Committee for Risk Assessment (RAC)

Opinion

on

the ECHA's draft review report on

"Evaluation of new scientific evidence concerning DINP and DIDP in relation to entry 52 of Annex XVII to Regulation (EC) No 1907/2006 (REACH)"

ECHA/RAC/A77-O-0000001412-86-10/F

adopted 8 March 2013

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Opinion of the Committee for Risk Assessment

on the draft review report of ECHA

"Evaluation of new scientific evidence concerning DINP and DIDP in relation to entry 52 of Annex XVII to Regulation (EC) No 1907/2006 (REACH)"

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the draft review report of ECHA "Evaluation of new scientific evidence concerning DINP and DIDP in relation to entry 52 of Annex XVII to Regulation (EC) No 1907/2006 (REACH)".

	IUPAC NAME	EC NUMBER	CAS NUMBER
DINP	1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich	271-090-9	68515-48-0
	di-"isononyl" phthalate	249-079-5	28553-12-0
DIDP	1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich	271-091-4	68515-49-1
	di-"isodecyl" phthalate	247-977-1	26761-40-0

PROCESS FOR ADOPTION OF THE OPINION

Rapporteur, appointed by RAC: *Helmut GREIM*

The Executive Director of ECHA requested RAC on 25 April 2012 to provide an opinion on the draft review report of ECHA "Evaluation of new scientific evidence concerning DINP and DIDP in relation to entry 52 of Annex XVII to Regulation (EC) No 1907/2006 (REACH)".

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ECHA's draft review report was made publicly available at http://www.echa.europa.eu/web/guest/addressing-chemicals-of-concern/restriction/consultations-draft-review-report on 7 May 2012. Interested parties were invited to submit comments and contributions by 31 July 2012.

RAC was requested to assess ECHA's draft review report as well as the comments received on the report during public consultation and to adopt an opinion as soon as possible and not later than December 2012.

On 5 February 2013, the Executive Director of ECHA extended the deadline for adoption to 31 March 2013.

The RAC opinion was adopted by consensus on 8 March 2013. The opinion takes into account the comments of interested parties provided during public consultation.

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TERMS OF REFERENCE

RAC is requested, pursuant to Article 77(3)(c) of REACH, to:

Adopt an opinion on ECHA's draft report "Evaluation of new scientific evidence concerning DINP and DIDP in relation to entry 52 of Annex XVII to Regulation (EC) No 1907/2006 (REACH)". Comments from the public consultation should be taken into account by RAC.

A) RAC should assess in its opinion the overall scientific quality of the report, its completeness, potential weaknesses, as well as the scientific validity of the conclusions drawn. If RAC disagrees with the conclusions, it is invited to elaborate on its reasons.

B) The opinion should in particular respond, based on the available evidence presented in the draft review report, to the following questions:

1) Is the selection of no observed adverse effect levels (NOAELs) and assessment factors (AF) to derive the derived no effect levels (DNELs) appropriate and sufficiently justified?

2) Does RAC support the assumptions and conclusions of the exposure assessment?

3) Does RAC agree to the conclusions of the draft review report that exposure to DINP and DIDP from mouthing of toys and childcare articles would present a risk, if the existing restriction was lifted?

4) Does RAC agree to the conclusions of the draft review report regarding consumer risk from the presence of DINP and DIDP in articles other than toys and childcare articles?

5) Does RAC agree to the conclusions of the draft review report regarding the risk from combined exposure[1] to DINP and DIDP?

[1] 'Combined exposure' includes all routes, pathways, and sources of exposure to multiple chemicals (as defined in the joint opinion of SCHER, SCENIHR and SCCS "Toxicity and Assessment of Chemical Mixtures" from 2011).

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OPINION

Based on the evaluation of the information presented in the draft review report, and taking into account information from the public consultation, RAC responds as follows to the questions in the Terms of Reference. RAC refers to the supporting document to the opinion for more details and a better understanding to the opinion and its justifications.

A) RAC should assess in its opinion the overall scientific quality of the report, its completeness, potential weaknesses, as well as the scientific validity of the conclusions drawn. If RAC disagrees with the conclusions, it is invited to elaborate on its reasons.

RAC concludes that the overall scientific quality of the report is good, and the report is considered to be complete in that it addresses and discusses all necessary information to evaluate whether the existing restriction on DINP and DIDP in toys and childcare articles, which can be placed in the mouth by children is justified.

B) The opinion should in particular respond, based on the available evidence presented in the draft review report, to the following questions:

1) Is the selection of no observed adverse effect levels (NOAELs) and assessment factors (AF) to derive the derived no effect levels (DNELs) appropriate and sufficiently justified?

Modification of the dose descriptor for DINP and DIDP

RAC considers that adult rats orally absorb about 50-70% and humans 100%, and that therefore a modification of the dose descriptor with a factor of two can be justified.

RAC noted however, that the estimated absorption rate of 50% in adult rats might underestimate the actual absorption at low dose levels (see sections 1.1 and 1.5 of the supporting document). For that reason RCRs have been also calculated without the modification of the dose descriptor.

DINP

RAC agrees with the selected NOAELs and assessment factors applied to derive the DNELs for reproductive toxicity for DINP in the ECHA draft report.

With regard to repeated dose toxicity, RAC discussed two key studies for DNEL derivation, the Aristech (1994) and Exxon (1986) studies with NOAELs of 88 and 15 mg/kg/d respectively. Considering the dose spacing in those studies, in particular the Exxon study with 152 mg/kg as the next higher dose, the true NAEL (No Adverse Effect Level) could be argued to be somewhere between 88 and 152 mg/kg/day. However, there were differences in methodology between both studies: the Exxon (1986) study evaluated 4-5 liver sections, whereas the Aristech (1994) study examined 1-2 sections. It was argued that as a result of this methodological difference, the Exxon (1986) study was the most appropriate to use. RAC supported the NOAEL for DINP of 15 mg/kg as proposed by ECHA noting that the NAEL could be higher given the large dose spacing in this study.

Overall, RAC agrees with the selected NOAELs and assessment factors applied to derive the DNELs for repeat dose toxicity for DINP in the ECHA draft report.

DIDP

RAC agrees with the selected NOAELs and assessment factors applied to derive the DNELs for reproductive toxicity for DIDP in the ECHA draft report.

However, RAC questioned the LOAEL proposed in the ECHA draft report for DIDP repeated dose toxicity. As described in section 1.2.2 of the supporting document to the opinion, it can be questioned whether the LOAEL in the Cho et al. (2008/2010) study is dose related. Furthermore, RAC is aware that the relevance of spongiosis hepatis for humans has been ques-

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tioned. Thus, RAC does not recommend to exclusively use the Cho et al. study to identify the repeated dose NOAEL for DIDP. Instead, RAC proposes to use the NOAELs from the 90 days studies in dogs (Hazleton 1968b, NOAEL 15 mg/kg) and rats (BASF 1969, NOAEL 60 mg/kg) in addition, as described further in section 1.1 of the supporting document.

