

Helsinki, 12 September 2013  
**RAC/26/2013/07 Rev.1**  
**(Agreed at RAC-26)**

## **APPLICATION FOR AUTHORISATION: ESTABLISHING REFERENCE DNELS FOR BBP**

### **Background**

At the 22<sup>nd</sup> meeting of the Committee for Risk Assessment (RAC) in September 2012, the ECHA Secretariat presented a proposal to set DNELs and dose-response curves for substances prior to receiving applications for authorisation (AfAs). This was approved by RAC as a trial exercise.

The DNELs and dose response curves so derived will serve as non-legally binding 'reference' values. They would provide applicants with a clear signal as to how RAC is likely to evaluate these important elements of the risk assessment of AfA.

This initiative is intended to improve the efficiency of the AfA process as a whole by discussing and when possible publishing reference values in advance of applications, so providing greater consistency and better use of the legally defined period of opinion-development in the RAC. The trial will be evaluated in terms of efficiency after the first applications have been discussed in Committee.

### **Requested action**

Following the Committee's agreement on the document, it will be published on the ECHA website at:

<http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information>.

### **Progress**

The trial was started with two substances, RAC agreeing to establish 'reference' DNELs for DEHP (diethylhexyl phthalate) and TCEP (tris(2-chloroethyl)phosphate). However, it was later decided that DBP (dibutyl phthalate) had greater urgency and this substance was therefore selected as a second candidate instead of TCEP.

The Secretariat prepared this document for the substance BBP (benzyl butyl phthalate) which was reviewed at RAC 26, commented on by the advisory group consisting of RAC members, then revised accordingly and agreed.

The current document builds on conclusions previously drawn in RAC when the substance was discussed in relation to a restriction proposal, as well as on recent discussions related to the DNEL derivations for DEHP and DBP.

Annex: Reference DNELs derived for BBP

Annex I Reference DNELs for selected substances on Annex XIV of the REACH Regulation (EC) No 1907/2006

SUBSTANCE NAME	EC NUMBER	CAS NUMBER
Benzyl butyl phthalate (BBP)	201-622-7	85-68-7

**Table 1. Overview of derivation of reference DNELs for workers and general population (adults and children) exposed to BBP derived according to the document**

Point of departure for DNEL derivation for BBP by ECHA		
Rat 2-generation study, oral NOAEL in mg/kg/d	50	
Dosing regime (days per week)	7	
Oral absorption percentage	100%	
Derivation of Reference DNELs		
	WORKERS	GENERAL POPULATION
<i>Assessment Factors</i>		
Interspecies, AS <sup>1</sup>	4	4
Interspecies, remaining differences	2.5	2.5
Intraspecies	5	10
Dose response	1	1
Quality of Data Base	1	1
<i>Days per week</i>	5	7
ORAL		
Absorption percentage	(100%)	100%
NOAEL (corrected)	(not relevant)	50
<b>Reference DNELs<sup>2</sup> ORAL in mg/kg/d</b>	<b>(not relevant)</b>	<b>0.5</b>
DERMAL		
Absorption percentage	5%	5%
NOAEL (corrected)	1400	1000
<b>Reference DNELs<sup>2</sup> DERMAL in mg/kg/d</b>	<b>28</b>	<b>10</b>
INHALATION		
Absorption percentage	100%	100%
Standard respiratory volume in m <sup>3</sup> /kg bw per day	0.38 <sup>3</sup>	1.15
NOAEC (corrected)	123	43.5
<b>Reference DNELs<sup>2</sup> INHALATION in mg/m<sup>3</sup></b>	<b>9.9</b>	<b>1.7</b>

<sup>1</sup> Not to be applied when calculating inhalation DNEL

<sup>2</sup> Not legally binding

<sup>3</sup> The respiratory volume was further adjusted for light work (10/6.7)

## Relevance of endpoints

For applicants applying for authorisation under Article 60(2) (adequate control route), in order to conclude whether the adequate control is demonstrated, only endpoints (i.e. properties of concern) for which the substance is included in Annex XIV need to be addressed in the hazard assessment<sup>4</sup>. However, information on other endpoints might be necessary for comparing the risks with the alternatives.

