Scientific Committee on Health and Environmental Risks

SCHER

Opinion on phthalates in school supplies

The SCHER adopted this opinion by written procedure on 17 October 2008

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SCHER

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1. BACKGROUND

Phthalates used as plasticizers in products for children, such as toys and childcare articles, have been of concern. Following assessment of the risks under Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1], and the evaluation of CSTEE and SCHER of such assessments[2,3,4,5,6,7,8], Directive 2005/84/EC of the European Parliament and of the Council of 14 December 2005 prohibits the marketing and use of the following phthalates[9]:

- Bis (2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) and benzyl butyl phthalate (BBP) in all toys and childcare articles;
- Di-isononyl phthalate (DINP) and di-isodecyl phthalate (DIDP) in toys and childcare articles which can be placed in the mouth by children.

A further plasticizer, di-n-octyl phthalate (DNOP), was banned from toys and childcare articles which can be placed in the mouth by children on the basis of a CSTEE evaluation on the risks of phthalates in general[10].

Study of the Danish Environmental Protection Agency

The Danish Environmental Protection Agency (EPA) has recently analysed phthalates in school supplies such as school bags, play bags, pencil cases and erasers. In addition, the Danish EPA identified DEHP (and small amounts of DBP) in a pencil case. It furthermore found phthalates, without identifying them individually, when screening other school supplies such as pencil cases, toy bags and school bags.

The Danish EPA concluded that “In general, the content of the above-mentioned substances [isophorone, Butylated hydroxytoluene, cyclohexanone, phenol, toluene, DIBP, DEHP, 2-heptanone, tert-butyl alcohol, methyl propionate, p-xylene] in the tested products does not present any health risk at normal use of the products; neither in the individual products nor if children are exposed to several products at once - for instance through use of pencil case, eraser and school bag - at exposure via both inhalation and migration for artificial sweat".

However, "Some of the studied erasers are made of PVC (9 of 26) and four of these erasers have a content of DEHP as plasticizer. Daily intake of a small amount (cube of approx. 4 mm) of eraser with a content of DEHP during a longer period may represent a health risk. Correspondingly, it may represent a health risk if a child daily sucks on an eraser with a high content of DEHP during a longer period.", and)”, "The calculations are generally based on the analyzed values for a few selected school bags, toy bags, pencil

[1] OJ L 84, 5.4.1993, p. 1.

[2] Opinion on Phthalates in Toys, SCTEE, 24 April 1998.

[3] Opinion on Phthalate Migration from Soft PVC Toys and Childcare Articles, 6th SCTEE plenary meeting, 26/27 November 1998.

[4] DINP: Opinion on the results of the Risk Assessment of: 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate. Report version (Human Health Effects), 27th CSTEE plenary meeting, Brussels, 30 October 2001.

[5] DEHP: Opinion on the results of the Risk Assessment of Bis (2-ethylhexyl) phthalate (DEHP). Report versions: Environment / Human Health, September 2001. Opinion expressed at the 29th CSTEE plenary meeting, Brussels, 09 January 2002.

[6] DIDP: Opinion on the results of the Risk Assessment of: 1,2-Benzenedicarboxylic acid di-C9-11-branched alkyl esters, C10-rich and di-"isodecyl"phthalate - Report version (Human health effects): 24th CSTEE plenary meeting, Brussels, 12 June 2001.

[7] DBP: Opinion on the results of the risk assessment Report of DIBUTYLPHTHALATE, 23rd CSTEE plenary meeting, Brussels, 24 April 2001.

[8] BBP: Scientific Committee on Health and Environmental Risks opinion on: Risk Assessment Report on Benzyl Butyl Phthalate (BBP) Human Health Part CAS No.: 85-68-7 EINECS No.: 201-622-7. Adopted by the SCHER during the 3rd plenary meeting of 28 January 2005.

[9] OJ L 344, 27.12.2005, p. 40.

[10] See: Opinion on Phthalate Migration from Soft PVC Toys and Childcare Articles, 6th SCTEE plenary meeting, 26/27 November 1998.

cases and erasers. It cannot be excluded that there may be products with a higher content than found in the products tested in this project. Furthermore, there may be other sources to the same chemical substances in the child's surroundings which will contribute to the total exposure."

