

THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS
INTENDED FOR CONSUMERS

OPINION

CONCERNING

IODOPROPYNYL BUTYLCARBAMATE

COLIPA n° P91

Adopted by the SCCNFP on 1 July 2004
By means of the written procedure

1. Terms of Reference

1.1. Context of the question

3-Iodo-2-propynyl-butylcarbamate is listed in Annex VI part 1, n° 56 as a preservative. Its maximum authorised concentration in the finished products is 0.05% under the conditions required by the SCCNFP in its opinion SCCNFP/0193/99 (adopted on 23 June 1999). These conditions are:

- not to be used in oral hygiene and lipcare products
- if the concentration in products intended to remain on the skin exceeds 0.02 %, add the phrase 'Contains Iodine'.

This provision was introduced by the 24th technical adaptation of Directive 76/768/EEC (OJ L56, 1.3.2000, p. 42).

1.2. Request to the SCCNFP

In 2000 and 2001, the Commission received requests from Norway and Denmark which were the basis of the following questions to the SCCNFP:

- *Does the safety profile documented in the submission of the Norwegian Food Control Authority support the statement that the use of the preservative 3-Iodo-2-propynyl-butylcarbamate in cosmetic products increases the risk of attracting thyroid hormonal disturbances, including auto-immune thyroid disease, to the consumer?*
- *Does the SCCNFP, on the basis of the document submitted by the Norwegian Food Control Authority, find any arguments to undertake a renewed appraisal of the safety issue pertaining the preservative 3-Iodo-2-propynyl-butylcarbamate with particular reference to the toxicity end-points mentioned?*
- *Has the SCNFP assessed child safety aspects of the preservative 3-Iodo-2-propynyl-butylcarbamate in cosmetic products, in the former opinion of the SCCNFP (SCCNFP/0193/99)?*
- *If not, does the SCCNFP find it safe to use the preservative 3-Iodo-2-propynyl-butylcarbamate in cosmetic products intended for children?*
- *Does the SCCNFP propose any specific restrictions or conditions for use of the preservative 3-Iodo-2-propynyl-butylcarbamate in cosmetic products intended for children?*

1.3. Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.

The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

2. Toxicological Evaluation and Characterisation

3-Iodo-2-propynyl-butylcarbamate (IPBC) is listed in Annex VI part 1, n° 56 of the Cosmetics Directive 76/768/EC. Since 1990, twelve submissions (I to XII) with the results of scientifically based investigations have been presented.

The SCCNFP adopted in its plenary meeting of 23 June 1999 a statement on the Safety Assessment of IPBC:

The assessment followed the Notes of Guidance under scientifically based premises of consumer safety and leads to a classification 1 for the intended use.

Evaluation of acute toxicity (oral, dermal), skin and mucous membrane irritation, sub-chronic toxicity (oral), sensitisation, reproductive toxicity (oral), genotoxicity, percutaneous absorption, dose-dependent adverse effects (Cholinesterase activity inhibition) have shown that the compound can be safely used under the conditions stated in the Opinion. The same is valid for an evaluation of possible influences of IPBC (especially its iodine contents) on endocrine functions.

As well as an opinion on the use of IPBC was published in Internet by the EC: (SCCNFP 0193/99):

Opinion

The SCCNFP is of the opinion that 3-Iodo-2-propynyl-butylcarbamate (IPBC) is safe for use in cosmetic products as a preservative at a maximum concentration of 0.05 %.

The SCCNFP proposes the following further restrictions or conditions for its use in cosmetic products: the substance should not be used in oral hygiene and lip products. Leave-on products, containing more than 0.02 % of 3-Iodo-2-propynyl-butylcarbamate (IPBC), must be labelled 'Contains Iodine'.

In a letter, dated 07 April 2000 the Norwegian Food Control Authority raised concern pointing to the question to which extend iodine in cosmetic products in general, and especially from the IPBC molecule could be influenced by appropriate enzymes (e.g. deiodinases) with the effect of

a liberation of free iodine and consequently unwanted interactions on the thyroid gland and general metabolism, respectively.

Thus the SCCNFP in amending its formal opinion asked for further specific information in which a health effects based evaluation of small (additional) amounts of iodine/iodide should be established - closely connected with the physiological role of iodine [18].

These investigations should give a base to determine quantitatively the liberation rate of iodine from IPBC and thus figures on the bioavailability of the (additional) iodine/iodide in appropriate pharmacokinetic scenarios. This should be done in both, *in vitro* and *in vivo* (human clinical) studies. Moreover the trials should reflect the different epidemiological situation in Europe compared with e.g. North America/Canada.

