RepDose and FeDTex
Two databases focusing on systemic toxicity

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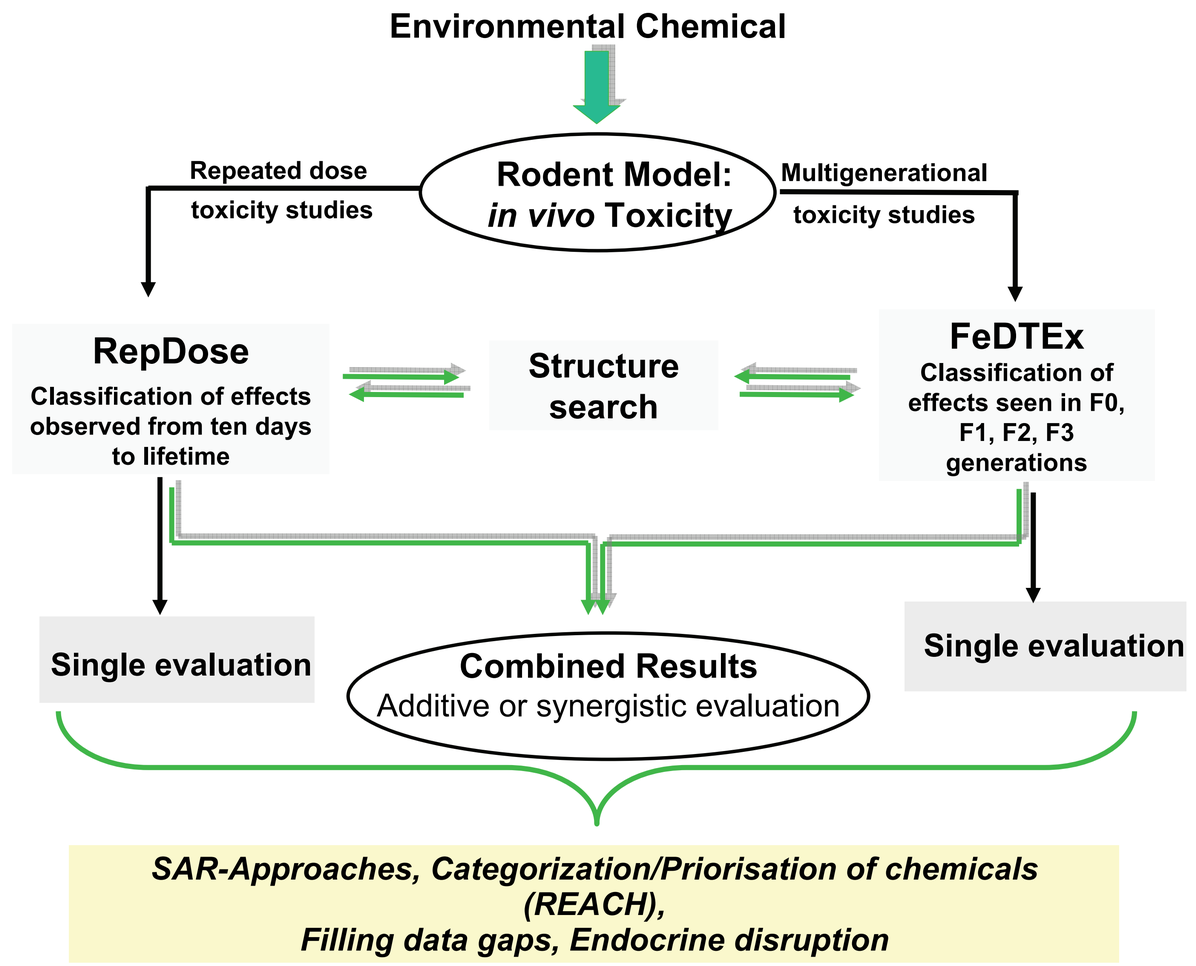
Introduction

New regulations for chemicals, biocides and cosmetics require the a thorough and careful data mining either for the applicability of SAR approaches or for the priorisation and planning of animal experiments needed. One tool to support this work is the data compilation in form of endpoint specific databases. Currently, two databases for in vivo toxicology are under construction at Fraunhofer ITEM on behalf of CEFIC LRI.

Short description of the databases

RepDose contains data from repeated dose toxicity studies; FeDTEx addresses reproductive toxicity including one-, two- and three-generational studies.

- RepDose contains at present repeated dose toxicity information for more than 400 industrial chemicals; effects in test groups observed from ten days to lifetime were collected here (*REPDOSE: A database on repeated dose toxicity studies of commercial chemicals--A multifunctional tool. Regul Toxicol Pharmacol. 2006 Dec;46(3):202-10).*
- FeDTEx is designed comparably and the data entry has been started for reprotoxic effects seen in F0, F1, F2, F3 generations.