For an additional plasticizer identified in the school supplies but not covered by Directive 2005/84/EC, Di-isobutyl phthalate (DIBP), the Danish EPA considered that "All the calculated MOS [Margins of Safety] of the individual products are significantly above 100 and this assessment is thus they do not represent any health risk with regard to DIBP. Exposure to DIBP both by inhalation and through skin absorption from several products at the same time is not estimated to represent any health risk for the examined products."

Finally, in a separate assessment of DINP, the Danish EPA concludes that "the exposure to phthalates through erasers is unacceptable."

Separate from the Danish study, there are claims that phthalates other than those banned are used in consumer products, however without sufficient knowledge about their risks. Although such claims are unconfirmed so far, it appears plausible that such phthalates may be used in order to avoid a conflict with the ban.

2. TERMS OF REFERENCE

Against the above background, SCHER is requested:

A) To assess the overall scientific quality of the report on the phthalates analysed, in particular DEHP and DINP, and to comment in particular on its completeness and reliability, and on the validity of its conclusions. If SCHER disagrees with such conclusions, it is invited to elaborate on the reasons. If SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

In particular, does the Committee agree with the approach adopted in which:

- The articles were cut into very small pieces of 2g for migration measurement (p. 38 of the report)?
- Artificial sweat was used as a surrogate for saliva (pp. 9 and 38 of the report)?
- It is assumed that children bite off pieces of articles (especially erasers) and swallow them. Is it considered appropriate to compare such exposure, when happening daily, to a NOAEL derived from chronic animal studies (pp. 64 - 66 of the report)?

B) To express an opinion on the specific issues including

- Whether the six phthalates covered by Directive 2005/84/EC may present a risk in certain or all school supplies;
- Whether the exposure to the six phthalates covered by Directive 2005/84/EC from school supplies, in addition to the exposure from toys and childcare articles and other sources indoor such as PVC-floorings, may present a risk;
- Whether the exposure to other phthalates than those covered by Directive 2005/84/EC may present a risk, taking into account recent scientific information.

3. OPINION

3.1. General Description of the Danish EPA study

The Danish Environmental Protection Agency investigated the exposure and possible risk of chemicals in consumer products and articles. Within this program, a"Survey as well as health assessment of chemical substances in school bags, toy bags, pencil cases and erasers" has been performed. After a market survey, a number of school bags, toy bags,

pencil cases and erasers were purchased and analysed. The chemical analysis was of a screening character and was performed in a tiered approach. The content of chlorine in the articles was investigated to identify PVC-containing articles, Fourier Transform InfraRed (FT-IR) spectroscopy was used on some samples to characterise polymer types, and X-ray analysis assessed the presence of chlorine or bromine (indicative of the presence of flame retardants), and of tin, sulphur and nickel. Head-space analyses were performed to investigate release of volatile chemicals. Extracts of some of the articles were analysed for selected metals, colouring agents, anti-oxidants and perfluorinated compounds. The migration of substances to artificial sweat and saliva was also studied for some of the samples.

A quantitative assessment of the content of chemicals was performed in 46 products including 26 erasers. There is some uncertainty regarding sample 16 as it is identified as pencil case in Table 2.3, but it is used in the risk assessment of erasers. Nine of the erasers contained phthalates; three of them contained 22-44% of DEHP and six contained 32-70% DINP. Some of the investigated products also contained DIBP and di-n-butyl phthalate (DNBP), as indicated by the migration analysis, but the total content of these phthalates was not determined.

The migration of chemicals from 14 products (none of these were erasers) into artificial sweat was studied for 2 g samples into 25 ml artificial sweat at 40°C under static conditions. Detailed information regarding the surface area of the samples is not given, the surface area was “varying”. The migrated chemicals were analysed by GC-MS employing solid phase micro extraction. The results showed that DIBP (maximum 88 µg/g/h), and DEHP (maximum 6 µg/g/h) migrated from 11 and 5 products respectively.

