National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-48
April 14-16, 2009

Hilton- Old Town Alexandria
1867 King Street
Alexandria, VA

AGENDA

Tuesday, April 14, 2009

10:00 a.m.	*Development team meetings: Phosgene oxime; Perfluoroisobutylene; Perchloryl fluoride
11:00	Introductory remarks and approval of NAC/AEGL-47 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:15	Chemical List Update (Paul Tobin)
11:30	Status Update/ Insufficient Data Chemicals: Diacetylmorphine; Fluoroacetate salts; Methyl fluoroacetate; Methoxyethylmercuric acetate; Monofluoroacetic acid; Paraquat; Phencyclidine; Sodium fluoroacetate; Tetraethylpyrophosphate; Tetramethylenedisulfotetramine; Tungsten hexafluoride (Cheryl Bast/ Bob Young) Methyl Iodide- Status Update (Alan Becker/Sylvia Talmage)
11:35	Arsenic pentoxide and Arsenic trichloride- Discussion of potential approach for AEGL Derivation (Bob Young)
12:00 p.m.	Lunch
1:00	Discussion on Oral to Inhalation Extrapolation (George Rusch)
1:30	Review of Calcium cyanide, potassium cyanide, and sodium cyanide (Ralph Gingell/Cheryl Bast)
2:15	Review of Phosgene oxime (Jim Holler/BobYoung)
3:15	Break
3:30	Review of Perfluoroisobutylene (George Rusch/Cheryl Bast)
4:30	Revisit of Ricin- New data (Jim Holler /Bob Young)
5:30	Adjourn for the day

Wednesday, April 15, 2009

8:30 a.m.	*Development team meetings: Carbamate Pesticides (Aldicarb, Carbofuran, Methomyl, oxamyl); Tellurium hexafluoride
9:30	Discussion of data for Gasoline AEGLs (Russ White, American Petroleum Institute)
10:30	Phosgene- Discussion of recent data (Juergen Pauluhn, Bayer HealthCare AG)
12:00 p.m.	Lunch
1:00	Review of Aldicarb (Paul Tobin/Sylvia Talmage)
2:00	Review of Carbofuran (Paul Tobin/Bob Young)
3:00	Break
3:15	Review of Oxamyl (Paul Tobin/Sylvia Talmage)
4:15	Review of Methomyl (Paul Tobin/Sylvia Talmage)
5:30	Adjourn for the day

Thursday, April 16, 2009

8:30 a.m.	Review of Tellurium hexafluoride (Roberta Grant/Jennifer Rayner/Cheryl Bast)
9:30	Review of Perchloryl fluoride (Glenn Leach/Dana Glass)
11:00	Administrative matters
11:30	Adjourn meeting

*See page 2.

ANY INFORMATION DISCUSSED AT THE NAC/AEGL MEETINGS IS CONSIDERED PUBLIC INFORMATION.

Pre-meeting Small Discussion Groups: NAC-48

	Chemical	Staff Scientist	CM	Reviewer	Reviewer	Other Attendees
Tues. 4/14/09						
	Phosgene oxime	Young	Holler	Becker	Willhite	Anderson, Benson, Cushmac, Niemeier, Sudakin
	Perfluoroisobutylene	Bast	Rusch	Ripple	Freshwater	Beasley, Bernas, Gingell, Heinz, Woolf
	Perchloryl Fluoride	Glass/Talmage	Leach	Hinz	Chapman	Baril, Camacho, Grant, van Raaij, Woodall
Wed. 4/15/09	Carbamates: Aldicarb Carbofuran Methomyl Oxamyl	 Talmage Young Talmage Talmage	Tobin	Anderson	Sudakin	Becker, Benson, Camacho, Freshwater, Gingell, Hinz, Holler, Neimeier,Ripple, Rusch, Willhite, Woolf
	Tellurium hexafluoride	Rayner/Bast	Grant	Woodall	Beasley	Baril, Bernas, Chapman, Cushmac, Heinz, Leach, vanRaaij

At this time, the following chemicals do not have a formal pre-meeting discussion scheduled: Cyanide salts; Ricin

NAC/AEGL Meeting 48: April 14-16, 2009

Chemical: ATTENDANCE **CAS Reg. No.:** PLEASE INITIAL + RETURN TO PAUL TOBIN!