First examples from analyses of repeated dose toxicity and reprotoxicity studies

RepDose and FeDTex can be used as stand alone databases or in combination to identify chemical structures responsible for specific effects or target organs. Within RepDose a broad spectrum of targets and effects can be addressed. In FeDTex, queries on selected effects in parent and offspring generations are possible. Combined use of both databases will provide an improved tool for substance toxicity profiling e.g. for early indication of reprotoxic properties.
51 chemicals are identical in both databases. An evaluation of toxicity profiles for these chemicals is presented in Fig 1.

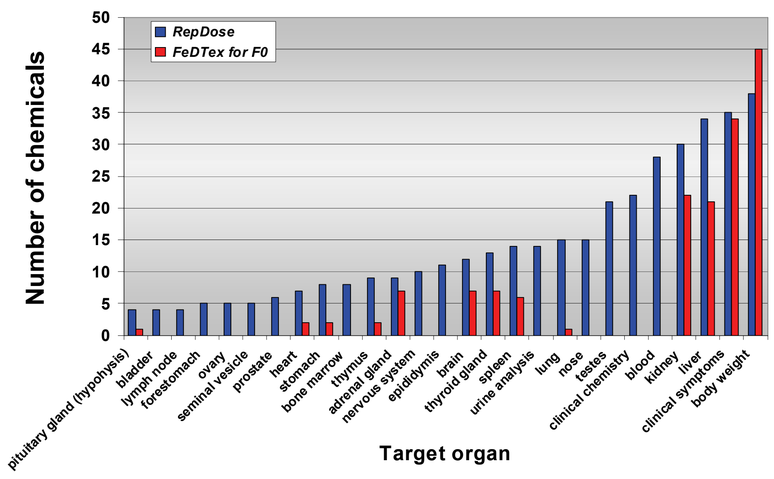


Fig 1. Distribution of target organs for general toxicity in RepDose and FeDTex

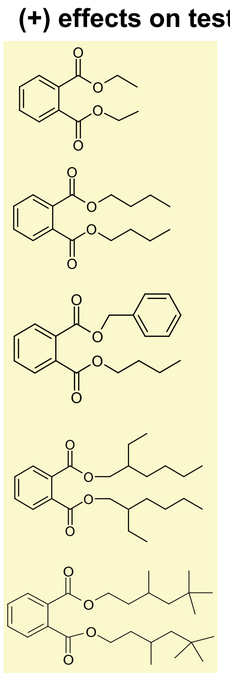
Queries for phthalic acid derivatives

The query in both databases for effects of phthalic acid derivatives shows the possibilities of combined queries and proves the applicability and data consistency for a group of chemicals with known effects on the reproductive system.

- **9 phthalic acid derivatives are listed in RepDose**
- **7 phthalic acid derivatives are listed in FeDTex in multi-generation studies**

RepDose

(+) effects on testes



CAS 84-66-2
LOEL = 3160 mg/kg bw/d
oLOEL= 150 **mg/kg bw/d**

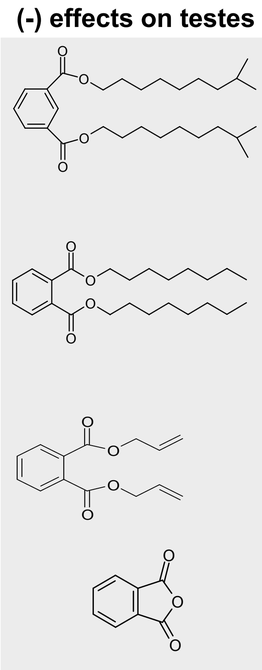
CAS 84-74-2
LOEL = 4.4 mg/kg bw/d
oLOEL= 0.04 **mg/kg bw/d**

CAS 85-68-7
LOEL = 180 **mg/kg bw/d**
oLOEL= 1250 **mg/kg bw/d**

CAS 117-81-7
LOEL = 600 **mg/kg bw/d**
oLOEL= 300 **mg/kg bw/d**

CAS 28553-12-0 / 68515-48-0
oLOEL = 125 **mg/kg bw/d**
$LOEL_{(testes)}$ = 500 **mg/kg bw/d**

