Review

Recent European Food Safety Authority toxicological evaluations of major phthalates used in food contact materials

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During the 1980s and 1990s, and at the EU level, the Scientific Committee for Food evaluated a number of phthalates that were being used, or were requested for use, as additives in plastics. At this time, peroxisome proliferation was considered as the pivotal effect on which toxicological evaluation of these chemicals was based. At the end of 1990s, a general consensus has been agreed that rodents are highly sensitive to the phenomenon of peroxisome proliferation and that this particular effect should not be used for human risk assessment. Consequently in 2004, it was requested from the newly created European Food Safety Authority to perform a new evaluation of the mainly used phthalates on the basis of existing data. This paper summarizes evaluations of butylbenzylphthalate, dibutylphthalate, diethylhexylphthalate.

Keywords: European Food Safety Authority / Food contact materials / Phthalates / Toxicological evaluation

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1 Introduction

During the 1990s and at the EU level, the Scientific Committee for Food (SCF) evaluated a number of phthalates that were being used, or were requested for use, as additives in plastics. These included a few extensively investigated substances, butylbenzylphthalate (BBP), dibutylphthalate (DBP), diethylhexylphthalate (DEHP), di-isononylphthtalate (DINP), and di-isodecylphthtalate (DIDP), as well as a large number of phthalates for which there was little or no toxicity information.

For the studied phthalates, the most sensitive change observed in rodents at that time was peroxisome proliferation in the liver. It was unclear then whether the peroxisome proliferation seen at relatively low doses was mechanistically linked to the development of liver tumors seen in rodents after chronic treatment with much higher doses. Although limited evidence at that time indicated that liver cells from humans and from some other nonrodent species were relatively nonresponsive to induction of peroxisome proliferation by phthalates, the possibility that such agents might pose a carcinogenic risk to humans could not be ruled out.

In 1994, faced with these uncertainties, the SCF pursued a prudent approach and set a tolerable daily intake (TDI) for many phthalic esters, based on the NOEL for peroxisome proliferation in rat liver. Five phthalates, *i.e.*, BBP, DBP, DEHP, DINP, and DIDP, were classified in SCF list 2 and the values for their TDIs were based on their peroxisome proliferation potencies. Since, it was also known that some other structurally-related alkyl esters also induced peroxisome proliferation, the SCF issued an opinion in 1995 covering all the alkyl esters requested for use in food contact materials [1]. In this opinion, a requirement was set for peroxisome proliferation studies to be submitted on those alkyl esters for which migration exceeded 0.05 mg/kg of food, unless there was evidence from structure–activity considerations that peroxisome proliferation would not be expected to occur. Since, that SCF report, a general consensus, expressed by IARC [2], has been agreed that rodents are highly sensitive to the phenomenon of peroxisome prolifer-

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Abbreviations: AGD, anogenital distance; **BBP,** butylbenzylphthalate; **DBP,** dibutylphthalate; **DEHP,** diethylhexylphthalate; **DiBP,** diisobutyl phthalate; **DIDP,** di-isodecylphthtalate; **DINP,** di-isononylphthtalate; **EFSA,** European Food Safety Authority; **GD,** gestational day; **LC,** Leydig cell; **MBP,** monobutyl phthalate; **SCF,** Scientific Committee for Food; **TDI,** tolerable daily intake; **TDS,** testicular dysgenesis syndrome

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ation and that this particular effect should not be used for human risk assessment.

As a consequence, it was requested to perform a new evaluation of phthalates on the basis of existing data and no longer considering the use of peroxisome proliferation studies as pivotal studies.

The present paper summarizes the toxicological evaluations performed in 2004–2005 by the European Food Safety Authority (EFSA) panel on food additives, flavorings, processing aids, and materials in contact with food (AFC) [3–8]. These evaluations are part of the opinions published later on the EFSA website and in the EFSA Journal (EFSA, 2005).

