

## **Risk assessment on the use of triclosan in cosmetics**

### **II: Toxicity of triclosan in cosmetic products**

The objective of the present toxicological evaluation is, as stated in the terms of reference, to review and update the toxicological information and assess the margin of safety in the use of triclosan (cas no. 3380-34-5) in cosmetics. There is an extensive database on the toxicology of triclosan, which covers acute-, subchronic- and chronic toxicity, carcinogenicity, reproductive- and developmental toxicity, genotoxicity, irritation/sensitisation studies, toxicokinetic data as well as studies in humans (1-4). Triclosan is approved for use in cosmetic products in the European Union. However, we have not been able to find any toxicological evaluation (by e.g. SCCNFP) underlying this approval. Triclosan is approved in EU for use in food contact material made of plastic and in that context in 2000 the EU Scientific Committee on Food (SCF) did a toxicological evaluation of triclosan (5). The safety of triclosan in cosmetic products has been evaluated by the cosmetic industry (1-4). Particularly the Environ Corporation Expert Panel report on the safety of triclosan in toothpaste and oral rinse products (1) is an extensive review of existing data updated until 1992. Except for one study on toxicokinetics the studies evaluated by SCF in 2000 are covered in The Environ Corporation Expert Panel Report (1). Very few toxicological studies have been published in the open literature since 1990. The reviews made by industry and SCF are based mainly on a large number of unpublished industry reports as well as on published works. In the context of this report where the microbiological issues are in the focus, we only summarise the toxicological data as they appear in the reviews (1-5). We did not have access to the original toxicological reports.

#### *Acute toxicity*

The acute oral LD<sub>50</sub> is > 5000mg/kg/day based on studies that involve several species and routes of administration.

#### *Irritation and sensitisation*

Products containing triclosan have been tested for irritation, sensitisation, and photosensitisation potential in animals and clinical studies. Triclosan is moderately eye and skin irritating, and there is no evidence of contact sensitisation reaction or phototoxic/photoallergic response.

#### *Subchronic toxicity*

In numerous animal studies employing several species and routes of administration the subchronic toxicity of triclosan has been described. Although the toxicity varied by route of administration and by species, it was primarily linked to hepatic effects with minimal renal and haematopoietic changes noted in several species. In a 90-day dietary feeding study with rats a NOAEL = 100 mg/kg/day was identified. In hamsters administered orally for 13 weeks the NOAEL was 75 mg/kg/day (2). SCF (5) reviewed a 90 day study in rats and noted that no toxic effect was seen at a dose of 1000 ppm in the diet (equivalent to 50 mg/ kg bw/day) whereas toxic effects were seen at 3000 ppm in the diet (equivalent to 150 mg/ kg bw/day).

#### *Chronic toxicity/carcinogenicity*

In rats exposed to dietary triclosan for 2 years, it was observed dose-related changes in mean body weight gain, as well as selected haematology, clinical chemistry, and urinalysis parameters. Toxicity was mainly hepatic in nature as identified by centrilobular hypertrophy at a dose of 3000 ppm in the diet, and associated clinical chemistry changes. No putative preneoplastic or neoplastic lesions were found in the liver. A NOAEL (No observed adverse

effect level) (rats) of 52 mg/kg/day was identified (1). SCF (5) reviewed the same 2-year bioassay in rats, dose levels were 0, 300, 1000, 3000 and 6000 ppm in the diet (equivalent to  $\approx$  0, 15, 50, 150 and 300 mg/kg bw/day). Red cell counts were significantly reduced at all dose levels at 104 weeks, however, the effect was not more pronounced at 3000 ppm than at 300 ppm. Reduced red cell counts appeared at an earlier stage at higher doses in comparison with the lower. The animals did not appear anaemic. SCF noted that the 300 ppm dose, equivalent to 15 mg/kg bw/day can be regarded as a marginal effect level. In hamsters exposed to dietary triclosan for 90-95 weeks, there were dose-related changes in body weight gain and parameters of haematology, clinical biochemistry and urinalysis. Histological changes were seen in kidney, testes and stomach. No carcinogenic effects were seen. A NOAEL (hamsters) of 75 mg/kg/day was identified (2).

#### *Reproductive and developmental toxicity*

Pregnant rats exposed to triclosan by gastric intubations showed changes in food consumption, foetal and litter incidence, and in retardation of several ossification sites. In this study the NOAEL was 50 mg/kg/day for both maternal and foetal toxicity (1-4).

In a similar experiment with rabbits the NOAEL for maternal toxicity was 50 mg/kg/day for maternal toxicity and 150 mg/kg/day for developmental toxicity. In mice the NOAEL was 25 mg/kg/day for both maternal and developmental toxicity (1).

