ENCLOSURE IV

To letter 24 September 2004 from the Norwegian Food Safety Authority to the EU Commission asking for prohibition of the preservative IPBC in cosmetics products

INGREDIENTS APART FROM IPCB THAT CONTAIN IODINE AND THAT MAY BE OR ARE USED IN COSMETICS

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Identification of the other iodine-containing ingredients

In the following we mention those that figure in the EU Cosmetics Inventory (the INCI list) and the International Cosmetic Ingredient Dictionary and Handbook (9th Edition 2002) that is issued by the American branch organisation the CTFA. Listing in these two sources doesn’t necessarily mean that the ingredient concerned is actually being used today. It’s difficult to know exactly which is currently being applied and which isn’t. We have tried to find out about this by

- going through Nordic inspection records issued by the controlling authorities
- searching on the Internet
- checking with a freely available database on the web that has been established by an environmental organisation that has inspected the ingredients-list of very many products on the market in recent years

It appears from other chapters of this paper, which ingredients seem to be in use.

The INCI-list and that of the CTFA are not complete in any way and new ingredients are being launched to the marketplace of cosmetics every day (as IPBC was in the early 90s).

Iodine-containing molecules often show bioactive properties and some of the compounds are – or have been - used in topical medicinal products. Due to spin-offs from the pharmaceutical industry it may sometimes happen that these medicinally active principles find their way to
the “active cosmetics” area. As should appear from the comments to the list below, many of those compounds that figure on them actually also are active principles in medicinal products. Potassium iodide (KI) is one example. This salt is being used as an expectorant, as an anti-fungi remedy and as an iodine fortifier in foodstuffs (governmental programs) to prevent endemic goitre in iodine deficient geographical areas. For reasons as given in a letter to the EU Commission 26 October last year, we are of the view that in principle such substances should be reserved for the area of medicinal products only. The four iodine-containing substances figuring on the Annex II already are of the typical “medicinal” kind and were at the time placed there mostly because of that.

