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

Opinion on the results of a second Risk Assessment of:

BIS(2-ETHYLHEXYL) PHTHALATE [DEHP] HUMAN HEALTH PART

CAS No.: 117-81-7

EINECS No.: 204-211-0

Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]

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

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[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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Terms of Reference

A CSTEE opinion was delivered on the human health risk assessment of DEHP in January 2002. Since then further data have become available. The Rapporteur has considered the additional data on reproductive toxicity, used as a basis for risk characterisation for both testicular and developmental toxicity, and on biomonitoring in humans, used as the basis of the risk characterisation for the regional environmental exposure assessment.

The CSTEE is invited to examine the following issue on the basis of the new information:

Does the CSTEE agree with the results of the risk assessment based on the new information?

In particular the opinion of the CSTEE is sought on:

- the Margin of Safety for newborns exposed through breast milk;

- the DEHP exposure estimated derived from the biomonitoring data based on urinary metabolites.

GENERAL COMMENTS

The RAR has used a new NOAEL of 4.8 mg/kg bw/day for testicular toxicity and developmental toxicity derived from a recent 3-generation reproductive study in rats. The CSTEE supports this since the results seen in this newer study are more robust than those underpinning the previous NOAEL of 3.7 mg/kg bw/day.

The RAR advocates the use of measured urinary DEHP metabolites in order to calculate DEHP exposure in adults. The CSTEE is in agreement with this and recommends the biomonitoring of MEHP, 5OH-MEHP and 5oxo-MEHP for such calculations, rather than relying solely on the lesser metabolite MEHP. However, the CSTEE is not in agreement with the Technical Meeting that has preferred to use the MEHP conversion factor of 13% derived from a study of Anderson *et al.* (2001) to calculate the DEHP exposure. On the other hand, the Rapporteur may have estimated a too high DEHP exposure by using conversion factors for the DEHP metabolites from a study by Schmid and Schlatter (1985). A very recent study by Koch *et al.* (2003b) indicates higher urinary metabolite excretion. Given this new information, the CSTEE judges that there is an acceptable safety margin for regionally exposed adults. However, the CSTEE points out that greater

confidence in the risk characterisation will be achieved by broadening the database on DEHP metabolism and excretion in humans.

The safety margin with respect to testicular toxicity in infants exposed to DEHP from breast milk may be adequate. However, considerable uncertainty exists in the database, both with respect to DEHP levels in milk and to combined exposures in children aged 0-3 years, especially from indoor air. Thus, the CSTEE recommends the conclusion i) in order to gain more confidence in the exposure estimates.

SPECIFIC COMMENTS

Exposure assessment

For man exposed indirectly via the environment, the RAR has estimated exposure of adults as calculated from urinary excretion of DEHP-metabolites. In this estimate, there is a divergence of opinion between the Rapporteur and the Technical Meeting. The Technical Meeting advocates an estimation of DEHP exposure by using urinary measurements of the primary metabolite MEHP using a conversion factor. This conversion factor of 13% is derived from a study measuring urinary MEHP levels after administering a mixture of DEHP and diisooctylphthalate (DIOP) to human volunteers (Anderson *et al.*, 2001). From this, an exposure of 7.1 μg DEHP/kg bw/day is estimated. The Rapporteur criticises this calculation, both because MEHP is a lesser metabolite of DEHP and since the conversion factor is too large because it was derived from a study administering a mixture of DEHP and DIOP (both forming MEHP but DIOP is presumably more slowly further metabolised than DEHP). The CSTEE supports the arguments put forward by the Rapporteur in the RAR that a conversion factor from the Anderson *et al.* (2001) study is scientifically not sound.