The resulting exposure estimates for some of the identified substances were integrated in a health risk assessment. The conclusion in the report is that, in general, the investigated exposures do not present a health risks for the children. The only exception was exposure to DEHP from erasers through sucking and chewing. In a separate memorandum entitled “Erasers containing DEHP” (Danish EPA, 22 June 2007), it is described that two of the three erasers containing DEHP have been described as toys and thus been banned. In another memorandum entitled “Erasers containing DINP” (Danish EPA, 22 June 2007), of six erasers contained DINP, five were described to be toys and were thus banned.

The main focus of this opinion will therefore be to evaluate the potential for exposure to DEHP from uses of DEHP-containing erasers by children. The major exposure route to phthalates from the items investigated in the Danish study is by licking and chewing on the items as well as swallowing small pieces of the item. The most relevant items in school supplies are erasers due to their small size, as more frequent biting and licking on bags and cases is considered as unlikely. SCHER agrees with the conclusion that erasers may be the only relevant source for phthalates from the selection of school supplies investigated.

Validation exercises within the EU and CEN have shown that migration of phthalates into artificial saliva of several compositions, at neutral pH, were comparable (Bouma and Schakel, 2002; Earls et al. 2003; CSTEE, 1998). Thus, it is expected that phthalate migration into artificial sweat will be comparable with that into artificial saliva and the data obtained from the migration studies using artificial sweat can therefore be extrapolated to migration into artificial saliva. The experiments using artificial sweat are performed under static conditions at 40°C and the content of phthalates in the products used for these experiments is not known. Therefore, no conclusions are possible.

3.2. General conclusions based on the reviewed study report

In general, the study design and the report contain several weaknesses, which hamper its evaluation and the ability to come to conclusions based on the results. The report is confusing as not all details required for an evaluation are included; some information is given in the section on exposure, some in the section on risk assessment. Furthermore,

only limited and sometimes diverging information on quality assurance of the analyses is provided.

However, SCHER agrees that the presence of phthalates in school supplies other than erasers is of low concern since dermal contact may be the only reasonable exposure pathways for children. Exposure from this pathway is expected to be very limited due to limited skin contact and inefficient dermal uptake.

Erasers may be of concern when they contain phthalates. However, based on the report, a science-based risk assessment of this potential exposure cannot be performed due to the following deficiencies in the report:

- The migration of DEHP into artificial saliva (pH 5.0) was only studied from one eraser (DEHP content 44%, w/w) in a 1 g sample cut into small pieces (cubes) with a width of 2-3 mm at 37°C for one hour. This procedure gives a much larger area for migration, and thus results in excessive leaching of the plasticizer. The study authors have calculated a six fold overestimation. The analysis of chemicals migrated into artificial sweat was performed correctly using an extraction technique that only measures dissolved substances. The phthalate data from this investigation are much lower than the DEHP migration from the eraser into artificial saliva.
- Small pieces of the eraser material suspended in the artificial saliva at the end of the migration experiment were not removed before extraction, which may further overestimate DEHP migration.
- It is not clear whether the extraction was performed under static or under dynamic (= shaking) conditions since, in a memorandum called “Erasers containing DINP” (Danish EPA, 22 June 2007), the same experiment is described as “the sample was shaken with the artificial saliva”.
- The uncertainty of the determinations has been reported to be 50% - which is considered to be indicative of a low quality of the chemical analyses, especially as stable isotope-labelled DEHP was used as an internal standard.
- To obtain information on a potential phthalate release from swallowed eraser particles, the migration of phthalates should be analysed using artificial gastric juice, normally 0.05% HCl.

In summary, SCHER considers that, due to the many weaknesses in this study and its reporting, firm conclusions on release of DEHP and DINP from the erasers as a basis for an assessment of potential health risk cannot be made.

However, SCHER will use some of the data presented in the Danish EPA report for a screening risk assessment of the exposures to phthalates from erasers to indicate the magnitude of a possible problem and information needs.