In the submissions XI (November 2002) and XII (February 2003) the results of extensive investigations in the requested sectors were presented by the claimant. It has to be acknowledged that the applicant made an extraordinary effort to answer and elucidate the pending questions.

Because of the unusual nature of the subject, the SCCNFP established a working party dealing solely with an evaluation of the endocrine effects of substances, amongst others iodine, used as ingredients of cosmetic products. The '*ad hoc*' Task Force invited highly specialized external experts from different EU Member States to participate and contribute to the scientific discussion.

As a result of the work of the Task Force "Endocrine functions" the following position statements were established:

2.1. General Statements concerning validity and extrapolation of results of animal experiments, especially the rat, for extrapolation and potential action in humans with special focus on the thyroid hormone axis

2.1.1. Initial comment

The rat is the animal model most extensively studied with respect to thyroid hormone synthesis metabolism and action, as well as in terms of studies on metabolism, action, and toxicity of various chemicals. Due to the well established information, many of the results obtained in experimental rat models, both during development and in the adult animal, provided the solid scientific basis for further studies and extrapolations in other mammals as well as for human relevance. In spite of the information, limits exist with respect to extrapolation of rodent, here rat, experimental results to human physiology/pathophysiology and risk assessment, which are due to some major differences, especially in thyroid hormone physiology between rats and humans.

2.1.2.1. Thyroxine-binding globulin (TBG), the major human thyroxine-binding protein, is not the major thyroid hormone-binding protein in rats.

TBG, the low capacity-binding protein for thyroxine and also T₃ in humans, produced and secreted by the liver of humans and a few higher mammals, is not expressed to a significant amount in the normal adult rat. TBG expression has been found in pregnant as well as ageing

female rats and under conditions of starvation [1]. Nevertheless, it does not play the major role in thyroxine or T_3 -binding in the rat. Due to this major difference, some of the key issues of thyroid hormone physiology differ between species. First of all, the major thyroxine-binding protein in the normal adult rat is transthyretin (TTR) the most conserved and ancient thyroxine-binding protein in vertebrates, which has medium capacity and medium affinity [2]. The third thyroid hormone-binding protein of relevance is albumin, a high capacity – low affinity-binder, which is both present in rats and humans. From these considerations, it has to be appreciated that compounds interfering with thyroid hormone-binding in the serum might provide different results in rodents compared with humans, depending on their site of interaction, either with or without TBG or transthyretin. This is of importance, as in the absence of the high affinity - low capacity-binding protein TBG, many phenolic, aromatic and polycyclic, natural and synthetic compounds appearing in our environment, either from nutrition or other types of exposure, might lead to more prominent changes in the rodent[3]. Due to displacement of thyroid hormones from transthyretin in the human, such displacement effects might be buffered by the high affinity-binding protein TBG.

It is also of special importance that TBG levels increase during pregnancy, due to steroid-dependant alterations in TBG degradation[4]. Whether similar events also play a role in pregnant rats, remains to be established. However, so far, these changes have not attracted major attention. One other implication of these differences is relevant for analysis of thyroid hormone levels in animals, as in many experimental studies a simple transfer of human thyroid function tests to rodent sera, blood or tissue is performed without controlling for differences in thyroid hormone binding in two species. Several data are biased, due to inappropriate methodology. This has been of major importance during time periods where free hormone measurements were performed without taking into consideration the different matrix effects of human versus rodent serum. A further implication of these species differences in thyroid hormone binding is the different half life of thyroid hormones, which is much shorter in the rodent, due to the fact that the high affinity binding protein TBG is missing in the normal adult animal. Therefore, in rodent models hypothyroidism, especially primary hypothyroidism, occurs rather quickly, compared with man, where a large pool of TBG prevents these rapid changes. For example, carbohydrate starvation of an adult rat leads to hypothyroidism within 3–4 days [5]. Again, many experimental models do not take into account direct, indirect and delayed effects of altered thyroid hormone axis regulation in rodent models.

