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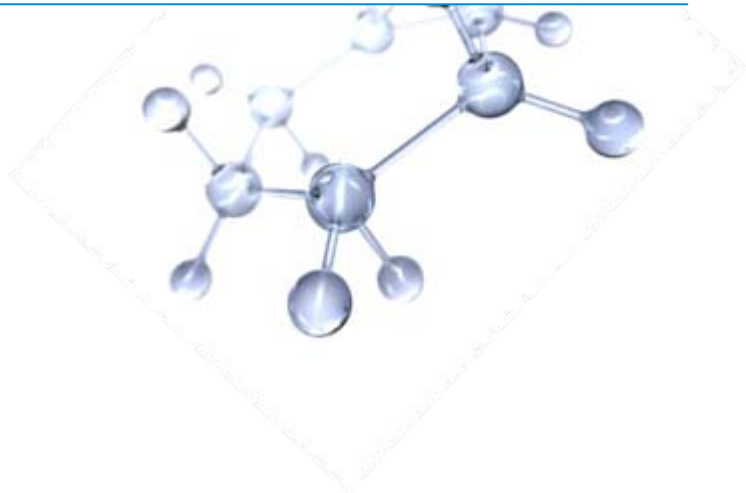
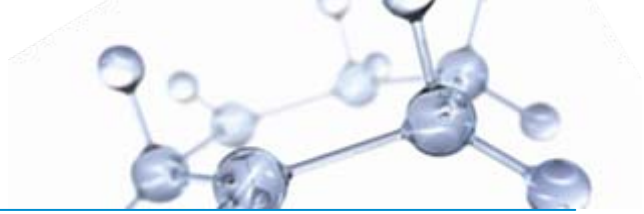


DINP and DIDP

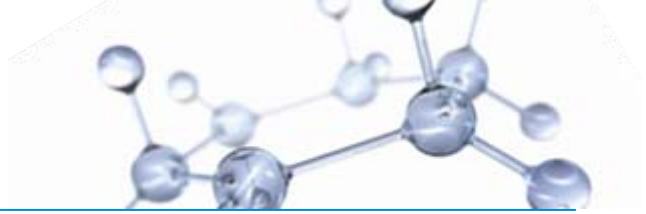
Ammie Bachman PhD
ExxonMobil Biomedical Sciences, 2010

Agenda



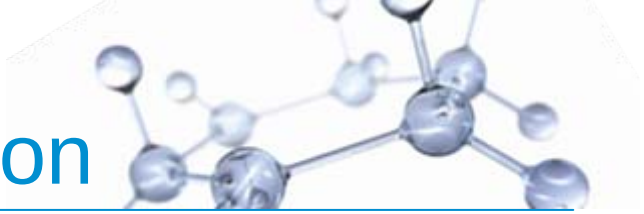
- Phthalate Chemistry
- Hazard Characterization Comparison
- Cumulative Risk
- Summary

“Phthalates” . . .



- Constitute a broad class of chemicals with a range of physical, chemical and toxicological properties
  - The properties are structure-dependent
    - Phthalates are NOT all the same, and
    - They are NOT all toxicologically equivalent
- Are widely used because they have technical properties suitable to many applications
  - But suitability is related to specific technical properties
  - Phthalates are sometimes interchangeable
    - But interchange of phthalates are not appropriate for all uses
  - Non-phthalate alternatives exist for some applications
    - But are not always as:
      - Technically suitable
      - Well characterized toxicologically
      - Readily available and/or cost competitive

Overall Hazard characterization

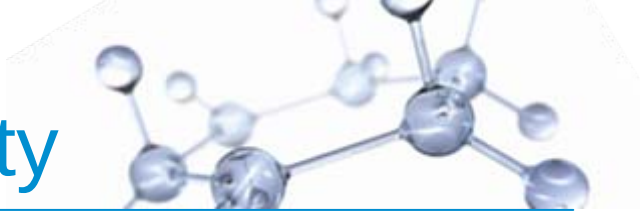


- DINP and DIDP have low toxicity on par with the most likely alternatives.

