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-'isodecyl' phthalate (DIDP)

CAS No 26761-40-0 AND 68515-49-1
EINECS No 247-977-1 AND 271-091-4

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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 DIDP and the two other non-classified phthalates (i.e. DINP[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 DIDP.

Properties of (and risks from) DIDP are often investigated together with those of (from) DINP; some "*read-across*" from data on DINP to DIDP is sometimes suggested.

Therefore, as it is for DINP, most of the new available information on DIDP 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. Many new biomonitoring studies on phthalates in human body fluids as proxy to overall exposure are also reported.
Compared to other restricted phthalates, and in particular to DINP, it appears however that less new information on uses and potential exposure to DIDP has been made

[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-'isononyl' phthalate; CAS No 28553-12-0 and 68515-48-0 / Einecs No 249-079-5 and 271-090-9

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

available since the EU RAR was agreed. This is particularly the case for the use of DIDP in products for children, or other consumer products to which children may be exposed.

It appears from contacts with manufacturers of DIDP (industry) that the substance is currently, with DEHP and DINP, a phthalate of high commercial interest in Europe. A registration dossier was submitted[7] to ECHA for DIDP (CAS No 68515-49-1) in December 2009.

[7] by the lead registrant

2. Information on uses of the substance

Total use of DIDP:
Due to its long backbone carbon chain, DIDP 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 DIDP a "*general purpose*" phthalate, such as DEHP or DINP. DIDP (and DINP) also show a particular compatibility for uses requiring long term performance or durability. Therefore, DIDP 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), ECPI, 2007). The main applications of DIDP are similar to those of DINP.
DIDP is primarily used to soften PVC. HMW phthalates, and DIDP in particular, can be used in wire and cables (e.g. heat-resistant electrical cords), flexible PVC sheets and films, coated fabrics, automotive applications (e.g. synthetic leather for car interiors, car undercoating), building and construction applications (e.g. waterproofing), swimming pools, ponds liners and PVC flooring (EU, 2003; www.didp-facts.com; ECPI, 2010a). According to Industry, DIDP is also preferably used in car interior trims meeting the low fogging thresholds set by car manufacturers, usually not met by DINP or LMW phthalates (ECPI, 2010a). Available information also mentions the use of DIDP in some vinyl gloves. Information made available by Industry indicates that DIDP is preferably used in extruded and calendered articles (such as cables, profiles, roofing sheets, ponds liners, etc.); however, similarly to DINP, DIDP can also be blended into a paste (so-called "*plastisol*") for coating (such as tarpaulins, synthetic leather, flooring, wall covering, etc.) (ECPI, 2010; ECPI, 2010a).
Other typical uses of DIDP are in anti-corrosion and anti-fouling paints, sealing compounds and textile inks, but in much lower volumes (EU, 2003; www.didp-facts.com).

A consequence of the harmonised classification and labelling of LMW phthalates (Toxic to Reproduction, category 1B according to new CLP Regulation[8]) and the overall conclusions of the EU Risk Assessment Reports (EU RARs) 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 DIDP (ECPI workshop, 2009). This transfer can be illustrated by the following figures and facts:

- DINP, DIDP and DPHP[9] 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 use of plasticisers, for 50% for DEHP (ECPI workshop, 2009);

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

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

– 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, 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 and DPHP – which is a new substance developed during the last five years – has appeared on the EU market (CEFIC, 2010; CEFIC, 2010a). As far as DIDP is concerned, the current EU consumption for DIDP appears to be approximately the same as was reported in the EU RAR for this substance for the year 1994 (CEFIC, 2010);

– 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 identification of DEHP, BBP and DBP as Substances of Very High Concern (SVHC) 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.

One company has already registered (as lead registrant) the substance with CAS No 68515-49-1 / Einecs No 271-091-4 (*1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich*) under the REACH Regulation, in December 2009. However, many other legal entities pre-registered DIDP[10], and in particular the substance with CAS No 26761-40-0 / Einecs No 247-977-1 (*di-"isodecyl" phthalate*), with a first registration deadline on 30 November 2010.

