Regulatory Toxicology and Pharmacology 62 (2012) 248–256

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A comprehensive review of intake estimates of di-isononyl phthalate (DINP) based on indirect exposure models and urinary biomonitoring data

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ARTICLE INFO

Article history:
Received 24 June 2011
Available online 11 January 2012

Keywords:
Di-isononyl phthalate
DINP
Biomonitoring
Exposure estimates
Human
Urine

ABSTRACT

Di-isononyl phthalate (DINP) is a high molecular weight general purpose plasticizer used principally in the manufacture of flexible polyvinyl chloride (PVC) articles. DINP metabolites can be measured in biological media such as blood and urine. However, measurement of a substance in the blood or urine does not by itself mean that the chemical causes or is associated with adverse health outcomes. This is particularly pertinent given the advances in modern analytical techniques whereby ever diminishing trace amounts of substances can be detected. Therefore, it is a scientific necessity that risk assessors understand the relationship of biomonitoring data to estimation of exposure so that appropriate comparisons can be made to the no observed adverse effects levels (NOAELs) or other points of departure from toxicological studies in animals. In this paper, estimates of daily DINP intake are calculated for various population segments based on urinary biomonitoring data and are compared to estimates of exposure based on indirect methods and to health-based exposure guidance values. In general, intake estimates converge on a mean of 1–2 μg/kg/day regardless of source of exposure or population cluster; a value 2-orders of magnitude lower than health-based exposure guidance values, ranging from 120 to 290 μg/kg/day, which have been established by regulatory authorities and other authoritative bodies as representing acceptable levels.

1. Introduction

Di-isononyl phthalate (DINP, CAS Nos. 68515-48-0 and 28553-12-0) is a high molecular weight, general purpose plasticizer used primarily in the manufacture of flexible polyvinyl chloride (PVC) articles. DINP can be used in most general purpose PVC applications including flooring, wall coverings, automotive applications, wire and cable sheathing, and in a wide range of durable goods. Due to its physical properties, DINP is not suitable for use in personal care products, such as perfumes, and according to a recent summary, was not identified as a constituent in a survey of such products (Witorsch and Thomas, 2010).

Although plasticizers such as DINP are not directly bound to the PVC polymer structure, there are a number of forces at the atomic and molecular levels that promote retention of the plasticizer within the polymer matrix. The interaction of DINP with PVC is not covalent bonding but rather a complex of other inter-atomic attractions including hydrogen bonding (acid/base or Lewis force), polar forces (dipole/dipole or Keesom force and induced dipole or Debye force) and dispersion (London force) (Sears and Darby, 1982). Coupled with a low vapor pressure and water solubility, under normal use, DINP does not readily migrate (i.e. the process by which phthalates leave the matrix based on physical/chemical considerations) from the PVC polymer matrix (Cousins and Mackay, 2000). In fact, the usefulness of DINP depends on being retained in the vinyl; without the plasticizer, the vinyl would become brittle and subject to cracking and breakage.

There have been numerous regulatory reviews of the potential risks from exposure to DINP. The European Union conducted a risk assessment of DINP under the Existing Substances Regulation that had broad coverage of applications and potentially exposed groups (European Chemicals Bureau, 2003). The National Toxicology Program Center for Evaluation of Health Risks (NTP-CERHR) concentrated on the potential risks for developmental and

Abbreviations: ADI, acceptable daily intake; CE, creatinine excretion rate; CERHR, Center for the Evaluation of Risks to Human Reproduction; CPSIA, Consumer Product Safety Improvement Act of 2008; DINP, diisononyl phthalate; F_{UE}, fractional urinary excretion; MINP, monoisononyl phthalate; MHNP, OH-MINP (mono-hydroxyl-isononyl phthalate); MONP, oxo-MINP (mono-oxo-isononyl phthalate); MCOP, carboxy-MINP (mono-carboxy-isooctyl phthalate); NHANES, National Health and Nutrition Examination Survey; NOAEL, no observed adverse effect level; NTP, National Toxicology Program; pTDI, provisional tolerable daily intake; PVC, polyvinyl chloride; TDI, tolerable daily intake; UC, urinary metabolite concentration – creatinine corrected; UC_{pm}, urinary metabolite concentration; UV_{24}, 24-h urinary volume.

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doi:10.1016/j.yrtph.2012.01.001

reproductive effects (Kavlock et al., 2002; NTP-CERHR, 2003). Several assessments of potential risks to children from exposure to DINP from toy use have been conducted as well (Babich et al., 2004; Chronic Health Advisory Panel, 2001; CSTEE, 2001; European Chemicals Bureau, 2003; Gill et al., 2001; Health Canada, 1998; Konemann, 1998; United States Consumer Products Safety Commission, 1998, 2003). Although these assessments have all concluded that exposures to DINP are well below no observed adverse effect levels (NOAELs), precautionary consideration has led to restrictions on the use of DINP in toys and childcare articles which can be placed in the mouth in some countries. For example, in the United States, legislation was introduced implementing a temporary prohibition of DINP in children's toys that can be placed in a child's mouth or child care articles, pending a review by the CPSC Chronic Hazard Advisory Panel (CHAP) of relevant scientific data on phthalate esters and phthalate alternatives, [Consumer Product Safety Improvement Act of 2008, Pub. L. No. 110–314, 122 Stat. 3016 (2008)] even though a previous CHAP found the risk from DINP to be low or non-existent (Chronic Health Advisory Panel, 2001).