The Rapporteur favours the estimation of DEHP exposure from a study by Koch *et al.* (2003a), where the metabolites MEHP, 5OH-MEHP and 5oxo-MEHP have been measured in urine from 85 non-occupationally exposed Germans. It is recognised that these data may not represent DEHP exposures throughout Europe. In order to convert these measured levels to DEHP exposure, conversion factors were calculated based on a human volunteer study with two individuals administered unlabeled DEHP (Schmid and Schlatter, 1985). By this procedure, the regional exposure estimate for DEHP becomes 52.1 μg/kg bw/day, i.e. approximately 7 times higher than the estimate supported by the Technical Meeting. The CSTEE is in agreement with the Rapporteur that derivation of the DEHP exposure by taking into account all the three metabolites (MEHP, 5OH-MEHP and 5oxo-MEHP) is better than relying solely on MEHP which is further metabolised. However, the levels of these metabolites in the Schmid and Schlatter study (1985) are considerably lower than what has been found in a very recently published study with a single human volunteer administered deuterium-labelled DEHP (Koch *et al.*, 2003b). Whereas Schmid and Schlatter (1985) reported MEHP levels in urine of 1.0 and 2.4%, Koch *et al.* (2003b) found a MEHP level of 7.3%. It should be noted that Schmid and Schlatter (1985) only detected 10-25% of the DEHP dose excreted in the urine, whereas Koch *et al.* (2003b) reported an excretion percentage of 47%. Thus, the question arises whether the conversion factor used by the Rapporteur from the Koch *et al.* 2003a-study could be too low and thus the DEHP exposure estimate too high. Another point to mention is that both the Koch *et al.* 2003b-study and that of Barr *et al.* (2003) report that 5OH-MEHP and 5oxo-MEHP are excreted in the urine in higher concentrations than MEHP, emphasising that measurements of the sum of these metabolites should be a much better biomarker for DEHP exposure than measurements of MEHP alone.

Data are available for 10 individual breast milk samples where the highest measured concentration was 160 μg DEHP/kg milk. This was converted to the following worst case exposure doses: 21 μg/kg bw/day for 0-3 month and 8 μg/kg bw/day for 3-12 month old infants.

A total of 39 individual samples of 14 different brands of infant formulae have been analysed and the measured concentrations used for calculation of DEHP exposure. The highest concentration of 440 μg DEHP/kg dry powder has been used as a worst case in these calculations. This resulted in the following DEHP exposures: 13 μg/kg bw/day for 0-3 month and 8 μg/kg bw/day for 3-12 month old infants.

The exposure of young children to DEHP from toys is presumably low, since it is assumed that the legislation prohibiting the placing on the market of the toys and childcare articles made of, or in part made of, soft PVC containing more than 0.1% by weight of DEHP that may be mouthed by children aged 0-3 years (Commission Decision 1999/815/EC, as last amended by Commission Decision 2003/819/EC) is respected.

The RAR has estimated indoor air exposure to DEHP by using the concentration of 5.3 μg/m^3 at saturated vapour pressure conditions. This level has been multiplied by 3 in order to account inhalation of DEHP bound to particles, arriving at a total air concentration of 21.2 μg/m^3. From this worst case scenario, children 0.5-3 years have been estimated to have an indoor air exposure of 22 μg/kg bw/day. The CSTEE points out that the worst case air concentration used in the RAR is approximately 100-fold higher than the 90th percentile of 240 ng/m^3 (aerosol + gas phase) reported from daytime (12 hours) air concentration measurements in a study of 125 Californian homes (Sheldon *et al.*, 1993)

Effects assessment

In a previous CSTEE opinion (CSTEE, 1998b), testicular toxicity was identified as the critical end-point for DEHP from a 13-week dietary study in Sprague-Dawley rats, and a NOAEL was set at 3.7 mg/kg bw/day based on mild Sertoli cell vacuolation (Poon *et al.*, 1997). Since that time, the results of a new multigenerational reproductive toxicity study of DEHP in Sprague-Dawley rats has become available (Wolfe and Layton, 2003). The RAR has evaluated the unaudited draft of that study. Three generations were fed DEHP in the diet at concentrations of 1.5 (DEHP-content in the control feed), 100, 300, 1000, 7500 and 10000 ppm corresponding to doses of 0.1, 0.5, 1.4, 4.8, 14, 46, 359 and 775 mg/kg bw/day. There were dose-dependent effects on numerous testis-related parameters (decreased testicular weight, small or aplastic testes, seminiferous tubular atrophy, infertility at high doses). The NOAEL for both testicular toxicity and developmental toxicity from this experiment was arrived at 4.8 mg/kg bw/day. The CSTEE agrees with the RAR to use this NOAEL rather than the 3.7 mg/kg bw/day derived from the study of Poon *et al.* (1997), since the endpoints seen in the Wolfe and Langley (2003) study are more robust.

