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Di-iso-nonyl phthalate (DINP)

A health risk assessment for nurses who might be exposed to DINP leaching from gloves

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EXECUTIVE SUMMARY

Di-iso-nonyl phthalate (DINP) was identified as an extractable when three types of vinyl gloves were extracted with synthetic perspiration. The gloves are used by nurses on a daily basis, and DINP might leach from the gloves during use and make contact with the skin. Subsequently, some DINP might be absorbed through the skin and become systemically available.

Bibra was told to assume that a nurse might wear up to 32 pairs of gloves during an 8-hour shift, and was asked to assess whether the potential DINP exposure might pose any significant health risks to the nurses. Bibra was told to assume that nurses might use the gloves for 48 weeks/year for 40 years.

The toxicology profile of DINP has been well investigated. Consequently, this health risk assessment relies heavily on Expert Group summaries and opinions, and the REACH dossiers. This approach was supplemented by a search of more recent primary literature, to ensure that no critical data were missed.

There is consensus among Expert Groups that the available studies provide sufficient evidence to conclude that DINP lacks significant mutagenic character and, consequently, it was assessed in this report as a threshold toxin. This is also the approach adopted by most Expert Groups in deriving tolerable exposure figures for DINP, with the exception of CalEPA's OEHHA who are currently proposing a non-significant risk level (NSRL) figure based on conservative modelling appropriate to a mutagenic carcinogen.

It was estimated that DINP concentration in perspiration while wearing gloves might be approximately 8 µg/ml (about 0.0008%). As even undiluted DINP has shown very little potential to irritate intact or abraded skin, it seems clear that the nurses would not be at any significant risk of skin irritation from any extracted DINP.

The available skin sensitisation studies in guinea pigs and humans indicate that the nurses would not be at significant risk of skin sensitisation from any extracted DINP.

At most, the nurses might experience a DINP dose of 5.2 µg/kg bw on a working day. As the margin between this exposure and the acute dermal dose that caused no deaths in rabbits

(3160 mg/kg bw) is >607,000, it is clear that the potential exposure would not pose any significant acute systemic health risks to nurses.

In the worst-case scenario being assessed, a nurse might be exposed dermally to DINP at 5.2 µg/kg bw/day on any working day, which is about 3.7 µg/kg bw/day when averaged over a working week and 2.0 µg/kg bw/day when averaged over a 70-year lifetime. The averaged lifetime dermal exposure level (2.0 µg/kg bw/day) is 940 times lower than the derived no-effect level (DNEL; 1.88 mg/kg bw/day) generated by the European Chemicals Agency (ECHA) for tolerable long-term dermal exposure of the general population. Consequently, it can be confidently concluded that nurses would not be at any significant systemic toxicity risks from repeated exposure to any DINP leaching from the gloves.

This conclusion, based on a conservative tolerable dermal exposure figure derived by EU regulatory health risk experts, is supported by a number of tolerable values derived by Expert Groups for oral exposure. The relevant values (2.1, 75, 120 and 150 µg/kg bw/day (from OEHHA, ECHA, US CPSC and EFSA, respectively) are 1-75 times higher than the (dermal) exposure level being assessed (2.0 µg/kg bw/day). Moreover, when route-specific absorption is taken into account (4 and 100% for dermal and oral exposures, respectively), the estimated nurses' systemic (absorbed) exposure level (0.08 µg/kg bw/day, expressed as a lifetime average) is 26-1875 times lower than the systemic (absorbed) dose level that would arise from exposure at the tolerable oral dose levels set by these four agencies.

Overall, it is confidently concluded that, based on the analytical extraction study provided to bibra, any leaching DINP would not pose any significant health risks to nurses using the gloves.

BACKGROUND

Di-iso-nonyl phthalate (DINP) was identified as an extractable when three types of Medline vinyl gloves were extracted with synthetic perspiration. The gloves are used by nurses on a daily basis, and DINP might leach from the gloves during use and make contact with the skin. Subsequently, some DINP might be absorbed through the skin and become systemically available.

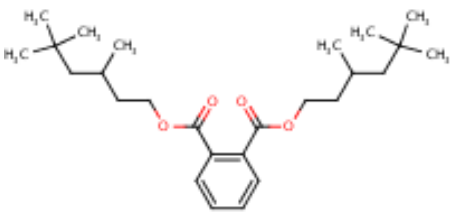
Bibra was told to assume that a nurse might wear up to 32 pairs of gloves during an 8-hour shift, and was asked to assess whether the potential DINP exposure might pose any significant health risks to the nurses.

EXPERTISE

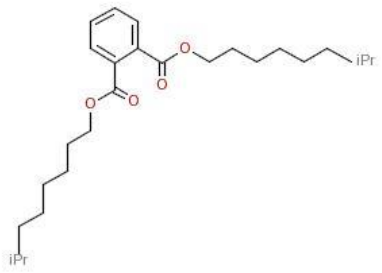
Bibra was founded (as the British Industrial Biological Research Association) in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have a >50-year record of objectivity and scientific excellence. All of the senior scientists in the current team are accredited and listed in the EUROTOX and UK Royal Society of Biology/British Toxicology Society Registers, and are thus bound by their specific codes of conduct. Peter Watts, the bibra Director of Toxicology and author of this report, is a graduate chemist and has 37 years' experience in reviewing and critically evaluating toxicological data and other scientific information on a wide range of chemicals.

