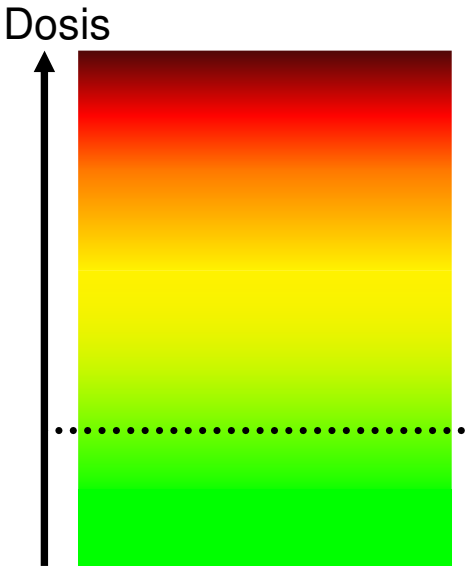
BfR
Risiken erkennen – Gesundheit schützen

Critical Appraisal on DNEL Derivation on PFOA

Ulrike Bernauer

BfR, Department Safety of Chemicals
Unit: Toxicology of Chemicals

What is a DNEL ?



Derived **N**o-**E**ffect **L**evel

REACH Tool for human Risk Assessment

Exposure level, above which humans should not be exposed (REACH Annex I, 1.0.1)

DNEL used for: Risk characterisation

DNEL: is there a risk ? The risk to humans can be considered to be adequately controlled if the exposure levels do not exceed the appropriate DNEL

Risk Characterisation

$$\textbf{Risk Characterisation Ratio (RCR)} = \frac{\textbf{Exposure}\ \textbf{(combined)}}{\textbf{DNEL}}$$

1) If exposure < DNEL: risk is adequately controlled

2) If exposure > DNEL: risk is not adequately controlled

Consequence of 2: Further action necessary

Regulatory actions: Restriction ??

Risk Management Measures (RMM)

Risk assessment of Perfluorooctanoic Acid (PFOA) as part of a strategic partnership between German authorities and industry

Chemical Safety Report (CSR) according to the provisions of the European REACH Regulation No. 1907/2006

Project participants

From industry:

- Du Pont de Nemours
- Miteni Spa
- European Photographic Industry Association
- 3M Medical Department

From authorities:

- Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety
- BAuA (Federal Institute for Occupational safety and Health) Division 5 (lead project co-ordination)
- BfR (Federal Institute for Risk Assessment)
- UBA (Federal Environmental Agency)

Risk assessment of Perfluorooctanoic Acid (PFOA) as part of a strategic partnership between German authorities and industry

Basis:	OECD Draft SIDS Report version 18 March 2007 Supplemented by studies published until June 2008
Industry:	Draft report Steps of DNEL derivation Suggestions for DNEL: Industry
Authorities:	Written Comments and Suggestions
Industry + Authorities:	Meetings for clarifications and discussions

Addressed here: DNEL for Man exposed via Environment (MvE)/Consumers

Final report: some disagreements concerning Human Health

DNEL- Derivation – the ideas behind

ADI/TDI	**DNEL**
(NOAEL/AF x AF) Usually AF = 10 i.e. 10 x 10	considers that different NOAELs might be associated with different uncertainties
	Differentiates between • Populations (workers, consumers, susceptible subpopulations) • Exposure routes (dermal, oral, inhalation) • Duration of exposure • Systemic and local effects
	Enables flexibility concerning assessment factors
MOS (NOAEL/Exposure) Discussion of the “margin”	Gives more detailed guidance

→ Separate DNELs possible for one substance

Tran

How to derive a DNEL ?

Step 1:

Gather typical dose-descriptors
(e.g. NOAELs, LOAELs) for each endpoint

Step 2:

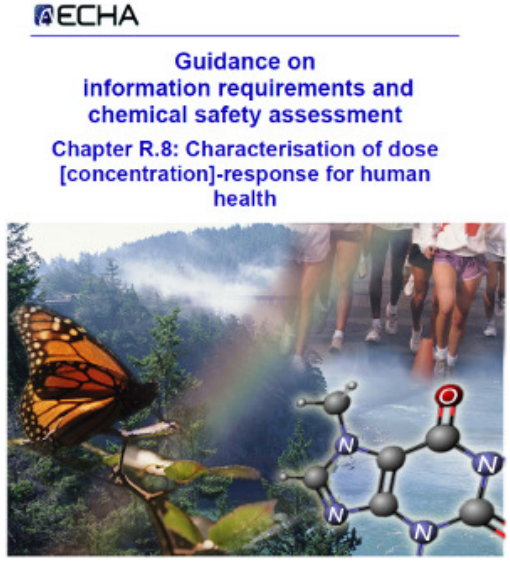
Modify the dose descriptor
to the correct starting point
(comparability with target population)