2 Butylbenzylphthalate (BBP)

The following studies on reproduction and development toxicities have been considered in 2005 by the EFSA AFC panel for the determination of an NOAEL which could be used as a basis for a TDI calculation.

A 26 wk oral study in F344 rats resulted in decreased testicular weights, atrophy of seminiferous tubules, a near total absence of mature sperm production and marked hypospermia in the epididymis at dose level of 2.5% in the diet (1417 mg/kg bw (body wieght)/day) [9].

In conjunction with the NTP carcinogenicity study on BBP a 10 wk modified mating study in rats was also performed [10]. Decreases in epididymal spermatozoal concentrations have been reported at dose levels of 200 and 2200 mg/kg bw/day, with a NOAEL of 20 mg/kg bw/day and a LOAEL of 200 mg/kg bw/day. However, accompanying histopathological effects on the testes and adverse impact on fertility was only seen at 2200 mg/kg bw/day [11].

A NOAEL of 20 mg/kg bw/day was reported from a two-generation study [12], based on increased serum follicle stimulating hormone (FSH) concentrations in the F0 parental males. The corresponding LOAEL was 100 mg/kg bw/day. In the F1 generation, the NOAEL was 100 mg/kg bw/day based on offspring bodyweight at birth (while viability was not affected). Furthermore, in the same study all other examined end-points had a NOAEL of 100 mg/kg bw/day.

In an other developmental toxicity in the rat using a multiple dose study design [13], BBP induced increased liver and kidney weights in dams, accompanied by liver enzyme increases in maternal serum. Observed foetotoxicity included increased resorptions, reduced foetal weights, increased incidence of skeletal anomalies, and reduced foetal testis weights in the presence of an increased incidence of retarded testicular descent. As embryotoxicity was found at lower dosages compared to observed maternal toxicity, BBP appeared to be a specifically embryotoxic compound. The overall benchmark dose was assessed at 95 mg/kg/day, based on a 1% increase in abnormal testis location. Benchmark doses for frequency of resorptions, relative testis weights and extra lumber rib 13 are respectively 199, 172, and 171 mg/kg/day.

In a multi-generation study [14, 15], BBP was administered in the diet at 0, 750 (50), 3750 (250), and 11 250 ppm (750 mg/kg bw/day) ad libitum. Adult F0 systemic toxicity and adult F1 systemic and reproductive toxicity were present at 11 250 ppm (750 mg/kg bw/day). At 11 250 ppm, there were reduced F1 and F2 male anogenital distance (AGD) and body weights/litter during lactation, delayed acquisition of puberty in F1 males and females, retention of nipples and areolae in F1 and F2 males, and male reproductive system malformations. At 3750 ppm (250 mg/kg bw/day), only reduced F1 and F2 offspring male AGD was present. There were no effects on parents or offspring at 750 ppm (50 mg/kg bw/day). The F1 parental systemic and reproductive toxicity NOAEL was 3750 ppm. The offspring toxicity NOAEL was 750 ppm (50 mg/kg bw/day), based on the presence of reduced AGD in F1 and F2 males at birth at 3750 ppm, but no effects were observed on reproductive development, structures, or functions.

Based on all the available toxicological evidence, it was concluded that effects on reproduction and development are the most sensitive end-points on which to base the risk assessment. Previous reviews have identified as pivotal several rat reproduction studies conducted in the last decade, which gave NOAELs or LOAELs in the region of 20–100 mg/kg bw/day, with the critical effect being on male reproductive development.

Based on the current literature on BBP testicular toxicity and on the presence of reduced AGD in F1 and F2 males at birth at 250 mg/kg bw/day (NOAEL 50 mg/kg bw/day) in the Tyl study, the AFC panel has allocated a TDI of 0.5 mg/kg bw/day, issued from a NOAEL of 50 mg/kg bw/day and making use of an uncertainty factor of 100.

