BEFORE THE
CHRONIC HAZARD ADVISORY PANEL
ON PHTHALATES AND PHTHALATE SUBSTITUTES

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COMMENTS OF THE

PHTHALATE ESTERS PANEL
OF THE
AMERICAN CHEMISTRY COUNCIL

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I. Introduction

The Phthalate Esters Panel of the American Chemistry Council[1] appreciates the opportunity to provide comment to the Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Substitutes. Demand for plasticizers is estimated to total about 1.5 billion pounds in the United States, about 70 percent of which is comprised of 14 commercial phthalates. The vast majority of phthalate use is to make polyvinyl chloride (PVC or vinyl) flexible for a wide variety of consumer, commercial, industrial, and medical applications.

Section 108 of the Consumer Product Safety Improvement Act (CPSIA) gives the CHAP a broad mandate to complete an examination of the full range of phthalates that are used in children's products. Included in this mandate are the requirements to –

- examine the likely levels of exposure to children, pregnant women, and others to phthalates, considering all routes of possible exposure from all sources;

- consider all potential health effects of each of the full range of phthalates, both in isolation and in combination with other phthalates;

- consider the levels of phthalate exposure at which there is a reasonable certainty of no harm; and

- consider the possible similar health effects of phthalate alternatives used in children's toys and child care articles

While daunting, the CHAP can draw on a considerable amount of information that already exists for the six phthalates addressed by the CPSIA. Among this information is the review of a previous CHAP completed in 2001 that considered the use of one of the CPSIA products, diisononyl phthalate (DINP), in children's products. As a result of this comprehensive review, the Consumer Product Safety Commissioners denied a petition to ban the use of phthalates in children's toys.

The comments provided below attempt to address the questions raised in the June 3 *Federal Register* notice[2] announcing the CHAP public comment session. In addition, specific comments on the Commission staff's toxicity reviews of the six CPSIA phthalates are included as Appendix A.

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[1] The Panel represents the four North American manufacturers of phthalates: BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, and Ferro Corporation. These companies also manufacture non-phthalate plasticizers that can be used in some flexible vinyl applications. Teknor-Apex Company, a major compounder of flexible vinyl, also is a Panel member.

[2] 75 *Federal Register* 31426.

II. Current and Future Uses of Phthalates

The primary phthalates to be considered by the CHAP possess a range of physical and chemical properties, from the fast fusing properties of dibutyl phthalate (DBP) and benzyl butyl phthalate (BBP), to the transitional properties of di(2-ethylhexyl) phthalate (DEHP), to the lower volatility characteristics of DINP and diisodecyl phthalate (DIDP) and the linear C_6-C_{10} phthalates that contain di-n-octyl phthalate (DnOP). The functionality of the various phthalates varies considerably and their interchangeability for use in children's and other consumer products needs to be evaluated on a case-by-case basis. For example, DBP is not used extensively in PVC formulations because of its relatively high volatility at typical processing temperatures.[3] This volatility makes the use of DBP in certain processing equipment (e.g., calendar rolls) difficult and results in shrinkage of the vinyl product during use. As a result, only a small amount can be used in PVC without incurring fusion/volatility problems. Similarly, BBP is used in specialty applications like PVC flooring and caulks, sealants, and adhesives and is not used in more general vinyl applications.[4]

Dibutyl Phthalate (DBP) – While not used extensively in PVC formulations, DBP has been used in certain personal care products (i.e., nail polish) and enteric coatings for some medicines. Dibutyl phthalate (DBP) has been found to be safe and effective for use in making nail polish flexible and resistant to chipping, and numerous reviews in the United States and Europe suggest, however, that exposure to DBP through regular use of nail polish products poses little or no risk to humans. Restrictions on its use in nail polish and other cosmetics in Europe, however, have caused many manufacturers to eliminate the use of DBP in nail products both in Europe and North America. Currently, the PE Panel does not believe that DBP is used in nail polish.

Although several authors (e.g., Hauser *et al*, 2004)[5] have estimated potential exposures from medicinal coatings, the PE Panel estimates that use of DBP in pharmaceuticals is minimal. This is based on information available on domestic production and import/export data. Anecdotal reports of significant exposures to DBP resulting from medicines are not representative of the general population.

Butyl Benzyl Phthalate (BBP) – BBP is used in several specialty applications like PVC flooring and caulks, sealants, and adhesives. A survey conducted by Health Canada in 2007 found no

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[3] Chemical Economics Handbook (CEH) Marketing Research Report – Plasticizers, SRI Consulting (January 2007), at 52.

[4] *Id*, at 50.

[5] Hauser R et al. Medications as a source of human exposure to phthalates. *Environ Health Persp* 112(6):751-753 (2004).

children's products containing BBP.[6] This finding is consistent with the conclusions of the European Chemicals Bureau that "BBP is not intentionally used in toys and childcare articles in the EU but may be present as impurity in trace amounts"[7] and the analysis conducted by the Australian Department of Health and Aging.[8]

Di-n-octyl Phthalate (DnOP) – DnOP is an ester of a straight chain 8-carbon (C_8) alcohol. It is not commercially available except as a mixture with the straight chain 6-carbon (C_6) alcohol and the straight chain 10-carbon (C_{10}) alcohol where it may comprise 20 percent of the mixture.[9] The C6-C10 mixture occurs as a result of one particular process for producing the alcohol. Rather than separate the alcohols, manufacturers esterify the alcohol mixture, resulting in a range of phthalates with alcohol chain lengths of C6, C8, and C10.52 Although it is possible to clean up the stream to produce concentrated DnOP, the additional expense would make the resulting product cost-prohibitive for toy applications.

DnOP terminology is not consistent in the technical literature, with the substance sometimes being referred to as "dioctyl phthalate." As noted in the assessment by Health Canada, [T]his has led to confusion with the branched-chain isomer, bis(2-ethylhexyl) phthalate (DEHP), also sometimes referred to as "dioctyl phthalate" or "DOP".[10] The assessment further explains that "the frequency of occurrence of DnOP in the environment may have been overestimated, since reports of environmental concentrations of „dioctyl phthalate" could pertain to DEHP, which has been used in much higher quantities than DnOP."

