



**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-n-octyl phthalate (DNOP)**

**CAS No 117-84-0
EINECS No 204-214-7**

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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/EEC¹ (i.e. DEHP², DBP³ and BBP⁴) the restriction covers the placing on the market and use in any type of toys and childcare articles. For DNOP and the two other non-classified phthalates (i.e. DINP⁵ and DIDP⁶) 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 DNOP.

The new available information related to DNOP is limited: within the information submitted by stakeholders to the European Commission or ECHA, there is no precise information available on the possible current uses of DNOP in EU, nor any study specifically dedicated to the exposure to DNOP and potential related risks. Some information on the health hazard properties of DNOP was identified both in the submitted information and in the specific literature search performed by ECHA.

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

2. Substance identity

From the available information and information further provided by Industry (European Council for Plasticisers and Intermediates, ECPI workshop, 2009), it appears that there may be confusion between “di-n-octyl phthalate” (DNOP; CAS No 117-84-0 / EINECS No 204-214-7) and “*di-octyl phthalate*” (DOP), which is usually claimed to be an alternative (synonym) name for DEHP (www.dehp-facts.com, “About DEHP”).

In the European chemical Substances Information System (ESIS, <http://ecb.jrc.ec.europa.eu/esis/>), the name of the substance to which CAS No 117-84-0 and EINECS No 204-214-7 are associated is “*dioctyl phthalate*”, without any further details on the precise structure of its alkyl chains, apart from the proposed chemical structure (which is with linear (“*n*”) alkyl chains, but just indicative).

It has also to be noted that another name and CAS No have been used for DNOP: until it was deleted and replaced by CAS No 117-84-0, CAS No 8031-29-6 was also used by Industry, associated with the substance name “*1,2-Benzenedicarboxylic acid, 1,2-dioctyl ester*” and with several synonyms like “*Di-n-octyl phthalate*” or “*DNOP*”.

3. Information on uses of the substance

As further described in the following paragraphs, the available information on current uses of DNOP in EU appears to be very limited and contradictory. Compared to the other phthalates, there is almost no data on DNOP specifically and in particular on its uses, in the available sources of information.

Although Industry (the European Council for Plasticizers and Intermediates, (ECPI workshop, 2009)) indicate that, to their knowledge, there is currently no commercial use of DNOP within EU, the results of a new survey on the exposure of 2 years-old children to chemical substances in consumer products conducted for the Danish Environmental Protection Agency (EPA) (Danish EPA, 2009) show that DNOP has been found in some soap packaging products; in that case, a clear reference to CAS No 117-84-0 is made.

Furthermore, information submitted by third parties in the context of this review reports on the detection of DNOP in the environment and house dust samples in Europe (Bulgaria) as well as in toys that can be found on the US market (California), as reported by the Agence française de sécurité sanitaire de l'environnement et du travail (AFSSET, 2009). DNOP metabolites were also reported to have been found in urinary samples of pregnant women in Israel (Berman T. *et al*, 2008). However, none of these sources provide the CAS No to which the substance they refer to should be associated; therefore, confusion on the substance identity cannot be excluded.

Moreover, it has to be noted that the substance with CAS No 117-84-0 (Einecs No 204-214-7, and named “*dioctyl phthalate*”) has been pre-registered under REACH by ca. 350 legal entities (including Only Representatives having created several legal entities), with a first registration deadline on 30 November 2010. If registration(s) will be received⁷, some clarifications and further information on the current uses of this substance may be brought by the registrant(s) by the end of this year.

In addition, the substance associated with CAS No 8031-29-6 (and no existing Einecs No) and called “*di-n-octyl phthalate*” (see “*2.Substance identity*”) has been pre-registered by ca. 500 legal entities; however, a great majority of the pre-registrants for this substance are plastics recyclers and, although one company (with different subsidiaries) indicated an envisaged registration deadline of 30 November 2010, the highest tonnage band pre-registered was 100 – 1,000 t/y (associated in the REACH Regulation to 31 May 2013 as deadline for registration). At the time when this review report was finalised no registration dossier had been submitted to ECHA for DNOP.

⁷ It has to be noted that raw pre-registration statistics should be considered with all the necessary precautions, even though it already gives an idea on whether registration dossiers should reasonably be expected to be submitted or not. In the specific case of DNOP, it has to be noted that at pre-registration step, several legal entities informed ECHA 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.

