	Page 15

### 1. Identification of substance

<b>Chemical name (IUPAC):</b>	Acetanilide
<b>INCI</b>	Acetanilid
<b>Synonyms</b>	N-phenylacetamide
<b>CAS No.</b>	103-84-4
<b>EINECS No.</b>	203-150-7
<b>Molecular formula</b>	C <sub>6</sub> H <sub>5</sub> NH(COCH <sub>3</sub> )
<b>Chemical structure</b>	
<b>Molecular weight</b>	135.16
<b>Contents (if relevant)</b>	
<b>Physiochemical properties</b>	Appearance: solid, white crystalline substance, Density: 1.22 g/cm <sup>3</sup> (20 °C) Boiling point: 304 °C (1013 hPa) Melting point: 115 °C Flash point: 173 °C DIN 51758 log P <sub>ow</sub> : 1,16 (no bioaccumulation; log P <sub>ow</sub> 1-3) Vapor pressure: 0.002 hPa (20 °C) Solubility (water): 5 g/l (20 °C) pH: 5 - 7 (at 10 g/l, H <sub>2</sub> O, 25 °C)  References: (1, 2)

## 2. Uses and origin

<b>Uses</b>	<p>➤ <b>Cosmetic products:</b></p> <p><b>Functions according to</b></p> <ul style="list-style-type: none"><li>○ <i>CosIng database:</i> “Masking”- reduces or inhibits the basic odor or taste of the product “Stabilizing” - improves ingredients or formulation stability and shelf-life</li><li>○ <i>In-market surveys by competent authorities</i> Perfuming (masking),  H<sub>2</sub>O<sub>2</sub> stabilizer in hair coloring /bleaching products and also in tooth whitening /bleaching products</li></ul> <p><b>Concentrations being applied</b></p> <ul style="list-style-type: none"><li>○ Perfuming (masking) : maximally 0,025 % <sup>1</sup></li><li>○ H<sub>2</sub>O<sub>2</sub> stabilizer / Tooth bleaching/whitening: 0.001 - 0.5 % <sup>2</sup>.</li><li>○ H<sub>2</sub>O<sub>2</sub> stabilizer / Hair coloring: maximally 0.2 % in products placed on the scalp.</li></ul> <p>In Norway during the 80s, the cosmetics industry requested to use acetanilide as a stabilizer for H<sub>2</sub>O<sub>2</sub> in two-component hair coloring products, with one part containing H<sub>2</sub>O<sub>2</sub> and Acetanilide (up to 0.4 %) and the other part containing the dyestuff with auxiliary ingredients. These two components are normally mixed 1:1 before usage. According to the current Norwegian Cosmetics regulation (Norwegian Law and Jurisdiction), it is not allowed to use more than 0.2 % (2000 ppm) in the mixture being placed on the scalp. We cannot exclude that even in the market of today, consumers are exposed to products containing that much – or even more. The current regulation will be lifted 11 July 2013.</p>
-------------	---

<sup>1</sup> This figure is assumed taking into consideration that according to an earlier German cosmetic products regulation no more than 0,025 % was allowed. If the concentration is higher the usage becomes unacceptable for health reasons applying an sufficiently high margin of safety of 100

<sup>2</sup> Confer the USPTO Patent Application 20080044796, a teeth whitening system and a method for whitening teeth. The application can be retrieved from the internet at the address:  
<http://www.freshpatents.com/A-teeth-whitening-system-and-a-method-for-whitening-teeth-dt20080221ptan20080044796.php>

	<p><b>Frequency of use</b></p> <ul style="list-style-type: none"> <li>○ <i>Fragrance:</i> <p>Acetanilide is reported as used in fragrance compounds in 2008 (IFRA Fragrance Ingredient List<sup>3</sup>).</p> <p>When finding use as a component in a fragrance mixture Acetaldehyde is not declared – only the fragrance is. We have no data, therefore, that could indicate with what frequency it occurs in cosmetic products as a fragrance. Because of lack of data we in accordance with SCCS guidance apply the default value it is in all cosmetic products. Confer that near to all cosmetic products contain a fragrance ingredient.</p> <p>The perfuming properties of Acetanilide are also used to remove/mask unwanted odor from the product (CosIng). When employed as a separate masking ingredient Acetanilide has to appear in the list of ingredients.</p> <p>In the German database Codecheck<sup>4</sup>, one fine perfume product is mentioned that according to the list of ingredients contain Acetanilide. No products or brands listed in the EWG cosmetic database (see EWG, 2011)<sup>5</sup>; The limited listing of Acetanilide-containing perfumes 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.</p> </li> <li>○ <i>As H<sub>2</sub>O<sub>2</sub> stabilizer</i> <p>Data indicate that still Acetanilide is one of the main H<sub>2</sub>O<sub>2</sub> stabilizers.<sup>6</sup> Therefore, it is assumed that Acetanilide occurs to a large extent in cosmetic products wherein H<sub>2</sub>O<sub>2</sub> is employed as an ingredient. The cosmetics then concerned would mainly be the oxidative hair coloring products and the tooth bleaching products.</p> <p>Because of lack of data we in accordance with SCCS guidance apply the default value it is present in every oxidative hair coloring product – and also is present in every tooth bleaching H<sub>2</sub>O<sub>2</sub> based product currently being placed on the market in Europe.</p> <p>The German database Codecheck, mentions only two hair coloring products that according to the list of ingredients contain Acetanilide. It is apparent that Acetanilide is together with hydrogen peroxide. These two products contains all together 45 different ingredients. The Acetanilide is in the 14<sup>th</sup> place in the list of ingredients and we judge that the</p> </li> </ul>
--	--

<sup>3</sup> [http://www.ifraorg.org/en-us/Ingredients\\_2](http://www.ifraorg.org/en-us/Ingredients_2)

<sup>4</sup> <http://www.codecheck.info>

<sup>5</sup> <http://www.ewg.org/skindeep/ingredient/716277/ACETANILID/>

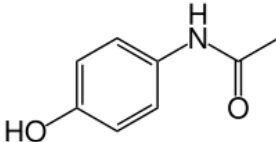
<sup>6</sup> <http://www.foodgradeH2O2.com/101/247/typ/secure/ebv3.pdf>