IDENTIFICATION OF DINP

CHEMICAL STRUCTURE



As depicted in ChemIDplus



As depicted in PubChem and a REACH dossier

DINP refers to mixtures of certain alkyl diesters of ortho-phthalic acid. The alkyl side chains (derived from the alcohols) are said to be C8-C10 (C9-rich), mainly dimethylheptanols and methyloctanol. DINP can exist as DNIP 1, DNIP 2 or DINP 3. The following text is taken from an expert report from the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS): "Structurally, phthalate esters are characterized by a diester structure consisting of a benzenedicarboxylic acid head group linked to two ester side chains. DINP is not a single compound, but a complex mixture containing mainly C8, C9-branched isomers. DINP has two CAS numbers. The composition of DINP (CAS No 68515-48-0) is represented as mixed phthalates with side chains made up of 5-10% methyl ethyl hexanol, 45-55% dimethyl heptanol, 5-20% methyl octanol, 0-1% n-nonanol, and 15-25% isodecanol. The composition of DINP (CAS No 28553-12-0) is represented as mixed phthalates with side chains made up of 5-10% methyl ethyl hexanol, 40-45% dimethyl heptanol, 35-40% methyl octanol, and 0-10% n-nonanol. Thus, DINP [side chains of dimethyl heptanol (i.e. isononanol)] makes up about 50% of the two DINP mixtures available on the market. The above structural formulas [given in the NICNAS report] are those associated with the CAS numbers given but they do not reflect the complexity of the commercially available phthalate mixtures" (NICNAS, 2008).

DINP is considered to be a "high MWt" phthalate (US EPA, 2010).

CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBERS (CAS RNS)

DINP 1	68515-48-0
DINP 2	28553-12-0
DINP 3	28553-12-0

ANTICIPATED USE OF GLOVES BY NURSES

Bibra was told to assume that a nurse might wear up to 32 pairs of gloves (64 gloves) during an 8-hour shift.

For this report, it was assumed that a nurse would work an 8-hour shift on 5 days/week, during 48 weeks/year, for 40 years over a 70-year lifetime. This is anticipated to reflect a worst-case scenario.

A use rate of 64 gloves/day on a work day equates to[1] averaged use rates of 45.7 gloves/day over a working week, and 24 gloves/day over a 70-year lifetime.

EXTRACTION TESTS AND RESULTS

In total, 120 gloves (40 per type) were extracted, each with by 125 ml synthetic perspiration at 37°C for 20 minutes (ARDL, 2014).

[1] 64 gloves/day x (5 days/7 days) = 45.7 gloves/day averaged over a working week.
64 gloves/day x 5 days/week x 48 weeks/year x 40 years = 614,400 gloves/lifetime. Lifetime = 365 days/year x 70 years = 25,550 days. Averaged glove use over a lifetime = 614,400 gloves/25,550 days = 24 gloves/day.

The total amount of extracted DINP from sets of 40 gloves was 154.4, 277.2 and 158.1 µg for the three glove types, respectively.

ESTIMATED DERMAL (EXTERNAL) DINP EXPOSURE

Bibra was asked to base the health risk assessment on the average leaching value for the three gloves type i.e. 196.6 µg per 40 gloves, equivalent to 4.91 µg/glove.

During an 8-hour working day when 64 gloves are worn, a nurse might experience a dermal DINP dose of 314.2 µg, which equates to about 5.2 µg/kg bw/day for a nurse weighing 60 kg.

Over a working week, the averaged dermal DINP dose would be about 3.7 µg/kg bw/day.

Over a lifetime, the averaged external dermal exposure could be **2.0 µg/kg bw/day, or 120 µg/day** for a 60-kg nurse (as a lifetime averaged exposure level).

This is clearly a "worst case" exposure estimate because it assumes that:

(a) a nurse's normal hand perspiration production is equally efficient at extracting DINP as was the large volume of synthetic perspiration;
(b) a nurse changes gloves every 15 minutes, every day for a working lifetime (40 years);
(c) a nurse works 8-hour shifts every working day for 40 years.

ESTIMATED SYSTEMIC (ABSORBED) DINP EXPOSURE

NICNAS experts have noted that bioavailability via dermal (skin) absorption is expected to be not greater than 4% in humans (NICNAS, 2012, 2013). The two REACH dossiers on DINP summarise a study where radiolabelled 14C-DINP was applied to the intact skin of rats at about 1.2 ml/kg bw and rats were killed after 1, 3 or 7 days. Based on radiolabel determinations in excreta, gastrointestinal tract, blood and selected tissues, only 2-4% of the applied dose was absorbed during the 7-day period (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014).

Experts note that the low dermal absorption of DINP is in marked contrast with absorption following oral exposure, where data indicate complete and rapid absorption (NICNAS, 2012, 2013). European Chemicals Agency (ECHA) experts have also recently indicated that about 50 and 100% of DINP is absorbed following oral exposure of rats and adult humans, respectively (ECHA, 2013).

Adopting an absorption figure of 4% for the estimated dermal DINP dose level (2.0 µg/kg bw/day as an averaged lifetime dose level) leads to an estimated absorbed (systemic) exposure level of **0.08 µg/kg bw/day, or 4.8 µg/day** for a 60-kg nurse (as a lifetime averaged systemic exposure level).

TOXICITY DATA SEARCHES

Bibra has access to a wide range of toxicity data sources. Searches were carried out for key toxicity data on DINP using the relevant CAS RNs (28553-12-0 and 68515-48-0). Sources included the bibra TRACE database (see Appendix A for details), the Toxnet system of databases (see Appendix B), eChemPortal (see Appendix C) and RTECS.

