

## RISK PROFILE

### *Cosmetic ingredients containing iodine*

This concerns iodine containing cosmetic ingredients that are not regulated specifically in the REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products

Date of reporting 30.10.2013

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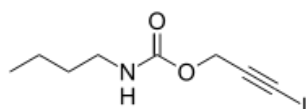
### 1. Identification of substance

<b>General explanation</b>	<p>The substances concerned contain iodine either because they are iodine salts (<math>I^-</math> or <math>I_3^-</math> anions) or organic iodine molecules (I bound covalently). Additionally, there are also a few brown and red algae extracts like, for example, extracts of the seaweed bladderwrack that contain iodine to the extent it is utilized as a rich source of iodine. All these substances are mentioned as non-specifically regulated ingredients in the CosIng database of the European Commission that is freely available on the internet (Online – CosIng – see references).</p> <p>So, this risk evaluation concerns ingredients that, currently, are allowed unconditionally in cosmetic products. The CosIng database is occasionally extended when more ingredients become available to the cosmetics industry. At present it contains 24 unconditionally allowed iodine ingredients counting in 5 seaweed extracts of potential interest<sup>1</sup> as separate ingredients. For practical reasons only 10 of these 24 ingredients</p>
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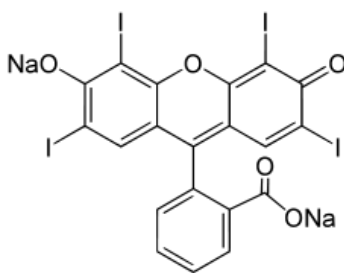
<sup>1</sup> The following 5 seaweed species stand out as particularly rich in iodine and are, therefore, of potential interest to the cosmetic products industries placing anti-wrinkling and the alike anti-age products on the market: *Laminaria digitata*, *Fucus vesiculosus*, *Laminaria saccharina*, *Laminaria hyperborea* and *Gracilaria verrucosa* (Sources: Marchal P *et al* (2000) , André S (1971), CEVA ( 2004) and document prepared by the organisation UNITIS that was distributed at a meeting of the European Commission Working Party for cosmetic products in 2006. UNITIS is identical to the European Organisation of Cosmetic Ingredients Industries and Services).

are mentioned in particular in the below text. The other ones are mentioned only briefly in Appendix 1.<sup>2</sup>

Observe that the conclusion reached in this document is valid not only for the 10 selected specific substances but for **all** iodine containing cosmetic products ingredient **except** for those that are mentioned in the Annexes III-VI of the Regulation (EC) No 1223/2009 (Cosmetic Product Regulation). Currently, this concerns only the following two ingredients that can be used on specific conditions in cosmetic products in the EEA area. They are;



- 3-Iodo-2-propynyl-butylcarbamate (IPBC)  
(preservative, see Annex V position 56)



- CI 45430 (ACID RED 51, erythrosine)  
(colorant, see Annex IV – but forbidden as hair dye  
– see Annex II position 1337)

IPBC is a much used preservative. The Codecheck database (*inter alia*) mentions 903 products containing IPBC. The regulation of IPBC was made stricter in 2006 because it became clear that the regulation introduced a couple of years before would allow for a usage being that extensive it would involve an unacceptable risk for thyroid disruptions/sicknesses.<sup>3</sup> Subsequent to uptake in the body the covalently bonded iodine is set free from IPBC metabolically.

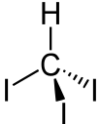
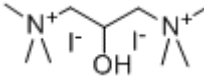
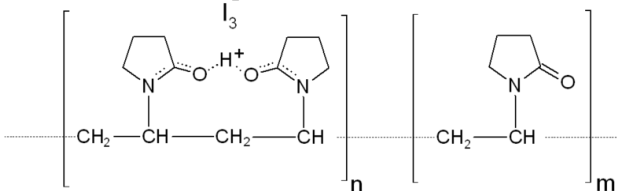
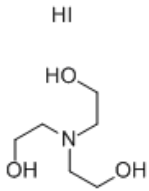
<sup>2</sup> Over the years up till 2008 the Norwegian medicinal products agency (mpa) was contacted by market players asking whether a specific drug (i.e. an active principle in pharmaceutical products) might be allowed in a cosmetic product on certain conditions. Among these were also the 10 mentioned selected iodine containing ingredients. For health reasons and because they would cause pharmacological effects even at low concentrations in a cosmetic product, the mpa rejected the applications made.

<sup>3</sup> Norway made aware of the problem in letter from the former Norwegian Food Control Authority (SNT) to the European Commission 7 April 2000 (ref: 99/00952/322/HJT/tso). An enclosure to letter contained a safety assessment that also is shown in the Commission working paper document 00/ENTR/COS/20, Annex 3 (presented to the Working Party for cosmetic products). This Norwegian initiative prompted a work at the level of the scientific committee of the European Commission (SCNFP) that delivered an opinion on the IPBC 1 July 2004 (SCCNFP/0826/04). The references pertaining to the risk for thyroid disruption are contained in that opinion.

	<p>In connection with the IPBC/iodine case back in 2006<sup>4</sup> the European Commission at one point in time also proposed to prohibit the colorant CI 45430 (erythrosine) entirely. That seemed necessary in order to prevent a much too high total intake of iodine. However, industry defended the use of CI 45430 in toothpaste explaining usage would lead to only minute exposure employing a concentration of not more than 25 ppm (0.0025 %). In 2010, The scientific committee of the European Commission found no safety concerns related to such limited usage. However, from the Codecheck database it appears that as of today the CI 45430 ingredient is present in 700 products of <i>all</i> kinds of coloured cosmetics and not only in toothpaste. Similar to nearly all iodine containing organic molecules, also the CI 45430 molecule releases covalently bonded iodine upon intake into the body. Dependent upon the magnitude of the iodine exposure, the thyroid functioning might get disrupted to the extent it would cause health damage<sup>5</sup>.</p> <p>Over the years a whole series of other iodine containing molecules have been prohibited and placed in Annex II of the cosmetic product regulation. On this confer the positions 5, 9, 68, 137,156, 192, 213, 329, 361, 1046, 1096 and 1336. The position 213 is for iodine itself; I<sub>2</sub></p> <p>Besides, the European Commission apparently consider ingredients that are complexes between the I<sub>2</sub> molecule and another molecule to fall under the entry 213 of the Annex II. This would be ingredients that release elemental iodine – i.e. the molecule I<sub>2</sub> – upon use. One such ingredients is MEA-iodine with the structure:</p> $\text{HO-CH}_2\text{-CH}_2\text{-NH}_2 \odot \text{I}_2$ <p>The few ingredients in question are mentioned in the CosIng database under entry 213. Hence, according to CosIng they all are forbidden in cosmetics products.</p> <p>The wording is solely “<i>iodine</i>” in entry 213 of the Annex II of the Regulation (EC) No 1223/2009. Authentic law is the regulation and not the CosIng database. However, as long as the European Commission, apparently, interpret “<i>iodine</i>” to mean that I<sub>2</sub> complexes are included also and that the industry represented by the branch organisation Cosmetics Europe seems to have accepted that interpretation, we also consider them banned in cosmetics products.</p>
<p><b>Chemical name (IUPAC):</b></p>	<p>For the chemical names of the selected 10 iodine-containing ingredients, see their respective INCI names in the CosIng data base</p>
<p><b>INCI</b></p>	<p>The 10 selected ingredients are:</p> <ul style="list-style-type: none"> <li>• Ammonium iodide</li> <li>• Potassium iodide</li> <li>• Sodium iodide</li> <li>• Iodoform</li> <li>• PVP-iodine,</li> <li>• Hydroxypropyl bistrimonium diiodide</li> <li>• TEA- hydroiodide</li> </ul>

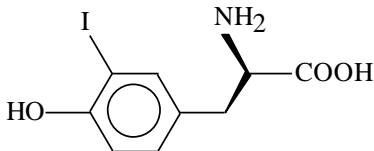
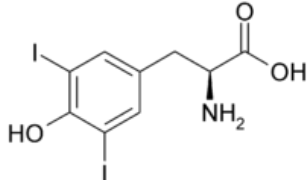
<sup>4</sup> Reference is made to the risk management process that took place at the level of the Working Party (WP) of the European Commission the WP dealing with the SCCNFP opinion on IPBC as from 1 July 2004.

<sup>5</sup> The scientific committee in its opinion SCCS/1314/ as of 22 June 2010 also stated that thyroid tumours and effects on the thyroid were the most prominent adverse treatment-related effects after administration of erythrosine.....These observation support the hypothesis, that long-term dietary administration of erythrosine to rats produces a situation of hyper-stimulation of the thyroid which could ultimately end-up in thyroid tumours (ref. Couch *et al.*, 1983 in the opinion).

	<ul style="list-style-type: none"> <li>• Ethiodized oil</li> <li>• <i>Fucus vesiculosus extract</i></li> <li>• <i>Laminaria digitata extract</i></li> </ul>
<b>Synonyms</b>	<p>Synonyms that also are INN names – i.e. generic pharmaceutical names:</p> <p><i>Prolonium iodide</i> for Hydroxypropyl bistrimonium diiodide  <i>Povidone - iodine</i> for PVP-iodine</p> <p><i>Besides Iodotrat</i> is synonymous with TEA-hydroiodide; <i>ethiodol</i> is synonymous with ethiodized oil, whereas bladderwrack is the English name for the herb <i>Fucus vesiculosus</i> and oarweed is <i>Laminaria digitata</i></p>
<b>CAS No.</b>	See CosIng
<b>EINECS No.</b>	See CosIng
<b>Molecular formula</b>	-
<b>Chemical structure</b>	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p><math>\text{NH}_4\text{I}</math> <b>Ammonium iodide</b></p>  <p><b>Iodoform</b></p> </div> <div style="text-align: center;"> <p><math>\text{KI}</math> <b>Potassium iodide</b></p>  <p><b>Hydroxypropyl bistrimonium diiodide</b></p> </div> <div style="text-align: center;"> <p><math>\text{NaI}</math> <b>Sodium iodide</b></p> </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="text-align: center;">  <p><b>PVP-iodine</b></p> </div> <div style="text-align: center;">  <p><b>TEA- hydroiodide</b></p> </div> </div> <p><b>Ethiodized oil</b> is composed of iodine (37%) combined with ethyl esters of fatty acids of poppy seed oil primarily as ethyl mono-iodostearate and ethyl diiodostearate. The precise structure is not known (RcList <sup>6</sup> and Martindale) but complies, probably, with the following one <sup>7</sup>;</p> $\text{CH}_3-(\text{CH}_2)_n-\text{CHI}-(\text{CH}_2)_m-\text{CHI}-(\text{CH}_2)_p-\text{COOC}_2\text{H}_5$

<sup>6</sup> RcList is an online service to the medicinal profession in their search for adequate remedies : confer <http://www.dino-online.de/leiste/?url=http://www.rxlist.com/cgi/generic2/ethiodol.htm>

<sup>7</sup> <http://www.drugbank.ca/system/msds/DB00965.pdf?1265922744>

	<p>The <b>algae</b> in question - i.e. primarily the two selected seaweeds <i>Laminaria digitata</i> (<i>brown algae</i>) and <i>Fucus vesiculosus</i> (<i>brown algae</i>) - may contain up till 0.8 % and 0.2 % iodine as dried raw material respectively (Council of Europe 1<sup>st</sup> plant book in 1989 as concerns <i>fucus vesiculosus</i>).<sup>8</sup> A large percentage of the iodine content in algae is in the form of organic iodides; up to 37% in the <i>brown ones</i> and up to at least 50% in the <i>red ones</i>. The organic iodides consist of the following two tyrosine iodine derivatives:</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p><b>3-iodotyrosine (MIT)</b> (CAS No 70-78-0) 41 % iodine</p> </div> <div style="text-align: center;">  <p><b>3,5-diiodotyrosine (DIT)</b> (CAS No 66-02-4) 59 % iodine</p> </div> </div> <p>These molecules are precursors in the metabolic formation of the T3 and T4 thyroid hormones:</p> <p>MIT + DIT → T3 (triiodothyronine) DIT + DIT → T4 (thyroxine)</p> <p>(Marchal P <i>et al</i> 2000, Hou X <i>et al</i> 1997, André S 1971, textbooks). The bioavailability over the gut epithelia of iodine in MIT is about as high as for potassium iodide (KI); 80.0% compared to 96 % (Aquaron R <i>et al</i> 2002).</p> <p>The Council of Europe 1<sup>st</sup> plant book in 1989 mention that when extracts are made using propylene glycol as percolating agent, the <i>Fucus vesiculosus extract</i> obtained contains at least 0.2 % total iodine.</p>
<b>Molecular weight</b>	-
<b>Contents (if relevant)</b>	See above for the algae extracts
<b>Physiochemical properties</b>	-

