Yrkeseksponeringsgrenser og arbeidsmiljø

BIO4530 Regulatorisk toksikologi

Steinar Øvrebø

Koksproduksjon

Yrkesmessig PAH eksponering i Norge

Norsk aluminiumsverk

Beskyttelse av arbeidstakere

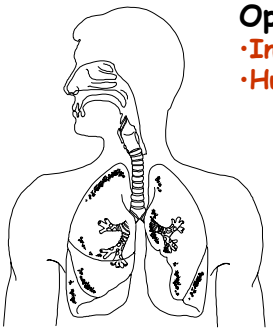
- Yrkeseksponering hovedsakelig innånding av luftbåren forurensning
- Hudopptak kan bidra til eksponeringen
- Hvorledes sikre at arbeidstakerene ikke blir utsatt for farlige stoffer?
- Metoden har vært å sett en øvre grense for mengde forurensing i luften

Hvilke påvirkninger i arbeidsmiljø - hvem gjør hva?

- Sikkerhet (safety) ikke med i STAMI sin 'portefølje'
- Arbeidspsykologi metoder
- Arbeidsfysiologi
- Arbeidsmedisin
- Radioaktiv stråling, elektromagnetisk stråling og støy

Opptak

- Innånding
- Hud

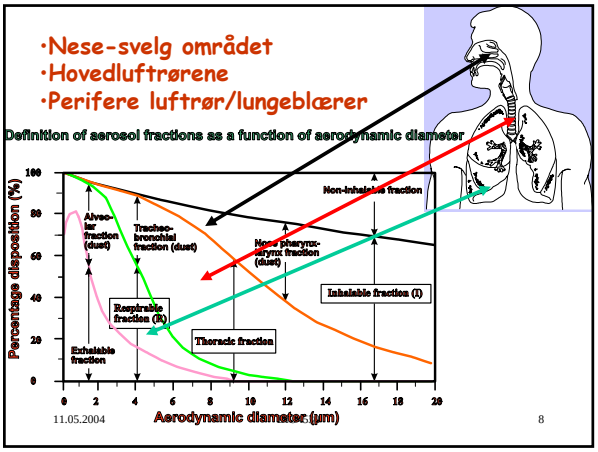


Forurensning i arbeidsatmosfære

Hovedtema blir eksponering for industrielle kjemikalier

Begreper i forurensing av arbeidsatmosfære
- Gass
- Aerosoler
  - Støv
  - Fiberformig støv
  - Røyk (fast stoff i luft)
  - Tåke (væske i luft)

- Nese-svelg området
- Hovedluftrørene
- Perifere luftrør/lungeblærer



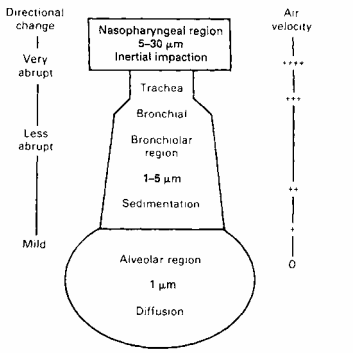


Figure 15–4. Parameters influencing particle deposition. [Fro Casarett, LJ: The vital sacs: Alveolar clearance mechanisms in inha lation toxicology, in Blood FR (ed): Essays in Toxicology. New York Academic Press, 1972, vol 3.]

Partikkel deponering

Deposition mechanisms - occurs primarily by interception, impaction, sedimentation, and diffusion (brownian movement).

interception - sperre, kommer fore nær veggene
impact - kollidere fortsetter i samme bane
diffusion - diffusjon

Aerodynamisk diameter
- Fallhastigheten beregnes for den aktuelle partikkelen eller fiberen.
- Den aerodynamiske diameteren er lik diameteren til en partikkel med egenvekt =1 som faller med samme hastighet

