EVALUATION OF NEW SCIENTIFIC EVIDENCE CONCERNING THE RESTRICTIONS CONTAINED IN ANNEX XVII TO REGULATION (EC) NO 1907/2006 (REACH)

REVIEW OF NEW AVAILABLE INFORMATION FOR

di-'isononyl' phthalate (DINP)

CAS No 28553-12-0 AND 68515-48-0
EINECS No 249-079-5 AND 271-090-9

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REVIEW REPORT

JULY 2010

1. Introduction

Entries 51 and 52 of Annex XVII to REACH include the restrictions on the placing on the market and use of certain phthalates in toys and childcare articles, as initially introduced by Directive 2005/84/EC of the European Parliament and of the Council of 14 December 2005. As explained in the recitals of this Directive, the six restricted phthalates were sorted into two groups associated with a different scope for the restriction. For the three phthalates which are classified as reprotoxic, category 2 according to Council Directive 67/548/EEC[1] (i.e. DEHP[2], DBP[3] and BBP[4]) the restriction covers the placing on the market and use in any type of toys and childcare articles. For DINP and the two other non-classified phthalates (i.e. DIDP[5] and DNOP[6]) the restriction covers the placing on the market and use in toys and childcare articles which can be placed in the mouth by children. In addition and as explicitly mentioned in entries 51 and 52 of Annex XVII, the Commission was to evaluate the restrictions concerning these six phthalates in the light of new scientific information by 16 January 2010, and if justified, these restrictions shall be modified accordingly.
The European Commission requested ECHA to review the available new scientific information for these phthalates and to evaluate whether there is evidence that would justify a re-examination of the existing restrictions.
According to the work plan agreed between ECHA and the European Commission, this document provides ECHA's report on its review of the new available information related to DINP.

Recent scientific studies related to non-classified phthalates seem to have given main focus to DINP. Most of the new available information consists of reports on studies on the hazard properties of the substance; some of the available articles also report on concerns about potential long term health effects on children due to their exposure at foetal and/or neonatal stages. A number of new biomonitoring studies on phthalates in human body fluids as proxy to overall exposure are also reported.
In addition, new reports on studies aiming at evaluating the actual exposure of children via their use of toys are brought. Finally, the use in school supplies, and in particular PVC-containing erasers, has been investigated as an additional route of exposure for children.
It appears from contacts with manufacturers of DINP (industry) that the substance is currently, with DEHP and DIDP, the phthalate of highest commercial interest in Europe. Registration dossiers for each CAS No of DINP have been submitted by their respective lead registrants to ECHA in February 2010.

[1] Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. According to the CLP Regulation (Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures) these three phthalates are classified as Toxic to Reproduction, category 1B.

[2] bis (2-ethylhexyl) phthalate; CAS No 117-81-7 / Einecs No 204-211-0

[3] dibutyl phthalate; CAS No 84-74-2 / Einecs No 201-557-4

[4] benzyl butyl phthalate; CAS No 85-68-7 / Einecs No 201-622-7

[5] di-'isodecyl' phthalate; CAS No 26761-40-0 and 68515-49-1 / Einecs No 247-977-1 and 271-091-4

[6] di-n-octyl phthalate; CAS No 117-84-0 / Einecs No 204-214-7

2. Information on uses of the substance

Total use of DINP:
Due to its long backbone carbon chain, DINP is usually described as part of the sub-group of "*High Molecular Weight (HMW)*" phthalates, in contrast to "*Low Molecular Weight (LMW)*" phthalates such as DEHP, DBP and BBP. Its profile in terms of processability, performance, availability and economics makes DINP a "*general purpose*" phthalate, such as DEHP or DIDP. DINP (and DIDP) also show a particular compatibility for uses requiring long term performance or durability. Therefore, DINP appears to be an alternative to most of the uses of DEHP (EU, 2008; www.dehp-facts.com), with the main exception for use in medical devices (European Council for Plasticisers and Intermediates, ECPI, 2007). About 95% of DINP is used in PVC applications. HMW phthalates can be used in (electrical) wire and cables, flexible PVC sheets, coated fabrics, automotive applications (synthetic leather for car interiors, car underbody coatings, cables), building and construction (e.g. waterproofing) and (vinyl) flooring (www.dinp-facts.com). Other reported uses are in shoe soles, sealings, paints and lacquers, same as for DEHP (EU, 2003; ECHA, 2009a), as well as in footwear in general and in swimming pools and ponds liners (www.dinp-facts.com). According to Industry, DINP can be blended into a paste (so-called "*plastisol*"), which makes it particularly fitted for coating (such as tarpaulins, synthetic leather, flooring, wall covering, etc.) and rotomoulding (such as some toys and sporting articles) applications; although it can also be used in "*plastisols*", DIDP is preferably used in extruded and calendered articles, such as cables, profiles, roofing sheets or ponds liners (ECPI, 2010; ECPI, 2010a). Phthalates, including DINP, have also been mentioned to be used in children's clothing (ECPI newsletter, summer 2009, issue 16; see also "*Use in other articles for/in contact with children*" section below).

A consequence of the harmonised classification and labelling of LMW phthalates (Toxic to Reproduction, category 1B according to new CLP Regulation[7]) and the overall conclusions of the EU Risk Assessment Reports prepared in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances was a move to the use of general purpose non-classified HMW phthalates, and in particular to DINP (ECPI workshop, 2009). This transfer can be illustrated by the following figures and facts:

- DINP, DIDP and DPHP[8] represent nowadays ca. 65% of the overall consumption of plasticisers in Western Europe, for only ca. 16% for DEHP (in 2008, ECPI workshop, 2009; ECPI, 2010; CEFIC, 2010); in comparison, at global level DINP and DIDP represent only ca. 30% of the total consumption of plasticisers, for 50% for DEHP (ECPI workshop, 2009);

- in 1999, DINP and DIDP were representing only 35% of the consumption of phthalates in Western Europe, for 42% for DEHP (ECPI workshop, 2009). Industry confirmed that the current trend is the replacement of DEHP (and other LMW phthalates) by HMW phthalates (DINP, DIDP, DPHP) (CEFIC,

[7] Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

[8] di-propylheptyl phthalate; CAS No 53306-54-0 / Einecs No 258-469-4 (CEFIC, 2010)

2010a). The manufacture of DEHP has indeed decreased from 595,000 tonnes/year in EU-15 in 1997 to 340,000 tonnes/year in EU-25 in 2007 (ECHA, 2009a), for a total use of DEHP of only 221,000 tonnes/year in 2004 (EU, 2008) and ca. 210,000 tonnes/year in the last few years (ECPI workshop, 2009); on the contrary, the use of DINP has constantly increased since 1994[9] (ECPI workshop, 2009);

– all in all, putting the effects of the economic recession to one side, the total use of plasticisers, including phthalates, is steady to slightly declining within the EU during the last 10 years, driven by the increasing manufacture of PVC articles outside the EU. While on a global scale producers still foresee an increase in total manufacture and consumption of plasticisers, consumption within the EU is likely to continue to be steady to slightly declining (ECPI workshop, 2009; CEFIC, 2010a).