Confusion over the nomenclature may explain why DnOP, although included in restrictions imposed by the European Parliament, is not classified in Annex I of the European Commission's Classification and Labeling Directive (67/548/EEC), is not listed in Annex 1 of the Export and Import of Dangerous Chemicals Regulation (689/2008), and is not reported in the European Union as a high, or low, production volume chemical (HPVC or LPVC).[11]

Di(2-Ethylhexyl) Phthalate (DEHP) – Principal markets for DEHP include medical devices (e.g., blood and intravenous solution bags, tubing), weather stripping, garden hoses, wall coverings,

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6 Notice on Publication of Phthalates Regulations, 143 *Canada Gazette* Part I: 1849 (June 20, 2009)

7 European Union Risk Assessment Report – Benzyl Butyl Phthalate (BBP) (2007), at VII.

8 Australian Government Department of Health and Aging, Existing Chemical Hazard Assessment Report – Benzyl Butyl Phthalate (2008), at IV.

9 Australian Government Department of Health and Aging, Existing Chemical Hazard Assessment Report Di-n-Octyl Phthalate (2008), at IV.

10 Canadian Environmental Protection Agency, Priority Substances List Assessment Report: Di-n-Octyl Phthalate (1993), at 5.

11 This information is taken from the European Inventory of Existing Commercial Chemical Substances (EINECS) and is available at http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ora.

furniture upholstery, and consumer applications such as baggage and footwear. It has been replaced in applications such as automotive upholstery and wire and cable insulation because of the improved performance of other phthalates. As a result of concerns about exposure to infants and small children, DEHP was removed from soft buccal products (teething rings and pacifiers) over a decade ago. DEHP remains the preferred plasticizer in medical applications in part because it is one of the few plasticizers certified for such uses by the US Food and Drug Administration (FDA).

Di-isononyl Phthalate (DINP) – DINP is commonly used in many general-purpose plasticizer applications. Principal applications of DINP include PVC film and sheeting, coated fabrics, dip plastisol coatings, electrical jacketing, and resilient vinyl flooring. As with DEHP, it was voluntarily removed from pacifiers and teething rings several years ago. This voluntary restriction has effectively removed the highest potential source of exposure to DINP to children under 3 years of age.

Diisodecyl Phthalate (DIDP) – DIDP is used commonly in wire & cable insulation, automotive interiors, and coated fabrics. Although DIDP has applicability in a broad range of markets, the plasticizer was not found in any of the children's products sampled by Health Canada. Since the products were selected in mid-2007, prior to the implementation of CPSIA restrictions, the absence of DIDP suggests other considerations (e.g., cost) may create a significant disincentive to its use in children's products. Of the thirty five toys sampled by the National Toxicology Program's Expert Panel, none contained DIDP.[12] Similar studies conducted in the UK in 1992 and 1996 yielded the same result.[13]

III. Exposure Pathways

Exposure to the CPSIA phthalates and other plasticizers may result from food, air, drinking water, soil, and dust. Human exposure to DBP, BBP, DEHP, and DINP have been evaluated by Dr. Kathy Clark using information in a comprehensive data base maintained by the PE Panel (Clark *et al.* in press).[14] The ACC database is comprised of more than 500 references reporting measurements of PEs in various media. The references have been reviewed and categorized in terms of data quality, on the basis of analytical and sampling methodologies and reporting of quality assurance and quality control measures; data categorized as "not reliable" are not included in the analysis.

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[12] National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, Expert Panel Report on Di-Isodectyl Phthalate (2000), at 3. (NTP-CERHR DIDP Report)

[13] *Id,* at II-30.

[14] The Panel's data base has been provided to Commission staff. The article by Clark *et al.* has been accepted for publication in the *Journal of Human and Ecological Risk Assessment (*Appendix B).

The primary route of exposure is generally believed to be through food, although the pathway by which the phthalates get into the food is not well understood. Exposure via food may be evaluated by determining concentrations in a wide variety of foods (often called market basket surveys) and then quantifying typical consumption of each of those foods. The market basket survey data for the phthalates were collected 20 years ago (e.g. Page and Lacroix 1995),[15] however, when phthalates were more commonly used in food processing equipment. More recent measurements of phthalates in foods tend to be for composite diets (e.g. Fromme *et al.* 2007)[16] or for a few selected foods and not for a wide range of foods typical of the diets of most individuals.

Although many of the indirect studies have evaluated only selected exposure pathways (e.g. ingestion of food and exposure to environmental media), Wormuth *et al.* (2006) study also included exposure to consumer products via ingestion, inhalation, and dermal contact.[17] Inclusion of consumer products provides a more comprehensive evaluation of potential exposures to the users of those products; however, it will overestimate exposures for individuals who are not product users. In addition, the estimates of exposure due to use of consumer products are confounded by very limited information concerning the concentrations of PEs in the products, the scenarios of use including intake rates, and absorption factors. Also, as indicated above, none of the phthalates of primary interest to the CHAP currently are used to a great extent in consumer products.

The lowest estimates of daily intake of DBP are those based on diet only (e.g. Tsumura *et al.* 2003)[18] or diet and inhalation of air (Franco *et al.* 2007).[19] In the evaluation by Clark *et al.*, ingestion of food is estimated to account for about 75 percent of total exposure for the adult, teen, child, and toddler, with the remainder due to inhalation of indoor air and incidental ingestion of dust. For the formula-fed infant, ingestion of food accounts for 46% of exposure, followed by ingestion of dust (38%) and inhalation of indoor air (15%). For the breast-fed infant, ingestion of dust is the dominant exposure pathway (62% of total exposure), followed by inhalation of indoor air (25%) and ingestion of food (13%).

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[15] Page BD Lacroix GM. The occurrence of phthalate ester and di-2-ethylhexyl adipate plasticizers in Canadian packaging and food sampled in 1985 - 1989: A survey. *Food Addit Contam* 12:129-51 (1995).