The toxicology profile of DINP has been well investigated. Consequently, this health risk assessment relies heavily on Expert Group summaries and opinions, and the REACH dossiers. This approach was supplemented by a search of more recent primary literature, to ensure that no new critical data were missed.

DINP HEALTH RISK ASSESSMENT

GENERAL

An early step in this process is an assessment of genotoxicity potential. It is important to assess whether a substance has mutagenic (DNA-reactive) properties or not, because this will determine whether it is assessed as a mutagen (potentially lacking a threshold dose for mutagenic/carcinogenic effects) or a non-mutagen (where the substance is likely to show a threshold for its toxic effects).

GENOTOXICITY OVERVIEW

DINP showed no genotoxic activity in the classical three key in vitro screening assays. These consisted of an Ames bacterial mutation assay in five strains of *Salmonella typhimurium*, a mammalian gene mutation test in mouse lymphoma cells, and a test for chromosome damage (aberrations) using hamster ovary cells. In all three systems, testing was carried out with and without an added metabolic activation fraction derived from rat liver (S9). In addition, DINP showed no ability to induce DNA damage when incubated with rat liver cells (hepatocytes) in a UDS assay. In the only in vivo assay available for review, DINP did not cause chromosome damage in the bone marrow cells of rats when given at up to 5 ml/kg bw/day for 5 days, by gavage[2] (NICNAS, 2008, 2012).

Industry has submitted two DINP-relevant REACH dossiers to ECHA. One was registered as di-"isononyl" phthalate with the CAS RN 28553-12-0 (BASF SE et al. 2015) and the other as 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich with the CAS RN 68515-48-0 (Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014). Both dossiers contain summaries of the same six genotoxicity studies. In the only in vivo study, DINP did not cause chromosome damage in the bone marrow cells of rats when given at up to 5 ml/kg bw/day by gavage for 5 days. In vitro, DINP did not induce bacterial mutations in three Ames tests, mammalian gene mutations in mouse lymphoma cells, or chromosome aberrations in hamster ovary cells. In the in vitro assays, testing was carried out both with and without rat liver S9 (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014).

An expert report from the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) briefly mentions a second in vivo test on

[2] Several Expert Group reviews incorrectly give the maximum tesed dose as 5 mg/kg bw.

DINP, in which no ability to induce micronuclei was seen in male mice dosed at up to 2000 mg/kg bw/day for 2 days. The OEHHA report does not disclose the exposure route [presumably oral] or the tissue that was examined (OEHHA, 2013).

Although no dermal 2-year studies were identified, NICNAS evaluations of DINP's carcinogenicity potential noted a 2-year dietary study in mice and three 2-year dietary studies in rats. Kidney tumours were increased in male rats, but understood to arise by a mode-of-action involving formation of alpha-2µ-globulin. As this protein is specific to male rats, these tumours were deemed irrelevant for humans. The liver tumours induced in rats and mice were held to arise as a result of persistent peroxisome proliferation, to which humans are generally considered refractive. Finally, mononuclear cell leukaemia (MNCL) incidence was increased in F344 rats, but this cancer is regarded as a common neoplasm in aged F344 rats with no comparable tumour type in humans (NICNAS, 2008, 2012). Overall, NICNAS concluded that these tumours are not relevant to humans (NICNAS, 2012).

ECHA agreed that the renal tumours seen in rats stem from an alpha-2µ-globulin mode-of-action that is not relevant for humans. The increased incidences in MNCL in rats might have a human counterpart but, as MNCL is likely to follow a threshold mode-of-action with a NOAEL equal to that for repeated dose toxicity, the finding was not a driver for the health risk assessment. ECHA was a little more circumspect in regard to the liver tumours, noting that the mechanisms of liver carcinogenicity in rodents with peroxisome proliferators have not entirely been elucidated and that multiple pathways seem to exist. "Some of those pathways seem to be PPARα-independent, which might indicate a need for some caution when interpreting the relevance of rodent carcinogenicity with DINP to humans" (ECHA, 2013).

ECHA, OECD and Health Canada experts have all concluded that DINP is not mutagenic in vivo or in vitro (ECHA, 2013; ECHC, 2015; OECD, 1999), a conclusion in line with recent reports from the Danish Environmental Protection Agency (Danish EPA, 2014) and the EU Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR, 2015). A NICNAS Factsheet noted that DINP "is not genotoxic or carcinogenic" (NICNAS, 2013) although presumably NICNAS was referring to a lack of cancer potential in humans, since high dose levels clearly have induced tumours in rodents. OEHHA agreed that DINP is inactive in the available genotoxicity tests but pointed out that it has not been adequately tested for induction of oxidative DNA damage (OEHHA, 2013). However, such an effect is widely assumed to have a practical threshold, partly as a result of efficient repair mechanisms.

A Toxtree (version 2.6.6 with plug-ins) analysis showed the DINP lacks any structural alerts for bacterial (Ames) mutagenicity or genotoxic carcinogenicity.

Consequently, DINP is assessed here as a threshold toxin.

ABSORPTION

NICNAS notes that bioavailability via dermal (skin) absorption is expected to be not greater than 4% in humans. This is in marked contrast with the oral route, where data indicate complete and rapid absorption (NICNAS, 2012, 2013).

