Proposed Approach to Conducting a Cumulative Risk Assessment for 6 Phthalates (DINP, DIDP, DnOP, DEHP, DBP, and BBP)

ExxonMobil Chemical Company

July 19, 2010

Section 108 of the Consumer Product Safety Improvement Act of 2008 (CPSIA) directs that the Consumer Product Safety Commission (CPSC) appoint a Chronic Hazard Advisory Panel (CHAP) to assess phthalates used in children's toys and childcare articles. Among other things, the CHAP is to consider the cumulative effect of total exposure to phthalates.

The term "phthalate" is used to refer to a dialkyl ester of *ortho*-phthalic acid, where the alkyl portion is a hydrocarbon chain with one or more carbons.[1] The hydrocarbon may be linear (e.g., di-n-octyl phthalate (DnOP)) or branched (e.g., di(2-ethylhexyl) phthalate (DEHP); diisononyl phthalate (DINP)). In this paper we refer to the longest portion of a branched chain as the "backbone" of the associated phthalate; the length of the backbone is designated as Cx, where x is the number of carbons in the backbone.

Although sharing a common name, the phthalates show a large diversity in function and toxicology. The lowest molecular weight phthalates (C1 to C4) generally are not useful as vinyl plasticizers, whereas the higher molecular weight phthalates (C7 and greater) have few applications other than as vinyl plasticizers. In terms of toxicology, a division can be made between low molecular weight (LMW) phthalates with a backbone of six carbons or less (≤ C6), and high molecular weight phthalates (HMW), having a backbone of seven or more carbons (≥ C7), with the latter having very low toxicity in general. With respect to reproductive/developmental toxicity, C4 to C6 phthalates (e.g., dibutyl phthalate (DBP, BBP, and DEHP) have shown clear developmental and reproductive effects warranting classification under the EU Classification, Labelling and Packaging (CLP) Regulation and the UN Globally Harmonized System (GHS); HMW phthalates show little to no such toxicity based on comprehensive testing and are not classified under the EU CLP and UN GHS

Of the HMW phthalates, DINP and diisodecyl phthalate (DIDP) have the highest volumes of commercial distribution. DINP is almost exclusively the phthalate used in children's toys.

Overview of Cumulative Risk Approaches

Cumulative risk typically refers to the accumulation of risk from multiple chemical and/or non-chemical stressors that may interact to produce an additive, synergistic, or antagonistic effect. This is different from aggregate risk assessment which refers to the sum of the risks resulting from exposures to the same chemical via multiple sources and multiple routes. Chemical mixture risk assessment is encompassed within cumulative risk: two or more chemicals are involved which may cause the same or different effects to a target population (e.g., different organophosphates with the same mode of action, tailpipe exhaust with multiple chemicals having similar and different effects, etc.). Cumulative risk may also be defined broadly to refer to risk from multiple unrelated sources (e.g., combined chemical and non-chemical risks).

Current approaches to cumulative risk assessment (CRA) include: 1) the hazard index (HI) approach using health indexes such as acceptable daily intakes (ADI), reference doses (RfD) or

[1] Although benzyl technically is not an alkyl group, 'phthalate" also usually encompasses butyl benzyl phthalate (BBP).

benchmark doses (BMD); 2) the toxicity equivalency factor (TEF) or margin of exposure approach using TEFs; and 3) biologically based assessments.

The HI approach is by many standards an overly conservative and crude model which considers only whether similar endpoints are affected. Using this approach, an HI is calculated for a mixture by taking the sum of the hazard quotients for the individual compounds present in that mixture. A hazard quotient (HQ) is the ratio of the estimated exposure to the acceptable level of exposure (e.g., RfD). The HI approach has the advantage of being a defined, transparent methodology where extensive data are not needed and uncertainty is well incorporated. The limitations of this method, causing it to be overly conservative, include: (1) a common mode of action is not needed to apply the HI approach; (2) dose addition is assumed even at low levels for which the dose response curve may not be defined; and (3) toxicokinetic and toxicodynamic differences are not fully accounted for among the chemicals in the mixture.

Under the toxic equivalency factor (TEF) approach, each chemical is assigned a TEF which represents the toxic potency of the individual chemical relative to the potency of a reference chemical. TEFs essentially normalize the doses of chemicals in the mixture so that they can be summed. Here the advantage is that the methodology is such that potency can be factored into the calculations and a defined mixture with a clear mode of action can be determined. However, as with the hazard index approach, there are a number of limitations inherent to the methodology including: (1) the assumption that there are no significant interactions among the chemicals; (2) the sensitivity of the TEF value to the selected reference compound; and (3) reliance on a single endpoint effect and associated parameter (e.g., a No Observed Adverse Effect Level (NOAEL)).