[16] Fromme H *et al.* Intake of phthalates and di(2-ethylhexyl)adipate: results of the Integrated Exposure Assessment Survey based on duplicate diet samples and biomonitoring data. *Environ Int* 33:1012-20 (2007)

[17] Wormuth M *et al.* What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Analysis* 26(3):803-24 (2006).

[18] Tsumura Y *et al.* Estimated daily intake of plasticizers in 1-week duplicate diet samples following regulation of DEHP-containing PVC gloves in Japan. *Food Addit Contam* 20(4):317-24 (2003).

[19] Franco A *et al.* Comparison and analysis of different approaches for estimating the human exposure to phthalate esters. *Environ Int* 33:283–91 (2007).

In the recent dietary study by Fromme *et al.* 2007, BBP was detected in only 35 of 350 composite samples (detection limit of 0.01 mg/g). Despite this low frequency of detection of BBP in composite foods, *Clark et al* estimate that ingestion of food accounts for 68% to 77% of total exposure for the adult, teen, child, and toddler, with the remainder primarily due to incidental ingestion of dust and a minor contribution due to inhalation of indoor air. For both the formula-fed and breast-fed infants, ingestion of dust accounts for approximately 94% of exposure, with ingestion of food comprising most of the remainder.

For DEHP, Clark *et al* estimate the highest intake to be among toddlers, followed by children. For the adult, teen, child, and toddler, ingestion of food is the predominant exposure pathway, accounting for approximately 95% of total exposure. Most of the remainder is due to incidental ingestion of dust. For the formula-fed infant, incidental ingestion of dust accounts for 63% of total exposure, ingestion of food 34%, and ingestion of drinking water 2%. For the breast-fed infant, ingestion of food accounts for 76% of total exposure and incidental ingestion of dust 24%. In the indirect estimates by Wormuth *et al.* (2006), ingestion of food accounts for more than 95% of total exposure to the adult, teen, and child. For the toddler and infant, ingestion of food and ingestion of dust are the predominant exposure pathways, having approximately equal importance.

Clark *et al.* estimate that intake of DINP among infants and teens are comparable to those for adults, but are higher for the child and toddler. For the adult, teen, child, and toddler, ingestion of food accounts for 61% to 71% of intake, depending on the age group. The remainder of the exposure for these age groups (and all of the exposure to the infant) is due to ingestion of dust.

IV. Pharmacokinetics and Metabolism

Phthalates are well absorbed and rapidly metabolized in rats and other experimental animals, and metabolism appears to be qualitatively similar in humans (Koch *et al.*, 2005).[20] Recent efforts in the United States, Germany, and elsewhere have resulted in a growing data base of measured concentrations of phthalates in blood and urine samples taken from the general population.

[20] Koch HM *et al.* New metabolites of di(2-ethylhexyl) phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. *Arch Toxicol* 79:367-76 (2005).

a. Estimating Exposure from Biomonitoring Data

Interpretation of these data requires an understanding of the metabolism to relate the biomonitoring results to exposure. Fortunately, the following equation, from David (2000)[21] as expressed by Koch *et al.* (2003b)[22], can be used to estimate the daily intake:

$$DI = (UE \times CE)/(1000 \times F_{UE}) \times (MW_d/MW_m)$$

where:

DI = daily intake of diester (mg/kg/d)
UE = creatinine-corrected urinary metabolite concentration (mg/g)
CE = creatinine clearance rate normalized by body weight (mg/kg/d)
F_{UE} = molar conversion factor that relates urinary excretion of metabolite to diester
MW_d = molecular weight of diester (g/mol)
MW_m = molecular weight of monoester (g/mol)

For short chain PEs the simple monoesters appear to be the major metabolites (Wittassek and Angerer 2008).[23] Thus, for DBP and BBP, the estimates of intake are based on measurements of the following metabolites in urine: monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP).

For DEHP and DiNP, the oxidized (secondary) metabolites have been found to be more suitable biomarkers of exposure because they are produced in greater quantity compared with the primary metabolites and they are not susceptible to external contamination, as are the primary metabolites (Wittassek and Angerer 2008). For DEHP, intake estimates are based on measurements of mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(2-carboxymethylhexyl) phthalate (MCMHP), and mono-2-ethylhexyl phthalate (MEHP). For DINP, intake estimates are based on measurements of mono(hydroxyisononyl) phthalate (MHiNP), mono(oxoisononyl) phthalate (MOiNP), mono(carboxyisononyl) phthalate (MCiNP), and monoisononyl phthalate (MiNP).[24]

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[21] David RM. Exposure to phthalate esters. *Environ Health Persp* 108(10):A440 (2000)

[22] Koch HM *et al.* An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. *Int J Hyg Environ Health* 206:77-83 (2003).

[23] Wittassek M & Angerer J. Phthalates: metabolism and exposure. *Int J Andrology* 31(2):131-8 (2008)

[24] Some DINP is produced from a mixed isomeric alcohol unlike the other phthalates, which are esters of single structures of alcohols. Therefore, DINP is a blend of chromatographic peaks which makes measuring the metabolites in the urine more challenging.