3.3. Possible contribution of erasers to phthalate exposures in children

The internal exposure of a child to DEHP and DINP from erasers by licking and chewing is dependent on the following factors:

1. the migration of the substance to saliva
2. the time the user is sucking/chewing on the eraser and how it is done
3. the amount of particles swallowed from the eraser
4. the migration of the substance from the particles into gastric juice
5. the bioavailability of the substance from saliva and the gastrointestinal tract

For a screening assessment, the data for the Danish EPA study are used to represent a worst case situation acknowledging that this may be an overestimation regarding the

release from sucking and licking. In the Danish study, 0.1% of DEHP migrated to artificial saliva within one hour from an eraser containing 44% of DEHP. As this was obtained after cutting the eraser into smaller pieces the authors estimated it to give a 6-fold overestimation. As an example, an eraser measuring 11*18*40 mm has a surface of 8 cm^2 and a weight of 13 g. The DEHP migration measured in the Danish study then corresponds to a release of more than 120 $\mu g/cm^2/h$. This is almost ten times higher than what was found for DINP migration in two European chewing studies (Könemann, 1998; Steiner et al., 1998), but comparable to the highest values found in a US study (US CPSC, 1998). A worst-case release of DEHP may thus indeed be 120 $\mu g/cm^2/h$.

A more difficult parameter to estimate is the suction time. Most children will never put an eraser into their mouth, and there are probably some that do it more frequently, and a few may do it over longer time periods. In the Danish report, it is assumed that a child sucks on a piece of eraser (1 gram) for one hour per day. SCHER has no other information and will use this assumption as a reasonably worst case.

Bioavailability of phthalates from saliva or swallowed particles is assumed as 100 %, but the amount of small eraser particles swallowed after chewing is very difficult to estimate. However, practical experience shows that small particles bitten off an eraser are sharp and not easily swallowed. In the Danish report, the exposure via swallowed particles was calculated for 8, 50 and 100 mg of particles per day. SCHER considers higher particle consumptions as unrealistic and will concentrate on the lowest level (8 mg of particles) in its exposure assessment. In addition, it is not known how frequently biting and swallowing occurs in children. This represents the largest uncertainty factor in this assessment.

With these assumptions, the total exposure to DEHP from 1 cm^2 of an eraser containing 44% DEHP may be 0.1 mg/child from sucking and licking. Biting off pieces and swallowing these particles may result in an intake of up to 4 mg DEHP/child. It is obvious that the swallowed fraction may be the dominant exposure pathway, but the uncertainty regarding the relevance of the pathway for overall DEHP-exposure is high. Combining all these worst-case scenarios it results in an exposure of 4.1 mg/child or 0.2 mg/kg for a 6 years old child of 20 kg of weight. This exposure is 4-fold above the EFSA TDI of 0.05 mg/kg/day for DEHP and with a MOE (margin of exposure) of 25 to the NOAEL for DEHP of 4.8 mg/kg bw/day identified by CSTEE (2004), derived with a major contribution from swallowed particles. Uptake of DEHP by licking only, even when using a conservative assessment, will not exceed the afore-mentioned highly conservative EFSA TDI for DEHP.

However, swallowing of a larger number of particles from an eraser containing DEHP likely represents an infrequent event due the nature of the particles (see above) and the fact that only a very small number of children in the groups where DEHP intake was assessed by biomonitoring (see below) exceeded the TDI. In addition, licking on erasers and swallowing particles bitten off an eraser represents a short-time habit of children resp. a one-time event as outlined in the report. Therefore, due to the short exposure time, it is inappropriate to use the TDI (derived for lifetime exposures) from a chronic study for risk assessment due to the rapid biotransformation and excretion of phthalates. Moreover, the assessment of exposure by swallowing particles relies on a single exploratory experiment, which needs to be repeated to confirm the findings.

3.4. New information on exposure and toxicity of phthalates

SCHER has no information on use patterns, occurrence, and human exposures to diisodecyl (DIDP) and di-n-octyl phthalate (DNOP). For DEHP, DINP, DIBP, DNBP, and DBP, a large number of studies relevant to exposure and risk assessment of phthalates are available including recent risk assessment reports (RAR). Therefore, the following text only gives short summaries.

3.4.1 Exposure assessment

Detailed exposure assessment using concentrations of phthalates in food, environmental media and materials including predictions by modelling have been performed in the EU-RARs. For an additional detailed overview on occurrence of phthalates and assessments of human exposures, see Heudorf et al., 2007.