(-) effects on testes



CAS 26761-40-0
oLOEL=
40 **mg/kg bw/d**

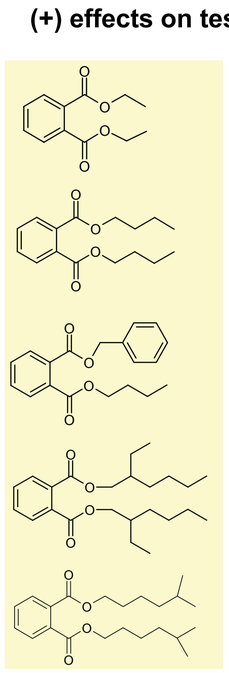
CAS 117-84-0
oLOEL=
1906 **mg/kg bw/d**

CAS 131-17-9
oLOEL=
70 **mg/kg bw/d**

CAS 85-44-9
oLOEL=
375 **mg/kg bw/d**

FeDTEx

(+) effects on testes and/or sperm parameters



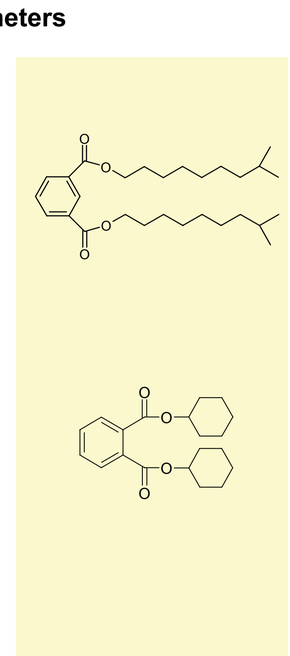
CAS 84-66-2
$LOEL_{(sperm)}$= 150 mg/kg bw/d

CAS 84-74-2
$LOEL_{(testes)}$ = 0.5 mg/kg bw/d

CAS 85-68-7
$LOEL_{(testes)}$= 100 mg/kg bw/d
$LOEL_{(sperm)}$= 563 mg/kg bw/d

CAS 117-81-7
$LOEL_{(testes)}$ = 135 mg/kg bw/d

CAS 71888-89-6
C7_rich > 80%; C6-C8
$LOEL_{(testes)}$= 400 mg/kg bw/d
$LOEL_{(sperm)}$= 50 mg/kg bw/d



CAS 68515-49-1
C10_rich; C10-C12
$LOEL_{(testes)}$= 40 mg/kg bw/d

CAS 84-61-7
$LOEL_{(testes)}$= 60 mg/kg bw/d
$LOEL_{(sperm)}$= 60 mg/kg bw/d

Comparison of target organs in RepDose and FeDTex for 4 phthalates

	84-66-2	Diethyl phthalate	84-74-2	Di-n-butyl phthalate	85-68-7	Butyl benzyl phthalate	117-81-7	di-sec-octyl Phthalate
	RepDose	FeDTex	RepDose	FeDTex	RepDose	FeDTex	RepDose	FeDTex
adrenal gland	X	F0, F1, F2						
bladder					X			
blood			X		X		X	
body weight/body weight gain	X	F0, F1, F2	X	F1	X	F0, F1, F2	X	F1
brain	X	F2	X			F0, F1, F2		F1
clinical chemistry	X	F1	X		X			
clinical symptoms			X		X	F0, F1	X	
endocrine system		F0				F0, F1		F1
epididymis		F0	X	F1		F0, F1		
gall bladder			X					
heart	X					F1		
intestine	X				X			
kidney	X	F1, F2	X		X	F0		F0
liver	X	F1, F2	X		X	F0, F1	X	F0, F1
lung			X			F0, F1	X	
mammary gland						F0		
ovary						F0, F1, F2		
pancreas					X			
pituitary gland (hypophysis)	X	F1				F1	X	
prostate		F1		F1	X			
spleen	X	F1, F2	X			F1, F2		F1
stomach	X							
testes	X			F1	X	F0, F1, F2	X	
thymus		F1, F2				F0, F1, F2		
thyroid gland	X	F1				F1		
urine analysis					X	F0, F1		
uterus		F1, F2						

Testes are predominant target organs of phthalatic acid derivatives after repeated dose application and in reprotoxicity studies. Neither testes nor other reproductive organs in RepDose do determine the overall LOEL in the examined studies (data not shown). A lower dosing in multi-generation studies may account for the seen discrepancies in the observed F0_male effects in RepDose and FeDTEx.
Toxicity seems to be dependent on the length of the aliphatic substituent. In RepDose C2-C6 substituted phthalic acids induce toxic effects on testes, substitutents with chain length of C8 and more do not have any activity on testes, as well as isophthalic and condensed ring derivatives. FeDTEx_data confirme that C2-C6 substituted derivatives show effects on sperm parameters and testes. Unexpectedly, diisodecylphthalate is toxic to testes in subsequent offspring generations.
All over the results fit well with the hypotheses published for the reprotoxic effects of phthalates and, thus, confirm the value of combined queries within both databases.

Acknowledgement

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LRI The Long-range Research initiative
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