The replacement of DEHP by DINP in many of its applications was a reason for identifying the need for further biomonitoring of DINP as reported by the Scientific Committee on Health and Environmental Risks (SCHER) (SCHER, 2008).

The identification of DEHP, BBP and DBP as Substances of Very High Concern and their inclusion in the Candidate List and prioritisation by ECHA for inclusion in Annex XIV (List of substances subject to authorisation) will most likely further accelerate the transfer from LMW to HMW phthalates.

Two companies (one for each CAS number) have already registered (as lead registrants) the substance under the REACH Regulation, in February 2010; another registrant for CAS No 28553-12-0 has also submitted his dossier to ECHA in March 2010. Many other legal entities pre-registered DINP with a first registration deadline on 30 November 2010[10]; however, it has to be noted that many legal entities informed ECHA already at pre-registration step that they were not intending to register the

[9] according to Industry, there are four EU producers of DINP (www.dinp-facts.com; ECPI, 2010a); furthermore, the current EU consumption for DIDP is approximately the same as it was reported in the EU RAR for this substance for the year 1994, while DPHP – which is a new substance developed during the last 5 years – has now become available on the EU market and is produced nowadays in significant quantities (CEFIC, 2010; CEFIC, 2010a)

[10] DINP was pre-registered by 886 legal entities in total, with a first registration deadline on 30 November 2010 announced by 73 legal entities in total.
Both CAS numbers have been pre-registered, for all the different tonnage bands. The precise distribution is as follows:

- di-'isononyl' phthalate – CAS No 28553-12-0 / Einecs No 249-079-5 :
  - 1000 t : 41 pre-registrations
  - 100 – 1000 t : 99
  - 10 – 100 t : 118
  - 1 – 10 t : 374

- 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich - CAS No 68515-48-0 / Einecs No 271-090-9 :
  - 1000 t : 32 pre-registrations
  - 100 – 1000 t : 34
  - 10 – 100 t : 70
  - 1 – 10 t : 118

substance, and in particular plastics recyclers who intended to benefit from Art. 2.7 (d) provisions of REACH.

Use in toys and childcare articles:

A recent publication of the Danish Environmental Protection Agency (EPA) (Danish EPA, 2009) does not bring any new critical information on the use of DINP in toys and childcare articles which may affect the exposure and risk assessments that were conducted in the framework of the EU Risk Assessment Report. However, it has to be noted that phthalates (mainly DEHP and DBP, but also potentially DINP) have been detected in erasers (designed as fruits or food with related smell) and (parts of) bags which can be categorised as toys rather than school supplies (Force Technology, 2007). Some of these items may easily be placed in the mouth by children, and therefore contribute to the overall burden in phthalates. From another survey, it appears that all of the tested erasers which were containing phthalates were not CE marked (Phthalates in PVC erasers, LGC Ltd, UK).

Furthermore, information from Industry shows that plasticisers, and therefore potentially DINP, are used in outdoor/playgrounds applications such as play, gym and bouncing balls, swimming pools or inflatable castles/toboggans (ECPI workshop, 2009). Playground equipment intended for public use is not covered by the Toys Directive; however, similar products are also supplied for private use.

Finally, it has to be noted that a new survey and health assessment of the exposure of 2 year-old children to chemical substances in consumer products recently published by the Danish authorities (Danish EPA, 2009) gives an overview of several previous surveys aiming at analysing the presence of DINP in different consumer products, and in particular in toys and childcare articles. This shows that, in years the 2002-2008, DINP could be found in plasticine, in several categories of toys (plastic books, balls, dolls and Disney/cartoons' characters, inflatable feeding bottles, swords,…) whose purpose was not but could easily be placed in the mouth, as well as in baby products like baby changing mats/cushions. In some of these articles which should be considered as toys or childcare articles[11], DINP could be found in concentrations higher than 0.1%, like in some baby changing mats/cushions (in concentrations of ca. 15 % and potentially more, according to a study from 2008), in plasticine (ca. 10 % according to a study from 2002), and in so-called "*mucous toys*" found in day-care centres (in maximum concentration of 0.18 % according to a study from 2006). In the context of this survey, a series of products to which children are highly susceptible to be exposed, and in particular diapers, bed linen[12] and soft toys, were also analysed[13], but DINP is not reported to have been found in those products. The restrictions on the

[11] according to the definition of « *childcare articles* » as introduced by Directive 2005/84/EC of the European Parliament and the Council of 14 December 2005 amending for the 22nd time Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (phthalates in toys and childcare articles)

[12] note that ECHA considers these products as childcare articles that can be placed in the mouth according to Guidance Document on the interpretation of the concept "*which can be placed in the mouth*" as laid down in the Annex to the 22nd amendment of Council Directive 76/769/EEC (available at: http://ec.europa.eu/enterprise/sectors/chemicals/files/markrestr/guidance_document_final_en.pdf)

[13] for each category of product (i.e. jackets, mittens, rubber clogs, rubber boots, pacifiers (including their coverage), soap packaging, non slip figures and (bath/shower) mats, soft toys, diapers, bed linen) five (5) products were analysed

use of DINP in toys and childcare articles which can be placed in the mouth as introduced in REACH Annex XVII entry 52 should have led in the EU to the prohibition of the selling of these DINP-containing articles as of 16 January 2007. However, there is no further available information on the compliance of producers and importers with this restriction, and the possible remaining level of DINP in these categories of products.

Use in school supplies:
It appears from the available information that DINP is used as plasticiser in some PVC-containing school supplies, and in particular in non-toy erasers. A survey conducted for the Danish EPA (Force Technology, 2007) showed that 10 out of 26 (38.5%) tested erasers were containing phthalates; among the nine (9) erasers which were further analysed, six (6) were containing DINP (67%) in concentrations between 32 and 70% w/w, and an additional one at the level of traces. The results and conclusions of a new survey and health assessment of the exposure of 2 year-old children to chemical substances in consumer products (Danish EPA, 2009) confirms that such erasers, and in particular erasers containing aromas/fragrance (categorised as "*scented toy/eraser*"), could theoretically[14] be found in day-care centres.
DINP was also found in the PVC-made component of one pencil case[15], but at the traces level (Force Technology, 2007).
Finally, it has to be mentioned that some phthalate-containing PVC was also found in all of the four (4) school bags analysed in the framework of this study, without further investigations on which particular phthalate was concerned (Force Technology, 2007).

