

Het afleiden van grenswaarden in de praktijk

CGC - NVT bijeenkomst 'Quick & Dirty?'

Fenneke Linker

March 12, 2015

HEALTH · NUTRITION · MATERIALS



Inhoud

1. Afleiden van veilige grenswaarden op de werkplek
2. Beperkte dataset
3. Read across
4. Health Hazard Bands
5. OECD toolbox



Praktijk: vaak combinatie van benaderingen,
case by case assessments!




Afleiden van veilige grenswaarden op de werkplek

1. Opzoek naar data:
 - REACH dossier?
 - ChemIDplus databases?
 - Clinical data?

Page 2




 [Start New Query](#) [Modify Query](#) [Search History](#) [Show Query](#)
[Switch to Summary View](#)

Substance Name: Benzene
RN: 71-43-2
InChIKey: UHOVQNZJYSORNB-UHFFFAOYSA-N

Note
Toxic, volatile, flammable liquid hydrocarbon byproduct of coal distillation. It is used as an industrial solvent in paints, varnishes, lacquer thinners, gasoline, etc. Benzene causes central nervous system damage acutely and bone marrow damage chronically and is carcinogenic. It was formerly used as parasiticide.

Molecular Formula
C₆H₆

Molecular Weight
78.1134



[←](#)
[↻](#)
[Na +](#)
[🔍](#)
[3D](#)

All [Classifications](#) [Links to Resources](#) [Names & Synonyms](#) [Registry Numbers](#) [Structure Descriptors](#) [Toxicity](#) [Physical Properties](#)

Classification Codes [↔](#)

Classification Codes

Agricultural Chemical	Human Data	Out-dated pesticide	Skin / Eye Irritant
Drug / Therapeutic Agent	Mutation data	Reproductive Effect	Tumor data

Superlist Classification Codes


2007 CERCLA Priority List, Rank: 6	Known to be a carcinogen	Reportable Quantity (RQ) = 10 lb	TWA see 1910.1028; Also see Table Z-2 for the limits applicable in the operations or sectors excluded in 1910.1028
2011 CERCLA Priority List, Rank: 6	Overall Carcinogenic Evaluation: Group 1	TWA 0.5 ppm; STEL 2.5 ppm; skin; Confirmed human carcinogen; BEI	

Links to Resources [↔](#)

NLM Resources (File Locators)

CCRIS	MeSH	TRI2000	TRI2011
ClinicalTrials.gov	MeSH Heading	TRI2001	TRI2012
DART	PubChem	TRI2002	TRI95
DrugPortal	PubMed	TRI2003	TRI96
EMIC	PubMed AIDS	TRI2004	TRI97
GENETOX	PubMed Cancer	TRI2005	TRI98
Haz-Map	PubMed Toxicology	TRI2006	TRI99
Household Products	RTECS	TRI2007	WebWISER
HSDB	Tox Town	TRI2008	MedlinePlusAll
IRIS	TOXLINE	TRI2009	
ITER	TOXMAP	TRI2010	

Page 3



Afleiden van veilige grenswaarden op de werkplek

1. Opzoek naar data:
 - REACH dossier?
 - ChemIDplus databases?
 - Clinical data?
2. Vaststelling **kritisch effect** (LOAEL of NOAEL)
3. Veiligheidsfactoren kiezen
 - Interspecies
 - Intraspecies
 - Studieperiode
 - Blootstellingsroute
 - LOAEL/NOAEL
 - Betrouwbaarheid dataset
4. Huid als blootstellingsroute?