A biologically based cumulative risk assessment improves upon the former two approaches as it accounts for physiological, toxicokinetic and toxicodynamic parameters through quantitative modeling and takes into account temporal considerations. Again the underlying assumption is that chemicals act independently of one another. Fundamentally, this approach is highly data intensive and reliant on extensive mechanistic research. When extensive data is available, this type of assessment yields a much more comprehensive assessment and reduces the amount of uncertainty associated with the conclusions.

A recent recommendation described in a National Research Council (NRC) report (NRC, 2009) broadens the scope of cumulative risk to include non-chemical stressors (e.g., psychosocial risk, dietary risk, physical factors), all routes and pathways of exposure, and varying susceptibilities of the population (burden of disease). All other assessments would then be termed mixture risk assessments as they consider aggregate exposure to multiple chemicals in the same family but do not consider other components previously mentioned. A separate NRC report (NRC, 2008) recommended that phthalates and other chemicals that affect male reproductive development in animals, including anti-androgens, be considered in a CRA. These approaches would be all-encompassing, highly-complex assessments without precedent. While this type of assessment would provide a complete understanding of how all chemical and non-chemical stressors contribute to an individual's risk, the data development and methodological validations would be vast, complex and time intensive.

For the purposes of the CPSC CHAP, a simple or less data intensive method may be appropriate as an initial screen to begin to understand which phthalates drive the toxicity of a phthalate mixture and the likelihood of an adverse effect from the mixture based on the predicted exposures to the chemicals.

One example of an approach to conducting a CRA specifically for a group of phthalates was reported by (Benson, 2009). The author employed a hazard index (HI)/relative potency factor (RFP) approach for six phthalates (DBP, diisobutyl phthalate (DiBP), BBP, DEHP, dipentyl phthalate (DPP), and DINP) with the underlying assumption that all the phthalates have a similar mechanism of action. A reference dose for each of the phthalate esters was derived, based on adverse male reproductive and/or developmental effects, and a potency factor relative to DEHP was assigned. Using exposure data from (Wittassek and Angerer, 2008) and (Kohn *et al.*, 2000) for EU and US populations, respectively, hazard quotients were calculated and then summed to determine the HI. Although some limitations of the methodology were identified (see Appendix 1), the HI approach was useful. It not only demonstrated that humans are likely not suffering adverse developmental effects from current environmental exposures to the six phthalates as a mixture of exposures, but also identified which phthalates in the mixture are most likely to drive the risk. Consistent with each individual chemical's ability to induce developmental and reproductive effects in rodents, the hazard quotients for DEHP and DBP were much larger than for DINP, indicating that the lower molecular weight phthalates likely drive the toxicity and risk of the mixture.

CRA requires extensive scientific knowledge and currently has significant uncertainty. Expert testimony at the February 4, 2010 hearing of the Senate Environment and Public Works Committee's Subcommittee on Superfund, Toxics, and Environmental Health on "Current Science on Public Exposures to Toxic Chemicals" supported this view. For example, the National Institute of Environmental Health Sciences (NIEHS) Director, Linda Birnbaum, recognized that the science of cumulative risk was only beginning to develop and that much research was still needed[2]. However, under CPSIA Section 108, the CHAP was asked to consider the potential health effects of phthalates in combination. Therefore, ExxonMobil's recommended approach to addressing this charge is presented in this document.

Given the state of the science in cumulative risk assessment; there exists no methodology at present to incorporate comprehensive cumulative risk, including chemical and non-chemical stressors, as a routine component of chemical analysis. Only for purposes of the CPSIA direction to consider cumulative effects, ExxonMobil suggests a modified HI approach using selected points of departure (POD) modified by uncertainty factors (Wilkinson *et al.*, 2000) as providing a conservative (overestimate of risk) approach. This document uses those phthalates named by the CPSIA to illustrate the modified HI approach, though other phthalates could be added. This is similar to the approach used by the Environmental Protection Agency (EPA) for CRA on organophosphate pesticides, additionally outlined by the ILSI Cumulative Risk Assessment Framework (ILSI, 1999). Including non-chemical stressors and additional chemicals not named in the CPSIA is not recommended as the science has not yet advanced to the point where that type of comprehensive assessment is feasible. As demonstrated in this document, using the suggested, conservative method, no significant risk from the phthalate mixture (i.e., DEHP, DBP, BBP, DINP, DIDP, and DnOP) is predicted and an extensive assessment is not warranted at this time.

Conservatism and Limitations of the HI Approach

The HI approach is an overly conservative first-pass screen for mixture toxicity used to determine if a more stringent methodological assessment is required, such as a biologically based CRA.