	<p>concentration is above 0.1 %. No products or brands listed in the EWG cosmetic database (see EWG, 2011);</p> <p>The limited listing of Acetanilide containing 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.</p> <p>➤ <b>Food</b> (data not retrieved)</p> <p>➤ <b>Medicinal products /applications</b></p> <p><u>History:</u>  For many years after its discovery in 1886, Acetanilide was used as an alternative to aspirin (i.e. acetyl salicylate) - an analgesic (painkiller) and antipyretic (fever reducing) drug to relieve e.g. headache, menstrual pain, and rheumatic pain. Under the name "Acetanilide" it formerly appeared in the formula of a number of patent medicines and over the counter drugs. In 1948, Julius Axelrod and Bernard Brodie discovered that Acetanilide is much more toxic in these applications than other drugs, causing methemoglobinemia and ultimately causing damage to the liver and kidneys. Thus, Acetanilide has largely been replaced by less toxic drugs, in particular acetaminophen (i.e. paracetamol), which is a metabolite of Acetanilide and whose use Axelrod and Brodie suggested in the same study (8).</p> <p>A product containing H<sub>2</sub>O<sub>2</sub> with Acetanilide (not over 0.017 per cent) is used in the treatment of <i>rhus dermatitis</i> (<a href="http://jama.ama-assn.org/content/146/7/612.extract">http://jama.ama-assn.org/content/146/7/612.extract</a>)</p> <p>Disinfectant:  In the hospital sector Acetanilide appears to have been used with as much as 5000 ppm (i.e. 0.5 %) in H<sub>2</sub>O<sub>2</sub> solutions (19).</p> <p>➤ <b>Other consumer products</b></p> <p><i>Household products:</i>  Acetanilide is one of the most frequently used stabilizers for hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), at concentrations in the range of 25 -250 ppm. <a href="http://www.foodgradeh2o2.com/101/247/typ/secure/ebv3.pdf">http://www.foodgradeh2o2.com/101/247/typ/secure/ebv3.pdf</a></p>
<p><b>Origin</b>  Natural (exo /endo)  Synthetic</p>	<p><b>Synthetic origin:</b>  Antipyretic analgesic drugs were derived as by-products of the German dye industry in the late nineteenth century, and Acetanilide was first made by Gerhardt in 1853 by reacting aniline with acetylchloride or acetic anhydride (2, 4, 5).</p>

### 3. Regulation

<b>Norway</b>	According to the current Norwegian Cosmetics it is not allowed to use more than 0.2 % (2000 ppm) in the mixture being placed on the scalp. The current regulation will be lifted 11 July 2013
<b>EU</b>	Acetanilide is not mentioned in any of the annexes of the EU cosmetics directive.  It for a long time – but not anymore now - appeared in lists displaying drugs in some of the EU member states and so was allowed in cosmetics on specific terms only. In Germany, in earlier times the cosmetic industry was allowed to use acetanilide up till the low limit of 0.0025 % in fragrances. This national regulation no longer exists.

### 4. Relevant toxicity studies

<b>Absorption</b> Skin GI tractus	Theoretical default value equal to 100% is applied since no experimental values is available (section 5) (SCCS recommendation)
<b>Distribution</b> <b>Metabolism</b>	<p>It was established in 1948 already that acetanilide is mainly metabolized to p-hydroksyacetanilide (paracetamol) in humans, and that paracetamol is responsible for the analgesic and antipyretic properties (7, 8).</p>  <p>Occurrence of methemoglobinemia and cyanosis after acetanilide administration is due to the small proportion of acetanilide being hydrolyzed to aniline in the human body (7).</p> <p>Acetanilide is converted to a phenolic metabolite in the human body which gives it an analgesic effect, but some is converted to aniline (aminobenzene) which is toxic. It has been found that for a single dose of 10 mg/kg of acetanilide, the half-life in blood plasma is <math>191.5 \pm 27.8</math> min. of in 25 subjects (human) and the metabolic clearance rate observed was <math>14.1 \pm 2.8</math> liter/h of (Kellerman et al., 1978; cited in ref. 6).</p>
<b>Excretion</b>	Elimination of acetanilide takes place in two phases: first through oxidation to p-hydroxy acetanilide (paracetamol) in the liver, and then through the formation of water soluble glucuronide and sulphate conjugates (conjugation in the hydroxyl group), that is excreted in the urine (ca. 70-90 % of applied dose). Under normal circumstances, a limited amount of paracetamol is converted via the microsomal enzyme system to a toxic metabolite, NAPQI (N-acetyl-p-benzoquinone imine), which in turn is detoxicated by conjugation with reduced glutathione. If glutathione is depleted, covalent binding to macromolecules may lead to chronic hepatitis (hepatocellular necrosis), mainly related to abuse,

	<p>alcoholism or cachexia (Vandenberghe, 1996, ref. 18; see also Annex 3). Detailed information is obtainable in ref. 7.</p> <p>The diagram illustrates the metabolic pathways of Acetanilide. It starts with Acetanilide (a benzene ring with an -NHCOCH<sub>3</sub> group). An arrow points to N-Acetyl p-Aminophenol (a benzene ring with an -NHCOCH<sub>3</sub> group at the top and an -OH group at the para position). From N-Acetyl p-Aminophenol, three arrows branch out: one to the right to Conjugated N-Acetyl p-Aminophenol (a benzene ring with an -NHCOCH<sub>3</sub> group at the top and an -OR group at the para position, where R = Glucuronic Acid); one down to Phenylhydroxylamine (a benzene ring with an -HNOH group at the top); and one down to Aniline (a benzene ring with an -NH<sub>2</sub> group at the top). A question mark is placed between the N-Acetyl p-Aminophenol and Phenylhydroxylamine arrows.</p>
<p><b>Local toxic effects</b> Irritation Sensitivity</p>	<p>Acetanilide is not irritating to skin but slightly irritating to the eyes in animals. Seemingly, there is no information available in the public domain for skin sensitization (6). See Annexes 1 and 2.</p>
<p><b>Systemic toxic effects</b></p> <p>Acute</p> <p>Repeated</p> <p>Mutagenicity/genotoxicity</p> <p>Carcinogenicity</p> <p>Reprotoxicity / teratogenicity</p>	<p>References: A review of toxicological data and human health effects of acetanilide has previously been published by OECD SIDS Initial Assessment Report of Acetanilide (6). Other references: (6, 10, 11b) and Annex 1 (RTECS #AD7350000-Chemical Toxicity Database) (section 10). Toxicological data are summarized in Annex 2 -excerpt from ref. 6.</p> <p><i>Acute oral toxicity</i> of acetanilide in rats is considered to be low, with LD<sub>50</sub> of 1959 mg/kg body weight (corresponding LD<sub>50</sub> mouse: 1210 mg/kg). (<b>Annex 2</b>).</p> <p><i>Repeated dose toxicity</i>: LOAEL = 22 mg/kg/day (both sexes; rats) (6, <b>Annex 2</b>).</p> <p><i>Mutagenicity/genotoxicity in vitro</i>: negative test</p> <p><i>Carcinogenicity</i>: tumor formation not detected (rat, mouse, hamster)</p> <p>(<a href="http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+103-84-4">http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+103-84-4</a>)</p> <p><i>Reproduction toxicity</i>: NOAEL = 200 mg/kg/day (rats) <i>Teratogenicity /developmental disturbances offspring</i>: NOAEL = 67 mg/kg/dag</p>