Use in other articles for/in contact with children:
The results and conclusions of a new survey and health assessment of the exposure of 2 year-old children to chemical substances in consumer products were recently published by the Danish authorities (Danish EPA, 2009). In this context, a series of products to which children are highly susceptible to be exposed, such as outdoor clothes (jackets and mittens), footwear (rubber clogs and rubber boots), pacifiers (including their coverage), bath soap packaging, non-slip figures and (bath) mats[16], and soft toys, were analysed[17]. It appears that DINP has been found in the label of two (2) mittens (label with product name on the back of the hands) in concentrations of 7.8% and 8.6%, in one (1) PVC-containing soap packaging in a concentration of 8.8% and one (1) shower mat in a concentration of 14.6%; DINP was also found in the coverage of a pacifier, but at a low concentration (i.e. around 0.1 %). In the health risk

[14] note that there is no clear indication in the above mentioned reports whether these products have actually been found in day-care centres, or if it is just considered as a reasonable assumption that they can be used in such places

[15] out of seven products analysed for this category of school supplies

[16] note that, according to Guidance Document on the interpretation of the concept "*which can be placed in the mouth*" as laid down in the Annex to the 22nd amendment of Council Directive 76/769/EEC (available at: http://ec.europa.eu/enterprise/sectors/chemicals/files/markrestr/guidance_document_final_en.pdf) non-slip figures and (bath) mats may also be regarded as childcare articles

[17] for each category of product (i.e. jackets, mittens, rubber clogs, rubber boots, pacifiers (including their coverage), soap packaging, non slip figures and (bath/shower) mats, soft toys, diapers, bed linen) five (5) products were analysed

assessment, the potential exposure from baby changing mats/cushions has also been considered (dermal route) (see paragraph 4.3. a)).
It has also to be mentioned that, in the proposed overview of several previous surveys aiming at analysing the presence of DINP in different consumer products, it is reported that DINP was found in some (children) clothes, in concentrations of up to 32% (Greenpeace – Toxic textiles by Disney, 2003).

Use in medical devices:
According to Industry (ECPI workshop, 2009), DINP is not used in medical devices such as medical tubing and blood bags; Industry also mentions that DINP is not included in the European Pharmacopeia for this application. In its opinion "*The safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups at risk*" of 6 February 2008, the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) (SCENIHR, 2008) identifies DINP as a potential alternative to DEHP in medical devices, but concludes that a risk assessment should be made in order to confirm that DINP could be considered as an acceptable alternative to DEHP for this application.

3. Information on human health hazards

3.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Some available sources report on studies discussing the different metabolites of some phthalates (including DINP), and in particular their secondary (oxidized) metabolites and their possible use as reliable and appropriate biomarkers for biomonitoring and exposure assessment purposes. However, no new information on toxicokinetics specifically applied to human health hazards assessment was identified during the review.

3.2 Acute toxicity

No new information assessing acute toxicity of DINP was found during this review.

3.3 Irritation

No new information assessing irritation effects of DINP was found during this review.

3.4 Corrosivity

No new information assessing corrosivity effects of DINP was found during this review.

3.5 Sensitisation

In the EU Risk Assessment Report for DINP (EU RAR, 2003) four *in vivo* studies on sensitisation were reported of which three were considered valid (one with limitations). One of these studies was positive (in Guinea pigs), while the other two (one in Guinea pigs and one in humans) were negative, and the overall conclusion in the RAR was that there was weak evidence that DINP may cause sensitisation in humans. The data was not considered enough to justify classification of DINP as a sensitizer.

During the review, some new information was found. Several epidemiological studies investigating the potential impact of chemicals present in the environment on asthma/allergies were found. Many of these studies were of a more general nature, i.e. not assessing the correlation between specific phthalates and asthma. Some studies indicating a correlation between DEHP levels in the environment and asthma/allergy were found, but in no one there was a correlation between DINP and asthma/allergy. In a review and meta-analysis of several of the sensitizing studies on DINP and other phthalates (Jaakkola & Knigth, 2008), the conclusion was that there is some evidence which supports the hypothesis that phthalate emissions from PVC materials increase the risk of asthma and allergies. It was also concluded that heated PVC fumes can possibly contribute to the development of asthma in humans and that epidemiological studies in children show associations between phthalate exposure (e.g. through dust) and risk of asthma and allergies. However, as mentioned above, it is difficult to draw any conclusion on specific phthalates and their individual contribution to the effects seen.

Also, some new animal studies were reported. In a hypersensitivity test in mice, DINP did not show any hypersensitisation properties in contrast to some of the other tested phthalates (Imai *et al*, 2006). In one mouse study (Butala *et al*, 2004), when comparing IgE levels between the DINP exposed animals and the positive controls, there were some indications of a sensitisation potential. However, no significant effects of DINP exposure on IgE, IL-4 or IL-13 levels were seen. Also, other phthalates were assessed in this study with the same negative result. In another mouse study (Larsen *et al*, 2002), adjuvant effects of several phthalates, including DINP, were assessed. Adjuvant effect varied strongly between the phthalates investigated. Phthalates with 8 or 9 carbon atoms in the alkyl side chains were the stronger adjuvants whereas phthalates with shorter or longer alkyl side chains possessed less adjuvant activity. For DINP, after the first booster injection there was an adjuvant effect on IgE and IgG at 200 mg/ml even though it was not concentration dependent. After the second booster injection, the adjuvant effect was apparent on the IgG antibody level both at the 200 and at the 2000 mg/ml levels with a clear concentration-effect relationship. No adjuvant effect on IgE levels was observed after two boosters, which is consistent with the results from the other mouse study. In a third mouse study (Lee *et al*, 2004) the results suggest that both DEHP and DINP enhance allergenic responses by enhancement of IL-4 production in CD4+ T cells via stimulation of NF-AT-binding activity.

The new studies give some evidence of a sensitizing potential of DINP, but the studies would need an in-depth assessment to evaluate the reliability and relevance to conclude on whether or not the results would lead to a different conclusion compared to the one drawn in the EU RAR.

3.6 Repeated dose toxicity

The liver has previously been identified as the target organ for DINP effects. In the EU RAR several studies were included indicating that DINP acts as a peroxisome proliferator (PP), a mechanism which is considered to be of low or no relevance to humans. The PP effects of DINP have been tested in monkeys and no effects were seen which further supports this. In the EU RAR a NOAEL of 88 mg/kg bw/day was determined, based on a well-conducted chronic/carcinogenicity study in rats. The NOAEL was based on hepatic biochemical changes (increased ALT, AST), liver weight increase in both sexes together with histopathological findings (not related to specific PP effects).