[2] http://epw.senate.gov/public/index.cfm?FuseAction=Hearings.Hearing&Hearing_ID=8a722315-802a-23ad-4e9a-b8477139e63f

In terms of a CRA, the HI approach represents a worst-case scenario. Three significant layers of conservatism inherent to the HI approach are as follows:

1. Dose-addition (DA) – Dose addition is based on the idea that all components in a mixture behave as if they are simple dilutions of one another. DA implies that every toxicant in the mixture contributes, in proportion to its toxic unit, to the overall mixture toxicity. Since a complete dose-response assessment for the phthalates of interest is lacking, it is assumed that dose addition occurs across the entire dose-response continuum, introducing a level of conservatism into the approach.

2. No Observed Effect Level (NOAEL)/Lowest Observed Effect Level (LOAEL) to describe dose-response data – Point estimates, such as NOAELs and LOAELs, neither represent effect concentrations nor effect levels. Both are empirically based on experimental design and are not an accurate representation of the intrinsic hazard value of a chemical. Since point estimates do not represent equi-effective doses, the use of them in a CRA introduces an additional layer of conservatism into the HI approach.

3. Modified Points of Departure (MPOD) – Adjustment/uncertainty factors used in the calculation of the MPOD are quantitative judgments of qualitative deficiencies in the database and are typically based on default values. The use of these uncertainty factors results in the conservative estimate of an MPOD, and by extension, a conservative HI value.

A major limitation in the HI approach is that it does not fully account for toxicokinetic and toxicodynamic differences among chemicals. For example, experimental parameters such as species choice and exposure duration are a source of uncertainty. Additionally, the use of the HI approach does not allow for low dose extrapolation because hazard indices are simply ratios of exposure and effect level. In addition, since the use of the HI approach cannot take into consideration the shape of the dose response curve, information on the relative potencies of chemicals in a mixture will be unknown. The HI approach implicitly assumes that summation of the ratios provides a valid representation of potential toxicity.

HI Methodology

1. DEFINE THE PHTHALATE MIXTURE AND IDENTIFY COMMON TOXICOLOGICAL ENDPOINTS– Fundamental to the hazard index approach is that a common mode or mechanism of action is *not* required for the chemicals comprising the mixture. Since no mode or mechanism of action needs to be defined, endpoints should be chosen based on a similar toxicological endpoint. In order to logically define the phthalate mixture for a common endpoint, a decision framework was created (Figure 1). The only relevant, common, endpoint of concern for all six phthalates named in the CPSIA is repeated dose toxicity.

   Repeated dose effects: Increased liver weight and increased palmitoyl - CoA oxidase activity are markers of peroxisome proliferation via activation of the peroxisome proliferator activated receptor α (PPAR α), a common toxicological endpoint for phthalate esters. Sustained activation of PPARα in rodents eventually results in liver tumorigenesis. A strong body of evidence and reviews by several expert bodies indicate that this mode of action is not relevant for humans.

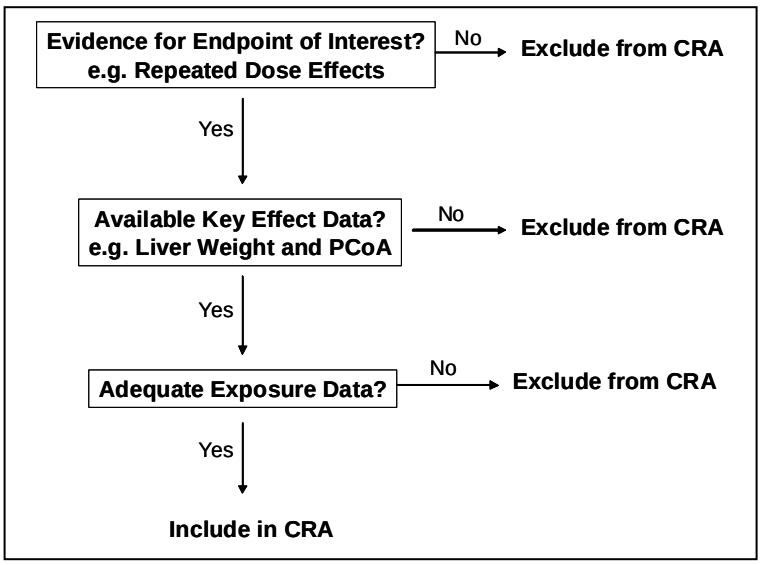

Figure 1 Cumulative risk assessment (CRA) decision framework for defining the phthalate mixture for a selected endpoint.

Six phthalates are named in the CPSIA: DEHP, DBP, BBP, DnOP, DINP and DIDP. Each phthalate was evaluated using the framework for potential inclusion in the mixture assessment. Supporting data for repeated dose effects is presented in Table 1. The framework for inclusion in the CRA also includes availability of biomonitoring data from which exposure could be calculated or indirect exposure estimations.

Based on the availability of published data indicating repeated dose effects, specifically decreased liver weight and increased palmitoyl CoA, the CRA was conducted on DBP, BBP, DEHP, DnOP, DINP and DIDP.