Action: Proposed_____ **Interim**_____ **Other**____ ATTACHMENT 2

Sylvia Talmage
Cheryl Bast
Robert Young

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					John Hinz				
Marc Baril					Jim Holler				
Lynn Beasley					Glenn Leach				
Alan Becker					Richard Niemeier				
Robert Benson					Susan Ripple				
Edward Bernas					George Rusch, Chair				
Iris Camacho					Daniel Sudakin				
Gail Chapman					Marcel vanRaaij				
George Cushmac					Calvin Willhite				
David Freshwater					George Woodall				
Ralph Gingell					Alan Woolf				
Roberta Grant					Ernest V Falke				
Dieter Heinz									
P. TOBIN					TALLY				
SIGNATURE					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** _____ **Second by:** _____
AEGL 2 **Motion by:** _____ **Second by:** _____
AEGL 3 **Motion by:** _____ **Second by:** _____
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 4/14/09

ARSENIC COMPOUNDS

- **Attempt at arsenic trichloride AEGL 1997 (aka "building a chimney with no bricks" approach)**
  - **AEGL-1: no data**
  - **AEGL-2 : elemental equivalence to arsenic trioxide**
  - **AEGL-3: 1- hr LC_{50} (Flury, 1921)**
  - **data are no better today**

- **Assumptions for elemental equivalence approach**
  - **the arsenic moiety is the sole determinant of toxicity**
  - **the mode of action is similar for all trivalent arsenicals**
  - **the metabolism and disposition of arsenic trichloride and arsenic trioxide will both yield the arsenic moiety in a similar state of bioavailability and the internal dose rate for the arsenic will be similar**

ARSENIC COMPOUNDS

- trivalent (arsenite) and pentavalent (arsenate)
  - metabolic conversion of pentavalent to trivalent
  - most toxicity attributable to arsenite
  - methylation

- absorption of arsenic is via passive diffusion in humans and mice; possible carrier-mediated cellular transport in rats
  - rats sequester arsenic in erythrocytes – bad model for humans
  - metabolism in humans appears to vary from that in most rodents

- mode of action of As+3 and As+5
  - ultimately, most toxicity is due to As+3
  - interaction with thiols, altered redox status, energy production, cytotoxicity

- surrogate arsenicals
  - As_2O_3 – also limited data
  - pentavalent arsenicals - conversion issues

- Why is arsenic trichloride of special interest ????
  - volume of production
  - precursor to many arsenicals including lewisite

ATTACHMENT 4

RICIN AEGL
REVISIT – NEW DATA

NAC/AEGL-48
Hilton-Old Town Alexandria, VA
April, 2009

AEGL Program

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	NR	NR	NR	NR	NR
AEGL 2	NR	NR	NR	NR	NR
AEGL 3*	0.033 mg/m^3	0.010 mg/m^3	0.0048 mg/m^3	NR	NR

*estimated lethality threshold (LC_{01}) in rats (Griffiths et al., 1995a); values incorporate a 2.7-fold reduction for potency variability; UF=10 (3x3); n=0.95

NR = Not recommended due to insufficient data

Acute inhalation toxicity of ricin in rats and mice (Gomez et al. 2009)		
Exposure concentration	**Exposure duration (min)**	**Response (lethality)[a]**
Rats		
0.12 µg/L (0.12 mg/m^3)	10	1/6
	20	6/6
	30	6/6
	40	6/6
	50	6/6
Mice		
0.01µg/L (0.01 mg/m^3)	10	0/6
	20	0/6
	40	6/6
	60	5/6
	80	6/6

[a] mean survival ≤ 2 days for rats (6.2 days for lowest dose); 2-7 days for mice; 7-day observation

- 0.15 µg/kg rats (no c.i.)
- 0.56 µg/kg mice (0.36-0.79 c.i.)

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	NR	NR	NR	NR	NR
AEGL 2	NR	NR	NR	NR	NR
AEGL 3	0.033 mg/m^3 0.0040 mg/m^3	0.010 mg/m^3 0.0013 mg/m^3	0.0048 mg/m^3 0.00067 mg/m^3	NR	NR

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

Selected Cyanide Salts

Sodium Cyanide (CAS No. 143-33-9)
NaCN

Potassium Cyanide (CAS No. 151-50-8)
KCN

Calcium Cyanide (CAS No. 592-01-8)
$Ca(CN)_2$

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ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ralph Gingell

Chemical Reviewers: George Cushmac and Ed Bernas

- The cyanide salts are solids.
- Inhalation of dusts may result in ionization in the nasal or lung mucosal fluids to yield CN^-.

  The salts may also react with water in humid air and be inhaled as HCN.