Based on these three studies and applying appropriate inter- and intra-species assessment factors, and extrapolation from subchronic to chronic exposure, RAC noted that the resulting DNEL for DIDP would be similar to the DNEL for DINP.

2) Does RAC support the assumptions and conclusions of the exposure assessment?

RAC generally supports the assumptions and conclusions of the exposure assessment for adults and for children.

It is noted that the exposure assessment for children is driven by exposure to DINP and DIDP from mouthing of articles, which heavily depends on the migration rates of phthalates from the mouthed article and the mouthing time per day. RAC notes that there is a high uncertainty of the migration rates and mouthing times. RAC took note of the error in the reported value from Greene (2002) in ECHA's draft review report, but concluded it did not have significant consequences on the mouthing time assumptions for a reasonable worst case exposure estimate. RAC supports to use a mouthing time of 2 hour per day for children until 18 months of age as a reasonable worst case.

RAC supports to lower the exposure estimates for sex toys containing DINP or DIDP (see section 2.2 of the supporting document).

3) Does RAC agree to the conclusions of the draft review report that exposure to DINP and DIDP from mouthing of toys and childcare articles would present a risk, if the existing restriction were lifted?

The reasonable worst case exposure estimates from toys and childcare articles alone, would result in RCRs exceeding 1 for all age groups for both DINP and DIDP (RCRs of 2.0 for 0-6 months, 1.6 for 6-12 months and 1.3 for 12-18 months respectively) based on DNELs of 0.075 mg/kg for both DINP and DIDP, which includes a modification of the dose descriptor of a factor 2. Combined exposure of the two phthalates based on reasonable worst case exposure estimates for toys, dermal contact, air/dust and food, results in a maximum RCR of 2.4 for 6-12 month old children (RCRs of 2.2 for 0-6 months, 2.4 for 6-12 months and 2.0 for 12-18 months respectively).

As an uncertainty assessment, taking into account that the RCRs based on combined exposure[1] of the two phthalates used the reasonable worst case exposure scenarios, RAC also calculated RCRs without use of the dose descriptor modification factor of 2 (thus using DNELs of 0.15 mg/kg). The resulting RCRs for combined exposure of the two phthalates are still slightly above 1 (RCRs of 1.15 for 0-6 months; 1.23 for 6-12 months and 1.04 for 12-18 months respectively). If in addition, in the case of DINP, a higher NOAEL were to be used, then the RCRs for children of all ages would be below 1 (see discussion on NOAEL selection in section 1.2.1 of the supporting document).

Overall, RAC concludes that a risk from mouthing of toys and childcare articles with DINP and DIDP cannot be excluded if the restriction were lifted.

4) Does RAC agree to the conclusions of the draft review report regarding consumer risk from the presence of DINP and DIDP in articles other than toys and childcare articles?

RAC agrees with the conclusion that the major exposure of adults to DINP and DIDP results

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from the use of sex toys (RCRs for the reasonable worst case of 0.4 for both phthalate esters). RAC noted that there are substantial uncertainties to exposure duration and migration rates of the phthalate esters from sex toys. A risk from use of sex toys can be considered unlikely. Dermal exposure for example from PVC garments is not anticipated to result in a risk for the adult population and the developing foetus in pregnant women. Exposure from food and the indoor environment is not considered to constitute a risk for adults or children.

5) Does RAC agree to the conclusions of the draft review report regarding the risk from combined exposure[2] to DINP and DIDP?

RAC supports the concept to apply dose/concentration addition for assessing the risk from combined exposure to DINP and DIDP. However, as stated in the draft review report, for the purposes of the assessment of exposure to articles from mouthing or dermal contact (direct exposure to articles), it was assumed that the articles either contain DINP or DIDP. Therefore, dose addition does not apply to direct exposure to articles. It however applies to exposure via food and the indoor environment.

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Basis for the opinion
The supportive document gives the detailed grounds for the opinion.

[2] 'Combined exposure' includes all routes, pathways, and sources of exposure to multiple chemicals (as defined in the joint opinion of SCHER, SCENIHR and SCCS "Toxicity and Assessment of Chemical Mixtures" from 2011).

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ANNEX

SUPPORTING DOCUMENT TO THE OPINION

This supporting document shall be regarded as further reference material to the opinion of the Committee for Risk Assessment. It contains further details and assessment and may be used to better understand the opinion and its justifications.

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1 Human health hazard assessment (question 1)

RAC agrees with the conclusions drawn in the ECHA draft review report regarding all human health endpoints, with the exception of the repeated dose toxicity endpoint and the oral absorption part. These aspects are commented on below. In addition, RAC commented on the DNEL derivation by ECHA.

1.1 Toxicokinetics: oral absorption

1.1.1 DINP

Animal studies with DINP

Hazleton (1972) administered about 2500 mg/kg/day over 6 days to albino rats (4 treated, 2 controls). The amount excreted radioactivity in urine ranged from 8-18%. Considering the high dose, the absorption process was probably saturated (EC 2003a).

Midwest Research Institute (1983), also cited as McKee et al (2002), treated Fischer 344 rats with a single radioactive dose of 50 and of 500 mg/kg, with recoveries in urine of 49% and 43% respectively (after normalizing to 100% total recovery, which was 99 and 91% at 50 and 500 mg/kg, respectively). In a repeated dose study over 5 days with 50, 150 and 500 mg/kg, recoveries in urine were 52, 60 and 55 % respectively (after normalizing to 100% total recovery, which was 123, 117 and 115% at 50, 150 and 500 mg/kg, respectively).

Human volunteer studies with DINP

Koch and Angerer (2007) described elimination of major DINP metabolites via urine in a study where one human volunteer was dosed 1.27 mg/kg (n = 1). A recovery of 43.6% of the custom synthesised DINP-2 was calculated in urine measurements during 48h of four metabolites. Four metabolite 'groups' of structural isomers were measured. Other possible metabolites (with two or more functional groups or shortened side chains) were not measured. The recovered percentage is thus likely an underestimation of the actual elimination of DINP via urine (Koch and Angerer 2007).

Anderson et al. (2011) studied the kinetics of DINP and DEHP in 10 male and 10 female human volunteers (n = 20). Two dose levels were used of the deuterium labelled DINP and DEHP, which were for DINP 0.78 mg (0.010 mg/kg for males and 0.011 mg/kg for females) and 7.3 mg (0.090 mg/kg for males and 0.107 mg/kg for females). A recovery of 32.9 ± 6.4% of the labelled DINP was calculated in urine measurements during 48 h of four metabolites (the same metabolites as in Koch and Angerer).