4. Information on human health hazards

In studies on health hazard effects there is as well confusion on the substance identity, in some cases. In the review references have only been considered if it is specified that the substance is equal to di-n-octyl phthalate (DNOP). If di-octyl phthalate (DOP) is mentioned in the study, the study has only been considered if the CAS number corresponding to DNOP is specified.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The toxicokinetics of DNOP in female adult Sprague Dawley (SD) rats was studied by Silva *et al*, 2005. The excretion of DNOP metabolites in urine after oral administration (300 mg/kg) was monitored, and phthalic acid (PA), mono-n-octyl phthalate (MNOP), as well as the major DNOP metabolite mono-(3-carboxypropyl) phthalate (MCP) were found. They also identified five additional urinary DNOP oxidative metabolites based on their chromatographic behaviour and mass spectrometric fragmentation pattern, which were postulated to be mono-carboxymethyl phthalate (MCMP), mono-(5-carboxy-n-pentyl) phthalate (MCPeP), mono-(7-carboxy-n-heptyl) phthalate (MCHpP), and isomers of mono-hydroxy-n-octyl phthalate (MHOP; e.g., mono-(7-hydroxy-n-octyl) phthalate) and of mono-oxo-n-octyl phthalate (MOOP; e.g., mono-(7-oxo-n-octyl) phthalate). The urinary excretion of DNOP metabolites followed a biphasic excretion pattern. The metabolite levels decreased significantly after the first day of DNOP administration although MCP, MCHpP, MHOP, and MOOP were detectable after 4 days. They also studied the *in vitro* metabolism of DNOP and MNOP by rat liver microsomes, and found that DNOP produced MNOP, MHOP, and PA *in vitro* whereas, MNOP produced MHOP and PA *in vitro* at detectable levels.

No further information on toxicokinetics of DNOP was found during the review.

4.2 Acute toxicity

In the National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) Monograph on DNOP (2003), LD₅₀ values for mice and rats were given as 15 g/kg bw and 53.7 g/kg bw, respectively. Dermal LD₅₀ values were 75 mL/kg bw for guinea pigs. The doses are very high and our conclusion is that DNOP can be considered to be of low acute toxicity.

4.3 Irritation

No information on the irritation potential of DNOP was found during this review.

4.4 Corrosivity

No information on the corrosive potential of DNOP was found during this review.

4.5 Sensitisation

Some studies assessing the sensitizing potential of DNOP are available. A review and meta-analysis have been done on several of the sensitizing studies on DNOP and other

phthalates (Jaakkola & Knigth (2008). Their general conclusion it that there are some evidence which support the hypothesis that phthalate emissions from PVC materials increase the risk of asthma and allergies, 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 the same article it is reported that in one study, subcutaneous injection (s.c.) of MnOP to mice, provoked a statistical increase in antibodies in response to one booster of ovalbumin (100 µg/mL: increase in IgE; 10 µg/mL: increase in IgG). In another similarly designed study, 2.000 µg/mL of DnOP gave an increase in IgG1 and IgE levels. The extent of adjuvancy provoked by individual phthalates has been shown to be structure related, and mono phthalates with 8 (MEHP and MnOP) or 9 (MiNP) carbons caused a greater increase in antibodies than those with 4, 7 or 10. It is also reported that in another of the evaluated studies, the degree of increase of antibodies was generally shown to be concentration-dependent and that DNOP has been found to produce a concentration-dependent increase in production of IgG1 but not IgE. It is also reported that one *in vitro* study has shown that phthalates with 8 carbon atoms alkyl side chain length (DEHP and DNOP, including their respective metabolites MEHP and MNOP are the strongest histamine release potentiators.

There are indications of a potential sensitizing activity of DNOP, but before a conclusion can be drawn, an in-depth evaluation of the original studies is needed to evaluate the reliability and relevance of the results.