The EU Cosmetics inventory contains these iodine-containing ingredients

<table>
<thead>
<tr>
<th>INCI Name</th>
<th>INN</th>
<th>Pharm Eur Name</th>
<th>CAS Nr</th>
<th>EINECS Nr</th>
<th>Chemical name</th>
<th>Restriction</th>
<th>Function</th>
<th>Function (In italics is mentioned some other functions according to CTFA)</th>
<th>(Numbers refer to comments below the table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACID RED 51, CI 45430</td>
<td>Erythro-sine</td>
<td>16423-68-0</td>
<td>240-474-8</td>
<td></td>
<td>Disodium 2-(2, 4, 5, 7-tetraiodo-6-oxido-3-o xo xanth en-9- yl)benzoate (CI 45430)</td>
<td>IV/1</td>
<td>hair dyes</td>
<td>colorant</td>
<td></td>
</tr>
<tr>
<td>ACID RED 95, CI 4525, CI 45480</td>
<td></td>
<td>3329-19-9</td>
<td>251-419-2</td>
<td></td>
<td>Disodium 2-(4, 5-diodo-6-oxido-3-o xo xanth en-9-yl)benzoate (CI 45380)</td>
<td>VI/1</td>
<td>hair dyes</td>
<td>colorant</td>
<td></td>
</tr>
<tr>
<td>ALGEOA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fucus vesiculosus, ext. Extractives and their physically modified derivatives such as tinctures, concretes,</td>
<td></td>
<td>botanicals</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>AMMONIUM IODIDE</td>
<td></td>
<td></td>
<td>12027-06-4</td>
<td>234-717-7</td>
<td>Ammonium iodide</td>
<td></td>
<td>antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIODOMETHYL-TOLYSULFONE</td>
<td></td>
<td></td>
<td>20018-09-1</td>
<td>243-468-3</td>
<td>P-[diiodomethyl)sulphonyl]-toluene</td>
<td></td>
<td>antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIMETHYLAMINO-STYRYL HEPTYL METHYL THIAZOLIUM IODIDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thiazolium, 3-heptyl-4-methyl-2-[2-[4-dimethylaminophenyl] ethenyl]-, iodide</td>
<td></td>
<td>antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETHIODIZED OIL</td>
<td>ethiodized oil</td>
<td>8008-53-5</td>
<td></td>
<td></td>
<td>Fatty acids, poppy seed, iodinated, ethyl esters</td>
<td></td>
<td>emollients</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>FUCUS VESICULOSUS</td>
<td>fucus</td>
<td></td>
<td>84696-13-9</td>
<td>283-633-7</td>
<td>Fucus vesiculosus, ext. Extractives and their physically modified derivatives such as tinctures, concretes,</td>
<td></td>
<td>botanicals</td>
<td>(3)</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Description</th>
<th>CAS Number(s)</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROXYPROPYL BISTRIMONIUM DIIODIDE</td>
<td>Prolonium iodide</td>
<td>123-47-7, 204-630-9</td>
<td>Antimicrobials (skin conditioning agent) (4)</td>
</tr>
<tr>
<td>IODIZED CORN PROTEIN</td>
<td>Proteins, corn, iodinated</td>
<td></td>
<td>Botanicals (skin conditioning agent)</td>
</tr>
<tr>
<td>IODIZED GARLIC</td>
<td>Allium sativum, garlic, iodinated</td>
<td></td>
<td>Botanicals</td>
</tr>
<tr>
<td>IODIZED GARLIC EXTRACT</td>
<td>Allium sativum, garlic, ext., iodinated</td>
<td></td>
<td>Botanicals</td>
</tr>
<tr>
<td>IODIZED HYDROLYZED ZEIN (Iodoprolamina)</td>
<td>Protein hydrolyzates, zeins, iodinated</td>
<td></td>
<td>Biological additives (5)</td>
</tr>
<tr>
<td>MEA-IODINE (Iodamicid)</td>
<td>2- aminoethanol, compound with iodine</td>
<td></td>
<td>Antimicrobials (hair conditioning agent)</td>
</tr>
<tr>
<td>NONOXYNOL-12 IODINE</td>
<td>Poly(oxy- 1, 2-ethanediyl), a- (nonylphenyl)- ?- hydroxy-, compd. with iodine</td>
<td></td>
<td>Antimicrobials</td>
</tr>
<tr>
<td>NONOXYNOL-9 IODINE</td>
<td>26- (p- nonylphenoxy)- 3, 6, 9, 12, 15, 18, 21, 24- octaoxahexacosan- 1- ol, compound with iodine</td>
<td></td>
<td>Antimicrobials</td>
</tr>
<tr>
<td>POTASSIUM IODIDE</td>
<td>Potassium iodide</td>
<td></td>
<td>Antimicrobials (6)</td>
</tr>
<tr>
<td>PVP-IODINE</td>
<td>2- pyrrolidinone, 1- ethenyl- , homopolymer, compd. with iodine</td>
<td></td>
<td>Antimicrobials (7)</td>
</tr>
<tr>
<td>QUATERNIUM-45</td>
<td>3, 4- dimethyl- 2- [2- (phenylamino)vinyl] oxazolium iodide</td>
<td></td>
<td>Antistatic agents (8)</td>
</tr>
<tr>
<td>QUATERNIUM-51</td>
<td>2- [2- [(5- bromo- 2- pyridyl)amino]vinyl]- 1-ethyl- 6- methylpyridinium iodide</td>
<td></td>
<td>Antistatic agents (8)</td>
</tr>
</tbody>
</table>
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| QUATERNIUM-73 | 15763-48-1 | 239-852-5 | 3-heptyl-2-[(3-heptyl-4-methyl-3H-thiazol-2-ylidene)methyl]-4-methylthiazolium iodide | (9) antistatic agents (8) |
| SODIUM IODATE | 7681-55-2 | 231-672-5 | Sodium iodate | VI/1,10 preservatives |
| SODIUM IODIDE | sodium iodide | natrii iodidum | 7681-82-5 | 231-679-3 | Sodium iodide | antimicrobials |
| SOLVENT RED 73 | 38577-97-8 | 254-010-7 | 3', 6'-dihydroxy-4',5'-diiodospiro[isobenzofuran-1(3H), 9'-[9H]xanthene]-3-one (CI 45425) | IV,1 hair dyes |
| TEA-HYDROIODIDE (Iodotrat) | 7601-53-8 | 231-508-2 | 2, 2', 2''-nitrilotrisethanol hydroiodide | additives |

Comments:

(1): Normally, different algae, like for example FUCUS VESICULOSUS (see below) contains fairly high amounts of iodine. Other kelp types that figure as separate cosmetic ingredients and that haven’t been mentioned specifically in the above list, is for example: Macrocystis pyrifera, Laminaria digitata, Laminaria hyperborea extract, Ascophyllum nodosum, Gigartina stellata, and Sargassum vulgare.