## 2. Uses and origin

<b>Uses</b>	<p>➤ <b>Cosmetic products:</b></p> <p><i>Functions according to:</i></p> <ul style="list-style-type: none"> <li>○ CosIng database (CosIng [online]).</li> </ul> <table border="1" style="width: 100%; margin-top: 10px;"> <thead> <tr> <th style="width: 60%;"><i>Ingredient(s)</i></th> <th><i>Functioning</i></th> </tr> </thead> <tbody> <tr> <td>NH<sub>4</sub>I, KI, NaI, HCl<sub>3</sub></td> <td></td> </tr> </tbody> </table>	<i>Ingredient(s)</i>	<i>Functioning</i>	NH <sub>4</sub> I, KI, NaI, HCl <sub>3</sub>	
<i>Ingredient(s)</i>	<i>Functioning</i>				
NH <sub>4</sub> I, KI, NaI, HCl <sub>3</sub>					

<sup>8</sup> Wikipedia: The iodine content of Kelp range from 89 microgram /g to 8165 microgram/g; that is from 0.009 % to 0.8 %, which corresponds to the range 89 ppm to 8165 ppm

	Hydroxypropyl bistrimonium diiodide, PVP-iodine	Antimicrobial
	TEA- hydroiodide	Buffering and skin conditioning
	<i>Laminaria digitata extract</i>	Skin protecting
	<i>Fucus vesiculosus extract</i>	Emollient, skin conditioning, smoothing, soothing
	Ethiodized oil	Emollient

○ Council of Europe 1<sup>st</sup> plant book 1989 as concerns *fucus vesiculosus*

- Soothing, smoothing, emollient, stimulant.

○ Other as concerns the *algae extracts*

Finnish authorities observed that out of 32 **anti-cellulite products** studied 11 contained different algae extracts (Sainio EL 1997). Most probably the purpose of using these extracts in anti-cellulite products differs from the functioning mentioned in the CosIng.

Confer also Appendix 2 about special algae treatments being offered in some spas.<sup>9</sup>

○ Council of Europe (2008) as concerns PVP-iodine (taken from Appendix 4)

One of the cosmetic usages of PVP-iodine is in **oral-care hygiene products**, mouth rinses. The iodine wiper represents a new technology for the application of antimicrobial materials to the hands of food processing / food handling personnel.

*Frequency of use*

○ According to the German **Codecheck** database the frequency of use was as follows 28 October 2013

<i>Ingredient</i>	<i>Number of products containing ingredient</i>	<i>Type of product (number of products identified in parentheses)</i>
NH <sub>4</sub> I	0	
Nal	0	

<sup>9</sup> The appendix text is taken from an enclosure to a letter that the Norwegian Food Safety Authority submitted to the European Commission March 7, 2005; letter reference number is 05/8762. The letter can be obtained upon request to the Norwegian Food Safety Authority. The information about the spa algae treatments (*Thalasso procedure*) was the basis for the Working Party on cosmetics products of the European Commission, discussing at the time proposal for adjusted maximum use requirements for the preservative IPBC.

	KI	32	Face masks (7) Shampoo (3) Soaps (2) Body lotion (2) Shower gel (2) Peeling cream (2) Face water (2) Face lotion (2)  Face care gel (1) Tanning cream (1) Hand cream (1) Cleaning of face (1) Day cream (1) Body styling cream (1) Mouth care (1) Various products (3)
	Iodoform	0	
	Ethiodized oil	0	
	Hydroxypropyl bistrimonium diiodide	1	Face mask
	PVP-iodine	1	Hair spray
	TEA- hydroiodide	1	Body contouring
	<i>Laminaria digitata</i> extract	210	Various kinds
	<i>Fucus vesiculosus</i> extract	295	Various kinds  40 arbitrarily picked products:  Face mask: (10) Soap (4) Shampoo (4) Anti – wrinkle (3) Body lotion /gel (4) Other hair care (4) “slimming” (2) Some face product (4) Nail product (1) Mud pack (1) Other (3)

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- A search at **EWG`s Skin Deep** (EWG's Skin Deep [online]) showed 35 products containing KI and 82 products containing *fucus vesiculosus* extracts.

The types of products concerned correspond closely to the ones observed in the Codecheck database. In many instances KI is present together with the algae in the product.

Besides, the EWG database lists one foot soap product – that contains **iodoform**, and also a product claimed to be slimming and contouring cream that contains **TEA-hydroiodide**.

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- According to the source **Goodguide**<sup>10</sup> KI and the two seaweed extracts are present in the following product types

Type of product	Number of products that contain		
	KI	<i>Laminaria digitata extract</i>	<i>Fucus vesiculosus extract</i>
Lipstick	30		
Hair colour and bleaching	21	2	
Bath oils/salt/soak	15	2	
Eye shadow	13		
Lip liner	11		
Bath and shower cleaner	10		
Bleach products	6		
Blush	5		
Sunless tanning	4	1	
Foot cleansing	4		
Mask	3	14	12
Makeup	3		
Eye liner	3	9	
Facial moisturizer	1	13	2
Bath and shower	1		
Corn	1		
Moisturizer	1	3	7
Foot	1	2	2
Bar soap	1		1
Baby care	1		1
Anti-aging	1	16	1
Facial cleanser		17	4
Shampoo		16	
Conditioner		15	2
Body wash and cleanser		12	7
Shampoo + conditioner		10	
Eye cream		10	1
Mascara		10	1
Body firming lotion		8	2
Hair spray		7	
Anti Frizz		5	
Concealer		4	
Skin toner		4	3
Styling gel/mouse		5	2

<sup>10</sup> <http://www.goodguide.com/ingredients/117059-potassium-iodide>  
<http://www.goodguide.com/>

Goodguide is an American database that in its presentation also conveys that: "To address the consumer marketplace's need for better information, GoodGuide has assembled a team of scientific and technology experts to take on the challenge of organizing the world's product information. Our Chief Scientist is Bill Pease, an expert in chemical risk assessment and creator of the web's top pollution information resource, scorecard.org. His science team includes specialists in life cycle assessment, environmental engineering, chemistry, nutrition and sociology. Together we are working to acquire and compile high quality data, which we then organize and transform into actionable information for consumers.



Body and foot scrub		3	2
Other eye makeup		2	1
Facial scrub		2	1
Sunscreen		2	
Hand cream		2	1
Foundation		2	
Hair relaxer		1	
After shave		1	
Hair care general		1	
Eye makeup remover		1	
Detangler		1	
Bubble bath		1	
Skin care		1	
Skin lightener		1	
Body oil		1	
Stretch mark		1	
Anti-dandruff		1	
Body powder		1	
Facial powder			3
Liquid had soap			2
Scalp treatment			1
Shaving cream			1
Sum number of products	106	206	60

The Goodguide database also contains the same **iodoform** foot soap as does the EWG database.

- Potassium iodide (KI) is used also in iodized bathing salts - see Appendix 3

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- Other as concerns TEA-hydroiodide

On the internet a lot of so-called body countering products are announced, for example the following five:

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*Concentrations applied*<sup>11</sup>

- **Potassium iodide (KI)**

<sup>11</sup> The data shown under this title are mainly collected from a letter (enclosure IV) from the Norwegian Food Safety Authority to the European Commission 24 September 2004 (our ref 04/4053). The Norwegian Food Safety Authority can provide the letter upon request. The data were laid to ground the Working Party on cosmetics products of the European Commission discussing at the time proposal for adjusted used conditions for the preservative IPBC. The enclosure IV is presented in Appendix 3. It can even be reached on the internet at [http://www.mattilsynet.no/kosmetikk/stoffer\\_i\\_kosmetikk/enclosure\\_iv\\_letter\\_to\\_eu\\_commission\\_on\\_theipbc\\_case\\_24\\_september\\_2004.10800/BINARY/ENCLOSURE%20IV%20-%20letter%20to%20EU%20Commission%20on%20theIPBC%20case%2024%20September%202004](http://www.mattilsynet.no/kosmetikk/stoffer_i_kosmetikk/enclosure_iv_letter_to_eu_commission_on_theipbc_case_24_september_2004.10800/BINARY/ENCLOSURE%20IV%20-%20letter%20to%20EU%20Commission%20on%20theIPBC%20case%2024%20September%202004)

	<p>Iodized bath salt (Appendix 3): 1.2 - 2.0 gram KI per kg product. 500 g is sufficient for 3-4 baths</p> <ul style="list-style-type: none"> <li>• <b>NH<sub>4</sub>I, NaI, HCl<sub>3</sub> (iodoform), Hydroxypropyl bistrimonium diiodide (Prolonium iodide), Ethiodized oil</b></li> </ul> <p>No data is presently available in the public domain. These 5 ingredients seem to be used only very sparingly.</p> <ul style="list-style-type: none"> <li>• <b>PVP-iodine</b> (Council of Europe 2008, Appendix 4)</li> </ul> <p>Mouth waters: 1 % Fluid in wipes: 5 %</p> <ul style="list-style-type: none"> <li>• <b>TEA- hydroiodide</b></li> </ul> <p>Anti-cellulite: 0.8 % (Appendix 3) Emulsions, gels, massage creams: from 0.6 to 3%. Foam baths 8% (Producer)</p> <ul style="list-style-type: none"> <li>• <b>Laminaria digitata extract</b>, (Appendix 3)</li> </ul> <p>Spa treatment involves whole body application of 200 g extract that contains 0.3 -0.8 % iodine.</p> <ul style="list-style-type: none"> <li>• <b>Fucus vesiculosus extract</b> (Council of Europe 1<sup>st</sup> plant book 1989)</li> </ul> <p>Slimming (shower, gels, cream): 10 % Massage creams: 10% Iodine content in extract: minimum 0.2%</p> <p>Maximum up to ca. 5 % extract (based on impression from commercial announcements)</p> <p>➤ <b>Medicinal products/applications</b></p> <ul style="list-style-type: none"> <li>○ KI is perhaps the most used remedy against iodine deficiency (iodine fortified foodstuffs). It is also used medicinally as an expectorant and as a remedy against certain fungus infections (<i>spingo tricosis</i>) (taken orally).</li> <li>○ Iodoform is used for wound disinfection. Then the usage and consumption are 4% -6% in gauze and 5% - 10% in topical ointment.<sup>12</sup></li> <li>○ 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 (Martindale).</li> <li>○ PVP-iodine also is known as Betadine and is among the leading antiseptics used in hospitals today. 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 medicinal mouthwashes for prevention of peridontitis and infections that might arise in the mouth in the connection with piercing.</li> <li>○ Ethiodized oil is used in medicine as a contrast medium. It was the first</li> </ul>
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<sup>12</sup> <http://www.chemyq.com/En/xz/xz13/120591fonll.htm>

	<p>iodinated contrast agent (used for myelography). Further, because it is slowly metabolised to release iodine it is used in the management of iodine deficiency (Martindale)</p> <ul style="list-style-type: none"> <li>○ Extracts of <i>fucus vesiculosus</i> (as dried seaweed) is an ingredient of a number of herbal preparations given for various disorders including obesity, constipation and iodine deficiency (Martindale).</li> </ul> <p><i>Fucus vesiculosus</i> was the original source of iodine, discovered in 1811, and was used extensively to treat goitre (wikipedia).</p> <p>➤ <b>Food and drinking water</b></p> <p>Because iodine is an essential trace mineral required for thyroid hormone synthesis, in many countries KI is added to fodder, table salts and/or other foodstuff in order to secure a good iodine status in the general population.</p> <p>Kelp – including bladderwrack – is foodstuff raw material in many countries.</p>
<b>Origin</b> Natural (exo/endo) Synthetic	Synthetic except for KI and the seaweed extracts. Iodoform is a synthetic product, but occurs also naturally in the non-edible mushroom <i>Mycena arcangeliana</i>

### 3. Regulation

<b>Norway</b>	No regulation at present. Up to 2008 the Norwegian regulation was such that in case any of the 10 particular ingredients were present in a topical product that product automatically was considered falling within the scope of the Norwegian medicinal products legislation. This implied that in effect the 10 ingredients were not allowed in cosmetic products. This regulation was withdrawn October 2008.
<b>EU</b>	No regulation
<b>Rest of the world</b>	No regulation, with the exception that in the US some of these compounds are not allowed in cosmetics because the US foods and drugs administration (FDA) considers them medicinal remedies in themselves. This concerns for example the PVP-iodine.