2.1.2.2. The pattern of expression of deiodinases in humans and rats is different.

The thyroid gland secretes the pro-hormone thyroxine (T_4), which is then either activated to the thyromimetically active hormone T_3 or inactivated to yield reverse T_3 (rT_3). This metabolism of the pro-hormone T_4 as well as the resulting T_3 and rT_3 is predominantly catalysed by three deiodinases, which are selenocysteine-containing enzymes. Two of the deiodinases can activate T_4 to T_3 . This is the type I (D1) and the type II 5'-deiodinase (D2), whereas degradation of T_4 to the inactive reverse T_3 and degradation of T_3 to lower iodinated iodothyronines is catalysed by the type III 5'-deiodinase (D3), as well as, to some extent, also by type I 5'-deiodinase, which is of limited substrate specificity. The pattern of expression of the three deiodinases is development- and tissue-specific and subject to marked alterations by both physiological and pathophysiological conditions [6]. This explains, why tissue-specific levels of thyroid hormones are not reflected in all conditions by serum thyroid hormone levels, as T_3 is produced and degraded in some tissues and organs independent of circulating thyroid hormone levels. These recent discoveries have markedly complicated interpretation of thyroid hormone economy and

regulation. Under these conditions, it is also of major importance that the relative expression levels of these enzymes also show species differences. Whereas it is generally believed that type I 5'-deiodinase is the major enzyme producing T_3 found in circulation and detected in serum, the type II 5'-deiodinase is held responsible for local production of thyroid hormones in tissues which are independent from systemic (hepatic) T_3 supply. Prominent among these tissues are the brain, the brown adipose tissue in rodents and also the skin. Type III deiodinase activity also shows an expression pattern different from type I and type II. Type III deiodinase is considered to be an enzyme preventing the production or accumulation of the thyromimetically active hormone T_3 in appropriate location, time or concentration. Initial characterisation of the developmental and tissue-specific expression patterns of deiodinases have been performed in rats and recently also, in context of knock-out mouse models, in mice and have then been extrapolated or controlled or specifically analysed in several other species, such as fish, amphibians, a few higher vertebrates and mammals, including men. Recently, it became more and more evident that in contrast to the rat, man is much more dependent on type II 5'-deiodinase expression in several tissues. Whereas the rodent brain and pituitary, for example, expresses both type I and type II deiodinase activity, the human brain seems to express different patterns. Type II seems to be much more important in the human central nervous system and the pituitary, but also in other tissues [7]. Special differences have been observed for the thyroid. Whereas the rat thyroid does not express type II deiodinase activity to a significant extent, the human deiodinase at least expresses transcripts for type II deiodinase and enzyme activity, especially in stimulated thyroid glands, such as under conditions of hyperthyroidism or in Graves' Disease, an auto-immune disease, where auto-antibodies stimulate the human thyroid gland [8]. This difference and the different ratio of D1 and D2 activity in the pituitary leads to some difficulties in extrapolation of the thyroid hormone feedback from the rodent model to the human application. Here, new and more detailed analysis and experiments are required before rodent data can be extrapolated to the human. Nevertheless, the rodent models have provided tremendous and important insight into mechanisms of hormonal regulation, especially also for the thyroid hormone axis. A very recent, unexpected development has been shown in man, but not yet in as much detail in the rat : under several conditions, where physiology is disturbed either by disease processes or external intervention (e.g. drugs, other agents or related to the so-called low T_3 or non-thyroidal illness syndrome) it becomes apparent that re-expression of the type III deiodinase activity occurs in tissues which normally do not express this activity in the adult human (e.g. liver, heart, muscles or other tissues). This observation might be interpreted as a type of embryonal expression pattern of deiodinase enzymes; however, the final understanding of mechanisms of these alterations is far from being reached. However, these data are of major importance in terms for pharmacological and toxicological studies, where interference with the thyroid hormone axis occurs. Whether those findings also occur in rodent or other animal models remains to be established.

2.1.2.3. Species differences also exist with respect to conjugating mechanisms of thyroid hormone metabolism and elimination

As thyroid hormones contain a highly acidic phenolic group in 4'-position, activated by iodine substituents in the ortho position, and an alanine side chain. Thyroid hormones undergo several metabolic reactions, modifying the 4'phenol group, either by sulfation or glucuronidation, which make thyroid hormones more water-soluble and directs them either to excretion via the bile or direct the conjugated hormones to enterohepatic circulation, where deconjugation then occurs by the intestinal flora, thus providing active thyroid hormone again [9]. On the other hand, the amino acid side chain, which in effect is alanine, might also undergo metabolic

reactions which, however, are less well examined and understood. It is well-known, that sulfation and glucuronidation reactions requiring co-factors and co-substrates, show marked differences between species. In addition to species differences, these enzymes are also under control of various steroids and other natural or synthetic environmental compounds. Therefore, agents disturbing conjugation reactions might also impact on thyroid hormone economy and metabolism. These differences are not well understood at the moment and therefore no definite conclusions can be drawn at this point.