(2): According to the source Martindale ETHIODIZED OIL is used in medicine as a contrast medium. Further, because it is slowly metabolised to release iodine it is used in the management of iodine deficiency.

(3): Extracts of the algae FUCUS VESICULOSUS is used to some degree in anti-cellulite products. It contains fairly high amounts of iodine: 0.03 – 0.2 % free and organically bonded (dry weight). Fucus (as dried seaweed) is an ingredient of a number of herbal preparations given for various disorders including obesity, constipation and iodine deficiency (Martindale).

(4): According to Martindale Prolonium iodide has been given by injection as a source of iodine as part of treatment of thyroid storm and for pre-operative management of hyperthyroidism.

(5): Zein is an alcohol-soluble protein obtained from corn, Zea mays

(6): KI is perhaps the most used remedy against iodine deficiency (iodine fortifying of foodstuffs). It is also used medicinally as an expectorant and as a remedy against certain fungus infections (spingotricosis) (taken orally)

(7): PVP-iodine that also is known as Betadine is among the leading antiseptics used in hospitals today. It is widely available. Its usefulness includes wound disinfection and irrigation, sterilization of instruments and surfaces, as well as for water purification. It is also used as an antimicrobial in hand-cleaning products in the food industry and in mouthwashes for prevention of periodontitis and infections that might arise in the mouth in the connection with piercing.

(8): Also used as a photosentizing dye meant for diagnostic purposes.

(9): Quaternium -73 was a temporarily approved preservative up till 21 February 1989 (89/174/EEC). It held the position 5 in Annex VI Part 2. It was deleted from Annex VI without being placed on Annex II. Apparently, the Scientific Committee (SCC) never gave an opinion. So, formally, the reason for suppressing this ingredient was that industry had lost interest in it as a preservative. As a temporary preservative it was allowed up till no more than 0.002% - and only in creams, lotions and shampoo. At the time it wasn’t allowed in higher concentrations for non-preservative purposes. Now, it’s used for
antistatic purposes – and such ingredients are normally used in fairly high concentrations; ca 1-2% it seems. Quaternium-73 and the other anti-microbials also being photosensitizing dyes are currently allowed as preservatives in all cosmetics in Japan up till 0.002% (all such compounds in total).

The International Cosmetic Ingredient Dictionary and Handbook (9th Edition 2002) also contains these molecules that are not in the INCI-list. They are not forbidden in the EU:

<table>
<thead>
<tr>
<th>INCI Name</th>
<th>INN</th>
<th>Pharm Eur Name</th>
<th>CAS Nr</th>
<th>EINECS Nr</th>
<th>Chemical name</th>
<th>Restriction</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IODOFORM</td>
<td></td>
<td></td>
<td>75-47-8</td>
<td>200-874-5</td>
<td>Triiodomethane</td>
<td>Cosmetic biocide</td>
<td></td>
</tr>
<tr>
<td>IODIZED HYDROLYZED EXTENSIN (Pronalen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>PLATONIN</td>
<td>3571-88-8</td>
<td>222-681-5</td>
<td></td>
<td></td>
<td>Thiazolium, 2,2’-(3-(2-(3-heptyl-4-methyl-4-thiazolin-2-ylidene)ethylidene)propenylene)bis(3-heptyl-4-methyl-, diiodide</td>
<td>Skin-Conditioning Agent Miscellaneous (*)</td>
<td></td>
</tr>
</tbody>
</table>

(*) Platonin is developed as a photosentizing dye meant for diagnostic purposes

Iodine weight percentage of molecules/ingredients that seems to find use

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Iodine percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI 45430 (organic iodide)</td>
<td>57,7 (508 x 100/880)</td>
</tr>
<tr>
<td>ETHIODIZED OIL (organic iodide)</td>
<td>35-39</td>
</tr>
<tr>
<td>It contains 37% iodine organically combined with ethyl esters of the fatty acids (primarily as ethyl monoiodostearate and ethyl diiodostearate) of poppyseed oil. Stabilized with poppyseed oil, 1%. The precise structure of Ethiodol is unknown (RxList – confer references /Martindale) Ethyl stearate: CH₃(CH₂)₁₆COOEt</td>
<td></td>
</tr>
<tr>
<td>IODIZED GARLIC EXTRACT (organic iodide and I₂)</td>
<td>Ca 70%</td>
</tr>
<tr>
<td>Medicinally used garlic oil consists nearly exclusively of allylsulphides of different kinds (Lawson LD 1998). When I₂ is added to the oil one would believe that they are reacted, at last some to degree, into iodine derivatives like for example ICH₂=CHI-CH₂-S-S-CH₂=CHI-I (M= 654 out of which 77,7% is due to iodine). The ingredient probably also contain much complexed I₂</td>
<td></td>
</tr>
</tbody>
</table>
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IODIZED HYDROLYZED EXTENSIN (organic iodide and I\textsubscript{2})