In a two-generation study in rats exposed to dietary triclosan (doses: 0, 300, 1000 and 3000 ppm in the diet) a NOAEL = 150 mg/kg/day for reproductive performance in the adults and a NOAEL = 50 mg/kg/day for effects on the offspring were established (2). SCF (5) noted that an unequivocal NOEL could not be established due to effects on the body weight at some stages even at the lower dose and that 300 ppm in the diet could be regarded as a marginal effect level.

#### *Genotoxicity*

Triclosan was not genotoxic in numerous *in vitro* and *in vivo* assays

#### *Absorption, distribution and excretion*

Triclosan is rapidly absorbed in mice, rats, hamsters and humans and maximum concentration is reached after 4 hours. The excretion is almost complete in rats and mice after 48 hrs. The major part is excreted in faeces and a minor part in urine as sulphate and glucuronide conjugates, whereas in hamsters the excretion is complete after 7 days and the major part is excreted in urine. Humans exposed to triclosan in the drinking water or in toothpaste during 21 days obtained a steady state level in plasma after 7 days and excreted most of the triclosan 4-5 days after cessation of exposure. Compared with exposure through an aqueous solution no more than 14 % of the triclosan in toothpaste after brushing and expectoration was absorbed. Blood levels obtained were about 1000 times lower than the blood levels of rats at hepatotoxic levels of triclosan (1,3,5,6,10).

*NOAEL*

The different NOAELs presented in the reviews (1-5) are summarised in the table.

Type of study	Species	Exposure	NOAEL (mg/kg/day)
Subchronic	rat	90 days	50 100
	hamster	13 weeks	75
Chronic/carcinogenicity	rat	2-years	52 15 (NOEL, marginal effects)
	hamster	90-95 weeks	75
Reproductive/developmental	rat	2-generation	50 150 (reproductive performance) 50 (offspring) 15 (NOEL, marginal effects)
			mouse

In the following safety evaluation of triclosan in cosmetic products we choose to use a NOAEL of **25 mg/kg/day** for maternal and developmental toxicity in mice as suggested by The Environ Corporation Expert Panel Report on the safety of triclosan in toothpaste and oral rinse products (1). An alternative would be to use 15 mg/ kg/day in order to take into account uncertain and marginal effects (5).

*Exposure*

We used the SCCNFP notes of guidance to calculate the global estimate of exposure of preservatives based on extensive use scenarios (7). The exposure calculations are based on the maximum allowed concentration of triclosan in cosmetics in Norway (0.5 % in soaps and rinse-off products and 0.3 % in leave-on products) (8). The exposure of triclosan from other sources, which is considered to be very small, is not taken into account.

The calculations are based on the following premises:

- 0.3 % triclosan in oral hygiene products, eye products and non rinse-off products, and 0.5 % in rinse-off products
- For a mouthwash 10 % of the amount used is ingested
- For a toothpaste 17 % of the amount used is ingested
- 100 % of ingested triclosan is absorbed
- 25 % dermal absorption of the applied triclosan dose for the eye products, non rinse-off products and 10 % for the rinse-off products (2)
- Body weight = 60 kg
- NOAEL = 25/mg/kg/day
- The exposure of triclosan from other sources, which is considered to be very small, is not taken into account

Exposure from the 4 main types of cosmetic products:

Oral Hygiene products

Toothpaste	$0.48 \text{ g/day} \times 0.3 \% = 1.4 \text{ mg/day}$ or $0.023 \text{ mg/kg/day}$
Mouthwash	$3.00 \text{ g/day} \times 0.3 \% = 9.0 \text{ mg/day}$ or $0.150 \text{ mg/kg/day}$
Lipstick	$0.04 \text{ g/day} \times 0.3 \% = 0.1 \text{ mg/day}$ or $0.002 \text{ mg/kg/day}$
Total	$3.52 \text{ g/day} \times 0.3 \% = 10.5 \text{ mg/day}$ or $0.175 \text{ mg/kg/day}$
Systemic exposure with 100 % absorption = <b>0.175 mg/kg/day</b>	

Eye products

Total	$0.05 \text{ g/day} \times 0.3 \% = 0.2 \text{ mg/day}$ or $0.003 \text{ mg/kg/day}$
Systemic exposure with 25 % absorption = <b>0.0008 mg/kg/day</b>	

Non rinse-off products

Total	$13.5 \text{ g/day} \times 0.3 \% = 40.5 \text{ mg/day}$ or $0.675 \text{ mg/kg/day}$
Systemic exposure with 25 % absorption = <b>0.168 mg/kg/day</b>	

Rinse-off products

Total	$0.75 \text{ g/day} \times 0.5 \% = 3.75 \text{ mg/day}$ or $0.063 \text{ mg/kg/day}$
Systemic exposure with 10 % absorption = <b>0.006 mg/kg/day</b>	