2.1.2.4. Relevance of other animal models, such as the dog

Dogs are a popular animal model, also in thyroid hormone research. However, recent studies have shown that, again, major differences exist between both the human and the rat thyroid physiology. For example is TSH regulation of thyroid function markedly different between rats, dogs and humans, not only with respect to species differences of glycosylation forms of TSH but also for the subsequent signalling of the TSH receptor, which is a 7 transmembrane G protein-coupled receptor [10;11]. In terms of thyroid hormone synthesis and secretion studies, the two most popular models are porcine thyroids, which can also easily be re-constituted to intact follicles, which is much more difficult with the rat thyroid. On the other hand, a series of important findings have been established on thyroid cell lines especially in the rat context (see the most extensively studied cell line FRTL-5), which however lacks some specific characteristics of an intact thyroid epithelial follicular cell. An alternative to porcine thyrocytes are primarily cultures or reconstituted cultures of dog thyroid cells. Again, these species differences are of relevance, as for example, dog thyroid hormone metabolism differs from that of human and rat in so far as dog type I 5' deiodinase is less active versus thyroid hormones compared to rat or human enzymes [12]. On the other hand, a series of well controlled and systematic studies have been published on thyroid hormone metabolism in porcine models, both during development and in the adult animal by the group of Slebodzinski et al. [13].

2.1.2.5. Alternative models for thyroid hormone metabolism, action and interference

Apart from these rodent and higher mammalian models, marked insight in regulation of hormone synthesis, metabolism and action comes from fish and amphibian models, as well as from bird models, especially the chicken. Again, as indicated above, for the mammalian models also marked differences exist between these models. Among these species, not only in terms of developmental expression, but also with respect to absolute expression of the deiodinase enzymes, for example, type I deiodinase is less important. Probably, in the aquatic species and in the bird models, the thyroid hormone axis is regulated by hormone systems differently than in the rodent models.

<h4>2.1.2.6. Thyroid hormone metabolism in the skin / Interaction iodide and the skin</h4>

Recently, the highly efficient transport systems for iodide across epithelial cells have been characterised in more detail. The most important molecule active in this process is the so-called sodium-iodide-symporter (NIS), which is mainly expressed in the thyroid but also found in several tissues, especially those exposed to inner surfaces, but also, to a low extent, in the skin [14]. The non-thyroidal expression, regulation and function of NIS is less well understood and requires more studies. However, the data available at this point allow a much better understanding of thyroidal iodide uptake, as well as understanding of disturbance of iodide metabolism, for example, the so-called Wolff-Chaikoff effect, which is partially under control of iodide by altering NIS expression and half life. With respect to the issue of iodine-containing compounds, it is of importance that recent evidence suggests that skin expresses several components of the thyroid hormone axis molecule, including not only NIS, the TSH receptor, but also deiodinases, especially type II and type III deiodinase (see recent publication by Slominski et al., *Journal of Invest. Dermatol.* 2002). The exact role of these thyroid hormone-, metabolism- and function-related molecules in skin is not well understood. However, local T₃ production has to be assumed for maintenance of integrity of the body surface, as well as mucosa, which requires expression not only of thyroid hormone receptors, but also components of thyroid hormone metabolism. Whether skin expression of NIS thyroid hormone receptors and deiodinases also is of phylogenetic and ontogenetic importance (see intrauterine aquatic environment) remains to be established. The fact that components of thyroid hormone metabolism and action are found in skin, however, opens the possibilities for interference by environmental, natural or synthetic compounds, entering the body via the skin.

2.1.2.7. Specificity of deiodinases in terms of dehalogenation versus deiodination

Currently available evidence suggests that deiodinases are highly specific enzymes, which in spite of their limited substrate specificity allowing reaction with several iodinated compounds, such as T₄, reverse T₃, T₃ or other iodine containing aromatic compounds. They have been shown to be specific in terms of deiodination versus dehalogenation. All attempts, so far, to demonstrate debromination or dechlorination of compounds by deiodinases failed or revealed results, indicating rather low turn-over rates for brominated and minimal turnover of chlorinated compounds, suggesting that deiodinases are highly specific for deiodination of phenolic and potentially aromatic iodinated compounds.