The values for F_{UE} are critical to the calculation of exposure. For example, a value of 0.059 for MEHP was derived by Koch *et al*. (2004)[25] based on a single individual (as are the values for the oxidative metabolites of MEHP), while a value of 0.12 was derived by Anderson *et al*. (2001) [26] using eight subjects (oxidative metabolites were not analyzed). Clearly, the value selected has an impact on the exposure calculated; additional volunteer studies are necessary to determine more accurate values. The following is a list of values used in the above equation: 0.69 for MBP (Anderson *et al.* 2001); 0.73 for MBzP (Anderson *et al.* 2001); 0.12 for MEHP (Anderson *et al.* 2001); 0.233 for MEHHP, 0.15 for MEOHP, 0.042 for MCMHP, and 0.185 for MECPP (Koch *et al*. 2005); 0.02 for MiNP, 0.106 for MOiNP and 0.202 for MHiNP (Koch and Angerer, 2007).[27]

Since the measured urinary concentrations in a spot sample can vary by a factor of 2 or 3 based on the hydration status of the individual, a correction also is required for the creatinine excretion rate. While creatinine rates will vary among individuals, estimates for male and female, and adult, child, and infant populations are generally used. The values for creatinine clearance rate are: 23 and 18 mg/kg/d for male and female adults, respectively (Kohn *et al.* 2000)[28]; and 20, 11, and 9.8 mg/kg/d for all adults combined, children, and infants, respectively (Calafat and McKee 2006).[29] Normalization to creatinine excretion per kg body weight is thought to reduce the diurnal variability in urinary output and the inter-individual variability in urinary output (David 2000).

b. Diurnal Variability in Metabolite Levels

Estimation of exposure from biomonitoring data for the phthalates also is complicated by the relatively short half-life of the excretion of the metabolites. Anderson et al (2001) found no detectable labeled metabolite of DBP eliminated after the first 24 hours, suggesting a half live for the metabolite of less than 6 hours. As a consequence, urinary concentrations are likely to vary substantially over the course of 24 hours. Using a simple pharmacokinetic model for DEHP, which has metabolites with half-lives to those of DBP, Lorber et al (2010) demonstrated that for a given daily exposure rate, spot urinary samples could be expected to produce

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[25] Koch HM *et al.* Di(2-ethylhexyl) phthalate (DEHP) metabolites in human urine and serum after a single oral dose of deuterium labelled DEHP. *Arch Toxicol* 78:123-30 (2004).

[26] Anderson WA *et al.* A biomarker approach to measuring human dietary exposure to certain phthalate diesters. *Food Addit. Contam.* 18, 1068–1074 (2001).

[27] Koch HM & Angerer J. Di-iso-nonyl phthalate (DINP) metabolites in human urine after single oral dose of deuterium-labelled DINP. *Int J Hygiene Environ Health* 210:9-19 (2007)

[28] Kohn MC *et al.* Human exposure estimates for phthalates. *Environ Health Persp* 108(10):A440-2 (2000)

[29] Calafat AM & McKee RH. Integrating biomonitoring exposure data into the risk assessment process: Phthalates (diethyl phthalate and di[2-ethylhexyl] phthalate) as a case study. *Environ Health Persp* 114(11):1783-9 (2006)

concentrations 2 to as much as 5 times higher than the average urinary concentration.[30] For this reason, Hays *et al.* (2008) have suggested that biomonitoring data for compounds with short biological half-lives (like phthalates) should be evaluated on a population basis using the central tendency of the population rather than the extremes.[31]

The analysis by Lorber et al also suggests that more 24-hour urine collections likely produce more reliable estimates of exposure than spot urine samples (Aylward *et al.*, 2009).[32]

IV. Exposure Estimates

The biomonitoring data collected by the Center for Disease Control and Prevention (CDC) as part of its National Health and Nutrition Examination Survey (NHANES) suggest that exposures to five of the six phthalates of primary interest to the CHAP are generally well below the reference dose levels established by EPA and others. Based on the data provided in the Fourth National Report,[33] mean exposures to the phthalates can be estimated as indicated in Table 1.

The estimated exposures also are below the reference dose at the 95th percentile of the biomonitoring data.

While biomonitoring data for DIDP is not available from CDC, NTP-CERHR estimated that exposure to DIDP in the general adult population is lower than for DEHP, based on the "physicochemical characteristics of DIDP and limited monitoring data."[34] Müller *et al.* (2003)[35] estimated total oral exposure to DIDP to be 3 µg/kg/day for adults. While the estimates for children were higher, the European Food Safety Authority (EFSA) noted that these exposures were based on oral exposure from toys and were probably overestimated. EFSA assumed a value of 7 µg/kg/day as a worst case estimate of dietary exposure to DIDP and concluded that these exposures were "well below" the tolerable daily intake of 150 µg/kg/day.

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[30] Lorber M *et al.* A simple pharmacokinetic model to characterize exposure of Americans to Di-2-ethylhexyl phthalate. *J Exp Sci and Environ Epidemol* 20:38-53 (2010)

[31] Hays SM *et al.* Guidelines for the derivation of Biomonitoring Equivalents: report from the Biomonitoring Equivalents Expert Workshop. *Regul Toxicol Pharmacol* 51, S4–15 (2008).

[32] Aylward LL *et al.* Derivation of Biomonioring Equivalents for di-n-butyl phthalate (DBP), benzylbutyl phthalate (BzBP), and diethyl phthalate (DEP). *Regul Toxicol Pharmacol* 55:259-267 (2009)

[33] CDC, Fourth National Report on Human Exposure to Environmental Chemicals (2009)

[34] NTP-CERHR DIDP Report, at 7.

[35] Müller AM *et al.* Ministeriet for Fødevarer, Landbrug og Fiskeri Veterinær- og Fødevaredirektoratet (2003). Human exposure to selected phthalates in Denmark, rapport 2003: 15. (cited in EFSA, 2005)

Table 1. Geometric Mean Exposures (µg/kg/day)[1]

		Total Population	Age Groups			Gender		Reference Dose[2]
			6-11	12-19	20+	Male	Female	
DBP	MnBP	0.720	0.768	0.727	0.665	0.656	0.811	**100**
BBP	MBzP	0.431	0.658	0.554	0.367	0.442	0.433	**200**
DEHP	MEHP	1.048	0.786	0.986	1.019	1.101	1.029	**20**
	MEHHP	2.326	2.446	2.418	2.144	2.479	2.248	**20**
	MEOHP	2.417	2.6	2.595	2.204	2.514	2.384	**20**
	MECPP	4.446	4.613	4.555	4.105	4.674	4.357	**20**
DnOP	MOP	*	*	*	*	*	*	**3500**
DINP	MINP	*	*	*	*	*	*	**120**
DIDP	MIDP	--	--	--	--	--	--	**150**

[1] The urinary concentrations of phthalate monoesters reported by CDC were converted to daily intake of the parent phthalate using the methodology described in David, R. (2000).