3 Dibutylphthalate (DBP)

The following studies on reproduction and developmental toxicity have been considered in 2005 by the EFSA AFC panel for the determination of an NOAEL which could be used as a basis for a TDI calculation.

In a one-generation reproduction study with DBP in mice [16, 17], the NOAEL was 0.3% in the diet, equivalent to 420 mg/kg bw/day, based on effects on maternal fertility and embryotoxicity.

In a one-generation reproduction studies in rats [18], in which females and males were exposed to DBP separately, NOAELs of 50 mg/kg bw/day in females (urogeniatal abnormalities) and 500 mg/kg bw/day in males (delayed puberty) have been reported.

In a two-generation reproduction study in rats, a LOAEL (52 mg/kg bw/day for males and 80 mg/kg bw/day for females) based on embryotoxic effects was reported [19, 20].

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In the reproduction study performed by Mylchreest *et al*. an NOAEL (50 mg/kg bw/day) and LOAEL (100 mg/kg bw/day) for toxicity of DBP on male reproductive development in the F1 generation have been observed [21].

A more recent developmental toxicity study in the rat [22], with dietary exposure to DBP during the period from late gestation (gestational day (GD) 15) to the end of lactation (postnatal day 21), has shown effects on the development of male and female offspring at lower doses than those found previously, having examined the development of reproductive tissues in considerable detail at various ages postnatally. Reduction of testicular spermatocyte development and mammary gland changes at low incidence in both sexes of offspring were seen at PND 21 at the lowest dose tested of 20 ppm (1.5–3.0 mg/kg bw/day) and above, with dose-dependent increased incidence or/and severity. Loss of germ cell development was no longer present at 20 ppm at postnatal week 11, but was still present with dose-dependency from 200 ppm (14–28 mg/kg bw/day) to 10 000 ppm (712–1372 mg/kg bw/day). Nondose-related, but statistically significant effects on the mammary gland persisted to postnatal week 11 in males at all doses, but by postnatal week 20, significant effects were only seen from 200 ppm and above. Based on loss of germ cell development and mammary gland changes at 20 ppm in the diet (the lowest tested dose) a NOAEL could not be established. However, given the reversibility of the effects at all dose levels and especially at the lowest dose level (20 mg/kg feed, which corresponds to 1.5 to 3 mg/kg bw/day) and also given that in several reproductive toxicity studies with longer exposure periods only approximately 30-fold higher NOAELS or LOAELS have been determined, a safety factor of 200, to derive a TDI for DBP based on the LOAEL of 20 mg/kg feed from the Lee *et al*. study is considered sufficient.

According to the above statement, the AFC panel has allocated a TDI for DBP of 0.01 mg/kg bw/day, based on a LOAEL of 2 mg/kg bw/day and making use of an uncertainty factor of 200.

4 Diethylhexylphthalate (DEHP)

Available data demonstrate that exposure to DEHP affects both fertility and reproduction in rodents of both sexes and also produces developmental effects in offspring. In males, DEHP induces severe testicular effects, including testicular atrophy. Developing male rats have been found to be more sensitive to DEHP-induced testicular toxicity than sexually mature animals by Gray and Butterworth [23], and Sjöberg *et al*. [24, 25]. The onset of the lesion in young animals is also more rapid. Irreversible effects occur in rats exposed prenatally and during suckling [26].

The following studies on reproduction and development toxicities have been considered by the EFSA AFC panel for the determination of an NOAEL which could be used as a basis for a TDI calculation.

Testicular effects have been observed in several repeated dose toxicity studies in rats, mice, and ferrets [27–38]. In addition, minor effects were observed in hamsters exposed to DEHP and more severe effects were induced by MEHP [30]. In the available studies marmosets were not sensitive to DEHP [39, 40]. No studies on testicular effects in rabbits are available.

The lowest identified NOAEL for testicular effects in the diet corresponding to 3.7 mg/kg bw/day in rats, is based on a high incidence (7/9) of Sertoli cell vacuolation at the next higher dose level (500 ppm equivalent to 37.6 mg/kg bw/day) in a 13 wk guideline study [36].