### 4. Relevant toxicity studies

<b>Absorption</b> Skin	Skin penetration rates as basis for systemic exposure estimates:		
	Ingredient	Penetration rate (%)	Reference
	Iodopropynyl butylcarbamate (IPBC)	20	Opinion SCCNFP/0826/04 of the European Commission scientific committee SCCNFP as of 1 July 2004 (can also be retrieved on the internet via CosIng).

	CI 45430 (Erythrosine)	No indications of systemic bioavailability could be observed (references Carson, 1983; and Hazleton Laboratories, 1969 in the opinion)	Opinion SCCS/1314/10 of the European Commission scientific committee SCCS as of 22 June 2010 (can be retrieved on the internet via CosIng)
		0.13 ethanol - water 1:1  0.04 oil in water emulsion	<i>In-vitro</i> percutaneous absorption through human skin  Franz TJ, 1984  (the above mentioned SCCS opinion do not mention this reference)
	The iodide anion (I <sup>-</sup> ) as in the salts <ul style="list-style-type: none"> <li>• KI , NaI, NH<sub>4</sub>I</li> <li>• TEA- hydroiodide,</li> <li>• Hydroxypropyl bistrimonium diiodide</li> </ul>	0.1	See reasoning in Appendix 3
	I <sub>3</sub> <sup>-</sup> anion that form part of the PVP-iodine salt	0.06	Council of Europe publication 2008 on use of active ingredients in cosmetics. The Council refer to a SCCNFP opinion as of 1 July 2004 (SCCNFP/0826/04) SCCNFP opinion from 2004. Confer Appendix 4
	Iodoform  Ethiodol  3-Iodotyrosine,  3,5-Diiodotyrosine	100	In lack of data we apply the default value of 100 % skin penetration which is in compliance with the guidelines of the scientific committee of the European commission /SCCS).
<b>Distribution</b>	No data available ( <i>inter alia</i> – see Council of Europe monograph as presented in Appendix 4)		
<b>Metabolism</b>	No data available ( <i>inter alia</i> – see Council of Europe monograph as presented in Appendix 4)		
<b>Excretion</b>	No data available ( <i>inter alia</i> – see Council of Europe monograph as presented in Appendix 4)		
<b>Local toxic effects</b>	<b>PVP-iodine</b>		

<p>Irritation Sensitivity</p>	<p>The PVP-iodine complex slowly releases iodine when in contact with skin. Only a small amount of iodine is released at any time, giving PVP-iodine a lower irritant potential than more conventional iodine solutions such as tinctures of elemental iodine. Albeit an uncommon occurrence, irritant contact dermatitis induced by PVP-iodine can be an unfortunate adverse reaction complicating its use as an antiseptic (Murthy MB <i>et al</i> 2009). The skin lesions of irritant contact dermatitis may clinically and histologically resemble the lesions of toxic epidermal necrolysis (Vandegriff TW <i>et al</i>).</p> <p><b>Iodide</b></p> <p>When patch testing has been conducted, positive reactions may be seen with PVP-iodine, but not with iodine (I<sub>2</sub>) or potassium iodide (KI) (Katelaris CH, 2009). None of five patients with a history of contact dermatitis after PVP-iodine reacted to patch testing with KI solution, whereas all reacted to PVP-iodine (Van Ketel WG 1990).</p> <p><b>Iodoform</b></p> <p>In connection with use as an antiseptic in dental dressing stomatis dermatitis has been reported (reference in Appendix 3)</p>
<p><b>Systemic toxic effects</b></p>	<p><i>Iodine bound in organic molecules are liberated entirely when taken up in the body</i></p> <p>The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) in its opinion SCCNFP/0826/04 assumes that covalently bound iodine in the molecule IPBC is entirely liberated from the molecule and becomes systemically available subsequent to uptake in the skin. The SCCNFP explains as follows about the mechanism behind the splitting off of the iodine substituent:</p> <p style="padding-left: 40px;">Oxidative dehalogenative metabolism of iodinated compounds might occur via enzymes related to thyrooxidase (ThOx) or by processes know from activated leukocytes, macrophages etc., where oxidative dehalogenation occurs, leading to the liberation of iodide, which then can either be incorporated into proteins of any source or end up in the thyroid via accumulation by the NIS (sodium iodide symporter), highly efficient and expressed in the human thyroid.</p> <p>Hence, this probable mechanism applies to splitting off of iodine irrespective of the individual organic molecule concerned. E.g. it applies not only to de-iodination of IPBC but to de-iodination of all organic molecules containing an iodine-carbon covalent bond. The molecules concerned includes also the following ones: <i>erythrosine</i>, <i>iodoform</i>, <i>ethiodized oil</i><sup>13</sup>, the <i>iodine derivatives of tyrosine</i> as well as the molecule <i>diiodomethyltolylsulfone</i> and the different iodized plant extracts mentioned in Appendix 1.</p> <p>As a further confirmation that this mechanism applies is the observation that thyroid disruption / hypothyroidism, thyroid cancers occur also in connection with iodine containing drugs and other molecules. On this see Appendix 6.</p>

<sup>13</sup> As concerns ethiodol it has been found that urinary excretion in the form of inorganic iodine was the chief mode of iodine loss from the system. Iodine is split off from fatty compounds and becomes free iodine in the body (Drugs Com) : <http://www.drugs.com/pro/ethiodol.html>.

Drugs.com presents itself as the largest, most widely visited, independent medicine information website available on the Internet. (<http://www.drugs.com/support/about.html>)

So topical application of IPBC, and all other iodine containing molecules for that sake, is in effect a way of supplying the body with iodine. There is no indication that the route of iodine intake influences the effect of iodine in the organism (SCCNFP/0826/04).

*Comparatively narrow gap between recommended daily intake and toxic levels*

The recommended daily intake (RDI) of iodine via the food in Europe is 150 microgram in adults. At somewhat higher levels (TI) iodine cause systemic toxic effects. The gap between RDI and TI appears to be narrow. Thus, contribution to iodine exposure by other sources than food is problematic from a public health perspective (*inter alia*).

*The toxic effects and the thyroid gland*

The only known adverse health effects associated with variation in iodine intake is related to the thyroid gland and its diseases. Larger amounts of iodine than recommended may have a variety of direct toxic effects. These are described at length in the Council of Europe monograph as presented in the Appendix 4.

*Different levels of toxicity*

Back in 1995 it was commonly believed that it would be safe for adult people having a healthy thyroid, to take in 1000 microgram iodine per day. Currently the assumed safe level is no more than 600 microgram/day. So over the years there has been a downward trend new scientific data becoming available. The former Scientific Committee on Food (SCF)<sup>14</sup> in 2003 arrived at a tentative "Tolerable Upper Intake Level" (tUL) amounting to 600 microgram/day<sup>15</sup>. There might be a risk for enlarged thyroid volume at an even lower level (Zimmermann MB *et al* 2005). So 600 microgram /day is no more than a temporary estimate. The SCCNFP (SCCNFP/0826/04) referred to the SCF opinion launching the tUL (SCF/CS/NUT/UPPLEV/26; 7 October 2003).

In a report delivered in 1995 the Nordic Council (Nord 1995:18) concluded as follows:

"It may be stated that there are large individual differences when it comes to thyroid function disturbances following increased iodide intake in some individuals. The intake of up to 1 000 microgram iodine/day is usually safe, but not for individually disposed people, as will appear also from the following compilation (Bürgi *et al* 1982):

Intake of iodine microgram /day)	Effects of different doses of iodine intake of thyroid functioning
0-50	<i>Iodine deficiency. Goitre, hypothyroidism</i>
(50) -100-300	<i>Normal thyroid functioning</i>
300 - 1000	<ol style="list-style-type: none"> <li>1. <i>Increasing rate of lympholytic thyroiditis (*)</i></li> <li>2. <i>Lower remission rate of auto-immune hyperthyroidism</i></li> <li>3. <i>Relative increase in the rate of papillary thyroid carcinoma and decrease in follicular carcinoma</i></li> <li>4. <i>Iodine Basedow (**)</i></li> </ol>

<sup>14</sup> The Scientific Committee on Food (SCF), established in 1974, was the main committee providing the European Commission with scientific advice on food safety, until its responsibilities have been transferred to the European Food Safety Authority (EFSA).

<sup>15</sup> The tUL is based on elevations in TSH levels after iodine intake and an enhanced response in TSH levels to TRH stimulation. These effects are of a biochemical nature and are not associated with any clinical adverse effects

1000 – 10 000	1. <i>Iodine Basedow</i> 2. <i>Iodine goitre and hyperthyroidism</i>
> 10 000	<i>Gradual reduction in thyroid hormone production</i>

(\* ) Same as Hashimoto's disease (\*\* ) Same as Grave's disease

SCCNFP (SCCNFP/0826/04) cites studies with healthy volunteers and variable intake of iodine. 750 microgram /day intake caused biological disturbances as manifested by changes in the circulatory levels of the hormones T4, TSH and TRH. At 500 microgram/day results were variable from one study to the other, whereas at 250 microgram /day biological changes were not observed. (An extrapolation of these data to chronic administration appeared difficult).

Thyroid autoimmunity disease is very common and thyroid abnormalities, in general, are very common in the population. Focal lymphocytic infiltration of the thyroid was found in around 50 % of middle aged and elderly Caucasian women at autopsy. In Denmark, 30 % of elderly women had circulating antibodies against one or more thyroid proteins. And 30 % of elderly women had thyroid nodules. Both thyroid autoimmunity and thyroid nodularity are often undiagnosed, and both conditions may predispose to iodide induced abnormalities in thyroid function. (SCCNFP/0826/04).

People with thyroid autoimmunity and/or thyroid nodularity may experience hyper (Grave's disease) or hypothyroidism (Hashimoto's disease).

The Nordic Council (Nord 1995:18) was of the opinion that even for iodine sensible people –i.e. including also those having attracted the mentioned thyroid abnormalities – a daily intake up to 300 microgram would be safe. Hence, the difference between RDI and this upper limit is only 150 microgram per day.

The average intake of iodine *via* foodstuff may be high in some countries. In the Nordic countries the picture is somewhat diverse. As appears from the below table the average daily intake in Norway complies with what is recommended because of the need of the body for iodine (150 - 200 microgram/day).