  In both cases, there will be systemic absorption of cyanide ion

- One mole of sodium cyanide or potassium cyanide may react with water or moisture to produce a maximum of one mole of hydrogen cyanide as follows:

  $NaCN + H_2O \rightarrow HCN + NaOH$

  $KCN + H_2O \rightarrow HCN + KOH$

- One mole of calcium cyanide may react with water or moisture to produce a maximum of two moles of hydrogen cyanide as follows:

  $Ca(CN)_2 + 2H_2O \rightarrow 2HCN + Ca(OH)_2$

- Hydrolysis rates were not located

  The rate of cyanide generation may be dependent on ambient temperature and humidity and the chemical structure of the cyanide

  Water solubility/reactivity is described as "forms hydrogen cyanide" for sodium and potassium, and "gradually liberates hydrogen cyanide" for calcium cyanide (HSDB, 2008)

- The cyanide moiety is responsible for acute toxicity from cyanide salts.

•Qualitative:

Cyanide-induced clinical effects are indistinguishable following inhalation or dermal exposure to HCN vapor, or oral exposure to the cyanide salts NaCN and KCN, for both humans and animals.

Headaches, dizziness, nausea, inability to concentrate, thoracic oppression, palpitation, numbness, weakness, rapid pulse, face flushing, unconsciousness, and death.

•Quantitative: Rat oral LD_{50} values

The CN adjusted values for hydrogen, sodium, and potassium cyanides are comparable

Adjusted value for calcium cyanide is much greater (suggesting a less toxic compound) than would be expected on a molar basis for CN.

May be due to a slower hydrolysis rate, allowing for more efficient detoxification, relative to the other cyanide salts.

Rat oral lethality data			
Compound	LD_{50} (mg/kg)	Adjusted LD_{50} (mg/kg CN)	Reference
HCN	8.5	8.2	Cohrssen, 2001
NaCN	15	7.9	Smyth et al., 1969
KCN	16	6.4	IUCLID, 2000
$Ca(CN)_2$	39	22	Smyth et al., 1969

- Appropriate chemical-specific inhalation data are not available for derivation of AEGL values for cyanide salts.

- Hydrogen cyanide values are final and published in Volume 2.

- AEGL-1, AEGL-2, and AEGL-3 values for cyanide salts will be based on hydrogen cyanide AEGL-1, AEGL-2, and AEGL-3 values, respectively, using a molar equivalence approach.

- The hydrogen cyanide AEGL values will be used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values.

  Calculations assume 25 degrees C and 760 mm Hg and complete hydrolysis

AEGL VALUES FOR METAL CYANIDE SALTS*

Compound	Classification	10-min	30-min	1-hr	4-hr	8-hr
Sodium Cyanide	AEGL-1	5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3
	AEGL-2	34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3
	AEGL-3	54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3
Potassium Cyanide	AEGL-1	6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3
	AEGL-2	45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3
	AEGL-3	72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3
Calcium Cyanide**	AEGL-1	4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3
	AEGL-2	32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3
	AEGL-3	51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3

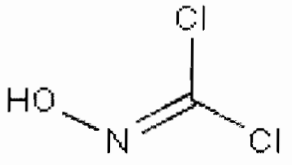
*These airborne concentrations will produce the equivalent AEGL values for hydrogen cyanide.

** *Although the adjusted rat oral LC value for calcium cyanide is much greater (suggesting a less toxic compound) than would be expected on a molar basis for CN, the production of two moles of HCN was assumed per mole of calcium cyanide. This assumption will yield protective AEGL values.*

ATTACHMENT 6

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PHOSGENE OXIME (CAS Reg. No. 1794-86-1)



PHOSGENE OXIME

- **Urticant/nettle agent causing instant intolerable pain, erythema, wheals and urticaria**

- **Corrosive; causes extensive damage to tissue**

- **Initially developed (1929) as a possible warfare agent (mask breaker)**

- **Precise mechanism of action is not fully understood**
  - **skin lesions similar to those made by a strong acid**
  - **necrotizing effects of the chlorine, direct effect of the oxime or effect from the carbonyl group**

- **Nasty stuff with a relatively poor data base**

PHOSGENE OXIME - Human Data

- Malatesta et al. (1983)
  - six volunteers (including investigators) exposed to phosgene oxime
  - methods for determination of exposure concentrations were not specified
  - "threshold of physiologic sensitivity": 1 mg/m^3 (0.21 ppm), minimal concentration over a 10-minute period
    - awareness of the chemical by ocular sensitivity, taste, and odor
  - "threshold of pathologic sensitivity": ~3 mg/m^3 (0.63 ppm)
    - minimal concentration of a product after one minute of exposure causing an unpleasant or irritating sensation on the conjunctiva, nose (assumed to refer to nasal mucosal surfaces), or skin.
- U.S. Army (2005)
  - estimated LCt_{50} of 3200 $mg \cdot min/m^3$ (based upon a 10-minute exposure) for phosgene oxime vapor

PHOSGENE OXIME - Animal Data

- limited data
  - exposure-response data ? lethality threshold estimate ?
  - experimental protocols ?