## 5. Exposure estimate and critical NOAEL / NOEL

<p><b>NOAEL/NOEL critical</b></p>	<p>Estimation of NOAEL is based on long term effects in animal experiments (OECD SIDS, ref. 6). Oral tube feeding of rats with acetanilide (12 /dose, males; 12/dose, females) at doses of 22, 67, 200 and 600 mg/kg/day over a period of 30 days (males) or 39-50 days (females).</p> <p>Histopathological examinations demonstrated hyperplasia of blood cells in the spleen ("red pulp"; removal of damaged blood cells), hyperplasia of red blood cells in the bone marrow (most likely a compensatory response on hypoxia/anemia caused by acetanilide), as well as reduced values of hemoglobin and certain other blood parameters.</p> <p>Interspecies variations are known to exist with regard to the effect of Acetanilide on the formation of hemoglobin, with reduced sensitivity in the order: cat &gt; humans &gt; dog &gt; rat (10).</p> <p>LOAEL for 'repeated dose toxicity': 22 mg/kg/day (both sexes; rats) (6).</p> <p>NOAEL (estimated) = LOAEL/3 (empirical factor of 3 is used when the exact value is missing) = 22 (mg/kg) /3 = 7 mg/kg</p>
<p><b>Exposure cosmetic products</b></p>	<p><i>Systemic exposure dose (SED) for Acetanilide in humans:</i></p> <ul style="list-style-type: none"> <li>○ <i>Masking ("perfuming") usage</i></li> </ul> <p><i>Default values: cf. SCCS guide.</i></p> <p>Skin area (total body) = 17800 cm<sup>2</sup> (SCCS)  Amount of product applied pr. cm<sup>2</sup>: 1 mg (SCCS)  Absorbance of product through the skin: 100 % (SCCS)  Body weight: 60 kg (SCCNFP)</p> <p>Maximum (earlier allowed) concentration of product for "masking": 0.025 %</p> <p>SED: 17800 mg (i.e.17800 cm<sup>2</sup> x 1 mg/cm<sup>2</sup>) x 0.00025 / 60 kg = 0.074 mg/kg</p> <ul style="list-style-type: none"> <li>○ <i>Tooth bleaching</i></li> </ul> <p>Cf. Hydrogen peroxide, in its free form or when released, in oral hygiene products and tooth whitening products (SCCP/1129/07). For calculations - see <b>Annex 4</b>.</p> <p>From the exposure studies, the systemic absorption of hydrogen peroxide is estimated to be in the range from 0.03 mg/kg bw/day to 0.2 mg /kg bw /day. Consequently, an exposure from tooth whitening products with 6% hydrogen peroxide of 0.2 mg /kg bw /day may be used in safety calculation.</p> <p>For gel strips it has been reported that users occasionally may swallow the strip, resulting in an exposure of about 12 mg hydrogen peroxide (0.2 mg/kg bw).</p>

	<p>The amount of gel: <math>Y \times 0,06 = 12 \text{ mg}</math> ; <math>Y = 200 \text{ mg}</math></p> <p>Maximum concentration of Acetanilide being use in tooth bleaching products: 0,4 % (used for illustrative purpose)</p> <p>SED (acetanilide): <math>200 \times 0,004 = 0,8 \text{ mg}</math> or <math>0.013 \text{ mg /kg bw /day}</math></p> <ul style="list-style-type: none"> <li>○ Hair coloring products (oxidative hair dying)</li> </ul> <p>50 g hair coloring product is applied to hair (default – SCCNFP) 100 % skin absorbance (default; same as for fragrances /perfume)</p> <p>Maximum concentration of Acetanilide in 1:1 mixture placed on the scalp: 0,2 % (industry / application)</p> <p>SED (acetanilide): <math>50000 \times 0,002/60 = 1,7 \text{ mg /kg bw /day}</math></p>
<b>Margin of Safety (MoS)</b>	<p><i>MoS pertaining to current usage:</i></p> <p>MoS for “masking” /perfuming: <math>7 / 0.074 = 95</math></p> <p>MoS for tooth bleaching: <math>7 / 0.013 = 538</math> (<i>The maximum allowed level corresponding to a MoS equal to 100 is 2.1 %.</i>)</p> <p>MoS for oxidative hair dying: <math>7/ 1,7 = 4,1</math> (<i>The maximum allowed level corresponding to a MoS equal to 100 is 0,0084 %.</i>)</p>

## 6. Other sources of exposure than cosmetic products

<b>Food stuffs</b>	<i>No data retrieved</i>
<b>Pharmaceuticals</b>	<p>Acetanilide is no longer used as a drug in its own right, but the success of its metabolite – paracetamol (acetaminophen) – is well known as a safer alternative (9). Thus, the following observations might be relevant for total exposure assessments.</p> <p>Using painkillers such as ibuprofen, aspirin and paracetamol in pregnancy may harm development of the sex organs in unborn boys, warn Kristensen and coworkers (12). The condition known as <i>cryptorchidism</i> is a risk factor for reduced fertility and increased risk of testicular germ cell tumors later in life (12, 14-16). The second trimester is especially vulnerable, because the risk was doubled with ingestion of one analgesic drug during this period, and increased 16 times when more than one drugs were used simultaneously (16). Both the Danish and the Finnish cohort consisted of more than 2000 pregnant women. However, the lower limit for safe usage of these painkillers in relation to development of cryptochidism is not known.</p> <p>Although the mechanism is not known, a separate study in rats appeared to confirm the link between painkillers and undescended testicles. It was also demonstrated that mild analgesics reduced levels</p>