The REACH dossiers summarise a study where radiolabelled 14C-DINP was applied to the intact skin of rats at about 1.2 ml/kg bw and rats were killed after 1, 3 or 7 days. Based on radiolabel determinations in excreta, gastrointestinal tract, blood and selected tissues, only 2-4% of the applied dose was absorbed during the 7-day period (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014).

SKIN IRRITATION

No irritation was seen when undiluted DINP was applied to the covered skin of volunteers for 24 hours (NICNAS, 2008). A 4-hour semi-occlusive application of undiluted DINP to the intact skin of six rabbits resulted in very slight, transient erythema in 2/6 rabbits. In two other rabbit studies (including a study involving a 24-hour exposure to abraded skin), only slight erythema and oedema were observed (NICNAS, 2008, 2012).

When undiluted DINP was applied, under occlusive conditions for 24 hours, to intact and abraded skin sites of rabbits (4/group) at 0, 0.5 or 2.5 ml/kg bw/day, on 5 days/week for 6 weeks, no significant irritation was seen at 0.5 ml/kg bw/day. Slight or moderate erythema and slight desquamation were observed at 2.5 ml/kg bw/day (NICNAS, 2008, 2012).

If it is assumed that a nurse produces perspiration at a rate of just 100 ml/hour while at work, and that the hands represent about 5% of body area, then the hands might produce an estimated 5 ml perspiration per hour. If the nurses wear four pairs of gloves during that hour, and extract DINP at 4.91 µg/glove, then they might extract 39 µg DINP in that hour. This equates to a DINP concentration in the perspiration of about 8 µg/ml (approximately 0.0008%). As even undiluted DINP has shown very little potential to irritate intact or abraded skin, it seems clear that the nurses would not be at significant risk of skin irritation from any leached DINP.

SKIN SENSITISATION

Following an evaluation of two Buehler skin sensitisation tests in guinea pigs and a repeated insult patch test in humans, NICNAS experts concluded that DINP is “unlikely to cause skin sensitisation” (NICNAS, 2008, 2012).

A Toxtree (version 2.6.6 with plug-ins) analysis showed the DINP lacks any structural alerts for skin sensitisation.

It is concluded that the nurses would not be at significant risk of skin sensitisation from any extracted DINP.

ACUTE DOSE DERMAL TOXICITY

The occlusive 24-hour skin application of DINP at doses of up to 3160 mg/kg bw did not cause any clinical toxicity in rabbits (4/dose level). Thus the acute dermal LD50 is >3160 mg/kg bw (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014; NICNAS, 2008, 2012), indicating a very low degree of acute dermal toxicity.

The nurses are likely to experience a worst-case dose of 5.2 µg/kg bw on a working day. The margin between this exposure and the acute dermal dose that caused no deaths in rabbits is >607,000.

It is clear that even the very worst-case estimate of exposure would not pose any significant acute systemic health risks to nurses.

REPEATED DOSE DERMAL TOXICITY

Information on toxicity following repeated dermal dosing appears to be limited to a single study, where the covered 24-hour application of DINP to intact and abraded skin sites of rabbits (4/group) at 0, 0.5 or 2.5 ml/kg bw/day, on 5 days/week for 6 weeks, caused no systemic toxicity. Clinical signs were recorded daily, haematology and urinalysis were undertaken initially and terminally, and histopathology was performed on the liver, kidneys and skin. The systemic toxicity no-observed-adverse-effect level (NOAEL) was 2.5 ml/kg bw/day (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014; NICNAS, 2008). [See SKIN IRRITATION section above for data on local effects.]

Taking the density of DINP as 0.97 g/ml (BASF et al. 2015), the NOAEL in the above rabbit study equates to 2425 mg/kg bw/day (5 days/week), which is equivalent to 1732 mg/kg bw/day when the 5 days/week dosing schedule is accounted for. This dermal NOAEL is 866,000 times higher than the (worst-case) estimate of dermal exposure being assessed here (2.0 µg/kg bw/day). Although the benchmark study is limited in nature (e.g. short duration, restricted examination, small groups), this large margin provides a degree of reassurance over potential health risk from DINP exposure in the nurses.

Fortunately, a considerable amount of useful data is available from repeated oral dose studies, and these [see below] provide valuable insights into potential health risks from dermal exposure.

REPEATED DOSE ORAL TOXICITY

As noted above, a considerable number of repeated oral dose studies are available for DINP, investigating both systemic toxicity endpoints and reproductive and developmental toxicity endpoints. Unlike certain other (lower MWt) phthalates, reproductive/developmental toxicity is not considered to be the key health effect of DINP (CERHR, 2003; ECHA, 2013; EFSA, 2005; NICNAS, 2008, 2012).

The US National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR) considered DINP to be of "minimal concern" in regard to both human reproductive and developmental toxicity. Tolerable doses were not derived (CERHR, 2003). Experts from the European Food Safety Authority (EFSA) summarised the relevant information on reproductive and developmental toxicity as follows: "No overt toxicity was observed on reproductive organs in rats. No observed adverse effect levels (NOAEL) of 500 mg/kg bw/day and 622 mg/kg bw/day were established for minor developmental effects and decreases in live birth and survival indices, respectively. Maternal toxicity was limited to lower mean body weight and hepatic changes with a lowest observed adverse effect level

(LOAEL) of 114 mg/kg bw/day" (EFSA, 2005). A more recent, comprehensive evaluation by experts from ECHA identified the key data as an NOAEL of 50 mg/kg bw/day for reduced foetal testosterone level, an LOAEL of 159 mg/kg bw/day for decreased body weight in offspring, and an NOAEL of 100 mg/kg bw/day for skeletal variations. Effects on fertility occur at higher dose levels, with a NOAEL for decreased live birth and survival indices of 622 mg/kg bw/day and a NOAEL of 276 mg/kg bw/day for decreased testicular weights (ECHA, 2013).