Extensins are homologous hydroxyproline-rich glycoproteins found in the plant extracellular matrix. When hydrolysed the aminoacid hydroxyproline is formed. Possibly, iodisation involves formation of either an iodine derivatives of this aminoacid (3-Iodo-4-hydroxy-L-proline) or a charge-transfer complex between this molecule and I\textsubscript{2}. No information about iodine content is found. (*)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Rate (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPCB (organic iodide)</td>
<td>45</td>
<td>(127 x 100/280)</td>
</tr>
<tr>
<td>KI (I\textsuperscript{-} anion)</td>
<td>76,5</td>
<td>(127 x 100/166)</td>
</tr>
<tr>
<td>Laminaria hyperborea extract (organic iodide and I\textsuperscript{-})</td>
<td>This particular dried herb contains 0,55 – 0,70 % iodine by weight. Others may contain somewhat less.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEA-IODINE (HO-CH\textsubscript{2}-CH\textsubscript{2}-NH\textsubscript{2} ⊙ \textsuperscript{I\textsubscript{2}}) (releases I\textsubscript{2})</td>
<td>80,6</td>
<td>(254 x 100 /315)</td>
</tr>
<tr>
<td>PVP-IODINE ((C\textsubscript{6}H\textsubscript{9}NO)x . xHI\textsubscript{3}) (releases I\textsubscript{2})</td>
<td>9-12</td>
<td></td>
</tr>
<tr>
<td>QUATERNIUM-51 (I\textsuperscript{-} anion)</td>
<td>28,5</td>
<td>(127 x 100/446)</td>
</tr>
<tr>
<td>QUATERNIUM-73 (I\textsuperscript{-} anion)</td>
<td>31,2</td>
<td>(127 x 100/407)</td>
</tr>
<tr>
<td>TEA-Hydroiodide (HOCH\textsubscript{2}CH\textsubscript{2}NHI (I\textsuperscript{-} anion )</td>
<td>45,8</td>
<td>(127 x 100/277)</td>
</tr>
</tbody>
</table>

(*) Example of product containing product (“Iodized Hydrolyzed Extensin /Anti cellulite product”) is found on the Internet at [http://www.maxworth.co.th/3associate.htm](http://www.maxworth.co.th/3associate.htm)

Skin penetration rates

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Rate (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPBC</td>
<td>20 (SCCNFP)</td>
<td>Concerns IPBC- molecule as such</td>
</tr>
<tr>
<td>CI 45430</td>
<td>0,13 (Franz TJ, 1984)</td>
<td>Concerns CI 45430 – molecule as such</td>
</tr>
<tr>
<td>PVP-Iodine</td>
<td>0,06 (SCCNFP)</td>
<td>Concerns iodine bound electro statically as I\textsuperscript{-} anion in the special PVP-Iodine complex (special monograph exists)</td>
</tr>
<tr>
<td>I\textsubscript{2} as in tincture</td>
<td>10 (see below)</td>
<td>Concerns the elemental iodine molecule I\textsubscript{2} in ethanol solution. Probably, when engaged in weak charge-transfer bonds as in for example HO-CH\textsubscript{2}-CH\textsubscript{2}-NH\textsubscript{2} ⊙ \textsuperscript{I\textsubscript{2}} (MEA-iodine) the rate is relatively similar (may be somewhat less).</td>
</tr>
<tr>
<td>I</td>
<td>0,1 (see below)</td>
<td>Concerns iodide anion as in water solvable salts</td>
</tr>
</tbody>
</table>