	<p>of testosterone in the testes of rats by approx. 50 %. Some researchers believe that endocrine disruptors play roles in increasing reproductive problems in young men in the Western World. Medicinal active ingredients are, however, not included in the EU listing of endocrine disruptors so neither paracetamol nor salicylates figure in that list. <a href="http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm">http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm</a>. Clearly further research is needed.</p> <p>Similarly, Jensen et al. (2010) reported a moderate increase of cryptorchidism with the intake of acetaminophen (i.e. paracetamol) for more than 4 weeks during pregnancy, in particular the first and second trimester (16), but did not find any effect of aspirin and ibuprofen. Data were collected from 47400 boys-mothers in the "Danish National Birth Cohort", during the period 1996-2002.</p> <p>Results were reportedly adjusted, at least partly, for potential underlying chronic disease.</p> <p>These findings are important because more than 50 % of pregnant women in the western world are using pain relieving drugs, with a majority using paracetamol (Werler et al., 2005; cited in ref. 12).</p> <p>Norwegian Directorate of Health, National <b>Poison</b> Centre in Norway (Giftnformasjonen i Helsedirektoratet) has noticed a doubling of inquiries in relation to paracetamol poisoning later years, from less than 500 in 2003 (when paracetamol became an over the counter non-prescription drug) to more than 1 000 in 2009. Paracetamol is most frequently related to selfinflicted overdose and overdoses caused by medication errors, cf. Berit Moan Norwegian Directorate of Health (Apotekforeningens journal). In the period 2003 – 2008, misuse of paracetamol caused 35 deaths (13). The same trend is seen in the UK and US, where the FDA has recently lowered the maximum limit for content of paracetamol in one tablet to 325 milligram in order to reduce the risk of liver toxicity (17).</p>
<p><b>Other sources</b></p>	<p><i>Hydrogen Peroxide Stabilizers in the Marketplace</i> I) Hydrogen peroxide is fairly stable in concentrations of up to 40 percent. It does, however, break down with exposure to water, sunlight, and over time, into water and oxygen.</p> <p>However, hydrogen peroxide that is produced for the technical industry, as well as over the counter drug store hydrogen peroxide, is all treated with a number of possible stabilizing agents to retard dissociation of the hydrogen peroxide into its water and oxygen components. The most common stabilizing agents include "Acetanilide", "phenol", "tin", "colloidal stannate", "sodium pyrophosphate" (present at 25 - 250 mg/L) and "organophosphonates", "nitrate".</p> <p>Most of these stabilizing agents are toxic to humans. They are used in hydrogen peroxide stabilizing for specific applications, none of which include regular household cleaning, bathing, food preparation etc. For this reason perhaps it is best to avoid use of these grades of hydrogen peroxide around the home <a href="http://www.foodgradeh2o2.com/101/247/typ/secure/ebv3.pdf">www.foodgradeh2o2.com/101/247/typ/secure/ebv3.pdf</a></p> <p>II) Hydrogen peroxide solutions contain 3% of H<sub>2</sub>O<sub>2</sub> in water with 0.5% of Acetanilide or acetophenetidin as a stabilizing agent [American Hospital</p>

	<p>Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984.,p. 52:28]</p> <ul style="list-style-type: none"> <li>o For pharmaceuticals of H<sub>2</sub>O<sub>2</sub> , an excellent stabilizer is 0.02 % quinine SO<sub>4</sub></li> <li>o Acetanilide 0.03% is present in H<sub>2</sub>O<sub>2</sub>, to protect from it from the effects of sunlight, since it is light sensitive</li> </ul> <p><a href="http://bit.ly/hn0n69">http://bit.ly/hn0n69</a></p>
<p><b>Adverse side effects apart from cosmetics</b></p>	<p>In 1948, Brodie &amp; Axelrod (7) reported that Acetanilide users developed a non-lethal blood disease, known as methemoglobinemia, which was ascribed to the small proportion of Acetanilide that is hydrolyzed to aniline in the body. Methemoglobin is a modified molecular form of hemoglobin responsible for disrupting the normal ability of hemoglobin to transport oxygen, thereby causing functional anemia. Thus, while Acetanilide and paracetamol both are associated with increased risk for liver and kidney damage, Acetanilide is considered to be more toxic by also causing methemoglobinemia.</p> <p>Examples of acute poisoning related to therapeutic usage or abuse of Acetanilide are known from the literature (7, 8), reviewed in a report by EC Joint Research Centre (JRC) (10). <i>Symptoms:</i> methemoglobinemia, cyanosis (blue coloring of the blood), hemolytic anemia and alterations in blood parameteres. <i>Other key symptoms:</i> increased temperature, increased heartrate, nausea, vomiting, followed by extreme cyanosis and slight jaundice over the whole body.</p> <p>Reduced kidney function, liver failure and alcoholism results in increased risk for kidney- and liver damage related to usage of acetanilide (and paracetamol) (Biam2, ref. 8). Intake of ethanol inhibits microsomal oxidation and increases the half-life of acetanilide in the circulation (11).</p> <p><b><u>Interaction:</u></b> High doses of paracetamol increases INR*, resulting in <i>increased risk for bleeding</i>  (<a href="http://www.legemiddelverket.no/templates/InterPage_82950.aspx">http://www.legemiddelverket.no/templates/InterPage_82950.aspx</a>)</p> <p>*) INR: International normalized ratio;  <a href="http://www.labtestsonline.org/understanding/analytes/pt/test.html">http://www.labtestsonline.org/understanding/analytes/pt/test.html</a></p>

## 7. Assessment

The total exposure of acetanilide in the human body is the sum of contributions from cosmetic products and other sources (e.g. environmental exposure and pharmaceutical drugs).

Presumably, Acetanilide is still used in a number of cosmetic products on the market today, perhaps most frequently as a stabilizer of H<sub>2</sub>O<sub>2</sub>, most notably in hair coloring / bleaching products, but also in cosmetic products for bleaching discolored nails and cleaning / peeling skin – although perhaps not that much when it comes to the big brands. Probably, Acetanilide has to some extent been replaced by less toxic H<sub>2</sub>O<sub>2</sub> stabilizers over the years (e.g. sodium stannate - Na<sub>2</sub>Sn(OH)<sub>6</sub>). Data on the extension to which Acetanilide has been replaced does not exist in the public domain.

Acetanilide as a H<sub>2</sub>O<sub>2</sub> stabilizer in tooth bleaching products is a potential new application area for this substance; cf. Dahl J (NIOM, Norway).

In addition, acetanilide is also used as a “masking agent” (cf. CosIng database); i.e. it “perfumes” the product by removing disagreeable smell from the product itself when added as an ingredient. However, we have not been able to retrieve products in which acetanilide has this function.

The estimated NOAEL of 7 mg/kg/day for acetanilide with a MOS of approx. 100 is based on cosmetics solely, and does not consider contributions from other sources.