KEY EXPERT GROUP DERIVATIONS OF TOLERABLE DERMAL EXPOSURES

ECHA has generated a derived no-effect level[3] (DNEL) of 1.88 mg/kg bw/day for systemic effects in the general population exposed long-term by the dermal route. The key oral NOAEL of 15 mg/kg bw/day was adjusted to a dermal NOAEL of 187.5 mg/kg bw/day by application of a factor reflecting differences in absorption between the routes (50% oral; 4% dermal). An Assessment Factor (AF) of 100 [two factors of 10 to account for potential interspecies and intraspecies differences] was then applied to generate the DNEL of 1.88 mg/kg bw/day (ECHA, 2013).

In contrast, both of industry's DINP REACH dossiers propose a DNEL of 220 mg/kg bw/day for general systemic effects in the general population exposed long-term by the dermal route (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014). Details of the derivation were not given by the dossier submitters, but it appears that the oral NOAEL of 88 mg/kg bw was adjusted to a dermal value of 4400 mg/kg bw/day (assuming 100 and 2% absorption from oral and dermal exposure, respectively), and application of an AF of 20. [In bibra's opinion, this industry derivation is not adequately health precautionary.]

Summary of tolerable long-term dermal exposure figures and margins of exposure

Source	Tolerable lifetime figure	Estimated exposure of nurses (worst-case)	Margin of Exposure	Reference
ECHA DNEL	1.88 mg/kg bw/day	2.0 µg/kg bw/day	940	ECHA, 2013
Industry DNEL	220 mg/kg bw/day	2.0 µg/kg bw/day	110,000	BASF SE et al. 2015 Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014

As a very worst-case scenario, a nurse might be exposed dermally to DINP at 2.0 µg/kg bw/day as an averaged figure over a 70-year lifetime. This dermal exposure level is 940 times lower than the ECHA DNEL for tolerable long-term dermal exposure of the general population (1.88 mg/kg bw/day), and 110,000 times lower than industry's equivalent figure (220 mg/kg bw/day). The ECHA derivation is considered to be more robust, and it can be confidently concluded that

[3] A DNEL is the level of exposure to the substance above which humans should not be exposed. Health risks are considered to be adequately controlled if exposures are kept below the DNELs. Industry-derived DNEL values included in REACH dossiers represent the views of the submitting consortium. In general, the amount of information disseminated on the ECHA website is insufficient for easy or independent verification of these industry DNELs.

nurses would not be at any significant systemic toxicity risks from any DINP leaching from the gloves.

KEY EXPERT GROUP DERIVATIONS OF TOLERABLE ORAL EXPOSURES

Several Expert Groups have derived tolerable exposure figures for the oral route, and these can be used, together with information on dermal absorption, to draw health-precautionary conclusions regarding potential health risks from dermal exposure.

EFSA concluded that the pivotal toxicological effect for orally-administered DINP is certain hepatic changes seen in various studies. Liver peroxisome proliferation was considered as irrelevant for human risk assessment. The key study was a 2-year chronic toxicity study in rats showing an increased incidence of spongiosis hepatis, accompanied by increased serum levels of liver enzymes and increases in absolute and relative liver and kidney weights in both sexes (Exxon Biomedical Sciences, 1986). The EFSA experts used the NOAEL of 15 mg/kg bw/day for these non-peroxisomal proliferation-related chronic hepatic and renal effects, and applied an uncertainty factor (UF) of 100 to derive a tolerable daily intake (TDI) of 0.15 mg/kg bw/day (EFSA, 2005).

The US Consumer Product Safety Commission (CPSC) selected the same key study, NOAEL and UF as EFSA did, but evidently applied the UF to the "maximum likelihood estimate of the BMD05"[4] for histopathological liver effects, leading to an oral acceptable daily intake (ADI) of 0.12 mg/kg bw/day (CPSC, 2010).

More recently, ECHA proposed an oral DNEL of 0.075 mg/kg bw/day for DINP. The key rat NOAEL of 15 mg/kg bw/day was adjusted to 7.5 mg/kg bw/day (to reflect the view that oral absorption is about 50% in rats and 100% in adult humans). An Assessment Factor (AF) of 100 was applied to generate the DNEL (ECHA, 2013).

Both DINP REACH dossiers propose a DNEL of 4.4 mg/kg bw/day for general systemic effects in the general population exposed long-term by the oral route (BASF SE et al. 2015; Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014). The derivation is not fully explained by the dossier submitters, but seems to have involved the application of an AF of just 20 to an NOAEL of 88 mg/kg bw/day, seen in another 2-year rat feeding study. The selection of study and (apparently inadequate) AF is not justified in the dossier that is publically available.

A further tolerable exposure figure has recently been proposed by experts from the Reproductive and Cancer Hazard Assessment Branch of the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA). These experts have proposed to list DINP as a known carcinogen and to adopt a Non-Significant Risk

[4] A benchmark dose (BMD) approach involves fitting a mathematical model to the entire dose-response dataset for an endpoint, and allowing the model to estimate the threshold dose corresponding to a level of benchmark response (BMR). This BMR is set at a certain level (e.g., 1%, 5%, 10%) as defined by the risk assessor. The BMD05 is the model's best estimate of the effective dose (ED) at a BMR of 5%.