[2] The Reference Doses for DBP, BBP, and DEHP are the RFD's derived by EPA, as presented in the Integrated Risk Information System (IRIS). The value for DINP is the acceptable daily intake from 2001 CPSC CHAP. The value for DIDP is based on the Tolerable Daily Intake reported by the European Food Safety Authority.[36,37] The value for DnOP is based on a NOAEL of 350 mg/kg/day reported by the NTP-CERHR.

* Below the limit of detection.

V. Toxicity Data

As indicated by the summaries prepared by the Commission staff, there is a large body of toxicity information available for the phthalates. Historically, concern about the potential of one or more of the phthalates to produce adverse health effects in humans is based on results of laboratory studies indicating an increased incidence of liver tumors and male reproductive anomalies in rodents. A number of reviews have been conducted to assess the potential significance of these animal data to humans. These reviews have generally concluded that the mechanism by which tumors result in laboratory rodents is not relevant to humans. More recent data on developmental effects in male mice and marmosets further suggest that the rat is not a good model for predicting human effects.

[36] European Food Safety Authority (EFSA). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food (AFC) on a request from the Commission related to Di-Butylphthalate (DBP) for use in food contact materials. *The EFSA Journal* 242: 1-17 (2005).

[37] EFSA. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Material in Contact with Food (AFC) on a request from the Commission related to Di-isodecylphthalate (DIDP) for use in food contact materials. *The EFSA Journal* 245: 1-14 (2005).

a. Rodent Liver Tumors

There is a robust body of data indicating that the liver tumors observed in rodent studies are due to a mode of action involving the peroxisome proliferator-activated receptor-α (or PPARα). The progression of liver effects caused by peroxisome proliferating compounds (PPCs), leading up to and including tumors, has been well characterized, and there is a strong scientific consensus that such effects are not relevant for human risk assessment (Klaunig *et al.,* 2003).[38] The liver effects observed in the rodent studies conducted with the phthalates, with the possible exception of spongiosis hepatis (a spontaneous lesion in rats), were consistent with the PPARα mode of action. In contrast, no such effects were seen in the primate studies, even at doses of 2500 mg/kg/day (e.g., Hall *et al.,* 1999; Pugh *et al.,* 2000).[39,40]

The potential human response to PPCs also has been examined in liver biopsies from patients treated with hypolipidemic drugs (i.e., fibrates) which are potent PPCs. Morpohometric measurements in liver biopsies did not reveal evidence for peroxisome proliferation. As noted by IARC, the potential carcinogenic risk of hypolipidemic therapy with fibrates has been evaluated in two limited clinical trials with no evidence for carcinogenesis. (IARC, 1996)[41]

A review of peroxisome proliferation by IARC concluded that rats and mice had a much higher propensity for peroxisomal proliferation than other species including humans (IARC, 1995).[42] More specific to phthalates, IARC revised its classification of DEHP in 2000 from "possibly carcinogenic to humans" (Group 2B) to "not classifiable as to its carcinogenicity to humans" (Group 3)[43] based in large part on its consideration of the relevance of the rodent liver tumors. In summarizing its conclusion, IARC explained –

> In making its overall evaluation of the carcinogenicity to humans of [DEHP], the Working Group took into consideration that (*a*) [DEHP] produces liver tumours in

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38 Klaunig J *et al.* PPARα agonist-induced rodent tumors: Modes of action and human relevance. *Crit Rev Toxicol* 33(6): 655–780 (2003).

39 Hall M *et al.* Effects of di-isononyl phthalate (DINP) on peroxisomal proliferation markers in the marmoset – DINP is not a peroxisome proliferator. *Toxicol Sci* 24(3): 237-244 (1999).

40 Pugh G *et al.* Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in Cynomolgus monkeys. *Toxicol Sci* 56: 181-188 (2000).

41 IARC. Evaluations for clofibrate and gemfibrozil. IARC monographs on the evaluation of carcinogenic risks to humans, some pharmaceutical drugs. Vol. 66, Lyon (1996).

42 IARC. Peroxisome proliferation and its role in carcinogenesis: Views and expert opinions of an IARC Working Group Lyon 7-11 December, 1994. IARC Technical Report No. 24, International Agency for Research on Cancer, Lyon, France (1995). Available at http://monographs.iarc.fr/ENG/Publications/techrep24/IARCrep24.pdf.

43 IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 77 - Some Industrial Chemicals. World Health Organization. Lyon, France (2000).

> rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (*b*) peroxisome proliferation and hepatocellular proliferation have been demonstrated under the conditions of the carcinogenicity studies of [DEHP] in rats and mice; and (*c*) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to [DEHP] nor in the liver of exposed non-human primates. Therefore, the mechanism by which [DEHP] increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans.[44]

In 2003, a workgroup of the ILSI Risk Science Institute reviewed the relationship of peroxisome proliferation and liver tumors in rodents. The results of that workshop are presented in a paper titled "PPAR*α* Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance" (Klaunig *et al.,* 2003). The workshop concluded –

> In summary, the weight of evidence overall currently suggests that the rodent [mode of action] for liver tumors is not likely to occur in humans, taking kinetic and dynamic factors into account. This conclusion is based upon evaluation of the existing body of evidence and would apply to the consequences of exposure to known examples of PPAR*α* agonists.[45]

Other reviews support the ILSI and IARC conclusions. For example, CPSC's 2001 CHAP concluded "that DINP causes liver cancer in rodents by a PPARα-mediated mechanism that is pronounced in rodents and believed not readily induced in humans, especially at doses resulting from current use of consumer products."[46] Subsequently the CPSC staff, based on the CHAP and on the ILSI workshop, "concluded that DINP, which is a peroxisome proliferator, is not likely to present a cancer risk in humans" (CPSC, 2003).[47]
Similarly, the European Union (EU) in its risk assessment of DINP concludes –

> The current literature suggests that only rats and mice are responsive to the carcinogenic effects of peroxisome proliferator, while dogs, non-human primates and humans are essentially non-responsive or refractory. In this way, it should be noted that in monkey, following oral administration of DINP for 14 days or 13 weeks there was no evidence of peroxisome proliferation. This indicates that

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[44] *Id*, at 124.