However, biological data both in animal models and in the human indicate that deiodinases are not the only enzymes able to liberate iodine from aromatic or phenolic compounds. A second group of enzymes, the so-called dehalogenases, have recently been characterized in more detail. Whereas deiodination by the deiodinases strictly requires reducing conditions (though the physiological co-factor has not yet been identified). Dehalogenation generally proceeds in a oxidative reaction, leading in some cases to the oxidative destruction of the phenolic or aromatic rings. Recently described dehalogenases resemble the enzymes of the respiratory burst or oxidative enzymes activating during phagocytosis of leukocytes, activated macrophages or related processes. Therefore, dehalogenation reactions occurring by oxidative pathways have to be considered. So far, no reliable information is available as to whether dehalogenases are expressed in the skin.

Alterations of thyroid functions are a frequent finding in animal experiments and toxicity studies. The continuous production of H₂O₂ in the thyroid gland by the recently discovered thyrooxidases (ThOx1,2) might provide an environment of continuous oxidative exposure,

conditions leading to alteration of several biological molecules and chemical compounds, especially aromatic or phenolic compounds, which might be accumulated in the thyroid, due to the extremely high perfusion rate of the endocrine organ, where most follicular cells are supplied by microcapillaries [15;16]. It has to be assumed that there is an excess of endothelial cell versus thyrocytes in thyroids of several species.

2.1.2.8. Preliminary summary of the experimental and molecular effects

The rodent model is one of the best examined and well established models for studying thyroid hormone axis physiology and pathophysiology, as well as thyroid hormone synthesis, metabolism and action. A large data collection is available on interference of natural and synthetic compounds with the thyroid hormone axis. These data are in the majority of cases compatible with findings in other rodents, and even fish or chicken. However, some species differences have to be observed and considered. Much of data can also be extrapolated to humans, provided that agents or compounds do not interfere primarily first with the serum hormone binding proteins (normal adult rodents do not express the high affinity T₄ binding protein TBG), that they do not directly interfere with deiodinases (rodents and humans have different development- and tissue-specific deiodinase expression patterns) and if compounds do not markedly alter enzyme systems involved in conjugation of thyroid hormones.

N.B.

Marked sex differences also exist in tissue and development specific expression of several components of the thyroid hormone axis, as evident from the female preponderance of several thyroid-related diseases, such as autoimmunity, thyroid cancer etc. in man. The rodent model is sensitive to alterations in thyroid hormone axis, due to rapid turnover of thyroid hormones compared with man, partially due to the lack of TBG, but also to other factors. Animal models have to be carefully analysed with respect to alterations in thyroid hormone status, as both hypo- and hyperthyroidism are much more rapidly induced by simple manipulations, such as carbohydrate starvation or conditions leading to the non-thyroidal illness like euthyroid sick syndrome conditions. The interrelationship between thyroid hormones and the growth hormone IGF axis is much more pronounced in humans, as these pathways are directly regulated by thyroid hormones in rodents. Several of the interactions of thyroid hormones with lipid metabolism in the rat resemble that of the human, but there are also some exceptions, for example processing and editing of the apolipoprotein B48/100. Identification of alterations of bone formation, development, and ossification might be an indicator of altered thyroid hormone availability, metabolism or action at the tissue-specific level.

In summary, recent research has identified tissues and development-specific expression of thyroid hormone dependent genes which are not reflected by circulating pool levels of thyroid hormones, but are governed by local activation and inactivation of thyroid hormones at the tissue level, might it be target tissue or tissues where action of thyroid hormone is prevented by inactivation, catalysed by the type III deiodinase or in some instances also by type I 5'-deiodinase. These species differences exist between the rodent and the human. Rodent models provide important data with respect to extrapolation to higher mammals, including the human, provided that species differences in development and other differences in hormone physiology and pathophysiology are not neglected but carefully applied and critically considered.

2.1.2.9. Special statement IPBC (P 91)

Submission XI and XII relate to studies and *in-vivo* tests in pigs, rabbits and humans. A special part of these studies has addressed the question of bioavailability of free or absorbed iodine. In this context, the recent identification of the sodium iodide symporter (NIS) is of relevance. NIS is mainly expressed in the human thyroid, but transcripts protein and immunoreactivity and in a few instances function has also been described for other tissues, in the rat as well as in other species. It has to be appreciated that species differences exist, not only in iodide uptake, but also in deiodinases and receptor expression together with expression of thyroid hormone metabolising enzymes [18]. So far, no systematic analyses have been performed, as to whether iodinated compounds of this type are subject to deiodinases. Available evidence would contradict such an assumption. However, oxidative dehalogenative metabolism of iodinated compounds might occur via enzymes related to thyrooxidase (ThOx) or by processes known 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, highly efficient and expressed in the human thyroid. Whether molecules of the thyroid hormone axis, known to be present in the skin from recent studies, might be affected by these compounds, remains to be established. Currently available data do not provide strong evidence for this assumption.