For applicants aiming at authorisation based on Article 60(4) (socio-economic analysis route) Article 62(4)(d) also applies and the socio-economic analysis (SEA) route will as a consequence focus on the risks that are related to the intrinsic properties specified in Annex XIV. The SEA should in turn consider the impacts related to such risks. In practice the applicant is expected to provide this information in their CSR for which an update may be advisable. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' become relevant in order to demonstrate that no suitable alternative is available.

BBP was included on Annex XIV due to its reprotoxic properties. For that reason the DNELs proposed in the present document are only based on reprotoxicity<sup>5</sup>. In this case it is also the most sensitive endpoint, but this may not necessarily be the case with all substances.

## Previous discussions on DNEL(s) for BBP in RAC

During its opinion-making process for a Danish restriction proposal addressing four classified phthalates (*Diethylhexyl phthalate*, DEHP; *Dibutyl phthalate*, DBP; *Di-isobutyl phthalate*, DIBP; and *Benzyl butyl phthalate*, BBP) RAC made an extensive evaluation of the available information related to the hazard profile of the substances. The conclusions related to toxicokinetics, endpoint of concern, identification of a N(L)OAEL, and justification for assessment factors given below have been compiled based on that RAC opinion<sup>6</sup>, which was adopted in the Committee's 21<sup>st</sup> meeting in June 2012.

### *Toxicokinetics and absorption*

Following oral administration, phthalates are generally rapidly absorbed from the gastrointestinal tract (probably in monoform). Phthalates can also be absorbed through the lungs, whereas absorption through the skin appears to be limited.

For BBP absorption fractions established in the EU-RAR were considered appropriate (Table 2).

---

<sup>4</sup> Article 60(2) states "...an authorisation shall be granted if the risk to human health or the environment from the use of the substance arising from the **intrinsic properties specified in Annex XIV** is adequately controlled".

<sup>5</sup> To the authorisation relevant endpoints refers also section 5 of the document: "How RAC and SEAC intend to evaluate the applications (common approach of RAC and SEAC in opinion development on applications for authorisation, agreed RAC-20/SEAC14, 24/03/2012). Link: <http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information>

<sup>6</sup> The RAC opinion on the restriction proposal for four phthalates is available here: <http://echa.europa.eu/previous-consultations-on-restriction-proposals/-/substance/490/search/+term>

**Table 2. Absorption percentages for humans used in the RAC opinion<sup>6,7</sup>**

	Oral absorption	Dermal absorption	Inhalatory absorption
BBP	100% (adults and children)	5% (adults and children)	100% (adults and children)

#### *Reprotoxicity of BBP*

As DEHP and some other phthalates, BBP is classified as toxic to reproduction on the evidence of adverse effects on the reproductive organs in rodents, which are attributed to an anti-androgenic mode of action. When examining the relevant reproduction toxicity studies, RAC recognised that more than one toxic mechanism may have occurred at the same time, leading to several effects which however all seem to follow an anti-androgenic mode of action. Effects attributable to an anti-androgenic mode of action (be it functional or an early marker) are relevant endpoints, since they are so consistently observed in the available studies. Therefore, the most sensitive of these effects resulting in the No-Observed-Adverse-Effect Level (NOAEL), was chosen for use in the establishment of Derived No-Effect Levels (DNEL) for BBP.

#### *Selection of the starting point for DNEL derivation*

For BBP, RAC concluded in their opinion on the Danish restriction proposal addressing four classified phthalates that reduced AGD in male rats was the most sensitive endpoint. This effect was found at LOAELs of 500, 250 and 100 mg/kg bw/day in two-generation studies by Nagao et al. (2000), Tyl et al. (2004) and Aso et al. (2005), respectively. The overall NOAEL for this effect was 50 mg/kg bw/day from the Tyl et al. study. RAC noted that this NOAEL was also selected in the EU-RAR on BBP and by EFSA when establishing a TDI of 0.5 mg/kg bw for BBP.

#### *Assessment factors*

In deriving a DNEL for BBP RAC concluded that assessment factors need to be applied for intra- and interspecies differences. Other assessment factors were not found to be needed.