Yrkehygienisk viktige partikler

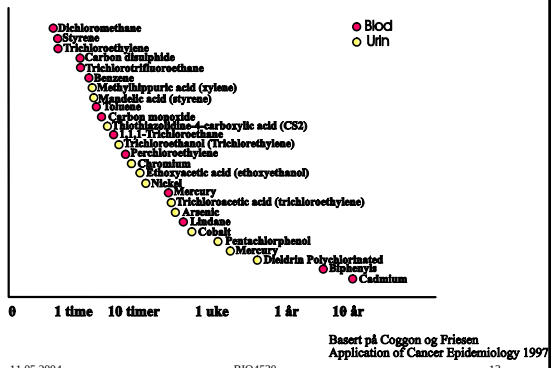
Krystallinske partikler - kvarts, silikose
Amorfe partikler - silika
Fibrer - asbest
Ultrafine partikler - diameter < 100nm

Permissible levels - tillatte nivåer

Allowable atmosfæriske verider

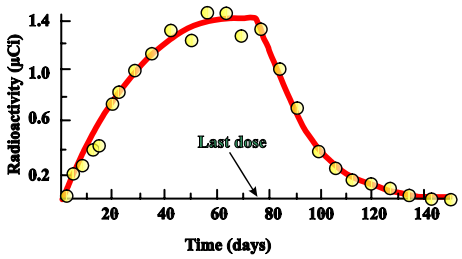
- MACs - Maksimum tillatte konsentrasjoner (D)
- TLVs - Terskel grenseverdier ® (ACGIH) (USA)
- TWA - Tidsvektet gjennomsnitt
- OEL - Yrkeseksponeringsgrenser
- STEL - Korttids eksponeringsverdier
- OESs - Terkselverdi (UK)
- MELs - Ikke sikre verdier (UK)
- Biologisk monitorering
  - BEI (USA)
  - BAT Werte
  - Bly i blod

Utskillelse og halveringstider for flere biomarkører - blod og urin



Basert på Coggon og Friesen
Application of Cancer Epidemiology 1997

Accumulation of hemoglobin adducts resulting from chronic administration of 4 aminobiphenyl in rats



Exposure Standards and Guidelines

Environmental Exposure Standards and Guidelines

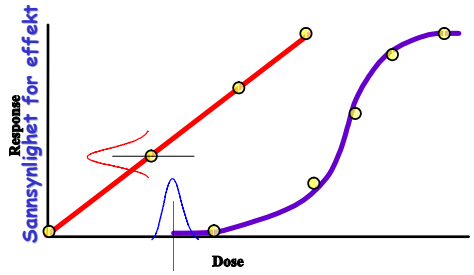
HA - Health advisories (EPA)
Limits for:
1 - Day exposure
10 - Day exposure
Longer term exposure
Liftime exposure

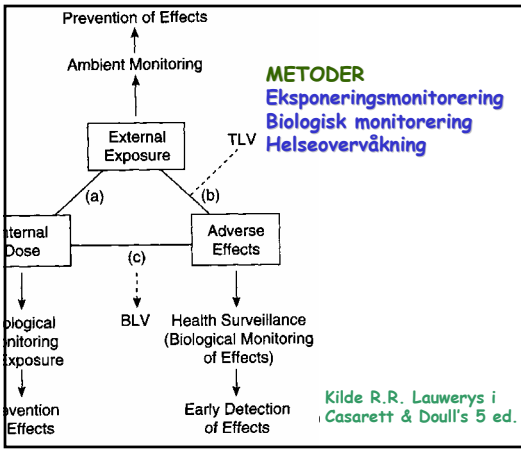
Occupational Exposure Standards and Guidelines

PEL - Permissive exposure limits (OSHA)
TWA - Time Weight Average PEL
STELs - Short Time Exposure Limits
Ceiling Limit PELs

TLVs Threshold Limit Values (ACGIH)
RELs Recommended Exposure Levels (NIOSH)
OEL Occupational Exposure Limits (International)
AN Administrativ Norm (Norway)

Dose respons





METODER
Eksponeringsmonitorering
Biologisk monitorering
Helseovervåkning

Kilde R.R. Lauwerys i Casarett & Doull's 5 ed.

Helseovervåkning og biologisk overvåkning

Metoder for å sette grenser

OEL Occupational exposure limits
MAK Maksimale arbeids konsentrasjonen
TLV Treshold limit values
PEL Permissible exposure levels
REL Recommenden exposure levels
OES Occuaptional exposure levels
MEL Maximum exposure levels
AD Administrative normer
YG Yrkeshygieniske grenseverdier

Hvilke metoder benyttes?
Metodene varier fra land til land og organisasjon til organisasjon

Harmonisering - Vil vi det?