[45] Klaunig *et al.,* 2003, at 693.

[46] Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), Report to the US Consumer Product Safety Commission (2001), at 122.

[47] CPSC. Response to additional question from Commissioner Moore on Petition HP 99-1 to Ban Polyvinyl Chloride In Toys and Other Products. Memorandum from M. Babich, M. Wind, and L. Martin to the Commission (Feb. 13, 2003). Available at http://www.cpsc.gov/library/foia/foia03/brief/response.pdf.

> monkeys and subsequently probably humans are far less sensitive than rodents to peroxisome proliferation and its relative liver effects. It should be noted that recently IARC gave a ruling on the carcinogenicity of DEHP and concluded that the mechanism (peroxisome proliferation and PPARα activation) by which DEHP increased the incidence of liver tumours in rodents was not relevant to humans.[48]

The conclusion that activation of the PPARα receptor is the key event in the induction of liver tumors in the laboratory animals is supported by the absence of tumors in nine PPAR-α–null (knock-out, or KO) mice exposed to a strong peroxisome proliferator (Wy-14,643) after 11 months, whereas each of the six similarly exposed wild-type mice had multiple hepatocellular neoplasms (Peters *et al.*, 1997).[49] Subsequent work further suggested that DEHP failed to induce peroxisomal enzymes and peroxisome proliferation in KO mice after 24 weeks of exposure (Ward *et al.* 1998).[50]

Recent studies conducted in Japan using KO mice by Ito *et al.* (2007),[51] however, have led some to suggest that liver tumors might occur in wild-type mice via a PPARα-independent mechanism and that the observed liver tumors may therefore have relevance to humans (Ito *et al*., 2007; Guyton *et al.*, 2009).[52] The Japanese researchers observed that chronic exposure to DEHP resulted in a low level of liver tumors in the KO mice. No such tumors were observed in wild-type mice with an intact PPAR receptor, however, and the relevance of these tumors in KO mice to humans and the PPARα mode of action is unclear. The unusually high survival rates reported by Ito et al. also raise serious questions about their data. Ito et al. did not address in their paper why the survival rate in their study for both the wild-type and KO mice was so different from that reported in Howroyd *et al.* (2004).[53] In addition, data confirming that Ito et al. had in fact knocked out the PPARα alleles was not included in the published report, key information for validating their model and their results.

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[48] European Chemicals Bureau (ECB). 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate (DINP), CAS Nos: 68515-48-0 and 28553-12-0, EINECS Nos: 271-090-9 and 249-079-5, Summary Risk Assessment Report, Special Publication I.03.101, p. 18 (2003), at 243. Available at http://ecb.jrc.ec.europa.eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/dinpreport046.pdf.

[49] Peters JM *et al.* Role of PPAR alpha in the mechanism of action of the nongenotoxic carcinogen and peroxisome proliferator Wy-14,643. *Carcinogenesis* 18, 2029–2033 (1997).

[50] Ward JM *et al.* Receptor and nonreceptor-mediated organ-specific toxicity of di(2-ethylhexyl)phthalate (DEHP) in peroxisome proliferator-activated receptor alpha-null mice. *Toxicol Pathol* 26(2):240–246 (1998).

[51] Ito Y *et al.* Di(2-ethylhexyl)phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor alpha-independent pathway. *J Occup. Health* 49:172–182 (2007).

[52] Guyton KZ *et al.* A reexamination of the PPAR-α activation mode of action as a basis for assessing human cancer risks of environmental contaminants. *Environ Health Persp* 117:1664–1672 (2009).

[53] Howroyd P *et al.* Decreased longevity and enhancement of age-dependent lesions in mice lacking the nuclear receptor peroxisome proliferator-activated receptor α (PPARα). *Toxicol Pathol* 32:591-599 (2004).

Ito *et al*. proposed an alternative mechanism for rodent liver tumors that is independent of PPARα activation. Their hypothesis suggests increased production of reactive oxygen species as a result of increased oxidative stress in mouse hepatocytes due to DEHP exposure. However, as suggested previously (Kostadinova *et al*., 2005; Balkwill and Couseens, 2005)[54,55] the underlying increased susceptibility of the KO mice to tumorigenesis in the absence of chemical treatment may be due to fundamental mechanistic differences limiting the applicability of the model for testing the proposed hypothesis. Spontaneous tumors are known to occur in the KO mice at 24 months (Takashima *et al*., 2008).[56] The utility of this mouse model to assess alternative mechanisms of tumorigenesis, therefore, is problematic as is its relevance to humans. Importantly, there are no known reports on the ability of DINP to induce production of reactive oxygen species in livers of rodents, humans or non-humans primates, or in cultured liver cells from these species.

Subsequent analysis of gene expression in wild-type and KO mice by Ren *et al.* (2010)[57] indicate that transcriptional responses to DEHP and other peroxisome proliferating chemicals are overwhelmingly dependent on PPARα. Ren *et al.* point out that a number of their findings argue against the view that the induction of tumors in the KO mice supports a mode of action other than PPARα activation in wild-type strains –

> First, the transcript profile comparison in the present study showed that the vast majority of genes altered by DEHP in wild-type mice were not similarly altered in PPARα-null mice. Thus, the DEHP-induced tumors in wild-type mice could only be PPARα independent if the ~6% of the PPARα-independent gene changes were responsible for the tumors, an unlikely scenario given the magnitude of the PPARα-dependent effects. Second, wild-type and PPARα-null mice exhibited differences in DEHP-induced carcinogenesis. DEHP did not induce equivalent levels of tumors in the wild-type and PPARα-null mice; there were no statistically significant increases in liver tumors in the wild-type mice under these exposure conditions (200 ppm). DEHP increased the expression of growth control genes in PPARα-null mice but not in wild-type mice at equivalent doses (Ito *et al.*, 2007). Transcript profiling and RTPCR showed highly dissimilar changes in gene expression in the liver tumors from the wild-type and PPARα-null mice,

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54 Kostadinova R *et al.* PPARs in diseases: control mechanisms of inflammation. *Curr Med Chem* 12:2995-3009 (2005).