Therefore, even though it has to be noted that such raw pre-registration statistics should be considered with all the necessary precautions, it already gives an idea on

[10] both CAS numbers have been pre-registered, for all the different tonnage bands. The precise distribution is as follows:

– di-'isodecyl' phthalate – CAS No 26761-40-0 / Einecs No 247-977-1 :
  - 1000 t : 27 pre-registrations
  - 100 – 1000 t : 49
  - 10 – 100 t : 84
  - 1 – 10 t : 342

– 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich - CAS No 68515-49-1 / Einecs No 271-091-4 :
  - 1000 t : 24 pre-registrations
  - 100 – 1000 t : 38
  - 10 – 100 t : 88
  - 1 – 10 t : 175

whether registration dossiers should reasonably be expected to be submitted or not. 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 substance, and in particular plastics recyclers who intended to benefit from Art. 2.7 (d) provisions of REACH.

Use in toys and childcare articles:
The restrictions on the use of DIDP 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 DIDP-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 DIDP in these categories of products.

The available information on the use of DIDP in toys and childcare articles appears to be limited and does not bring new information which may affect the exposure and risk assessments that were conducted in the framework of the EU Risk Assessment Report (RAR).

Information from Industry shows that plasticisers, and therefore potentially DIDP, 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.

It has also to be noted that phthalate-containing PVC was detected in some bags which can be categorised as toys rather than school supplies (Force Technology, 2007), without further investigations on which phthalate was concerned.

Use in school supplies:
In the framework of this review, no new precise information on the possible use of DIDP in school supplies was made available by stakeholders. In particular, a survey and health assessment of chemical substances in school bags, toy bags, pencil cases and erasers (Force Technology, 2007) performed for the Danish authorities did not specifically investigate the presence of DIDP in that category of articles. However, it has to be noted that, in the framework of this study, phthalate-containing PVC was found in four (4) pencil cases (out of seven (7) analysed in total) and elements of all (4) tested school bags, without further investigations on which particular phthalate was concerned (Force Technology, 2007).

Use in other articles for/in contact with children:
There is no information available on the potential use of DIDP in other articles for/in contact with children. In particular, the 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) - which brings information related to other phthalates, and in particular DINP - does not investigate the presence and the related risks of DIDP in such products.

Use in medical devices:
According to Industry (ECPI workshop, 2009), DIDP is not used in medical devices such as medical tubing and blood bags. Industry also mentions that DIDP is not included in the European Pharmacopeia 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, and in particular their secondary (oxidized) metabolites and their possible use as reliable and appropriate biomarkers for biomonitoring and exposure assessment purposes. However, neither new information on toxicokinetics specifically applied to human health hazards assessment, nor specific information related to DIDP's metabolites was identified during the review.

3.2 Acute toxicity

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

3.3 Irritation

No new information assessing irritation was found during this review.

3.4 Corrosivity

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

3.5 Sensitisation

In the EU RAR (EU, 2003) several studies on the sensitising effects of DIDP are reported. One study (according to Buehler) gave a clear positive response, but the results were questioned due to a surprisingly strong irritant effect. Two other tests (one Buehler test and one maximisation test according to Magnusson and Kligman) were negative, but presented several weaknesses. Human patch tests performed did not show any positive reactions. Only one case has been reported, where DIDP gave rise to allergic contact dermatitis in one woman. It was concluded in the EU RAR that the weight of evidence was insufficient to justify a classification of DIDP as sensitising.

During the review, some new information was found. However, some of the information was of a more general nature, not evaluating the correlation between specific phthalates and the sensitizing potential and is not described here in further detail. In a review and meta-analysis of several of the sensitizing studies on DIDP and other phthalates (Jaakkola & Knight, 2008), the conclusion was that there are some evidence which support 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 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, it is difficult to draw any conclusion on specific phthalates and their individual contribution to the effects seen. In one study (Larsen *et al*, 2002) adjuvant effects of DBP, DNOP, DINP and DIDP were studied in a screening model in mice. The evaluation of adjuvant effect of DIDP on the IgG1 level after two boosters gave rise to ambiguous results, and a final conclusion about the adjuvant effect of DIDP on the IgG1 production after two boosters could not be

reached. However, it was concluded that all evaluation parameters suggested that DIDP is a weaker adjuvant than DNOP, DEHP and DINP. After one booster, DIDP showed a significantly increased IgE production in the highest exposure group (2000 mg/ml), indicating concentration-dependent effects.

