Approach To Cumulative Risk

U.S. Consumer Product Safety Commission
Bethesda, MD
March 23, 2010

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Agenda

• Introductions

• Recap

• CPSIA CHAP Charge

• Cumulative Risk Approach

• Backup
  – Previous CPSC CHAP DINP Conclusions
  – New Reviews/Assessments
  – Differences in Phthalates
Recap

• ExxonMobil met with CPSC July 2009
  – Commitment to safety of our products
  – CPSIA support
  – Differences in phthalates and commercial uses
  – CHAP review
  – Scientific DINP/DIDP review
  – Cumulative risk assessment

• Fully support the CHAP
  – Approach to cumulative risk assessment
  – Willing to submit all available toxicological and environmental data on DINP and DIDP
CPSIA CHAP Charge

• The Panel shall complete an examination of the full range of phthalates and phthalate alternatives that are used in products for children

• And shall...
  – Examine health effects from full range of phthalates
  – Consider health effects from each phthalate and in combination
  – Examine exposure levels of all phthalates in humans and subpopulations (i.e. children and pregnant women) from children's products
  – **Consider cumulative effect of total exposure to all phthalates in children’s products and in other products**
  – Review all relevant and objective studies of phthalates and phthalate alternatives
  – Consider health effects from exposure to phthalates from all exposure sources in addition to ingestion
  – Consider safe level of phthalates for humans and subpopulations
  – Consider health effects from phthalate alternatives
Overview

• Cumulative risk assessment: the accumulation of risk from multiple chemical and/or non-chemical stressors that may interact to produce an additive, synergistic, or antagonistic effect

• Aggregate risk assessment: the sum of the risks resulting from exposures to the same chemical via multiple sources and multiple routes

• Chemical mixtures 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)
Cumulative Risk

• Scientific community has several definitions of cumulative risk
  – EPA and World Health Organization’s International Program on Chemical Safety - cumulative risk for categories of structurally-related chemicals which share a common mode of action
    • 2008 – recommends assessing all chemicals showing common adverse health outcomes; these chemicals would not need to act through a common mechanism of toxicity
    • 2009 – recommends the incorporation of interaction between chemical and non-chemical stressors in cumulative risk assessments

• Data Requirements vs. Available Data
  – 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
Cumulative Risk, cont.

• Existing Methodology Overview
  – Hazard Index (HI) using reference and benchmark doses
  – Margin of Exposure (MoE) using Toxicity Equivalency factor (TEF)
  – Biologically based assessments

• ExxonMobil Suggested Methodology
  – Only for purposes of the CPSIA direction to consider cumulative effects, ExxonMobil suggests a modified HI approach as providing a conservative (overestimate of risk) approach

• Results
  – Hazard index approach clearly demonstrates that even for highly sensitive populations such as children and women of reproductive age, phthalates do not pose a cumulative risk for the demonstrated endpoint. As the HI methodology likely overestimates risk, further efforts to develop a more complex assessment are not justified
Accepted Approaches for Well Defined Mixtures

• Hazard Index Approach
  – Advantages
    + defined, transparent methodology; extensive mechanistic research data are not needed; uncertainty is well incorporated
  – Limitations
    + A common mode of action is not required, only a defined endpoint effect; dose addition is assumed at low levels; does not account for toxicokinetic and toxicodynamic differences; relative potency is not determined

• Toxic Equivalency Factor Approach
  – Advantages
    + A mode of action is defined for the mixture; potency is incorporated; can be used as a combined approach with the hazard index methodology
  – Limitations
    + Assumes no significant interactions among the chemicals; requires confidence in a single endpoint effect and associated parameter; determination of most potent/toxic compound can be subjective

• Biologically Based/Physiologically Based Pharmacokinetics Approach
  – Advantages
    + Highly comprehensive; lower uncertainty
  – Limitations
    + Highly data intensive and reliant on extensive mechanistic research
Recently Proposed Approaches

• Benson, 2009 -- Employed relative potency factor/hazard index approach for six phthalates demonstrating that humans are likely not suffering adverse developmental effects from current environmental exposure to the mixture
  – Advantages
    + Transparent methodology; mixture composition was based on a common mode of action; potency was considered
  – Limitations
    + Common toxic effect was broadly defined; calculation of point of departure (POD) was inconsistent

