



Scientific Committee on Consumer Safety

SCCS

## **OPINION ON**

# **Clarification of Annex II, entry 168 of the Cosmetic Directive: Choline salts and their esters e.g. Choline chloride (INN)**



The SCCS adopted this opinion at its 4<sup>th</sup> plenary meeting of 13 October 2009

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e.g. Choline chloride (INN)**

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In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

**SCCS**

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## 1. BACKGROUND

Annex II - list of substances which must not form part of the composition of cosmetic products – of Directive 76/768/EEC contains under entry no 168: choline salts and their esters, e.g. choline chloride. This entry has been part of the Cosmetic Directive since its original adoption in 1976, and for that reason no scientific opinion is available as the basis for this entry.

A related substance, acetylcholine, is also banned from use in cosmetic by entry 2 in Annex II: 2-Acetoxyethyltrimethylammonium hydroxide (acetylcholine) (INN) and its salts.

### **Need for clarifications of the scope of entry II/168:**

The German Authorities have asked the Commission for clarification whether lecithin, which is an ester of choline, is covered by entry II/168. At the same time they have pointed out that different wordings for this entry exist in different languages versions of the Cosmetics Directive.

In 2008, EFfCI requested advice from the Commission on the scope of entry II/168, as a member company has an interest in using stearic acid choline ester as a cosmetic ingredient. In Annex II of the Cosmetics Directive, no definitions are given for salts and esters. However, for salts and esters in connection with Annex VI, preservatives, a set of definitions is set out. They are:

- "Salts" is taken to mean: salts of the cations sodium, potassium, calcium, magnesium, ammonium and ethanolamines: salts of the anions chloride, bromide, sulphate, acetate.
- "Esters" is taken to mean: esters of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl

The Commission services identified from the Cosmetic Ingredients Information system (CosIng) and the Inventory of ingredients employed in cosmetic products, some substances which could be considered covered by entry II/168:

CAS number	Substance	INN
856676-23-8	Choline fenofibrate	Choline fenofibrate [USAN]
2016-36-6	Choline salicylate	Choline salicylate
507-30-2	Choline gluconate	Choline gluconate
4499-40-5	Cholinate theophylline	Cholinate theophylline; Oxtriphylline [USAN]
28319-77-9	Glycerophosphocholine	Choline alfoscerate

INN: International Nonproprietary Names, USAN: United States Adopted Name

However, entry II/168 has been interpreted by the responsible Commission services not to cover hydrogenated lysophosphatidylcholine, hydrogenated phosphatidylcholine, phosphatidylcholine, polyphosphorylcholine glycol acrylate and lecithin, which are choline derivatives also present in inventory part of the CosIng database.

### **Discrepancy in wording in different language versions:**

The following versions of entry II/168 of Directive 76/768/EEC exist:

- "Choline salts and their esters, e.g. choline chloride" (EN)
- "Ester von Cholin und Methylcholin und ihre Salze" (DE)
- "Esters de la choline et de la methylcholine et leur sels" (FR)

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These latter versions, which are equivalent also to the wording used in e.g. the IT, ES, PT versions, translates into

"Esters of Choline and Methylcholine and their salts".

## **2. TERMS OF REFERENCE**

1. *Based on the chemical structure and/or behaviour of the listed substances, does the SCCS consider that entry II/168 does cover:*

1a. *Choline fenofibrate  
Choline salicylate  
Choline gluconate  
Choline theophylline  
Glycerophosphocholine*

1b. *Choline esters of stearic acid, as asked for by EffCI, and other long alkyl chain carboxylic acids*

1c. *Hydrogenated lysophosphatidylcholine  
Hydrogenated phosphatidylcholin  
Phosphatidylcholine  
Polyphosphorylcholine glycol acrylate  
Lecithin*

2. *Based on its chemical structure and/or behaviour, does the SCCS consider it justified to include methylcholine together with choline in entry II/168, as presently the case in some language versions?*

## **3. OPINION**

### **3.1. General aspects**

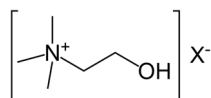
In general chemical terms, a salt is a chemical compound composed of two or more ions, often a positively charged metal ion (cation) and a negatively charged non-metallic ion (anion), so that the chemical compound is neutral. Salts may also be composed of a non-metallic cation, for example ammonium ( $\text{NH}_4^+$ ) ion. Anions can be inorganic, e.g. chloride ( $\text{Cl}^-$ ), sulphate ( $\text{SO}_4^{2-}$ ), or organic e.g. acetate ( $\text{CH}_3\text{COO}^-$ ).