4.6 Repeated dose toxicity

In the NTP-CERHR Monograph (2003), four studies in rats are mentioned. It is reported that DNOP had no effects on testes weight or gross appearance of the testes, kidney or pancreas. Two of the studies assessed effects after three weeks of DNOP exposure. Liver weight was increased with concurrent liver histology and biochemistry changes seen. There was biochemical evidence for peroxisome proliferation (PP), a mechanism considered to have either low or no relevance for humans, but also other liver enzymes were affected. DNOP induced hepatic lipid accumulation and PP similar to DNHP, but dissimilar to DEHP. DEHP caused e.g. greater increase in liver weight and the biochemical evidence shows that PP occurred earlier with DEHP compared to DNOP, and was about 7-fold higher. The PP values seen after DNOP exposure were about twice those of the controls. There were also liver effects that indicate other types of liver damage, not related to PP. Thyroid effects included a decrease in serum thyroxine (T4) and microscopic effects indicating thyroid hyperactivity. There were no effects on serum triiodothyronine (T3) levels. The LOAEL was determined to be ~1.821 mg/kg bw/day. In another study, no increase in peroxisome enzyme activity was seen after two weeks exposure to doses of 1.000 and 2.000 mg/kg bw/day. A small increase in liver weight was seen in the study. In a 13-week study, no effect was seen on organ or body weight at doses up to 350 (males) and 403 (females) mg/kg bw/day. At the highest dose, liver and thyroid effects were observed. DEHP was used as a positive control and was found to induce similar effects to those seen in the high-dose DNOP group. However, DEHP also induced PP and some biochemical changes and effects on reproductive organs which were not seen with DNOP.

Also some other information on effects of DNOP after repeated dose exposure was found. In the report from AFSSET (2009) on DNOP, similar conclusions as the ones made in the NTP-CERHR Monograph were drawn. The AFSSET report contains some references that were not included in the NTP Monograph. AFSSET concludes that DNOP does not appear to behave like other phthalates when it comes to PP, and hence the relevance for humans may be higher. They also report that DNOP may cause adverse hepatic effects in individuals living e.g. in the vicinity of hazardous waste sites if DNOP is present at sufficiently high levels in e.g. water consumed. In a report from the Agency for Toxic Substances and Disease Registry (ATSDR; 1997), a study where reductions in the size of thyroid follicles and mild decreases in colloid density was seen were cited.

A more in-depth evaluation of the relevant studies would be needed to conclude on the effects of DNOP after repeated dose exposure, and to establish NOAELs/LOAELs. It should however be noted that DNOP seems to have different mechanisms for inducing liver effects compared to other phthalates which exert their effects on the liver through the PP mechanism, and that the human relevance of the liver effects seen in rodents may hence be higher compared to other phthalates.

4.7 Mutagenicity

There are both *in vivo* and *in vitro* studies on the mutagenic potential of DNOP available, but most of these are studies where only mixtures containing DNOP have been tested. Negative results have been seen in some of these studies, and in other studies the results have been inconclusive. No tests where only DNOP has been tested are reported in the NTP monograph and they only state that mixtures containing DNOP have not shown conclusive evidence of mutagenicity. In the AFSSET report it is concluded that the results of microbial testing indicates that DNOP is not a mutagen, without further specification of the tests performed.

4.8 Carcinogenicity

In the AFSSET report the conclusion is that based on available studies, there are no indications that DNOP causes cancer in humans, and that IARC or EPA has not classified DNOP as a carcinogen. In the ATSDR report (1997) it is concluded that there is some data suggesting that DNOP may promote preneoplastic lesions in the rat liver, probably by a mechanism that does not rely on PP. Further evaluation of the studies would be needed to conclude on this.

4.9 Toxicity for reproduction

4.9.1 Fertility

In the NTP monograph, some studies on reproductive toxicity are reported. In a continuous breeding design in mice no effects were seen (exposure up to 7500 mg/kg/d; this was not a true multi-generation study since an effective evaluation of the second generation was not performed). In a sub-chronic study in rats, no histological effects on reproductive organs were seen after exposure to doses of up to 350 or 403 mg/kg/d for males and females, respectively. No testicular lesions were