1.1.2 DIDP

Animal studies with DIDP

From a gavage study with radiolabeled DIDP in Sprague Dawley rats (General Motors Research Laboratories 1983), the total absorbed dose was roughly estimated to be 55.6% after 0.1 mg/kg, 45.9% after 11.2 mg/kg and 17.3% after 1000 mg/kg. This seems to indicate absorption is saturable. The recovered radioactivity from urine and feces was >99%.

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Human volunteer studies with DIDP

Not available.

1.1.3 DEHP

Animal studies with DEHP

Numerous studies have been performed to study the toxicokinetics of DEHP in different rat strains, and also in non-human primates, mice, hamster, guinea pigs, dogs, miniature pigs. Based on amongst others about 16 kinetic studies with DEHP in rats, RAC concluded in its opinion of 15 June 2012 on the Annex XV dossier proposing restrictions on four phthalates that the absorption of DEHP in rats can be estimated to be 70%.

In a first experiment studying kinetics, Sjöberg et al (1985) administered 1000 mg DEHP/kg to 25, 40 and 60 days old rats by gavage (9-10 animals per group). The mean AUC of MEHP of 25 day old rats (1213 µg h/ml) was significantly higher than that of the 40 and 60 day old rats (611 and 555 µg h/ml respectively). In a second experiment studying excretion, groups of 25 and 60 day old rats (6 animals per group) were administered 1000 mg ^{14}C-DEHP/kg by gavage. The cumulative excretion of radioactivity was 44% in 25 day old rats and 26% in 60 day old rats. The authors concluded that the observations suggest that the absorption, and therefore exposure, to MEHP and its metabolites was higher in young than in more mature rats.

In Study I of Kurata et al (2012), groups of 3 and 18 months old marmosets received 100 and 2500 mg/kg ^{14}C-DEHP by gavage (3 animals per group). At the low dose, the cumulative urinary excretion 7 days after dosing was higher in the younger (about 18%) than in the elder animals (13%). At the high dose the younger excreted about 10%, the elder 22% radioactivity in urine. Within one day after the low dose there was no difference between the two age groups (about 10% excretion), whereas at the high dose the excretion in the younger animals was less than in the elder ones (5 versus 15%). Two hours after dosing radioactivity in blood and bile was more than twofold higher in the younger animals at the low dose and about 40% lower at the high dose. Thus, within one day after the low dose, the younger animals absorb more than the elder ones. At the high dose younger animals show lower radioactivity in urine, bile and blood than the elder ones (about 40% less).

Based on the results from Study II of Kurata et al (2012), in which 4 week old rats and 3 months old marmosets received 100 mg/kg ^{14}C-DEHP by gavage, there might be large species differences in absorption between rat and marmosets. In rats at 1 day post-dose radioactivity excreted in urine accounted for 58% of the dose, whereas in marmosets this was only 8%.

Human volunteer studies with DEHP

Schmid and Schlatter (1985) studied excretion of DEHP taken orally by 2 volunteers (30 mg or about 0.4 mg/kg) and determined an excretion of 11 and 15% of the dose in urine by measuring 12 DEHP metabolites. DEHP taken by the same volunteers over a period of 4 days at a dose of 10 mg/day (about 0.13 mg/kg/day) resulted in 15 and 25% recovery in urine. The amount recovered for 5 of the 12 metabolites was less than 1%.

Koch et al (2005) measured 5 metabolites in one human volunteer after doses of 4.7, 28.7 and 650 µg/kg, with recoveries in urine of 66, 65 and 71% respectively (mean of 67%). This is indicative that at these low exposure levels there is no saturation of absorption.

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Anderson et al (2011) studied 10 male and 10 female human volunteers (n = 20) given deuterium labeled DEHP (and DINP, see above) at dose levels of 0.31 mg (0.004 mg/kg for males and 0.005 mg/kg for females) and 2.8 mg (0.034 mg/kg for males and 0.041 mg/kg for females). The recovery in urine was 47% based on measurement of 4 metabolites. Using the same 4 metabolites from the Koch et al (2005) results, this would in comparison have given 65%. Anderson et al (2011) noted that the higher results seen in the Koch study can be explained because it is based on a single individual (with results still within the observed standard deviation). The authors also noted that the consequence of the difference is that when calculating exposure from biomonitoring data the conversion factors and therefore the exposure will be slightly higher based on their results.

Kessler et al (2012) studied 4 male volunteers given 618-665 µg/kg labelled DEHP and found 31% of the dose excreted in urine based on measurement of 3 metabolites. The authors concluded that the results are in line with those from Anderson et al for the 3 metabolites (29.1 and 33.2%). The results from Koch et al gave 44.2% excretion in the urine of the 3 metabolites (Kessler et al 2012). The authors made the same remark as Anderson et al (2011) regarding the consequences to the estimation of exposure from biomonitoring results in urine.

1.1.4 Conclusion

Animal studies indicate that absorption of DINP and DIDP are saturable at high dose levels. Studies with DINP and DIDP indicate absorption rates of around 50%. A study with DINP indicates absorption of roughly 40-55% at dose levels as high as 500 mg/kg/day. As biliary excretion occurs, an unknown percentage of the radioactivity excreted in feces is to be added to the radioactivity excreted in urine to estimate the absorption. The absorption of DINP and DIDP can therefore be assumed to be in the range of 50-70% in the rat.

Human volunteer studies with DEHP clearly demonstrate that the amount recovered in urine is dependent on the type and amount of metabolites that are measured in those studies. Measuring all metabolites most likely would result in near to 100% recovery of radioactivity in urine. An unknown amount of excretion via bile contributes further to the absorption estimate. However, it is acknowledged that the studies in humans have not been designed to determine absorption.

RAC concludes that adult rats can be assumed to absorb 50-70%, whereas humans absorb 100% based on read-across from DEHP.

1.2 Repeated dose toxicity

1.2.1 DINP

In the RAR on DINP (EC 2003a) a number of repeated dose toxicity studies using rats, mice, rabbits, primates and dogs have been evaluated. The RAR concluded that *"...for effects on the liver and kidneys, a NOAEL of 88 mg/kg/day is determined in rats regarding results found in a chronic/carcinogenic study (Aristech, 1994)*". This NOAEL was taken because liver pathology unrelated to peroxisome proliferation was seen in this study.