Country	Intake microgram /day	
	Average Nordic Council report (1995)	Average and range
Denmark	Ca. 60	110  Both sexes Aalborg and Copenhagen in 2004-5. Denmark introduced iodine fortification some years before 2004. (Rasmussen <i>et al.</i> 2008)

Finland	300		
Iceland	300 – 350		
Norway	150 – 200	214±64, 103 - 355	Women in Oslo area in 2007 (Brantsæter <i>et al.</i> 2009)
Sweden	Ca. 200		

A study performed in 1988 covering 17 Norwegian communities – both inland and coastal ones – showed a geographical spread reaching from 129 to 364 microgram /day. Further, it has been shown that Norwegians eating no salt water fish takes in on average 127 microgram /day whereas those who include such fish in their diets 4 days out of 10, takes in on average 289 microgram /day (Frey *et al* 1993)

Especially in regions where people enjoy also seaweed (*Fucus Vesiculosus*) to some degree, the iodine intake can soar. In Okinawa where the kelp consumption is very high, the average urinary iodine excretion in a group of 1039 subjects studied was found to be 1500 microgram/day (Nagata *et al* 1998). Urinary iodine values as high as 3000 – 5000 microgram/day have been seen in the Japanese town Sapporo (Konno *et al* 1998).

The extraordinarily high intakes observed in Japan because of kelp have led to an increased frequency of disrupted thyroid functioning. “Sea tangle powder” is sometimes used to a great extent in Norway also, and there are several examples of deleterious effects on consumers of these products (Nordic Council report 1995). Data indicate intake values of 2000 microgram/day and above (Skare 1980). Kelp isn't a very uncommon health food supplement in other European countries also.



## 5. Exposure estimate and safe intake of iodine related to use of cosmetics

<p>Safe intake of iodine</p>	<p>The SCCNFP in its SCCNFP/0826/04 opinion expresses that available evidence suggests that the optimal iodine intake to prevent thyroid disorders in a population is within a relatively narrow range around the recommended daily intake of 150 microgram/day. In that connection the committee holds that the possible iodine intake from non-food sources like cosmetic products should be negligible. <b>In practical life</b> this means, the committee says, that over a period of for example one week the contribution of cosmetic products to iodine intake should be maximally 10 % to 20 % of recommended intake. Concluding it says that</p> <p><i>“Considering the biological and physiological properties of iodine in potentially different populations at risk in Europe, the SCCNFP is of the opinion that the daily bio available intake of iodine from cosmetic products should not exceed 20% of the recommended daily intake of 150 µg which is 30 µg/day.”</i></p> <p>Obviously, the assumed <i>“practical life quota”</i> of 30 µg/day has no scientific foundation. Had the committee chosen 10 % instead of 20 % of the recommended intake it would have been only half as big.<sup>16</sup> Therefore, in our opinion, the actual sizing of a quote is secondary to the fact that the SCCNFP is of the view that the contribution of cosmetics to the total exposure <b>should be negligible</b>.</p> <p>Iodine is an essential micro mineral for human nutrition. From a health perspective it is of great importance that populations have a satisfactory iodine status. In some countries measures in the form of enrichment of certain foodstuffs and/or fodder are taken from time to time in order to secure a satisfying iodine status in populations. For the measures to be as efficient and controllable as possible iodine should be taken up in the body exclusively via the foodstuffs. Uptake because of use of cosmetic products must, therefore, be negligible. This is of importance even in countries with iodine deficiency. It was never the purpose of cosmetic products that they should serve as a secondary source for iodine in the population. Hence, even from a nutritional perspective the iodine contribution of cosmetics should be near to nil.</p> <p>In Norway, among people with high intake of fish the exposure of iodine <i>via</i> food may reach about 400 microgram/day, or even higher if also some kelp based food is part of the diet. Among those consuming the most the probability is that rather many have thyroid autoimmunity and/or thyroid nodularity making them susceptible to deleterious effects as mentioned. There might be even a risk for thyroid cancer in some of these disposed people.</p> <p>So, because many Norwegians consume more fish than most Europeans the more or less arbitrarily set “European quota” of 30 µg/day of iodine from cosmetics is likely much too liberal from a Norwegian public health perspective. Thus, our principal view is that iodine should not be allowed in cosmetic products.</p> <p>In a letter to the European Commission April 7, 2000, the Norwegian Food Safety Authority delivered a safety assessment on the use of IPBC in cosmetics, in which we concluded that IPBC should not be allowed in cosmetics at all<sup>17</sup>.</p> <p>In the Council of Europe monograph concerning use of organically bound iodine in cosmetic products in 2008 (Appendix 4) concludes as follows:</p>
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<sup>16</sup> 30 microgram /day is precisely the amount needed to allow for the authorisation of the preservative IPBC in the cosmetic directive on such condition that IPBC would function sufficiently effective as a preservative. This implies that in reality it was a wish to allow for the use of IBPC in cosmetics that determined the size of the quota.

<sup>17</sup> It was this intervention that resulted in the opinion SCCNFP/0826/04 and the subsequent revision of the regulation of the IPBC ingredient. The regulatory tightening brought the maximum allowed systemic exposure because of cosmetics down from 788 to 30 microgram/day.

	<p><i>"The IPBC take up 93% of the "quota" of 30 µg/day, leaving only 2 µg/day for other iodine containing products. PVP-iodine containing mouthwash can give as much as 1500 or 3000 µg/day and wipes can give 4.8 µg/day. Consequently, PVP-iodine should not be used in cosmetic products".</i></p> <p>Hence, our view is in line with the Council of Europe opinion that the maximum limit of iodine in cosmetics should not exceed 30 microgram iodine per day. The limit of not more than 30 microgram per day is absolute.</p>
<p><b>Exposure cosmetic products</b></p>	<p>The current regulation of the IPBC has as a consequence that the maximum allowed usage of this preservative involves a daily systemic intake of 28.05 microgram iodine. This appears from the European Commission working paper 05/ENTR/COS/55 which is referred to by the Council of Europe monograph as presented in Appendix 4. It was the European cosmetics branch organisation at the time, the COLIPA - which today is called Cosmetics Europe - that arrived at the figure of 28.05 microgram per day.</p> <p>This means that the regulated IPBC ingredient takes up 93 % of the 30 microgram /day "allowed" for the cosmetic products as a group. This leaves as little as 1.95 microgram/day for all other iodine compounds.</p> <p>The other European Commission scientific committee, the SCCS, in its opinion 2010 (SCCS/1314/10) on the safety of use of the regulated colorant CI 45430 (erythrosine) in toothpaste calculated a daily intake of the colorant as such amounting to 12 microgram. The erythrosine contains 57.7 % iodine so this permitted use involves a daily <i>ingestion</i> of 6.9 microgram iodine. However, not all of this is taken up in the body over the gut epithelia. The SCCS assumed a worst case bio-availability of 10 % even though most studies pointed in the direction of only 1 %. Hence, we assume that use of erythrosine in toothpaste involves at most a systemic iodine exposure of 0.69 microgram per day.</p> <p>Subtracting 0.60 microgram/day from 1.95 microgram/day leaves marginal 1.35 microgram/day for other usage of the erythrosine + the 24 unregulated iodine containing ingredients.</p> <p>The erythrosine colorant is allowed in all kinds of cosmetics products and not only in toothpaste – confer entry 80 of the Annex IV of the cosmetics regulation. Among 50 arbitrarily picked products in the Codecheck database erythrosine was found in</p> <ul style="list-style-type: none"> <li>23 lip products; mainly lipstick</li> <li>10 tooth pastes</li> <li>7 rouge products</li> <li>7 eye shadows</li> <li>7 shaving gels</li> </ul> <p>Lipsticks usually contain 5-8 % colorants (RIVM 2006) Usually a lipstick contains several colorants and a composition containing 5 colorants is not unusual. Calculating the iodine systemic intake caused by use of erythrosine containing lipstick we, conservatively, use the premise that CI 45430 is present at a concentration of no more than 1%. Further, we apply the default value of the scientific committee of the European commission (SCCS) as concerns the amount of lipstick swallowed daily which 40 mg. Also we apply the premise of 10 % bioavailability as mentioned above. Using this set of premises we calculate the following daily systemic intake of iodine that can be attributed to lipstick usage of erythrosine:</p> $40\ 000 \times 0.01 \times 0.1 \times 0.577 = \mathbf{23.08} \text{ microgram}$ <p>So, clearly, only because of the widespread allowed regulated use of IPBC and the colorant CI 45430 the consumer is exposed daily to much more than 30 microgram iodine.</p> <p>On this background and because all the known ingredients may penetrate skin to a greater or</p>

lesser extent, we are of the opinion that no other iodine containing ingredient should be used in cosmetic products.

For the sake of completion we estimate the following systemic iodine exposure resulting from employment of some of the 10 particular iodine containing ingredients.

Ingredient	Product type	Premises	Daily systemic intake microgram
PVP-iodine	Mouth water (gargle)	3 ml (g) is swallowed (SCCS default value) 5 drops (0,25 ml) of mouthwash in a glass of water (50 ml) Concentration in mouthwash before pouring into the glass: 1.0 % Bio-availability: 100 %	<b>87</b>  <i>Calculation:</i>  $3000\ 000 \times 0,01 \times 0.25 \times 0.577/50$
KI	Face mask (face pack)	Single product use: 20 gram (RIVM 2006) Frequency of use: 1-2 times a week (RIVM 2006) Partition coefficient: 1 (typical leave on product) Concentration: 0.5 % (illustrative value that complies with position in list of ingredients for face masks) Skin penetration rate of iodide: 0.1% (Appendix 3)	<b>109</b>  <i>Calculation</i>  $20\ 000\ 000 \times 0.005 \times 0.76 \times 0.001 \times 1 / 7$
	Iodized bath salt	Bath is added 0,3 g KI (estimated on the basis of information in advertisement - see Appendix 3) Partition coefficient: 0,01 (SCCS guideline) Skin penetration rate for iodide: 0,1% (see Appendix 3)	<b>2.3</b>  <i>Calculation</i>  $300\ 000 \times 0,01 \times 0,001 \times 0.76$
TEA-hydroiodide	Body contouring Cream (skin conditioning cream)	Skin area treated: 1600 cm <sup>2</sup> . <sup>18</sup> Amount of product per cm <sup>2</sup> is set to 1 mg. <sup>19</sup> Skin penetration rate for iodide: 0,1% (see Appendix 3) 2 applications per day (announcements) Partition coefficient: 1 (typical leave on product) Concentration 0.8 % (Appendix 3)	<b>11.6</b>  <i>Calculation</i>  $1\ 600\ 000 \times 0,008 \times 0,001 \times 2 \times 0,45$
Fucus	Face mask	Single product use: 20 gram (RIVM	<b>210</b>

<sup>18</sup> Estimating this skin area we precluded that the part of the body affected 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<sup>2</sup>.

<sup>19</sup> This default is in accordance with the SCCS notes of guidance

	vesiculosus extract	(face pack)	<p>2006)  Frequency of use: 1-2 times a week (RIVM 2006)  Partition coefficient: 1 (typical leave on product)  Concentration: 10 % (Council of Europe 1<sup>st</sup> plant book).  Concentration of iodine in extract 0.4% (Council of Europe 1<sup>st</sup> plant book say <i>at least</i> 0.2 %).  Concentration of iodine tyrosine derivatives in extract 0.2 x 0.37 % (Marchal P <i>et al</i> 2000, André. S 1971)  Skin penetration rate for iodine tyrosine derivative: 100 % (SCCS default value). Iodine content in molecule: 50%</p> <p><i>More realistic premises</i></p> <p>Illustrative value of concentration that complies with position in list of ingredients for face masks; 5 %. Skin penetration 2 % (powerful enhancers are present in all the algae masks).</p>	<p>(worst case: concentration of extract: 10 % and 100 % skin penetration rate)</p> <p><i>Calculation</i></p> <p>20 000 000 x 0.1 x 0.004 x 0.37 x 0.5 /7</p> <p><b>2</b></p> <p><i>Calculation</i></p> <p>20 000 000 x 0.05 x 0.004 x 0.02 x 0.37 x 0.5 /7</p>
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## 6. Other sources of exposure than cosmetic products

Food stuffs	See above
Pharmaceuticals	See above
Other sources	-
Adverse side effects - from uses other than cosmetics	See above

## 7. Assessment

Iodine is an essential trace mineral required for thyroid hormone synthesis in the body. The recommended daily intake (RDI) is 150 micrograms for non-pregnant adults. Both insufficient and excessive iodine intake can result in thyroid disease. Keeping the intake/exposure of iodine in the population under control is an important nutritional/public health issue.