A two-generation reproduction study of DEHP in rats [41] has documented effects on reproductive performance and fertility in the F0 and F1 parental animals at 1088 mg/kg bw/day. Substance-induced signs of adverse developmental toxicity were noted in the progeny of the F0 and F1 parents from 340 mg/kg bw/day onwards. The NOAEL for reproductive performance and fertility was 340 mg/kg bw/day and for developmental toxicity 113 mg/kg bw/day, respectively.

Wolfe and Layton [38] studied the multigenerational reproductive toxicity of DEHP in Sprague–Dawley rats. The conclusions of this study were as follows:

(i) the NOAEL for testicular toxicity was 100 ppm (equivalent to approximately 8 mg DEHP/kg bw/day in the F0 animals and ~5 mg DEHP/kg bw/day in the F1 and F2 animals).

(ii) the LOAEL for testicular toxicity was set at 300 ppm (equivalent to ~23 mg DEHP/kg bw/day in the F0 animals and 14 mg DEHP/kg bw/day in the F1 and F2 animals).

(iii) macroscopic pathological findings in male accessory sex organs other than testes (epididymis, seminal vesicles, and prostate) were also present at this dose level and at higher doses.

(iv) the NOAEL for toxicity to fertility was 1000 ppm (equivalent to ~77 mg DEHP/kg bw/day in the F0 animals, and 48 and 46 mg DEHP/kg bw/day in the F1 and F2 animals, respectively.

(v) the NOAEL for developmental toxicity was 100 ppm (equivalent to ~8 mg DEHP/kg bw/day in the F0 animals and ~5 mg DEHP/kg bw/day in the F1 and F2 animals) and was based on the fact that the testicular effects were much more severe in the F1 and F2 generations than in F0, indicating the developmental phases as sensitive to the testicular toxicity of DEHP.

(vi) the NOAEL for effects not related to reproductive toxicity in adult animals was 300 ppm (equivalent to ~23 mg DEHP/kg bw/day in the F0 animals, and 14 mg DEHP/kg bw/day in the F1 and F2 animals) and was based on reductions in body weights.

(vii) Sertoli cell vacuolation was observed in the control group as well as in the 1000 and 7500 ppm F1 males. It was

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Table 1. Main pivotal studies for major phthalates (details and explanations can be found in the respective EFSA opinions)

Phthalate	Pivotal study	End-point	NOAEL/ LOAEL	Value (mg/kg bw/day)	Ref.
DBP	Developmental Toxicity in rats	Germ cell development	LOAEL	2	[22]
DEHP	Developmental and testicular toxicity in rats	Germ cell depletion ↓ testis weight	NOAEL	5	[38]
			NOAEL	5	
BBP	Testicular toxicity in rats	↓ epididymal spermatozoa concentration	NOAEL	20	[10]
	Developmental toxicity in rats	↓ AGD (F1, F2)	NOAEL	50	[14, 15]
DINP	Liver and kidney toxicity (nonrelated to PP) in rats	Spongiosis hepatis	NOAEL	15	[42, 43]
DIDP	Liver toxicity in dogs (nonrelated to PP)	Microscopic lesions	NOAEL	15	[44]
	Developmental toxicity in rats	↓ F2 offspring survival	NOAEL	30	[45]

not observed in the 10 000 ppm animals with diffuse seminiferous tubule atrophy. In the 7500 ppm males, Sertoli cell vacuolation was observed in seminiferous tubules without atrophy. This vacuolation was similar to that observed in the control group males. This observed vacuolation of the Sertoli cells resulted from distortion during fixation and processing of the tissues according to a pathology working group. This distortion could have obscured any minimal toxic effects that may have been present.

The methodology used in this study to a large extent complies with OECD Guideline 416. This study appears to be more robust than those underpinning the previous NOAELs based on reproductive toxicity.