In the Exxon study (Lington et al. 1997) using Fischer 344 rats, there was a dose-related increase in relative organ weights of liver and kidney in both males and females with a clear NOAEL of 15 (males) – 18 (females) mg/kg/day. In addition to the increased liver and kidney weights at the LOAEL of 152 (females) - 184 (males) mg/kg/day, males had increased

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incidences of spongiosis hepatis and serum levels of alkaline phosphatase and transaminases. Spongiosis hepatis was also seen in males in the Aristech study. In these studies the NOAEL/LOAEL for spongiosis hepatis are the same as for the increases in liver and kidney weights.

If both the Exxon and the Aristech studies would have been conducted under exactly the same conditions the dose response could have been expected to be the same in both studies. Considering the dose spacing in those studies, in particular the Exxon study with 152 mg/kg as the next higher dose, the true NAEL (No Adverse Effect Level) could be argued to be somewhere between 88 and 152 mg/kg/day. However, there were differences in methodology between both studies: the Exxon (1986) study evaluated 4-5 liver sections, whereas the Aristech (1994) study examined 1-2 sections. Comparison of Aristech (1994) data scaled to 4 slides, and another comparison with Exxon (1986) data scaled to one slide showed no statistical significant difference between the scaled data sets. This indicates that it is likely that the dose response from both studies would have been the same if the studies would've examined the same amount of liver sections.

It was argued that as a result of this methodological difference, the Exxon (1986) study was the most appropriate to use. RAC supported the NOAEL for DINP of 15 mg/kg as proposed by ECHA noting that the NAEL could be higher given the large dose spacing in this study.

1.2.2 DIDP

The NOAEL for DIDP has been discussed in the RAR (EC 2003b) by EFSA (2005), SCCP (2007), SCHER (2008), and the US CPSC (2010). The studies used for NOAEL setting in the EU RAR were subchronic studies. Since the peroxisome proliferation effects in the liver of rodents are generally seen as species-specific, dog was considered to be a more relevant species for human risk assessment. The dog study by Hazleton (1968b) resulted in a NOAEL of 15 mg/kg/day. However, because of the limitations of the dog study, a NOAEL of 60 mg/kg/day from a 90-day rat dietary test was considered in addition (BASF 1969). The EU RAR carried out risk characterisation for both NOAELs.

According to the EU RAR (EC 2003b), the NOAEL in another 90 day rat study by Hazleton (1968a) was 0.3% (approx. 200 mg/kg/day) and the LOAEL 1% (approx. 650 mg/kg/day). As the NOAEL of 200 mg/kg/day in the Hazleton (1968a) study is higher than the LOAEL in the BASF (1969) study (120 mg/kg/day), it is the BASF study that determines the overall NOAEL for a study of that duration in the rat. Therefore, RAC considered it not appropriate to consider the Hazleton study for DNEL calculation. This is consistent with the approach in the EU RAR for DIDP. It could be noted that furthermore the Hazleton study used 10 animals per dose group versus 20 in the BASF study, and 3 dose levels versus 4 dose levels respectively. Industry argued that the 90 day rat study (Hazleton 1968a) should be used in addition to determine DNELs for DIDP as it was conducted with the substance which is produced commercially within the EU today (CAS number 68515-49-1). RAC did not consider this argument to be convincing, noting that read-across between the two forms of DINP and between the two forms of DIDP is general practise both by industry and by regulatory authorities, and furthermore, imported articles might contain either form of DIDP.

A new study by Cho et al (2008, 2010) reported a 2 years dietary study in male and female F344 rats at daily doses of about 22, 120 and about 500 mg/kg/day. Significant toxicity was observed at the highest dose level and similar to the previous studies, spongiosis hepatis occurred in male rats. Since the effect was seen at the lowest dose, no NOAEL could be derived by ECHA. Spongiosis hepatis occurred in 3/48 (6.3%), 3/49 (6.1%), and 5/39 (12.8%) male rats at the low, middle and highest doses, respectively but not in the controls. The ECHA report concluded that the negative findings in the controls do not contradict the experience from other studies using F-344 rats, where this lesion occurred between 0 and 34% of the male controls (Karbe and Kerlin 2002). Thus, ECHA proposed a LOAEL of 22

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mg/kg/day to be derived from this chronic study. RAC questioned the reliability of the Cho et al. 2008 study to derive a LOAEL of 22 mg/kg/day DIDP as a starting point to set the DNEL (see also section 1.3).

The reliability of the Cho et al 2008 study has been extensively discussed. It can be argued that the incidences of the Cho et al study are all within the range of available controls from NTP studies, and that therefore the incidences should not be interpreted as a response to the administered dose. Alternatively, it can be argued that historical control data from NTP studies has limited relevance for evaluating the 0% incidence of spongiosis hepatis in the control of the Korean study by Cho et al: the uniformly low incidences seen in the study might be a consequence of the different breeder, possible differences in diagnosis, possible differences in amount of liver sections taken, etc. Thus, it could be argued that the statistical significance of the study is a relevant finding that is related to the dose. Moreover, a zero control incidence might not be a deviating finding, as the range of historical controls was reported to be 0-34% from 12 NTP studies, of which 1 showed a zero control incidence only. Moreover, in the 2 years' studies on DINP the incidences of spongiosis hepatis in the untreated Fischer rats were 24/81 animals (Exxon 1986) and 5/80 (Aristech 1994). Concerning the relevance of spongiosis hepatis for humans see section 1.3.

RAC recommended to use all three studies, i.e. the 90 day study in dogs (Hazleton 1968b), the 90 day and 2 year studies in rats (BASF 1969 and Cho et al 2008, 2010), in deriving the DNEL for DIDP.

1.3 Evaluation of human relevance of spongiosis hepatis

In the 2 year rodent carcinogenicity studies on DIDP (Cho et al 2008, 2010) and DINP (Exxon 1986 and Aristech 1994) histopathological changes in the liver included spongiosis hepatis at low but statistically significant incidences in all male treatment groups. The ECHA report discusses the relevance of these lesions in detail. The lesion occurs spontaneously in aging male rats and can be enhanced by genotoxic and non-genotoxic hepato-carcinogens but has not been described in dogs and non-human primates. According to the literature there is a controversial discussion whether spongiosis hepatis can be considered a proliferative change or may be regarded as a preneoplastic or even a benign neoplastic lesion.

ECHA concluded that the mechanisms of spongiosis hepatis are not known, but that they seem unrelated to peroxisome proliferation.

On behalf of the European Council for Plasticisers and Intermediates (ECPI) the significance of spongiosis hepatis for humans has been evaluated by Berry (2012), who concluded the following:

*"In my experience, there is no comparable human lesion, a view shared by expert human pathologists in this field. In Professor Sir Roderick MacSween's book the authors state "**to the best of our knowledge no human counterpart of spongiosis hepatis has ever been described**". The authors use the term **spongiocytic pericytoma** but are considering the lesion we discuss here and Bannasch is a contributor to the volume. Further, there was no evidence of a lesion resembling spongiosis hepatis in a review of 163 human livers conducted by members of the Bannasch laboratory (Su et al., 1997) nor in my autopsy study of 1500 livers at autopsy.*

The broad consensus of pathologists appears to support the view that spongiosis hepatis is a degenerative change. From NTP studies, spongiosis hepatis is a lesion that appears to be confined to rats, particularly male rats, and teleost fish."