Table 1 - Repeated Dose Toxicity: Increased Liver Weight and Palmitoyl CoA Activation

Phthalate ester	Key Effect Data Repeated Dose Toxicity: Increased Liver Weight and Palmitoyl CoA activity	Exposure Data	Include in CRA?
DBP	90-day study, Wistar rats, 0, 0.04, 0.2 and 1.0% in diet (~0, 30, 152, 752 mg/kg bw) (European Commission, 2004). NOAEL 0.2% ~ 152 mg/kg bw Changes in hematological parameters (decreased haemoglobin- and haematocrit-values and decreased erythrocyte counts), clinical chemical parameters (decreased triglyceride levels, increased serum glucose and albumin levels), a statistically significant increase in the activity of cyanide-insensitive palmitoyl-CoA oxidase (PCoA; is an indicator for peroxisomal proliferation), a statistically significant decrease in T3 and statistically significant increases in liver and kidney weights.	Biomarker Exposure Estimate – MBP, MiBP (Centers for Disease Control and Prevention, 2009) Indirect Exposure Estimate (soil, water, air) (Clark *et al.*, 2010)	Yes

Phthalate ester	Key Effect Data Repeated Dose Toxicity: Increased Liver Weight and Palmitoyl CoA activity	Exposure Data	Include in CRA?
BBP	21-day study, Fisher rats, 0, 0.6 1.2 or 2.5% in diet (European Commission, 2007). Increase in absolute weight and relative weight of the liver, serum triglyceride levels were lower in the treated males and higher in the treated females, while cholesterol levels were reduced in both sexes, cyanide-insensitive palmitoyl-CoA oxidation levels increased in a dose-dependent manner, moderate increase in peroxisome numbers and size. LOAEL 0.6% (639 mg/kg/day)	Biomarker Exposure Estimate –MBzP (Centers for Disease Control and Prevention, 2009) Indirect Exposure Estimate (soil, water, air) (Clark *et al.*, 2010)	Yes
DEHP	90-day study, Sprague Dawley rats, 0, 5, 50, 500 or 5000 ppm in diet) (European Commission, 2008). Liver enlargement, mile hepatocellular hypertrophy, increased number of peroxisomes. NOAEL 500 ppm (37.6 mg/kg/day)	Biomarker Exposure Estimate – MEHP, MEHHP, MEOHP (Centers for Disease Control and Prevention, 2009) Indirect Exposure Estimate (soil, water, air) (Clark *et al.*, 2010)	Yes
DINP	2-year study, Fisher rats, 0, 500, 1500, 6000, or 12000 ppm in diet (European Commission, 2003a). Increased liver weight, increased incidence of hepatocellular neoplasia. NOAEL 1500 ppm (88 mg/kg/day)	Biomarker Exposure Estimate – MINP (Centers for Disease Control and Prevention, 2009) Indirect Exposure Estimate (soil, water, air) (Clark *et al.*, 2010) Indirect Exposure Estimate (Mouthing Toys) (Babich *et al.*, 2004)	Yes
DIDP	90-day study, Fisher rats, 0, 0.05%, 0.3%, 1%(European Commission, 2003b). Increased liver weights. NOAEL 0.3% (150 mg/kg/day) 21-day feeding study, Fisher rats, 0, 0.3 1.2 or 2.5% in diet; increased liver weights; increased palmitoyl-CoA oxidation levels; marked but variable increase in peroxisome number and size (European Commission, 2003b) NOAEL 0.3% (264 mg/kg/day)	Biomarker Exposure Estimate – MINP (Centers for Disease Control and Prevention, 2009) Biomarker based exposure estimates calculated from the DINP metabolite data was used as a conservative estimate for DIDP (Silva *et al.*, 2007)	Yes
DnOP	21-day study, Wistar rats, 0, 20,000 ppm in diet; increased liver weights; increased palmitoyl-CoA oxidation levels (Hinton *et al.*, 1986) LOAEL 20,000 ppm (1821 mg/kg/day) 90-day study, rats, 0, 5, 50, 500, or 5,000 ppm in diet; no effects on liver weight noted (Poon *et al.*, 1997) NOAEL 36.8 mg/kg/day	Biomarker Exposure Estimate – MOP, MCPP (Centers for Disease Control and Prevention, 2009)	Yes

Abbreviations: MBP(mono-n-butyl phthalate), MiBP (Mono-isobutyl phthalate), MEHP (Mono-2-ethylhexyl phthalate), MBzP (mono-benzyl phthalate), MINP (mono-isononyl phthalate), MEHHP (Mono-2-ethyl-5-hydroxyhexyl phthalate), MEOHP (Mono-2-ethyl-5-oxohexyl phthalate), MOP (Mono-n-octyl phthalate), MCPP (Mono-3-carboxylpropyl phthalate)

2. IDENTIFY THE POINT OF DEPARTURE (NOAEL OR LOAEL) – Select the relevant NOAEL or LOAEL appropriate for the common endpoint of interest. The NOAEL/LOAEL does not represent the ideal point of departure in a CRA since these values are based upon the dose spacing selected for the experiment. Ideally, a more definitive evaluation of the dose-response curve, BMD or $EC_{50,}$ would be used in a cumulative risk assessment; however, this is not possible with the data currently available. In addition, the use of the NOAEL and LOAEL as points of departure disallows a potency calculation for phthalates since these values do not represent equi-effective doses and are merely a function of experimental design and not the intrinsic hazard of the chemical.