A NOAEL of 5 mg/kg bw/day for testicular toxicity and developmental toxicity has been derived by the AFC panel from this study.

5 Consideration on the possibility of allocating a group-TDI for phthalates

The panel was also requested by the EU Commission to made a statement about the possibility of allocating a group-TDI for BBP, DBP, DEHP, DINP, and DIDP. The panel after reviewing the recent literature on toxicological studies, has agreed the respective pivotal studies, summarised in Table 1, as relevant for the toxicological evaluation.

In the past, the AFC panel considered that a group TDI for health protection should be employed if:

(i) exposure to several members of a structurally related series of chemicals is likely to occur frequently, and

(ii) several members of the series have been demonstrated to have a common target organ(s), cellular target(s) and the same mode of action.

If the above mentioned criteria are met, individual members of the series should be assumed to have an additive effect. Even in cases where there are only limited toxicological data on one or more of the members it is assumed that these compounds contribute to the same effect on the target organ. Toxicological equivalence factors (TEF) can be introduced where there are adequate data and the potencies span three to five-fold or more. If this is not possible, the most potent member of the series is assumed to be representative for the purposes of standard setting.

According to the above mentioned pivotal studies,

(i) DBP and DEHP have pivotal effects on germ cell development/depletion,

(ii) BBP has pivotal effects on epididymal spermatozoa concentration,

(iii) DINP and DIDP have pivotal effects on the liver.

While it may appear that three phthalates (DBP, DEHP, and BBP) act on the same target organ (the testis), their profile of effects at the hormonal and cellular level are not identical and their individual modes of action have not yet been demonstrated.

Moreover, the two others, DIDP and DINP, primarily affect the liver rather than the testis. But even in this case, the end-points indicate that different mechanisms are involved. Consequently, a group -TDI cannot be allocated for BBP, DBP, DEHP, DINP, and DIDP.

6 Remark concerning a group-TDI for DBP, BBP, and DEHP

This remark is not a part of the EFSA opinions and cannot be considered as an EFSA statement.

Fetal exposure of male rats to phthalates as DBP, DEHP, or BBP induces reproductive disorders similar to those in human testicular dysgenesis syndrome (TDS), including infertility, cryptorchidism, focal "dysgenetic areas," and Sertoli cell-only tubules in the adult testis. Humans are widely exposed to DBP, but at much lower levels than those causing adverse effects in rats.

Accordingly, we need an answer to the following questions:

(i) What are actually the scientifically-based and most sensitive end-points to be used for TDS approach?

(ii) How to handle the recent literature on the phthalate cumulative approach in the light of the above question?

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(iii) What is the knowledge in different species, including man, about these TDS sensitive end-points?

(iv) How to introduce the last data about human phthalate exposure data on this?

Since 2005, many studies which have been performed and published are giving elements on the above statement.

6.1 Scientifically-based and most sensitive end-points to be used for testicular dysgenesis syndrome (TDS) approach

The objective of a study performed by Mahood *et al*. [46] was to evaluate end points affected by DBP action in rats in fetal and adult life that are relevant to human TDS, and to compare their dose sensitivity. Adult end points of TDS (infertility, cryptorchidism) and indicators within the fetal testis of dysgenesis (abnormal Leydig cell (LC) aggregation, multinucleated gonocytes (MNGs)), as well as conditions that may result from these indicators in adulthood (occurrence of focal dysgenetic areas) were recorded. Fetal testis weight and testicular testosterone levels were also evaluated. The fetal end points analyzed (testicular testosterone levels, abnormal LC aggregation, occurrence of MNGs) were most sensitive to disruption by DBP, as all were significantly affected at a dose of 100 mg/kg/day DBP, with a trend toward effects occurring at 20 mg/kg/day DBP; adult end points were affected consistently only by 500 mg/kg/day DBP. Consequently, fetal end points can be used when performing the health risk of exposure to DBP and other phthalates, as well as identifying DBP-sensitive fetal events that have adult consequences/end points that are identifiable in human TDS.