The expert also questioned the reliability of the Cho et al. 2008 study:

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"The authors make little note of the finding other than to note its presence and the overall conclusion made in the paper is that "The increases in the relative weights of the liver and kidney were not accompanied by any histopathologic lesions in those organs." There is little information presented in the paper to fully evaluate the lesion (i.e., correct diagnosis, information on severity, number of sections reviewed). As such, it would be difficult to utilize this endpoint as a point of departure in hazard identification and risk assessment. This is particularly the case, when as noted above, the changes observed have no relevance for human pathology."

He concluded that it would be difficult to utilize the endpoint spongiosis hepatis as a point of departure in hazard identification and risk assessment.

There are two publications reporting features resembling spongiosis hepatis in relation with hepatic adenomas that appeared in users of oral contraceptives (Nime et al. 1979 and Kaiserling and Müller 2005). Berry (2012) questioned the relation of these findings with spongiosis hepatis in rats however.

Considering the above, RAC noted that the relevance of spongiosis hepatis for humans has been questioned by some, while others have indicated that treatment-related lesions similar to spongiosis hepatic are described in human pathology (sinusoidal dilations or sinusoidal ectasia), but that the terminology differs.

1.4 Derivation of DNELs by ECHA

The DNELs for the different routes of exposures for adults, children (repeated dose effects and reproduction) and for foetal development in pregnant women as derived by ECHA are given in Table 1 and Table 2.

Table 1 DNELs (mg/kg/day) for DINP proposed by ECHA

Route	Repeated dose toxicity		Reproductive toxicity children	Foetal development in Pregnant Women
	Adults	Children		
Oral (mg/kg)	0.15	0.075*	0.25*	0.5
Inhalation (mg/m3)	0.35	0.26	0.87	1.16
Dermal (mg/kg)	1.88	1.88	6.25	6.25

*includes a dose descriptor modification with a factor of 2 for absorption

Table 2 DNELs (mg/kg/day) for DIDP proposed by ECHA

Route	Repeated dose toxicity		Reproductive toxicity children	Foetal development in Pregnant Women
	Adults	Children		
Oral (mg/kg)	0.073	0.037*	0.26*	0.17
Inhalation (mg/m3)	0.17	0.13	0.904	0.38
Dermal (mg/kg)	0.92	0.92	6.50	2.06

*includes a dose descriptor modification with a factor of 2 for absorption

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1.5 Comments from RAC on DNEL derivation by ECHA

1.5.1 Absorption

Based on a study from Sjoberg et al. (1985) which seemed to show a greater absorption of DEHP by the oral route in young rats compared to older ones (see section 1.1), the ECHA draft report differentiated between adults and children, assuming that the absorption rates in children are higher (100%) than in adults (50%). As a consequence, a lower DNEL for children was derived. This endpoint modification step is in line with the EU Risk Assessments for DINP, DIDP and DEHP. The RAC opinion on the Danish restriction proposal on four phthalates of 15 June 2012 also assumed 100% absorption in children.

RAC considers there is no indication that adults absorb less phthalate esters than children. The assumption of higher absorption by children in the draft ECHA review is based on DEHP data from adults (Koch et al 2005, Anderson et al 2011, Kessler et al 2012), from which a 50% absorption in adults has been estimated. However, these studies indicate a rather high absorption rate in adults taking into account that the amount recovered in the urine depends on the number of urinary metabolite measured, and the unknown amount of excretion via bile.

Since adults absorb almost 100% (see section 1.1) there is no need to assume an even higher absorption in children so that an additional factor to take into account differences in absorption between adults and children is not necessary. However, an endpoint modification is necessary considering the species differences in absorption: adult rats absorb about 50% whereas humans around 100%. As indicated in the ECHA guidance R.8, Appendix R.8.2-2, an endpoint modification is needed in that case. Indeed, the default situation, in the absence of information, is to assume the same bioavailability for experimental animals and humans for a particular exposure route. However, when available information indicates that at the relevant level of exposure humans absorb less (or more) than experimental animals, the dose descriptor needs to be corrected for this difference in bioavailability.[3]

RAC notes that Industry, by referring to the following text of the ECHA guidance R.8.4.3.1, page 24, questioned the justification for this endpoint modification: *"If no substance-specific data are available, the standard procedure for threshold effects would be, as a default, to correct for differences in metabolic rate (allometric scaling) and to apply an additional factor of 2.5 for other interspecies differences, i.e. toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part). In case substance-specific information shows specific susceptibility differences between species, which are not related to differences in basal metabolic rate, the additional factor of 2.5 for 'remaining differences' should be modified accordingly".* Accordingly, Industry concluded that for DINP and DIDP substance specific data are available, which was said to support that there is no need for the default factor of 2.5, giving an interspecies assessment factor of 4 (which together with

[3] ECHA guidance R.8, R.8.4.2, point b) 'Modify, when necessary, the relevant dose descriptor(s) per endpoint to the correct starting point' clarifies as follows: *"In a few situations, the effects assessment is not directly comparable to the exposure assessment in terms of exposure route, units and/or dimensions. In these situations, it is necessary to convert the dose descriptor for the threshold effect (e.g. N(L)OAEL, benchmark dose, LD/LC50) into a correct starting point (i.e., correct the unit of exposure, e.g. corrected N(L)OAEL). This applies to the following situations:*
1. If for a given human exposure route there is a dose descriptor for the same route in experimental animals but for that particular exposure route there is a difference in bioavailability between experimental animals and humans at the relevant level of exposure."
This is exemplified also in Appendix R.8.2-2, point B, a modification of starting point is necessary amongst others "*If for a given human exposure route there is an effect parameter for the same route (in experimental animals or humans) but for that particular exposure route there is a difference in absorption between experimental animals and humans at the relevant level of exposure."*

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an intraspecies factor of 10 gives an overall assessment factor of 40).

RAC notes however that "toxicokinetic differences not related to metabolic rate (small part)" in the above citation does not refer to absorption but to the other aspects of toxicokinetics, i.e. distribution, metabolism and elimination. Indeed, the guidance clearly specifies that the dose descriptor needs to be corrected separately in the step prior to applying assessment factors in case there are differences in bioavailability between experimental animals and humans.