	DINP	DIDP	DINCH	DOTP	DPHP
Acute	☑ Low	☑ Low	☑ Low	☑ Low	☑ Low
Irritation	☑ Slight	☑ Slight	☑ Slight	☑ Slight	☑ Slight
Sensitization	☑ Negative	☑ Negative	☑ Negative	☑ Negative	☑ Negative
Genotoxicity	☑ Negative	☑ Negative	☑ Negative	☑ Negative	☑ Negative
Mutagenicity	☑ Negative	☑ Negative	☑ Negative	☑ Negative	☑ Negative
Repeated Dose[1]	Liver and Kidney Effects	Liver Effects	Thyroid and Kidney Effects	Retinal Degeneration	Liver Effects
Carcinogenicity	Tumor formation - NOT relevant to humans		Thyroid Tumor Formation – (possibly secondary effect)	☑ Negative	No Data
Reproductive	☑ Negative	☑ Negative	☑ Negative	Lactational Maternal Death (> 1300 mg/kg)	☑ Negative
Developmental	Skeletal Variations	Skeletal Variations	Slight Decrease AGD/AGI (1000 mg/kg)	Skeletal Variation	High Rate of Resorptions; Skeletal Var.

[1]The relevance of the listed effects to humans is questionable.

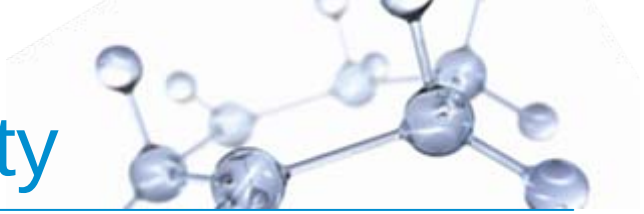
DINP Developmental Toxicity



- Minimal developmental effects thought to be due to maternal toxicity observed in standard assays
- Not classified under EU Classification, Labeling, Packaging Regulation and UN Globally Harmonized System

	DINP		
Reference	Nikoforov et al., 1994	Waterman et al., 1999 OECD 414	Hellwig et al., 1997
Species/Strain; Route	Crl:CDBR Rat; gavage	Wistar Rat; Gavage	Wistar Rat; Gavage
Dose Levels (mg/kg/day)	0, 40, 200, 500, 1000	0, 100, 500, 1000	0, 40, 200, 1000
Duration	GD 6-15	GD 6-15	GD 6-15
Critical Effect (Fetal)	No Effect	Skeletal Variations (Ribs) Dilated renal pelves at maternally toxic doses (Effect level: 1000 mg/kg)	Skeletal Variations (Ribs) at maternally toxic doses (Effect level: 1000 mg/kg)
NOAEL (Fetal)	**1000 mg/kg/day**	**500 mg/kg/day**	**200 mg/kg/day**
Critical Effect (Maternal)	No Effect	Reduced weight gain, food consumption	Reduced weight gain, kidney weight
NOAEL (Maternal)	**1000 mg/kg/day**	**500 mg/kg/day**	**200 mg/kg/day**

DIDP Developmental Toxicity



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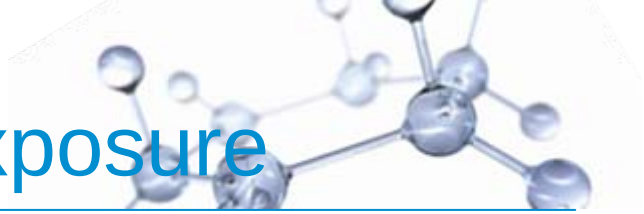
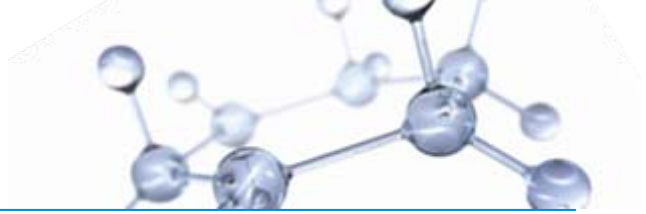
	DIDP	
Reference	Waterman et al., 1999 OECD 414	Hellwig et al., 1997 OECD 414
Species/Strain; Route	Crl: CDBR Rat; Gavage	Wistar Rat; Gavage
Dose Levels (mg/kg/day)	0, 100, 500, 1000	0, 40, 200, 1000
Duration	GD 6-15	GD 6-15
Critical Effect (Fetal)	Skeletal Variations (Effect level: 1000 mg/kg)	Skeletal Variations Dilated ureter (Effect level: 1000 mg/kg)
NOAEL (Fetal)	**500 mg/kg/day**	**200 mg/kg/day**
Critical Effect (Maternal)	Reduced weight gain	Increased liver weight
NOAEL (Maternal)	**500 mg/kg/day**	**200 mg/kg/day**