6.2 Recent literature on the phthalate cumulative approach

Using Sprague–Dawley rats, Howdeshell *et al*. [47] have observed that a DBP + DEHP dose increased the incidence of many reproductive malformations by > or = 50%, including epididymal agenesis, and reduced androgen-dependent organ weights in cumulative, dose-additive manner. Fetal testosterone production and expression of insl3 and cyp11a were also cumulatively decreased by the DBP + DEHP dose. Such data indicate that individual phthalates with a similar mechanism of action, but with different active metabolites (monobutyl phthalate (MBP) *versus* monoethylhexyl phthalate), can elicit dose-additive effects when administered as a mixture.

Howdeshell *et al*. [48] characterized also the dose response effects of six individual phthalates (BBP, DBP, DEHP, diethyl phthalate (DEP), diisobutyl phthalate (DiBP), and dipentyl phthalate (DPP)) at GD 18 using testicular testosterone production as fetal end-point. BBP, DBP, DEHP, and DiBP were equipotent (ED50 of 440 ± 16 mg/kg/day), DPP was about three-fold more potent (ED50 = 130 mg/kg/day) and DEP had no effect on fetal testosterone production. In a second study, dams were dosed at 100, 80, 60, 40, 20, 10, 5, or 0% of the mixture containing 1300 mg of total phthalates/kg/day including BBP, DBP, DEHP, DiBP (300 mg/kg/day *per* chemical), and DPP (100 mg DPP/kg/day). The testosterone production was reduced in a dose-additive manner. Several of the individual phthalates and the mixture also induced fetal mortality, due to pregnancy loss. These experiments demonstrate that individual phthalates with a similar mechanism of action can elicit cumulative, dose additive effects on fetal testosterone production and pregnancy when administered as a mixture.

6.3 Species differences of fetal TDS sensitive end-points

The rat has been explored in detail for its in utero susceptibility to male reproductive tract malformation following phthalate exposure. Few other species have been studied in detail, and it is important for both mechanistic and risk assessment purposes to understand the species specificity of this response.

Gaido *et al*. [49] investigated the response of the fetal mouse testis to phthalate exposure and compared these results with those previously obtained from the rat. Initial experiments using a variety of phthalate congeners (MBP, DBP, or mono(2-ethylhexyl) phthalate) and exposure paradigms did not reduce fetal mouse testis testosterone levels. Pharmacokinetic data after a single 500 mg/kg DBP exposure on mouse GD 18 demonstrated that the concentrations and kinetics of the active metabolite MBP in fetal and maternal plasma were similar to the rat. After a single 500 mg/kg or multiple day 250 mg/kg fetal mouse DBP exposure, rapid and dynamic changes in testis gene expression were observed, including induction of immediate early genes. Unlike the rat, expression of genes involved in cholesterol homeostasis and steroidogenesis were not decreased a. The Gaido's results demonstrate that fetal mouse and rat phthalate exposure both induce immediate early gene expression and disrupt seminiferous cord and gonocyte development. But, this response in the mouse occurs without a measurable decrease in testicular testosterone.

Tomonari *et al*. [50] have reported on male marmosets treated daily with 0, 100, 500, or 2500 mg/kg DEHP by oral gavage for 65 wk from weaning (3 month of age) to sexual maturity (18 month). No treatment-related changes were observed in male organ weights, and no microscopic changes were found in male gonads or secondary sex organs. Sperm head counts, zinc levels, glutathione levels, and testicular enzyme activities were comparable between groups. Electron microscopic examination revealed no treatment-related abnormalities in Leydig, Sertoli, or spermatogenic cells. Histochemical examination of the testis after 3β-hydroxysteroid dehydrogenase (3β-HSD) staining

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did not reveal any alterations in steroid synthesis in the LCs.