Summary of inhalation toxicity of phosgene oxime in animals				
Concentration	Exposure Duration	Species	Effect	Reference
100-500 mg/m^3	30 min.	mice, guinea pigs, rabbits	All concentrations: no deaths; lacrimation, agitation and respiratory difficulty resolved by day 3 post-exposure	Malatesta et al., 1983
1.5- 2.0 mg/L (1,500-2,000 mg/m^3)	30 min.	dogs (n =8)	7 of 8 dogs died; surviving dog received intensive treatment	Tschanatschev and Dronzin, 1957
1.5-3 mg/L (1,500-3,000 mg/m^3)	30 min.	dogs	100% lethality	Balev and Andreev, 1957

PHOSGENE OXIME
AEGL-1

AEGL-1 values for phosgene oxime					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	**0.17 mg/m^3**	**0.17 mg/m^3**	**0.17 mg/m^3**	**0.17 mg/m^3**	**0.17 mg/m^3**

Key Study: Malatesta, P., B. Bianchi and C. Malatesta. 1983. [Acute Thionyl Chloride Poisoning Contributo allo studio delle sostanze orticanti: Nota 1. Boll. Chim. Farm 122: 96-103.

Critical Effect: Awareness of chemical by ocular, nasal, and dermal sensation following 10-minute exposure of 6 informed human volunteers to 1 mg/m^3

Uncertainty Factors: 3; direct contact irritant (ocular, nasal, dermal contact) requiring no metabolism/disposition processes; initial awareness is not expected to vary among individuals

Modifying Factor: 2; limited data

Time Scaling: No time scaling applied for direct-contact irritation that is primarily a function of concentration and not expected to have a significant temporal component.

PHOSGENE OXIME
AEGL-2

AEGL-2 values for phosgene oxime					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-2	**0.50 mg/m^3**	**0.50 mg/m^3**	**0.50 mg/m^3**	**0.50 mg/m^3**	**0.50 mg/m^3**

Key Study: Malatesta, P., B. Bianchi and C. Malatesta. 1983. [Acute Thionyl Chloride Poisoning Contributo allo studio delle sostanze orticanti: Nota 1. Boll. Chim. Farm 122: 96-103.

Critical Effect: Unpleasant (likely intolerable) irritation of eyes, nasal tissue, and skin following 1-minute exposure of 6 informed human volunteers to 3 mg/m^3

Uncertainty Factors: 3; direct contact irritant (ocular, nasal, dermal contact) requiring no metabolism/disposition processes; initial awareness is not expected to vary among individuals