3. DEVELOP A MODIFIED POINT OF DEPARTURE (MPOD) - Once the studies and POD for an endpoint have been identified, a MPOD is calculated to convert the animal data into an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. This involves the modification of the POD by a series of uncertainty factors, Table 2 and 3.

$$MPOD = POD / (UF_1 * UF_2 * \ldots UF_{n)}$$

Table 2 - Uncertainty Factors

Source of Uncertainty	Uncertainty Factor
Interspecies Differences	10
Intraspecies Differences	10
Use of a LOAEL	3
Subacute to Chronic Adjustment	6
Subchronic to Chronic Adjustment	2

Table 3 - Critical Endpoint, Point of Departure, and MPOD

REPEATED DOSE EFFECTS – Increased Liver Weight and PCoA Activity					
Key Effect	POD (mg/kg/d)	POD Type	Uncertainty Factors	MPOD	Reference
DBP	152	NOAEL	200	0.76	(Kaufmann, 1992; Schilling, 1992)
BBP	639	LOAEL	1800	0.36	(Barber *et al.*, 1987)
DEHP	37.6	NOAEL	200	0.19	(Poon *et al.*, 1997)
DINP	88	NOAEL	100	0.88	(Moore, 1998)
DnOP	36.8	NOAEL	200	0.18	(Poon *et al.*, 1997)
DIDP	150	NOAEL	200	0.75	(Hazelton Laboratories, 1968)

4. ESTABLISH EXPOSURE ESTIMATES – Accurate exposure estimates are critical to the CRA. Exposure data can be obtained by two methods, (a) exposures based on biomonitoring data, and (b) exposures based on the calculated concentration of each phthalate ester in each medium of exposure combined with the rate of intake. As defined in the CPSIA, the populations of interest are children, women of reproductive age, and the total population.

    a. BIOMARKER EXPOSURE ESTIMATES – Biomarker exposure estimates are "back" calculated from biomonitoring data. In this case, the monoester metabolite data

Phthalates have been shown to undergo secondary metabolism from the monoester into various oxidative metabolites. Secondary metabolite data from the CDC National Exposure Report is available for DEHP and DnOP, but not other phthalates. Calculations with the secondary metabolites of DEHP did not significantly impact the exposure estimates; therefore, exposure estimates are based only on the monoester data (see Appendix 2).

Exposure estimates are based on the equation below (David, 2000; Kohn *et al.*, 2000) and the parameters defined in Table 4. Table 5 presents calculated exposure data for the 95th percentile of the populations of interest including children ages 6 – 11 yrs and females ages 6 – 60 yrs in addition to the total population ages 6+ yrs. Exposures calculated based on the 95th percentile metabolite concentrations are highly conservative.

$$DI = (UC \times CE / (F_{ue} \times 1000)) \times (MWd/MWm)$$

where:

DI = Daily intake (µg/kg/day)
UC[3] = Urinary concentration (metabolite) – creatinine corrected (µg/kg)
CE[4] = Creatinine excretion (mg/kg/day)
F_{ue}[5] = Fractional urinary excretion of the metabolite (unitless)
MWd = Molecular weight of the diester
MWm = Molecular weight of the metabolite

Table 4 – Equation Parameters for Exposure Calculations from Biomonitoring Data

Phthalate	Molecular Weight	Monoester	Molecular Weight	F_{ue}	Reference
DBP	278.35	MBP	222.24	0.69	(Anderson *et al.*, 2001)
BBP	312.39	MBzP	256.35	0.73	(Anderson *et al.*, 2001)
DEHP	390.56	MEHP	278.38	0.059	(Koch *et al.*, 2005)
DINP	418.62	MINP	292.37	0.0212	(Koch and Angerer, 2007)
DnOP	390.62	MnOP	278.44	0.059[6]	(Koch *et al.*, 2005)

Table 5 - Phthalate Exposure Calculations Based on the 95th Percentile Creatinine Corrected Urine Concentration (ug/g) of the Corresponding Monoester from the NHANES 4th Report

Phthalate	Calculated Daily Intake (ug/kg/d) – 95th Percentile		
	Children (6 – 11 yrs)	Females (15 – 44 yrs)	Total Population (6+ yrs)
DBP	2.74	3.42	3.33
BBP	4.21	1.91	2.34
DEHP	7.51	14.58	12.08
DINP	2.43	2.92	3.94
DnOP	0.84	1.38	1.38
DIDP[7]	2.43	2.92	3.94