seen in a study in male rats after exposure to 2800 mg/kg/d for 4 days. The conclusion by NTP is that DNOP is not likely to affect the human reproductive system. A NOAEL of 7500 mg/kg/d in mice and 350 mg/kg/d in rats was determined. Since no effects on fertility were seen, no LOAEL could be established. Some studies suggest that DNOP produces some effects on the male reproductive system similar to those seen with other (short-chain) phthalates, but that DNOP is most likely much less potent. Also AFSSET (2009) and ATSDR (1997) conclude in their reports that the potential of DNOP to cause adverse reproductive effects should be considered to be low. In a cohort study in Mexican women (Meeker *et al*, 2009), mean urine concentrations of some phthalates, including mono(3-carboxylpropyl) phthalate (MCP; a metabolite of DNOP, but also of DBP), were higher in women who subsequently delivered preterm. The authors concluded that there may be an association between some phthalates and preterm birth, and that additional research, including larger human studies and experimental studies, is warranted to further investigate the relationship between phthalate exposure and preterm birth. Also, since MCP is a metabolite of both DNOP and DBP, no firm conclusion on the potential contribution of DNOP to the preterm birth in these women can be drawn based on this study and it can only be seen as additional information.

4.9.2 Developmental toxicity

In the NTP Monograph as well as in the information from AFSSET (2009) and the ATSDR report (1997), it is said that DNOP has been shown to cause some developmental toxicity, but only very high doses have been tested. For example, in one study an increase in malformations was seen after i.p. injection of 4890 mg/kg/d of DNOP (it should be noted that i.p. injection is not the preferred way of administration). It is also said that the limitations in the study design did not provide a basis for determining a dose-response relationship, nor any NOAELs or LOAELs. The available data were not considered enough to conclude that DNOP is not a developmental toxicant, but they indicate that DNOP has a very low potential to induce adverse developmental effects.

4.9.3 Endocrine disruption

In the AFSSET report it is reported that DNOP has been shown to affect Leydig cells in rats, and incubated Leydig cells were found to have a decreased testosterone production when incubated with MNOP, the primary metabolite of DNOP. No effects on testicular function or morphology have been seen. In the NTP Monograph it is reported that *in vitro* tests assessing the potential estrogenic activity of DNOP were negative. Also an *in vivo* study in ovariectomized rats was negative. In an *in vitro* study (Krüger *et al*, 2008) no effect of DNOP on the androgen receptor was observed. Overall, there are limited indications that DNOP may cause endocrine disrupting effects on the reproductive system.

4.10 Other effects

The ATSDR concluded that there is limited data suggesting that DNOP can exert immunotoxicological effects in rats and mice after acute oral exposure to relatively high doses. These effects are reflected in changes in the weight and morphology of various lymphoreticular organs (thymus, spleen, and lymph nodes), altered activity of

humoral antibody-forming cells and cellular mediators of immunity, and reduced resistance to bacterial, viral, protozoan, or other parasitic infection.

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

Further evaluation of the data would be needed before any calculation of DNELs/DMELs may be done.

5. Information on exposure and related risk

From the available information it appears that, even though DNOP can be found in the (indoor) environment (e.g. in indoor dust) and some consumer products to which children can be exposed, the estimated levels of exposure are very low and as such do not represent a risk for human health. In particular, migration rates from products such as soap packaging appear to be very low, below the current analysis detection limits (Danish EPA, 2009).

6. Conclusions and suggestions for further action

In conclusion, it appears that the possible confusion around the substance identity of DNOP on the one hand, and the contradictory information on the actual commercial use of this substance in Europe on the other hand, require further clarifications before it can be assessed whether there is actually new information available which would argue in favour of reopening the discussions on the current restrictions or not.

The information on hazard properties of, and exposure to DNOP is limited. However, the only conclusions in terms of risks from the presence of DNOP in indoor dust and some (limited) consumer products which are reported in the available documentation indicate that there is no risk for human health.

There is currently not available new information on hazards of or exposures to DNOP which would justify the re-examination of current restriction. This review revealed that DNOP may not be commercially used within the EU. Therefore, ECHA suggests to wait for the first registration deadline has passed after which the Commission may decide on any further actions on DNOP. If any of the companies which pre-registered DNOP actually register it in quantities at or above 1000 t/year, this could bring some clarity on the uses within the EU and potentially also further information on the properties of DNOP. It is noted that the lack of EU manufacturing and use does not alone justify the re-examination of the current restriction. This is because DNOP can still be used outside the EU and imported to the EU in articles if the restriction is removed.

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