• NRC 2008, 2009 -- Recommended that phthalates and all other chemicals that affect male reproductive development in animals be assessed. Includes consideration of chemical and non-chemical stressors (e.g. psychosocial risk, dietary, physical factors), all routes and pathways of exposure, and varying susceptibilities of the population (burden of disease)
  – Advantage
    + All encompassing assessment of probability for adverse outcome of interest
  – Limitations
    + Highly complex; no currently acceptable methodology; time intensive; data intensive
Objectives

• Meet the charge defined in the CPSIA to consider cumulative health effect of total exposure to all phthalates in children’s products and in other products.

• Employ a currently accepted method using available objective hazard and exposure data

• Understand which phthalates drive the toxicity of the mixture and the likelihood of an adverse effect from the mixture based on the predicted exposures to the chemicals

• Focus on sensitive subpopulations
  – children, especially those mouthing toys
  – women of reproductive age
Proposal

• Use the Hazard Index Approach, a currently accepted methodology, to conduct a practical screening assessment for mixture toxicity
  – Identify phthalates that likely drive the toxicity of the mixture

• For simplicity of the example, first conduct the assessment on those phthalates named in the CPSIA: DBP, DEHP, BBP, DIDP, DINP, DnOP.
  – A focused cumulative risk assessment, limited to those phthalates named in the CPSIA will help inform whether further assessment is needed

• Use common toxicological endpoints such as repeated dose effects (i.e. increased liver weight and Palmitoyl CoA induction)

• Use either biomonitoring data to calculate estimated exposures or indirect exposure estimates for the populations of interest

• If indications of risk are identified, develop data necessary to conduct a more extensive assessment
Hazard Index Approach

- Overestimates risk; first-pass screen for mixture toxicity to determine whether more extensive assessment is necessary

- Levels of conservatism toward overestimating risk
  - Dose-addition – 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
  - NOAEL/LOAEL – Point estimates do not represent equi-effective doses
  - Modified Points of Departure – adjustment factors used in the calculation of MPOD are quantitative judgments of qualitative deficiencies in the database
Hazard Index Approach

- Identify common toxicological endpoint
- Define the phthalate mixture
- Evaluate evidence and quality of data
- Identify point of departure (NOAEL or LOAEL)
- Develop a Modified Point of Departure (MPOD)
- Establish exposure estimates
- Calculate the hazard quotient for each phthalate
- Sum the hazard quotients to calculate the hazard index
Identify Endpoint

- Endpoints should be chosen based on the commonality of the endpoint, availability of adequate published data, and toxicological concern.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Key Data</th>
<th>Observed</th>
<th>Not Observed</th>
<th>No Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Repeated Dose Effects/ Peroxisome Proliferation</strong>[1]</td>
<td>Increased Liver Weight, Increase in Palmitoyl CoA activity</td>
<td>DBP, BBP, DEHP, DINP, DIDP, DnOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male Reproductive/ Developmental Indicators</strong>[3]</td>
<td>Decrease in Anogenital Distance</td>
<td>DBP, BBP, DEHP</td>
<td>DINP[2], DIDP</td>
<td>DnOP</td>
</tr>
<tr>
<td></td>
<td>Nipple Retention</td>
<td>DBP, BBP, DEHP</td>
<td>DINP[2], DIDP</td>
<td>DnOP</td>
</tr>
<tr>
<td></td>
<td>Alterations in the weight of sexual organs and accessory glands</td>
<td>DBP, BBP, DEHP</td>
<td>DINP, DIDP</td>
<td>DnOP</td>
</tr>
<tr>
<td></td>
<td>Decreased Testosterone</td>
<td>DBP, BBP, DEHP</td>
<td>DINP[2]</td>
<td>DIDP, DnOP</td>
</tr>
</tbody>
</table>

[1] Peroxisome Proliferation is not considered a relevant endpoint for assessment of human risk. For the purposes of demonstrating cumulative risk methodology it is included.
[3] Significant reproductive and developmental adverse effects are only observed for low molecular weight phthalates (DEHP, BBP, DBP) and NOT for high molecular weight phthalates (DINP, DIDP).
Define the Phthalate Mixture

Evidence for Endpoint of Interest?
  e.g. Repeated dose toxicity

Yes → Available Key Data using relevant, objective studies?
  e.g. Increased liver weight

Yes → Adequate Exposure Data?

