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

CONCERNING

METHYL ACETATE

adopted by the SCCNFP during the 24th plenary meeting
of 24-25 June 2003

1. Terms of Reference

1.1 Context of the question

The Danish EPA has received a request from a poison information department in a hospital regarding the regulation of methyl acetate in cosmetics. A child had played with a nail polish remover containing 50 w/w % methyl acetate and there was suspicion that it had ingested some of the product.

Methyl acetate is very quickly hydrolysed to acetic acid and methanol both whether inhaled or ingested. It is also well known that humans are more sensitive to methanol poisoning than rodents. In order to evaluate the acute toxicity of methyl acetate in humans, it was found reasonable to consider the acute toxicity of methanol as reported by clinical cases of poisoning.

According to the IPCS report on methanol (Environmental Health Criteria 196, 1997), the lowest lethal dose in humans was considered to be 0.3-1.0 g/kg bw. Assuming a bodyweight of 10 kg for a child, the lowest lethal dose would be 3 g (or 0.09 mol) methanol, arising from the metabolism of 0.09 mol or 6.9 g methyl acetate.

At a concentration of 50 w/w % methyl acetate, the lethal dose for humans might be 14 g of nail polish remover. The Danish EPA found it not unlikely that children could risk methanol poisoning if nail polish removers are not properly stored/contained.

1.2 Request to the SCCNFP

The SCCNFP was asked to answer the following question :

* *Is the use of methyl acetate in cosmetic products safe?*

* *Is there a need for setting a concentration limit for the use of this substance in cosmetic products?*

* *Is there a need to set restrictions on which products methyl acetate can be used in?*

* *Is there a need for an obligatory warning label regarding the storage conditions, taking into account the risk for children using cosmetic products containing the ingredient ?*

2. Toxicological review

A wide variety of products contains methanol (CH_3OH) as a solvent or an ingredient, such as cosmetics, dyes, lacquers, wood stains, paint strippers, antifreeze, windshield washing solutions, and many other cleaning, painting and automotive products. It is also used as a chemical intermediate, industrial solvent and ethanol denaturant. Alcoholic beverages may contain low levels of methanol. The interest in its toxicity has increased because of the possible increased use of methanol in synthetic fuels (ref. 8, 11).

The acute per-oral LD_{50}-value of methanol for the rat is 5630 to 7500 mg/kg bw (ref. 1). The chemical is moderately irritating to the rabbit eye and has been found to be non-sensitising in a modified guinea pig Maximisation test. A mutagenicity / genotoxicity test battery is available, leading to some diverging results.
There is no evidence from animal studies to suggest that methanol is a carcinogen, although the lack of an appropriate animal model is recognised. There are some embryotoxic/foetotoxic effects, but only at high and maternally toxic exposure concentrations. Therefore, methanol is not considered as toxic for reproduction (ref. 8).

Through the Dangerous Substances legislation, methanol is classified as toxic and flammable [Dir. 98/98/EC] :

F (Highly flammable)
T (Toxic)

R11	:	Highly flammable.
R23/24/25	:	Toxic by inhalation, in contact with skin and if swallowed.
R39/23/24/25	:	Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.
C > 20%	:	T, R23/24/25-39/23/24/25
10% ≤ C < 20%	:	T, R20/21/22[1], 39/23/24/25
3% ≤ C < 10%	:	Xn, R20/21/22, 40/20/21/22[2]

Methanol is listed in Annex III, part 1, ref. n° 52 to Directive 76/768/EEC on cosmetic products. The field of application specified in Annex III is "denaturant for ethanol and isopropyl alcohol", with a maximum authorised concentration in the finished cosmetic product of 5% calculated as a % of ethanol and isopropyl alcohol.

It has been proven that not methanol, but its metabolite formic acid plays an important role in methanol toxicity. Studies on the kinetics of methanol metabolism revealed clear species-specific differences. In primates, metabolism by an alcohol dehydrogenase system occurs rapidly and yields the toxic intermediates formaldehyde and formic acid :

	Alcohol dehydrogenase or catalase		*aldehyde dehydrogenase or formaldehyde dehydrogenase*	
CH_3OH	→	HCHO	→	HCOOH
Methanol		*Formaldehyde*		*Formic acid*

Whereas formaldehyde is rapidly oxidised to formic acid, with a half-life of about 1,5 min, formic acid is only slowly metabolised to CO_2 (elimination in 20h), and therefore accumulates in the tissues, including the eye. A severe metabolic acidosis results, which precedes the most distinct aspect of methanol intoxication in man, visual impairment. In rodents, the reaction of

[1] R20/21/22: Harmful by inhalation, in contact with skin and if swallowed.
[2] R40/20/21/22 : Harmful : possible risks of irreversible effects through inhalation, in contact with skin and if swallowed.

formic acid to CO_2 occurs faster, and formic acid does not accumulate to the degree observed in primates. Thus, the results of methanol toxicity studies in rodents cannot predict its toxicity in primates, unless their formate oxidation pathway has been selectively inhibited (ref. 1, 6, 9).

For the general public, the usual route of elevated exposure to methanol is by ingestion either as a substitute for ethanol, in attempts to commit suicide, or in adulterated or mislabelled alcoholic beverages. Poisonings have involved many people and it has been shown that toxic effects caused by methanol are irrespective of the route of exposure. Moreover, the seriousness of the clinical case is often not correlated with the amount of methanol ingested (ref. 11).