ACGIH examples of low variability in Europe

Substances for which indicative limit values exist due to Commission Directive 91/322/EEC10												
		mg/m3										
Substance	CAS*	EU	Norge	Spania	Storbritannia	Tyskland	Sverige	Danmark	Australia	Ungarn	USSR	Japan
Nicotine	54-11-5	0,5	0,5	0,5	0,5	0,47	-	0,5	0,5	-		
Formic acid	64-18-6	9	9	9	9,6	9,5	5	9	9,4	5	STEL 1	9,4
Acetic acid	64-19-7	25	25	25	25	25	13	25	25	10	STEL 5	25
Methanol	67-56-1	260	130	266	266	270	250	260	262	50	STEL 5	260
Acetonitrile	75-05-8	70	50	68	68	68	50	70	70	50	STEL 10	
Picric acid	88-89-1	0,1	0,1	0,1	0,1	0,1	-	0,1	-	0,1	-	
Naphthalene	91-20-3	50	50	53	-	-	-	50	52	40	STEL 20	
Nitrobenzene	98-95-3	5	5	5	5,1	-	5	5	5	3		
Resorcinol	108-46-3	45	45	46	46	-	45	45	45	45		
Diethylamine	109-89-7	30	30	30	30	15	30	15	30	30		
Pyridine	110-86-1	15	15	16	16	16	7	15	16	5	STEL 5	
Carbon dioxide	124-38-9	9000	9000	9150	9150	9100	9000	9000	9000	ja9000		
Oxalic acid	144-62-7	1	1	1	1	-	1	1				
Cyanamide	420-04-2	2	2	2	2	-	2	2				
Calcium dihydroxide	1305-62-0	5	5	5	5	-	-	5				
Disphosphorus pentoxide	1314-56-3	1	1	1	2	1	1	1				
Disphosphorus pentasulphi	1314-80-3	1	1	1	1	1	-	1				
Cresols (all isomers)	1319-77-3	22	22	22	22	22	4,5	22				
Platinum (metallic)	7440-06-4	1	0,002	1	5	0,002	0,002	0,002				
Lithium hydride	7580-67-8	0,025	0,025	0,025	0,025	lib	-	0,025				
Bromine	7726-95-6	0,7	0,7	0,7	0,66	0,66	0,7	0,7				
Phosphorus pentachloride	10026-156	1	1	0,9	0,87	1	-	1				
Nitrogen monoxide	10102-43-9	30	30	31	31	-	30	30				
Pyrethrum	8003-34-7	5	5	5	5	5	-	5				
Barium (soluble compounds as Ba)		0,5	0,5	0,5	0,5	0,5	0,5	0,5				
Silver (soluble compound as Ag)		0,01	0,01	0,01	0,01	0,01	0,01	0,01				
Tin (inorganic compounds as Sn)		2	2	2	2	lib	-	2				

Worldwide occupational exposure limits (OEL) for formaldehyde in 1994

Country/agency	OEL (ppm)	Type of guideline
NIOSH	0.1	C (15 min)
World Health Organization (WHO)	0.24	TWA
ACGIH (1991)	0.3	C
Denmark	0.3	C
Germany	0.4	STEL
USSR (former)	0.4	TWA
Germany	0.5	TWA
U.S. Occupational Safety and Health Administration (OSHA, 1992)Hungary, Yugoslavia	0.75 0.8	TWA TWA
Finland, Norway, Sweden	1.0	C
ACGIH (1990), AIHA, Australia, Austria, Germany, Italy, the Netherlands, Switzerland/OSHA	1.0	TWA
Brazil, Chile	1.6	TWA
Bulgaria	0.8	STEL
Australia, Belgium, India, Japan, the Netherlands, Venezuela	2.0	C
ACGIH (1990), AIHA, Argentina, France, the Netherlands, OSHA, United Kingdom	2.0	STEL
Hungary	1.6	STEL
Czech Republic, Poland	1.6	TWA
Argentina, Mexico, United Kingdom	2.0	TWA
People's Republic of China	2.5	TWA
Australia	3.0	STEL
Rumania	3.2	C
Czech Republic	4.1	C
Indonesia	5.0	C
Egypt, Republic of China	5.0	TWA