Yes → Include in CRA

No → Exclude from CRA

No → Exclude from CRA

No → Exclude from CRA
Determine POD and Develop MPOD

- Application of uncertainty Factors

<table>
<thead>
<tr>
<th>Source of Uncertainty</th>
<th>Uncertainty Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interspecies Differences</td>
<td>10</td>
</tr>
<tr>
<td>Intraspecies Differences</td>
<td>10</td>
</tr>
<tr>
<td>Use of a LOAEL</td>
<td>3</td>
</tr>
<tr>
<td>Subacute to Chronic Adjustment</td>
<td>6</td>
</tr>
<tr>
<td>Subchronic to Chronic Adjustment</td>
<td>2</td>
</tr>
</tbody>
</table>

[1, 2] Only applicable to the Repeated Dose endpoint

- Calculation of MPOD

<table>
<thead>
<tr>
<th>Key Effect</th>
<th>POD (mg/kg/d)</th>
<th>POD Type</th>
<th>Uncertainty Factors</th>
<th>MPOD</th>
<th>Reference for POD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>152</td>
<td>NOAEL</td>
<td>200</td>
<td>0.76</td>
<td>EU Risk Assessment, 2004</td>
</tr>
<tr>
<td>BBP</td>
<td>639</td>
<td>LOAEL</td>
<td>1800</td>
<td>0.36</td>
<td>EU Risk Assessment, 2007</td>
</tr>
<tr>
<td>DEHP</td>
<td>37.6</td>
<td>NOAEL</td>
<td>200</td>
<td>0.19</td>
<td>EU Risk Assessment, 2006</td>
</tr>
<tr>
<td>DINP</td>
<td>88</td>
<td>NOAEL</td>
<td>100</td>
<td>0.88</td>
<td>EU Risk Assessment, 2003</td>
</tr>
<tr>
<td>DnOP</td>
<td>36.8</td>
<td>NOAEL</td>
<td>200</td>
<td>0.18</td>
<td>Poon et al., 1996</td>
</tr>
<tr>
<td>DIDP</td>
<td>150</td>
<td>NOAEL</td>
<td>200</td>
<td>0.75</td>
<td>EU Risk Assessment, 2003</td>
</tr>
</tbody>
</table>

Hazelton Laboratory, 1968
Establish Exposure Estimates

• Biomarker Exposure Estimates (CDC NHANES Data)
  – Calculate daily intake (ug/kg/d) of diester from creatinine corrected urinary metabolite levels for each of the phthalates except DIDP and DnOP for the 50th and 95th percentiles
  – Populations of interest
    + Children ages 6 – 11 yrs
    + Females ages 15 – 44 yrs
    + Total Population 6+ yrs

• Indirect Exposure Estimates (Clark et al., 2009, unpublished)
  – Use of the concentration of the phthalate ester in each medium of exposure and the rate of intake of that medium to quantify exposure
  – Populations of Interest
    + Children ages 5 – 11 yrs
    + Toddlers ages 6 months – 4 yrs
    + Adults ages 20+ yrs

• Exposure from Toys
  – Used estimated oral exposure (99th percentile) to DINP from soft plastic toys based on mouthing and migration studies (Babich et al., 2004)
  – This estimated exposure was added to daily intake estimates of toddlers ages 6 mos – 4 yrs
Biomarker Exposure Estimates

- 3rd and 4th Centers for Disease Control and Prevention (CDC) reports based on National Health and Nutrition Examination Survey (NHANES) data—measurement of phthalate ester metabolites in urine to back calculate exposure to the parent diester

- David, 2000; Kohn et al., 2000 Methodology

\[
\text{DI} = \left(\frac{\text{UC}^{[1]} \times \text{CE}^{[2]}}{(\text{F}_{\text{ue}}^{[3]} \times 1000)}\right) \times \left(\frac{\text{MWd}}{\text{MWm}}\right)
\]