Modifying Factor: 2; limited data

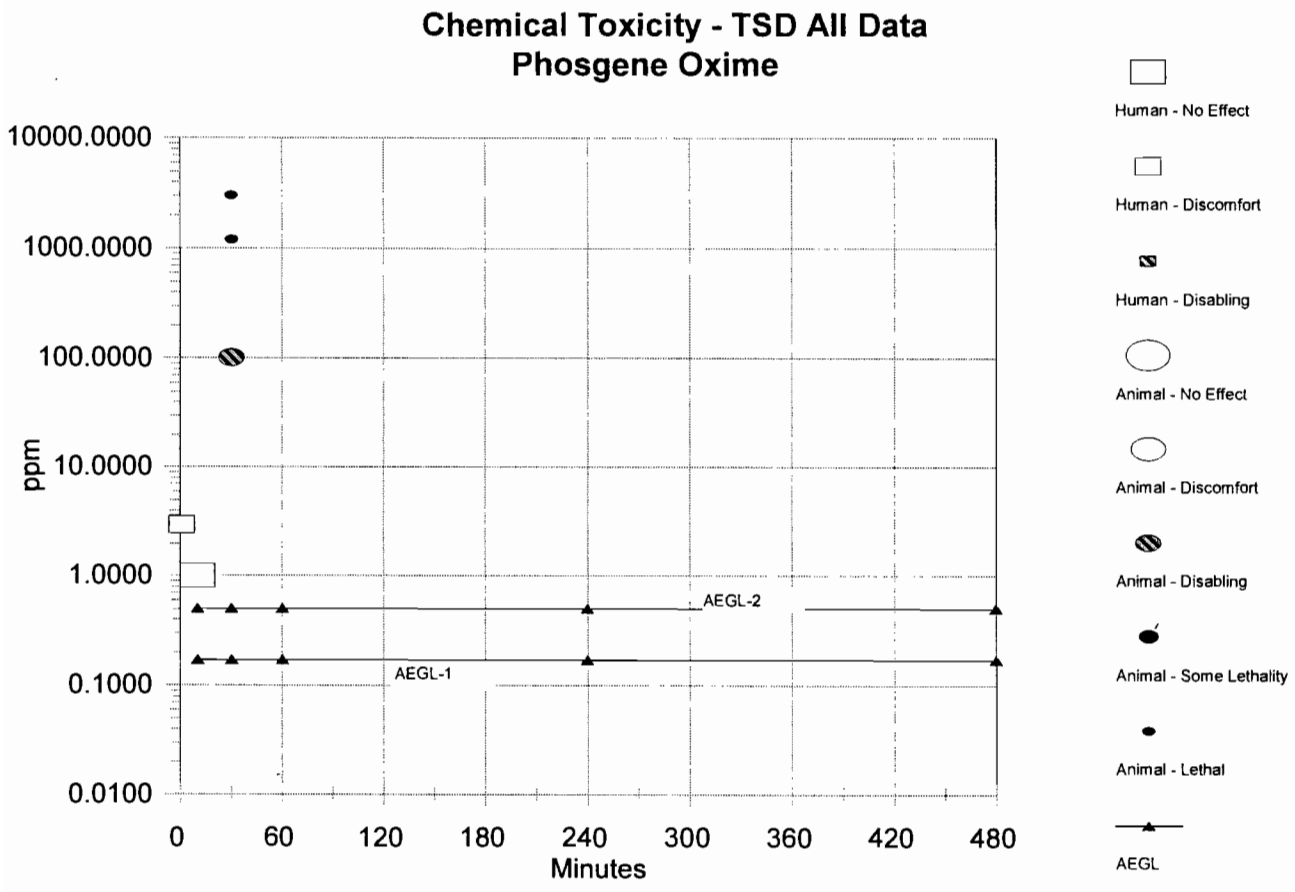
Time Scaling: No time scaling applied for direct-contact irritation that is primarily a function of concentration and not expected to have a significant temporal component.

PHOSGENE OXIME
AEGL-3

- **Insufficient data**
  - **Estimate of lethality threshold not possible**
  - **Lethality response basically 100%**
  - **Human LCt50 estimate ??????**

AEGL values for phosgene oxime (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	**0.17 mg/m^3**	**0.17 mg/m^3**	**0.17 mg/m^3**	**0.17 mg/m^3**	**0.17 mg/m^3**
AEGL-2	**0.50 mg/m^3**	**0.50 mg/m^3**	**0.50 mg/m^3**	**0.50 mg/m^3**	**0.50 mg/m^3**
AEGL-3	**NR**	**NR**	**NR**	**NR**	**NR**

- **Values for 4 and 8 hrs ???????**


Chemical Toxicity - TSD All Data
Phosgene Oxime
10000.0000
1000.0000
100.0000
10.0000
1.0000
0.1000
0.0100
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

ATTACHMENT 7

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PERFLUOROISOBUTYLENE (PFIB)

NAC/AEGL-48
April 14-16, 2009
Alexandria, VA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Rusch

Chemical Reviewers: Susan Ripple and David Freshwater

Colorless gas

Formed during the production of tetrafluoroethylene and chlorodifluoromethane

Produced in relatively small amounts during the heated decomposition of polytetrafluoroethylene (PTFE or Teflon®) and some closely related plastics.

"Heavy products/High-boilers" are by-products formed at high temperatures (700°C) during the synthesis of tetrafluoroethylene from chlorodifluoromethane. Certain volatile and relatively inert by-products readily dissipate; however, other heavier more unstable by-products with high boiling points (above 40°C) accumulate at the base of the distillation column. The physical properties of these compounds lead to the name "heavy products/high boilers." Analyses of these "heavy products/high boilers" suggested that PFIB (found in concentrations ranging from 0.1 to 3%) is responsible for the high toxicity of "heavy products/high boilers".

No production volume information was located.

Exact mechanism of action is not known.

Highly electrophilic chemical, likely undergoes electron transfer that leads to several highly reactive intermediates

Reacts with almost all known nucleophiles.

Pattern of pulmonary damage is characteristic of highly hydrophobic gases that penetrate into the deep lung.

Little evidence of direct pathological damage to tissues outside the respiratory tract.

All PFIB-induced tissue damage appears to result from rapid interaction with cells that are either in, or in close proximity to, the respiratory airways.

Produces pulmonary permeability-type edema (similar to phosgene)

<u>Human Data-</u>

Limited to occupational exposures with no definitive concentration or duration parameters.

Clinical signs included cough, difficulty breathing, wheezing, nausea, chest pain, weakness, and bad taste.