Level[5] (NSRL) of 146 µg/day under Proposition 65, a figure that equates to 2.1 µg/kg bw/day for a 70-kg person. Using the OEHHA (2013) review as its basis, the derivation is described in an undated OEHHA "Initial Statement of Reasons" document (OEHHA, [undated]). OEHHA noted that the mechanisms by which DINP induces tumours are unknown and, although none of the possible mechanisms discussed in the supporting report (OEHHA, 2013) involved a DNA-reactive (mutagenic) mechanism, applied the default linearized multistage polynomial model to four sets of tumour incidence data (liver and leukaemia combined [using benchmark dose software] in male rats in two studies, and liver tumours in female rats in two studies). This is a conservative model traditionally used to assess cancer risks at low exposure to known mutagenic carcinogens and assumes that cancer risk reduces in a linear fashion as exposure approaches zero. The experts estimated cancer slope factors (CSFs) for the four chosen rat tumour data sets, converted these to human CSFs (by multiplying the rat CSF by the ratio of human-to-rat body weight, raised to the one-fourth power, and derived a geometric mean human CSF of 0.0048 per mg/kg bw/day of exposure. From this, the exposure associated with a (negligible) cancer risk of 1 in 100,000 can be calculated to be 2.08 µg/kg bw/day, or 146 µg/day for a person weighing 70 kg (OEHHA, [undated]).

Summary of tolerable long-term oral exposure figures and margins of exposure

Source	Tolerable lifetime figure	Estimated (worst-case) systemic exposure of nurses assuming 4% dermal absorption	Margin of Exposure	Reference
OEHHA NSRL	146 µg/day (2.1 µg/kg bw/day)	0.08 µg/kg bw/day (4.8 µg/day)	26	OEHHA, [undated]
ECHA DNEL	0.075 mg/kg bw/day	0.08 µg/kg bw/day (4.8 µg/day)	940	ECHA, 2013
US CPSC ADI	0.12 mg/kg bw/day	0.08 µg/kg bw/day (4.8 µg/day)	1500	CPSC, 2010
EFSA TDI	0.15 mg/kg bw/day	0.08 µg/kg bw/day (4.8 µg/day)	1875	EFSA, 2005
Industry DNEL	4.4 mg/kg bw/day	0.08 µg/kg bw/day (4.8 µg/day)	55,000	BASF SE et al. 2015 Dow Benelux B.V. and ExxonMobil Chemical Holland B.V., 2014

Over a lifetime, the nurses could experience an averaged external dermal exposure of 2.0 µg/kg bw/day, or 120 µg/day for a 60-kg nurse. This is lower even than the most

[5] An NSRL is defined as the daily intake level for a chemical calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure to the chemical at the level in question.

conservative of the oral tolerable exposure values, the OEHHA draft NSRL of 2.1 µg/kg bw/day (actually published as 146 µg/day for a 70-kg person). The other Expert Group figures for tolerable oral exposure (0.075-0.15 mg/kg bw/day) are some 38-75 times higher than the assessed nurses' dermal exposure level (2.0 µg/kg bw/day).

The margins are even more reassuring when the differences in absorption between exposure routes are taken into account. Using the figures favoured by Expert Groups (4 and 100% absorption in humans exposed dermally and orally respectively), the nurses' systemic (absorbed) dose is 0.08 µg/kg bw/day (expressed as an averaged lifetime daily dose). In comparison, even the most conservative, OEHHA NSRL (systemic dose level 2.1 µg/kg bw/day) is 26-fold higher than the (worst-case) estimate of systemic (absorbed) exposure from gloves. The OEHHA NSRL is clearly highly conservative because its derivation assumed that a non-threshold, mutagenic mode-of-action underpinned the observed rat tumours. In contrast, other Expert Groups view DINP as lacking mutagenic potential, in line with the available test data both on DINP itself and with other dialkyl phthalates as a generic class. These groups have set tolerable oral exposure levels (daily for lifetime) of 0.075-0.15 mg/kg bw/day, which equate (as oral absorption is 100%) to systemic (absorbed) dose levels of 0.075-0.15 mg/kg bw/day, which are 940-1875 times higher than the averaged systemic exposure (0.08 µg/kg bw/day) that could arise in the nurses from glove DINP exposure.

Clearly, the nurses would not be at any significant systemic toxicity risk from repeated dermal exposure to any DINP leaching from the gloves.

CONCLUSION

There is consensus among Expert Groups that the available studies provide sufficient evidence to conclude that DINP lacks significant mutagenic character and, consequently, it was assessed in this report as a threshold toxin. This is also the approach adopted by most Expert Groups in deriving tolerable exposure figures for DINP, with the exception of CalEPA's OEHHA who are currently proposing an NSRL based on modelling appropriate to a mutagenic carcinogen.

It was estimated that the DINP concentration in perspiration might be approximately 8 µg/ml (about 0.0008%). As even undiluted DINP has shown very little potential to irritate intact or abraded skin, it is inconceivable that the nurses would be at significant risk of skin irritation from any extracted DINP.

The available skin sensitisation studies in guinea pigs and humans indicate that the nurses would not be at significant risk of skin sensitisation from any extracted DINP.

