Mutation Research 751 (2012) 82–157

Contents lists available at SciVerse ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

DEHP: Genotoxicity and potential carcinogenic mechanisms—A review☆

Jane C. Caldwell *

National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Mail Code: 8623P, Washington, DC 20460, United States

ARTICLE INFO

Article history:
Received 18 January 2012
Received in revised form 22 March 2012
Accepted 22 March 2012
Available online 3 April 2012

Keywords:
Genotoxicity
Epigenetics
Carcinogenicity
DEHP
di(ethylhexyl) phthalate

ABSTRACT

Di(ethylhexyl) phthalate (DEHP) is a manufactured chemical commonly added to plastics: it is a ubiquitous environmental contaminant to which humans are exposed through multiple routes. DEHP is a rodent carcinogen with an extensive data base on genotoxicity and related effects spanning several decades. Although DEHP has been reported to be negative in most non-mammalian *in vitro* mutation assays, most studies were performed under conditions of concurrent cytotoxicity, precipitation, or irrelevant metabolic activation. However, a number of *in vitro* rodent tissue assays have reported DEHP to be positive for effects on chromosomes, spindle, and mitosis. A robust database shows that DEHP increases transformation and inhibits apoptosis in Syrian hamster embryo cells. In a transgenic mouse assay, *in vivo* DEHP exposure increased the mutation frequency only in the liver, which is the target organ for cancer. *In vitro* exposure of human cells or tissues to DEHP induced DNA damage; altered mitotic rate, apoptosis, and cell proliferation; increased proliferation, tumor mobility, and invasiveness of tumor cell lines; and activated a number of nuclear receptors. DEHP has been shown to be an agonist for CAR2, a novel constitutive androstane receptor occurring only in humans. Environmental exposures of humans to DEHP have been associated with DNA damage. After taking into account study context and relevant issues affecting interpretation, *in vitro* studies reported that a similar DEHP concentration range induced both mutagenic and non-mutagenic effects in human tissues and, using a much more limited rodent database, transformation of embryonic rodent tissues. The human and rodent data suggest that DEHP induces cancer through multiple molecular signals, including DNA damage. The analyses presented here may provide guidance for similar data sets used in structure–activity relationships, computational-toxicology extrapolations, and attempts to extrapolate *in vitro* results to predict *in vivo* effects for hazard characterization.

Published by Elsevier B.V.

Contents

☆ *Disclaimer*: The views expressed in this article are those of the author, and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Abbreviations: ADME, absorption, distribution, metabolism and elimination; CAR, constitutive androstane receptor; CERHR, NTP Center for the Evaluation of Risks to Human Reproduction; CHO, Chinese hamster ovary; CYP, cytochrome p450; CpG, cytosine guanine dinucleotide; DEHP, di(ethylhexyl) phthalate, di(2-ethylhexyl) phthalate; DMSO, dimethylsulfoxide; Dnmt, DNA methyltransferases; EPA, Environmental Protection Agency; FSK, Forskolin; FRAP, FKBP12-rapamycin-associated protein; GJIC, gap junction intercellular communication; GST, glutathione-S-transferase; HCC, hepatocellular carcinoma; IARC, International Agency for Research on Cancer; IC_{50}, inhibitory concentration of 50%; IPCS, International Programme on Chemical Saftey; IKK, IkappaB kinase; LDH, lactate dehydrogenase; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MMP, matrix metalloproteinase; NADP, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NFκB, nuclear factor kappa B; NIEHS, National Institute of Environmental Health Science; NTP, National Toxicology Program; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; QSAR, quantitative structure–activity relationship; ROS, reactive oxygen species; RT-PCR, real-time polymerase chain reaction; S-9, rat microsomal activation system; SCE, sister chromatid exchange; SHE, Syrian hamster embryo; SXR, steroid and xenobiotic receptor; TIMP-2, tissue inhibitor of matrix metalloproteinase-2; WHO, World Health Organization.

* Correspondence address: 821 Bluestone Road, Durham, NC 27713, United States. Tel.: +1 919 541 4768.
E-mail address: Caldwell.jane@epa.gov.

1383-5742/$ – see front matter. Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.mrrev.2012.03.001

1. Introduction: occurrence, human exposure, and pharmacokinetic considerations in humans

Human exposure to di(ethylhexyl) phthalate (DEHP) can occur *via* the dermal, inhalation, oral, and intravenous routes of exposure and, when released from medical equipment to patients in the neonatal intensive care unit, levels can be high [178]. The toxicokinetics (absorption, distribution, metabolism and elimination [ADME]) of DEHP in humans, experimental animals and, where relevant, cellular systems, plays an important role in discerning potential adverse effects. The carcinogenic hazard of DEHP has been reviewed previously by the International Agency for Research on Cancer (IARC) [87,88] with a more recent evaluation that occurred in 2011 published as a brief summary of findings [72]. DEHP reproductive hazard has been evaluated twice by expert panels convened by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR), a joint venture between the The National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences (NIEHS) [96,97]. Both the previously published IARC and CERHR efforts contained discussed DEHP exposure and ADME. However, more recent studies in humans have been published after the finalization of these reviews [107–109] that provide critical information for the interpretation of human studies and relevance of rodent and marmoset models.