During the review information was found that confirms the liver as the target organ for effects of DINP, and it has been further shown in mouse studies that DINP works through a PP mechanism (Kaufmann *et al*, 2002; Valles *et al*, 2003). In a report from the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2001) a lower NOAEL of 15 mg/kg bw/day based on findings of spongiosis hepatis in rats was determined. The reference on which this NOAEL is based was included in the EU RAR, but there is a difference in interpretation of spongiosis hepatis between the EU RAR and the CSTEE report and hence, this leads to differences in determination of the NOAEL. This is also mentioned in the communication from the Commission to the European Parliament on the restriction of the phthalates (http://eur-lex.europa.eu, CELEX: 52005PC0143). In this communication it is said that the CSTEE concluded that there is a need for limiting the risks based on this

finding, while in the EU RAR it was concluded that there is no need for further information/testing or for risk reduction measures beyond those being already applied. The ECPI does not support the lower NOAEL concluded by the CSTEE, but instead agrees on the NOAEL from the EU RAR. Their argument for this is presented in their "Review of Recent Scientific Data on Di-isononyl Phthalate (DINP) and Risk Characterisation for its use in Toys and Childcare articles" (ECPI, 2009), where it is *i.a.* stated that spongiosis hepatis is considered to be degenerative change in ageing rats, with no known counterpart in humans. It is also stated that the change seems to be male specific. An in-depth evaluation of the relevant information is needed before a firm conclusion on the NOAEL for liver effects can be determined.

3.7 Mutagenicity

In the EU RAR, the conclusion was that DINP is not mutagenic *in vitro*, based on bacterial mutation assays or mammalian gene mutation assay, nor clastogenic in one *in vitro* cytogenicity assay and one *in vivo* assay on bone marrow cells (Fisher 344 rats).

No new information on assessing mutagenic effects of DINP was found during this review.

3.8 Carcinogenicity

In the EU RAR, studies in rats and mice were reported where a significant increased incidence of neoplasia, primarily in the liver, was seen after DINP exposure. However, several studies have shown that DINP acts PP, which is, as mentioned above, a mechanism to which human cells are considered to be refractory or non-responsive. Induction of PPAR-responsive genes is less in human cells compared to rat or mouse cells. It was therefore concluded that the liver neoplasia seen in rodent studies were not likely to be relevant for humans. In studies on monkeys no changes related to PP were reported, which gives further support to the conclusion that primates are less sensitive than rodents to this specific effect. Two other neoplasms were also discussed, mononuclear cell leukaemia (MNCL) and kidney tumours, but the conclusion in the EU RAR was that the findings in the rat studies were not relevant to humans.

During the review more information indicating that DINP is a PP was found, which confirms the conclusion from the EU RAR (Kaufmann *et al*, 2002; Valles *et al*, 2003).

3.9 Toxicity for reproduction

3.9.1 Fertility

In adult rats, some effects were reported in the EU RAR, e.g. increased and decreased absolute and relative testis weight, but adverse effects were not histologically confirmed. The NOAEL for 276 mg/kg bw/day was assumed based on testicular effects. Based on the studies evaluated in the EU RAR, it was concluded that DINP does not cause any adverse effects on fertility.

During the review some new information was found. In two reports (National Toxicology Program, Centre for the Evaluation of Risks to Human Reproduction (NTP CERHR, 2003); Agence française de sécurité sanitaire de l'environnement et du travail - AFSSET (AFSSET, 2009)) the EU RAR conclusion that DINP does not impair fertility was confirmed. However, the NTP report doesn't give reference to any new information compared to the EU RAR and hence can not be considered as giving new information.

In one study, not included in the EU RAR (Lee *et al*, 2006), doses of 40, 400, 4.000 and 20.000 ppm DINP were tested in rats (gestational day (GD) 15-postnatal day (PND) 21). Effects seen were e.g. a significant decrease in the lordosis quotient, a measure of sexual responsiveness in females perinatally exposed to DINP (at all doses tested). There was also decreased copulatory behaviour (number of mounts, intromissions and ejaculations) in males but this effect was only seen at the lowest dose tested and is not considered to be related to DINP exposure. There were no effects on LH, FSH or testosterone in male rats. Effects on genes previously identified as sex-steroid regulated genes in the neonatal rat hypothalamus were also seen, but not at all dose levels tested. No effect on delivery in dams was seen in the study, nor any effects on serum levels of LH, FSH or oestradiol, or on the oestrus cycle. There was no calculation of corresponding doses in mg/kg bw/day, and this would be needed to determine a NOAEL from this study. However, looking at other rat studies, a dose of 40 ppm would likely correspond to a dose of ~2 mg/kg bw/day. The study is not considered to justify a change in the NOAEL for fertility determined in the EU RAR because of the suggestive nature of the study. However, the results should be considered in conjunction with the other studies indicating a potential endocrine disrupting (ED) effect of DINP and with the studies included in the EU RAR. (see Sections 3.9.2, 3.9.3 and 3.10).

3.9.2 Developmental toxicity

In the EU RAR, several studies evaluating the developmental toxicity of DINP were reported. A decrease in live birth and survival indices was observed in a one-generation study, but not in a two-generation study in rats. A NOAEL of 622 mg/kg bw/day was determined based on the decrease in life birth and survival indices. In developmental studies, visceral and skeletal variations in the absence of maternal toxicity, or together with only slight maternal toxicity, were significantly increased and the NOAEL was determined to be 500 mg/kg bw/day. A decrease in mean offspring bodyweight was observed in one- and two-generation studies at the lowest dose tested and the LOAEL was estimated to be 159 mg/kg bw/day, the lowest value of the maternal dose range post-partum. This LOAEL was used for risk characterisation.