In conclusion, there are some indications of a sensitizing effect of DIDP, but the new information found during this review is not considered enough to change the conclusion made in the EU RAR.

3.6 Repeated dose toxicity

The liver was identified as the target organ in the EU RAR. The NOAELs from rat studies were derived from liver effects related to peroxisome proliferation (PP), a mechanism which is species-specific and considered to be of low, or no, relevance to humans. In a dog study (Hazelton laboratories, 1968; EU, 2003), a NOAEL of 15 mg/kg bw/day was identified and although the study had several limitations it was considered relevant for risk characterisation. The dog also seemed to be a more relevant species for human risk assessment since it is non-responsive/refractory to PP. From the rat studies a NOAEL of 60 mg/kg bw/day was identified, based on increased liver weights in female rats. It was concluded that the effects seen did not justify a classification of DIDP with Xn; R48.

During the review one new study on the long-term effects of DIDP was found (Cho *et al*, 2008). The relative kidney and liver weights of both male and female rats exposed to 8000 ppm were significantly increased compared to the controls. No treatment-related changes were observed in the relative organ weights for the spleen, testes, ovary, brain, adrenal glands and heart. The rats in this study were exposed to dose levels of 400 – 8000 ppm in diet. However, the calculated dose levels in mg/kg bw/day (0.53 – 13.36 and 0.85 – 17.37 mg/kg bw/day in females and males, respectively) are very low compared to calculated dose levels normally seen in other studies, which makes them questionable and it is hard to draw any conclusions on NOAELs from this study. According to Industry (in a Chemical Safety Report submitted specifically in the framework of this review (CSR; 2009)) they have been in contact with the main author of the Cho *et al* article who has confirmed that the calculated doses are incorrect. The correct calculated average daily doses for 400, 2000, and 8000 ppm DIDP for male rats should, according to the CSR, be 21.9, 110.3 and 479.2 mg/kg/d, and for female rats 22.9, 128.2 and 619.6 mg/kg/d.

Industry (CSR; 2009) did not carry forward the NOAEL from the dog study (15 mg/kg bw/day) due to the limitations of the study, and considers a NOAEL of 150 mg/kg bw/day to be correct based on a 90-day study in rats[11]. This rat study was included in the EU RAR. The limitations of the dog study were recognised and

[11] in the CSR (2009) the NOAEL of 60 mg/kg bw/day from a rat study, used in the EU RAR, was not carried forward. The argument for this was that the underlying data were not available for evaluation, because the test substance was described by a CAS number that is different from the CAS number that describes the substance for which the document was developed, and because the results are not consistent with other, more recent studies. As previously mentioned, there are two existing CAS numbers available for DIDP and this review report, as well as the EU RAR, covers both of these CAS numbers without differentiating between them. Hence the NOAEL of 60 mg/kg bw/day is considered valid.

mentioned in the EU RAR but the NOAEL (15 mg/kg bw/day) was still considered relevant and used for risk characterisation. It was also mentioned that the dog appeared to be, in this case, a more relevant species for human risk assessment since the dog is considered not responsive or refractory to peroxisome proliferation. No new information has been found during this review that would lead to a different conclusion on the study and the NOAEL is considered to be relevant with the same note on study limitations as mentioned in the EU RAR. Due to the limitations in the dog study, in the EU RAR also a NOAEL of 60 mg/kg bw/day was identified from a 90-day rat study, based on increased liver weights in female rats and this NOAEL is also considered valid. The European Food Safety Agency (EFSA, 2005), in its opinion on the use of DIDP in food contact materials, supports the NOAEL of 15 mg/kg/d from the dog study. This NOAEL was the lowest overall NOAEL determined for effects of DIDP in the EU RAR.