 OEL (mg/m³ of µg/m³)

Page 4



Beperkte dataset

1. Wel een LD50 (rat, oral)?
2. Geen indicatie voor CMR eigenschappen?

 MTD methode

- Berekening mbv LD50 (rat, oral) en LogKow geeft een **Maximum Tolerated Dose** (expected to produce limited toxicity)

Advised assessment factors:

- 10 (LOAEL -> NOAEL)
- 4 (rat -> man)
- 3 (intraspecies, workers)

Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances, ECETOC TR 101 (2006)
APPENDIX D: PREDICTION OF AN ORAL MTD FROM AN LD50 AND A LOG KOW

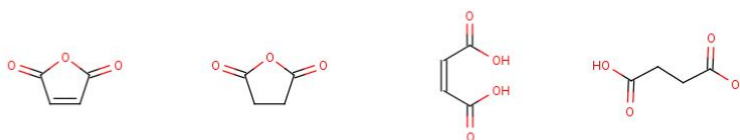
Page 5



Read across

Vergelijkbare stoffen waar wél data van beschikbaar is?

- Zoeken op molecuulstructuur
- Kijken naar te verwachten metaboliëten



Page 6



Health Hazard Bands (1)

Kwantitatieve parameters

	Band 1	Band 2	Band 3	Band 4	Band 5
				HIGH POTENCY COMPOUNDS	
OEL ($\mu\text{g}/\text{m}^3$)*	>1000-2000	100-1000	10-100	1-<10	<1
Sensitizing Potency** (EC3% value)	Non-sensitizing	Weak (10-100)	Moderate (1-10)	Strong (0.1 - 1)	Extreme (<0.1)
Therapeutic Dose (mg/day)	>100	10-100	1-<10	0.1-<1	<0.1

Page 7



Health Hazard Bands (2)

Kwalitatieve parameters

	Band 1	Band 2	Band 3	Band 4	Band 5
				HIGH POTENCY COMPOUNDS	
Hazard Potential	Slight	Moderate	High	High	Very High
Systemic Effects / Treatable?	Minor Fully Treatable	Acutely toxic	Significant Acute / Chronic Toxicity	Toxicity Serious Acute / Chronic	Very serious effects / Possibility of chronic disability or death.
Reversibility	Reversible	Reversible	Chronically reversible	Possibly Irreversible	Irreversible
FDA Pregnancy Category¹	A,B	C	D	X	X
Reproductive / Developmental Toxicity	Negative	Suspect (evidence from animals studies)	Moderately reprotoxic, low potency teratogen. R62; R63; R64	Confirmed reprotoxic defects in animals and/or suspected or proved in humans R60; R61	Confirmed reprotoxic defects in animals and/or suspected or proved in humans R60; R61
Medical Intervention	Not required	Not Required / First Aid	First Aid / Medical Examination	Medical Examination	Emergency medical treatment
LD50 Rat Oral (mg/kg)	>2000	200-2000	25-200	0.5-25	<0.5
Genotoxicity / Mutagenicity	Negative	Suspect	Evidence of mutagenicity	Confirmed mutagen	Confirmed mutagen

OECD toolbox

1. Profileren op basis van molecuulstructuur - alerts
2. Ophalen dataset verschillende databases ☺
3. Vergelijken data andere stoffen
4. *Voorspellen van eindpunten mbv data andere stoffen*
 - *Ja/nee (bijv. Sensitizer)*
 - *Schatting NOAEL of LOAEL*

Praktijk: vaak combinatie van benaderingen, case by case assessments!

Conclusie

1. Dataprofiel
2. Interpretatie
3. Transparant documenteren!



Praktijk: vaak combinatie van benaderingen,
case by case assessments!

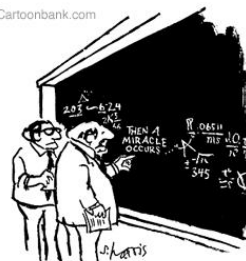
Page 10



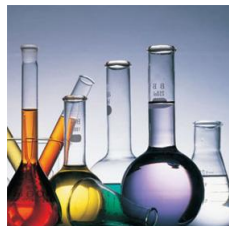
Vragen???



© Cartoonbank.com



"I think you should be more explicit here in step two."



Page 11