Risk characterisation

For the risk characterisations of adults exposed indirectly via the environment, the diverging exposure estimates of 7.1 μg/kg bw/day (Technical Meeting) and 52.1 μg/kg bw/day (Rapporteur), result in MOS values of 676 and 92, respectively, when the NOAEL of 4.8 mg/kg bw/day is applied. The Rapporteur thus has arrived at conclusion iii), whereas the Technical Meeting arrived at conclusion ii). Since the exposure estimate used by the Rapporteur may be somewhat too high (v.s.) and the corresponding MOS value is close to 100, the CSTEE supports a conclusion ii) for the indirect exposure of adults from the environment, mainly from food products. However, it must be emphasised that the database underlying the use of conversion factors to transform urinary metabolite levels into DEHP exposure estimates is very small. Thus, more confidence in the risk characterisation will be achieved with a broadened database on DEHP metabolism and excretion in humans.

For children exposed through breast milk a MOS value of 229 for testicular toxicity is derived based on an exposure of 21 μg/kg bw/day and the NOAEL of 4.8 m/kg bw/day. The RAR argues for a MOS of around 250 for testicular effects and fertility should be an acceptable cut off for newborns (0-3 months) due to a number of reasons: 1) Testicular toxicity is a serious end point especially during the sensitive developing life-stage, 2) There is DEHP exposure of infants through several different routes, 3) There is a likely exposure of infants to other phthalates with similar mechanisms of action, and 4) There is considerable uncertainty in the exposure estimates. The CSTEE judges these arguments in the following fashion: 1) The testicular toxicity was revealed in a 3-generation reproductive study, this being a test method especially designed to detect reproductive effects during sensitive phases of a developing individual. Thus it is difficult to see why an additional assessment factor than the conventional factor of 100 used by the CSTEE (CSTEE, 2001), should be introduced. 2) Although infants probably are exposed to DEHP via other sources than breast milk, it is highly unlikely that an infant would be exposed to the worst case scenario for breast milk and infant formulae at the same time. Further, the CSTEE judges that the worst case scenario calculated for indoor air exposure to DEHP may be unrealistically high in comparison with measured data. However, should the calculation of indoor exposure in children be correct, this would result in a MOS value of 218 (exposure 22 μg/kg bw/day, NOAEL 4.8 mg/kg bw/day). The exposure of children 0-3 to DEHP from toys and other PVC products that may be mouthed is presumably low given the current EU regulation. 3) The CSTEE agrees that there is exposure of infants to other phthalates and that they may possibly act in an additive fashion, however phthalates such as DBP are considerably less potent than DEHP (CSTEE, 1998). 4) The CSTEE agrees with the RAR that there is uncertainty in the exposure estimates given the limited number of analysed milk samples.

There was disagreement among the member states in the Technical Meeting with respect to accepting the minimal MOS value (250) for testicular toxicity for young children (0-3 months) exposed to DEHP via breast milk. This minimal MOS value was also proposed to account for exposures from all routes and sources. Although the database on DEHP in breast milk is rather limited, the estimated worst case exposure of infants of 21 μg/kg bw/day would lead to a MOS of 229 for this source. The CSTEE concludes that this MOS value would not give rise to concern. However, given the uncertainties especially with respect to the data base for exposure from indoor air, the CSTEE recommends conclusion i) giving the possibility to improving the data base on combined DEHP exposure to young children and thus giving greater confidence to the risk characterisation.

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