<table>
<thead>
<tr>
<th>where:</th>
<th>DI = Daily intake (µg/kg/day)</th>
<th>UC = Urinary concentration – creatinine corrected (µg/kg)</th>
<th>CE = Creatinine excretion (mg/kg/day)</th>
<th>F_{ue} = Fractional urinary excretion of the metabolite (unitless)</th>
<th>MWd = Molecular weight of the diester</th>
<th>MWm = Molecular weight of the metabolite</th>
</tr>
</thead>
</table>

\[^{[1]}\] Urinary concentrations were for the phthalate’s respective monoester

\[^{[2]}\] Constants were used for total population (20 mg/kg/day), children (11 mg/kg/day), and females (18 mg/kg/day)

\[^{[3]}\] \text{F}_{\text{ue}} \text{ values were derived from several published studies concerning the metabolism of phthalates}
Biomarker Exposure Estimates

- Exposure calculations based on monoester data mainly from the CDC 4th report (2003-2004 data)
- Calculated Daily Intake (ug/kg/d) – 95th Percentile

<table>
<thead>
<tr>
<th>Phthalate</th>
<th>Children (6 – 11 yrs)</th>
<th>Females (15 – 44 yrs)</th>
<th>Total Population (6+ yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>2.7</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>BBP</td>
<td>4.2</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>DEHP</td>
<td>7.5</td>
<td>14.6</td>
<td>12.1</td>
</tr>
<tr>
<td>DnOP¹</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>DINP</td>
<td>2.4</td>
<td>2.9</td>
<td>3.9</td>
</tr>
<tr>
<td>DIDP²</td>
<td>2.4</td>
<td>2.9</td>
<td>3.9</td>
</tr>
</tbody>
</table>

¹DnOP data only available in CDC NHANES 1999-2000 data set
²DINP data used for DIDP (Silva et al., 2007)
Indirect Exposure Estimates

- Clark, 2009 unpublished: Use of the concentration of the phthalate ester in each medium of exposure and the rate of intake of that medium to quantify intake of the phthalate ester

\[ D = \sum (C_i \times I_{Ri} \times A_i / BW) \]

where:
- \( D \) = Absorbed dose of PE (µg/kg/d)
- \( C_i \) = Concentration of PE in medium (µg/g)
- \( I_{Ri} \) = Intake rate of medium (g/d)
- \( A_i \) = Absorption factor (unitless)
- \( BW \) = Body weight (kg)

- Calculated Daily Intake (µg/kg/d) – 95th Percentile

<table>
<thead>
<tr>
<th>Phthalate</th>
<th>Toddler (0.5 – 4 yrs)</th>
<th>Children (5 – 11 yrs)</th>
<th>Adult Population (20+ yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>12</td>
<td>8.1</td>
<td>3.0</td>
</tr>
<tr>
<td>BBP</td>
<td>6.1</td>
<td>4.0</td>
<td>1.4</td>
</tr>
<tr>
<td>DEHP</td>
<td>124</td>
<td>81</td>
<td>31</td>
</tr>
<tr>
<td>DnOP</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>DINP</td>
<td>8.7</td>
<td>5.5</td>
<td>2.0</td>
</tr>
<tr>
<td>DIDP</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = No data
Indirect Exposure Estimates

• Additional DINP Exposure from Mouthing of Toys

• Estimated oral exposure (99\textsuperscript{th} percentile) to DINP from soft plastic toys based on mouthing and migration studies (Babich et al., 2004)
  – This estimated exposure (1.5 ug/kg/d) was added to the DINP daily intake estimate of toddlers ages 6mos – 4 yrs

• Calculated Daily Intake (ug/kg/d) – 95th Percentile

<table>
<thead>
<tr>
<th>Phthalate</th>
<th>Toddler (0.5 – 4 yrs)</th>
<th>Toddler (0.5 – 4 yrs) + DINP Exposure from Toys</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>BBP</td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td>DEHP</td>
<td>124</td>
<td>124</td>
</tr>
<tr>
<td>DnOP</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>DINP</td>
<td>8.7</td>
<td>10.2</td>
</tr>
<tr>
<td>DIDP</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = No data
Phthalate Mixture

- Repeated dose data for the effect of increased liver weight and increased Palmitoyl CoA activity is available for all 6 phthalates