55 Balkwill F & Coussens LM. Cancer: an inflammatory link. *Nature* 431:405-406 (2004).

56 Takashima K *et al.* Different mechanisms of DEHP-induced hepatocellular adenoma tumorigenesis in wild-type and PPARα-null mice. *J Occup Health* 50:169-180 (2008).

57 Ren H *et al.* Characterization of peroxisome proliferator–activated receptor α—independent effects of PPARa activators in the rodent liver: di-(2-ethylhexyl) phthalate also activates the constitutive-activated receptor. *Toxicol Sci* 113(1):45-59 (2010).

> indicating different molecular mechanisms of their origins (Takashima *et al.*, 2008). Lastly, in the absence of PPARα, DEHP altered a unique set of genes not similarly altered in wild-type mice. Some of these genes are known targets of [constitutive-activated receptor or CAR]. Taken together, these data indicate that although DEHP can induce marginal increases in liver tumors in PPARα-null mice, the mode of action is different from that in wild-type mice. The transcriptional responses induced by DEHP in wild-type and nullizygous mouse strains indicate that CAR is important in the induction of tumors in PPARα-null mice.[58]

Ren *et al.* point to evidence that PPARα and CAR have antagonist properties and note that "[t]he expression of the CAR gene itself was increased by DEHP in PPARα-null but **not** in wild-type mice." (emphasis added) CAR activation is a minor pathway in wild-type mice and this activation, likely by MEHP, would, in essence, be "swamped out" by the activation of PPARα and its ensuing effects. The minor contribution of DEHP-induced CAR activation to liver tumorigenesis in the wild-type mouse is not sufficient to drive tumorigenesis independent of PPARα.

To date, there has only been one study which investigated the ability of DEHP and MEHP to activate human CAR (DeKeyser *et al.*, 2009).[59] In human livers, the CAR gene expresses a number of differentially spliced mRNA transcripts, (Savkur *et al.*, 2003; Arnold *et al.*, 2004; Jinno *et al.*, 2004; Lamba *et al.*, 2004).[60],[61],[62],[63] The CAR2 splice variant, which lacks constitutive activity, is expressed at approximately 30% of the reference transcript level in human hepatocytes (Xu *et al.*, 2004; DeKeyser *et al.*, 2009).[64] The CAR2 transcript cannot be generated in marmoset, mouse or rat, indicating that CAR2 may be unique to humans (Kent *et al.*, 2002; DeKeyser *et al.*, 2009).[65] DEHP has been shown to activate CAR2 in vitro in a transactivation

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[58] *Id.,* at 55-56.

[59] DeKeyser J *et al.* Di(2-ethylhexyl) phthalate is a highly potent agonist for the human constitutive androstane receptor splice variant, CAR2. *Molec Pharmacol* 75:1005-1013 (2009).

[60] Savkur R *et al.* Alternative splicing within the ligand binding domain of the human constitutive androstane receptor. *Mol Genet Metab* 80:216-226 (2003).

[61] Arnold K *et al.* Alternative splicing affects the function and tissue-specific expression of the human constitutive androstane receptor. *Nucl Recept* 2:1 (2004).

[62] Jinno H *et al.* Identification of novel alternative splice variants of human constitutive androstane receptor and characterization of their expression in the liver. *Mol Pharmacol* 65:496-502 (2004).

[63] Lamba J *et al.* Expression of constitutive androstane receptor splice variants in human tissues and their functional consequences. *J Pharmacol Exp Ther* 311:811-821 (2004).

[64] Xu R *et al.* A structural basis for constitutive activity in the human CAR/RXRalpha heterodimer. *Mol Cell* 16:919-928 (2004).

[65] Kent W *et al.* The human genome brower at UCSC. *Genome Res* 12:996-1006 (2002).

study in which CAR2 was added to a kidney epithelial cell line derived from the African green monkey (*i.e.*, COS-1). However, when MEHP was tested in the same assay, only weak activity was demonstrated even at a concentration of 10uM. From this, DeKeyser *et al.* (2009) concluded that DEHP, not MEHP, is a potent agonist of CAR2. However, this conclusion is inconsistent with the prevailing hypothesis that MEHP is the active metabolite in animals and humans due to the high rate of metabolism of the parent compound (see, e.g., ECB, 2008; Rhodes *et al.*, 1996; Tomita *et al.*, 1982).[66],[67],[68] Thus, these data suggest that activation of CAR2 is not a plausible mode of action whereby DEHP could cause cancer in humans (or even mice).

b. Male Developmental Effects

Various reports have suggested adverse trends in male reproductive health, citing an increase in the incidence of both congenital malformations (hypospadias, cryptorchidism) and adult onset diseases (lowered sperm counts, testis germ cell cancer). While the suggestion of a downward trend in several of these effects is contradicted by clinical results (Fisch, 2009; Fisch et al. 2010)[69,70], these reports have led to the suggestion of a "testicular dysgenesis syndrome" to explain the interrelated nature of these diseases (Skakkebaek et al. 2001).[71] According to this hypothesis, perturbations of the developmentally-critical *in utero* or perinatal environment, possibly due to the suppression of fetal androgen production and/or increased estrogen exposure, may result in subsequent malformation of the male reproductive tract. Phthalates, such as DBP and DEHP, have been implicated in the development of testicular dysgenesis (Fisher 2004; Latini et al. 2006)[72,73] due to their ability to induce reproductive tract abnormalities in rats following *in utero* exposure. In particular, phthalate-induced suppression of fetal steroidogenesis in rats has been cited as a main driving-force in the expression of concern by an Expert Panel for the Center of the Evaluation of Risks to Human Reproduction

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66 ECB. bis(2-ethylhexyl)phthalate (DEHP), CAS No: 117-81-7, EINECS No: 204-211-0, European Union Risk Assessment Report, PL-2 80, EUR 23384 EN, European Chemicals Bureau. (2008) Available at http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/ RISK_ASSESSMENT/REPORT/dehpreport042.pdf.