Esters are chemical compounds derived by the chemical reaction of an alcohol or phenol with an acid. Esters can be derivatives of carboxylic acids (e.g. ethyl acetate) or inorganic acid (e.g. dimethyl sulfate).

Annex II of Directive 76/768/EEC does not contain a definition of 'salts' and 'esters'. The definition of salts and esters described in the preamble of Annex VI for preservatives of Directive 76/768/EEC on Cosmetic Products is very restrictive and does not include other salts and esters that could be used as preservatives in cosmetic products. The scientific rationale for this restrictive definition is not set out in any supporting documentation. The SCCS does not see a scientifically valid reason for the limitation of the definition used in Annex VI and considers that from the chemical point of view, the term "Choline salts and their esters" should in principle cover all possible salts and esters without exception and should not be limited to those listed in Annex VI.

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Choline is a quaternary saturated amine with the chemical formula  $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{OH X}^-$ , where the positively charged choline is the cation and the negatively charged  $\text{X}^-$  is the anion (also called counterion) e.g. chloride, hydroxide, tartrate, etc.



Choline in its free form (in basic pH environments) is a strong quaternary ammonium base. However, when salts of choline are used in cosmetic formulations at neutral or slightly acidic pH, choline is not expected to be found in its free form (i.e. dissociated), but it will be associated with the specific counterion used in the salt (e.g. chloride, salicylate, gluconate, etc.). The toxicological profile of choline in cosmetic formulation at neutral or slightly acidic pH will relate to that of the specific choline salt. This in practice means that a risk assessment on a specific choline salt will be necessary to support its use in cosmetic products. When choline salts are used in formulations at basic pH, the safety profile of free choline should be considered for the purpose of product safety evaluation.

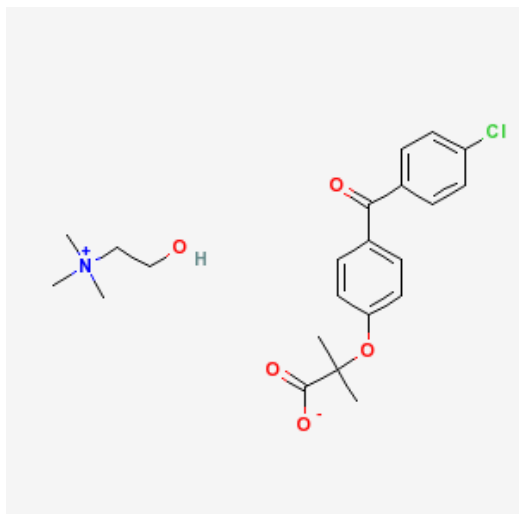
When the hydroxyl group of choline is esterified, the choline is in the form of a salt of the choline ester  $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{OOR X}^-$ , where R is the alkyl chain of the carboxylic acid used for the esterification. The same situation as described above applies to salts of choline esters. In cosmetic formulations at neutral or slightly acidic pH, they may remain undissociated, and thus, safety evaluation of specific salts of choline esters would be required before their use. When salts of choline esters are used in formulations at basic pH, the toxicological profile of the choline ester should be considered for the risk assessment. An important parameter to be considered in the risk assessment of choline esters is the fact that non-specific esterases, present in the skin, are expected to hydrolyse various choline esters to liberate the constituents of the choline ester, namely choline itself and the acid used for the esterification

The scientific reasons to introduce entry 168: choline salts and their esters, e.g. choline chloride in Annex II of the Cosmetic Directive is not known to SCCS, as no scientific assessment that might have formed the basis for this entry is available to the Committee. The possible reason for not permitting the use of these compounds may be that they are quaternary ammonium compounds (QAC), and thus, they may have intrinsic irritation/sensitisation potential, similar to many other known QAC. Individuals exposed to quaternary ammonium compounds can exhibit irritant contact dermatitis (IPCS/INCHEM 1999); and Weston and Assem (1994) have shown immunological cross-reactivity between different QAC. Study performed by Weston and Assem (1994) also indicated that QAC may be both sensitizers and histamine releasers. Recently, Nielsen et al. (2007) described QAC as well established adjuvant in animal studies.