Conservative exposure assessments for DEHP, DINP, DIBP, DNBP, and DBP are given in the available RARs. However, more recent studies derived human exposures to phthalates by biomonitoring of metabolite excretion since this results in a more precise estimate of average exposures and the range of exposures as compared to exposure estimates based on concentrations of phthalates in environmental media and food and assumptions on uptake of these media. The linear two-compartment model published by Kohn et al. (2000) and David (2000) based on the creatinine adjusted concentrations of phthalate ester metabolites in urine and the molar fraction of the urinary excreted metabolite related to the parent compound (Koch et al. 2004a) were used to derive estimates of phthalate exposure in children (Table 1). If available, results for adults are presented for comparison.

The most representative biomonitoring data from two surveys are available on DEHP. Within the US-National Health and Nutritition Examination Survey (NHANES) 2001-2002, information of urinary levels of phthalate metabolites were collected from 2782 participants aged 6 years and older (NCEH 2005). In the pilot study for the German Environmental Survey on Children (GerES IV), urinary levels of phthalates were determined in random urine sample of 254 children aged 3 to 14 years (Becker et al. 2004). In comparison to the NHANES subpopulation of children aged 6 to 11 years, the median levels of DEHP metabolites were slightly higher in the German samples, while the 95^{th} percentiles were lower. In the German sample, the concentrations of secondary metabolites in urine were increased in boys as compared to girls and were significantly higher in children aged 6-7 years compared to children in the age group 13-14 years.

Table 1: Urinary concentrations of mono-(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP), mono-isobutyl phthalate (MIBP), and mono-benzyl phthalate (MBeP) to assess daily intakes of di(2-ethylhexyl)phthalate (DEHP), mono-butyl phthalate (MmBP), di-n-butyl phthalate (DNBP), di-isobutyl phthalate (DIBP), and benzylbutyl phthalate (BBP).

	Metabolite concentration (µg/g creatinine)			Phthalate intake (µg/kg b.w.)			year of sampling	Reference
Age, number	**Median**	**95th Percentile**	**Max**	**Median**	**95th Percentile**	**Max**		
DEHP (EFSA TDI of 50 µg/kg bw/day)								
USA								
6-11 y, n: 392	34.2	211	-	3.8	24	-	2001/02	NCEH 2005
>20 y, n: 1638	*15.0*	*134*	-	*1.7*	*15*	-		
6-9 y; n: 90	43.8 [a]	-	-	5.0	-	-	2004/05	Wolff et al. 2007
6-10 y; n: 35	76.4	592	1101	8.7	67	125	2004	Teitelbaum et al. 2008
Germany								
3-14 y, n: 254	39.9	170	1990	4.5	19	227	2001/02	Becker et al. 2004
2-7 y; n: 36	55.8	107	129	6.4	12	15	2003	Koch et al. 2004b
20-59 y; n: 19	*28.1*	*64*	*103*	*3.2*	*5.7*	*12*		
DNBP (EFSA TDI of 10 µg/kg bw/day)								
USA								
6-11 y, n = 392	35.1	146	-	1.3	5.3	-	2001/02	NCEH 2005
>20 y, n: 1638	*15.4*	*71.6*	-	*0.6*	*2.6*	-		
6-9 y; n: 90	44.1[a]	-	-		-	-	2004/05	Wolff et al. 2007
6-10 y; n: 35	52.6	165.1	661	1.9	6.0	24.0	2004	Teitelbaum et al. 2008
Germany								
2-14 y, n = 239	136	491	2102	4.9	17.8	76	2001/02	Koch et al 2007
DIBP (no TDI allocated)								
USA								
6-11 y, n: 392	5.2	24	-	0.2	0.9	-	2001/02	NCEH 2005
>20 y, n: 1638	*2.2*	*11*	-	*0.1*	*0.4*	-		
6-9 y; n: 90	11.1	-	-	0.4	-	-	2004/05	Wolff et al. 2007
6-10 y; n: 35	15.6	50.9	158	0.7	1.8	5.7	2004	Teitelbaum et al. 2008