Although acetanilide is no longer used as a pharmaceutical drug in its own right, the success of its metabolite – paracetamol (a.k.a. acetaminophen) – is well known as a safer alternative (9). However, paracetamol has the potential to cause serious side effects in humans, including increased risk for liver necrosis (7, 8). Prolonged use of paracetamol in pregnancy has recently been reported to harm development of the sex organs (i.e. cryptorchidism) in unborn boys (12, 16), thereby increasing the risk for poor sperm quality and testicular cancer in later life.

A single paracetamol tablet (500 mg) contains more “endocrine disruptor potency” than the combined exposure to the ten most prevalent of the currently known environmental endocrine disruptors during the whole pregnancy, according to Dr. Leffers, a senior author of one of the Danish studies (12; see also EC Cordis News, 2010, ref. 15). Nonetheless, the direct role of paracetamol in the etiology of cryptorchidism remains to be established, and there is a gap in our knowledge concerning the lower limit for safe usage of this and other mild analgesics in relation to this potential reprotoxic effect.

The environmental exposure to acetanilide is considered to be very low, and is most likely via direct dermal contact and inhalation at the production site (only two geographic locations in Korea and the US) (6). Likewise, we have not been able to retrieve data for acetanilide in food stuffs.

## 8. Conclusion

The toxicological profile of acetanilide is well known. There is no evidence that acetanilide is mutagenic (i.e. genotoxic). However, the **NOAEL** value is as low as **7 mg /kg body weight /day** on the basis of a long term repeated dose study in rats.

We have estimated the margin of safety (MoS) for three different product categories of acetanilide: (i) as a fragrance with “masking” function (cf. CosIng), and as a H<sub>2</sub>O<sub>2</sub> stabilizer in (ii) tooth bleaching and (iii) hair coloring products.

MoS “perfume”:  $7 \text{ (mg/kg)} / 0.074 \text{ (mg/kg)} = 95$  (0.0025 % use level and 100 % skin penetration rate in order to keep MoS below 100)

MoS tooth bleaching products:  $7 / 0.013 = 538$  (the maximum allowed levels of acetanilide corresponding to MoS = 100: 2.1 %).

MoS hair coloring products:  $7 / (50000 * X / 60) = 100$   
 $7 * 60 = 50000 * X * 100$ ;  $X = \underline{0.0084 \%}$ ; (i.e. maximum allowed levels of acetanilide in ready-to-use hair coloring product is 0.0084 %).

In conclusion, we propose that the following maximum usage limits for acetanilide in cosmetic products should apply:

Perfume /fragrances (“masking”): 0.0025 %

Tooth bleaching: 2.0 %

Hair coloring, including hair bleaching: 0.01 %

## 9. References

1. Merck – MSDS according to Regulation (EC) nr. 1907/2006 (revised 10.11.2010). Cat.nr. 100011: Acetanilide test substance for elementary analysis.  
[http://www.merck-chemicals.kr/pharmaceutical-ingredients/en\\_US/Merck-KR-Site/USD/ViewProductDocuments-File?ProductSKU=MDA\\_CHEM-100011&DocumentType=MSD&DocumentId=%2Fmda%2Fchemicals%2Fmsds%2Fno-NO%2F100011\\_NO\\_NO.PDF&DocumentSource=GDS&Country=KR&Channel=Merck-KR-Site](http://www.merck-chemicals.kr/pharmaceutical-ingredients/en_US/Merck-KR-Site/USD/ViewProductDocuments-File?ProductSKU=MDA_CHEM-100011&DocumentType=MSD&DocumentId=%2Fmda%2Fchemicals%2Fmsds%2Fno-NO%2F100011_NO_NO.PDF&DocumentSource=GDS&Country=KR&Channel=Merck-KR-Site)
2. <http://en.wikipedia.org/wiki/Acetanilide>
3. <http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=31571>
4. <http://www.yourdictionary.com/acetanilide>
5. Botting R (2004) Antipyretic therapy. *Frontiers in Bioscience* 9: 956-966
6. OECD SIDS (2003) Acetanilide, SIDS Initial Assessment Report, Geneva: United Nations Environment Programme, September 2003. <http://webnet.oecd.org/hpv/ui/Default.aspx>; [www.inchem.org/documents/sids/sids/Acetanilide.pdf](http://www.inchem.org/documents/sids/sids/Acetanilide.pdf)
7. Brodie, B. B.; Axelrod, J. (1948), "The fate of acetanilide in man", *J. Pharmacol. Exp. Ther.* 94 (1): 29–38, PMID 18885611, [http://profiles.nlm.nih.gov/HH/A/A/A/D/\\_/hhaaad.pdf](http://profiles.nlm.nih.gov/HH/A/A/A/D/_/hhaaad.pdf)
8. <http://www.biam2.org/accueil.html>; <http://www.biam2.org/www1/Sub1367.html>  
[http://translate.googleusercontent.com/translate\\_c?hl=no&sl=fr&u=http://www.biam2.org/www1/Sub1367.html&prev=/search%3Fq%3Dfrench%2Bbiam%2Bdatabase%26hl%3Dno%26prmd%3Ddivns&rurl=translate.google.no&usq=ALKJrhj6Er\\_ZaWsLXbODcN9gPrFCmMjFrw#SubEII](http://translate.googleusercontent.com/translate_c?hl=no&sl=fr&u=http://www.biam2.org/www1/Sub1367.html&prev=/search%3Fq%3Dfrench%2Bbiam%2Bdatabase%26hl%3Dno%26prmd%3Ddivns&rurl=translate.google.no&usq=ALKJrhj6Er_ZaWsLXbODcN9gPrFCmMjFrw#SubEII)
9. <http://www.ask.com/wiki/Acetanilide>
10. <http://ecb.jrc.ec.europa.eu/exportfiles/103-84-4.exp>
11. McKay J, Rawlings MD, Cobden I & James OFW (1982) The acute effects of ethanol on acetanilide disposition in normal subjects, and in patients with liver disease. *Br. J. clin. Pharmacol.* 14: 501-504.
- 11b. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+103-84-4>
12. Kristensen, D. M., et al. (2010) Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Human Reproduction* (in press), published online 8 Nov. DOI: 10.1093/humrep/deq323.
13. <http://www.forskning.no/artikler/2010/desember/274634/print>
14. <http://www.forskning.no/artikler/2010/november/270178>
15. [http://cordis.europa.eu/fetch?CALLER=EN\\_NEWS\\_FP7&ACTION=D&DOC=2&CAT=NEWS&QUERY=012c39e73fea:6d92:4c017339&RCN=32749](http://cordis.europa.eu/fetch?CALLER=EN_NEWS_FP7&ACTION=D&DOC=2&CAT=NEWS&QUERY=012c39e73fea:6d92:4c017339&RCN=32749)
16. Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, Henriksen TB, Olsen J. (2010) Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology* 21:779-85.
17. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm239894.htm>

18. Vandenberghe J (1996). Hepatotoxicology: mechanisms of liver toxicity and methodological aspects. In: Niesink RJM, deVries J and Hollinger MA (eds.) Toxicology. Principles and Applications. CRC Press. pp. 707-708.