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2.2. General Statements concerning Iodine Intake and Risk of Disease in Humans

2.2.1. Initial comment

Iodine is an essential part of thyroid hormones and the only known effect of variation in iodine intake within a wide range is related to the thyroid gland and its diseases. Very large amounts of iodine may have a variety of direct toxic effects on the body. This is considered irrelevant for the discussion on the use of iodine containing preservatives in cosmetic products.

Knowledge on the association between iodine intake and the risk of thyroid disease in *humans* has been derived from studies of individuals or small groups of patients and healthy subjects. Another approach has been epidemiological studies evaluating the association between iodine intake in a cohort and the prevalence and incidence of thyroid diseases.

To be taken up by the thyroid gland, iodine has to present in blood as iodide. The amount of iodide available for thyroid uptake is reflected by the iodide excretion in urine. Approximately 90 % of iodine in diet is excreted in urine as iodide. There is no indication that the route of iodine intake influences the effect of iodine in the organism.

The recommended daily intake of iodine in Europe is 150 µg. The dietary sources of iodine differ between populations. In many countries dairy products are a main source of iodine. The amount of iodine in milk varies with the iodine content of dairy cows feeding, and may be influenced by the use of iodine containing disinfectants by farmers or in the dairy industry. In

many European countries (and elsewhere) salt is enriched with iodide or iodate because the average iodine intake with diet is insufficient.

2.2.2.1. Effect of excess iodine in normal young subjects

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 [1] studied 9 euthyroid men age 34 ± 3 years (mean \pm SE) and 23 euthyroid women (age 32 ± 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 μ g. Nine men and nine women received 750 μ g iodine as NaI in water every 12 hour for 14 days. Nine women received 250 μ g and nine received 125 μ g every 12 hour for 14 days. Some of the women participated in more than one study. The administration of 1500 μ 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 ± 0.2 to 2.8 ± 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 μ 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 μ g iodide per day increased the TSH response to TRH in normal volunteers in another study from the United States.

2.2.2.2. Occurrence of thyroid abnormalities in the population

Evaluation of iodine effects in normal healthy young subjects is not sufficient when discussing public health effects of iodine intake, because thyroid abnormalities are very common in the population. The prevalence rate of various types of thyroid abnormalities depends on genetic and environmental factors. Nearly all thyroid abnormalities are more frequent in women. Thyroid autoimmunity is very common in Caucasians but less so in the Japanese or Black American 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. In populations with insufficient iodine intake nodular thyroid disease is very common. In Denmark, 30 % of elderly women had thyroid nodules. Around 5 % of women develop transient thyroid function abnormalities during

the postpartum period. This is around 50 % of women with measurable thyroid antibodies. Both thyroid autoimmunity and thyroid nodularity are often undiagnosed, and both conditions may predispose to iodide induced abnormalities in thyroid function.

2.2.2.3. Effect of excess iodine in individuals with thyroid abnormalities

Iodine intake above recommended levels may lead to hypothyroidism in a substantial proportion of individuals with thyroid autoimmunity. Chow et al [2] in the UK performed a randomized controlled trial in healthy women and women with thyroid autoantibodies. Free thyroxin and TSH in serum was measured before and after 14 and 28 days of administration of 500 µg 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 [3] gave 250 µg 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 [4] assigned 62 subjects with euthyroid diffuse endemic goitre randomly to 200 µg iodine per day or placebo for 12 months. Basic urinary iodine excretion was 34 µg/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.

2.2.2.4. Iodine intake and the epidemiology of thyroid disease

The above mentioned studies performed in relatively few subjects suggest that even relatively small differences in iodine intake may influence the occurrence of thyroid disease. This hypothesis is supported by epidemiological studies. The conclusion is further substantiated by the results of the monitoring of the Danish iodine supplementation program (DanThyr). 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 µg/day. Intake above this level is associated with more hypothyroidism and intake below with more goitre and hyperthyroidism caused by autonomous thyroid nodules.

2.2.2.5. Preliminary summary of the human part

Iodine intake of a population should be monitored and adjusted to achieve optimal prevention of thyroid disease. A most severe abnormality which may be associated with abnormal thyroid function is developmental CNS damage caused by lack of thyroid hormones during foetal or the first years of life. Iodine deficiency may lead to such developmental brain damage, and hypothyroidism with elevated serum TSH in pregnant women is also associated with a decrease in IQ in the child. As elevated TSH is more common during excessive iodine intake, both low and high iodine intake levels should be avoided.

