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SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

OPINION ON THE RISK ASSESSMENT FOR ACETYL TRIBUTYL CITRATE (ATBC) PLASTICIZER USED IN CHILDREN'S TOYS

Adopted by the CSTEE during the 41st plenary meeting of 8 January 2004

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Terms of Reference

Plasticizers are necessary to manufacture flexible PVC products. A number of plasticizers can be used in PVC although in Western Europe more than 90% are phthalates. Concerning the possibility of using alternative plasticizers to phthalates, the CSTEE has earlier concluded that there were significant gaps in the amount of scientific information on the potential substitutes which needed to be filled before their use in PVC toys and childcare articles could be properly evaluated.

The DG Enterprise has now obtained from industry a risk assessment report on acetyl tributyl citrate (ATBC) as plasticizer used in children's toys. The CSTEE has therefore received the following questions:

1. Is the CSTEE of the opinion that the risk assessment is of a good quality?

2. Is the CSTEE of the opinion that the risk assessment has provided sufficient sound scientific evidence to show that toys plasticized with acetyl tributyl citrate can be safely used by children?

GENERAL COMMENTS

The CSTEE is of the opinion that the current risk assessment report (Nikiforov, 2003) is of a good quality. In addition, the CSTEE is of the opinion that the risk assessment has provided sufficient sound scientific evidence to show that toys plasticized with acetyl tributyl citrate (ATBC) can be safely mouthed by children.

SPECIFIC COMMENTS

Exposure assessment

In the CSTEE opinion of 28th September 1999 on the toxicological characteristics and risks of certain citrates and adipates used as a substitute for phthalates as plasticizers in certain soft PVC products (CSTEE, 1999), gaps in the data base on ATBC were noted. It was concluded that it was not possible to do a proper risk assessment, especially because the lack of exposure information. Therefore, a study examining the extraction of ATBC from PVC disks cut from a custom molded ball and two commercially available toys has been performed with human volunteers (5 males and 5 females, 18 to 30 years old) (Bestari *et al.*, 2002). Volunteers were instructed to move the disks in their mouths, draw upon, apply pressure with the tongue or lightly chew the disks for four consecutive 15 minute intervals. All saliva was collect for subsequent analysis of ATBC content. The mean rates for ATBC migration rates were 1.53, 1.75 and 2.19 μg/min for the custom molded

ball, a yellow rubber duck toy and a blue shampoo bottle top, respectively. The two largest subjects had considerably higher migration rates than the other volunteers, the highest migration rate was found to be 10.1 μg ATBC/min.

In its earlier CSTEE opinion on phthalate migration from soft PVC toys and childcare articles (CSTEE, 1998), 6-12 months old children weighing an average of 8.0 kg were considered to maximally be mouthing toys for 180 minutes per day. This is considerably longer than the data provided by the Dutch Consensus Group study of Groot *et al.* (1998), where 3-12 months old children on average were determined to be mouthing toys for 12.0 minutes per day and for 2.1 minutes per day for 13-26 months old children.

Using the highest ATBC migration rate of 10.1 μg/min at a maximum mouthing duration of 180 min for a child weighing 8.0 kg and assuming that all the extracted ATBC is swallowed, an estimated daily intake via oral exposure becomes 227 μg per kg bodyweight. This is clearly a worst-case situation since the maximal extraction rate from a large, male adult and a mouthing duration of 180 minutes were used in the calculation.

Effects assessment

In the CSTEE opinion in 1999 (CSTEE, 1999) it was noted that an acceptable chronic toxicity/-carcinogenicity for setting an ADI for ATBC was not available. From a 2-generation reproduction toxicity study and a 90-day repeated dose study, a NOAEL of 100 mg/kg bw/day was indicated.

The present report (Nikiforov, 2003) argues that when considering the age of the animals when exposure to the test substance begins, the duration of the exposure period and time period at which evaluations are conducted with the test animals, a dietary 13-week study with an *in utero* exposure phase design much more closely mimics the exposure that children aged 0 to 36 months might have from mouthing soft PVC toys as compared to a chronic toxicity/carcinogenicity study design. A 13-week study with an *in utero* exposure phase in rats is about 20% of the two-year lifetime of the animals, whereas a 36-month exposure period of children to ATBC via mouthing of soft PVC toys is about 4% of their 75 year lifetime. The CSTEE supports the notion that a 13-week study with an *in utero* exposure phase is a valid test design on which to assess the potential risks for young children mouthing PVC toys containing ATBC as a plasticizer.

The influence of ATBC on systemic toxicity, reproduction and sexual maturation endpoints was assessed in a GLP 13-week dietary study using Han Wistar rats, which had direct and indirect exposure to the test material from before conception (Chase and Willoughby, 2002). Parental (F_0) animals were exposed to ATBC continuously in the diet at target doses of 0, 100, 300 and 100 mg/kg bw/day for four weeks before pairing and throughout mating. The offspring (F_1 generation) were exposed to the test material *in utero* and from birth until the start of the 13-week study. During the 13-week study, the F_1 animals were administered ATBC in the diet at the same target doses as the parental animals. Parental animals were evaluated for reproductive endpoints and F_1 animals were evaluated for sexual maturation, oestrous cyclicity, physical appearance, ophthal-mologic effects, neurobehavioral effects, growth, food consumption, survival, haematology, blood chemistry, urinalysis, peroxisome proliferation, organ weights, gross pathology and histopathology.

There were no effects of ATBC on any of the reproductive endpoints. Litter size, survival and growth were similar in all groups. Also, there were no indications of any endocrine effects of ATBC treatment. There were no findings at necroscopy of parental animals or surplus offspring that were considered to be treatment related. Treatment in the 13-week toxicity phase resulted in a slight reduction in body weight gain in both sexes at the highest dose (1000 mg/kg bw/day). Liver weights were increased and hepatic hypertrophy occurred at 1000 mg/kg bw/day in both sexes.

Weak peroxisome proliferation was measured in males at 300 mg/kg bw/day and both sexes at 1000 mg/kg bw/day. Slight variations in urinary composition and in plasma electrolyte concentrations indicated an effect on renal function at the two higher dose levels. The NOAEL for ATBC in this 13-week toxicity study with an *in utero* exposure phase were considered by the authors of the study report to be 100 mg/kg bw/day for males and 300 mg/kg bw/day for females [The CSTEE notes that it has reviewed the Chase and Willoughby (2002) study and that the Committee is in agreement with the description and evaluation of this study by Nikoforov (2003)].

Risk characterisation

From a mouthing study of PVC-disks containing ATBC in human volunteers, a maximum daily oral exposure dose of 227 μg/kg bw has been estimated. A new 13 week study in rats with an *in utero exposure has identified a NOAEL of 100 mg/kg bw/day. Since this study is judged to have an adequate design for addressing the potential risk for young children mouthing PVC-toys containing ATBC as a plasticizer, the CSTEE does not see a need for a chronic toxicity study. It is assumed that the risk assessment report is a correct reflection of the study outcome.* When comparing the estimated exposure dose with the NOAEL, a Margin of Safety (MOS) of 440 can be calculated. Since the exposure dose clearly is a worst-case estimate, the actual MOS for children up to 36 months of age presumably is considerably larger. Therefore, the CSTEE concludes that there is no safety concern when young children are mouthing PVC-toys containing ATBC as plasticizer.

References

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