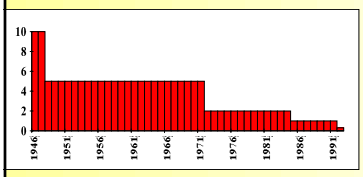
Note. All limits were obtained from one of the following publications: WHO (1977), Cook (1986), AIHA (1990), ACGIH (1989, 1992). C, ceiling value (maximum instantaneous concentration). STEL, short-term exposure limit (15 min; up to 4 times per day). TWA, time-weighted average (8 h/d).

from: D. Paustenbach J Toxicol Env Health 50 (1997) 217-263

Changes in the ACGIH TLV for formaldehyde and the rationale (1946-1992)

Year	Concentration (ppm)	Guideline	Rationale
1946-1947	10	MAC-TWA	Prevent skin and mucous membrane irritation
1948-1962	5	TLV[a]-TWA	Protective of respiratory injury
1963-1971	5	TLV-Ceiling	Protective of respiratory injury
1972-1984	2	TLV-Ceiling	Protective of eye irritation, mucous membrane irritation, disturbed sleep
1985	1	TLV-TWA	Prevent eye and nose irritation
1985	2	TLV-STEL	Minimize cancer hazard
1992	0.3	Ceiling	Eliminate eye and upper respiratory tract irritation; de minimis cancer risk

Note. MAC, maximum allowable concentration; TWA, time-weighted average; STEL, short-term exposure limit; Ceiling, maximum instantaneous concentration. [a]*MACS become TLVs during this time period.*



from: D. Paustenbach J Toxicol Env Health 50 (1997) 217-263

Distribution of Criteria Used to Develop ACGIH TLVs for 414 Substances Through 1968a

Criteria[b]	Number	Percent	Criteria	Number	Percent[a]
Organ or organ system affected	201	49	Biochemical changes	8	2
Irritation	165	40	Fever	2	0.5
Narcosis	21	5	Visual changes (halo)	2	0.5
Odor	9	2	Visibility	2	0.5
Organ function changes	8	2	Taste	1	0.25
Allergic sensitivity	6	1.5	Roentgenographic changes	1	0.25
Cancer	6	1.5	Cosmetic effect	1	0.25

[a]Exclusive of inert particulates and vapors.
[b]Number of times a criterion was used of total number of substances examined x 100, rounded to nearest 0.25 percent. Total percentages exceed 100 because more than one criterion formed the basis of the TLV of some substances.

Source: Stokinger (1970)

Framgangsmåter for å sette OELs og administrative normer

- Basert på data fra epidemiologiske undersøkelser, forsøk med mennesker eller dyreforsøk

- Setter så en grense basert på disse dataene der ingen skader på kort eller lang sikt oppstår - er det mulig?

SCOEL

Scientific Committee Group on Occupational Exposure Limits

Gruppen har utarbeidetdokumentet: Methodology for the derivation of occupational exposure limits: Key documentation

Se også: TNO report V98.1304 Methods for the establishment of Health-Based Occupational Reference Values for New and Existing Substances -Version 2-

Effektstudier og dose respons

Eksempelet Bly
- Toksikokinetikk; opptak, fordeling og utskillelse og eventuelle lager i kroppen
- Perifere nerveskader
- Hematologiske effekter
- Nyre toksisitet
- Hjerte kar effekter
- Reproduktive effekter
- Kreftfremkallende effekt

Pb Effect	Blood Lead Levels (µg/dL) Adult	Children
Nevrologisk		
Encephalopathy (overt)	80 -100	100 - 120
Hearing deficits	20	-
IQ deficits	10 -15	-
In utero effects	10 - 15	-
Nerve conduction velocity ↓	40	40
Hematologic		
Anemia	80 - 100	80 - 100
U-ALA ↑	40	40
B-EP ↑	15	15
ALA-D inhibition	10	10
Renal		
Nephropathy	40	40 - 60
Vitamin D metabolism	<30?	-
Blood pressure		30?
Reproductuction		
Males		40
Females		?