Step 3:

Apply Assessment factors
to the correct starting point to obtain the DNELS
(address different uncertainties)

Step 4:

Select the leading health effects



DNEL-Derivation on PFOA

DNEL derivation for **MvE/Consumers**

Endpoint	Species	Reference	Dose Descriptor	Modified dose-descriptor [serum PFOA concentration (µg/ml)]	Assessment Factors							DNEL [serum PFOA concentration (µg/ml)]
					Interspecies							
					Allometric Scaling	Remaining Differences	Intra-species	Exposure duration	Dose-response	Quality of whole database	Overall	
Epidemiologically based health parameters	Human	Olsen et Zobel, 2007	NOAEL	5	1	1	3.2	1	1	2	6.4	0.8
Reproductive toxicity – Fertility Impairment	Rat	Butenhoff et al., 2004	NOAEL	39	1	2.5	3.2	1	1	1	8	4.9
Reproductive Toxicity - Development	Mouse pup	Lau et al., 2006	$BMCL_5$	16	1	2.5	3.2	1	1	1	8	2
Repeated Dose Toxicity	Monkey 6 months	Butenhoff et al., 2002	$BMCL_{10}$	60	1	2.5	3.2	1	1	1	8	7.5
Carcinogenicity	Rat – 2 year study	Sibinski, 1987	$BMCL_{10}$	125	1	2.5	3.2	1	3	1	24	5.2

DNEL derivation PFOA – specifics (I)

PFOA: Species differences in half-life	
Species /sex	Half-life [days]
Rat, female Rat, male	0.08 – 0.07 4 - 6
Dog, female Dog, male	8 – 13 20 - 30
Cynomolgus monkey, female Cynomolgus monkey, male	33 31
Macaccus monkey, female Macaccus monkey, male	2.7 5.6
Human, female Human, male	Not available 1400 (3.8 years !)
References: Lau et al., 2006; Noker and Gorman, 2003	

Use of internal values as modified dose-descriptor (Plasma PFOA levels)

Requires back calculation to external values

- Justified
- Unusual (with respect to guideline)

DNEL derivation PFOA – specific issues (III)

Guideline (REACH Guidance R.8) states:*

„However, the DNEL may be expressed as internal biomarker values, but this only applies to the limited number of substances, where internal values, i.e. biomonitoring data (e.g. biomarkers) are available and have been reliably associated with effects…“

*http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r8_en.pdf?vers=20_08_08

DNEL-Derivation on PFOA

DNEL derivation for **MvE/Consumers**

Endpoint	Species	Reference	Dose Descriptor	Modified dose-descriptor [serum PFOA concentration (µg/ml)]	Assessment Factors							DNEL [serum PFOA concentration (µg/ml)]
					Interspecies							
					Allometric Scaling	Remaining Differences	Intra-species	Exposure duration	Dose-response	Quality of whole database	Overall	
Epidemiologically based health parameters	Human	Olsen et Zobel, 2007	NOAEL	5	1	1	3.2	1	1	2	6.4	0.8
Reproductive toxicity – Fertility Impairment	Rat	Butenhoff et al., 2004	NOAEL	39	1	2.5	3.2	1	1	1	8	4.9
Reproductive Toxicity - Development	Mouse pup	Lau et al., 2006	$BMCL_5$	16	1	2.5	3.2	1	1	1	8	2
Repeated Dose Toxicity	Monkey 6 months	Butenhoff et al., 2002	$BMCL_{10}$	60	1	2.5	3.2	1	1	1	8	7.5
Carcinogenicity	Rat – 2 year study	Sibinski, 1987	$BMCL_{10}$	125	1	2.5	3.2	1	3	1	24	5.2

DNEL derivation PFOA – specific issues (II)

The critical study – the critical DNEL (Olsen and Zobel, 2007)

Background: PFOA-induced peroxisome-proliferator (PPAR) mediated effects on lipid metabolism

Investigation of possible association between PFOA serum levels and serum lipid, hepatic, and thyroid parameters in a total of 506 male employees, investigaion of „standard“ clinical parameters

⟶ No association

DNEL derivation PFOA – specific issues (III)

CAVE

Were the parameters investigated adequate to assess possibly adverse health effects ?

Emmet et al.(2006): Exposure to Perfluorooctanoate: Relationships between Serum Levels and Certain Health Parameters : „Other endpoints need to be addressed….“

Adequacy with respect to effects not mediated by PPAR ?

Adequacy with respect to target population (developmental effects) ?

(source population: male workers target population: women of child-bearing age?)

