



## **DINP and DIDP are not endocrine disruptors**

Second Meeting of the Chronic Hazard Advisory Panel on Phthalates

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## What are DINP and DIDP?

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- DINP: Di-isononyl phthalate
  - is a substance composed of esters of phthalic acid and isononanol
  - is a commonly used plasticiser, 95% of which is used in PVC applications. More than half of the DINP used in non-PVC applications involves polymer related-uses (e.g. rubbers).
- DIDP: Di-isodecyl phthalate
  - is a substance composed of esters of phthalic acid and isodecanol
  - is a common phthalate plasticiser, used primarily to soften Polyvinyl chloride (PVC). It has properties of volatility resistance, heat stability and electric insulation and is typically used as a plasticiser for heat-resistant electrical cords, leather for car interiors, and PVC flooring.

For further information, see: <http://www.dinp-facts.com/> and <http://www.didp-facts.com>

- Endocrine disruption is not considered a toxicological end point per se but a functional change that leads to adverse effects
- Definition of an endocrine disruptor
  - Weybridge definition (1996) :
    - "An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function."
  - IPCS definition (2002):
    - "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

# How do you identify an endocrine disruptor?

## OECD Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals

<p><b>Level 1</b> Sorting &amp; prioritization based upon existing information</p>	<ul style="list-style-type: none"> <li>- physical &amp; chemical properties, e.g., MW, reactivity, volatility, biodegradability,</li> <li>- human &amp; environmental exposure, e.g., production volume, release, use patterns</li> <li>- hazard, e.g., available toxicological data</li> </ul>	
<p><b>Level 2</b> <i>In vitro</i> assays providing mechanistic data</p>	<ul style="list-style-type: none"> <li>- ER, AR, TR receptor binding affinity</li> <li>- Transcriptional activation</li> <li>- Aromatase and steroidogenesis <i>in vitro</i></li> <li>- Aryl hydrocarbon receptor recognition/binding</li> <li>- QSARs</li> </ul>	<ul style="list-style-type: none"> <li>- High Through Put Prescreens</li> <li>- Thyroid function</li> <li>- Fish hepatocyte VTG assay</li> <li>- Others (as appropriate)</li> </ul>
<p><b>Level 3</b> <i>In vivo</i> assays providing data about single endocrine Mechanisms and effects</p>	<ul style="list-style-type: none"> <li>- Uterotrophic assay (estrogenic related)</li> <li>- Hershberger assay (androgenic related)</li> <li>- Non-receptor mediated hormone function</li> <li>- Others (e.g. thyroid)</li> </ul>	<ul style="list-style-type: none"> <li>- Fish VTG (vitellogenin) assay (estrogenic related)</li> </ul>
<p><b>Level 4</b> <i>In vivo</i> assays providing data about multiple endocrine Mechanisms and effects</p>	<ul style="list-style-type: none"> <li>- enhanced OECD 407 (endpoints based on endocrine mechanisms)</li> <li>- male and female pubertal assays</li> <li>- adult intact male assay</li> </ul>	<ul style="list-style-type: none"> <li>- Fish gonadal histopathology assay</li> <li>- Frog metamorphosis assay</li> </ul>
<p><b>Level 5</b> <i>In vivo</i> assays providing data on effects from endocrine &amp; other mechanisms</p>	<ul style="list-style-type: none"> <li>- 1-generation assay (TG415 enhanced)<sup>1</sup></li> <li>- 2-generation assay (TG416 enhanced)<sup>1</sup></li> <li>- reproductive screening test (TG421 enhanced)<sup>1</sup></li> <li>- combined 28 day/reproduction screening test (TG 422 enhanced)<sup>1</sup></li> </ul> <p><sup>1</sup> Potential enhancements will be considered by VMG mamm</p>	<ul style="list-style-type: none"> <li>- Partial and full life cycle assays in fish, birds, amphibians &amp; invertebrates (developmental and reproduction)</li> </ul>

# OECD conceptual framework: Level 1

<p><b>Level 1</b> Sorting &amp; prioritization based upon existing information</p>	<ul style="list-style-type: none"> <li>- physical &amp; chemical properties, e.g., MW, reactivity, volatility, biodegradability,</li> <li>- human &amp; environmental exposure, e.g., production volume, release, use patterns</li> <li>- hazard, e.g., available toxicological data</li> </ul>
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Level 1 Endpoints	DBP	DEHP	DINP	DIDP
Physical & chemical properties	Di-n-butyl phthalate CAS RN 84-74-2  C4 alcohol + phthalic anhydride	Di-ethylhexyl phthalate CAS RN 117-81-7  C8 alcohol + phthalic anhydride	Di-isononyl phthalate CAS RN 68515-48-0 CAS RN 28553-12-0  C9 alcohol + phthalic anhydride	Di-isodecyl phthalate CAS RN 68515-49-1  C10 alcohol + phthalic anhydride
Human & environmental exposure	PVC plasticisers, physically bound to the polymer matrix			
Hazard	<b>Classified:</b> EU CLP Repr.1B Aquatic Acute 1	<b>Classified:</b> EU CLP Repr.1B	Not classified	Not classified

**Conclusion:** comprehensive hazard assessment datasets are already available, sufficient to demonstrate that not all phthalates are the same and enable (non)-classification decisions