- Exposure data is not available for DIDP; however, DINP exposure was used as a conservative estimate of exposure to DIDP (Silva et al., 2007)

- DnOP total population exposure estimate was used for the female 15-44 yrs population

<table>
<thead>
<tr>
<th>Population</th>
<th>Phthalates Included in Cumulative Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker-Based Exposure Estimate</strong></td>
<td></td>
</tr>
<tr>
<td>Children (6 – 11 yrs)</td>
<td>DBP, BBP, DEHP, DINP, DnOP, DIDP</td>
</tr>
<tr>
<td>Females (15 – 44 yrs)</td>
<td>DBP, BBP, DEHP, DINP, DnOP, DIDP</td>
</tr>
<tr>
<td>Total Population (6+ yrs)</td>
<td>DBP, BBP, DEHP, DINP, DnOP, DIDP</td>
</tr>
<tr>
<td><strong>Indirect Exposure Estimate</strong></td>
<td></td>
</tr>
<tr>
<td>Toddlers (6 mos – 4 yrs)</td>
<td>DBP, BBP, DEHP, DINP</td>
</tr>
<tr>
<td>Children (5 – 11 yrs)</td>
<td>DBP, BBP, DEHP, DINP</td>
</tr>
<tr>
<td>Total Population (20+ yrs)</td>
<td>DBP, BBP, DEHP, DINP</td>
</tr>
</tbody>
</table>
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:

\[ HQ = \frac{\text{Exposure metric}}{\text{MPOD}} \]

### Phthalate Ester

<table>
<thead>
<tr>
<th>Phthalate Ester</th>
<th>Using Bio Marker Based Exposure</th>
<th>Using Indirect Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPOD</td>
<td>Exposure 95th Percentile (mg/kg/day) Children 6 – 11 yrs(^{[1]})</td>
</tr>
<tr>
<td>DBP</td>
<td>0.76</td>
<td>0.0027</td>
</tr>
<tr>
<td>BBP</td>
<td>0.36</td>
<td>0.0042</td>
</tr>
<tr>
<td>DEHP</td>
<td>0.19</td>
<td>0.0075</td>
</tr>
<tr>
<td>DINP</td>
<td>0.88</td>
<td>0.0024</td>
</tr>
<tr>
<td>DIDP</td>
<td>0.75</td>
<td>0.0024</td>
</tr>
<tr>
<td>DnOP</td>
<td>0.18</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

\(^{[1]}\) Children as defined by the CDC NHANES dataset are 6-11 yrs

\(^{[2]}\) Children as defined by the Clark, 2009, unpublished data are 5-11 yrs

ND = No data
Calculate 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
  - \( HI = \sum (HQ)_i \) (i for n chemicals in set)

<table>
<thead>
<tr>
<th>Repeated Dose Effects</th>
<th>Toddlers (6 mo - 4 yrs) 95th%</th>
<th>Toddlers (6 mo – 4 yrs) 95th% + DINP Toy Exposure (12-23 mos.) 99th%[1]</th>
<th>Children 95th%[2]</th>
<th>Females (15 – 44 yrs) 95th%</th>
<th>Total Population 95th%[3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Exposure</td>
<td>0.70</td>
<td>0.70</td>
<td>0.46</td>
<td>0.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Biomarker-Based Exposure</td>
<td></td>
<td></td>
<td>0.07</td>
<td>0.1</td>
<td>0.09</td>
</tr>
</tbody>
</table>

[1] The 99th percentile estimated mean exposure to DINP is 1.5 \( \mu \text{g/kg/day} \) 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, 2009, unpublished data.
[2] Children as defined by the CDC NHANES dataset are 6-11 yrs. Children as defined by the Clark, 2009, unpublished dataset are 5-11 yrs.
[3] Total Population as defined by the CDC NHANES dataset is 6-60 yrs. Adult population as defined by the Clark, 2009, unpublished dataset are 20+ yrs.
Summary of Results

Cumulative Risk Assessment for Phthalate-Induced Repeated Dose Effects Using the Hazard Index Approach for Various Populations