[3] Urinary concentrations were for the phthalate's respective monoester
[4] Constants were used for total population (20 mg/kg/day), children (11 mg/kg/day), and females (18 mg/kg/day)
[5] F_{ue} values were derived from several published studies concerning the metabolism of phthalates
[6] DEHP Fue value of 0.059 was used for DnOP as both are C8 phthalates.
[7] DINP exposure data is a conservative estimate of DIDP exposure, because as phthalates increase backbone length, they have lower vapor pressures, lower water solubilities, and lower skin absorption rates.

b. INDIRECT EXPOSURE ESTIMATES – Indirect exposure estimates are based on mathematical calculations that aggregate potential exposure based on measurements of the subject chemical in various media. The general procedure used to estimate intake includes the following steps: description of exposure scenarios (i.e., the pathways of exposure to the various media containing the phthalate esters: food, incidental soil, and incidental dust); assigning a concentration of the phthalate ester in each medium; and assigning an intake rate for that medium (Clark *et al.*, 2010). Inclusion of absorption factors for the various media converts the estimated intakes into uptakes, facilitating a more direct comparison with the biomarker studies. Uptake is calculated for each medium and then summed, using the following equation:

$$D = \Sigma\ (Ci \times IRi \times Ai\ /\ BW)$$

where:

D	=	Absorbed dose of PE (µg/kg/d)
Ci	=	Concentration of PE in medium (µg/g)
IRi	=	Intake rate of medium (g/d)
Ai	=	Absorption factor (unitless) (Assumed to be 100%)
BW	=	Body weight (kg)

Table 6 presents calculated exposure data for the 95th percentile of the populations of interest including toddlers and children ages 6 months – 4 yrs and 5 – 11 yrs, respectively, in addition to adults ages 20 – 70 yrs. Again, use of exposure data for the 95th percentile of the populations of interest is highly conservative. Of the six phthalates of interest, only data for DBP, BBP, DEHP, and DINP were available from (Clark *et al.*, 2010).[8]The authors indicate that DIDP has previously been analyzed, but not detected, in several types of food and in air, and that DIDP has been quantified in fish and dust. However, there is insufficient information for most other media with which to characterize total human exposure to DIDP. DnOP was not included due to a lack of available measurements.

Children have been identified as a sensitive sub-population which may experience additional phthalate exposure (primarily to DINP) through the mouthing of toys or childcare articles. While no biomonitoring data exists for this age range (i.e., <6 yrs), an indirect exposure estimate has been determined (Babich *et al.*, 2004). The 99th percentile estimated mean exposure to DINP, as calculated in (Babich *et al.*, 2004), is 1.5 µg/kg/day for children aged 12- 23 months. This exposure estimate has been added to the toddler (6 months – 4 yrs) 95th percentile exposure estimate based on ingested soil, dust, water, and food and inhalation of indoor and outdoor air calculated by (Clark *et al.*, 2010) to address this uncertainty. In doing so, estimated exposure to DINP increases from 8.7 ug/kg/day to 10.2 ug/kg/day, Table 6.

[8] The report does include data for di-methyl phthalate, di-ethyl phthalate and di-isobutyl phthalate.

Table 6 - Phthalate Exposure Calculations Based on Indirect Estimates

Phthalate	Calculated Daily Intake (ug/kg/d) - 95th Percentile			
	Adult (20-70 yrs)	Child (5-11 yrs)	Toddler (6 mos - 4 yrs)	Toddler (6 mos – 4 yrs) + 99th% Toy Exposure Estimate[9]
DBP	3.0	8.1	12	12
BBP	1.4	4.0	6.1	6.1
DEHP	31	81	124	124
DINP	2.0	5.5	8.7	10.2

5. CALCULATE HAZARD QUOTIENT FOR EACH PHTHALATE- The hazard quotient (HQ) is a ratio of the expected exposure to a chemical compared to the modified point of departure (MPOD) value for that chemical. Table 7 presents an example of hazard quotient calculations based on both biomarker data and indirect exposure estimates for children ages 6-11 or 5-11yrs, respectively for the repeated dose endpoint.

$$HQ = \text{Exposure metric} / MPOD$$

Procedurally, the point of departure (MPOD or RfD) and the exposure estimates are converted to molar equivalents prior to HQ calculation. However, this is not necessary as the final calculations are not significantly altered by this extra mathematical manipulation