During the review new information on developmental toxicity was found. In one study (Borch *et al*, 2004), 750 mg/kg bw/day of DINP caused a reduction in testosterone content and production in testes of male rat foetuses on GD 21, but no statistical significant change in plasma testosterone levels was found. There was a tendency towards decreased plasma testosterone levels and elevated plasma LH levels. Also DEHP was tested in this study, and when comparing the effects DINP showed similar effects, but DINP seemed to have a lower potency. For DEHP, assessment of e.g. AGD and nipple retention was done in additional experiments

reported in the article, but for DINP this was not assessed. There was also an assessment of combined effects of DINP and DEHP. The results of this study could indicate an anti-androgenic action of DINP. In the rat study by Lee *et al* (2006; see also Section 3.9.1) a small but significant decrease in neonatal foetal bw as well as a decreased anogenital distance (AGD; PND 1) was seen in male offspring at all doses tested also after bodyweight correction, and an increase in AGD was seen in females, but only at the highest dose tested. There was no dose-dependent change in serum estradiol or testosterone levels (PND 7). In another rat study (Masutomi *et al*, 2003) some significant effects on organ weights (adrenals, uterus, brain) were seen in offspring after *in utero* and postnatal exposure to DINP, but only at the highest dose tested (20.000 ppm, corresponding to a maternal intake of approx. 1165 mg/kg bw/day during gestation, and approx. 2646 mg/kg bw/day during lactation). However, the changes were not consistent when comparing absolute and relative weights. At the same dose toxic effects on both dams and offspring were seen. There was also a decreased body weight gain in offspring (both sexes), as well as a decrease in testes weight, both absolute and relative. The decrease in testes weight could indicate an anti-androgenic action of DINP, but the dose level where it was seen was high, and the effect seemed to be transient as there was no significant change at final necropsy. A change in degeneration of stage XIV meiotic spermatocytes and vacuolar degeneration of Sertoli cells were observed in the testes. The changes were only slight/minimal, but were present in 80% of the animals. There were no effects on puberty onset or on oestrous cyclicity. In another study in rats by the same authors (Masutomi *et al*, 2004), no effects on offspring after maternal exposure to DINP were seen.

In the ECPI review on DINP, the validity of some of the studies is questioned. The NOAELs in most of these studies are higher than the ones determined in the EU RAR. In the study by Lee *et al* (2006) no calculation of doses in mg/kg bw/day had been done, but when comparing the doses with other rat studies, a dose of 40 ppm would correspond to approximately 2 mg/kg bw/day. The results of this study is not considered enough to justify a change in the NOAEL for developmental toxicity determined in the EU RAR and can only be used as additional information. However, the results should be assessed in conjunction with the other studies indicating a potential endocrine disrupting (ED) effect of DINP and with the studies included in the EU RAR (see Sections 3.9.3 and 3.10).

3.9.3 Endocrine disruption

In vitro tests reported in the EU RAR did not reveal any estrogenic activity of DINP. Neither any reproducible, dose-dependent estrogenic effects were seen in the uterotrophic assay/vaginal cell cornification assay. Regarding anti-/androgenic activities, there was one *in vivo* study in rats (Gray *et al*, 2000) reported in which males with areolas were observed, but no details on incidence were given. There were also indications of anti-androgenic effects seen and the DINP treatment group were reported to have malformations of testis, epididymis, accessory reproductive organs and external genitalia.

During the review several new studies evaluating potential effects of DINP on the endocrine system were reported. Masutomi *et al* (2003) studied the effects of DINP exposure in rats (400, 4.000 and 20.000 ppm) and concluded that the highest dose

tested caused degeneration of meiotic spermatocytes and Sertoli cells in the testis and decrease of corpora lutea in the ovary at week 11, although changes remained minimal or slight. In another study with a similar exposure (Masutomi *et al*, 2004), no effects of DINP on luteinising hormone (LH), follicle stimulating hormone (FSH) or prolactin levels were found. In an *in vivo* study (Hershberger assay in castrated male SD rats; Lee & Koo, 2007) there are indications that DINP may cause anti-androgenic effects. A decrease in seminal vesicle weight was seen at 100 and 500 mg/kg /d, and a decrease in levator ani/bulbocavernosus muscles (LABC) weights at 500 mg/kg bw/day. One new study (Main *et al*, 2006) was found where they studied whether phthalate monoester contamination of human breast milk had any influence on the postnatal surge of reproductive hormones in newborn boys as a sign of testicular dysgenesis. Mono-isononyl phthalate was found in the highest concentration of all phthalate monoesters included in the study. In the study a correlation was found between the metabolite MINP and LH levels, where MINP dose dependently increased serum LH. This was the only effect which reached statistical significance. There was a tendency towards a positive correlation between MINP and e.g. increasing total testosterone, and the LH:free testosterone ratio. No correlation with cryptorchidism was seen. Also two reviews (Lottrup *et al*, 2006; Swan, 2008) were found discussing this issue. However, in these reviews, no new information related to DINP and effects in humans other than the Main *et al* study was referred to. In an *in vitro* study by Ghisari & Bonefeld-Jorgensen (2009) no effects of DINP on the oestrogen receptor was found.

There is some new information indicating that DINP could be an ED substance, while in other studies no ED effects are seen. In their review of DINP, ECPI questions the validity of some of the positive studies, including the one by Gray *et al* included in the EU RAR, and their conclusion is that DINP should not be regarded as an ED. Our conclusion is that the new information would need a more in-depth assessment to evaluate the reliability and relevance of the studies. All the studies evaluating the potential endocrine disrupting (ED) effects of DINP should be assessed together, including the studies in the EU RAR.

3.10 Other effects

The thyroid was not identified as a target organ after DINP exposure in the EU RAR. Only slight and transient effects on thyroid weight were seen in a few studies. During the review no new studies evaluating the effects of DINP on the thyroid *in vivo* were found. However, some new information on ED of the thyroid *in vitro* was found. In one *in vitro* study assessing the thyroid hormone-like and estrogenic activities of several phthalates, all phthalates, including DINP, showed an effect on the TH-dependent rat pituitary GH3 cell proliferation (T-screen) (Ghisari & Bonefeld-Jorgensen, 2009). In another *in vitro* study (Wenzel *et al*, 2005) DINP caused an enhancement of iodide uptake, without causing cytotoxicity. In yet another study (Breous *et al*, 2005), no effect of DINP or DEHP on the sodium/iodide symporter (NIS; mediating the active transport of I- in the thyroid) was found, while other phthalates seemed to affect the NIS in different ways. No effects on the thyroid have been seen *in vivo*, other than slight and transient effects on thyroid weight. However, since effects on thyroid hormones have been seen also with other tested phthalates, our conclusion is that these studies would need further assessment.

3.11 Derivation of DNEL(s)/DMEL(s)

In one study (Lee *et al*, 2006) some effects were seen at a dose levels of 40 ppm and higher. In the study there was no information on the corresponding doses in mg/kg bw/day, but if comparing the doses to other rat studies a dose of 40 ppm would correspond to approximately 2 mg/kg bw/day. This is lower than the lowest overall NOAEL determined in the EU RAR. However, as mentioned earlier, the study can only be seen as supporting information and would not lead to a changed NOAEL. Concerning the different interpretations of the effect spongiosis hepatis and its relevance to humans, this would also need further assessment to reach a conclusion on the NOAEL.