As calls for risk characterization to advance from single substances to mixtures (i.e. cumulative risk) increases, it is imperative that the fundamental principles of risk characterization (hazard assessment, dose response characterization and exposure assessment) be understood for a particular substance prior to its consideration for inclusion in a cumulative risk assessment. Assessment of phthalate exposure has historically been conducted by indirect methods, i.e. by measuring chemical concentrations in various sources (diet, air, soil, etc.) and then applying these concentrations to develop estimates of intake from these sources. Models have been developed to improve exposure estimates that address variability around various inputs such as time activity or intake rates (ECETOC, 2001; United States Environmental Protection Agency, 1997, 2008).

In recent years the development of techniques to quantify trace levels of phthalate metabolites in human urine (Blount et al., 2000a,b) and the initiation of large screening programs to investigate trace urinary levels of phthalate metabolites in representative US populations (CDC, 2010), have provided data that can be used to estimate phthalate exposures (David, 2000; Kohn et al., 2000). Since these initial investigations, additional phthalate metabolites have been identified in urine and more extensive collections of urinary metabolite data have become available (Koch and Calafat, 2009; Wittassek et al., 2010). These more recent data are useful in addressing some of the exposure-related questions raised in the previous assessments and can provide additional certainty in addressing exposure.

In this paper, DINP urinary biomonitoring data are tabulated and reviewed. From these data, daily intake estimates are calculated and compared to estimates from the historical indirect intake assessments and to health-based exposure guidance values developed by multiple regulatory authoritative bodies to assess the potential risks from DINP exposure.

2. Methods for estimating DINP exposure

The ability to characterize phthalate exposure has progressed rapidly in recent years. Methods used to estimate exposure can be grouped into two types: indirect methods that use information about the concentration of the phthalates in particular media (e.g. air, water, food, consumer product, etc.) and the rate of intake from that media (e.g. inhalation or ingestion rates) to estimate intake; and direct methods that use urinary metabolite data to calculate daily intakes of the parent phthalate diesters utilizing physiological excretion constants.

2.1. Indirect methods

DINP exposure has been assessed by estimating the concentrations of DINP in different media and the intake of those media. These estimates have been used to approximate intake broadly from multiple sources (Clark et al., 2011; Sugita et al., 2003; Wormuth et al., 2006) or have focused on specific applications or sources, such as exposure from toys (Babich et al., 2004). There is uncertainty associated with these estimates including variations in reported concentrations and intake of various media, the potential for sample contamination, and reliance on surveys of product use. As a consequence, there is a tendency to default to worst case inputs to conservatively address the uncertainty.

2.2. Biomonitoring studies (direct methods)

An alternative method of intake estimation is to calculate external exposure from urinary metabolite data. Blount et al. (2000a,b) provided initial data on phthalate metabolites in urine collected from a human reference population. Intake estimates of phthalate esters were calculated (Eq. (1)) from creatinine corrected spot urinary metabolite levels reported for phthalate monoesters including the monoester of DINP, mono-iso-nonyl phthalate (MINP) (David, 2000; Kohn et al., 2000) by the following equation:

$$\mathrm{DI} = [\mathrm{UC} \times \mathrm{CE}/(F_{\mathrm{UE}} \times 1000)] \times [\mathrm{MWd}/\mathrm{MWm}] \quad (1)$$

in which, DI is daily intake (μg/kg/day), UC is the creatinine corrected urinary metabolite concentration (μg/g), CE is the creatinine excretion rate (mg/kg/day) for adults (Tietz, 2006) and children (Remer et al., 2002) and is used to account for differences in urine dilution (Preau et al., 2010), F_{UE} is the fractional urinary excretion rate of the metabolite (unitless) (Anderson et al., 2011; Koch and Angerer, 2007). MWd and MWm are the molecular weights of DINP and the metabolite, respectively (David, 2000; Kohn et al., 2000). This equation can be applied to any of the metabolites for DINP for which an F_{UE} value has been determined.

A second equation for estimating intake is used when 24-h voids are collected (Wittassek et al., 2007). In this equation:

$$\mathrm{DI} = [\mathrm{UC}_{\mathrm{pm}} \times \mathrm{UV}_{24}/(F_{\mathrm{UE}} \times \mathrm{BW})] \times [\mathrm{MWd}] \quad (2)$$

DI is daily intake (μg/kg/day), $\mathrm{UC}_{\mathrm{pm}}$ is the urinary metabolite concentration (μmol/l), UV_{24} is the 24-h urine volume (l/day), F_{UE} is the fractional urinary excretion rate of the metabolite (unitless) (Anderson et al., 2011; Koch and Angerer, 2007), BW is body weight (kg) and MWd is the molecular weight of DINP.

A third equation proposed by Lin et al. (2011) is similar to Eq. (2):

$$\mathrm{DI} = [\mathrm{UC}/(F_{\mathrm{UE}}] \times \mathrm{UV}_{24}/ \times [1/\mathrm{BW})] \times [\mathrm{MWd}/\mathrm{MWm}] \quad (3)$$

DI is daily intake (μg/kg/day), UC is the urinary metabolite concentration (μg/l), UV_{24} is the 24-h urine volume (l/day), F_{UE} is the fractional urinary excretion rate of the metabolite (unitless) (Anderson et al., 2011; Koch and Angerer, 2007), BW is body weight (kg), and MWd and MWm are the molecular weights of DINP and the metabolite, respectively.

Intake estimates from urinary metabolite data is dependent upon several factors such as the precision of the metabolite measurements and the sampling procedures. When calculations are based on spot urine samples, assumptions may need to be made regarding the representative nature of the samples to capture variability in sample concentrations with time. For example, there can be significant variability in metabolite urinary concentrations throughout the day due to the relatively short half-lives of phthalates (Hildenbrand et al., 2009; Preau et al., 2010; Wittassek et al., 2010). Large biomonitoring programs, such as NHANES, circum-