Summary of LOEL for Lead related Health effects, Casarett & Doull's

Kritisk effekt for bly

Encephalopathy (overt)	80 -100	
Hearing deficits	20	(3)
IQ deficits	10 -15	(1)
In utero effects	10 - 15	(1)
Nerve conduction velocity ↓	40	
Hematologic		
Anemia	80 - 100	
U-ALA ↑	40	
B-EP ↑	15	(2)
ALA-D inhibition	10	(1)
Renal		
Nephropathy	40	
Vitamin D metabolism	<30?	

Betyr det noe for vurderingen av usikkerhetsfaktorer om vi velger effekter på hjernen eller endringer i blod parametere?

Risikovurdering 1

- Rotte dårlig modell for mennesker
- Ikke humane primater god modell
- Ikke tilstrekkelig dose respons data
- Tradisjonell risikovurdering ikke mulig

Risikovurdering 2

- Mange undersøkelser av oralt inntak (ulykker) av metanol - død og synsskade
- Yrkeseksponering med sprit duplikator
  - (1) opp til 365 - 3080 ppm Svimmelhet, kvalme, synsforstyrrelser
  - (2) opp til 375 ppm Hodepine
  - (3) opp til 1075 ppm Svimmelhet, kvalme, synsforstyrrelser
  - (4) 20-25 ppm Ingen syns- eller CNS-skader

Risikovurdering 3

260 mg/m^3 = 198 ppm

(mg/m^3)
100.000_____
---LC_{50} (rotter) 83.894
10.000_____

1.000_____
---ACGIH TLV 260 mg/m^3
100_____

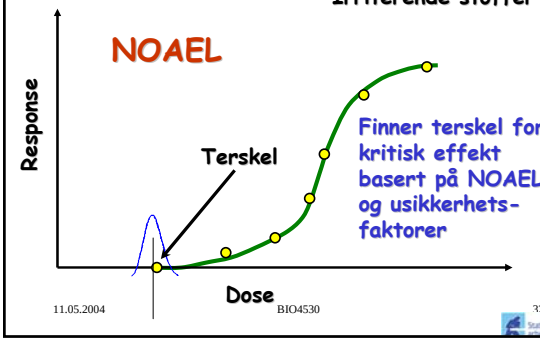
Risikovurdering 4

Sammenheng mellom eksponering og effekt for metanoleksponering

Eksponering	Varighet	Effekt
Lakkering i dårlig ventilerte rom med metanolholdig lakk	2-3 dager	Blindhet og død
86.000 mg/m^3	5 min	Utålelig nese- og øyeirritasjon
1.000 - 10.000 mg/m^3	flere år	Synsskade
1.245 - 1.441 mg/m^3	flere timer pr. dag	Øyeirritasjon, tåkesyn, hodepine, kvalme og svimmelhet
20 - 490 mg/m^3	flere timer pr. dag	Hodepine

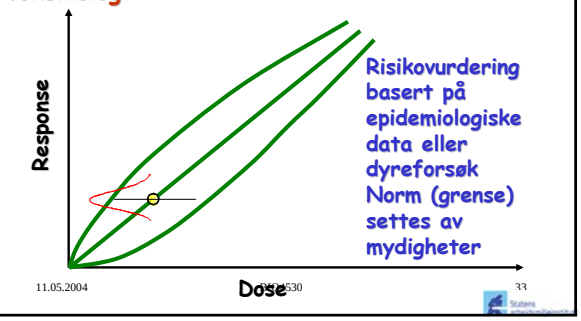
Stoffer som en antar effekten har/viser en terskel

- Ikke genotoksiske karsinogener
- Organ skadende stoffer
- Irriterende stoffer

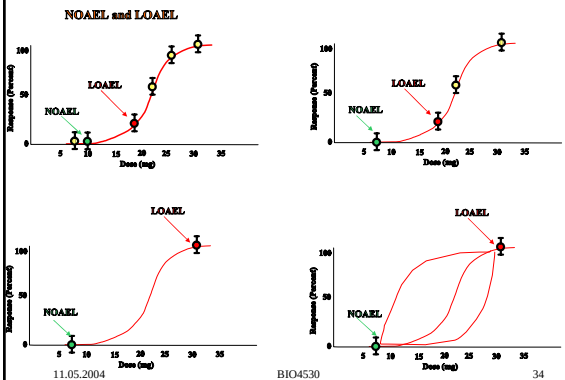


Stoffer som en antar ikke har/viser 'terskel toksikologi'