- **Indirect Exposure Data**
- **Biomarker-Based Exposure Data**

<table>
<thead>
<tr>
<th>Hazard Index</th>
<th>Toddlers (6 mo - 4yrs) - 95th% Exposure</th>
<th>Toddlers (6 mo - 4yrs) - 95th% Exposure + DINP Exposure from Toys</th>
<th>Children 95th Percentile</th>
<th>Females 95th Percentile</th>
<th>Total Population 95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indirect Exposure Data</td>
<td>Biomarker-Based Exposure Data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• The HI approach provides a conservative determination of potential risk
  – Overestimates risks due to conservatism, design and assumptions

• For phthalate esters, no concern from cumulative risk assessment observed for repeated dose effects
  – Assessment conservative in that
    + Default uncertainty factors accounted for in calculation
    + Generally in rodents, MPOD for repeated dose effect is lower than that for other effects
    + Effect not relevant to humans
    + Use of indirect exposure artificially increases the exposure estimate; biomonitoring data is more representative of total exposure to phthalates including that from consumer products

• Exposure to DINP from mouthing of toys does not substantially impact HI
CHAP/CPSC History

- CPSC staff risk assessments in 1998 concluded that few, if any, children are at risk of organ toxicity from mouthing teether, rattles and toys made of DINP-plasticized PVC.

- CPSC recommended convening a CHAP to evaluate whether there are chronic hazards from exposure to DINP, and conducting additional studies to better define potential exposure to DINP.

- In Nov 1998, NGOs submitted request to CPSC to ban PVC in products for children 5 years of age and under, and issue a national advisory on health risks of vinyl toys.

- Commission voted to convene CHAP in Dec 1998.

Previous CHAP Determination

• Conclusions

– Cancer/Tumors -- Although DINP is clearly carcinogenic in rodents inducing liver tumors in rats and mice of both sexes, kidney tumors in male rats and mononuclear cell leukemia in male and female rats, the human risk from cancer induced by DINP is **negligible or non-existent**.
  + Liver cancer -- DINP causes liver cancer by a mechanism known as peroxisome proliferation. The peroxisome proliferator-activated receptor α (PPARα) mediated mechanism of hepatocarcinogenesis is pronounced in rodents, but believed not readily induced in humans, especially at the doses resulting from current use of consumer products.
  + Kidney tumors -- The male rat kidney tumors were viewed as rat specific since they met the criteria for supporting an α2μ-globulin mechanism of action, a mechanism accepted as unique to male rats. They were not used to predict human risk.
  + MNCL -- Mononuclear cell leukemia in Fischer 344 rats was viewed of questionable significance and was not used in human risk prediction.
  + Spongiosis Hepatis (liver lesions) -- No observed adverse effect levels identified in laboratory animals exposed to DINP

– Genotoxicity – DINP is **not genotoxic**.
  + Majority of data indicate DINP is non-genotoxic, consistent with results from other peroxisome proliferators. Bacterial mutation assays, mammalian gene mutation, in vivo and in vitro cytogenetic assays, and in vitro analysis of unscheduled DNA synthesis in rat hepatocytes all show no evidence of mutagenicity or genotoxicity.

– Reproductive/Development Toxicity – The risk to reproductive and developmental processes in humans due to DINP exposure is **extremely low or non-existent**.
  + Large margin between dose to pregnant women and those expected to be without effect in the animal assays.
Previous CPSC Review

• CPSC conducted a state-of-the-art mouthing study and migration studies

• Using its exposure data and the very conservative Acceptable Daily Intake (ADI) from the DINP CHAP report, CPSC staff conducted a worst-case risk assessment
  - “With this worst case analysis, even the 99\textsuperscript{th} percentile exposure would not exceed the acceptable daily intake (ADI)”
  - “The staff concluded that oral exposure to DINP from mouthing soft plastic toys, teethers, and rattles is not likely to present a health hazard to children. Since children mouth other children's products less than they do toys, teethers and rattles and since dermal exposure is expected to be minimal, staff does not believe that other children's products are likely to present a health hazard to children”

• The Commission voted to deny the petition to ban PVC in children’s products and issue a national advisory
What’s New Since Then

• 2003 National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction determined
  • DINP presents “minimal concern” for both developmental and reproductive adverse effects
  • DIDP presents “minimal concern” for developmental adverse effects and “negligible concern” for reproductive adverse effects

• 2003 European Chemical Bureau’s Risk Assessment report concluded “no risk reduction required” for DINP & DIDP