Pulmonary edema and congestion were noted at autopsy.

<u>Animal Data-</u>

Lethality data are available for rats, mice, guinea pigs, rabbits, and cats, with the most robust data sets being for rats and mice.

Clinical signs include dyspnea, cyanosis, face washing, hyperemia, sneezing, mild responsiveness, rapid respiration, and convulsions.

Steep concentration-response curve

Limited interspecies variability

Death is attributed to pulmonary edema, a consistent necropsy finding.

LIMITED INTERSPECIES VARIABILITY

TABLE 1. Comparison of PFIB LC_{50} values for various animal species

Duration	Species	LC_{50} (ppm)	Ratio of LC_{50} values (maximum)	Reference
1 minute	Mouse	107	1.1	Fusheng et al., 1992
	Rat	122		Smith et al., 1982
10 minutes	Mouse	11.8	1.4	Bide et al., 2000
	Rat	17		Smith et al., 1982
15 minutes	Mouse	6.1	1.1	Karpov, 1977
	Rat	6.7		Karpov, 1977
2 hours	Mouse	0.98	3.1	Paulet and Bernard, 1968
	Rat	1.05		
	Guinea pig	1.05		
	Rabbit	1.20		
	Mouse	1.6		Karpov, 1977
	Cat	3.1		Karpov, 1977
	Rat*	11.6*	11.8*	Karpov, 1977

*LC_{50} value inconsistent with overall data base
(Karpov (1977) 15-minute rat value and reports from other authors).

STEEP CONCENTRATION-RESPONSE CURVE

Duration	Concentration	Mortality	Reference
Rat			
0.25-min	228 ppm	0% (0/10)	Smith et al., 1982
	468 ppm	100% (10/10)	
5-min	20 ppm	0% (0/10)	
	32 ppm	90% (9/10)	
10-min	10 ppm	0% (0/10)	
	20 ppm	80% (8/10)	
4-hr	0.25 ppm	0% (0/6)	DuPont, 1966
	0.5 ppm	100% (6/6)	
Mouse			
1-min	98 ppm	0% (0/6)	Fushing et al., 1992
	116 ppm	100% (6/6)	
10-min	10 ppm	10% (2/20)	Bide et al., 2000
	65 ppm	100% (10/10)	
Rat, Mouse, Rabbit, Guinea Pig			
2-hr	0.70 ppm	0%	Paulet & Bernard, 1968
	1.5 ppm	100% (10/10 rats)	
		100% (10/10 mice)	
		100% (3/3 rabbits)	
		80% (4/5 GP)	

AEGL-1 Values for PFIB				
10-min	30-min	1-h	4-h	8-h
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

AEGL-2 Values for PFIB				
10-min	30-min	1-h	4-h	8-h
0.20 ppm	0.067 ppm	0.033 ppm	0.0083 ppm	0.0043 ppm

Endpoint: Three-fold reduction of AEGL-3 values

Justified by steep concentration-response curve.

AEGL-3 Values for PFIB				
10-min	30-min	1-h	4-h	8-h
0.59 ppm	0.20 ppm	0.10 ppm	0.025 ppm	0.013 ppm

Species: Rat
Concentration: 0.25 ppm
Time: 4-hours
Endpoint: Highest concentration causing no mortality. Mortality (100%; 6/6) observed at next highest concentration tested: 0.5 ppm)
Reference: DuPont, 1966

Time Scaling:

$c^n \times t = k$, where the exponent, n, is 1.0, derived from rat lethality data ranging from 0.25 to 120 minutes.

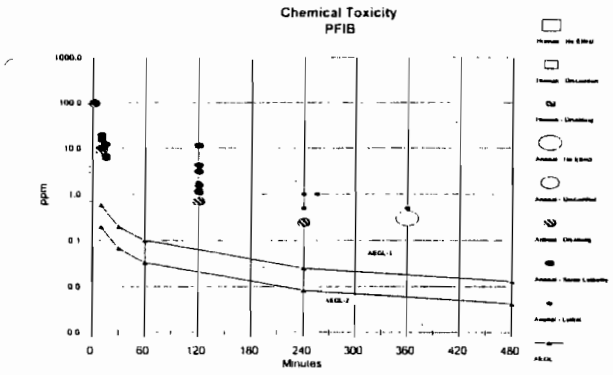
Time scaling from 4-hrs to 10-min is justified: No mortality was noted in rats exposed to 10 ppm PFIB (Smith et al., 1982) or mice exposed to 9.2 ppm PFIB (Bide et al., 2000) for 10-minutes. Applying an uncertainty factor of 10 to these concentrations, yields 10-min AEGL-3 values of 1.0 and 0.92 ppm, suggesting that the derived 10-min AEGL-3 value is reasonable.