Iodine intake shows considerable day to day variation in individuals, and the pituitary/thyroid/periphery axis is able to a large extent to adapt to such variations. Hence, minor amounts of extra iodine for a few days would probably be of little significance. On the other hand excessive intake for more than a week or two may lead to thyroid function abnormalities in some individuals

Optimally, iodine intake in a population should be part of a public health program. Sporadic excess iodine from environmental chemicals, cosmetics etc. should be kept low. It can be argued that such intake may be of value in areas with insufficient dietary iodine intake. However, this would only have sporadic effect and should be replaced by a proper public program of iodine supplementation in such areas.

The possible iodine intake from cosmetic products should be negligible. In practical life this means 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 [5].

Reference List (part 3.)

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5. Laurberg P. Personal communication to the SCCNFP

2.3. **The SCF Opinion on "The Tolerable Upper Intake Level of Iodine (SCF/CS/NUT/UPPLEV/26 final) 7 October 2002**

The former Scientific Committee on Food (DG SANCO) expressed in 2002 an Opinion on the Tolerable Upper Intake Level (UL) of Iodine. The SCCNFP regards this opinion as helpful in explaining the broad background of the physiological scenario of iodine effects.

Thus chapter 5 and 6 of this opinion are quoted in the complete text as an excerpt of the full paper.

(5.) DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The parameters altered in these dose-response studies included an evaluation of serum TSH levels in response to iodine intake and the enhanced response in TSH levels to TRH stimulation. They were all of a biochemical nature and not associated with any clinical adverse effects. However, elevated serum levels of TSH are not necessarily clinically adverse, but could be regarded as indicators of an existing risk of induced hypothyroidism. There is uncertainty

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whether the subtle changes observed, such as an enhanced response to TRH, would have significant adverse biological consequences even if sustained over longer periods, because all observed values remained within the normal ranges for the parameters determined. It remains uncertain whether chronic exposure to these small doses would have any relevant clinical consequences in normal euthyroid individuals.

An UL can be established on the basis that the noted biochemical changes in TSH levels and the TSH response to TRH administration were marginal and unassociated with any clinical adverse effects at estimated intakes of 1700 and 1800 µg/day.

Although the studies on which these UL estimates are based were all only of short duration, involved only a small number of individuals, and lacked precision of the actual total dietary intakes, their results were supported by the study covering a 5-year exposure at approximately similar iodide intake levels of 30 µg/kg bw/day (equivalent to approximately 1800 µg iodide/day) in which no clinical thyroid pathology occurred. An UL of 3 is thus considered adequate and provides an UL for adults of 600 µg/day.

The UL of 600 µg is also considered to be acceptable for pregnant and lactating women based on evidence of lack of adverse effects at exposures significantly in excess of this level.

Since there is no evidence of increased susceptibility in children, the ULs for children were derived by adjustment of the adult UL on the basis of body surface area (body weight^{0.75}).

<i>Age (years)</i>	<i>Tolerable Upper Intake Level (UL) for Iodine (µg per day)</i>
<i>1-3</i>	<i>200</i>
<i>4-6</i>	<i>250</i>
<i>7-10</i>	<i>300</i>
<i>11-14</i>	<i>450</i>
<i>15-17</i>	<i>500</i>

In the US the standing Committee on the Scientific Evaluation of Dietary References Intakes of the Food and Nutrition Board together with Health Canada are pursuing a joint project which proposes a tolerable upper level of intake for iodine for adults of 1100 µg/day (US Food and Nutrition Board, 2001). WHO has suggested a provisional maximal tolerable daily intake of 1 mg/day from all sources, equivalent to 17 µg/kg bw (WHO, 1988). In countries with long-standing IDD the intake should not exceed 500 µg/day to avoid the occurrence of hyperthyroidism. In France the Expert Committee on Human Nutrition has suggested an UL of 500 µg I/day in countries with long-standing IDD to avoid the occurrence of hyperthyroidism (AFSSA, 2001).

(6.) CHARACTERISATION OF RISK

Data from European populations indicate that the intakes of iodine from all sources in adults are unlikely to exceed the UL. For example, in the UK where iodine intake is considered to be high relative to other European countries, the 97.5 percentile intake in men is 434 µg/day.