For intraspecies differences, a factor of 10 (default) was suggested. The same factor of 10 (= 4\*2.5) was suggested for interspecies differences. RAC discussed lowering this latter default factor based on information on toxicokinetics (metabolism, distribution) and toxicodynamic data from studies in marmosets. It was felt that this information possibly points to reasons for lowering the assessment factor for interspecies differences in sensitivity to the reprotoxic effects of phthalates.

From the toxicokinetic data available it seemed that there were differences in metabolism and distribution between rats and primates, including humans. Whereas all species hydrolyse the phthalates into the monoform, which is subsequently further metabolised into oxidative metabolites, in contrast to primates, in rats there is no appreciable glucuronidation of the oxidative metabolites. It further appears that, whereas the distribution pattern is the same, rats show higher levels than marmosets of phthalate metabolites in tissues, including testes. In toxicity studies, marmosets appear less sensitive than rats for phthalate toxicity. It has been argued that marmosets are a more appropriate model species than rats to study the reproductive toxic effects of phthalates. These arguments for instance resulted in the use of an interspecies factor of 3 in the risk assessment of DEHP by the FDA, Health Canada and in Japan.

<sup>7</sup> EU RAR, <http://publications.jrc.ec.europa.eu/repository/bitstream/11111111/10948/1/benzylbutylphthalatereport318.pdf>

RAC however considered the toxicokinetic differences to be quantitative rather than qualitative, and judged the information on quantitative differences insufficient for providing convincing evidence for a reduced hazard. This is because of the complexity of the (multiple) mechanisms in play for the phthalates toxicity, not all of which may relate to reduced testosterone levels and/or steroidogenesis, and for which the ultimate toxic metabolites are unknown. One of the toxic metabolites is thought to be the mono-form, formed after enzymatic hydrolysis by e.g. lipase. Whereas some studies seemed to indicate that lipase activity is higher in rats than in marmosets, resulting in more toxic metabolites, other studies indicate the opposite or even that lipase activity in humans may be higher than in marmosets and rats. Moreover, studies in rats have shown variable sensitivity to phthalate toxicity depending on the life stage, with rats exposed prenatally and during suckling being much more vulnerable than e.g. sexually mature rats. For marmosets, however, limited data are available for in utero, peri- and neonatal exposure. There is no study with exposure during the entire life cycle such as the multigeneration studies in rats. In fact, there is only one developmental toxicity study (using a single high dose of MBP) with a period of exposure that covers the sensitive window for the programming of the male reproductive system, demonstrating some effects on the testes of neonatal marmosets of which the toxicological significance is unclear. This, combined with the relatively low number of (non-inbred) animals tested in the marmoset studies, makes it difficult to compare the results with those found in (inbred) rats.

All in all, RAC concluded that there is too much uncertainty in the data available to allow a conclusion on humans being less, equally or more sensitive than rats, and thus suggested not to deviate from the default interspecies factor of 10.

## Derivation of reference DNELs for BBP

Based on the previous conclusions in RAC referred to above, DNELs for the general population (children and adults) and workers have been derived for the oral, dermal and inhalation routes. As the DNELs are based on reprotoxicity they are most relevant for protection of pregnant women (and thus foetuses) and very small children. Other groups of the population would however also be protected as reprotoxicity is the most sensitive endpoint for BBP.

Placenta transfer is supposed to be the same in rats and humans and is not further adjusted for.

### Reference DNELs for the general population

Table 1 gives an overview of the derived reference DNELs for adult consumers and children exposed to BBP. As the same absorption and assessment factors were used for adults and children the DNELs for these two groups are identical.

An oral NOAEL in rat of 50 mg/kg bw/day for developmental toxicity was identified by RAC from the 2-generation reproductive toxicity study of Tyl et al. (2004) in their opinion on the Danish restriction proposal for four classified phthalates. An oral DNEL of 0.5 mg/kg bw/day was derived by RAC for the general population.

The oral NOAEL in rat (in mg/kg bw/day) was converted into an inhalatory corrected NOAEC (in mg/m<sup>3</sup>) by using a default respiratory volume for the rat corresponding to the daily duration of human exposure.