Uncertainty Factors:

Interspecies: 3- Lethality data from several animal species suggest little interspecies variability

Intraspecies: 3- Steep concentration-response curve implies limited intraspecies variability

Standards and Guidelines for PFIB					
Guideline	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.20 ppm	0.067 ppm	0.033 ppm	0.0083 ppm	0.0043 ppm
AEGL-3	0.59 ppm	0.20 ppm	0.10 ppm	0.025 ppm	0.013 ppm
ERPG-1 (AIHA)[a]			NA		
ERPG-2 (AIHA)[a]			0.1 ppm		
ERPG-3 (AIHA)[a]			0.3 ppm		
TLV-STEL (ACGIH)[b]	0.01 ppm (ceiling)				
MAC (The Netherlands)[c]					0.01 ppm



ACUTE EXPOSURE GUIDELINE LEVELS FOR OXAMYL

National Advisory Committee for AEGLs Meeting 48
Alexandria, VA
April 14-16, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Paul Tobin

Chemical Reviewers:
Henry Anderson
Daniel Sudakin

Properties

N-methyl carbamate pesticide
Crystalline solid with a low vapor pressure

Data Base

Human oral dosing study
Acute studies with rats
- 1 and 4 hours
- **dust** and aerosol studies
  - dust more toxic
- 1-hour LC_{50} values of 120 and 170 mg/m^3
- 4-hour LC_{50} values of 56 and 64 mg/m^3

Oral developmental/reproductive toxicity studies with rats and rabbits
Genotoxicity studies
Oral carcinogenicity studies with rats, mice and dogs

Mode of Action

Cholinesterase activity inhibition
- Erythrocyte acetylcholinesterase activity inhibition biomarker
- Sustained action of neurotransmitter acetylcholine

Plasma cholinesterase is butyl or pseudocholinesterase
Inhibition is reversible

Signs and symptoms of acetylcholinesterase activity inhibition (Paul 1987)
- miosis, lacrimation, salivation, tremors, convulsions....
- acetylcholinesterase depression is measured in relation to individual's baseline
- 0-15% = statistical error
- 25-35% slight poisoning
  - 30% activity inhibition from baseline = ACGIH-BEI
- 35-50% = severe poisoning

Uncertainty Factors

Taken from human and rat oral dosing studies with oxamyl
N-methyl carbamate pesticides do not have a port of entry effect, are expected to be rapidly absorbed and do not require activation. Therefore species differences and juvenile-adult differences in sensitivity in oral studies can be used as interspecies and intraspecies uncertainty factors in inhalation studies

Interspecies uncertainty factor: 3
- Differences in modeled erythrocyte acetylcholinesterase activity inhibition in humans and rats following oral dosing

Intraspecies uncertainty factor: 3.48
- Comparative brain acetylcholinesterase activity inhibition in post-natal-day 11 rats and adult rats following oral dosing

Total uncertainty factor: 10

Time-scaling
- n = 1.6 based on one 1-hour study and two 4-hour studies

Data for Derivation of AEGL-1
U.S. EPA 2000
4-hour study
male and female rats exposed to 0, 4.9 or 24 mg/m^3
endpoint of plasma, erythrocyte, and brain cholinesterase activity inhibition

4.9 mg/m^3: erythrocyte acetylcholinesterase activity inhibition of 28.5%
clinical signs similar to those of control rats
24 mg/m^3: 72-73% erythrocyte acetylcholinesterase activity inhibition

4-hour 4.9 mg/m^3 value divided by 10 and time-scaled using 1.6.

AEGL-1 Values for Oxamyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3

Data for Derivation of AEGL-2
No relevant data
Based on steep-concentration-response curve, divide AEGL-3 values by 3

AEGL-2 Values for Oxamyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3

Data for Derivation of AEGL-3
Well-conducted study of Kelly 2001
4-hour study
male and female rats exposed to 0, 50, 54, 65, 120 mg/m^3
endpoint of lethality: 2/10, 6/10, 7/10, 10/10 rats

Calculated 4-hour $BMCL_{05}$ of 22 mg/m^3:

4-hour 22 mg/m^3 value divided by 10 and time-scaled using 1.6.