In the UK survey data in young children aged 1½ - 4½ years have shown that iodine intakes may vary from 87-309 µg/day, with almost all iodine deriving from the consumption of milk. High

winter milk consumers may ingest up to 247-309 µg/day. The UK COT considered that the intake of iodine at the concentrations that have been found in cow's milk is unlikely to pose a risk to health even in those children who are high level consumers (COT, 2000). The SCF agrees with this and notes that an UL is not a threshold of toxicity but may be exceeded for short periods without an appreciable risk to the health of the individuals concerned.

Ingestion of iodine-rich algal products, particularly dried products, can result in dangerously excessive iodine intakes.

These ULs do not apply to IDD populations, as these are more sensitive to iodine exposure.

The UL is not meant to apply to individuals who are being treated with iodine under medical supervision.

2.4. Overall Summary

2.4.1. Daily iodine intake

The daily iodine intake varies according to countries and continents (100-200 µg/d in the UK, Germany and France, and it can reach more than 500 µg/d in the USA).

The daily-recommended dose in Europe is 150 µg/d (with an upper short term limit of 1000 µg/d).

2.4.2. Thyroid function and iodine overload

- * Thyroid function in humans is normally clinically estimated on plasma levels of T4, FT4, T3 and TSH (pituitary gland) and TRH test (hypothalamus). PBI is less used. Besides these parameters modern findings in thyroid function have lead to establish further measurements/methodological approaches which are at present only applied in special scientific questions. 24 hour iodine urinary excretion does not investigate thyroid function but is a good indicator for the total iodine intake.
- * The consequences of an iodine overload depends on its intensity, its duration, the chemical availability of iodine (iodide or organic iodine) and mainly on the functional status of the gland: classically, unwanted effects are seen among subjects with pre-existing dysthyroidism (iodine deficiency, hormonogenesis disturbances); but cases are also described in normal subjects.

2.4.3. Experimental data in man

Several exposure studies have been carried out in volunteers, inducing an iodine overload from 200 to 4500 µg/day; the duration of these studies varies, but unfortunately there is none of more than 11 weeks.

At 750 µg/day, biological disturbances can be seen for T4, TSH and in a TRH test. At 500 µg/day results are variable from one study to the other. At 250 µg/day, biological changes have not been observed. An extrapolation of these data to chronic administration is difficult.

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As to a “Tolerable Upper Intake Level of Iodine (UL)” it is also referred to an opinion of the EC-Scientific Committee on Food (SCF/CS/NUT/UPPLEV/26; 7 October 2003). Moreover in this paper the difficulties of an appropriate estimation/evaluation are described, including tentative UL depending on age of children.

2.4.4. 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 (0.06 % -600 µg out of 100 ml- is estimated to reach the systemic circulation.

2.4.5. IPBC-submissions XI & XII

The applicant has performed 5 new clinical studies, all carried out according to the same design:

6 days of a fixed daily diet.

3 days of cosmetic cream without IPBC application followed by 3 days of a cosmetic cream formulation containing IPBC application.

At day 0, day 3 and day 6, free plasma iodine and 24 hour urinary iodine excretion measurements.

Results

The increase between day 3 and day 6 are summarised as follows:

Substance	Iodide urinary excretion µg/24 h	
	<i>Volunteer 1</i>	<i>Volunteer 2</i>
0.01 % free IPBC *	70	65
0.02 % free IPBC *	131	167
0.02 % free IPBC *	143	53
0.02 % IPBC cyclodextrin complex *	223	43
Iodine 100 µg oral	103	84

* 14 g preparation on 7000 cm² surface (skin)

Based on historical data (no influence up to 500 µg/day on thyroid function) and on an agreed safety of a 100 µg/day added load, it was concluded that there is no risk linked to the use of IPBC.

2.4.6. Comments

The clinical studies include only 2 volunteers and were performed in North America/Canada (different status from Europe in terms of usual iodine intake). The duration of application is relatively short (3 days).

The new submissions do not answer directly the question: “Is IPBC safe for use in cosmetic products when potential for including hormonal disturbance is considered?”. What the submissions show: they do find in their volunteers the expected 24-hour iodine excretion after iodine 100 µg was given orally. The study performed with 0.01 % free IPBC meets the safety requirements in adults.

The oral study with 100 µg does not exclude possible problems in the subgroup population of dysthyroidism, when applied chronically.

The studies do not address the questions that can be raised for pregnant females with dysthyroidism, or for children between 0 and 3 years old; see also section 2.3 of this opinion.

3. OPINION

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 bioavailable 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%).

Moreover IPBC should not be used in oral hygiene and lip care products.