SCCNP concluded in their opinion that the intake of iodine from non-food sources i.e. cosmetic products *should be negligible only* (SCCNP, 2004), not exceeding 20% of the recommended daily intake of 150 µg, which is 30 µg/day (SCCNP, 2004). The preservative IPBC take up 93% of 30 µg/day, when used at the maximum permitted levels according to the Cosmetic Product Regulation), leaving only 2 µg/day for other cosmetic products which contain iodine.

The Norwegian Food Safety Authority has taken an even more restrictive view that “negligible” means nil, because there are a whole series of other iodine containing ingredients on the market – confer the information shown in Appendix 3 – which would likely result in much higher intake than what is considered to be safe.

For example, the colorant CI 45430 (erythrosine) contributes substantially to the exposure of iodine from cosmetics. Use of products containing IPBC as a preservative and lipsticks containing 1 % erythrosine might regularly contribute 51 microgram systemically per day - which is 34 % of the recommended daily intake (RDI) through the diet. This is much more than the EU scientific committee thought of as a maximum allowed amount of iodine originating from the use of cosmetic products. 51 microgram is not a negligible amount but rather a substantial one by comparison. A lipstick containing 5 % erythrosine instead of the conservatively put 1 % would alone contribute with 115 microgram - which is close to the average intake of iodine in the adult population via the diet. Another example is PVP-iodine containing mouthwash, which can give as much as 1 500 or 3 000 microgram /day (Council of Europe calculations).

Consequently, it is our view that neither PVP-iodine nor any other cosmetic ingredient containing iodine should be used in cosmetic products.

In a letter 9 January 2007, the European Commission requested the industry (COLIPA and UNITIS) to provide a list of substances containing iodine used in cosmetics, their levels in finished product, and the types of products in which they are used. In the interim, the industry was asked to focus on avoiding the use of substances containing high levels of iodine; and/or find ways of reducing the levels of iodine. The industry committed to provide the requested information on time, and COLIPA welcomed the opportunity to address the issue of iodine containing substances and would come back with an action plan in due time. The letters are shown in Appendix 7. See also Appendix 8 for more information about the IPBC/iodine risk management case.

We, now 7 years later, observe that the European Commission never informed about any feedback as promised by industry. Further, we observe that not only are there numerous products of all kinds on the market that contain IPBC and erythrosine but also many different products containing potassium iodide (KI) and extracts of seaweed that contain comparatively high amounts of iodine. 20 – 50 % of the iodine within the extracts is in the form of organic molecules that might easily cross over the skin with the help of enhancers. The products in question often contain powerful enhancers. The molecules in question are precursors in the metabolic formation of the T4 and T3 thyroid hormones. When taken up in the body they are likely to interfere with the functioning of the thyroid.

Industry defended only the marginal use of erythrosine in toothpaste but is using it today mostly in lipstick and other products. The other use is not prohibited, however. Hence, we cannot for the moment do much about it but to advice the public not to purchase products in which erythrosine is declared on the label. As concerns all the other unregulated iodine containing ingredients mentioned in this document, we urge industry not to market products containing any of them.

## 8. Conclusion

Based on opinions and recommendations by both the scientific committee of the European commission and also the Council of Europe, as described in the present risk profile, The Norwegian Food Safety Authority is of the opinion that for health reasons none of the 24 iodine containing substances/ingredients should be used in cosmetic products. The substances concerned are:

- Ammonium iodide
- Potassium iodide
- Sodium iodide

- Iodoform
  - PVP-iodine,
  - Hydroxypropyl bistrimonium diiodide
  - TEA- hydroiodide
  - Ethiodized oil
  - *Fucus vesiculosus extract*
  - *Laminaria digitata extract*
- 
- Diiodomethyltolylsulfone
  - Dimethylaminostyryl heptyl methyl thiazolium iodide
  - Platonin
  - Quaternium-45
  - Quaternium-51
  - Quaternium-73
  - *Laminaria hyperborea extract*
  - *Laminaria saccharina extract*
  - *Gracilaria verrucosa*
  - Iodized corn protein
  - Iodized garlic
  - Iodized garlic extract
  - Iodized hydrolysed extension
  - Iodized hydrolysed zein

Also any other iodine containing ingredient which is not yet listed in the CosIng database should not be used in cosmetics

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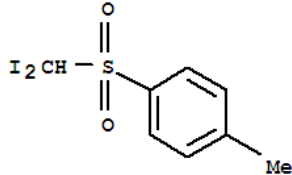
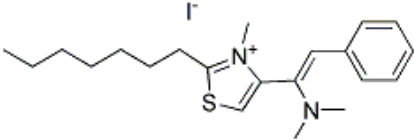
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## 10. Appendixes

### Appendix 1

#### The other iodine substances mentioned in CosIng

Ingredient (INCI name)	Number of products containing ingredient according to  A) The Codecheck B) The Goodguide	Structure
DIIDOMETHYLTOLYLSULFONE ( <i>amical</i> )	A): 0 B): 0	
DIMETHYLAMINOSTYRYL HEPTYL METHYL THIAZOLIUM IODIDE	A) 0 B) 0	
PLATONIN	A): 0 B): 0	



QUATERNIUM-45	A): 8 B): 0	<p>Functioning: antistatic</p>
QUATERNIUM-51	A): 6 B): 4	<p>Functioning: antistatic</p>
QUATERNIUM-73	A): 0 B): 8	<p>Appendix 3 provides some information about this molecule</p> <p>Function: antistatic</p>

Other algae extracts in question		
<i>Laminaria hyperborea</i> (LH) (brown algae)	LH: A): 14 B) 0	<i>Laminaria hyperborea</i> . The observed iodine values are between 5500 and 7000 ppm on the dry weight (0.55 – 0.7 %) (Marchal P <i>et al</i> 2000) 500 ppm hydroglycolic extract (UNITIS)
<i>Laminaria saccharina</i> (LS) (brown algae)	LS: A): 192 B): 0	<i>Laminaria saccharina</i> The observed iodine values are between 2789 and 5277 ppm on the dry weight (0.27 – 0.53 %) (CEVA 2004)
<i>Gracilaria verrucosa</i> (GV) (red algae)	GV: A): 0 B): 0	<i>Gracilaria verrucosa</i> Usually, the level observed are near 500 ppm (0.05 %) (Marchal P <i>et al</i> 2000)
IODIZED CORN PROTEIN	A and B: 0	
IODIZED GARLIC	A and B: 0	
IODIZED GARLIC EXTRACT	A and B: 0	Medicinally used garlic oil consists nearly exclusively of allylsulphides of different kinds (Lawson LD 1998). When I <sub>2</sub> is added to the oil we would believe that they are reacted, at least some to degree, into iodine derivatives like for example ICH <sub>2</sub> -CHI-CH <sub>2</sub> -S-S-CH <sub>2</sub> -CHI-CH <sub>2</sub> I (M= 654 out of which 77,7% is due to iodine). The ingredient probably also contain high amounts of I <sub>2</sub> complex(es).
IODIZED HYDROLYZED EXTENSIN	A and B: 0	Extensins are homologous hydroxyproline-rich glycoproteins found in the plant extracellular matrix. When hydrolysed the amino acid hydroxyproline is formed. Possibly, iodination involves formation of either iodine derivatives of this amino acid (5-Iodo- 4-hydroxy-L-proline) or a charge-transfer complex between this molecule and I <sub>2</sub> . No information about iodine content is found.
IODIZED HYDROLYZED ZEIN	A and B: 0	

## Appendix 2

The below text is taken from an enclosure to a letter from the Norwegian Food Safety Authority to the European Commission March 7, 2005.

### **Algae treatment**

The below picture illustrates how these products are applied so as to cover the body nearly entirely. They are applied either warm or cool. Following a scrub, body is painted with sea weed (Alga) paste and wrapped in a warm blanket. Usual procedure is to wear the product from 15 minutes to ½ hour per application. When taking part in the Thalasso procedure it's customary to go through 3 such application during a stay of one week at the enterprise offering the service.



### **Announcement collected from the Internet:**

The (*name of product*) is a classic European spa treatment. When powder is added to water it becomes a soft paste to be applied over the entire body. This firming treatment allows deep penetration of beneficial marine ingredients into skin cells. The combination of *Spirulina* and *Laminaria* seaweeds with horsetail and Kaolin increases the penetrating action of individual components on skin. The product provides a soothing effect as well as due to natural clay (Kaolin). *Spirulina* provides amino acids necessary to firm tissues.

#### LAMINARIA DIGITATA

Organic compounds 65 - 80 %

Mineral elements 25 - 28 %

Fucoïdine 4 - 7 %

Laminarine 10 -18 %

Mannitol (moisturizing) 7 - 16 %

Sulphur (purifying) 0.9 -1.5 %

Iodine (slimming) 0.3 -0.8 %

These figures come from scientific data and publications. They are not to be considered as guaranteed.<sup>20</sup>

#### DIRECTIONS FOR USE

Mix 200 g of powder with 400 ml of warm water to obtain a homogeneous paste. Apply directly to entire body. Wrap the client in a plastic sheet then in a warming blanket.

Treatment time: from 15 to 30 minutes.

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**Comments.** The above text was downloaded from an internet announcement 9 years ago. Similar announcements are still made in 2013/2014 – confer for example the following ones:

<sup>20</sup> Therefore, these concentrations need not be for this particular product.

## Appendix 3

Beneath is shown the enclosure IV of a letter sent 24 September 2004 from the Norwegian Food Safety Authority to the EU Commission asking for prohibition of the preservative IPBC in cosmetic products

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

#### Content

• Identification of the other iodine-containing ingredients.....	Page 1
• Iodine weight percentage of ingredients that seems to find use.....	Page 5
• Skin-penetration rates.....	Page 6
• Approximate exposure calculations for ingredients fining use.....	Page 7
• Safety data for some of the ingredients in question.....	Page 12
• Iodine-containing compounds banned in cosmetics.....	Page 14
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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 (9<sup>th</sup> 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

INCI Name	INN	Pharm Eur Name	CAS Nr	EINECS Nr	Chemical name	Restriction	Function (In it men som func accc CTF (Nurr to co below
ACID RED 51 CI 45430	Erythro-sine		16423-68-0	240-474-8	Disodium 2- (2, 4, 5, 7-tetraiodo- 6- oxido- 3- oxoxanthen- 9- yl)benzoate (CI 45430)	IV/1	hair color
ACID RED 95 CI 45425, CI 45480			33239-19-9	251-419-2	Disodium 2- (4, 5- diiodo- 6- oxido- 3- oxoxanthen- 9- yl)benzoate (CI 45380)	VI/1	hair color
ALGEA							botanical (1)
AMMONIUM IODIDE			12027-06-4	234-717-7	Ammonium iodide		antir
DIIDOMETHYL-TOLYLSULFONE			20018-09-1	243-468-3	P- [(diiodomethyl) sulphonyl]-toluene		antir
DIMETHYLAMINO-STYRYL HEPTYL METHYL THIAZOLIUM IODIDE					Thiazolium, 3- heptyl- 4- methyl- 2- [2- (4- dimethylaminophenyl) ethenyl]- , iodide		antir
ETHIODIZED OIL	ethiodized oil		8008-53-5		Fatty acids, poppy seed, iodinated, ethyl esters		emollient (2)
FUCUS VESICULOSUS		fucus	84696-13-9	283-633-7	Fucus vesiculosus, ext. Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from Fucus vesiculosus, Fucaceae		botanical (3)
HYDROXYPROPYL BISTRIMONIUM DIIODIDE	prolonium iodide		123-47-7	204-630-9	Prolonium iodide		antir (skin conditioning agent) (4)