3.7 Mutagenicity

In the EU RAR, it was concluded that DIDP is not mutagenic either *in vitro* or *in vivo*.

During the review, no new information on assessing mutagenic effects of DIDP was found.

3.8 Carcinogenicity

In the EU RAR, two *in vitro* studies assessing the transformation potential of DIDP were reported. One of these studies was negative and one was positive at the highest concentration tested (1 µl/ml). No long-term carcinogenicity studies *in vivo* were available. It was concluded that DIDP is likely to act as a PP, similar to what has been seen for DINP and DEHP in carcinogenicity studies, and that the relevance for humans is hence thought to be low.

During the review, one new study on the long-term effects of DIDP on rats was found (Cho *et al*, 2008). The authors concluded that no treatment related neoplastic lesions were observed in this study. The incidences of mononuclear cell leukemia (MNCL) in the male and female rats exposed to 8000 ppm were significantly increased compared with the vehicle control, but were within historical ranges of the controls. The C-cell adenomas of the thyroid gland were significantly decreased in the male exposed to 400 ppm and the females exposed to 2000 and 8000 ppm compared with the controls. The incidence was within the historical ranges. As mentioned in Section 3.6, the calculated doses from ppm to mg/kg/d were, according to the CSR submitted by Industry, incorrect in the article. However, the data does not seem to support a changed conclusion compared to the EU RAR.

3.9 Toxicity for reproduction

3.9.1 Fertility

In the studies reported in the EU RAR, there was no indication of any effects on fertility or reproductive organs in pubertal or adult animals.

During this review, no new information that would lead to a different conclusion compared to the one in the EU RAR was found.

3.9.2 Developmental toxicity

In the EU RAR, DIDP was concluded to have developmental toxic effects since in both the 2-generation studies reported a decrease in survival indices was observed. A NOAEL of 0.06% (~33 mg/kg bw/day) was determined and taken into account in risk characterisation. In developmental studies, an increased incidence of skeletal variations was seen at 1,000 mg/kg/d together with slight signs of maternal toxicity and this lead to a NOAEL of 500 mg/kg bw/day. In one two-generation rat study, body weight decrease was observed in offspring partly related to lactation at the highest dose of 0.8% and this lead to a NOAEL of 0.4% (ca 253-761 mg/kg bw/day depending on when in the dosing period the values were calculated). Those NOAELs were considered for risk characterisation. The effects seen were not considered severe enough to justify classification.

During this review, no new information was found. The conclusion, and the lowest NOAEL, from the EU RAR has been confirmed in two other reports, one from the National Toxicology Program, Center for the evaluation of risks to human reproduction (NTP CERHR, 2003) and one from Agence française de sécurité sanitaire de l'environnement et du travail (AFSSET, 2009). These reports, however, do not include any new information compared to the EU RAR. The NOAEL of 33 mg/kg/d was also considered by Industry (CSR, 2009), although it is argued that the effects may be secondary to maternal toxicity.

3.9.3 Endocrine disruption

Several *in vitro* and one *in vivo* test investigating the estrogenic activity of DIDP were reported in the EU RAR, and all of them were considered negative. It is stated in the EU RAR that *in vitro* tests evaluating the possible anti-androgenic mechanism of DIDP were ongoing when the RAR was written. Some alterations in male reproductive development, seen in one of the 2-generation studies, indicated a tendency for disturbance of male sexual differentiation through an endocrine-mediated mechanism: sex ratio (male/female) change (but only at the lowest dose in P2; 41.7/58.3% in treated versus 54.3/45.7% in controls), decreases of absolute but not relative testes weight in F1 and F2 offspring, cryptorchidism (3.25%) which usually occurred at a lower incidence (0.251%). Delay in body weight gain was considered responsible of the two later effects. No effects on any developmental landmarks were seen in the other 2-generation study. It was concluded that overall no ED related effects were observed for DIDP.