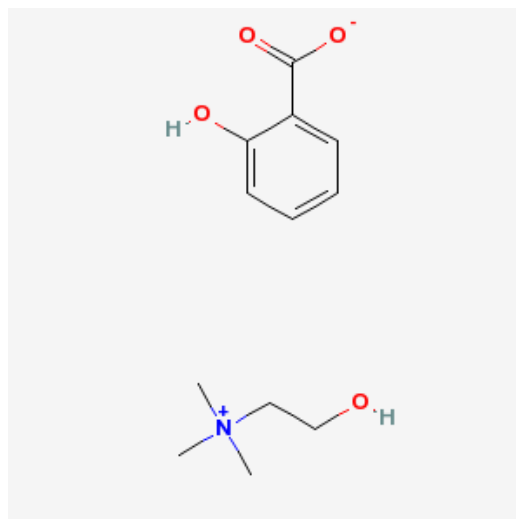
### **3.2. Choline fenofibrate, choline salicylate, choline gluconate, choline theophylline, glycerophosphocholine**

The substances choline fenofibrate, choline salicylate and choline gluconate are salts of choline; and choline theophylline is a choline compound with theophylline (1:1).

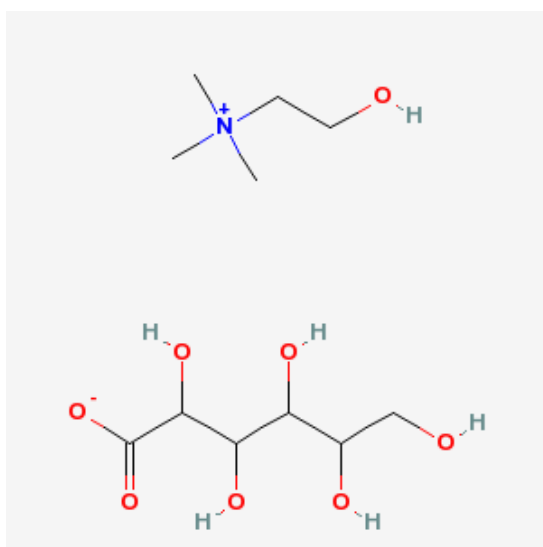
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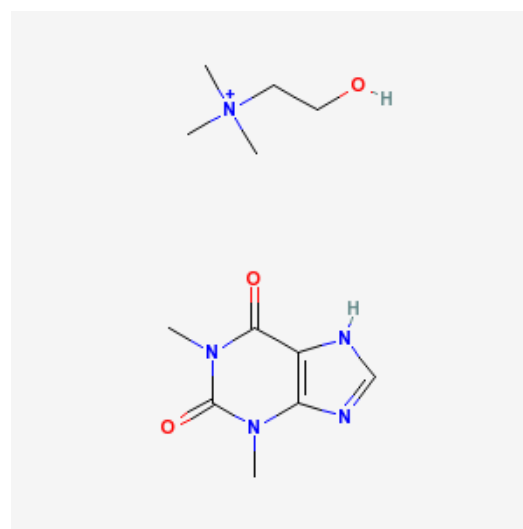
Choline fenofibrate



Choline salicylate



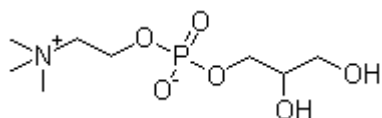
Choline gluconate



Cholineate theophylline

All four of these are quaternary ammonium compounds. These may be potential irritants and thus are covered by the entry no. 168 of the Directive 76/768/EEC.

Glycerophosphocholine, however, is a glycerol derivative of the phosphoric acid ester of choline, and thus, a derivative of a choline ester:



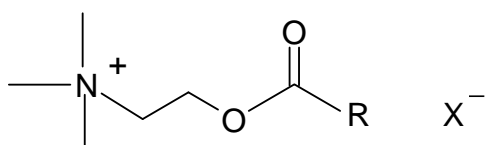
Glycerophosphocholine is a metabolite formed by hydrolysis of choline-containing phospholipids by phosphoesterases, which are widely present in living organisms. It is a zwitter ionic or neutral compound over a pH range from strongly acidic to strongly alkaline. Thus, in contrast to above mentioned choline salts/esters, it is not a 'cationic' quaternary ammonium compound similar to salts of choline or its esters and it is unlikely to be an irritant. Hence, glycerophosphocholine should not be covered by the entry 168 of Annex II of the Directive 76/768/EEC.