IODIZED CORN PROTEIN					Proteins, corn, iodinated		botan (skin conditi agent)
IODIZED GARLIC					Allium sativum, garlic, iodinated		botan
IODIZED GARLIC EXTRACT					Allium sativum, garlic, ext., iodinated		botan
IODIZED HYDROLYZED ZEIN (Iodoprolamina) (*)					Protein hydrolyzates, zeins, iodinated		biolog additi (5)
MEA-IODINE (Iodamicid)			94349-34-5	305-151-9	2- aminoethanol, compound with iodo		antim (hair c agent)
NONOXYNOL-12 IODINE			11096-42-7		Poly(oxy- 1, 2- ethanediyl), a- (nonylphenyl)- ?- hydroxy- , compd. with iodine		antim
NONOXYNOL-9 IODINE $C_{33}H_{60}O_{10} \cdot xI_2$			94349-40-3 11096-42-7	305-157-1	26- (p- nonylphenoxy)- 3, 6, 9, 12, 15, 18, 21, 24- octaoxahexacosan- 1- ol, compound with iodine		antim
POTASSIUM IODIDE	potassium iodide	kalii iodidum	7681-11-0	231-659-4	Potassium iodide		antim (6)
PVP-IODINE	povidone - iodine		25655-41-8		2- pyrrolidinone, 1- ethenyl- , homopolymer, compd. with iodine		antim (7)
QUATERNIUM-45			21034-17-3	244-158-0	3, 4- dimethyl- 2- [2- (phenylamino)vinyl] oxazolium iodide		antist agent (8)
QUATERNIUM-51			1463-95-2	215-976-5	2- [2- [(5- bromo- 2- pyridyl)amino]vinyl]- 1- ethyl- 6- methylpyridinium iodide		antist agent (8)
QUATERNIUM-73			15763-48-1	239-852-5	3- heptyl- 2- [(3- heptyl- 4- methyl- 3H- thiazol- 2- ylidene)methyl]- 4- methylthiazolium iodide	(9)	antist agent (8)
SODIUM IODATE			7681-55-2	231-672-5	Sodium iodate	VI/1,10	prese
SODIUM IODIDE	sodium iodide	natrii iodidum	7681-82-5	231-679-3	Sodium iodide		antim
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 d
TEA-HYDROIODIDE (Iodotrat)			7601-53-8	231-508-2	2, 2', 2''- nitrilotrisethanol hydroiodide		additi

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 (spingo tricosis) (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 peridontitis and infections that might arise in the mouth in the connection with piercing.

(8) Also used as a photosensitizing 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 (9<sup>th</sup> Edition 2002) also contains these molecules that are not in the INCI-list. They are not forbidden in the EU:**

INCI Name	INN	Pharm Eur Name	CAS Nr	EINECS Nr	Chemical name	Restriction	Function
IODIFORM			75-47-8	200-874-5	Triiodomethane		Cosme
IODIZED HYDROLYZED EXTENSIN (Pronalen)							Not rep
PLATONIN			3571-88-8	222-681-5	Thiazolium, 2,2'-(3-(2-(3-heptyl-4-methyl-4-thiazolin-2-		Skin-Cc Agent Miscol

ylidene)ethylidene)  
propenylene )bis( 3-  
heptyl-4-methyl-,  
diiodide

(\*)

. (\*) Platonin is developed as a photosensitizing dye meant for diagnostic purposes

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

Ingredient	Iodine percentage (%)
CI 45430 (organic iodide)	57,7 (508 x 100/880)
ETHIODIZED OIL (organic iodide)  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: CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> COOEt	35-39
IODIZED GARLIC EXTRACT (organic iodide and I <sub>2</sub> )  Medicinally used garlic oil consists nearly exclusively of allylsulphides of different kinds (Lawson LD 1998). When I <sub>2</sub> is added to the oil one would believe that they are reacted, at least some to degree, into iodine derivatives like for example ICH <sub>2</sub> -CHI-CH <sub>2</sub> -S-S-CH <sub>2</sub> -CHI-CH <sub>2</sub> I (M= 654 out of which 77,7% is due to iodine). The ingredient probably also contain much complexed I <sub>2</sub>	Ca 70%
IODIZED HYDROLYZED EXTENSIN (organic iodide and I <sub>2</sub> )  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 (5-Iodo- 4-hydroxy-L-proline) or a charge-transfer complex between this molecule and I <sub>2</sub> . No information about iodine content is found. (*)	?  Hydroxyproline – I <sub>2</sub> : 66
IPCB (organic iodide)	45 (127 x 100/280)
KI (I <sup>-</sup> anion )	76,5 (127 x 100 /166)
Laminaria hyperborea extract (organic iodide and I <sup>-</sup> )  This is only one of the many algae extracts being used within cosmetology.  Large percentages of the iodine content in algae are due to organic iodides. In the brow (red) algae this percentages amounts up till 37% (more than 50%). Organic iodides are in the form of 3,5-Diiodotyrosine [CAS NO 66-02-4] and 3-Iodotyrosine. These molecules are precursors in the metabolic formation of the T4 and T3 thyroid hormones (Marchal P <i>et al</i> 2000).	This particular dried herb contains 0,55 – 0,70 % iodine by weight. Others may contain somewhat less.  When industry make the different algae extracts meant for anti-cellulite products it would be of interest for some, one would think, to increase the content of the two thyroid hormone precursor.
MEA-IODINE (HO-CH <sub>2</sub> -CH <sub>2</sub> -NH <sub>2</sub> ⊙ I <sub>2</sub> ) (releases I <sub>2</sub> )	80,6 (254 x 100 /315)



PVP-IODINE ((C <sub>6</sub> H <sub>9</sub> NO) <sub>x</sub> · xHI <sub>3</sub> )	(releases I <sub>2</sub> )	9-12
QUATERNIUM-51	(I <sup>-</sup> anion)	28,5 (127 x 100/446)
QUATERNIUM-73	(I <sup>-</sup> anion)	31,2 (127 x 100/407)
TEA-Hydroiodide (HOCH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> NHI	(I <sup>-</sup> anion)	45,8 (127 x 100/277)

(\*) Example of product containing product ("Iodized Hydrolyzed Extensin /Anti cellulite product") is found on the Internet at <http://www.maxworth.co.th/3associate.htm>

### Skin penetration rates

Ingredient	Rate (%)	Comment
IPBC	20 (SCCNFP)	Concerns IPBC- molecule as such
CI 45430	0,13 (Franz TJ, 1984)	Concerns CI 45430 – molecule as such
PVP-Iodine	0,06 (SCCNFP)	Concerns iodine bound electro statically as I <sub>3</sub> <sup>-</sup> anion in the special PVP-Iodine complex (special monograph exists)
I <sub>2</sub> as in tincture	10 (see below)	Concerns the elemental iodine molecule I <sub>2</sub> in ethanol solution. Probably, when engaged in weak charge-transfer bonds as in for example HO-CH <sub>2</sub> -CH <sub>2</sub> -NH <sub>2</sub> · I <sub>2</sub> (MEA-iodine) the rate is relatively similar (may be somewhat less).
I <sup>-</sup>	0,1 (see below)	Concerns iodide anion as in water solvable salts

### Skin penetration rate of the I<sub>2</sub> molecule

Studies show that I<sub>2</sub> can penetrate the skin enough to blockade the uptake of <sup>131</sup>I (radioactive iodine) in the thyroid gland. A study involving 24 healthy male adult volunteers gave these results (Miller K 1989):

Form of iodine /Route of administration	Dose in micrograms	26 hour PA serum-I levels (pg/mm <sup>3</sup> )	Medium serum level of iodine (pg/mm <sup>3</sup> )	Thyroid uptake (%)
2% iodine tincture/8 ml on 200 cm <sup>2</sup> of abdomen	160 000 (on skin)	109-563	336	0,2 – 6,7
2% iodine tincture/ 4 ml on 100 cm <sup>2</sup> of forearm	80 000 (on skin)	30 -71	51	0,9 – 15,3
Orally / KI –tablets	99 000 (systemic)	125 - 1010	568	0 – 0,61
Controls	0	7,24 – 16,5	12	6,5 – 14,8

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<sup>-</sup>)

From an iontophoresis experiment on humans with Potassium iodide (KI) it appears that, when under the influence of an electrical field, the I<sup>-</sup> 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*

Premises:

Concentration: 100 ppm (experience with colour in toothpastes)

480 000 micrograms of toothpaste is ingested when brushing teeth (SCCNFP)

Daily intake:  $(480\ 000 \times 0,0001 \times 0,58 =)$  27 microgram

-----

Example of toothpaste announced on the Internet at

[http://www.beautycenter.co.uk/fiche\\_produit.php?id\\_rayon=312&id\\_article=231](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:  $(3\ 000\ 000 \times 0,0001 \times (0,25/50) \times 0,58 =)$  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](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:

$1000\ 000 \times 0,0013 \times 0,0001 \times 0,58 = 0,075$  microgram

### ***Ethiodized Oil***

Used in an anti-cellulite agent

Premises:

Skin penetration rate; 1 % (is guessed at – comparatively large lipophilic molecules)

Skin area: 1600 cm<sup>2</sup> – i.e. 1600 mg product used 2 times per day<sup>21</sup>

Concentration: 1% (CoE document on Active Ingredients)

Systemic daily dose:  $(1600\ 000 \times 0,01 \times 0,01 \times 0,35 \times 2) = 103$  microgram

-----

Example of product (“Super 'S' Cream®”) announced on the Internet at <http://www.healthandsunshine.com/s-cream.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<sub>2</sub>)

Daily use amount of product put into hair: 5 g

Partition coefficient: 0,1

Concentration: 2%

Systemic dose:  $(5\ 000\ 000 \times 0,02 \times 0,10 \times 0,10 \times 0,70) = 700$  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:  $300\ 000 \times 0,01 \times 0,001 \times 0,76 = 2,28$  microgram

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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 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.*

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<sup>21</sup> 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<sup>2</sup>.

### **MEA-IODINE (Iodamid)**

Product for cleaning the skin

Premises:

Skin area of hands: 1000 cm<sup>2</sup> – i.e. 1000 mg product applied

Partition coefficient: 0,1

Skin penetration rate for iodide: 10% (see estimate for I<sub>2</sub>)

Concentration: 0,45%

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

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Example of product announced on the Internet at [http://www.galena.com.br/produtos/produto.php?pro\\_codigo=4443](http://www.galena.com.br/produtos/produto.php?pro_codigo=4443)  
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 x 0,0075 x (0,25/50) =) 113 microgram

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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.pascualab.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/%280xd1545544gucz55xm2yka55%29/pdf/technical\\_information/PVP-iodine-grades.pdf](http://www.basf-pharma.com/%280xd1545544gucz55xm2yka55%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 hair 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 x 0,01 x 0,001 x 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: 2 000 cm<sup>2</sup> – i.e. 2 g

Skin penetration rate: 0,1% (see above)

Daily systemic use: (2 000 000 x 0,000020 x 0,001 x 0,31 =) 0,01 microgram

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Example of product ("Micro Skin Water") announced on the Internet at

<http://www.dhccare.com/Product.aspx?id=Micro+Skin+Water>

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<sup>2</sup> – i.e. 1600 mg product used<sup>22</sup>

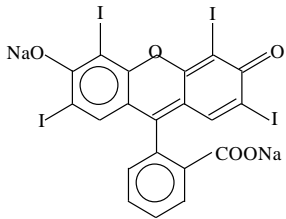
Concentration: 0,8% (Announcement)

Systemic dose: (1 600 000 x 0,008 x 0,001 x 0,45 =) 6 microgram

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Announcement/ deliverer of Iodotrat : [http://www.relata.info/html/healthy\\_5.html](http://www.relata.info/html/healthy_5.html)

### **Safety data for some of the ingredients in question**

CI 45430	<b>Acid red 51</b> <ul style="list-style-type: none"><li>• <b>Erythrosine</b> (used in connection with foodstuff)</li><li>• Food red 14</li><li>• FDA: <b>FD&amp;C Red No. 3</b></li><li>• E127</li></ul> Cas No: 16423-68-0	 <p>3',6'-Dihydroxy-2',4',5',7'-tetraiodospiro(iso-benzofuran-1(3H),9'(9H)xanthene)-3-one Disodium salt</p>
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As a foodstuffs additive Erythrosine 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 (37<sup>th</sup> report). The Erythrosine molecule contains much iodine and it has been demonstrated that it influences on the functioning of

<sup>22</sup> 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<sup>2</sup>.

the thyroid. JECFA considered that the occurrence of thyroid tumours in some long term rat-studies was most likely secondary to hormonal effects. Erythrosine 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).