Skin penetration rate of the I\textsubscript{2} molecule

Studies show that I\textsubscript{2} can penetrate the skin enough to blockade the uptake of \textsuperscript{131}I (radioactive iodine) in the thyroid gland. A study involving 24 healthy male adult volunteers gave these results (Miller K 1989):
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<table>
<thead>
<tr>
<th>Form of iodine /Route of administration</th>
<th>Dose in micrograms</th>
<th>26 hour PA serum-I levels (pg/mm³)</th>
<th>Medium serum level of iodine (pg/mm³)</th>
<th>Thyroid uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% iodine tincture/8 ml on 200 cm² of abdomen</td>
<td>160 000 (on skin)</td>
<td>109-563</td>
<td>336</td>
<td>0,2 – 6,7</td>
</tr>
<tr>
<td>2% iodine tincture/ 4 ml on 100 cm² of forearm</td>
<td>80 000 (on skin)</td>
<td>30 -71</td>
<td>51</td>
<td>0,9 – 15,3</td>
</tr>
<tr>
<td>Orally / KI – tablets</td>
<td>99 000 (systemic)</td>
<td>125 - 1010</td>
<td>568</td>
<td>0 – 0,61</td>
</tr>
<tr>
<td>Controls</td>
<td>0</td>
<td>7,24 – 16,5</td>
<td>12</td>
<td>6,5 – 14,8</td>
</tr>
</tbody>
</table>

Making some rough approximations we estimated skin penetrations rates on the basis of this information. As concerns the 160 mg dose on the abdomen we estimated a rate of 40%. As to the 80 mg dose on the arm, the rate amounted to 10%. This is, of course, a very coarse and imprecise way of obtaining information about the important skin penetrations rates. They should be treated with caution. Considering the smallness of the molecule and its partition coefficient (2,6), the relatively high figures make sense, though. Also reassuring is the higher percentage for the highest dose. Because, of the impreciseness of this estimation we cautiously decided to use the 10% figure when estimating the systemic exposure calculations as shown below.

**Skin penetration rate of the iodide anion (I⁻)**

From an iontopherosis experiment on humans with Potassium iodide (KI) it appears that, when under the influence of an electrical field, the I⁻ anion passes through the skin quite readily. The penetration rate amounted to around 10% (Puttemans FJ et al 1982). The authors stated that when the electrical field was swished off, the iodide anion didn’t penetrate the (intact) skin at all. However, the published measurement results on iodine amounts seem not entirely to exclude the possibility that a tiny amount did penetrate after all in this experiment. It has to be much lower than 1%, though. In their latest opinion on IPBC the SCCNFP informs that the sodium-iodide-symporter (NIS) is expressed to a slight degree in the skin tissues as well. NIS provide for active transport of iodide across biological membranes. Could it then not be that when applied to skin iodide anions have a certain tiny flux across the skin layers? We think the doubt should come to the benefit of the consumer of the cosmetics and uses an iodide skin penetration rate of low 0,1% when estimating the systemic iodine exposure for ingredients containing iodine in this form.

**Approximate exposure calculations for ingredients finding use**

**CI 45430**

Not used in lipsticks as colorant because of solubility problems (water soluble chemical).

*Presently it finds some use in certain toothpastes*
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Premises:
Concentration: 100 ppm (experience with colour in toothpastes)
480 000 micrograms of toothpaste is ingested when brushing teeth (SCCNFP)

Daily intake: (480 000 x 0,0001 x 0,58 =) 27 microgram
-----
Example of toothpaste announced on the Internet at http://www.beautycenter.co.uk/fiche_produit.php?id_rayon=312&id_article=231
Sales claims: Red, light reflecting formula toothpaste. Cleansing, polishing, antiplaque and gum protecting.
Indications: dental hygiene.

Is also is used in some mouthwashes:

Premises:
3 ml (g) is swallowed (SCCNFP)
5 drops (0,25 ml) of mouthwash in a glass of water (50 ml)
Concentration in mouthwash: 100 ppm

Daily intake: (3 000 000 x 0,0001 x (0,25/50) x 0,58 =) 0,87 microgram
-----
Example of mouthwash announced on the Internet at http://www.beautycenter.co.uk/fiche_produit.php?id_rayon=140&id_article=126
Information about product in the announcement:
• Advice for use: pour some drops into a glass of water, before or after brushing teeth.
  Counter-indications: not for children under 6.
Sales claims: Water of purifying and refreshing mouth.

Other products

CI 45430 could theoretically also be used in: shampoo, shower-bath, bubble bath, deodorants and eau de toilette.