At most, the nurses might experience an external dermal DINP dose of 5.2 µg/kg bw on a working day. As the margin between this exposure and the acute dermal dose that caused no deaths in rabbits (3160 mg/kg bw) is >607,000, it is clear that the potential exposure would not pose any significant acute systemic health risks to nurses.

In the worst-case scenario being assessed, a nurse might be exposed dermally to DINP at 5.2 µg/kg bw/day on any working day, which is about 3.7 µg/kg bw/day when averaged over a working week and 2.0 µg/kg bw/day when averaged over a 70-year lifetime. The averaged lifetime dermal exposure level (2.0 µg/kg bw/day) is 940 times lower than the ECHA DNEL (1.88 mg/kg bw/day) for tolerable long-term dermal exposure of the general population. Consequently, it can be confidently concluded that nurses would not be at any significant systemic toxicity risks from repeated exposure to any DINP leaching from the gloves.

This conclusion, based on a conservative tolerable dermal exposure figure derived by EU health risk experts, is supported by a number of tolerable values derived by Expert Groups for lifetime oral exposure. The relevant values (2.1, 75, 120 and 150 µg/kg bw/day (from OEHHA, ECHA, US CPSC and EFSA, respectively) are 1-75 times higher than the (dermal) exposure level being assessed (2.0 µg/kg bw/day). Moreover, when route-specific absorption is taken into account (4 and 100% for dermal and oral exposures, respectively), the estimated nurses' systemic (absorbed) exposure level (0.08 µg/kg bw/day, expressed as a lifetime average) is 26-1875 times lower than the systemic dose level that would arise from exposure at the tolerable oral dose levels set by these four agencies.

Overall, it is confidently concluded that, based on the analytical extraction study provided to bibra, any leaching DINP would not pose any significant health risks to nurses using the gloves.

REFERENCES

ARDL (2014). Akron Rubber Development Laboratory, Inc. Test Report PN 116295. Chemical Analytical Services. Report dated July 8, 2014. Report supplied to bibra.

BASF SE et al. (2015). REACH Registration Dossier for di-"isononyl" phthalate, joint submission to the European Chemicals Agency. Last updated in August 2015. http://apps.echa.europa.eu/registered/data/dossiers/DISS-828e025b-9dd6-1b22-e044-00144fd73934/DISS-828e025b-9dd6-1b22-e044-00144fd73934_DISS-828e025b-9dd6-1b22-e044-00144fd73934.html

CERHR (2003). US National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction, Research Triangle Park, NC, USA. Monograph on the Potential Human Reproductive and Developmental Effects of Di-isononyl Phthalate (DINP). NIH Publication No. 03-4484. http://ntp-server.niehs.nih.gov/ntp/ohat/phthalates/dinp/DiNP_Monograph_Final.pdf

CPSC (2010). US Consumer Product Safety Commission, Bethesda, MD, USA. Memorandum: Overview of Phthalates Toxicity. http://www.cpsc.gov//PageFiles/126521/phthalover.pdf

Danish EPA (2014). Danish Environmental Protection Agency. Survey of selected phthalates. Part of the LOUS-review. Danish Ministry of the Environment. Environmental Project No. 1541, 2014. http://www2.mst.dk/Udgiv/publications/2014/01/978-87-93026-95-7.pdf

Dow Benelux B.V. and ExxonMobil Chemical Holland B.V. (2014). REACH Registration Dossier for 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich. Last updated in March 2014. http://apps.echa.europa.eu/registered/data/dossiers/DISS-828e03e1-4edc-1b7a-e044-00144fd73934/DISS-828e03e1-4edc-1b7a-e044-00144fd73934_DISS-828e03e1-4edc-1b7a-e044-00144fd73934.html

ECHA (2013). European Chemicals Agency. Evaluation of new scientific evidence concerning DINP and DIDP. In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. August 2013. ECHA-13-R-07-EN. http://echa.europa.eu/documents/10162/31b4067e-de40-4044-93e8-9c9ff1960715

ECHC (2015). Environment Canada and Health Canada. State of the Science Report. Phthalate Substance Grouping. 1,2-Benzenedicarboxylic acid, diisononyl ester and 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich (Diisononyl Phthalate; DINP). http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=47F58AA5-1

EFSA (2005). European Food Safety Authority, Parma, Italy. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to Di-isononylphthalate (DINP) for use in food contact materials. The EFSA Journal 244, 1–18. http://www.efsa.europa.eu/en/efsajournal/doc/244.pdf

Exxon Biomedical Sciences (1986). Chronic Toxicity/Oncogenicity Study in F-344 Rats. Test Material: MRD-83-260. Project No 326075 performed at Exxon Biomedical Sciences, Inc., Unpublished Laboratory Report, January 13, 1986 (cited in EFSA, 2005).