DNEL derivation PFOA – specific issues (iii)

CSR regards literature until June 2008

Since that time: new studies, new publications:

C8 Health project USA (http://www.c8sciencepanel.org/study_results.html)

Study population: 69 030 community residents from 6 water districts in Ohio

Still ongoing, some reports available:

- PFOA and pregnancy outcome
- PFOA and immune biomarkers (clear associations with PFOA levels)
- PFOA and uric acid (clear associations with PFOA levels)
- PFOA and lipids (associations with PFOA levels)
- PFOA and diabetes (currently no association, but follow-up)

DNEL-Derivation on PFOA

DNEL derivation for **MvE/Consumers**

Endpoint	Species	Reference	Dose Descriptor	Modified dose-descriptor [serum PFOA concentration (µg/ml)]	Assessment Factors							DNEL [serum PFOA concentration (µg/ml)]
					Interspecies							
					Allometric Scaling	Remaining Differences	Intra-species	Exposure duration	Dose-response	Quality of whole database	Overall	
Epidemiologically based health parameters	Human	Olsen et Zobel, 2007	NOAEL	5	1	1	3.2	1	1	2	6.4	0.8
Reproductive toxicity – Fertility Impairment	Rat	Butenhoff et al., 2004	NOAEL	39	1	2.5	3.2	1	1	1	8	4.9
Reproductive Toxicity - Development	Mouse pup	Lau et al., 2006	$BMCL_5$	16	1	2.5	3.2	1	1	1	8	2
Repeated Dose Toxicity	Monkey 6 months	Butenhoff et al., 2002	$BMCL_{10}$	60	1	2.5	3.2	1	1	1	8	7.5
Carcinogenicity	Rat – 2 year study	Sibinski, 1987	$BMCL_{10}$	125	1	2.5	3.2	1	3	1	24	5.2

Risk Characterisation for PFOA (I)

$$RCR = \frac{\text{Exposure}}{\text{DNEL}}$$

- nonstick cookware
- stain resistant furniture, textiles, carpets
- oil repellant food packing materials
- water repellant, breathable functional clothing
- waterproofing spray for furnitures, textiles, footware
- fire fighting foams

Risk Characterisation for PFOA (II)

1. External exposure data for consumers (associated with uncertainties)

PFOA intake (worst case assumptions) [ng/kg bw/d]			
Reference	Infants (babies)	Infants (Toddlers)	Adults
EFSA 2008			10.0
Fromme et al., 2009			12.6
Trudel et al., 2008	114	93.6	44.1 (females) 39.3 (males)
Vestergreen et al., 2008	140	**150**	37.0 (females) 32.0 (males)
CSR 2009			40.0

2. Internal exposure data for consumers (from biomonitoring data)

Median values (general population): < 7 µg/l

(accidental high exposure not regarded)

Risk Characterisation for PFOA (II)

Back calculation from internal to external DNELs

external dose D = internal concentration $C_{internal}$ x (Clearance/absorbed fraction)

Clearance: 0.051 - 0.108 ml/day/kg absorbed fraction: 0.5 (from literature)

Reference	Internal DNEL	External DNEL
Epidemiological data **Olsen and Zobel, 2007** ???	**0,8 µg PFOA/ml Serum** ???	**0,08- 0,17 µg PFOA/kg/day** ???

Not considered: DNEL from probable PFOA precursors ???

PFOA: Risk characterisation for Consumers (I)

Risk characterisation under worst case assumptions

RCR = Exposure/DNEL

External DNEL calculated from internal DNEL

External dose

RCR =150 ng/kg/day (infant/toddler)/ 0.17 µg/kg/day = 0,9

Internal dose

RCR = 7 µg/l /0.8 µg/ml blood = 0,007µg/ml/0,8 µg/ml= 0,0087

Risks (apparently) adequately controlled

???

PFOA: Risk characterisation for Consumers -Conclusions (II)

Risk characterisation on PFOA based on uncertainties

with respect to DNEL-derivation

with respect to exposure assessment

New data have become available since finalization of the CSR report

PFOA: Risk characterisation for Consumers -Conclusions (III)

Are the Risks from Consumer Exposure to PFOA adequately controlled ?

Reliable answer requires

Half-life 3.8 years
Transfer in placenta and breast milk

- Consideration of new data
- Refinement of DNEL derivation
- Refinement of exposure assessment for MvE/Consumers (including PFOA precursors)

Special thanks to my colleagues

Prof. Dr. Ursula Gundert-Remy

Dr. Barbara Heinrich-Hirsch

Dr. Friederike Neisel

Dr. Ulrike Pabel

Dr. Agnes Schulte

FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

Thank you for your attention

Dr. Ulrike Bernauer

Federal Institute for Risk Assessment

Thielallee 88-92 • D-14195 Berlin

Tel. +49 30 - 84 12 - 3705 • Fax +49 30 - 84 12 - 3851

Ulrike.Bernauer@bfr.bund.de • www.bfr.bund.de