6.4 Last data about human phthalate exposure data

Based on the urinary metabolite excretion, Wittassek *et al*. [51] estimated daily intakes of the phthalates and investigated the chronological course of the phthalate exposure. The median daily intakes in the subsets between 1988 and 1993 were quite constant for DBP (~7 microg/kg bw/day) and DEHP (~4 microg/kg bw/day). However, from 1996 the median levels of both phthalates decreased continuously until 2003 (DnBP 1.9 microg/kg bw/day; DEHP 2.4 microg/kg bw/day). In contrast, the daily intake values for DiBP were slightly increasing over the whole time frame investigated (median 1988: 1.1 microg/kg bw/day; median 2003: 1.4 microg/kg bw/day). For BBP, we observed slightly decreasing values, even though the medians as of 1998 levelled off at around 0.2 microg/kg bw/day. Regarding daily DINP exposure, we found continuously increasing values, with the lowest median being 0.20 microg/kg bw/day for the subset of 1988 and the highest median for 2003 being twice as high. The trends observed in phthalate exposure may be associated with a change in production and usage pattern.

Compared to data from US National Health and Nutrition Examination Surveys (NHANES) exposure levels of the DBPs were generally higher in the German study population, while levels of BBzP were somewhat lower. Overall, for a considerable 14% of the subjects we observed daily DnBP intakes above the TDI value deduced by the EFSA (10 microg/kg bw/day). However, the frequency of exceedance decreased during the years and was beneath 2% in the 2003 subset. Even though transgressions of the exposure limit values of the EFSA and the US Environmental Protection Agency (US EPA) occurred only in a relatively small share of the subjects, one has to take into account the cumulative exposure to all phthalates investigated and possible dose-additive endocrine effects of these phthalates.

In an other study, Wittassek *et al*. [52] estimated the daily DEHP intake of 239 children aged 2–14 years by extrapolating from their urinary levels of the DEHP metabolites. Applying the volume or the creatinine-based calculation model, a median daily DEHP intake of 7.8 or 4.3 microg/kg bw/day and a 95th percentile of 25.2 or 15.2 microg/kg bw/day were found. Three children (1%) exceeded the value of the TDI of the EFSA of 50 microg/kg bw/day, while 7.5 or 3% (depending on the calculation model) exceeded the reference dose (RfD) of 20 microg/kg bw/day of the US EPA. In general, DEHP exposure was decreasing with increasing age and boys had higher exposures than girls.

These findings suggest that the majority of the children in the general population is exposed to quantities of DEHP below the TDI and the RfD.

Based on urinary phthalate metabolite concentrations, Wittassek and Angerer [53] estimated in 102 German subjects between 6 and 80 years of age, median daily intakes (microg/kg/day) of 2.7 for DEHP, 2.1 for DBP, 1.5 for DiBP, 0.6 for DINP, and 0.3 for butylbenzyl phthalate. In general, children have higher exposures compared to adults and seem to have a more effective oxidative metabolism of phthalates. These median daily intakes are lower than the corresponding EFSA phthalate TDI.

7 Conclusions

In rats some phthalates have been shown to act as endocrine disrupters *via* a common mechanism of action in a dose-additive manner. Therefore, the concept of a cumulative TDI value may be considered for phthalates. However, a TDS end-point without related species differences remains a need for establishing the potency relationship according the phthalate family which is larger than the usually tested phthalate.

According the research performed in this field, it seems that a good and sensitive scientifically based fetal end-point will be found soon. The use of it in reprotox studies according official guidelines would allow the establishment of new TDI values and to give the opportunity to have a good knowledge about the margins of safety. On this basis, it will be possible to decide if a cumulative TDI value is more appropriate for the consideration of the overall exposure and the potential human health risks resulting from everyday and simultaneous exposure to phthalates.

But such a decision is a risk management matter and is not in the scope of the present paper.

The author has declared no conflict of interest.

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