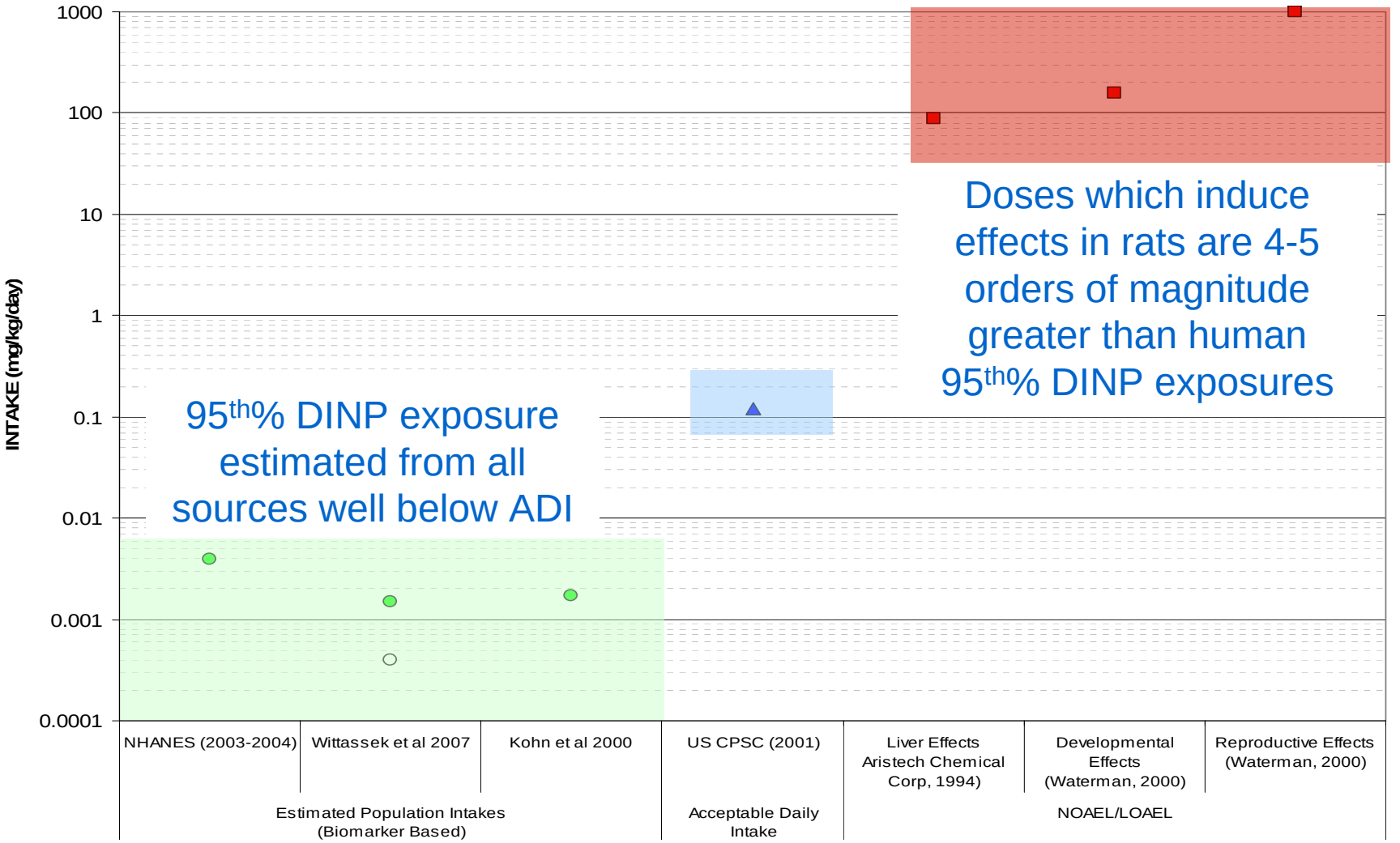
Phys/Chem Properties & Exposure



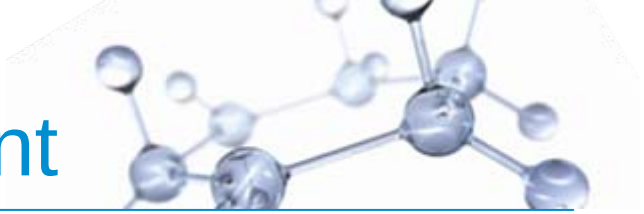
- DIDP and DINP are liquids with very low:
  - Vapor pressure
  - Water solubility
  - Dermal absorption (Elsisi et al., 1989)
- Exposures sufficiently high enough to induce adverse effects in humans are not plausible, given the inherent phys/chem properties of DIDP and DINP

Exposure to DINP/DIDP





HMW phthalates are different



Low molecular weight

BBP, DBP, DEHP

C3 to C8 alcohol + Phthalic Acid

- body weight decreases
- soft tissue & skeletal malformations
- decreased testosterone
- reduced anogenital distance
- nipple retention
- hypospadias
- cryptorchidism
- sex organ weight decreases
- adverse testis histopathology
- decreased fertility

CLASSIFIED FOR REPRO/DEV EFFECTS
UNDER EU CLP REGULATION AND UN GHS

High molecular weight

DINP & DIDP

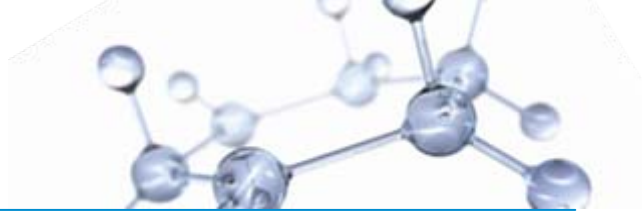
C9 & C10 Alcohol + Phthalic Acid

- body weight decreases
- no malformations - skeletal variations only
- decreased testosterone[1]
- no reduction in anogenital distance
- no nipple retention[2]
- no hypospadias