Gentoksiske karsinogener
Mutagene stoffer
Sensibiliserende stoffer
Reproduksjonstoksiske stoffer



Betydningen av godt datagrunnlag



·'health based' OELs - an OEL of this type may be established in those cases where a review of the total available scientific data base leads to the conclusion that it is possible to identify a clear threshold dose below which exposure to the substance in question is not expected to lead to adverse effects. Such OELs should meet the objective outlined above.

·'pragmatic' OELs - for some adverse effects (in particular genotoxicity, carcinogenicity and respiratory sensitisation) it may not be possible on present knowledge to define a threshold of activity. In such cases it must be assumed that any level of exposure, however small, might carry some finite risk and OELs for substances possessing these properties must be established pragmatically. Such OELs will be established at levels considered to carry a sufficiently low level of risk.

4.3 Individual susceptibility, special risk groups and sensitisation

The SCOEL will take into account available information on groups of people at special risk and this will be reflected in the advice it gives to the Commission. However, the variability of response between individuals at the same level of exposure, and the existence of special risk groups, may mean that the recommended OEL may not provide adequate protection for every individual. SCOEL will normally not recommend a health-based OEL for a respiratory sensitiser (Chapter 2, page 1).

Begrensninger i beskyttelse

ACGIH

…a small percentage of workers may experience discomfort...

EU/SCOEL

…may not provide adequate protection for every individual...

General principles graduation of effects

- No effects observed
- Compensatory effects or early effects of dubious significance without adverse health consequences
- Early health impairment (clear adverse effects)
- Overt disease, possible death

SCOEL

Responses to irritants graduation

- No effects observed; no awareness of exposure
- Very slight effects; awareness of exposure
- Slight irritant effects or nuisance (e.g. smell); easily tolerable
- Significant irritation/nuicance, overt health effects; barely tolerable
- Serious health effects (e.g. Pulmonary oedema); intolerable

SCOEL

(1) General procedure for setting OELs

- Assemble all available data on hazard of the substance
- Determine whether the database adequate for the setting of an OEL
- Identify the adverse effects that may arise from exposure to the substance
- Establish which adverse effect(s) is (are) considered to be crucial in deriving the level of the OEL
- Identify the relevant studies (in humans or animals) which characterise these key effects. Carefully review the quality of these studies
- Establish whether the substance acts via a non-threshold mechanism or whether a conventional (threshold) toxicological model can be used

SCOEL

(2) General procedure for setting OELs

- Assess the dose/response data for each key effect. Establish "no observed adverse effect levels" (NO(A)Els) wherver possible, otherwise establish "lowest observed adverse effect levels" (LO(A)Els)
- Decide whether a short term exposure limit (STEL) is required in addition to an 8 hr time weigthed (TWA) limit
- Establish a numerical value for an 8 hour TWA OEL
- Establish a numerical value for STEL (if required)
- Document the entire process such the rationale for the OEL is clear

SCOEL

Information relevant to the establishment of OELs

- Information on non-threshold effects
- Information on long term effects and the effects of repeated exposure by an apropriate route
- Information on short term (acute) effects (effects of a single exposure)
- Information of target organ(s) and the nature of the effects
- Information on the methodology of measurement of airborne levels

SCOEL

Human and animal data and laboratory studies

- Individual case reports, studies in human volunteers, cross-sectional studies and cohort and case-control studies
- Repeated exposure data, single exposure data, routes of exposure and toxicokinetic data
- Other information

Ethylene glycol - recommendation (1)

The study of Wills et al. (1974), establishing a NOAEL of 67 mg/m3, for irritation of the mucosae in human volunteers, was considered to be the best available basis for proposing occupational exposure limits. Because this study involved exposure for 20-22 h/d, and large differences in response were seen with continuous exposure compared with exposure for 8 h/d in the studies of Coon et al. (1970), uncertainty factor of 2 was considered adequate to allow for inter-individual variation and for the absence of long-term human data. Taking into account the preferred value approach, the recommended 8-hour TWA is 20 ppm (52 mg/m3). This is supported by the repeated exposure study of Coon et al. (1970).