• 2004 Organization for Economic Cooperation and Development’s HPV program concludes HMW phthalates are “low priority for further work”

• 2005 US CDC study showed that the general population has low ppb levels of DINP metabolites in urine
  • Recent research shows ppb levels for both DINP and DIDP metabolites - indicative of exposure well within safe limits

• 2006 Oslo-Paris North-East Atlantic Commission for protection of the marine environment concludes “DINP and DIDP are not PBT substances and “there is no indication of potential for endocrine disruption”

• Toxicological Literature search by ExxonMobil Biomedical Sciences (EMBSI) since 2002 indicates no new science to shift the opinion on DINP or DIDP
  • 31 studies on HMW phthalate (DINP/DIDP/DPHP) toxicology. References submitted by ExxonMobil to CPSC on Jan 12, 2009.

• 2009 “Review of Recent Scientific Data on DINP and Risk Characterization for its Use in Toys and Childcare Articles” completed by EMBSI
  • Submitted to European Commission for re-evaluation of the DINP/DIDP Toy Restriction
  • Report clearly demonstrates that there is an adequate margin of safety for DINP in toys that can be mouthed to support lifting toy restriction

• 2009 Successful REACH registration of DIDP

• 2010 “DINP Carcinogenicity Hazard Assessment” completed by ExxonMobil Biomedical Sciences (EMBSI)
  • Submitted to California Office of Environmental Health Hazard Assessment (OEHHA) for consideration in determining potential Prop 65 listing.
  • Listing consideration based on observance of tumors in rodents treated with high doses of DINP; however, robust database demonstrates rodent tumors are not relevant to humans.

• 2010 Successful REACH registration of DINP
### Not all Phthalates are the same

#### EU Evaluation of Plasticizers and PVC Toys

- Not all substances with the potential to be used are necessarily used in PVC toys.
- The table also shows the Category 2 CMR phthalates.

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>LMW phthalates Category 2 CMR</th>
<th>LMW phthalates Category 2 CMR</th>
<th>HMW phthalates</th>
<th>Other HMW phthalates</th>
<th>Linear phthalates</th>
<th>Other phthalates</th>
<th>Other plasticisers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasticisers</td>
<td>DEHP</td>
<td>DIBP</td>
<td>DINP</td>
<td>DPHP</td>
<td>Linear 810</td>
<td>Linear 911</td>
<td>BIMP</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>DIHP</td>
<td>DIDP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU Risk Assessment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EU Classification review</td>
<td>Yes - CMR Cat 2</td>
<td>Yes - CMR Cat 2</td>
<td>Yes - Not</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>classified</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Regulatory safety evaluation for use in toys</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Restrictions in all toys and childcare articles</td>
<td>Yes - all toys and childcare</td>
<td>Yes (Toy Safety Directive)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>articles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictions in toys and childcare articles that can be placed in the mouth</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- The table shows commercial plasticisers which are used in PVC toys, have the potential to be used in PVC toys, or which have been restricted in PVC toys.
- No restrictions and no EU regulatory evaluations for use in toys.
## Not all phthalates are the same

<table>
<thead>
<tr>
<th><strong>Low molecular weight</strong></th>
<th><strong>High molecular weight</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DEHP, BBP, DBP</td>
<td>DINP &amp; DIDP</td>
</tr>
<tr>
<td>C4 to C8 alcohol + Phthalic Acid</td>
<td>C9 &amp; C10 Alcohol + Phthalic Acid</td>
</tr>
<tr>
<td>Cat 2 Reproductive Agents</td>
<td>✓ Not CMR</td>
</tr>
<tr>
<td>Risk reduction required</td>
<td>✓ Not classified and labelled</td>
</tr>
<tr>
<td>REACH Candidate List</td>
<td>✓ No risk reduction required</td>
</tr>
<tr>
<td>Restricted in all toys and childcare</td>
<td>✓ Not endocrine disrupters</td>
</tr>
<tr>
<td>Articles pending scientific review</td>
<td>✓ REACH Registered</td>
</tr>
<tr>
<td></td>
<td>Temporary restriction in toys that can be placed in the mouth and childcare articles pending scientific review</td>
</tr>
</tbody>
</table>

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