BBP (EFSA TDI of 500 µg/kg bw/day)								
USA								
6-11 y, n = 392	37.2	195	-	1.2	6.5	-	2001/02	NCEH 2005
>20 y, n: 1638	*11.8*	*64.9*	-	*0.4*	*2.2*	-		
6-9 y; n: 90	28.7[a]	-	-	1.0	-	-	2004/05	Wolff et al. 2007
6-10 y; n: 35	36.6	288	824	1.2	9.6	27.5	2004	Teitelbaum et al. 2008
Germany								
2-14 y, n = 239	13.2	82.7	567	0.4	2.8	18.9	2001/02	Koch et al. 2007

[a] geometric mean

While in NHANES, no differences with respect to ethnicity were found, an association with ethnicity was observed in two other US studies. In an investigation of 90 girls from 4 US sites representing four racial/ethnic groups, exposure was found to depend on ethnicity with lowest concentrations observed for whites and on study site with differences of factor 1.7 (Wolff et al. 2007). These results were supported by Teitelbaum et al (2008) who observed a very high exposure to phthalates in 35 healthy Hispanic and black children.

Overall, it has to be considered that the knowledge of the toxicokinetic behaviour of DEHP and other phthalates in humans is still limited and age related differences have not been sufficiently evaluated. Despite these uncertainties, the average exposure of children is approximately twofold higher than that of adults. Different life style factors, eating behaviours, a higher dietary intake compared to body weight and the ingestion of dust from indoor surfaces may play a role. In a recent study from Germany, both urine samples and food duplicates were collected from 5-8 year old boys over 3 consecutive days (Heger 2007). The results indicated that diet (without beverages) was responsible for about 50 % of the exposure derived from biomonitoring (1.4 µg/kg b.w. vs. 3.1 µg/kg b.w.). Thus, other important sources, which are not yet identified, must exist. For adults, DEHP exposure is dominated by the dietary intake (Fromme et al. 2007), particularly from fatty foods.

Moreover, it has to be noted that using a scenario-based indirect approach no differences between adults and children 4-10 years old could be observed but a clearly increased exposure was calculated for children less than 4 years of age (Wormuth et al. 2006).

Since DINP replaces DEHP in many applications, an increase in the exposure to DINP occurs. Between 1999 and 2004, the proportion of DEHP to total phthalate usage decreased from 42% to 22% and the proportion of DINP and DIDP (no data specifically on DINP are available) increased from 35% to 58% (ECPI 2006). Beyond this, Wittassek et al. (2007) quantified the exposure to phthalate in 20-29 year old students from 1988 to 2003 in a retrospective study in Germany. A continuous decrease in DEHP exposure was observed from 1996 until 2003 with an increase in DINP (Median: 0.2 µg/kg b.w. to 0.4 µg/kg b.w.) exposure. At present, biomonitoring data on the metabolites of DINP or other phthalates in children are not available for exposure assessment and are needed.

DINP intake for children aged 3-12 months and 13-26 months was assessed by migration data and average mouthing times using statistical modelling (US-CPSC, 1998).Migration rates were developed from in-vitro experiments and scaled. These data were combined into an analytical model that used a lognormal distribution for human exposure duration, combining estimates from the separate experiments. The results showed a geometric mean average daily intake of 5.7 µg/child/day (95% confidence interval of 2.5 to 12.9) for children between ages 3 and 12 months (less then 1 µg/kg bw/day for an 8 kg child). The distribution was very skewed, with an estimate of 5% of children at an intake of 94.3 µg/child/day (more than 10 µg/kg bw/day for an 8 kg child) or more (95% confidence interval 50.1 to 225.6). The values for children at 13-26 months were considerably lower with a geometric mean of less than 1 µg/child/per day.

In conclusion, the exposure data based on biomonitoring indicate that average exposures are well below the TDI for DEHP, but the DEHP body burden may approach or even exceed the TDI in some highly exposed groups of population. For the other phthalates studied, the 95th percentile exposures derived are below the TDIs except for DNBP. For DNBP, a significant part of the population may be exposed to doses above the TDI indicating a need for further reductions in exposures.

3.4.2 Phthalate toxicity

The following contains a short synopsis of the toxicity of some widely used phthalates.