# OECD conceptual framework: Level 2

<b>Level 2</b> <i>In vitro</i> assays providing mechanistic data	<ul style="list-style-type: none"> <li>- ER, AR, TR receptor binding affinity</li> <li>- Transcriptional activation</li> <li>- Aromatase and steroidogenesis <i>in vitro</i></li> <li>- Aryl hydrocarbon receptor recognition/binding</li> <li>- QSARs</li> </ul>	<ul style="list-style-type: none"> <li>- High Through Put Prescreens</li> <li>- Thyroid function</li> <li>- Fish hepatocyte VTG assay</li> <li>- Others (as appropriate)</li> </ul>
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Level 2 Endpoints	DBP	DEHP	DINP	DIDP
Do data exist?	✓	✓	✓	✓
Indication of ED potential? yes (red) no (green) inconclusive (yellow)				

**Conclusion:** *in vitro* assay data already exist for these chemicals, sufficient to demonstrate that DINP and DIDP are not hormone receptor antagonists. *in vitro* data for other mechanisms is inconsistent.

# OECD conceptual framework: Level 3

<b>Level 3</b> <i>In vivo</i> assays providing data about single endocrine Mechanisms and effects	<ul style="list-style-type: none"> <li>- Uterotrophic assay (estrogenic related)</li> <li>- Hershberger assay (androgenic related)</li> <li>- Non -receptor mediated hormone function</li> <li>- Others (e.g. thyroid)</li> </ul>	<ul style="list-style-type: none"> <li>- Fish VTG (vitellogenin) assay (estrogenic related)</li> </ul>
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Level 3 Endpoints	DBP	DEHP	DINP	DIDP
Do data exist?	✓	✓	✓	✓
Indication of ED potential? yes (red) no (green) inconclusive (yellow)				

**Conclusion:** *in vivo* assay data already exist for these chemicals; the weight of evidence is sufficient to demonstrate that DINP and DIDP are not estrogen or androgen mediators

# OECD conceptual framework: Level 4

<p><b>Level 4</b> <i>In vivo</i> assays providing data about multiple endocrine Mechanisms and effects</p>	<ul style="list-style-type: none"> <li>- enhanced OECD 407 (endpoints based on endocrine mechanisms)</li> <li>- male and female pubertal assays</li> <li>- adult intact male assay</li> </ul>	<ul style="list-style-type: none"> <li>- Fish gonadal histopathology assay</li> <li>- Frog metamorphosis assay</li> </ul>
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Level 4 Endpoints	DBP	DEHP	DINP	DIDP
Do data exist?	✓	✓	✓	✓
Indication of ED potential? yes (red) no (green) inconclusive (yellow)				

**Conclusion:** *in vivo* assay data already exist for these chemicals, sufficient to demonstrate that DINP and DIDP are not reproductive system mediators

# OECD conceptual framework: Level 5

<p><b>Level 5</b> <i>In vivo</i> assays providing data on effects from endocrine &amp; other mechanisms</p>	<ul style="list-style-type: none"> <li>- 1-generation assay (TG415 enhanced)<sup>1</sup></li> <li>- 2-generation assay (TG416 enhanced)<sup>1</sup></li> <li>- reproductive screening test (TG421 enhanced)<sup>1</sup></li> <li>- combined 28 day/reproduction screening test (TG 422 enhanced)<sup>1</sup></li> </ul> <p><sup>1</sup> Potential enhancements will be considered by VMG mamm</p>	<ul style="list-style-type: none"> <li>- Partial and full life cycle assays in fish, birds, amphibians &amp; invertebrates (developmental and reproduction)</li> </ul>
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Level 5 Endpoints	DBP	DEHP	DINP	DIDP
Do data exist?	✓	✓	✓	✓
Indication of ED potential? yes (red) no (green) inconclusive (yellow)				

**Conclusion:** *in vivo* data from apical studies already exist for these chemicals, sufficient to support the position that DINP and DIDP are not endocrine disruptors

# Conclusion

- DINP and DIDP are not endocrine disruptors

OECD CF Level	Conclusions	
	DINP	DIDP
1	Comprehensive dataset already exists; shows that not all phthalates are the same	Comprehensive dataset already exists; shows that not all phthalates are the same
2	<i>in vitro</i> assay data exist; sufficient to demonstrate that DINP is not a hormone receptor antagonist	<i>in vitro</i> assay data exist; sufficient to demonstrate that DIDP is not a hormone receptor antagonist. <i>in vitro</i> data for other mechanisms is inconsistent
3	<i>in vivo</i> assay data exist; sufficient to demonstrate that DINP is not an estrogen or androgen mediator	<i>in vivo</i> assay data exist; the weight of evidence is sufficient to demonstrate that DIDP is not an estrogen or androgen mediator
4	<i>in vivo</i> assay data exist; sufficient to demonstrate that DINP is not a reproductive system mediator	<i>in vivo</i> assay data exist; sufficient to demonstrate that DIDP is not a reproductive system mediator
5	<i>in vivo</i> data from apical studies are sufficient to confirm that DINP is not an endocrine disruptor	<i>in vivo</i> data from apical studies are sufficient to confirm that DIDP is not an endocrine disruptor