Table 7 - Hazard Quotient Calculations for the Endpoint of Repeated Dose

Phthalate Ester	Biomarker-Based Exposure Estimate			Indirect Exposure Estimate		
	MPOD	Exposure 95th Percentile (mg/kg/day) Children 6 – 11 yrs	HQ	MPOD	Exposure 95th Percentile (mg/kg/day) Children 5 – 11 yrs	HQ
DBP	0.76	0.0027	0.0036	0.76	0.0081	0.0107
BBP	0.36	0.0042	0.0118	0.36	0.0040	0.0113
DEHP	0.19	0.0075	0.0399	0.19	0.0810	0.4309
DINP	0.88	0.0024	0.0026	0.88	0.0055	0.0063
DnOP	0.18	0.0008	0.0037	0.18	No Data	No Data
DIDP	0.75	0.0024	0.0045	0.75	No Data	No Data

6. SUM HAZARD QUOTIENT FOR HAZARD INDEX- The hazard index (HI) for a mixture is calculated by taking the sum of the hazard quotients for the individual compounds present in the mixture. If values are less than or equal to 1 then the risk is acceptable and no additional risk management measures are required. For values greater than 1, additional risk management measures are required. HIs calculated for the populations of interest based on both biomarker exposure data and indirect exposure estimates for the endpoint of repeated dose effects are presented in Table 8.

$$HI = \Sigma(HQ)_i$$

i for n chemicals in set

[9] For DINP, 1.5 ug/kg/day was added to account for the mouthing of toys (Babich *et al.*, 2004).

Table 8 - Hazard Index Calculations Phthalate-Induced Repeated Dose Effects

	Toddlers (6 mo - 4yrs) 95th%	Toddlers (6 mo – 4yrs) 95th% + DINP Toy Exposure (12-23 mos.) 99th%[10]	Children 95th%[11]	Females (6 – 60yrs) 95th%	Total Population[12] 95th%
Indirect Exposure	0.70	0.70	0.46		0.18
Biomarker-Based Exposure			0.07	0.10	0.09

Summary and Conclusion

Recently, cumulative risk has been defined broadly to refer to multiple unrelated stressors (e.g., combined chemical and non-chemical risks) (NRC, 2009). The scientific community has little experience with assessing multiple unrelated stressors (combined chemical and non-chemical risks) and there are few scientific data and no generally accepted methodology for conducting such assessments. NRC (2008) recommended that phthalates and other chemicals that induce the general "androgen-insufficiency syndrome" in animals, including anti-androgens, be considered in a CRA. While these broad, complex approaches to a CRA are ideal from a public health perspective, they are simply not feasible at this time based on the current state of the science and are not recommended for the CHAP's proposed assessment.

A highly conservative and less data intensive method is appropriate and can be adequately conducted as an initial screen to begin to understand which phthalates drive the toxicity of the mixture and the likelihood of an adverse effect based on the predicted exposures. The HI approach described here is an overly conservative, initial screen for risk of repeated dose effects associated with the 6 phthalates as a mixture. For each population of interest, regardless the exposure data set, the HI is substantially below 1 indicating that there is no cumulative risk posed by the phthalates examined. Furthermore, consistent with the hazard profile of each individual phthalate, the HQ values indicate that high molecular weight phthalates (DINP or DIDP) do not significantly contribute to the toxicity of the mixture.

In conclusion, for the purposes of the CHAP assessment, ExxonMobil recommends the hazard index approach which clearly demonstrates that even for highly sensitive populations such as children and women of reproductive age, phthalates do not pose a cumulative risk. The conservative HI methodology likely overestimates risk; further efforts to develop a more complex assessment are not justified.

[10]The 99th percentile estimated mean exposure to DINP is 1.5 µg/kg/day for children aged 12- 23 months (Babich *et al*., 2004). This exposure estimate has been added to the toddler (6 months – 4 yrs) DINP exposure estimate from Clark *et al*., 2010.

[11]The age range of children as defined by the CDC dataset is 6-11 yrs. The age range of children as defined by the Clark *et al*., 2010 dataset is 5-11 yrs.

[12] Total Population as defined by the CDC dataset is 6-60 yrs. Total population as defined by the Clark *et al*., 2010 dataset is 20+ yrs.

Appendix 1. Cumulative Risk Assessment, Phthalate Data and Potency Considerations

A cumulative risk assessment is highly dependent on the type and quality of the data for the endpoint of interest for each chemical included in the mixture. Ideally, a narrowly defined, common endpoint of interest should be chosen where evidence of the effect induced by each component of the mixture can be demonstrated using similar robust experimental designs. The methodology underlying the measurement of the effect should also be consistent for the dataset. As a category of chemicals, phthalates have been divided into two groups based on the principle that substances of similar structure have similar environmental and toxicological properties. Very distinct toxicological properties exist between low molecular weight phthalates (particularly phthalates with a 4 to 6 carbon backbone -- DBP, BBP, and DEHP) and high molecular weight phthalates (phthalates with greater than or equal to 7 carbon backbones, such as DINP, DIDP, and dipropylheptyl phthalate (DPHP)), especially for reproductive and developmental endpoints. Single studies testing all the phthalates for a common effect do not exist due to sheer complexity and expense. This impacts any cumulative assessment where only individual study data exist for the components of a mixture and a common effect or endpoint is key.