4. Information on exposure and related risk

4.1. General population - Overall exposure

Several recent studies based on new biomonitoring data confirm the exposure of the general population to DINP, covering several countries all over the world, including the EU. In these studies primary and secondary metabolites of DINP were indeed measured in several body fluids (e.g. urine, breast milk, saliva, serum) of different samples of the general population. An oxidative metabolite of DINP was for instance found in 21% of the breast milk samples from a 62-women cohort in southern Italy (Latini G *et al*., 2009), as well as in Finnish and Danish cohorts' breast milk samples (Main KM *et al*, 2006). DINP metabolites were also reported in urinary samples of pregnant women in Israel (Berman T. *et al*, 2008). In Germany, the regular measurement of the concentration of DINP metabolites in urinary samples from adult subjects showed a continuously increasing exposure over the last 20 years; however, the estimated level of exposure (lowest median value was of 0.2 µg/kg bw/day in 1988 highest median value 0.4 µg/kg bw/day in 2003) were still well below the agreed NOAEL in the EU RAR for DINP (88 mg/kg bw/day) (Wittassek M *et al*, 2007).

However, it also appears that new available biomonitoring data (various scientific articles under the scope of the review and quoted in ECPI, 2009) show that actual exposure of the general population (6 years old and over) is two orders of magnitude lower as was estimated in the EU RAR. Industry also launched a new biomonitoring study which aims at providing a robust basis for the back calculation from human urinary metabolites to actual exposure. According to Industry (ECPI), the final report[18] will confirm that existing urinary metabolite data from human biomonitoring can be used for exposure estimation and that:

- exposures to DINP are very low and well within safe limits,
- previous indirect exposures were overestimated,
- supports the conclusions of the EU risk assessment report for DINP.

Over the last years, particular attention has been paid to prenatal exposure of foetuses and to exposure of neonates/infants, in particular via breast feeding; certain recent studies mention that foetal exposure may be a route of exposure of higher concern than post-natal exposure.

Industry (ECPI workshop, 2009) indicated that phthalates-containing PVC has now been replaced in all food-packaging applications (e.g. in printing inks). If it was confirmed, the contribution of this potential source may need to be updated compared to the assumptions made in the framework of the EU RAR. However, it has to be noted that the hypothesis of replacement of DEHP by DINP in food contact materials was already investigated in the EU RAR (Appendices A and B) where it was concluded that conclusion (ii) ("*There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already*") was appropriate.

[18] according to ECPI, the final report will be published in a peer-reviewed journal in a short notice

4.2. Occupational exposure

There is no new information from the documents made available to ECHA, except a report from industry indicating that new measurements of occupational exposure levels at PVC articles production plants show actual exposure 60 to 140 times lower than those indicated in the EU RAR (ECPI, 2007).

4.3. Children's exposure

a) Exposure and risks from toys and childcare articles

As already mentioned above, although restrictions on the use of DINP in toys and childcare articles which can be placed in the mouth as introduced in REACH, Annex XVII, entry 52 should have led in the EU to a halt in the selling of these DINP-containing articles as of 16 January 2007, there is no further information available on the compliance of producers and importers with this restriction, and whether DINP is still present in these categories of products as a result of non-compliance with the existing restriction.

In the context of this review, Industry submitted documentation aiming at clarifying the uncertainties and conflicting information which led to the application of the precautionary principle when the existing restriction on the use of DINP in toys and childcare articles was introduced (ECPI, 2009). In particular, a review of (new) scientific information concludes that, for a NOAEL of 88 mg/kg bw/day (as determined in the EU RAR; see Section 3.6), and on the basis of a better estimation of the actual exposure (observational study of children's mouthing activities, new estimation of migration rates, biomonitoring data), margins of safety of at least 1,000 can be calculated compared with 176 for exposure via consumer sources only, and 107 for total exposure including exposure via the environment as calculated in the EU RAR (ECPI, 2009). An in-depth assessment of all the quoted new scientific evidence would be needed in order to confirm whether or not the new data lead to significantly different exposure levels that would change the earlier conclusion on the need for and scope of a restriction. However, it can already be mentioned that the main differences in the updated exposure estimations come from new mouthing durations' estimations from new behavioural studies (Consumer Product Safety Commission - CPSC, 2002; Babich *et al*, 2004; Sugita *et al*, 2003 as cited in ECPI, 2009)[19] which were not available when the EU RAR was agreed (between 1.8 and 105 min/day, to be compared with 180 min/day in the EU RAR) and consideration of biomonitoring data. As a result, the overall daily intake of DINP for children between 6 and 36 months is estimated by Industry (ECPI, 2009) to be between 2.03 and 70.2 µg/kg bw/day which is substantially less than the values of 200 µg/kg bw/day from toys and childcare articles only, and 410 µg/kg bw/day in total (with exposure via the environment) that were reported in the EU RAR. It has to be noted that new migration studies have also been announced to become available soon (announced at ECPI workshop, 2009; study report not yet available).

[19] note that these studies were not made available to ECHA in the framework of this review, but cited in ECPI, 2009

Furthermore, the new health risk assessment for the particular sub-population of 2-year old children recently published by the Danish authorities (Danish EPA, 2009) estimates the baby changing mats/cushions to contribute to a very low extend to the overall intake in DINP (9.10^{-4} µg/kg bw/day).

b) Exposure and risks from the use in school supplies

In 2007, a study was conducted for the Danish EPA in order to evaluate the potential risk from exposure of children to school bags, toys bags, pencil cases and erasers. According to the available information, the only potentially significant source of exposure of children to DINP from these categories of products are erasers where the major route of exposure would be via ingestion (sucking and/or swallowing) under specific conditions (daily intake of a significant amount of product, during a long period of time) (Danish EPA, 2007; Force Technology, 2007).
As far as the exposure to DINP from erasers is concerned, it was estimated a maximum possible daily intake of DINP for a 20 kg-child (i.e. approx. 6 year old) of 0.23 mg/kg bw/day (through sucking) and 2.7 mg/kg bw/day (through ingestion), leading to margins of safety of respectively 68.2 and 5.56 (i.e. < 100 which is usually considered as an acceptable cut-off limit for the considered end-points) for a selected NOAEL of 15 mg/kg bw/day (effects on liver and kidneys). On the basis of these estimations, it was concluded that the ingestion and/or sucking/chewing of erasers could constitute a risk for a certain sub-population of children and under certain conditions (i.e one hour daily exposure in an everyday exposure for a long period of time). It has to be noted that, if compared to the combined exposure (including toys) estimated at 0.02 mg/kg bw/day (children of 3-15 years old) to 0.41 mg/kg bw/day (infants of 0.5 to 3-year old) (EU, 2003), this additional route of exposure would also lead to an increase of the total daily intake of DINP with a factor of 150 for children of 3-15 years old and of 7 for infants of 0.5 to 3-year old. However, it is worth noting that, as explicitly stated in the study report (Danish EPA, 2007), the above estimations contain many uncertainties. In particular, the measured concentrations of DINP in artificial saliva that are used as a basis for the health risk assessment in connection with sucking of an eraser are "*probably overestimated by a factor of six*"; a correction of the estimated daily intake of DEHP by the same factor would lead to an updated margin of safety of ca. 400, and an acceptable level of risk. Similarly, the authors admit themselves that swallowing large pieces of erasers, which appears as the potential main contribution to daily intake of DINP, is not expected to be recurrent over a long period of time, but rather a one-time event.
Furthermore, the NOAEL selected for these calculations (15 mg/kg bw/day) differs from e.g. the NOAEL in the EU RAR for DINP (88 mg/kg bw/day, for repeated dose toxicity for effects on the liver and kidneys unrelated to PP). Although it is not clearly stated in the report from the Danish EPA on which study the NOAEL of 15 mg/kg bw/day is based it seems to be on the same study as for the NOAEL in the "*CSTEE opinion of 30 October 2001 on the results of the Risk Assessment for human health effects*" (12 mg/kg bw/day and 15 mg/kg bw/day for spongiosis hepatis; benchmark dose used for calculation)[20]. Even though they occur at the same dose, the critical effects on which these different NOAELs are based seem to be different.