NICNAS (2008). Australia National Industrial Chemicals Notification and Assessment Scheme. Existing Chemical Hazard Assessment Report. Diisononyl Phthalate. http://www.nicnas.gov.au/__data/assets/pdf_file/0004/4972/DINP-hazard-assessment.pdf

NICNAS (2012). Australia National Industrial Chemicals Notification and Assessment Scheme. Diisononyl phthalate. Priority Existing Chemical Assessment Report No. 35. September 2012. Available via eChemPortal. http://www.echemportal.org/echemportal/page.action?pageID=9

NICNAS (2013). Australia National Industrial Chemicals Notification and Assessment Scheme. Diisononyl phthalate (DINP) FactSheet. http://www.nicnas.gov.au/chemical-information/information-sheets/existing-chemical-info-sheets/diisononyl-phthalate-dinp-factsheet

OECD (1999). Organisation for Economic Co-operation and Development. 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich, and di-«isononyl» phthalate. SIDS INITIAL ASSESSMENT PROFILE. SIAM 9, 29 June-1 July 1999. http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=0EB98681-2455-4059-8890-49C5EBDC0A5B

OEHHA [undated but 2013 or later]. Office of Environmental Health Hazard Assessment. Initial Statement of Reasons. Title 27, California Code of Regulations. Proposed Amendment to:

Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Diisononyl phthalate (DINP). Safe Drinking Water and Toxic Enforcement Act of 1986. Proposition 65. Reproductive and Cancer Hazard Assessment Branch, California Environmental Protection Agency. Available via http://oehha.ca.gov/prop65/law/121914NSRL.html

OEHHA (2013). Office of Environmental Health Hazard Assessment. Evidence on the carcinogenicity of diisononyl Phthalate (DINP). October 2013. Reproductive and Cancer Hazard Assessment Branch, California Environmental Protection Agency. Available via http://www.oehha.ca.gov/serp.html?q=DINP&cx=001779225245372747843%3Av3sx-oyt7xc&cof=FORID%3A10&ie=UTF-8

SCENIHR (2015). Scientific Committee on Emerging and Newly-Identified Health Risks. SCENIHR Opinion on The safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update). http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.

US EPA (2010). US Environmental Protection Agency. Screening-level hazard characterization, phthalate esters category. Dated April 2010. http://www.epa.gov/hpvis/hazchar/Category_%20Phthalate%20Esters_March%202010.pdf

APPENDIX A

Bibra - toxicology advice & consulting

The TRACE database and databank

TRACE includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, TRACE covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMEA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, CRD, MHRA and VMD) and advisory committee (eg COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, CalEPA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- Bibra Toxicity Profiles

APPENDIX B

US National Library of Medicine

TOXNET network

TOXNET – Databases and databanks on toxicology, hazardous chemicals, environmental health, and toxic releases includes:

- Toxline – Toxicology literature online
- DART – Developmental Toxicology literature
- ChemIDplus – Chemical identification/Dictionary
- HSDB – Hazardous Substances Data Bank
- CCRIS – Chemical Carcinogenesis Information
- CPDB – Carcinogenic Potency Database
- GENETOX – Genetic Toxicology Data
- IRIS – Integrated Risk Information System
- ITER – International Toxicity Estimates for Risk
- LactMed – Drugs and Lactation Database
- TRI – Toxics Release Inventory
- TOXMAP – Environmental Health e-maps
- Haz-Map – Occupational Exposure/Toxicology

APPENDIX C

Organisation for Economic Co-operation and Development

eChemPortal

e-ChemPortal – The global portal to information on chemical substances

Databases currently participating in eChemPortal:

- ACToR - US Environmental Protection Agency Aggregated Computational Toxicology Resource
- AGRITOX - Base de données sur les substances actives phytopharmaceutiques
- APVMA-CR - Australian Pesticides and Veterinary Medicines Authority database of completed chemical reviews
- CCR - Canadian Categorization Results
- CESAR - Canada's Existing Substances Assessment Repository
- Combined Exposures - Collection of Case Studies on Risk Assessments of Combined Exposures to Multiple Chemicals
- ECHA CHEM - European Chemicals Agency's Dissemination portal with information on chemical substances registered under REACH
- EnviChem - Data Bank of Environmental Properties of Chemicals
- ESIS - European Chemical Substances Information System
- GDL - Gefahrstoffdatenbank der Länder [the Hazardous Substances Database of Countries] (Germany)
- GHS-J - The Result of the GHS Classification by the Japanese Government
- HPVIS - High Production Volume Information System
- HSDB - Hazardous Substance Data Bank
- HSNO CCID - New Zealand Hazardous Substances and New Organisms Chemical Classification Information Database
- INCHEM - Chemical Safety Information from Intergovernmental Organizations
- J-CHECK - Japan CHEmicals Collaborative Knowledge database
- JECDB - Japan Existing Chemical Data Base
- NICNAS Other - Australian National Industrial Chemicals Notification and Assessment Scheme assessments of existing chemicals other than Priority Existing Chemical assessments
- NICNAS PEC - Australian National Industrial Chemicals Notification and Assessment Scheme Priority Existing Chemical Assessment Reports
- OECD HPV - Organisation for Economic Cooperation and Development Existing Chemicals Database

- OECD SIDS IUCLID - Organisation for Economic Cooperation and Development Existing Chemicals Screening Information Data Sets (SIDS) Database
- SIDS UNEP - Organisation for Economic Cooperation and Development Initial Assessment Reports for HPV Chemicals including Screening Information Data Sets (SIDS) as maintained by United Nations Environment Programme (UNEP) Chemicals
- SPIN - Substances in Preparations In the Nordic countries
- UK CCRMP Outputs - UK Coordinated Chemicals Risk Management Programme Publications
- US EPA HHBP - US Environmental Protection Agency Human Health Benchmarks for Pesticides
- US EPA IRIS - US Environmental Protection Agency Integrated Risk Information System
- US EPA OPPALB - US Environmental Protection Agency Office of Pesticide Programs' Aquatic Life Benchmarks
- US EPA SRS - US Environmental Protection Agency Substance Registry Services