EPA recommends using the relative potency factor (RFP) approach to normalize and combine the different potencies among chemicals for cumulative risk assessment in an attempt to overcome limitations imposed by individual chemical study designs and varying toxicological properties. An initial step in the RPF approach is to identify a point of departure (POD). A POD is generally defined as a point estimate of the dose or exposure level that is used to depart from the observed range of empirical response data for the purpose of extrapolation. In the case of cumulative risk assessment, the POD is the dose reflecting a uniform response level for the common toxic effect for each chemical. This approach, coupled with the hazard index (HI) approach, was used by Benson (2009), where the common toxic effect was defined broadly as adverse effects on the male reproductive tract. Relative potency factors for the phthalates were then developed based on varying endpoints. Decreases in testosterone production were combined with structural malformations when determining the NOAELs/Bench Mark Doses (BMD) and calculating the reference dose (RfD) for effects on the developing male reproductive system. Varying calculations to arrive at bench mark doses in conjunction with a NOAEL (for DBP) and a LOAEL (for DINP) were used to derive RfDs. These inconsistencies are not considered best practice in applying the HI/RPF approach, as identification of a common mode of action and a discrete effect for the mixture enhances the reliability of the conclusions. The concept of toxic potency is important and was considered in Benson (2009); however it was ineffectively applied due to the lack of a consistent endpoint and the varying calculations used to arrive at a BMD plus use of both BMDs and NOAELs/LOAELs..

The HI approach as described in this document does not incorporate the concept of toxic potency, essentially assuming all the phthalates in the mixture are equi-potent. This is a grossly conservative assumption as differences in the effects on testosterone levels as a key measure of reproductive and developmental effects (i.e. anti-androgenicity) are clear between C4 to C6 low molecular weight phthalates (e.g., DEHP, DBP) and high molecular weight phthalates (e.g., DIDP, DINP). Some esters are not active: DIDP, DEP and DMP do not induce anti-androgenic changes at the phenotypic, molecular or gene level and are therefore considered not to be endocrine disrupters by internationally accepted definitions (e.g. WHO IPCS). For the other esters named in the CPSIA, DEHP, DBP and BBP are roughly equivalent in potency. DINP has been reported in one study to suppress fetal testosterone (Borch et al., 2004) while no effect has been reported in another study (Adamsson et al., 2009); no adverse health effects have been reported with DINP including in comprehensive 2-generation studies. It is therefore concluded that DINP is not an endocrine disrupter by internationally

accepted definitions. Even without the added complexity of potency, the recommended hazard index approach conservatively predicts no significant risk associated with the phthalate mixture for the defined endpoints.

Appendix 2 – Exposure Calculations for DEHP; Consideration of Oxidative Metabolites

Phthalate monoesters were chosen as the metabolite on which to base biomarker-based exposure back calculations. It has been established, at least for DINP and DEHP but likely other phthalates as well, that the metabolite monoesters can undergo further metabolism into various oxidative metabolite species, Table 2-1 (Koch *et al.*, 2005; Koch *et al.*, 2006; Koch and Angerer, 2007). Biomonitoring data is provided in the CDC 4th report for the oxidative metabolites of DEHP. DINP oxidative metabolites were not reported by CDC but are anticipated to be included in an update in the near future (personal communication with the CDC). To ensure consistency in estimating exposure based on a single dataset (i.e., CDC 4th Report) only the monoester metabolite data was used for each phthalate. It has been suggested that using the monoester in exposure estimates does not result in an accurate exposure estimate (Koch and Angerer, 2007). However, using DEHP as an example in the methodology previously described, regardless of metabolite species considered, the differences in exposure estimates were considered to be small (Tables 2-1 & 2-2) and did not impact the overall hazard index calculation for the mixture.

Table 2-1 - Molecular Information on the Monoester and Oxidative Metabolites of DEHP

Phthalate	Molecular Weight	Metabolite	Molecular Weight	F_{ue}	Reference
DEHP	390.56	MEHP	278.38	0.059	(Koch *et al.*, 2005)
		MEHHP	294.34	0.23	(Koch *et al.*, 2005)
		MEOHP	292.32	0.15	(Koch *et al.*, 2005)

Table 2-2 - Biomonitoring Exposure Estimates Based on the Monoester and Oxidative Metabolites of DEHP

Phthalate Metabolite	DEHP Calculated Daily Intake (ug/kg/d) Based on Biomonitoring Values for Oxidative Metabolites – 95th Percentile		
	Children (6 – 11 yrs)	Females (6 – 60 yrs)	Total Population (6+ yrs)
MEHP	7.51	11.56	12.08
MEHHP	13.39	17.76	21.00
MEOHP	11.86	18.92	21.00

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