[20] for further details on the selection of NOAELs for repeated dose toxicity, please refer to paragraph 3.6

In its opinion of 17 October 2008 (SCHER, 2008), SCHER concluded that, due to several deficiencies in the study report, in particular in terms of migration estimations, no firm conclusions in terms of potential additional risks can be drawn, and considers that clarifications and/or further studies would be needed, and in particular a new migration study should be conducted. It has not been possible to conclude in the framework of the present review whether new migration studies conducted meanwhile could contribute to such clarifications.

c) Exposure and risks from other sources / Overall exposure and risks

There appears to be no new available information related to exposures and risks from other sources, and more generally to overall exposures and risks, which would be applicable to sub-population of children as a whole.
However, in their new health risk assessment for the particular sub-population of 2-year old children (Danish EPA, 2009), the Danish authorities propose an estimation of the overall exposure to DEHP, but also include estimations of contributions from indoor climate (air and dust), food, toys, and other consumer products such as erasers, baby changing mats/cushions, as well as newly investigated items like mittens, pacifiers, bath/shower mats and soap packaging. This section presents the results and conclusions of this study with regard to all identified potential sources of exposure to DINP. It has to be noted that Industry (ECPI, direct submission by e-mail to ECHA on 11 December 2009) already commented on the results of this study, and in particular on the estimations made of the migration rates from articles and exposure from food and dust, as well as on the absence of comparison of estimated exposures with the available biomonitoring data.
Firstly, migration studies reported in the framework of the Danish report show that DINP does not migrate out of all newly investigated products, i.e. stickers on mittens, coverage of pacifiers, soap packaging and bath mats in concentrations above the detection limit. Therefore, the potential contribution of these categories of products was not taken into account in the risk assessment. As already indicated in a previous section, the potential contribution of baby changing mats/cushions was nevertheless considered; however, this was shown to contribute to a very low extend to the overall intake of DINP (9.10^{-4} µg/kg bw/day).
As far as toys are concerned, calculations come to an estimated daily intake of DINP (oral ingestion + dermal intake) of 3.91 µg/kg bw/day, which appears to be much lower than the 200 µg/kg bw/day selected as the worst-case scenario in the EU RAR. However, it has to be noted that this difference mainly comes from the fact that in the EU RAR the calculations were based on data for children of less than 1 year old, and it was already indicated that for 2-year old children the estimated exposure to DINP in teethers, rattles and toys was 4.4-16.2 µg/kg bw/day, which is in the same order of magnitude as the new estimations. The new estimation is also based on a different migration value of DINP from toys and a different method to evaluate the actual surface of dermal contact/sucking. On the contrary, the same oral contact duration has been used in the new estimation as in the EU RAR (3 hours), which was not the case in the assessment made by Industry and reported under paragraph a) above.
As for the contribution from food, the new study uses a maximum exposure of 10 µg/kg bw/day on the basis of the European Food Safety Authority (EFSA, 2005) estimates, to be compared to a total of 2.3 µg/kg bw/day from food and an additional 156 µg/kg bw/day due to food-contamination via the environment.

Finally, the new Danish study (Danish EPA, 2009) estimates the potential contribution of erasers to the total burden of 2-year old children in DINP at 10.96 µg/kg bw/day, i.e. to a level similar to other major contributors such as food or indoor climate. However, it has to be noted that this estimation is still well below the estimation made in a previous study on the exposure of children from the use in school supplies (see paragraph b) above), as it is assumed here that 2-year old children are in contact with erasers only 1 minute a day, when any other sibling are doing their homework.
All in all, this new Danish study estimates the maximum daily intake for 2-year old children in DINP from the various sources listed above (including baby changing mats/cushions listed under paragraph a)) at 37.54 µg/kg bw/day (in winter; in summer: 31.23 µg/kg bw/day), to be compared to a value of 410 µg/kg bw/day estimated in the EU RAR for infants of 0.5 to 3 years old. Even though the respective scope of exposure sources in these two estimations are not completely matching, ECHA considers that they are reasonably comparable, given that the main known and agreed contributors (food, indoor climate and toys) to the exposure of 2-year old children have been considered in both studies, except for erasers. Even if the contribution of erasers in the daily intake of DINP is taken into account as suggested in this new study, the total daily intake is still estimated to be below 0.5 mg/kg bw/day leading to a margin of safety above 100 when compared to the NOAEL of 88 mg/kg bw/day as used in the EU RAR.

Furthermore, in addition to substance-specific risk assessments for individual chemicals, the Danish report proposes cumulative Risk Characterisation Ratios for several substances which have been grouped as anti-androgenic substances, oestrogen like substances and substances that may have both effects. Different ratios have been calculated for winter and summer scenarios, taking into account the total chemical burden via the following routes:

- ingestion of food,
- ingestion of dust (50 mg in summer / 100 mg in winter),
- dermal contact with toys (9 hours in summer / 6 hours in winter),
- contact with other objects than toys, i.e. moisturising cream, bath articles and other textiles than winter clothing,
- contact with sunscreen lotion (summer only),
- contact with rubber clogs (summer only),
- contact with jackets/mittens (winter only).

In that report, DINP has been considered by the Danish authorities as an anti-androgenic substance with regard to its effects on testicular weight in mice with a NOAEL of 276 mg/kg bw/day which is considerably higher than the lowest overall NOAEL of 88 mg/kg bw/day retained in EU RAR which is based on liver and kidney effects.