Ethylene glycol - recommendation (2)

A STEL (15 mins) of 40 ppm (104 mg/m3) was proposed to limit peaks of exposure which could result in irritation. A 'skin' notation was recommended as dermal absorption could contribute substantially to the total body burden.

At the levels recommended, no measurement difficulties are foreseen.

Ethylbenzene - recommendation (1)

The report by Ruth (1986), of irritation in humans at 200 ppm (884 mg/m3), was considered to be the best available basis for proposing occupational exposure limits. The recommended 8-hour TWA is 100 ppm (442 mg/m3). A STEL (15 mins) of 200 ppm (884 mg/m3) was proposed to limit peaks of exposure which could result in irritation. These limits are not contradicted by the study of De Ceaurriz et al., (1981), reporting an RD50 of 1 430 ppm (6 321 mg/m3) for inhibition of respiratory irritation in mice.

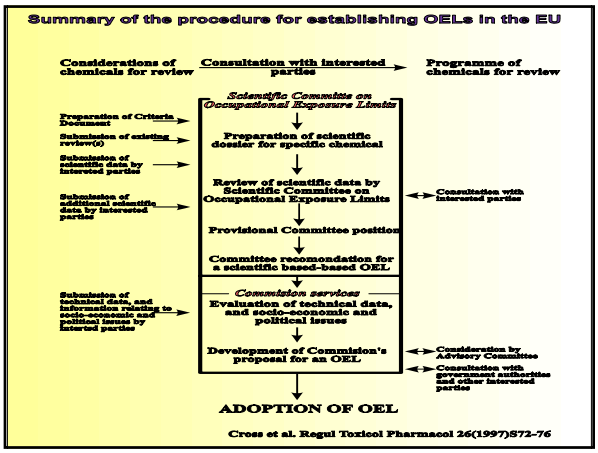
Ethylbenzene - recommendation (2)

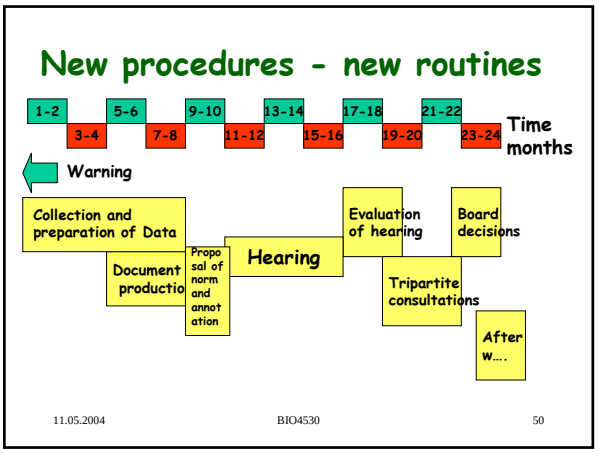
A 'skin' notation was recommended as dermal absorption could contribute substantially to the total body burden.

At the levels recommended, no measurement difficulties are foreseen.

Normer - Grenseverdier

Administrativ norm - Norge
Hygieniska gränsvärden - Sverige
Grænseværdier - Danmark
MAK Werte - Tyskland (Maximale Arbeitsplatzkonzentrationen)
MEL og OES - Storbritannia (Maximum Exposure Limits og Occupational Exposure Standards)
TLV® Threshold Limit Value (ACGIH) "USA"
PEL Permissible Exposure Limit (OSHA) - USA
REL Recommended Exposure Limit (NIOSH) - USA
BLV Binding Limit Value - EU
ILVs Indicative Limit Value - EU
OEL Occupational Exposure Limits
(Yrkes eksponerings grenser)





New procedures - new routines (4)

EXPERT GROUP

- Summary of important studies
- Dose response associations
- Critical effect(s)
- Recommendations
- Establish their own rules, key document

TEAN