In summary, RAC considers that a modification of the dose descriptor with a factor of 2 is justified. RAC notes however, that the estimated absorption rate of 50% in adult rats might underestimate the actual absorption at low dose levels, in particular given the contribution of biliary excretion, and that therefore the modification of the dose descriptor with a factor of 2 might be considered to be conservative.

With regards to the assumption for inhalation, RAC agrees with the assumption in the ECHA draft report of 75% absorption in adults and 100% absorption in children. The assumption of 100% absorption in children could be considered conservative.

1.5.2 DINP

RAC supports most DNELs derived by ECHA for DINP for repeated dose toxicity and reproductive toxicity, as shown in Table 3. For the oral route, however, RAC considers that the DNELs for adults and children should be the same. RAC further noted in section 1.2 that the NOAEL 15 mg/kg/day could be considered to be somewhat conservative.

Table 3 DNELs (mg/kg/day) for DINP supported by RAC

	Repeated dose toxicity		Reproductive toxicity	
Route	Adults	Children	Adults (pregnant women)	children
Oral (mg/kg)	0.075*	0.075*	0.25*	0.25*
Inhalation (mg/m3)	0.35	0.26	1.16	0.87
Dermal (mg/kg)	1.88	1.88	6.25	6.25

*includes a dose descriptor modification with a factor of 2 for absorption

1.5.3 DIDP

RAC supports the DNELs derived by ECHA for DIDP for reproductive toxicity, with the exception of the oral DNEL for pregnant women where RAC would apply a modification of the dose descriptor with a factor of 2 (see Table 4).

For the derivation of repeated dose DNELs for DIDP, RAC recommended (see section 1.2) the use of the NOAELs of the 90 days studies in rats (BASF 1969) and dogs (Hazleton 1968b) and the LOAEL of the 2 year study in rats (Cho et al 2008, 2010) by applying the appropriate interspecies scaling, the subchronic to chronic extrapolation and the intraspecies scaling. The oral DNEL without the modification of the dose descriptor can then be derived as follows:

- Dog 90 d study (Hazleton 1968b), NOAEL 15 mg/kg/day
  - Interspecies factor:
    a. AS (correction for differences in metabolic rate): 1,4

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b. remaining differences: 2,5

Intraspecies factor general population: 10
Exposure duration 90 day - chronic: 6[4]
Issues related to dose-response: 1
Quality of whole database: 1
Total factor: 210
DNEL: 0.07 mg/kg/day

- Rat 90 d study (BASF 1969), NOAEL 60 mg/kg/day
  Interspecies factor:
  c. AS (correction for differences in metabolic rate): 4
  d. remaining differences: 2,5
  Intraspecies factor general population: 10
  Exposure duration 90 day - chronic: 2
  Issues related to dose-response: 1
  Quality of whole database: 1
  Total factor: 200
  DNEL: 0.3 mg/kg/day

- Rat 2y study (Cho et al 2008, 2010), LOAEL 22 mg/kg/day
  Interspecies factor:
  e. AS (correction for differences in metabolic rate): 4
  f. remaining differences: 2,5
  Intraspecies factor general population: 10
  Exposure duration 90 day - chronic: 1
  Issues related to dose-response: 3
  Quality of whole database: 1
  Total factor: 300
  DNEL: 0.07 mg/kg/day

The average of the 3 DNELs is 0.15 mg/kg/day (unmodified). Following the modification of the dose descriptor with a factor of 2, the DNEL is 0.075 mg/kg/day.

The DNELs for DIDP for repeated dose toxicity and reproductive toxicity supported by RAC are shown in Table 4.

Table 4 DNELs (mg/kg/day) for DIDP supported by RAC

	Repeated dose toxicity		Reproductive toxicity	
Route	Adults	Children	Adults (pregnant women)	children
Oral (mg/kg)	0.075*	0.075*	0.08*	0.26*
Inhalation (mg/m3)	0.35	0.26	0.38	0.90
Dermal (mg/kg)	1.88	1.88	2.06	6.50

*includes a dose descriptor modification with a factor of 2 for absorption

[4] The default assessment factor for sub-chronic to chronic extrapolation is 2 for a rat 90 day study. The lifespan of a Beagle dog is around 13 year; thus, a study duration of 90 days covers roughly 2% of its lifespan. As a comparison between dog and rat, a 28 day study (subacute) covers 4% of the lifespan and a 90 day study (sub-chronic) covers 12% of a rat's life. Thus, a 90 day dog study covers about half of the length of a subacute study in rats. This justifies a default assessment factor of 6 for subacute to chronic extrapolation for the 90 day dog study (see Table R. 8-5 in ECHA guidance R.8).

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2 Exposure assessment (question 2)

In assessing exposure, the ECHA draft review report evaluated and documented a large number of studies and reports. RAC generally supported the exposure assessment in the ECHA draft review report, but provided comments on the exposure from toys and childcare articles, and on the exposure of adults from the use of sex toys (see below). In addition, RAC made a brief comment regarding the biomonitoring data for children.

2.1 Exposure from toys and childcare articles

Exposure is determined by the concentration of the leachable compound in the article, the migration rate and the duration of oral contact, which in the case of small children is mouthing time. The ECHA report presents a thorough evaluation of the available information. RAC noted the following regarding specifically the mouthing time assumption.

Mouthing time

The ECHA draft report used a study by Greene (2002) and Juberg et al. (2001) to derive a reasonable worst case mouthing time of 126 min/day.

During the opinion forming process, Industry commented that the ECHA report contained an error in the mouthing time it used from Greene (2002). In the room document RAC/23/2012/08, ECHA acknowledged that the draft report contained mistakes: ECHA had used a peer reviewed publication from Babich et al. (2004) which contained errors in the reported data from Greene (2002).

The correct 95th percentile mouthing time for the category "All soft plastic items except pacifiers" was not 127 minutes/day as reported by ECHA but 17.5 min/day.

In the room document ECHA assessed the corrected value in the context of all the available evidence, to derive a reasonable worst case estimate for mouthing of articles containing DINP or DIDP. Using a weight of evidence approach, ECHA referred to the following mouthing time results from the key studies:

- Greene (2002) reported 95th percentiles of 18 min/day for soft plastic items and 134 min/day for non-pacifiers for children of 3-11 months;
- Juberg et al. (2002) reported mean mouthing times for non-pacifiers of 70 min/day for 0-18 months old (without zeros, i.e. only taking into account children that mouthed, see Table 2 of Juberg et al.);
- Smith and Norris (2002) reported mean values for mouthing articles (excluding pacifiers and fingers) of 63 min/day for 6-9 month olds and 75 min/day for 5 year old children.

ECHA also pointed to a very large discrepancy between the maximum value of nearly 4 hours/day (227 min/day) for mouthing of toys by a child aged 6-9 months in Smith and Norris (2002) (with a mean of 39 min/day) and the highest 95th percentile of 18 min/day for 24-36 months old for mouthing of soft plastic items as calculated by a bootstrap procedure in Greene (2002).