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### 3.3. Choline esters of stearic acid and of other long alkyl chain carboxylic acids

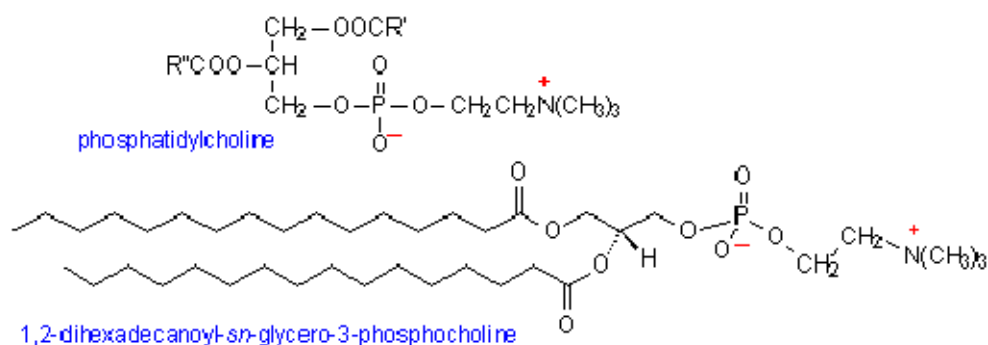
Choline esters of stearic acid and of other long alkyl chain carboxylic acids are quaternary ammonium compounds and will exist as salts at neutral or slightly acidic pH of cosmetic formulations. Having quaternary ammonium cation ( $\text{NR}_4$ , where R is an alkyl group)<sup>+</sup> as a part of their chemical structures, these may be potential irritant, and are covered by the entry no. 168 of the Directive 76/768/EEC.



*R* is alkyl chain of the carboxylic acid (for example stearic acid) and  $\text{X}^-$  is anion (for example,  $\text{Cl}^-$ ) of the salt of choline ester

### 3.4. Phosphatidylcholine, lecithin, hydrogenated lysophosphatidylcholine, hydrogenated phosphatidylcholine, polyphosphorylcholine glycol acrylate

Phosphatidylcholine is a diglyceride of fatty acids linked to glycerophosphocholine and lysophosphatidylcholine is a monoglyceride of a fatty acid linked to glycerophosphocholine. Phosphatidylcholine and lysophosphatidylcholine are widely present in living organisms. Industrial hydrogenation of unsaturated fatty acids of these compounds produces hydrogenated phosphatidylcholine and lysophosphatidylcholine. Lecithin is a fatty substance widely occurring in animal and plant tissues and in egg yolk. It is composed mainly of phosphatidylcholine together with small amounts of other phospholipids (phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine), sphingomyelin, glycolipids and triglycerides. The term lecithin is sometimes also used as a synonym for [phosphatidylcholine](#).



Phosphatidylcholine, hydrogenated phosphatidylcholine, lysophosphatidylcholine, hydrogenated lysophosphatidylcholine and polyphosphorylcholine glycol acrylate and lecithin are neutral or zwitterionic over a pH range from strongly acidic to strongly alkaline. These are not quaternary ammonium compounds similar to other salts of choline and its esters, and these are unlikely to be irritants. Thus, the entry no.168 of Annex II of Directive 76/768/EEC should not cover the above compounds.

### 3.5. Methylcholine

The term 'methyl choline', used in entry II/168 in some linguistic versions of the Cosmetics Directive is chemically poorly defined and can be interpreted as meaning alpha-

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methylcholine, beta-methyl choline, and/or o-methyl choline. In fact, these substances are different chemical species than choline. However, salts and esters of alpha-methylcholine and beta-methylcholine as well as salts of o-methylcholine will also have chemical properties of quaternary ammonium compounds similar to salts and esters of choline and they may also be potential irritant. Hence, the SCCS is of the view that salts and esters of methyl choline should also be part of entry no.168 of Annex II of the Cosmetic Directive.

**4. CONCLUSION**

The SCCS is of the opinion that, based on their structural and chemical properties the following substances listed in the Terms of Reference should fall under the scope of entry II/168:

- Choline fenofibrate
- Choline salicylate
- Choline gluconate
- Choline theophylline
- Choline esters of stearic acid and other long alkyl chain carboxylic acids
- Methylcholine and its salts and esters

The following substances, based on their structural and chemical properties, should not be considered to fall under the scope of entry II/168:

- Glycerophosphocholine
- Phosphatidylcholine
- Lecithin
- Hydrogenated lysophosphatidylcholine
- Hydrogenated phosphatidylcholine
- Polyphosphorylcholine glycol acrylate

**5. MINORITY OPINION**

Not applicable

**6. REFERENCES**

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