Erythrosine 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).

Erythrosine has been de-listed in the United States since 1990 following studies in rats that suggested that is was potentially carcinogenic for the thyroid gland (TD<sub>50</sub> 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 erythrosine 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 phototoxicity and photocarcinogenicity of dyes (NIEHS report October 2000). The colorant shows photoallergic reactions (Sugai T *et al* 1977)..

In-vitro percutaneous absorption through human skin:

Vehicle	Concentration (%)	% Dose absorbed in 48 hours
Mineral oil	1,0	0,003
Castor oil	1,0	0,002
Talc	1,0	0,0003
Ethanol water (50:50)	0,1	0,134
Oil-in water emulsion	0,1	0,040

(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-I 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 Groot1994).

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<sup>-</sup> 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-CH<sub>2</sub>-CH(OH)-CH<sub>2</sub>I) as the major component, is both genotoxic and carcinogenic: TD<sub>50</sub> (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 (I<sub>3</sub>HC) 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 placed there already in 1976

- Iodine – which is understood to mean the I<sub>2</sub> 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-3-iodophenoxy)-3,5-diiodophenyl)acetic acid and its salts (CAS 51-24-1) – Annex II position 5. It is also called triiodothyroacetic acid and Triacol. It is deaminated T3 and shows 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 –CH<sub>2</sub>-CH<sub>2</sub>-COOH moiety instead of a –CH<sub>2</sub>-COOH group. Also, this compound shows weak hormonal activity.

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

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KELP

## **Appendix 4**

### **Council of Europe monograph concerning use in cosmetic products of iodine containing products.**

This concern a monograph prepared and published by the Council of Europe. We show it with the kind permission of the Council. The monograph is contained in a Council of Europe publication issued in March 2008 and called "Safety survey of active ingredients used in cosmetics"<sup>23</sup> ISBN: 978-92-871-6298-4.

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[http://www.mattilsynet.no/kosmetikk/stoffer\\_i\\_kosmetikk/safety\\_survey\\_of\\_active\\_ingredients\\_used\\_in\\_cosmetics\\_monograph\\_on\\_iodine\\_containing\\_cosmetic\\_ingredients.10801/BINARY/Safety%20survey%20of%20active%20ingredients%20used%20in%20cosmetics%20-%20monograph%20on%20iodine%20containing%20cosmetic%20ingredients](http://www.mattilsynet.no/kosmetikk/stoffer_i_kosmetikk/safety_survey_of_active_ingredients_used_in_cosmetics_monograph_on_iodine_containing_cosmetic_ingredients.10801/BINARY/Safety%20survey%20of%20active%20ingredients%20used%20in%20cosmetics%20-%20monograph%20on%20iodine%20containing%20cosmetic%20ingredients)



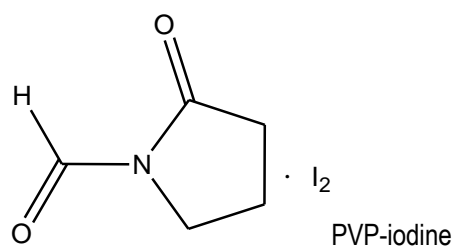
## 21. Iodine organically bound

<b>Chemical Name</b>	2,2',2'-Nitrilotrisethanolhydro-iodide 3',6'-Dihydroxy-2',4',5',7'-tetraiodospiro(iso-benzofuran-1(3H),9' (9H)xanthene)-3-one disodium salt
<b>INCI</b>	TEA-hydroiodide PVP-iodine
<b>CAS No</b>	TEA-hydroiodide: 231-508-2 PVP-iodine: 25655-41-8

**EINECS No** TEA-hydroiodide: 7601-53-8

**Molecular formula** PVP-iodine: C<sub>6</sub>H<sub>9</sub>I<sub>2</sub>NO

**Structural formula**



**Molecular Weight** 364.95

**Function in the EU inventory** Antimicrobial, buffering

### 1. Uses and natural occurrences

#### 1.1 Cosmetic products

One of the cosmetic usages of PVP-iodine is in oral-care hygiene products, mouth rinses. The iodine wiper represents a new technology for the application of antimicrobial materials to the hands of food processing / food handling personnel. Essentially, the wiper is a hand wipe towel that is comprised of a 5% Povidone-Iodine solution (PVP) coated onto a 100% polypropylene nonwoven wiper substrate. The PVP wiper is designed to provide a uniform amount of sanitizer to the surface of the hand. In its present embodiment, the treated wiper can be used to reduce microbial levels on worker hands via a 15 second wipe on hands that are dry or pre-wetted. The PVP solution is mechanically applied using processes similar to those employed in the preparation of the quat wiper (Barutha *et al.*, 1999).

#### Foodstuff:

#### 1.2 Other products

In plants, iodine predominantly occurs in inorganic form and the content varies with the iodine content in the environment. The iodine content of milk and milk products varies considerably depending on feed and use of iodine-containing disinfectants in connection with milking. The iodine content is generally higher in winter than in summer milk. The

iodine in drinking water varies considerably between regions and can locally be a significant iodine source. Fish, especially marine fish and shellfish, generally have high iodine content. Eggs can also be an important iodine source. Iodised table salt is available in at least Denmark, Sweden, Finland and Norway and contributes to iodine intake (reviewed in Nordic Nutrition Recommendations 2004).

Medicine:

Disinfectants.

## 2. Properties

### 2.1 Metabolism / Toxicokinetics

Absorption and distribution:

PVP-iodine is known to penetrate the skin.

Metabolism:

No data available.

Elimination:

No data available.

### 2.2 Local toxic effect

Skin irritation:

PVP-iodine is used as a disinfectant. It is antiviral, mainly for treatment of contaminated wounds and pre-operative preparations of the skin and mucous membranes. The complex slowly releases iodine when in contact with skin. Only a small amount of iodine is released at any time, giving PVP-iodine a lower irritant potential and longer duration of microbiocidal action than more conventional iodine solutions as for example tinctures of elemental iodine

Mucous membranes irritation:

No data

Skin sensitivity:

Iodide can give rise to sensitivity reactions such as urticaria (Scientific Committee on Food, 2002).

### 2.3 Skin penetration

PVP-iodine: It has been estimated that 600 µg iodine out of the 1 million µg total iodine in 100 ml 10% Betadine® reaches the systemic circulation through the skin (SCCNFP, 2004). This means that the skin penetration rate for iodine complexed in 10% PVP-iodine is (not more than) 0.06%.

### 2.4 Systemic toxic effects

Acute toxicity:

Animal

Excess iodine intake in animals leads to acute inhibition of iodine uptake. Laboratory animals, poultry, pigs and cattle have a high tolerance to large iodine intakes. Animal data are of limited value because of species differences in basal metabolic rate and in iodine metabolism (US Food and Nutrition Board, 2001). The non-obese diabetic mouse (NOD)-42<sup>h4</sup> develops spontaneously more frequent and severe autoimmune thyroiditis if iodine is added to the drinking water probably as a response to an increase in iodinated Tg (Scientific Committee on Food, 2002).

Human

Doses of 2 000-3 000 mg iodine (30-40 mg/kg bw) are probably lethal to humans but survival has been reported after ingestion of 10-15 g. Exposure to iodine vapour causes lung, eyes and skin irritation. Iodide in expectorant mixtures has been used at doses of 3.3 mg/kg bw mostly without adverse reactions. Iodine intakes >10 mg/day from drugs or accidental poisoning is toxic for some individuals (WHO, 1988).

### Short term toxicity:

#### Human

Young healthy subjects with no signs of thyroid abnormalities and a sufficient dietary iodine intake adapt to increases in iodine intake without measurable alterations in thyroid function or with only small changes. Paul *et al.* (1988) studied 9 euthyroid men age  $34 \pm 3$  years (mean  $\pm$  SE) and 23 euthyroid women (age  $32 \pm 2$  years). A careful history and physical examination revealed no evidence of thyroid disease in any, and none had detectable quantities of thyroid antibodies in serum. Average 24 hour urinary iodine excretion was 196  $\mu$ g. Nine men and nine women received 750  $\mu$ g iodine as NaI in water every 12 hour for 14 days. Nine women received 250  $\mu$ g and nine received 125  $\mu$ g every 12 hour for 14 days. Some of the women participated in more than one study. The administration of 1 500  $\mu$ g iodine per day induced a small but statistically significant fall in serum T4 and serum T3 and a statistically significant increase in serum TSH from  $1.9 \pm 0.2$  to  $2.8 \pm 0.4$  mU/l. Similarly, the TSH response to a TRH-test was significantly higher after iodine. The observed alterations are small. Still, some of the participants may have developed subclinical hypothyroidism with elevated serum TSH. This was not discussed.

Small but clear hypothyroid abnormalities with elevated serum lipids and a decrease in CNS function have been demonstrated in subclinical hypothyroidism, and some studies suggest that elevated serum TSH in pregnant women may increase the risk of abnormalities in CNS development of the foetus.

On the other hand, 250 or 500  $\mu$ g iodine per day for 2 weeks did not induce statistically significant alterations in serum TSH, although the risk of a type 2 statistical error is not negligible. Serum TSH was higher after both treatments and each group only included nine women.

The results of this and some related studies are the main basis for the idea that intake of iodine below 1 mg per day is safe because the normal thyroid gland is able to adapt to such an amount of iodide. Above this level of intake some degree of inhibition of thyroid function may occur. This would normally be fully reversible after normalization of iodine intake. It should be noted that 500  $\mu$ g iodide per day increased the TSH response to TRH in normal volunteers in another study from the United States.

Iodine intake above recommended levels may lead to hypothyroidism in a substantial proportion of individuals with thyroid autoimmunity. Chow *et al.* (1991) in the UK performed a randomised controlled trial in healthy women and women with thyroid auto antibodies. Free thyroxin and TSH in serum was measured before and after 14 and 28 days of administration of 500  $\mu$ g iodide per day. Significant impairment of thyroid function was obtained in both antibody positive and negative subjects receiving iodine, whereas no alterations were observed in controls. Abnormalities were larger in Ab+ subjects. Five of the 57 participants receiving iodide developed new or worsening biochemical abnormalities in thyroid function.

In Germany, Reinhardt *et al.* (1998) gave 250  $\mu$ g iodine per day for a mean period of 4 months to 40 patients positive for thyroidperoxidase (TPO) antibodies and/or with signs of thyreoditis by ultrasonography. Eight of the patients developed subclinical or overt hypothyroidism. Kahaly *et al.* (1997) assigned 62 subjects with euthyroid diffuse endemic goitre randomly to 200  $\mu$ g iodine per day or placebo for 12 months. Basic urinary iodine excretion was 34  $\mu$ g/day. Three out of 32 with iodine developed thyroid dysfunction. Relatively small amounts of iodine have been found to increase the risk of relapse of hyperthyroidism due to Graves' disease after previous medical therapy and to lead to an increase in cord serum TSH (SCCNFP, 2002).

### PVP-iodine

Iatrogenic iodine overload; clinical data:

Several publications refer to iatrogenic iodine overload and describe various clinical and biological aspects. 5 to 10% of hyperthyroidism (40% of hyperthyroidism in the elderly) may be the consequence of iodine overload. A good example of iodine overload induced by topical application is PVPI (e.g. Betadine®) a local antiseptic, which contains 1 g of iodine in 100 ml in the 10% concentration formulation (SCCNFP, 2004).