Single oral moderate to large doses of methanol (400 - 1000 mg/kg bw) are known to cause blindness (ref. 5). The minimum dose causing permanent visual defect is unknown, although blindness has been reported after ingestion of as little as 4 ml (± 53 mg/kg) of methanol. Other common clinical manifestations of methanol poisoning in humans include CNS depression, weakness, headache, and vomiting. The symptoms of methanol poisoning may be delayed for up to 24h owing to methanol oxidation to formic acid (ref. 1).
Susceptibility among individuals to the acute effects of methanol is highly variable.
Oral doses of 30 to 100 ml (± 395 to 1317 mg/kg) have shown to be life threatening to lethal, while in other cases, ingestion of up to 500 ml (± 1975 mg/kg) did not induce any apparent disability. The reasons for differences in individual susceptibility are unknown, but ingestion of ethanol is known to affect methanol metabolism, the amount of food in the stomach may affect absorption, and prior exposure to methanol on a regular basis may affect metabolism (ref. 9, 11).

The minimum acute lethal methanol dose is considered to be between 300 and 1000 mg/kg bw (ref. 1, 5, 6). Chronic intake of smaller amounts (e.g. by inhalation of vapours) may lead to mucosa irritation, numbness, dizziness, headache and body pains, cramps, functional disorders of the digestion and bladder, and visual disorders (ref. 9).

In occupational exposure, inhalation and skin absorption are the most important entry routes of methanol (ref. 1). Pure methanol has an anomalously high diffusion rate through the epidermis, compared to ethanol and isopropanol, because of the more severe damage it causes in the stratum corneum. It permeates the epidermis at a rate of 10.4 mg/cm² h (ref. 5, 9).
On the basis of clinical case reports and a small number of epidemiological studies, it has been suggested that prolonged exposures to ambient methanol concentrations above 260 mg/m³ impair human visual function (ref. 6).
Current general population exposures through air are typically 10000 times lower than occupational limits. The general population is exposed to methanol in air at concentrations ranging from less than 0.001 mg/m^3 (0.8 ppb) in rural air to nearly 0.04 mg/m^3 (30 ppb) in urban air. A widely used occupational exposure limit for methanol is 260 mg/m^3 (200 ppm), which is designed to protect workers from any of the effects of methanol-induced formic acid metabolic acidosis and ocular and nervous system toxicity. No other adverse effects of methanol have been reported in humans except minor skin and eye irritation at exposures well above 260 mg/m^3 (200 ppm) (ref. 8).

Treatment of acute methanol poisoning includes administration of ethanol and folic acid. Ethanol will compete for alcohol dehydrogenase and thus reduce formate production, while folic acid will enhance formate oxidation to carbon dioxide. Dialysis and alkalinisation of urine have also been used to increase the elimination of formic acid (ref. 1).

Some remarks on the use of methyl acetate as a cosmetic ingredient

Methyl acetate is not listed in any of the annexes to Dir. 76/768/EEC.

In the specific case report introduced by the Danish EPA, methyl acetate is used in a nail polish remover at 50%. The letter of the European Commission mentions that methyl acetate is nearly completely converted into methanol, while a report of the European Scientific Committee on Toxicity, Ecotoxicity and the Environment mentions a 60% conversion (ref. 4).

The legal basis for the safety evaluation of cosmetic products, as mentioned above, can be found in Article 2 of Directive 76/768/EEC and its Amendments :

Article 2 : *A cosmetic product put on the market within the Community must not cause damage to human health when applied* ***under normal or reasonably foreseeable conditions of use****, taking account, in particular, of the product's presentation, its labelling, any instructions for its use and disposal as well as any other indication or information provided by the manufacturer or his authorized agent or by any other person responsible for placing the product on the Community market.*

Methyl acetate is used in cosmetics as a nail polish remover (ref. 4) and in that case, the question which should be asked, is whether ingestion of such a product is to be considered as a normal or reasonably foreseeable condition of use. Since this is clearly not the case, it would be sufficient to insist on a childproof closure of the bottles, to take care that the colouring agents are not attractive to children and to place a warning label on the bottle.
In the case that methyl acetate occurs as an ingredient in other types of cosmetics, an uptake in Annex III could be considered, but then the study of its complete dossier must be carried out by the SCCNFP.

For its use as nail polish remover, a calculation has been carried out by the Danish EPA and the exposure amounts per day by inhalation by the consumer during normal use would maximally be 0.08 mg/kg bw/day, which is very low and of no toxicological concern.
Also a cumulative inhalation exposure of the consumer was calculated for all kinds of use and even then the exposure remained lower than 3 mg/kg bw/day.

3. Opinion

The SCCNFP is of the opinion that the use of methyl acetate, as such, in cosmetic nail polish removers can be considered as safe.

However, and in order to assess the risk when used in cosmetic products other than nail polish removers, a complete safety dossier, according to the Notes of Guidance (doc. n° SCCNFP/0321/00) should be submitted although it is unlikely that, considering its toxicity profile, methyl acetate would be used in cosmetic products other than nail polish removers.

Moreover, the imposition of safety measures, such as child-safe bottle, the use of colouring agents that are not easily confused with soft drinks or particular labelling, are considered as 'risk management measures' and therefore fall out of the field of competence of the SCCNFP.

4. References

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