Based on the above estimates, and considering the limitations and discrepancies in the da-

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ta, as well as the skewness and difficulties to determine appropriate article categories, ECHA considered that a mouthing time of 2 hour is appropriate for a reasonable worst case scenario for mouthing of articles containing DINP or DIDP by children up to 18 months old. Further details are available from the room document.

RAC took note of the error in the reported value from Greene (2002) and of the assessment by ECHA in the room document RAC/23/2012/08. RAC is of the opinion that the assumption of 2 hour mouthing time per day is appropriate for a reasonable worst case scenario for mouthing of articles containing DINP or DIDP by children. RAC notes that a mouthing time of 3 hours/day was assumed in the EU RARs from 2003 and that 3 hours mouthing time is also the recommended value for risk assessment according to the ECHA guidance.

RAC notes that according to RIVM 1998 and CHAP (2001) pacifiers are rarely made of soft PVC. They are typically made of latex or silicone. According to Tonning et al 2009 PVC may be used in the mouth shield and the handle only (see p. 197 of the ECHA report). RAC agrees with ECHA's conclusion to exclude pacifiers for exposure assessment.

RAC notes that the (small) change in mouthing time from 126 min/day to 2 h/day results in slightly lower reasonable worst case exposure estimates (see Table 5) than presented in the ECHA draft review report.

Table 5 Estimated daily reasonable worst case exposures to DINP or DIDP of children at ages 0-6, 6-12, and 12-18 months from mouthing articles

	0-6 months	6-12 months	12-18 months
Body weight (kg)	6.21	7.62	9.47
Mouthable surface (cm^2)	10	10	10
Daytime mouthing (min/day)	120	120	120
Migration rate ($\mu g/cm^2/h$)	45	45	45
Exposure mouthing articles (excl. pacifiers) (µg/kg/day)	**145**	**118**	**95**

2.2 Sex toys

Sex toys are mainly made of soft PVC or rubber latex. Concentrations of up to 60% w/w DINP have been measured in soft PVC sex toys. Being aware of large uncertainties in the frequency and duration of use of sex toys, migration rates from the different products and their content of phthalate esters, the ECHA report estimated typical and reasonable worst case exposures of 10 and 113 µg/kg bw/day respectively. Since migration rates of DINP and DIDP are similar, these values are applicable to both phthalate esters. In the absence of data on the absorption rates of phthalates from the vagina or rectum, the absorption was assumed to be 50%.

The draft ECHA report assumed a migration rate of 140 µg/cm2/h for the typical case and 217 µg/cm2/h for the reasonable worst case from respectively the average migration rate and the 75th percentile migration rate of DIDP in VWA (2009). The draft report pointed out that the migration rates from VWA (2009) were high in comparison with results from migration experiments with toys and childcare articles. Several possible explanations for the differences were identified. It was considered plausible that the PVC matrix of the tested articles in the VWA study was of bad quality, and three out of 6 sex toys contained very high levels of DINP (50-55% w/w). ECHA considered also that experimental factors might have

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been a cause for the high results.

In the draft responses to comments from public consultation, ECHA stressed that phthalates are highly lipophilic, and therefore fatty simulants can produce significant migration in contrast with non-lipophilic media. ECHA considers this an important point since oil-based personal lubricants are frequently used with sex toys. ECHA however suggested calculating a median and 75th percentile from the combined DINP and DIDP data from VWA might be appropriate. A median of 65 µg/cm2/h, a 75th percentile of 121 µg/cm2/h and a 95th percentile of 250 µg/cm2/h can be calculated from 19 samples in VWA (2009) (13 DINP and 6 DIDP samples).

Considering the uncertainties discussed, RAC considered that a migration rate of 65 µg/cm2/h for the typical case and 121 µg/cm2/h for the reasonable worst case would be appropriate assumptions for risk assessment. The estimated exposure of DINP and DIDP associated with the use of sex toys would then become 4.8 and 63 µg/kg/day respectively for typical and reasonable worst case exposures (see Table 6).

Table 6 Estimated exposure of DINP and DIDP associated with the use of sex toys

	Typical case	**Reasonable worst case**
Body weight (kg)	60	60
Migration rate (µg/cm^2/h)	65	121
Surface (cm^2)	125	125
Duration (min)	2.14	15
Exposure (µg/kg/day)	4.8	63.0

2.3 Biomonitoring data

RAC agreed with the assessment for adults in the ECHA report but notes that it did not sufficiently highlight the biomonitoring data for DINP for children from Becker et al. (2009, as cited in Kransler et al. 2012). The study reported 95th percentiles of up to 39.62 µg/kg/day for children between 3 and 11 years, which is considerably higher than found in other EU studies for children of that age (up to 10.4 µg/kg/day). How to interpret these findings in terms of exposure of children below 18 months old is, however, difficult.

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3 Risk characterisation (question 3, 4 and 5)

The previous sections demonstrate that DNELs derived for repeated dose toxicity (hepato-toxicity) are lower than those based on reproductive toxicity (Table 3 and Table 4). For that reason RAC recommends to only use DNELs for repeated dose toxicity when evaluating the risks posed by DINP and DIDP.

3.1 Children

In view of the (small) change in mouthing time and RAC's recommendation for a different DNEL for DIDP for repeated dose toxicity as compared to the ECHA draft review report, RAC notes that the risk characterisation ratios (RCRs) in the ECHA report need adjustment.

For toys and childcare articles, the adjusted RCRs for the reasonable worst case exposure from DINP and DIDP would become as presented in Table 7.

Table 7 Risk characterisation for the reasonable worst case exposure from DINP or DIDP in toys and childcare articles (repeated dose toxicity)

	0-6 months	**6-12 months**	**12-18 months**
Oral exposure (µg/kg/day)	145	118	95
$DNEL_{oral}$ (µg/kg/day)	75	75	75
RCR_{oral}	**1.93**	**1.57**	**1.27**
Dermal exposure (µg/kg/day)	54	50	49
$DNEL_{dermal}$ (µg/kg/day)	1880	1880	1880
RCR_{dermal}	**0.03**	**0.03**	**0.03**
RCR_{total}	**1.96**	**1.60**	**1.30**

For aggregated exposure[5] (for which in the ECHA draft review report RCRs have been calculated by adding the RCRs for the typical exposures from the indoor environment and from food to the RCRs for the reasonable worst case exposures for toys and childcare articles), the adjusted RCRs (using the DNELs recommended by RAC) would become as presented in Table 8 and Table 9.

[5] "Aggregated exposure" includes all routes, pathways, and sources of exposure to a given chemical (SCHER/SCENIHR/SCCS 2011).