### Long term toxicity and carcinogenicity:

The colorant CI 45430 (another iodine compound and which are regulated in the cosmetic directive, 76/768/EEC) has been de-listed in the United States since 1990, following studies in rats that suggested that that it was potentially carcinogenic for the thyroid gland (TD<sub>50</sub> value of 122 mg/kg bw). 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 (SCMPMD, 1998). FDA viewed the thyroid-cancer risk associated with erythrosine as small — about 1 in 100 000 over a 70–year lifetime.

### Sensitivity reactions to iodine:

Iodide can also give rise to sensitivity reactions such as urticaria, angioedema, polymyalgia, conjunctivitis, coryza, iodide fever, headache, salivary gland enlargement, cerebral symptoms and hypotension. Iododerma, eosinophilia, pruritic rashes, vesicular eruptions and fungoid eruptions may also occur (WHO, 1988). Some 3.2% of individuals treated with <sup>131</sup>I-labelled protein developed sensitivity reactions. Following amiodarone treatment about 0.4% developed erythema nodosum. In individuals with hyperthyroidism treated with iodide some 1.75% developed fever. In asthmatics/bronchitics treated with potassium iodide about 5% showed swollen salivary glands, 3% had runny noses, 2% headaches and 15% gastrointestinal complaints. In individuals treated with contrast media for urography (I content 4 935-5 150 mg/dose) some 1.7% experienced acute allergic reactions and 1.5% suffered from hives, sneezing, nasal congestion, pruritus and facial oedema, diffuse rash, hypotension, collapse, asthma, laryngeal oedema, grand mal seizures and parotid swelling (Scientific Committee on Food, 2002).

## 3. Exposure

IPBC: With the new regulation, COLIPA has calculated that IPBC amounts to 28.05 µg of

Amount per application (µg)	Application Frequency 1/day	Retention %	Topical exposure µg/day	PVP %	Topical iodine exposure PVP*0.10 <sup>24</sup>	Percutaneous Absorption%
10 000 000	3	10	3 000 000	1	3 000	100

SCCP's recommended upper intake from cosmetics (30µg/day), i.e. 93% (05/ENTR/COS/55). Leaving as little as 2 µg/day for other iodine compounds.

### PVP-iodine:

PVP-iodine (usually sold under the trade name Betadine®) is, among others, used in mouthwash and gargles.

Mouth waters contain 1% PVP-iodine solutions (Martindale). The use pattern is a little uncertain. If the product is not diluted before use, this will give the following exposure:

<sup>24</sup> Technical data, BASF – Pharma solutions

Systemic exposure to iodine: 3 000 µg/day.

However, if it is diluted (1 parts Betadine® with 2 parts water<sup>25</sup>), the systemic exposure to iodine will be 1 500 µg/day.

Iodine wipes:

Amount per application (µg)	Application Frequency 1/day	Retention %	Topical exposure µg/day	PVP %	Topical iodine exposure PVP*0.10	Percutaneous Absorption%
800 000	2	100	16 ^6 <sup>26</sup>	5	80 000	0.06

Systemic exposure to iodine: 4.8 µg/day.

Beside this, PVP-iodine may be used in other areas of cosmetic products.

In addition, Colorant 45430 (Acid Red 51) which is regulated in annex IV, column 1 will give as much as 422 µg/day, if the products contain 200 ppm. If the colorant is moved from column 1 to column 4, COLIPA has calculated that the colorant will give as little as 0.23 µg/day (05/ENTR/COS/55).

#### 4. Safety considerations

Opinion of SCCNP in 2004: "Considering the biological and physiological properties of iodine in potentially different populations at risk in Europe, the SCCNFP is of the opinion that the daily bio available intake of iodine from cosmetic products should not exceed 20% of the recommended daily intake of 150 µg (This is, for example, equivalent to approximately 0.002% IPBC in all cosmetic products at a daily use of 18 g and at a percutaneous absorption rate of 20%). IPBC should not be used in oral hygiene and lip care products." 20% of the recommended daily intake of 150 µg is 30 µg/day.

The IPBC take up 93% of 30 µg/day, leaving only 2 µg/day for other iodine containing products. PVP-iodine containing mouthwash can give as much as 1 500 or 3 000 µg/day and wipes can give 4.8 µg/day. Consequently, PVP-iodine should not be used in cosmetic products.

#### 5. Other considerations

##### Specific regulations and remarks:

TEA-hydroiodide:

CH: up to 500 µg/day tolerated

A: Should not be used in cosmetic products

PVP-iodine:

CH: banned

N: reserved in principle for the area of medicinal products.

E: Reserved for the area of pharmaceutical or biocidal products

<sup>25</sup> <http://www.purdue.ca/pdf/BetadineTopical.pdf>

<sup>26</sup> Calculated daily exposure of face cream is 1.6 g/day. We assume in this case that it is approximately the same for hands, even though these wipes probably is used more than two times a day.

Some other iodine compounds:

TEA-hydroiodide (CAS No: 7601-53-8): TEA-hydroiodide finds some use as an anti-cellulite ingredient.

*Fucus vesiculosus* L. (CAS No: 84696-13-9): Extracts of the algae *Fucus vesiculosus* L. 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).

Iodoform (CAS No: 75-47-8): Cosmetic biocide

Iodine containing compounds:

Ingredient	Iodine percentage (%)
<p>Ethiodised oil (organic iodide)</p> <p>It contains 37% iodine organically combined with ethyl esters of the fatty acids (primarily as ethyl monoiodostearate and ethyl diiodostearate) of poppy seed oil. Stabilized with poppy seed oil, 1%. The precise structure of Ethiodol is unknown (RxList – confer references /Martindale) Ethyl stearate: <math>\text{CH}_3(\text{CH}_2)_{16}\text{COOEt}</math></p>	35-39
<p>Iodised garlic extract (organic iodide and <math>\text{I}_2</math>)</p> <p>Medicinally used garlic oil consists nearly exclusively of allylsulphides of different kinds (Lawson 1998). When <math>\text{I}_2</math> is added to the oil one would believe that they are reacted, at least some to degree, into iodine derivatives like for example <math>\text{ICH}_2\text{-CHI-CH}_2\text{-S-S-CH}_2\text{-CHI-CH}_2\text{I}</math> (M= 654 out of which 77.7% is due to iodine). The ingredient probably also contain much complexed <math>\text{I}_2</math></p>	Ca 70%
<p>Potassium iodide (KI) (I<sup>-</sup> anion )</p>	76.5 (127 x 100 /166)
<p><i>Laminaria hyperborea</i> extract (organic iodide and I<sup>-</sup>)</p> <p>This is only one of the many algae extracts being used within cosmetology.</p> <p>Large percentages of the iodine content in algae are due to organic iodides. In the brow (red) algae this percentages amounts up till 37% (more than 50%). Organic iodides are in the form of 3, 5-Diiodotyrosine [CAS NO 66-02-4] and 3-Iodotyrosine. These molecules are precursors in the metabolic formation of the T4 and T3 thyroid hormones (Marchal <i>et al.</i>, 2000).</p>	<p>This particular dried herb contains 0.55 – 0.70 % iodine by weight. Others may contain somewhat less.</p> <p>When industry make the different algae extracts meant for anti-cellulite products it would be of interest for some, one would think, to increase the content of the two thyroid hormone precursor.</p>
<p>TEA-Hydroiodide (<math>\text{HOCH}_2\text{CH}_2)_3\text{NHI}</math> (I<sup>-</sup> anion )</p>	45.8 (127 x 100/277)

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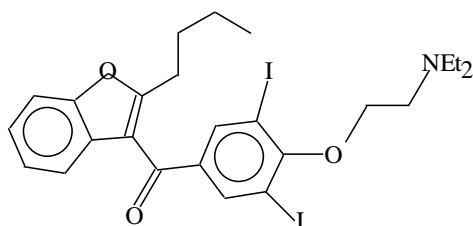
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## Appendix 6

### Drugs and other molecules causing thyroid disturbances when taken up in the body

Martindale: Iodides in general can produce goitre and hypothyroidism as well as hyperthyroidism

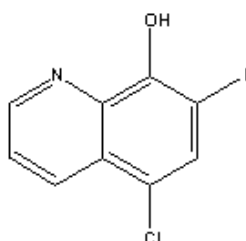
Some molecules:



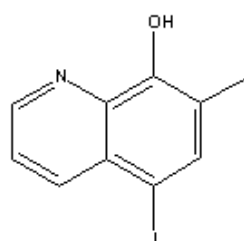
Amiodaron  $C_{25}H_{29}I_2O_3N$   $M = 645$   
Iodine fraction of M: 0.39

The drug **Amiodarone** is employed in the management of arterial fibrillation. Side effects: thyrotoxicosis and hypothyroidism. It reduces the peripheral transformation of T4 to T3 and increases the formation of reverse-T3. A large fall in serum T3 and T4 in hyperthyroid has been observed in patients treated with the drug. May lead to hypothyroidism in as many as 10% of the patients

Following amiodarone treatment about 0.4% developed erythema nodosum.



**Clioquinol** / 5-Chloro-7-iodo-8-hydroxyquinoline



**Diquinol**



Drugs used topically as an antifungal agent /skin infections, athletes foot. Oral preparations are banned. Clioquinol was withdrawn in 1983 due to neurotoxicity (Drugbank) Absorbs fairly easily through the skin. Topical use of clioquinol and Di-quinol, as well as other iodine-containing compounds, may increase the amount of protein-bound iodine (PBI) in patients with normal thyroid function and therefore may interfere with some thyroid function tests.

Drugbank:

“Topical absorption is rapid and extensive, especially when the skin is covered with an occlusive dressing or if the medication is applied to extensive or eroded areas of the skin. Clioquinol is absorbed through the skin in sufficient amounts to affect thyroid function tests.”

OCC(O)CI

### **3-iodo-1,2-propanediol**

Substance is both genotoxic and carcinogenic: Thyroide cancers.

TD50 (Gold and co-workers): 101 mg/kg bw/day in the rat and 138 mg/kg bw/day in the mouse. T25 (Dybing and Sanner): 52,6 mg/kg bw/day.

## **Appendix 7**

Letter from the European Commission 9 January 2007 to the European branch organisation COLIPA in connection with the “iodine-case” and industries response.



Adobe Acrobat  
Document

## **Appendix 8**

### ***Events that played in for the solution of the IBPC/iodine case / Risk management history***

During the course of the IBPC–case Norway always took the stand – and we as the competent authority in the product areas of both cosmetics and foodstuffs still think is right - that no contribution to the supply of iodine to the human body stem from use of cosmetic products. As said we are of the opinion that “negligible” means nil. The scientific committee, however, were of the view that up till 30 microgram would be acceptable. That was precisely the amount needed to allow for the authorisation of the preservative IPBC in the cosmetic directive on such use condition that IPBC would function sufficiently effective as a preservative. Hence, IPBC took up practically the whole “cosmetic quota” leaving only tiny 2 micrograms for other iodine containing ingredients. Norway made the Commission aware of a whole series of other iodine containing ingredients – confer the information shown in Appendix 3. Included were the preservative sodium iodate and the two colorants CI 45425 and CI 45430 (erythrosine). All three then figured in the positive lists at the time. Realizing that 2 micrograms was a much too little remain to accommodate for all these other ingredients the European Commission aiming for a subsequent regulatory amendment, initially proposed to remove sodium iodate and the two colorants from the respective positive lists and to allow for all other iodine ingredient up to a concentration of no more than 2 ppm. The latter was in effect to suggest a prohibition of all other iodine containing ingredients. On this reference is made to the working document 06/ENTR/COS/16b of the cosmetic products working party of the European Commission.

Later, a public consultation was carried out that revealed no-one wanted to defend the old authorisations of the sodium iodate preservative and the CI 45424 colorant which had never been subjected to a risk evaluation by the scientific

committee. Industry intervened, however, saying it would defend the use being made of CI 45430 (erythrosine) in toothpaste (only). Other interventions made the European Commission substitute the initial proposal of a ban of the unregulated ingredients with a letter to industry as shown in the Appendix 7. The sodium iodate and the other colorant were removed from the positive lists and can no longer be used for preservative or colouring purposes. There is no other use of these substances and the colorant also is prohibited as a hair dye.