The standard respiratory volume for rats is 0.2 l/min/rat (sRV<sub>rat</sub>) which corresponds to 0.8 l/min/kg or for 24 h of exposure 1.15 m<sup>3</sup>/kg bw. Thus when using the formula below, the corrected inhalatory NOAEC = 50 mg/kg bw/day x 1/1.15 m<sup>3</sup>/kg bw/24 h x 100/100 = 43.5 mg/m<sup>3</sup>.

For general population (in case of 24h exposure/d):

corrected inhalatory NOAEC =

$$\text{oral NOAEL} * \frac{1}{sRV_{rat}} * \frac{ABS_{oral-rat}}{ABS_{inh-rat}} * \frac{ABS_{inh-rat}}{ABS_{inh-human}}$$

$$= \text{oral NOAEL} * \frac{1}{1.15m^3/kg/d} * \frac{ABS_{oral-rat}}{ABS_{inh-human}}$$

ABS: Absorption; sRV: standard Respiratory Volume

The oral NOAEL rat (in mg/kg bw/day) was converted into a dermal corrected NOAEL (in mg/kg bw/day) by correcting for differences in absorption between routes (100% oral absorption in rats, 5% dermal absorption in humans), resulting in a dermal corrected NOAEL of 1000 mg/kg bw/day.

## Reference DNELs for workers

DNELs for workers were set using the same basic principles as for the general population.

The oral NOAEL rat (in mg/kg bw/day) was converted into an inhalatory corrected NOAEC (in mg/m<sup>3</sup>) by using a default respiratory volume for the rat corresponding to 8 h duration.

The standard respiratory volume for rats for 8 h exposure is 0.38 m<sup>3</sup>/kg bw, which corresponds to an 8 h standard respiratory volume in humans (70 kg) of 6.7 m<sup>3</sup>. The respiratory volume was further adjusted to compensate for a higher volume at light work (10 m<sup>3</sup>/8 h) in workers.

Thus when using the formula below, the corrected inhalatory NOAEC = 50 mg/kg bw/day x 1/0.38 m<sup>3</sup>/kg bw/day x 100/100 x 6.7/10 = 88.2 mg/m<sup>3</sup>.

For workers (in case of 8h exposure/d):

$$\begin{aligned} \text{corrected inhalatory NOAEC} &= \text{oral NOAEL} * \frac{1}{sRV_{rat}} * \frac{ABS_{oral-rat}}{ABS_{inh-human}} * \frac{sRV_{human}}{wRV} \\ &= \text{oral NOAEL} * \frac{1}{0.38m^3/kg/d} * \frac{ABS_{oral-rat}}{ABS_{inh-human}} * \frac{6.7m^3(8h)}{10m^3(8h)} \end{aligned}$$

ABS: Absorption; sRV: standard Respiratory Volume; wRV: worker Respiratory Volume

The NOAEC was further adjusted for an exposure duration of 5 days a week instead of 7 days in the experimental situation (88.2 mg/m<sup>3</sup> x 7/5 = 123 mg/m<sup>3</sup>).

The oral NOAEL rat (in mg/kg bw/day) was converted into a dermal corrected NOAEL (in mg/kg bw/day) by correcting for differences in absorption between routes, and further correcting for exposure during 5 days a week instead of 7 days a week. The dermal corrected NOAEL = 1400 mg/kg bw/day.

The default assessment factor of 5 for intraspecies differences was applied when deriving DNELs for workers. It was however noted by RAC that the DNELs for pregnant workers differ from those for pregnant women in the general population due to the differences in intraspecies assessment factors applied (5 versus 10)<sup>8</sup>. The ECHA guidance does not explicitly discuss assessment factors for pregnant women in a working environment. The general principle is that the worker population does not cover the very young, the very old, and the very ill and that therefore an AF of 5 is considered sufficient.

## References:

Tyl RW, Myers CB, Marr MC, Fail PA, Seely JC, Brine DR, Barter RA and Butala JH (2004). Reproductive toxicity evaluation of dietary Butyl Benzyl Phthalate (BBP) in rats. *Reprod. Toxicol.* 18, 241-264.

<sup>8</sup> The DNELs also differ due to differences in exposure conditions, but this does not lead to different no-effect levels if calculated on a weekly basis.