

Two databases focusing on in vivo toxicity: examples for application and combination

First examples from analyses of repeated dose toxicity (RepDose) and transgenerational toxicity (FeDTEEx) studies



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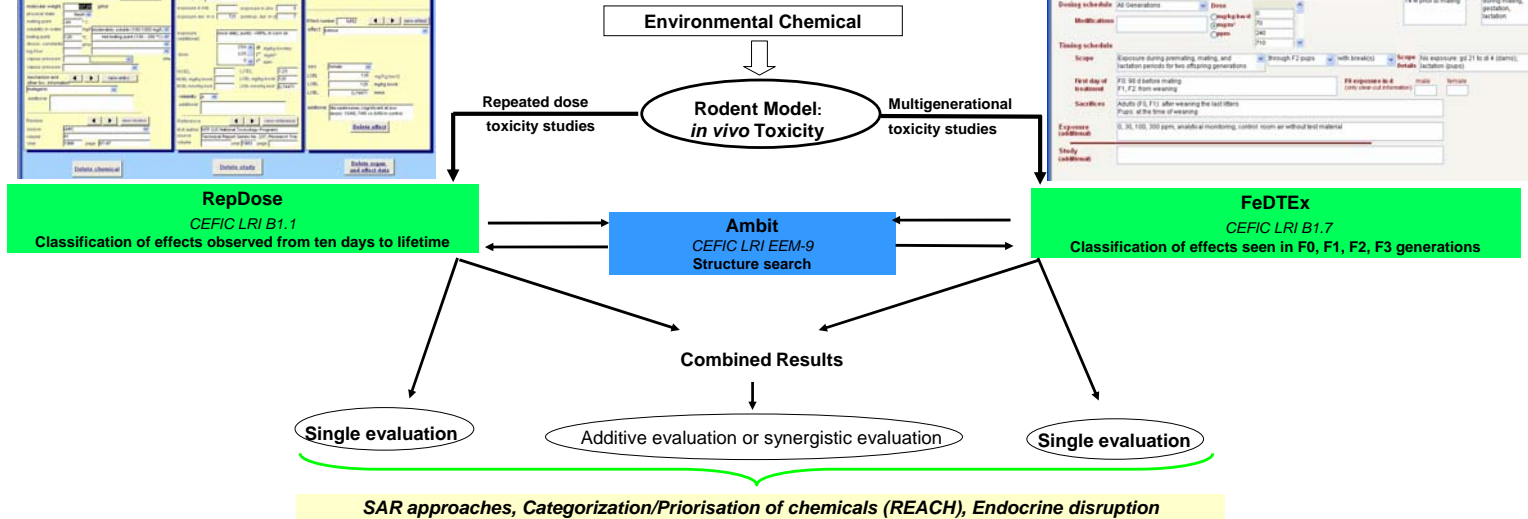
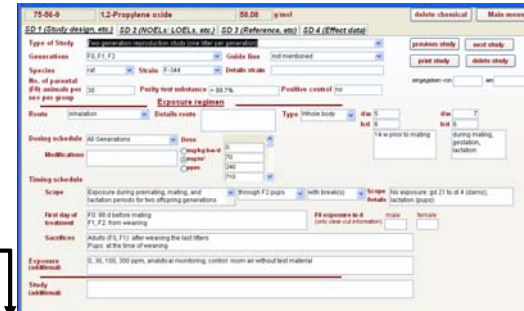
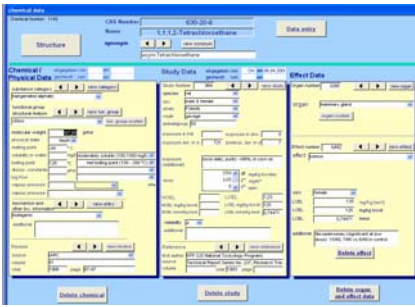
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New regulations for chemicals, biocides and cosmetics require the a thorough and careful data mining either for the applicability of SAR approaches or for the prioritisation and xx planning of animal experiments needed. One tool to support this work 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. RepDose (I) contains data from repeated dose toxicity studies; FeDTEEx (II) 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).

