



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?

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

OECD conceptual framework: Level 1

<p>Level 1 Sorting & prioritization based upon existing information</p>	<ul style="list-style-type: none"> - physical & chemical properties, e.g., MW, reactivity, volatility, biodegradability, - human & environmental exposure, e.g., production volume, release, use patterns - hazard, e.g., available toxicological data
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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	Classified: EU CLP Repr.1B Aquatic Acute 1	Classified: 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

Level 2 <i>In vitro</i> assays providing mechanistic data	<ul style="list-style-type: none"> - ER, AR, TR receptor binding affinity - Transcriptional activation - Aromatase and steroidogenesis <i>in vitro</i> - Aryl hydrocarbon receptor recognition/binding - QSARs 	<ul style="list-style-type: none"> - High Through Put Prescreens - Thyroid function - Fish hepatocyte VTG assay - Others (as appropriate)
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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

Level 3 <i>In vivo</i> assays providing data about single endocrine Mechanisms and effects	<ul style="list-style-type: none"> - Uterotrophic assay (estrogenic related) - Hershberger assay (androgenic related) - Non -receptor mediated hormone function - Others (e.g. thyroid) 	<ul style="list-style-type: none"> - Fish VTG (vitellogenin) assay (estrogenic related)
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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>Level 4 <i>In vivo</i> assays providing data about multiple endocrine Mechanisms and effects</p>	<ul style="list-style-type: none"> - enhanced OECD 407 (endpoints based on endocrine mechanisms) - male and female pubertal assays - adult intact male assay 	<ul style="list-style-type: none"> - Fish gonadal histopathology assay - Frog metamorphosis assay
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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>Level 5</p> <p><i>In vivo</i> assays providing data on effects from endocrine & other mechanisms</p>	<ul style="list-style-type: none"> - 1-generation assay (TG415 enhanced)¹ - 2-generation assay (TG416 enhanced)¹ - reproductive screening test (TG421 enhanced)¹ - combined 28 day/reproduction screening test (TG 422 enhanced)¹ <p>¹ Potential enhancements will be considered by VMG mamm</p>	<ul style="list-style-type: none"> - Partial and full life cycle assays in fish, birds, amphibians & invertebrates (developmental and reproduction)
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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