Total systemic exposure (SED) from all products = **0.350 mg/kg/day**

*Margin of safety (MoS)*

$$\text{NOAEL} = 25 \text{ mg/kg/day}$$

$$\text{SED} = 0.350 \text{ mg/kg/day}$$

$$\text{MoS} = \text{NOAEL}/\text{SED} = 25/0.350 = \mathbf{71.4}$$

*Comments*

The MoS is calculated to be 71.4. If uncertain and marginal effects are taken into account (NOEL = 15 mg/kg/day), the MoS are further reduced by 50 %. A MoS below 100 is a matter of concern (7) and warrants further analysis of the exposure data in order to identify problematic products. According to the model calculation, 50 % of the total triclosan exposure from cosmetic products is linked to the use of two types of products alone: mouthwash 43 % and toothpaste 7 %. The rest of the exposure derives practically in its entirety from all non rinse-off products (deodorants, creams, lotions etc), 48 %.

For mouthwash a concentration of 0.3 % was used in the calculation. However, according to a national survey carried out by The Norwegian Food Control Authority mouthwash sold on the Norwegian market in 2000 was reported to contain 0.03 % triclosan (9). With this concentration the MoS is calculated to be 125, a value still in the borderline range. In Norway the total quantity of triclosan used in toothpaste is approximately 850 kg/year since 2002 and 50 kg/year used in mouthwash (9). This proportion ( $850/50 = 17$ ) is not reflected in SCCNFPs notes of guidance for the application of toothpaste and mouthwash, which is:

#### Toothpaste

1.4 g x 2 times a day = 2.8 g/day, triclosan applied = 0.3 % x 2.8 g/day = 8.4 mg/day

#### Mouthwash

10g x 3 times a day = 30 g/day, triclosan applied = 0.03 % x 30 g/day = 9.0 mg/day

The proportion of applied triclosan in toothpaste/mouthwash =  $8,4/9 = 0.9$  in the calculation is very different from the proportion of triclosan in toothpaste/mouthwash = 17 used in the Norwegian marked. This difference may indicate that the group of mouthwash users in the population is small.

Non rinse-off products, which include a large number of products, contribute significantly to the total exposure of triclosan and the margin of safety for this group alone excluding all other exposures would be 149.

Eye products and rinse-off products, which contribute only 1.4 percent of the total exposure, do not represent a safety problem for human exposure. However, they may represent a significant source of exposure in the environment.

The exposure of triclosan from other sources such as food contact materials, household products and medicinal products, is not known in detail and therefore not included in the calculations. The contribution from these products to direct human exposure is expected to be very low. They may, however represent a significant source of exposure in the environment.

#### *Conclusion/recommendations*

Based on NOAEL = 25 mg/kg/day the margin of safety is less than 100 and the current regulation of triclosan content in cosmetic products is a matter of concern.

- The content of triclosan in mouthwash should be as low as possible
- The maximal level of triclosan allowed in non rinse-off products and toothpaste should be reduced
- The current maximal level in eye products and rinse-off products do not represent a safety problem

#### *References*

1. **Borzelleca, J.F., Frankos, V.H., Johnson, E.M., Jordan, W., Squire, R.A., and Weill, C.** 1992. Report of the expert panel on the safety of triclosan on toothpaste and oral rinse products. Environ Corporation Expert Panel Report.
2. **Ciba.** 2000. Triclosan: Justification of toxicological safety.
3. **Desalva, J., Kong, B., Lin, Y.-J.** 1989. Triclosan: A safety profile. American Journal of Dentistry **2**:185-196.
4. **Ciba Speciality Chemicals Holding Inc.** 1998. Irgasan Dp 300 Iracare MP. Toxicological and ecological data. Official registrations.
5. **SCF.** 2000. Opinion of the Scientific Committee on Food on the 10<sup>th</sup> additional list of monomers and additives for food contact materials.
6. **Nordberg P, Lindgren S and Svensson K.** Antimikrobiella medel, Rapport 16-2000, Livsmedelsverket/ National Food Administration, Uppsala, Sweden
7. **SCCNFP.** 2003. The SCCNFP's notes of guidance for testing cosmetics ingredients for their safety evaluation. 5<sup>th</sup> revision.

8. **Norwegian Food Control Authority (SNT)**. 1995. Generell forskrift for produksjon, import og frambud mv. av kosmetikk- og kroppspeieprodukter, nr 871 av 26. oktober 1995 <http://www.lovdata.no/for/sf/ho/to-19951026-0871-0.html>
9. **Norwegian Food Control Authority (SNT)**. SNT-rapport 1 – 2003. Analyse av triklosan i kosmetiske produkter. [http://snt.mattilsynet.no/dokumentasjon/rapporter/2003/snt\\_rapporter/200301.pdf](http://snt.mattilsynet.no/dokumentasjon/rapporter/2003/snt_rapporter/200301.pdf)
10. **Bagley D and Yi-Jong L**. Clinical evidence for the lack of triclosan accumulation from daily use in dentifrices. Am J Dentist, 2000;13:148-152