67 Rhodes C, et al. (1986). Comparative pharmacokinetics and subacute toxicity of di(2-ethylhexyl)phthalate (DEHP) in rats and marmosets: Extrapolation of effects in rodents to man. *Environ Health Persp* 65:299-308 (1986). Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474672.

68 Tomita I *et al.* Mutagenic/carcinogenic potential of DEHP and MEHP. *Environ Health Persp* 45:119-125 (1982).

69 Fisch, H. Declining Worldwide Sperm Counts: Disproving a Myth. Urol Clin N Am 35:137-146 (2008)

70 Fisch *et al.* Rising hypospadias rates: Disproving a myth. J Pediatric Urology 6(1):37-39 (2010).

71 Skakkebaek NE *et al.* Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 16(5): 972-978 (2001)

72 Fisher JS. Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. *Reproduction* 127(3):305-315 (2004).

73 Latini G *et al.* 2006. Phthalate exposure and male infertility. *Toxicology* 226(2-3):90-98 (2006).

(Kavlock et al. 2006).[74] DBP and other developmentally active phthalates have been shown to target a common set of genes involved in cholesterol transport in rat fetal Leydig cells, and the effects of these phthalates are due, at least in part, to lowered testosterone production as a result of decreased expression of these genes (Lehmann *et al.* 2004).[75]

The results seen in rats were not duplicated in mice, however, where steroidogenesis was not targeted (Gaido et al. 2007).[76] These results suggest that the action of phthalate esters on Leydig steroidogenesis and seminiferous cord development are mechanistically distinct and that mice appear to be resistant to the suppression of fetal Leydig steroidogenesis.[77]

The available data from primates also call into the question the value of the rat results for predicting potential effects in humans. In a significant study published in 2006, Tomonari *et al.* found that very high doses of DEHP administered to juvenile marmoset monkeys from weaning to sexual maturity had no negative effects on the development of the male reproductive tract.[78] In a study by McKinnell *et al.* (2009) pregnant marmosets were administered doses of a metabolite of DBP (MBP) of 500 milligrams per kilogram of body weight per day (mg/kg/day). Male offspring were followed through to adulthood, and showed no testicular damage or other reproductive system effects, and no reduction in germ cells. The authors concluded that "[f]etal exposure of marmosets to MBP does not measurably affect testis development/function or cause testicular dysgenesis."[79]

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[74] Kavlock R *et al.* NTP CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of di(2-ethylhexyl) phthalate. *Reprod Toxicol* 22(3):291-399 (2006).

[75] Lehmann KP *et al.* Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. *Toxicol Sci* 81(1): 60-68 (2004).

[76] Gaido KW *et al.* Fetal mouse phthalate exposure shows that Gonocyte multinucleation is not associated with decreased testicular testosterone. *Toxicol Sci* 97(2): 491-503 (2007).

[77] The PE Panel currently is sponsoring research at Brown University to delineate this species-specific response using a rat host xenotransplant model to examine phthalate-induced alterations of fetal testicular development.

[78] Tomonari Y *et al.* Testicular toxicity study of di(2-ethylhexyl) phthalate (DEHP) in juvenile common marmoset. *The Toxicologist* 72:385 (2003).

[79] McKinnell C *et al.* Effect of fetal or neonatal exposure to MBP on testicular development and function in the marmoset. *Hum Reprod*. 24:2244-2254 (2009).

VII. Cumulative Risk[80]

The results of cumulative exposure studies have been mixed. The research conducted by Gray and his coworkers have suggested dose-additivity in laboratory animals at relatively high-dose levels (~150 mg/kg body weight), but Foster *et al.*[81] was unable to produce additivity at lower doses (~100 mg/kg). More recent studies have suggested response additivity whereby substances may have the same effect by different mechanisms. These studies also have been conducted at high doses that are not reflective of environmental exposures.

The papers cited in the action plan are not able to address the fundamental question of whether the mode of action for the individual chemicals is dose dependent, or whether the model of combined action is also dose-dependent. This is a fundamental limitation of nearly all interaction and mixtures studies. The recommendation to apply dose addition broadly, and particularly to low doses, relies on a fundamentally weak assumption that cannot be validated and, in fact, that contradicts the available data.

Christensen *et al.* (2009) acknowledge that "our developmental rat model would not have produced any responses, had we combined all mixture components at [low, environmentally relevant exposure levels.]"[82] This finding is supported by earlier studies of up to 25 chemicals at environmental dose levels by Chapin *et al.* (1989)[83] and Heindel *et al.* (1995).[84]

The absence of a cumulative effect at environmental relevant levels is further supported by the evaluation conducted by Benson (2009) who concluded that "it is unlikely that humans are suffering adverse developmental effects from current environmental exposure to these phthalate esters."

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[80] Appendix C contains two publications on cumulative risk by Dr. Chris Borgert.

[81] Foster PMD *et al.* Antiandrogenic effects of a phthalate combination on *in utero* male reproductive development in the Sprague-Dawley rat: additivity of response?, Poster presentation at Society of Toxicology Annual Meeting (2002).

[82] Christiansen S *et al.* Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. *Environ Health Persp* 117(2):1839-1846 (2009).

[83] Chapin RE *et al.* Toxicology studies of a chemical mixture of 25 groundwater contaminants. III. Male reproduction study in B6C3F1 mice. *Fund Appl Toxicol*. 13(3):388-98 (1989).

[84] Heindel JJ *et al.* Assessment of the reproductive toxicity of a complex mixture of 25 groundwater contaminants in mice and rats. *Fund Appl Toxicol* 25(1):9-19 (1995).