19. "American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984.,pp. 52:28".

## 10. Annexes

### Annex 1. RTECS

#### RTECS #AD7350000-Chemical Toxicity Database

\*\*\* HEALTH HAZARD DATA \*\*\*

HUMAN:

\*\* ACUTE TOXICITY DATA \*\*

TYPE OF TEST : TDLo - Lowest published toxic dose  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Human  
DOSE/DURATION : 14 mg/kg/D  
TOXIC EFFECTS :  
Lungs, Thorax, or Respiration - cyanosis  
Kidney, Ureter, Bladder - changes in tubules (including acute renal failure,  
acute tubular necrosis)  
Blood - methemoglobinemia-carboxyhemoglobin  
REFERENCE :  
34ZIAG "Toxicology of Drugs and Chemicals," Deichmann, W.B., New York, Academic Press, Inc., 1969 Volume(issue)/page/year: -,62,1969

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Human - man  
DOSE/DURATION : 56 mg/kg/H-I  
TOXIC EFFECTS :  
Behavioral - hallucinations, distorted perceptions  
Gastrointestinal - decreased motility or constipation  
Nutritional and Gross Metabolic - body temperature decrease  
REFERENCE :  
AJMSA9 American Journal of the Medical Sciences. (Slack Inc., 6900 Grove Rd., Thorofare, NJ 08086) New series: V.1- 1841- Volume(issue)/page/year: 122,770,1901

TYPE OF TEST : TDLo - Lowest published toxic dose  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Human - man  
DOSE/DURATION : 405 mg/kg  
TOXIC EFFECTS :  
Behavioral - sleep  
Lungs, Thorax, or Respiration - cyanosis  
Lungs, Thorax, or Respiration - respiratory stimulation  
REFERENCE :  
JAMAAP JAMA, Journal of the American Medical Association. (AMA, 535 N. Dearborn St., Chicago, IL 60610) V.1- 1883- Volume(issue)/page/year: 12,103,1889

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Unreported  
SPECIES OBSERVED : Human - man  
DOSE/DURATION : 59 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
85DCAI "Poisoning; Toxicology, Symptoms, Treatments," 2nd ed., Arena,  
J.M.,  
Springfield, IL, C.C. Thomas, 1970 Volume(issue)/page/year: 2,73,1970

Dyr:

TYPE OF TEST : LD50 - Lethal dose, 50 percent kill  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Rodent - rat  
DOSE/DURATION : 800 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
JPETAB Journal of Pharmacology and Experimental Therapeutics. (Williams  
&  
Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10-  
Volume(issue)/page/year: 54,159,1935

TYPE OF TEST : LD50 - Lethal dose, 50 percent kill  
ROUTE OF EXPOSURE : Intraperitoneal  
SPECIES OBSERVED : Rodent - rat  
DOSE/DURATION : 540 mg/kg  
TOXIC EFFECTS :  
Nutritional and Gross Metabolic - body temperature decrease  
REFERENCE :  
JAPMA8 Journal of the American Pharmaceutical Association, Scientific  
Edition. (Washington, DC) V.29-49, 1940-60. For publisher information,  
see  
JPMSAE. Volume(issue)/page/year: 48,204,1959

TYPE OF TEST : LD50 - Lethal dose, 50 percent kill  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Rodent - mouse  
DOSE/DURATION : 1210 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
TXAPA9 Toxicology and Applied Pharmacology. (Academic Press, Inc., 1 E.  
First St., Duluth, MN 55802) V.1- 1959- Volume(issue)/page/year:  
19,20,1971

TYPE OF TEST : LD50 - Lethal dose, 50 percent kill  
ROUTE OF EXPOSURE : Intraperitoneal  
SPECIES OBSERVED : Rodent - mouse  
DOSE/DURATION : 500 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :



NTIS\*\* National Technical Information Service. (Springfield, VA 22161)  
Formerly U.S. Clearinghouse for Scientific & Technical Information.  
Volume(issue)/page/year: AD277-689

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Mammal - dog  
DOSE/DURATION : 500 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
HBAMAK "Abdernalden's Handbuch der Biologischen Arbeitsmethoden."  
(Leipzig,  
Ger. Dem. Rep.) Volume(issue)/page/year: 4,1290,1935

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Intravenous  
SPECIES OBSERVED : Mammal - dog  
DOSE/DURATION : 300 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
HBAMAK "Abdernalden's Handbuch der Biologischen Arbeitsmethoden."  
(Leipzig,  
Ger. Dem. Rep.) Volume(issue)/page/year: 4,1290,1935

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Mammal - cat  
DOSE/DURATION : 250 mg/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
JPHAA3 Journal of the American Pharmaceutical Association. (Washington,  
DC)  
V.1-28, 1912-39; New series: V.1-17, 1961-77. Volume(issue)/page/year:  
28,70,1939

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Intravenous  
SPECIES OBSERVED : Mammal - cat  
DOSE/DURATION : 8500 ug/kg  
TOXIC EFFECTS :  
Details of toxic effects not reported other than lethal dose value  
REFERENCE :  
JAPMA8 Journal of the American Pharmaceutical Association, Scientific  
Edition. (Washington, DC) V.29-49, 1940-60. For publisher information,  
see  
JPMSAE. Volume(issue)/page/year: 30,91,1941

TYPE OF TEST : LDLo - Lowest published lethal dose  
ROUTE OF EXPOSURE : Oral  
SPECIES OBSERVED : Rodent - rabbit  
DOSE/DURATION : 1500 mg/kg  
TOXIC EFFECTS :  
Peripheral Nerve and Sensation - spastic paralysis with or without  
sensory

change

REFERENCE :

JPETAB Journal of Pharmacology and Experimental Therapeutics. (Williams  
&  
Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10-  
Volume(issue)/page/year: 49,466,1933

TYPE OF TEST : LDLo - Lowest published lethal dose

ROUTE OF EXPOSURE : Oral

SPECIES OBSERVED : Rodent - guinea pig

DOSE/DURATION : 200 mg/kg

TOXIC EFFECTS :

Details of toxic effects not reported other than lethal dose value

REFERENCE :