- no cryptorchidism
- no sex organ weight decrease
- no adverse testis histopathology[3]
- no decreases in fertility

NOT CLASSIFIED
UNDER EU CLP REGULATION AND UN GHS

[1]One study reports decreased fetal testosterone (Borch et al., 2004), one study reports no effect on fetal testosterone (Adamsson et al., 2009)
[2]DIDP – not observed in 2-generation study (Waterman et al., 1999); DINP – 2/52 male pups exhibited nipple retention (Gray et al., 2000)
[3]DINP – not observed in 2-generation study (Waterman et al., 1999); Testis histopathology reported in a small number of animals (Gray et al., 2000)

Integrated data review



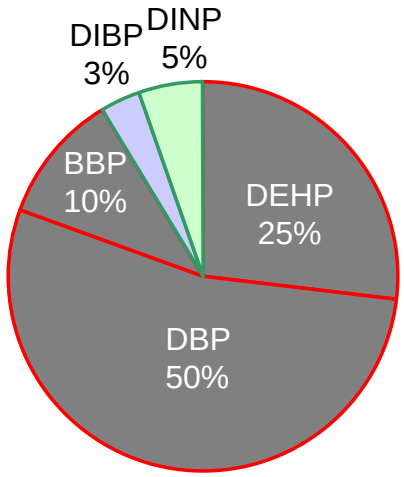
- NTP CERHR Review
  - DINP: *minimal concern for adverse reproductive or development effects*
  - DIDP: *negligible concern for adverse reproductive effects and minimal concern for adverse development effects*

- DINP and DIDP are not selective reproductive or developmental toxins
- DINP and DIDP are not endocrine disrupters: Weybridge definition, International Programme for Chemical Safety, and REACH
- DINP and DIDP do not pose a risk to male reproductive tract development