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Table 8 Risk characterisation for repeated dose toxicity from reasonable worst case exposure of children to DINP from toys and childcare articles combined with typical exposure estimates for exposure from the indoor environment and food

	0-6 months	6-12 months	12-18 months
RCR_{toys}	1.96	1.60	1.30
$RCR_{air/dust}$	0.039	0.112	0.091
RCR_{food}	<0.028	0.031	0.025
RCR_{total}	**2.03**	**1.74**	**1.42**

Table 9 Risk characterisation for repeated dose toxicity from reasonable worst case exposure of children to DIDP from toys and childcare articles combined with typical exposure estimates for exposure from the indoor environment and food

	0-6 months	6-12 months	12-18 months
RCR_{toys}	1.96	1.60	1.30
$RCR_{air/dust}$	0.019	0.056	0.045
RCR_{food}	0.013	0.016	0.013
RCR_{total}	**1.99**	**1.67**	**1.36**

When summing the RCRs for the reasonable worst-case exposures for all sources of exposure, the adjusted RCRs for aggregated exposure (using the DNELs recommended by RAC) would become as presented in Table 10 and Table 11.

Table 10 Risk characterisation for repeated dose toxicity from reasonable worst case exposures of children to DINP from all sources

	0-6 months	6-12 months	12-18 months
RCR_{toys}	1.96	1.60	1.30
$RCR_{air/dust}$	0.135	0.365	0.300
RCR_{food}	0.028	0.144	0.169
RCR_{total}	**2.12**	**2.11**	**1.77**

Table 11 Risk characterisation for repeated dose toxicity from reasonable worst case exposures of children to DIDP from all sources

	0-6 months	6-12 months	12-18 months
RCR_{toys}	1.96	1.60	1.30
$RCR_{air/dust}$	0.067	0.183	0.149
RCR_{food}	0.013	0.072	0.084
RCR_{total}	**2.04**	**1.86**	**1.53**

As can be seen from Table 8, Table 9, Table 10 and Table 11, the major contributor to the total RCR is the RCR from toys and childcare articles, with RCRs >1. The RCRs for the other exposure sources are well below 1.

Assuming the biomonitoring data by Becker et al (2009) for children is valid, an RCR of 0.53 for DINP for 3-11 years old children can be derived from the 95th percentiles. Most other studies report exposures of up to 10.4 µg/kg which corresponds to a RCR of 0.14 for children older than 2 years. The reasonable worst case exposure estimates from the indoor environment and food correspond very well with the 95th percentile estimates from Becker

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et al (2009) as can be seen in Table 10 and Table 11.

The ECHA draft review report also addressed combined exposure[6] from DINP and DIDP. Risk characterisation for combined exposure is justified on the basis of the similar liver findings and since DINP and DIDP are both used in a wide variety of consumer articles and construction materials, with largely overlapping uses. However, as stated in the draft review report, for the purposes of the assessment of exposure to articles from mouthing or dermal contact (direct exposure to articles), it was assumed that the articles either contain DINP or DIDP. Therefore, dose addition does not apply to direct exposure to articles. It however applies to exposure via food and the indoor environment.

Simultaneous exposure is confirmed by biomonitoring data, showing that metabolites of both DINP and DIDP (MCINP and MCIOP) were detected in most of the tested persons. According to Frederiksen et al. (2010), it seems that participants with a high exposure to one phthalate were also highly exposed to other phthalates. This might justify to add reasonable worst case estimates, although it should be acknowledged that this might lead to overestimation of actual exposures.

The adjusted RCRs (using the DNELs recommended by RAC) for this combined exposure would become as presented in Table 12.

Table 12 Risk characterisation for repeated dose toxicity from reasonable worst case exposures of children to DINP and DIDP from all sources (combined exposure of DINP and DIDP)

	0-6 months	6-12 months	12-18 months
RCR_{toys}	1.96	1.60	1.30
$RCR_{air/dust}$	0.202	0.548	0.449
RCR_{food}	0.041	0.216	0.253
RCR_{total}	**2.20**	**2.36**	**2.00**

3.2 Adults

In view of the changed exposures from sex toys and RAC's recommendation for different DNELs for DINP and DIDP for repeated dose toxicity as compared to the ECHA draft review report, RAC notes that the RCRs in the ECHA report need adjustment.

For sex toys, the adjusted RCRs for the typical and reasonable worst case exposure from DINP and DIDP would become as presented in Table 13.

Table 13 Risk characterisation for vaginal/rectal exposure to DINP or DIDP in adult sex toys

	Typical case	Reasonable worst case
Vaginal/rectal exposure (µg/kg/day)	4.8	63.0
$DNEL_{oral}$ * 2 (µg/kg/day)	150	150
RCR_{sex}	**0.03**	**0.42**

[6] Combined exposure" includes all routes, pathways, and sources of exposure to multiple chemicals (SCHER/SCENIHR/SCCS 2011).

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For aggregated exposure (combining the RCRs for the typical exposures from indoor environment, food and dermal exposure to articles to the RCR for the reasonable worst case exposure for sex toys), the adjusted RCRs (using the DNELs recommended by RAC) would become as presented in Table 14.

Table 14 Risk characterisation for reasonable worst case exposure of adults to DINP and for DIDP from sex toys combined with typical exposure estimates for exposure from the indoor environment, food and dermal exposure

	DINP	DIDP
$RCR_{sex\ toys}$	0.42	0.42
RCR_{dermal}	0.005	0.005
$RCR_{air/dust}$	0.008	0.005
RCR_{food}	0.002	0.001
RCR_{total}	**0.44**	**0.43**

When summing the RCRs for the reasonable worst case exposures for all sources of exposure, the adjusted RCRs for aggregated exposure (using the DNELs recommended by RAC) would become as presented in Table 15.

Table 15 Risk characterisation for reasonable worst case exposures of adults to DINP and for DIDP from all sources

	DINP	DIDP
$RCR_{sex\ toys}$	0.42	0.42
RCR_{dermal}	0.159	0.159
$RCR_{air/dust}$	0.030	0.018
RCR_{food}	0.053	0.027
RCR_{total}	**0.66**	**0.62**

The adjusted RCRs (using the DNELs recommended by RAC) for combined exposure to DINP and DIDP (with the exception of direct exposure to articles) would become as presented in Table 16.

Table 16 Risk characterisation for repeated dose toxicity from reasonable worst case exposures of adults to DINP and DIDP from all sources (combined exposure of DINP and DIDP)

$RCR_{sex\ toys}$	0.42
RCR_{dermal}	0.159
$RCR_{air/dust}$	0.048
RCR_{food}	0.08
RCR_{total}	**0.71**

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