HBAMAK "Abdernalden's Handbuch der Biologischen Arbeitsmethoden."  
(Leipzig,  
Ger. Dem. Rep.) Volume(issue)/page/year: 4,1290,1935

\*\* MUTATION DATA \*\*

TYPE OF TEST : Micronucleus test

ROUTE OF EXPOSURE : Intraperitoneal

TEST SYSTEM : Rodent - mouse

DOSE/DURATION : 50 mg/kg

REFERENCE :

JPMSAE Journal of Pharmaceutical Sciences. (American Pharmaceutical  
Assoc.,  
2215 Constitution Ave., NW, Washington, DC 20037) V.50- 1961-  
Volume(issue)/page/year: 80,761,1991

\*\*\* STATUS IN U.S. \*\*\*

EPA GENETOX PROGRAM 1988, Negative: Host-mediated assay

EPA GENETOX PROGRAM 1988, Inconclusive: Histidine reversion-Ames test

EPA TSCA Section 8(b) CHEMICAL INVENTORY

EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, JUNE 1998

## Annex 2. Systemic toxic effects

Excerpt summary table toxicological data (OECD SIDS, 2001): (ref 6)  
[www.inchem.org/documents/sids/sids/Acetanilide.pdf](http://www.inchem.org/documents/sids/sids/Acetanilide.pdf)

CAS NO:	103-84-4	SPECIES	PROTOCOL	RESULTS
B.	Non-Bacterial <i>in vitro</i> Test (Chromosomal aberrations)	Chinese hamster cell	Other (cytogenetic)	Negative (without metabolic activation)
5.6	Genetic Toxicity <i>in vivo</i>	Mouse	OECD TG 474	Negative
5.7	Carcinogenicity	Rat/mouse/hamster	Other	No tumorigenesis
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL=200 mg/kg/day
5.9	Developmental Toxicity / Teratogenicity	Rat	OECD TG 422	NOAEL (offspring toxicity) = 67 mg/kg/day
5.11	Experience with Human Exposure	Human	exposure in workplace, overdosing as a drug	Cyanosis, methemoglobinemia

TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD <sub>50</sub> 1959 mg/kg in male/ female LD <sub>50</sub> 2033 mg/kg in male LD <sub>50</sub> 1893 mg/kg in female
5.1.2	Acute Inhalation Toxicity			No data
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin Irritation	Rabbit	OECD TG 404	Not irritating
5.2.2	Eye Irritation	Rabbit	OECD TG 405	Slightly irritating
5.3	Skin Sensitisation			No data
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	LOAEL = 22 mg/kg bw/day
5.5	Genetic Toxicity <i>in vitro</i>			
A.	Bacterial Test (Gene mutation)	<i>S. typhimurium</i>	Other (Ames test)	Negative (with metabolic activation) Negative (without metabolic activation)

### Annex 3: Paracetamol metabolism

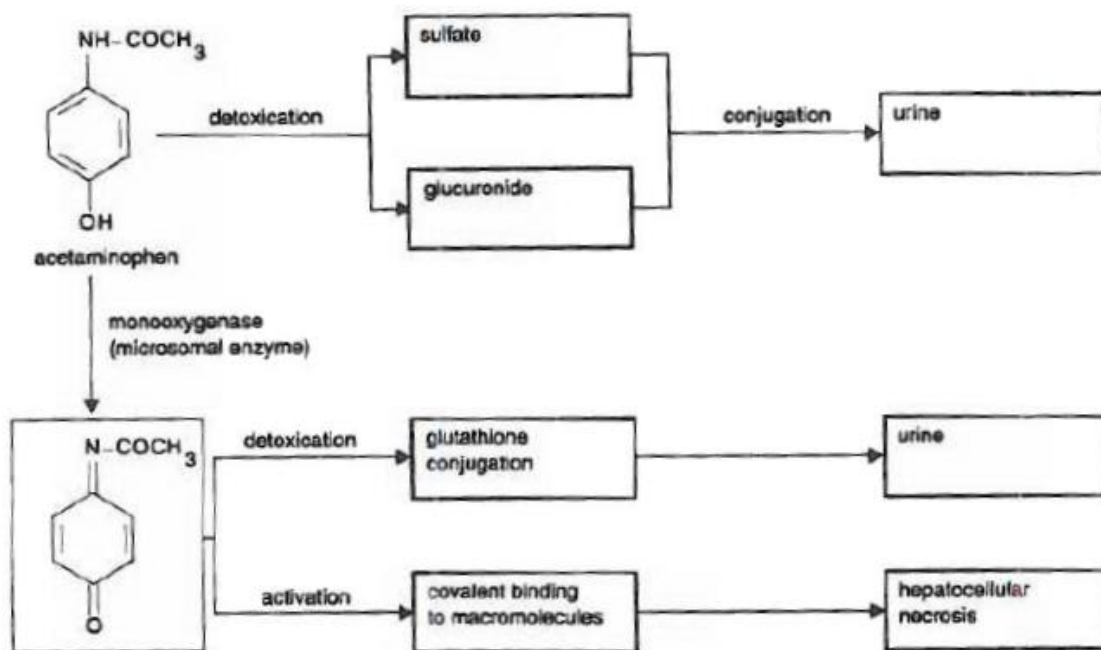
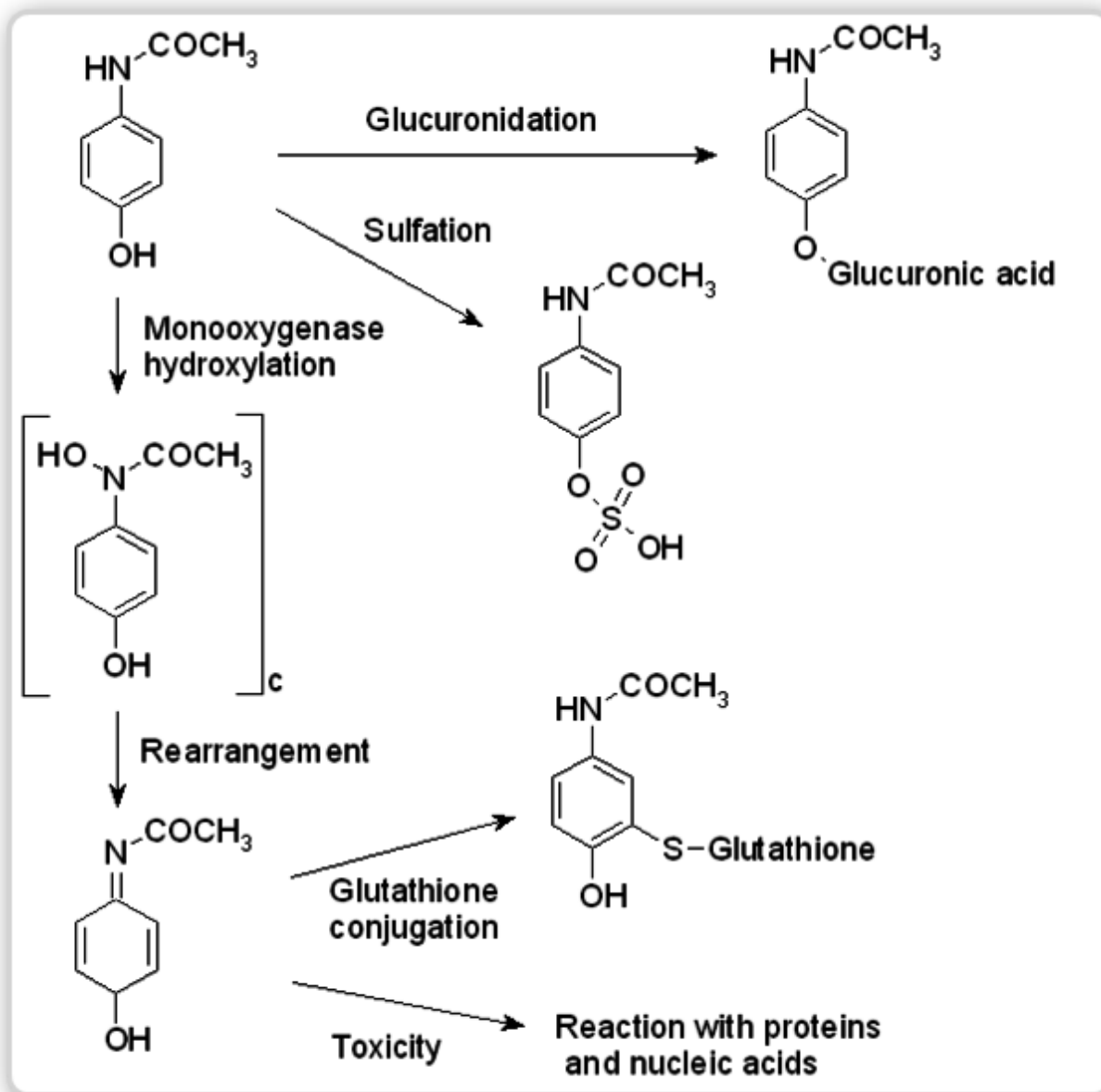