Upon ingestion by either rodents or humans, DEHP is rapidly metabolized by pancreatic lipases in the lumen of the gut to mono(2-ethylhexyl) phthalate (MEHP) and further metabolized into oxidative metabolites which can be glucuronidated before excretion in the urine and feces [7,8,178]. For humans the metabolism of DEHP is particularly complex and involves several oxidative metabolites. The data most cited and applicable to the characterization of DEHP ADME in humans is that of Koch et al. [107–109] and for rodents is Albro et al. [7–11]. Rodents and humans share many of these metabolites and pathways as shown in Fig. 1 (as adapted from Silva et al. [178]). One of the most studied DEHP metabolites, and the one implicated as responsible for many of DEHP's effects, is MEHP.

The study of DEHP ADME in either humans or experimental animal species is hampered by its ubiquitous presence in the environment, in laboratory equipment, and by its hydrolysis under abiotic conditions [65]. The most accurate estimate of DEHP ADME

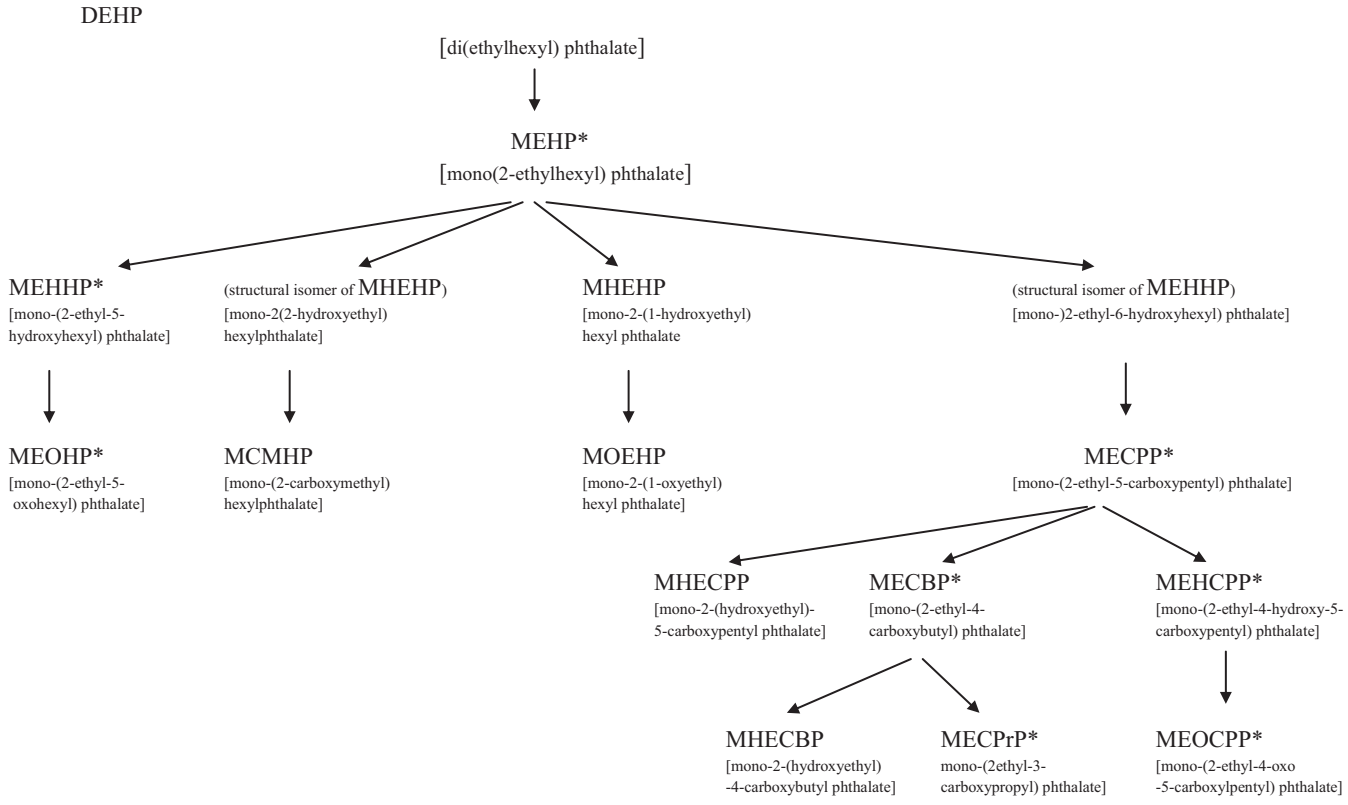

Fig. 1. Suggested metabolic scheme for DEHP metabolism in humans adapted from Silva et al. [178]. (*) Previously identified in rodents.