5. Conclusions and suggestions for further action

DINP appears to be overall used in much higher total volumes than those reported when the EU RAR was agreed. However, from the available information, there is not enough evidence of new significant categories of uses of DINP which were not already identified in the EU RAR. The new available information only shows that DINP is also used in some limited categories of school supplies and assimilated toys (erasers, (school) bags, pencil cases), as well as in some other specific consumer products to which children may be exposed (mittens, PVC-containing soap packaging, bath/shower mats, pacifiers' coverage, some (children) clothes). However, this information is based on a relatively limited number of products tested and DINP was finally detected only in a minor share of the tested articles. It has also to be noted that some of these products to which children may be exposed are childcare articles which can be placed in the mouth and should no longer be found on the market with a DINP content of more than 0.1% w/w. Therefore, there is a need to be cautious in drawing definitive conclusions in terms of the significance of the additional/new exposure. It has to be noted that the abstract of a study which was made available in the framework of this review indicates that, in general terms, the use of consumer products (that are not necessary specific to children) and the different indoor sources dominate the exposure to DINP of the general population, including children (Wormuth M *et al*, 2006). Various studies made available in the framework of this review also confirm the exposure of all groups of the general population to DINP.

As far as the hazard properties of DINP are concerned, there is some new information on the potential endocrine disrupting effects of DINP. In some studies DIDP has been shown to have endocrine disrupting effects, mainly anti-androgenic, while other studies are negative. Industry has questioned the validity of the positive studies and their arguments for this are presented in the ECPI review of DINP (2009). An in-depth assessment would be needed to draw a conclusion on the reliability and relevance of the results, but the results of these studies would most likely not lead to a change in the lowest overall NOAEL for DINP. Also the new information on spongiosis hepatis would need to be further assessed to draw a conclusion on the correct NOAEL for liver effects.

As for the risks from the use of DINP, particularly for children, the available information does not show that, in general, the above mentioned uses which were not specifically identified in the EU RAR would lead to major health concerns. For the use of DINP in school supplies, the available information tends to indicate that the only application which may raise concern is the use in erasers. However, there appears to be conflicting opinions on whether this use is actually of concern for children, depending on the estimation made of the probability and frequency of the exposure to DINP (via sucking/ingestion). Specific attention may also be needed for articles which may be categorised as toys, such as some erasers and so called "*toy bags*", and in particular on the correct application of the existing restrictions to these devices. As for the use of other articles to which children may be in contact, it appears from a recent study that DINP does not migrate out of these products in concentrations above the detection threshold (Danish EPA, 2009). Therefore, there is no new available information on the uses which were already assessed in the EU RAR which could lead to different conclusions in terms of risks. Indeed, even though there appears to be new information which may contribute to the clarification of some of

the uncertainties and conflicting information which played a role when introducing the existing restriction on the use of DINP in toys and childcare articles, in particular in terms of migration rates and children's mouthing behaviour, an in-depth assessment of the reported studies and access to some new study reports would be needed in order to be able to draw conclusions in terms of risks for children from the use of DINP-containing products, and consequently on the appropriateness of the existing restrictions and the possible need to amend them. Moreover, it has to be noted that some of these new study reports were not available to ECHA at the time when this review was performed. These reports may become available in the near future.
In conclusion, the available information does not bring evidence which would lead to different conclusions than those drawn in the EU RAR; a first tier overall assessment of the available information shows that there are no major risks from the current uses of DINP.

It has also to be mentioned that several scientific articles have indicated the need for further biomonitoring of phthalates in humans. After the EU RAR was agreed some new reports including biomonitoring data have been published and these may to a certain extent contribute to a better knowledge of the actual exposure of different groups of the population and the consequent potential risks for human health However, to date, ECHA does not have enough evidence to conclude that the latest biomonitoring data are sufficient to fill the gaps highlighted in the previous scientific articles.

ECHA considers that the available new information with regard to hazards and uses of and exposure to DINP does not bring a new perspective to the assessments which were carried out in the past and used as a basis for the current restrictions on DINP. Even though further in-depth assessment of the currently available information, and potentially further new information, would be needed to draw firm conclusions on the exact level of risks from certain uses of DINP, this information does not indicate the need for an urgent re-examination of the existing restriction on DINP.
Therefore, ECHA suggests to wait for all the registration dossiers to be submitted for DINP by the first registration deadline, after which the Commission may decide whether specific aspects of these registration dossier(s) should be assessed to confirm or contest the conclusion of this review, that there is no need to re-examine the current restriction. It is noted that substance evaluation under the REACH Regulation could be used, if further information to clarify any remaining concerns is deemed necessary.

It has also to be noted that the general topic of cumulative and/or synergistic effects of exposure to several chemicals, and in particular to several phthalates or other substances suspected to have endocrine disrupting effects, regularly appears through the documents which were under the scope of this review (e.g. in Borch *et al*, 2004; AFSSET, 2009; National Research Council, 2008, as cited in AFSSET, 2009; Ghisari & Bonefeld-Jorgensen, 2009; Tanida *et al*, 2009; Lottrup *et al*, 2006; Sharpe, 2008). It is suggested in some of these studies that, even though the exposure to individual phthalates may be not of concern for human health, except maybe for certain specific sub-populations, it cannot be excluded that the total exposure to all phthalates or to a phthalate together with other chemicals could raise health concerns, and this issue should therefore be further investigated. Furthermore, in its opinion of 6 February

2008 (SCENIHR, 2008), SCENIHR states that "*Combined exposure of different population and subpopulation is possible and may occur at different times or together. Due to the wide use of DEHP in society humans may be exposed from many different sources and exposed to other phthalates as well. It is obvious that combined exposure to DEHP, DBP, BBP, DIBP, and DINP having the same mechanism of action may potentially cause at least an additive effect. Combined exposure to DEHP and DINP had showed an additive effect (Borch* et al. *2004)*". The survey and health assessment of the exposure of 2 year-olds children to chemical substances in consumer products which was recently published by the Danish authorities (Danish EPA, 2009) also considers a cumulative risk assessment of potential endocrine-like substances, including DINP (as well as other phthalates DEHP, DBP, BBP and DiBP). The assessment of the potential combined effect of exposure to different phthalates goes beyond the scope of this evaluation of new scientific evidence concerning the current restrictions on DINP. Moreover, in the context of the Council discussion on this subject[21] the Commission has indicated that it will review the existing legislation in terms of its suitability to assess the effects of combined exposure.

[21] information from the Danish delegation on "*Combination Effects of Chemicals – children exposed to multiple endocrine disrupters*" dealt under "other business" at the meeting of the Council (Environment) on 21 October 2009 (Doc. ref. 14420/09 ENV 674 CHIMIE 79)

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