FIGURE 23.2  
The metabolism of acetaminophen and its hepatotoxicity



**NAPQI (N-acetyl-p-benzoquinone imine)** or systematic (IUPAC) name: N-(4-Oxo-1-cyclohexa-2,5-dienylidene)acetamide) is a toxic byproduct of paracetamol (acetaminophen). It is normally produced only in small amounts, and then almost immediately detoxified in the liver.

However, under some conditions in which NAPQI is not effectively detoxified (usually in case of paracetamol overdose), it causes severe damage to the liver. This becomes apparent after 3–4 days after ingestion and may result in death from fulminant liver failure several days after the overdose.

<http://en.wikipedia.org/wiki/NAPQI>

## Annex 4: Calculations

### Masking

17900 mg/ dag

$17900 \times 0,00025 / 60 = 0,07 \text{ mg/kg bw}$

$\text{MoS} = \text{NOAEL}/\text{SED} = 7 / 0,07 = 100$

*Maximum concentration of acetanilide allowed for masking purposes: 0,025 %*

### Tooth bleaching

Cf. SCCP (SCCP/1129/07): OPINION ON Hydrogen peroxide, in its free form or when released, in oral hygiene products and tooth whitening products

From the exposure studies, the systemic absorption of hydrogen peroxide is estimated to be in the range from 0.03 mg/kg bw/day to 0.2 mg/kg bw/day. Consequently, an exposure from tooth whitening products with 6% hydrogen peroxide of **0.2 mg/kg bw/day** may be used in safety calculation.

For gel strips it has been reported users occasionally may swallow the strip, resulting in an exposure of about 12 mg hydrogen peroxide (**0.2 mg/kg bw**).

The amount of gel is:  $Y \times 0.06 = 12 \text{ mg}$  ;  $Y = 200 \text{ mg}$

Maximum limit of 0.4 % acetanilide allowed in tooth bleaching products

i. e. SED for acetanilide:  $200 \times 0,004 = 0.8 \text{ mg}$  or  $0.013 \text{ mg /kg bw}$

$\text{MoS} = 7 / 0,013 = 538$

Upper maximum limit allowed: X % ( $7 \times 60 / (200 \times (X/100)) = 100$ )

$(7 \times 60 = 200 \times X)$ ; X = 2.1 %

<<<<<< Annen regnemåte

Dersom 6 % H<sub>2</sub>O<sub>2</sub> i produktet kan det være X % acetanilid i H<sub>2</sub>O<sub>2</sub>;  $0,06 \times X = 0,004$ ,  $X = 0,067$ , Dvs X kan være opp til 6,7 %

SED (tannbleking):  $0,2 \times 0,067 = 0,0134$  mg/Kg be

MoS =  $7 / 0,0134 = 522$  ergo 0,4 % i i tannblekeprodukt med 6 % H<sub>2</sub>O<sub>2</sub> er trygt i forhold til tannbleking

6% H<sub>2</sub>O<sub>2</sub> fører til systemisk opptak av 0,2 mg H<sub>2</sub>O<sub>2</sub> /Kg bw

Y er mengden tannblekemiddel som brukes i mg

Y x 0,06 er mengden H<sub>2</sub>O<sub>2</sub> i produktet

SED opp til 0,07 mg/Kg bw er trygt

$0,2 \times X_{\max} = 0,07$

X max = 0,35 dvs. opp til 35 % acetanilid i H<sub>2</sub>O<sub>2</sub> er trygg i tannblekeprodukter

Det kan tillates opp til  $35 \times 0,06 = 2,1$  %

***Maximum allowed tooth bleaching gel (filled in a tray): 2.1 %***

### **Hair coloring product**

50 g hair coloring product applied to hair (default)

100 % skin absorption (cf. perfume)

X % maximum allowed

SED  $50\,000 \times X / 60$

$7 / (50\,000 \times (X/60)) = 100$

$7 \times 60 = 50\,000 \times X \times 100$ ,  $X = 0,0084$  %

***Maximum allowed in mixed and ready-to-use hair coloring product added to the hair: 0.0084 %***