One would anticipate that worst-case use of such items involves a combined daily exposure of around 1 g (1 million micrograms). The skin penetration rate is very low, however: at most 0,13%. Hence, all the other product types combined one would believed involves a daily systemic dose of no more than:

1000 000 x 0,0013 x 0,0001 x 0,58 = 0,075 microgram

Ethiodized Oil

Used in as an anti-cellulite agent

Premises:
Skin penetration rate; 1 % (is guessed at – comparatively large lipophilic molecules)
Skin area: 1600 cm$^2$ – i.e. 1600 mg product used 2 times per day$^1$
Concentration: 1% (CoE document on Active Ingredients)

Systemic daily dose: $(1600000 \times 0,01 \times 0,01 \times 0,35 \times 2) = 103$ microgram

Example of product (“Super 'S' Cream®”) announced on the Internet at http://www.healthandsunshine.com/scream.htm
Use instruction in announcement: Use daily. Massage into clean skin. Work in thoroughly until completely absorbed, smoothing the skin. For best results, use morning and evening.
Sales claims: Smoothes the appearance of dimpled, irregular-looking skin often associated with cellulite

**Iodized garlic extract**

We saw it being used as the third most important ingredient in a particular hair tonic for prevention of hair loss and dandruff.

Premises:
- Skin penetration rate: 10% (is guessed at – small lipophilic molecules including much I$_2$)
- Daily use amount of product put into hair: 5 g
- Partition coefficient: 0,1
- Concentration: 2%

Systemic dose: $(500000 \times 0,02 \times 0,10 \times 0,10 \times 0,70 =) 700$ microgram

**KI**

Iodized salt in baths:

Premises:
- Bath is added 0,3 g KI (estimated on the basis of information in advertisement)
- Partition coefficient: 0,01 (SCCNFP)
- Skin penetration rate for iodide: 0,1% (see above)

Systemic dose from one bath: $300000 \times 0,01 \times 0,001 \times 0,76 = 2,28$ microgram

Example of product (“Iodized bathing salt”) announced on the Internet at http://www.solnemlyny.cz/eng/koupelove.html

Information about product in the announcement: Contains 1.2 to 2.0 g of KI per 1 kg of product., 1 bag (500 g) is sufficient for 3–4 baths.

Sales claims. Suitable addition to healthy régime and hygiene. Iodide contained in salt absorbs in skin and it has a positive impact on the function of thyroid gland and overall state of the body. Deficit of the supplies of

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$^1$ Estimating this skin area we precluded that the part of the body affected by the cellulite is the back of the thighs. According to the (rough) so-called Wallace’s “Rule of nine” (confer for example: http://www.gpnotebook.com/cache/201719886.htm) this skin surface amounts to 9% of the whole body surface – which according to the SCCNFP guidelines is 18 000 cm$^2$. 
iodide can be improved by means of iodized baths. Iodized bathing salt is also good for skin care. It has a positive impact on skin metabolism.

**MEA-IODINE (Iodamicid)**

Product for cleaning the skin

Premises:
Skin area of hands: 1000 cm$^2$ – i.e. 1000 mg product applied
Partition coefficient: 0,1
Skin penetration rate for iodide: 10% (see estimate for I$_2$)
Concentration: 0,45%

Systemic dose: $(1 000 000 \times 0,01 \times 0,1 \times 0,0045 \times 0,81) = 3,6$ microgram

Galena - Química e Farmacêutica Ltda.
Information about product in the announcement: Usual concentration: 0,2% to 0,45%:

**PVP-Iodine**

Used in some mouthwashes/gargles

Premises:
3 ml (g) is swallowed (SCCNFP)
5 drops (0,25 ml) of mouthwash in a glass of water (50 ml)
Concentration in mouthwash before pouring into the glass: 7,5 % (0,75% as iodine)

Daily intake: $(3 000 000 \times 0,0075 \times (0,25/50) =) 113$ microgram

Mostly PVP-Iodine-containing products are presented as medicinal commodities on the web but at least one firm, that we saw, markets them as plain consumer products also – i.e. as products falling under the definition of a cosmetic products: *Cream, Feminine Wash, Oral Antiseptic Solution, Skin Cleanser* (http://www.pascuallab.com/consumer/consumer.htm). It is also in product (wipes) meant for disinfection of hands of those working in the foodstuffs production industries (Barutha M 1999). Examples of typical formulations of PVP-Iodine-containing for different purposes are given in: [http://www.basf-pharma.com/%280xd154554qucz55xm2yka55%29/pdf/technical_information/PVP-iodine-grades.pdf](http://www.basf-pharma.com/%280xd154554qucz55xm2yka55%29/pdf/technical_information/PVP-iodine-grades.pdf)

**Quaternium-51**

Used as an anti-static agent in special products meant to remedy with thinning of hear and that is massaged into thinning scalp areas.