Di-(2-ethylhexyl) phthalate

The critical toxic effects of DEHP relate to reproduction. A 3-generation reproductive study in which DEHP was administered to rats in the diet gave a NOAEL of 4.8 mg/kg bw/day for testicular and developmental toxicity. A TDI of 0.05 mg/kg bw/day, based on this NOAEL, and the default uncertainty factor of 100, was established for DEHP by EFSA and is supported by SCHER.

Recent studies show that peroxisome proliferation may not represent a relevant mode-of-action for DEHP induced liver tumours, since peroxisome proliferator-activated receptor (PPAR) knockout mice also showed tumour induction after lifetime administration of DEHP. Alternative mechanisms for liver tumour induction have been outlined in the MAK-justification for DEHP with the conclusion that genotoxic events very unlikely are involved in the tumourigenicity of DEHP (MAK, 2002). At the DEHP-doses observed in humans, DEHP-exposure therefore does not represent a relevant cancer risk to humans. Therefore, the tumour induction by high doses of DEHP in rodents is not considered as an endpoint relevant for risk characterisation (MAK, 2002).

Di-isononyl phthalate

Di-isononyl phthalate (DINP) is a mixture of esters of o-phthalic acid with C8-C10 (C9 rich) alkyl alcohols. These alcohols can be obtained by different processes, yielding different ratios of chain length and branching distribution, which result in different DINP types. Presently, 2 different DINP types are used (CAS 68515-48-0 and CAS 28553-12-0). These DINP mixtures are considered together. Previously, a group TDI of 0.15 mg/kg bw/day (with di-isodecyl phthalate – (DINP + DIDP), was based on peroxisome proliferation in rodent liver, but peroxisome proliferation in rodents is not relevant for human risk assessment. In a 2-generation reproductive toxicity study with DINP, NOAELs of 500 mg/kg bw/day and 622 mg/kg bw/day were established for minor developmental effects and decreases in live birth and survival indices, respectively. The pivotal toxicological effects for DINP are hepatic changes. Using the NOAEL of 15 mg/kg bw/day for non-peroxisome proliferation-related chronic hepatic and renal effects and an uncertainty factor of 100, a TDI of 0.15 mg/kg bw/day was derived.

Di-isodecyl phthalate

There also are two different di-isodecyl phthalate (DIDP) products with different CAS numbers (68515-49-1 and 26761-40-0). The two phthalates are considered fully interchangeable and are considered together. There is no indication of reproductive organ effects for DIDP evidenced in repeated dose toxicity studies. In a 13-week oral study in dogs, a NOAEL of 15 mg/kg bw/day could be derived. Based on the liver effects in dogs (considered as a non-sensitive species to peroxisome proliferation) with a NOAEL of 15 mg/kg bw/day, a lowest overall NOAEL of 15 mg/kg bw/day could be considered. No TDI for DIDP is available, but low concern can be derived when exposures are below 0.15 mg/kg bw/day (MOE > 100).

Di-*n*-octylphthalate

The results of several acute- and intermediate-duration oral studies in rodents indicate that the potential of di-*n*-octyl phthalate (DNOP) to cause adverse reproductive and developmental effects is low. Unlike other phthalate esters such as DEHP, DNOP does not appear to affect testicular function or morphology (Hardin et al. 1987; Heindel et al. 1989). Observed hepatic effects in intermediate duration studies consisted of a statistically significant increase in hepatic ethoxyresorufin-0-deethylase activity and histological changes in hepatic architecture. Thyroid toxicity was also noted at this concentration. No chronic oral TDI is available for DNOP.

Benzylbutyl phthalate

A NOAEL of benzylbutyl phthalate (BBP) of 20 mg/kg bw/day for developmental effects was observed in a 2-generation study in rats (Nagao et al., 2000) based on a decreased body weight in offspring at the LOAEL of 100 mg/kg bw/day. The NOAEL for effects on reproductive organs was 100 mg/kg bw/day. A NOAEL of 50 mg/kg bw/day for developmental effects was also observed in a second 2-generation study (Tyl et al., 2004). Therefore, a TDI of 0.5 mg/kg bw/day based on a reduction of anogenital distance in the F1 and F2 generation with a LOAEL of 250 mg/kg bw/day was derived for BBP.