FeDTEEx is designed comparably and the data entry has been started for reprotoxic effects seen in F0, F1, F2, F3 generations (note: teratogenic effects are not within the focus of this database).

RepDose and FeDTEEx can be used either as single, stand alone databases or in combination. Single use could give information on e.g. chemical structures responsible for specific effects or the sensitivity of certain target organs (or relationship between exposure duration and LOELs). Within RepDose a broad spectrum of targets and effects can be addressed. In FeDTEEx queries on selected effects in parent and offspring generations are possible.



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 in 42 studies: 145 effects in 24 target organs
- 5 phthalic acid derivatives are listed in FeDTEEx in 7 studies (multi-generation)

RepDose

(+ effects on testes)		(-) effects on testes	
	CAS 84-66-2 LOEL = 3160 mg/kg bw/d oLOEL= 150 mg/kg bw/d		CAS 117-84-0 oLOEL= 1906 mg/kg bw/d
	CAS 84-74-2 LOEL = 4.4 mg/kg bw/d oLOEL= 0.04 mg/kg bw/d		CAS 121-91-5 oLOEL= 800 mg/kg bw/d
	CAS 85-68-7 LOEL = 1250 mg/kg bw/d oLOEL= 1250 mg/kg bw/d		CAS 26761-40-0 oLOEL= 40 mg/kg bw/d
	CAS 117-81-7 LOEL = 600 mg/kg bw/d oLOEL= 300 mg/kg bw/d		CAS 85-44-9 oLOEL= 375 mg/kg bw/d

FeDTEEx

(+ effects on testes and/or sperm parameters)	
	CAS 84-66-2 LOEL (sperm) = 150 mg/kg bw/d
	CAS 85-68-7 LOEL (testes) = 100 mg/kg bw/d LOEL (sperm) = 562,5 mg/kg bw/d
	CAS 84-61-7 LOEL (testes) = 60 mg/kg bw/d LOEL (sperm) = 60 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

	RepDose		FeDTEEx		
	N	N	F0_adult N	F1_adult N	F2_adult N
target total no. of chemicals	9	9	5	5	5
reproductive parameters		2		2	
endocrine system				1	
duration of pregnancy				1	
precoital interval				1	
reproductive organs		2		3	
epididymis				2	
ovaries				2	
pituitary gland		2		2	
prostate		1		4	
seminal vesicles				4	
sperm parameter				4	
testes		4		4	
thyroid gland		3		3	
uterus				4	1

	RepDose		FeDTEEx		
	N	N	F0_adult N	F1_adult N	F2_adult N
target total no. of chemicals	9	9	5	5	5
general toxicity		1		2	1
adrenal gland		1		1	
behaviour		1		1	
bladder		4		5	
blood		7		4	
body weight		2		1	3
brain		1		1	
forestomach		1		1	
gall bladder		1		1	
heart		1		1	
intestine		3		1	
kidney		6		4	5
liver		7		5	5
lung		3		1	1
pancreas		1		1	
spleen		2		1	2
stomach		1		1	3
thymus		1		1	1
urine analysis		2		1	1

Testes are predominant target organs of phthalic 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 42 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 FeDTEEx.

Toxicity seems to be dependent on the length of the aliphatic substituent. In RepDose C2-C6 substituted phthalic acids induce toxic effects on testes, substituents with chain length of C8 and more do not have any activity on testes, as well as isophthalic and condensed ring derivatives. FeDTEEx_data confirm that C2-C6 substituted derivatives show effects on sperm parameters and testes. Unexpectedly, diisododecylphthalate is toxic to testes in subsequent offspring generations. These results fit well with the hypotheses published for the reprotoxic effects of phthalates and, thus, confirm the value of combined queries within both databases.