Cumulative Risk

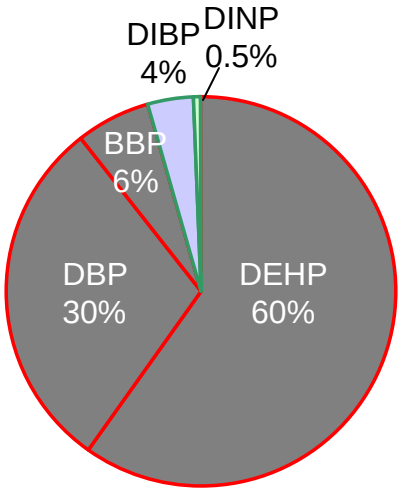
- Benson, 2009
- PODs based on BMDLs for decreased fetal testosterone or small/absent male reproductive organs[1]
- Exposure estimated from CDC NHANES 2003-2004 95th% Data

	Hazard Quotient
DBP	0.02
DEHP	0.01
BBP	0.004
DIBP	0.001
DINP	0.002



- Kortenkamp and Faust, 2010
- PODs based on BMDLs for decreased fetal testosterone or retained nipples in male offspring[1]
- Exposure estimated from CDC NHANES 2003-2004 95th% Data and from Kohn, 2000

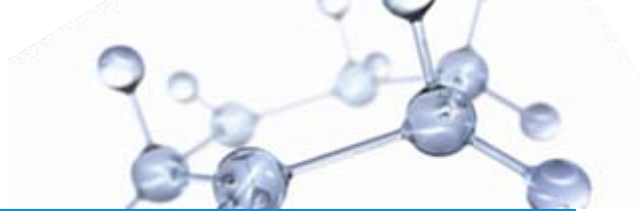
	Hazard Quotient
DBP	0.06
DEHP	0.12
BBP	0.012
DIBP	0.008
DINP	0.001



DINP and DIDP are minor contributors to the cumulative risk of the phthalate mixture
This is a function of low exposure and low (if any) toxicity for the endpoint of concern

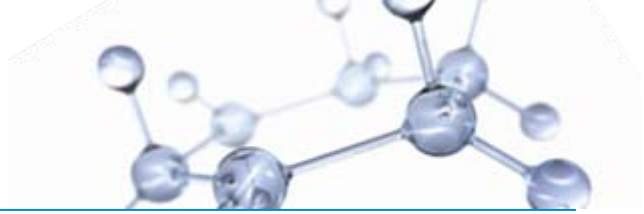
[1]See page 9 for clear differences between LMW phthalates (DEHP, DBP, BBP) and HMW phthalates (DINP, DIDP) with respect to these endpoints.

Conclusions



- HMW Phthalates (DINP and DIDP) are widely used in commerce
  - Uses relate to structures of specific molecules
  - HMW phthalates are not toxicologically equivalent to other phthalates
- DINP and DIDP have been extensively tested and widely assessed
  - ILSI RSI and the CPSC have assessed the carcinogenic potential
  - NTP assessed the reproductive/developmental effects
  - EU has conducted comprehensive risk assessments
  - Specific uses have been considered (e.g. CPSC, FDA, CIR)
  - Very low exposure has been estimated via biomonitoring data
  - DINP and DIDP are REACH registered
- Contribution to an overall cumulative risk of the phthalates by DINP and DIDP is minimal due to low exposure estimates and low toxicity

Independent Assessments of DINP/DIDP



2003	**US Consumer Product Safety Commission**	"**no demonstrated health risk**" from use of DINP in toys
2003	**National Toxicology Program**	"**minimal" and "negligible" concern** for reproductive / developmental toxicity of DINP & DIDP
2004	**OECD**	HMW phthalates (DINP/DIDP) are "**low priority for further work**" [1]
2005	**US Centers for Disease Control**	CDC (2005) report **indicates that exposure is well within safe limits**
2006	**European Union**	EU Risk Assessments find HMW phthalates (DINP & DIDP) **safe for use in current applications**[2][3]
2007	**US Consumer Product Safety Commission**	**"CPSC staff has kept abreast of the new research and has not seen anything that would cause a change in staff's position"** (Letter from CPSC staff to CA Senator Runner)
2009	**European Union**	DIDP registered under REACH
2010	**European Union**	DINP registered under REACH

[1] OECD comments for high molecular weight phthalates including DINP and DIDP
[2] In case DIDP were to be used in toys to substitute for other phthalates, risk reduction would be required for infants under 3 years of age
[3] ExxonMobil recommends the use of DINP for vinyl toys