During the review, some new information on the potential ED effects of DIDP was found. In one *in vitro* study (Ghisari & Bonefeld-Jorgensen, 2009) investigating the thyroid hormone (TH)-like and estrogenic activities of a range of widely used plasticizers and phenols, it was found that a majority of the tested compounds, including DIDP, affected the TH-dependent rat pituitary GH3 cell proliferation (T-screen). No estrogenic activity of DIDP was seen. In another *in vitro* study (Harris *et al*, 2007) there were indications that DIDP, and other phthalates tested, may negatively affect the sulphate supply pathway which could potentially lead to

increased levels of free hormones and decreased capacity for detoxification via sulphate conjugation. A potential negative effect on the sulphate pathway was also seen in an *in vitro* study by Turan *et al* (2005). In an *in vitro* study by Krüger *et al* (2008), DIDP was found to affect the aryl hydrocarbon receptor (AhR) but not the androgen receptor (AR). In an *in vivo* study (Hershberger assay in castrated male SD rats; Lee & Koo, 2007) ventral prostate weights and seminal vesicles were significantly decreased at a dose of 500 mg/kg/d of DIDP, which could indicate an anti-androgenic action. Similar effects were seen in animals treated with DEHP and DINP, but already at lower doses (DEHP: ventral prostate weight at 20 mg/kg/d and above; seminal vesicle weight at >100 mg/kg/d; DINP: seminal vesicle weight at >20 mg/kg/d). Our conclusion is that there are some indications that DIDP may exert anti-androgenic effects, although probably has a lower potency compared to for instance DEHP. No anti-androgenic activity has been shown *in vitro*. There is no data indicating an estrogenic activity. The new studies indicating a potential ED effect of DIDP would have to be further assessed regarding their reliability and the relevance of the findings to humans, and should be assessed together with the studies included in the EU RAR. However, the results from the *in vivo* study would most likely not lead to a lower overall NOAEL compared to the one determined in the EU RAR.

3.10 Other effects

In an *in vitro* study by Ghisari & Bonefeld-Jorgensen (2009; see also Section 3.9.3) DIDP affected the TH-dependent rat pituitary GH3 cell proliferation (T-screen). DIDP and other phthalates tested were shown to significantly enhance iodide uptake at concentrations between 10^{-4} M and 10^{-3} M in an *in vitro* study (Wenzel *et al*, 2005), due to modulation of sodium/iodide symporter (NIS) mediated iodide uptake activity.

Also for other phthalates there are indications of similar effects on the thyroid, but the studies would need further assessment to conclude on the reliability of the studies as well as the relevance of the findings to humans. Only *in vitro* studies were found and no NOAEL could hence be determined.

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

No new information was found during this review that would lead to a lower overall NOAEL than the one determined in the EU RAR (15 mg/kg bw/day).

4. Information on exposure and related risk

4.1. General population - General information/background exposure

Compared to other phthalates, and in particular DEHP and DINP, it appears that only a few biomonitoring studies aim at evaluating the presence of primary and secondary metabolites of DIDP in body fluids. However, one study reports the detection of a metabolite of DIDP in urine of pregnant women in Israel, however in a lower frequency (in 68% of the members of the cohort) and lower concentrations if compared to the metabolites of other phthalates such as DEHP, DBP or DINP (Berman T. *et al*, 2008).

Industry (ECPI workshop, 2009) indicated that phthalates-containing PVC has now been replaced in all food-packaging applications (e.g. from 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. Moreover, it has to be noted that the hypothesis of replacement of DEHP by DIDP in food contact materials was already investigated in the EU RAR (Appendices A and B) where it was concluded that, depending on the study selected to determine the NOAEL for repeated dose toxicity (rat or dog), conclusion (ii) ("*There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already*") or (iii) ("*There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account*") would apply for infants and newborns.

4.2. Occupational exposure

There is no new information from the documents made available to ECHA.