Di-n-butyl phthalate

The male reproductive system is also a main target of di-n-butyl phthalate (DNBP) toxicity with a NOAEL (50 mg/kg) and a LOAEL (100 mg/kg) for DNBP-effects on male reproductive development in the F1 generation (Mylchreest et al. 2000). In a 2-generation rat study, a LOAEL of 52 mg/kg for embryotoxicity in the F2-generation was observed.

A developmental toxicity study in the rat (Lee et al., 2004), with dietary exposure to DNBP during the period from late gestation (gestational day 15) to the end of lactation (Postnatal day 21), showed effects on the development of male and female offspring at lower doses than when examining the development of reproductive tissues at various postnatal ages in detail. Reduction of testicular spermatocyte development and mammary gland changes in both sexes of offspring were seen at PND 21 at doses of app. 1.5-3.0 mg/kg bw/day and above, with dose-dependent increased incidence and/or severity. Loss of germ cell development was no longer present at 1.5 to 3 mg/kg bw/day at postnatal week 11, but showed a dose-dependent increase in a dose range from 14-28 mg/kg bw/day to 712-1372 mg/kg bw/day. Based on loss of germ cell development and mammary gland changes at 1.5 to 3 mg/kg bw/day in the diet (the lowest tested dose), a NOAEL could not be established. EFSA has derived a TDI of 0.01 mg/kg bw/day using a high safety factor.

Di-isobutyl phthalate

DIBP, after giving rats high doses of 600 mg/kg bw/day day from gestational day (GD) 7 to either GD 19 or GD 20/21, induced testicular and developmental effects similar to DBP and DEHP. However, since no dose response was assessed, further developmental and postnatal studies are needed to characterize the reproductive effects of DIBP and derive a NOAEL for risk assessment (Borch et al. 2006). A TDI therefore has not been defined.

3.5. General conclusions

Based on the evaluation of the report of the Danish EPA on phthalates in school supplies, SCHER concludes that the phthalates in the articles tested do not significantly contribute to the body burden of phthalates in children. Analysis of exposure data on phthalates based on biomonitoring show that exposures to DEHP and other phthalates in the general population, except DNBP, are below the TDIs based on the comprehensive database on the toxicology of these compounds. However, DEHP exposures may exceed the TDI in specific populations (e.g. exposure from medical devices, see SCENHIR-opinion). Moreover, from the single available exploratory experiment SCHER has estimated that biting off pieces from an eraser and swallowing these particles also exceed the TDI by a factor of 4. This exposure is still 25-fold below the NOEL of DEHP, which has been obtained from long term experiments. Since swallowing particles bitten off an eraser represents a short-time habit of children or even a one-time event as outlined in the report it is unlikely that this exposure leads to health consequences. However, the SCHER stresses the great uncertainty of this evaluation and proposes a migration study as outlined in its opinion on Organic Chemicals in Toys (SCHER 2007).

4. LIST OF ABBREVIATIONS

BBP	Benzylbutyl phthalate
BHT	Butylated hydroxytoluene
CEN	European Committee for Standardization
DBP	Di butyl phthalate
DEHP	Di-(2-ethylhexyl) phthalate
DIBP	Di isobutyl phthalate
DIBP	Di-isobutyl phthalate
DIDP	Di-isodecyl phthalate
DINP	Di-isononyl phthalate
DNBP	Di n-butyl phthalate
DNOP	Di-n-octyl phthalate
ECPI	European Council for Plasticizers and Intermediates
EFSA	European Food Safety Authority
FT-IR	Fourier Transform InfraRed spectroscopy
GC-MS	Gas Chromatography-Mass Spectrometry
GD	Gestational day
LOAEL	Lowest Observed Adverse Effect Level
MAK	Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
MBeP	Monobenzyl phthalate
MEHHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
MIBP	Mono-isobutyl phthalate
MmBP	Mno-butyl phthalate
MOE	Margin of Exposure
MOS	Margin of Safety
NHANES	National Health and Nutritition Examination Survey
NOAEL	No Observed Adverse Effect Level
PND	Post Natal Day
PPAR	Proxisome proliferator-activated receptor
PVC	Polyvinyl chloride
RAR	Risk Assessment Report
TDI	Tolerable Daily Intake
US EPA	US Environmental Protection Agency

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