Premises:
Amount of product applied to skin daily: 2000 mg (anticipated from announcement)
Concentration: 1% (not untypical for anti-statics)
Skin penetration rate: 0,1% (see above)
Systemic dose: $(2000\,000 \times 0.01 \times 0.001 \times 0.285) = 5.7$ microgram

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Example of product announced on the Internet at http://fabaocanada.com/hair-loss-treatments/shen-min-topical.htm
Use instructions in the announcement:
Apply 10-12 drops directly onto thinning scalp areas every morning and evening. Use for at least 3-4 months.

Quaternium-73

Used de facto - but illegally in Europe - as a preservative in no higher concentration than 20 ppm

Skin water that is sprayed on (advertisement)

Premises:
Skin area exposed: $2000 \, cm^2$ – i.e. 2 g
Skin penetration rate: 0.1% (see above)

Daily systemic use: $(2000\,000 \times 0.000020 \times 0.001 \times 0.31) = 0.01$ microgram

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Sales claims: Let this nourishing toner relieve your skin with an instantly hydrating veil of moisture. This special formula balances your pH while it soothes and calms your complexion

TEA-Hydroiodide (Iodotrat)

Finds some use as an anti-cellulite ingredient.

Premises:
Skin penetration rate: 0.1% (see above)
Skin area: $1600 \, cm^2$ – i.e. 1600 mg product used
Concentration: 0.8% (Announcement)

Systemic dose: $(1600\,000 \times 0.008 \times 0.001 \times 0.45) = 6$ microgram

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Announcement/ deliverer of Iodotrat: http://www.relata.info/html/healthy_5.html

Safety data for some of the ingredients in question

2 Estimating this skin area we precluded that the part of the body affected by the cellulite is the back of the thighs. According to the (rough) so-called Wallace’s “Rule of nine” (confer for example: http://www.gpnotebook.com/cache/201719886.htm) this skin surface amounts to 9% of the whole body surface – which according to the SCCNFP guidelines is $18\,000 \, cm^2$. 
Appendix IV to letter to the EU Commission 24 September 2004 from the Norwegian Food safety Authority asking for prohibition of the preservative IPBC in cosmetics products

As a foodstuffs additive Erythrosin is allowed only in some cherries products but not in a higher concentration than 150-200 ppm. The EU Scientific Committee on Food (SCF) has determined an Acceptable Daily Intake (ADI) value of 0,1 mg/Kg body weight (opinion 1987). JECFA arrived at the same ADI in their latest opinion in 1991 (37th report). The Erythrosin molecule contains much iodine and it has been demonstrated that it influences on the functioning of the thyroid. JECFA considered that the occurrence of thyroid tumours in some long term rat-studies was most likely secondary to hormonal effects. Erythrosin has been considered non-genotoxic. JECFA concluded that it would be possible to establish the ADI from the NOAEL value determined in human studies (influence on thyroid function): 60 mg per day (60 Kg body weight and a safety factor of 10).

A WHO committee considered it unlikely that the daily intake exceed the ADI (WHO 2000).

Erythrosin is applied as a dental-plaque-disclosing agent (Martindale). When being used for medicinal purposes a daily intake of 0,013 mg/Kg body weigh is reckoned with (EU Scientific Committee for Medicinal Products and Medicinal Devices 1998).

Erythrosin has been de-listed in the United States since 1990 following studies in rats that suggested that it was potentially carcinogenic for the thyroid gland (TD_{50} value of 122 mg/Kg body weight). This move – that concerns also the molecules cosmetics use -was a result of the Delaney Clause, which restricts the use of any colorant shown to induce cancer in humans or animals, regardless of the amount (SCMPMD1998). FDA viewed the thyroid-cancer risk associated with erythrosin as small — about 1 in 100,000 over a 70–year lifetime.