4.3. Children's exposure

a) <u>Exposure and risks from toys and childcare articles</u>

As already mentioned above, although restrictions on the use of DIDP 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 DIDP-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 DIDP 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 DIDP in toys and childcare articles was introduced. This information package contained on the one

hand a Chemical Safety Report[12] (CSR, 2009), and on the other hand a "*Statement relevant to the re-evaluation of DIDP in toys and childcare articles as required by Directive 2005/84/EC*", which includes an updated risk characterisation for the use of DIDP in toys and childcare articles (DIDP Risk Characterisation, 2009). On the basis of a DNEL for repeated dose toxicity of 750 µg/kg bw/day[13], and an exposure of 70 µg/kg bw/day for children under 3 years age using read across from DINP for exposure estimations (exposure, migration and biomonitoring studies on DINP), a margin of safety[14] of 2,142 is calculated by Industry, which is to be compared with a value of 176 for exposure via consumer sources only, and a value of 107 for total exposure including the exposure via the environment as calculated in the EU RAR (DIDP Risk Characterisation, 2009). An in-depth assessment of all the quoted new scientific evidence, as well as the pertinence to use read across from DINP, would be needed in order to confirm that a comparison can actually be made with the previous assessments, and therefore to be able to draw conclusions on the appropriateness of the existing restrictions and the possible need to amend them. However, as mentioned for DINP, it can already be added that the main differences in the updated exposure estimation 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)[15], 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 from considering the biomonitoring data. As a result, the overall daily intake of DINP, and therefore by analogy for DIDP, for children between 6 and 36 months is estimated by Industry to be between 2.03 and 70.2 µg/kg bw/day, to be compared with 227 µg/kg bw/day from toys and childcare articles only, and 400 µg/kg bw/day in total (including exposure via the environment) as was estimated in the EU RAR (ECPI, 2009).
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).

b) Children - Exposure and risks from the use in school supplies

According to the available information, the presence/use of DIDP in school supplies (see "*2. Information on uses of the substance*") has not been specifically investigated. Therefore, no conclusion could be drawn regarding the potential exposure of children to DIDP from school supplies, and the related risks. However, it has to be noted that in erasers, which have been identified as the sub-category of school supplies whose use may be the only one raising health concerns for children (SCHER, 2008), only DEHP and DINP were detected in significant concentrations (up to 70% w/w). Other phthalates, such as for instance DIDP, appear to be present in erasers only in small

[12] "*Chemical Safety Report for 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich (EC No: 271-091-4 / CAS No: 68515-49-1)"*

[13] it is important to note that a DNEL of 750 µg/kg bw/day corresponds to a NOAEL of 150 mg/kg bw/day (with an assessment factor of 200), which is not consistent with the NOAEL used in the EU RAR – see Section 3.6 of this report for further details

[14] note that 100 is usually considered as an acceptable cut-off limit for the considered end-points

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

amounts, although further details on what this precisely means in terms of concentration ranges are lacking (Force Technology, 2007).

5. Conclusions and suggestions for further action

Although the *High Molecular Weight* phthalates appear to be nowadays overall used in much higher total volumes than those reported when the EU RAR for some of these substances were agreed, Industry indicates that the current EU consumption for DIDP is approximately the same as was reported in the EU RAR for this substance for the year 1994 (CEFIC, 2010). Moreover, from the available information, there is no evidence of new categories of uses of DIDP which were not already identified in the EU RAR.

As far as risks from the use of DIDP are concerned, particularly for children, the available information does not show that there are uses which were not specifically identified in the EU RAR that would lead to major health concerns. Similarly, there is no new available information on the uses which were already identified in the EU RAR which could lead to different conclusions in terms of their 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 DIDP 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 DIDP-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 DIDP.

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 previous scientific articles.

ECHA considers that the available new information with regard to hazards and uses of and exposure to DIDP 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 DIDP. 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 DIDP, this information does not indicate the need for an urgent re-examination of the existing restriction on DIDP.

Therefore, ECHA suggests to wait for all the registration dossiers to be submitted for DIDP[16] by the first registration deadline, after which the Commission may decide whether specific aspects of this(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. However, none of them reported specifically on DIDP.

[16] note that a registration dossier has been received for only one of the two CAS/Einecs numbers which are covered by the current restriction

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