Clinical data and anecdotal reports indicate that halogenated derivatives of fluorescein, are phototoxic under certain conditions of exposure. Fluorescein is frequently used in ophthalmic examinations and retinal angiography. There have been a number of anecdotal reports of ocular and cutaneous phototoxicity following intravenous administration of fluorescein for this application. Furthermore, halogenated fluorescein dyes are phototoxic if applied topically to scarified skin, but are not phototoxic if applied to intact skin. These results indicate that delivery of the dye to the skin is an important factor to consider in evaluating the potential

In-vitro percutaneous absorption through human skin:

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Concentration (%)</th>
<th>% Dose absorbed in 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mineral oil</td>
<td>1.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Castor oil</td>
<td>1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Talc</td>
<td>1.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ethanol water (50:50)</td>
<td>0.1</td>
<td>0.134</td>
</tr>
<tr>
<td>Oil-in water emulsion</td>
<td>0.1</td>
<td>0.040</td>
</tr>
</tbody>
</table>

(Ref: Franz TJ, 1984)

**Sodium iodate safety cannot be concluded**

There is a CIR report on the Sodium iodate ingredient concluding it cannot be considered safe in use until further data (eventually) show it is (ref: CIR). We never saw that further data were provided. It’s clear from the International Cosmetic Ingredient Dictionary and Handbook of the American branch organisation, the CTFA, that also in the year 2001 the CIR safety status of Sodium iodate is: “insufficient data to determine safety for use in cosmetics.” Seemingly, it doesn’t find any use these days as preservative.

Sodium Iodate is a retinotoxic compound. It may adversely affect the retina, blood-retinal barrier, pigment epithelium, rhodopsin regeneration, and ERG. It did not have mutagenic activity in the Ames, micronucleus, or recessive lethal test. Sodium DNA single-strand breaks were increased in cultures of E. coli strains B/r and Bs-l after irradiation when Sodium Iodate was added compared with those irradiated without Sodium Iodate addition. It decreased the survival of strain B/r, but it had no effect on E. coli strain pol A.

**PVP-iodine**

Many researchers and clinicians have described the toxic effects of PVP iodine (confer for example de Groot 1994). Use of the substance (10%) in clinical settings has caused hypothyroid reactions in elderly woman treated for leg ulcer.

**Alkyl iodides**

The iodised allyl sulphides within Iodized Garlic Extract belong to this class of chemical compounds. So do also the iodised ethyl stearates with in the Ethiodized Oil ingredient.

Because I⁻ is a good leaving group, many alkyl iodides are fairly strong alkylating agents. Some are known to possess genotoxic and carcinogenic properties. Examples: Methyl iodide (CAS No 74-88-4) is a Category 3 CMR (Cancer). Iodinated glycerol (CAS NO 5634-39-9), a complex mixture prepared by the reaction of iodine with glycerol and found to contain 33% 3-
iodo-1,2-propanediol (OH-CH2-CH(OH)-CH2I) as the major component, is both genotoxic and carcinogenic: TD50 (CPDB): 101 mg/kg bw/day in the rat and 138 mg/kg bw/day in the mouse. T25 (Dybing and Sanner 1997): 52.6 mg/kg bw/day. Thyroid cancers. Iodoform (I3HC) possibly still finds some use as an antiseptic in dental dressing. Reported side effect is stomatitis dermatitis. Also, severe iodoform toxicity from iodine absorption leading to coma has been reported (de Groot et al 1994).

Iodine-containing compounds banned in cosmetics
Annex II contains the following 4 compounds that were place there already in 1976

- Iodine – which is understood to mean the I2 molecule (position 213).
  This substance is used in medicine as a disinfectant on the skin (I tinctures).
  High concentrations cause skin corrosion.

- Thymol iodide (4,4′-Bis(iodoxy)-2,2′-dimethyl-5,5′-bis(1-methylethyl)-1,1′-biphenyl)
  (CAS No 552-22-7) – confer Annex II position 362.
  Thymol iodide is used as a dental hygienic agent.
  Thymol iodide was formerly used as external antiseptic.

- (4-(4-hydroxy-3iodophenoxy)-3,5-diiodophenyl)acetic acid and its salts (CAS 51-24-1) – Annex II position 5.
  It is also called triodothyroacetic acid and Triacol. It is deaminated T3 and show weak hormonal activity.
  Intake can give serious adverse effects and years ago FDA warned people to take this drug (was sold on the internet as a dietary supplement); could give stroke.

- Thyropropic acid (CAS No 51-26-3). It’s identical to Triacol except that it has a –CH2-CH2-COOH moiety instead of a –CH2-COOH group. Also, this compound shows weak hormonal activity.

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CPDB: The database of Gold and co-workers at the Berkeley University that can be retrieved at the following Internet address: http://potency.berkeley.edu/cpdb.html. See also the address http://potency.berkeley.edu/text/ToxicolPathol.pdf


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RxList is an online service to the medicinal profession in their search for adequate remedies: confer
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