AEGL-3 Values for Oxamyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 mg/m^3

Proposed AEGL Values for Oxamyl					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3
AEGL-2	5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3
AEGL-3	16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 mg/m^3

AEGL-1: based on 28.5% acetylcholinesterase activity inhibition in rats, 4.9 mg/m^3, 4 hours. Interspecies and intraspecies uncertainty factors of 3 and 3.5, respectively, for a total of 10 were applied.
AEGL-2: based on steep concentration-response curve, derived by dividing the AEGL-3 by 3.
AEGL-3: based on threshold for lethality (4-hour $BMCL_{05}$ of 22 mg/m^3). Inter- and intraspecies uncertainty factors of 3 and 3.5, respectively, for a total of 10 were applied.

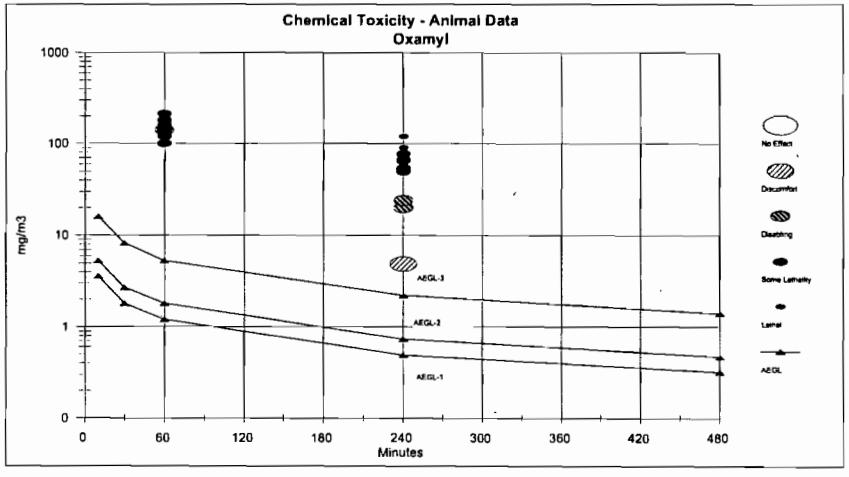
OXAMYL

Human Oral Data…..
40 healthy male subjects
Groups of 5; 10 controls
Doses of 0.005, 0.015, 0.03, 0.06, 0.09, or 0.15 mg a.i./kg
Clinical signs and symptoms and plasma and erythrocyte cholinesterase measured pre-dose and at set times post-dose
Clinical signs not dose-related
Erythrocyte acetylcholinesterase activity inhibition:
peak effect at 30-45 minutes; recovery by 2-3 hours post-dose
0.005, 0.015, 0.03, 0.06 mg/kg: similar to controls
0.09 mg/kg: 7%
0.15 mg/kg: 28%

Inhalation calculation:
0.15 mg/kg x 70 kg adult = 10.5 mg
Look at 4-hour value: 10.5 mg/(20 m^3/24 hours)(4 hours)($1_{absorption}$) = 3.15 mg/m^3
Divide by intraspecies UF of 3.5: (3.15 mg/m^3)/3.5 = 0.90 mg/m^3
(10-minute value would be 22 mg/m^3)

OXAMYL

Category graph of toxicity data and AEGL values



ACUTE EXPOSURE GUIDELINE LEVELS FOR METHOMYL

National Advisory Committee for AEGLs Meeting 48
Alexandria, VA
April 14-16, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Paul Tobin

Chemical Reviewers:
Henry Anderson
Daniel Sudakin

Properties

N-methyl carbamate pesticide
Crystalline solid with a low vapor pressure

Data Base

Human oral dosing study
Acute studies with rats
- all studies were for 4 hours
- **vapor**, powder and **aerosol** studies
  - vapor and aerosol studies well conducted
- 4-hour LC_{50} value of 258 mg/m^3 (aerosol)

Repeat-exposure study
Oral developmental/reproductive toxicity studies with rats and rabbits
Genotoxicity studies
Oral carcinogenicity studies with rats, mice and dogs

Mode of Action

Cholinesterase activity inhibition
- Erythrocyte acetylcholinesterase activity inhibition biomarker
- Sustained action of neurotransmitter acetylcholine

Plasma cholinesterase is butyl or pseudocholinesterase
Inhibition is reversible

Signs and symptoms of acetylcholinesterase activity inhibition (Paul 1987)
- miosis, lacrimation, salivation, tremors, convulsions....
- acetylcholinesterase depression is measured in relation to individual's baseline
- 0-15% = statistical error
- 25-35% slight poisoning
  - 30% activity inhibition from baseline = ACGIH-BEI
- 35-50% = severe poisoning

Uncertainty Factors

Taken from human and rat oral dosing studies with methomyl
N-methyl carbamate pesticides do not have a port of entry effect, are expected to be rapidly absorbed and do not require activation. Therefore species differences and juvenile-adult differences in sensitivity in oral studies can be used as interspecies and intraspecies uncertainty factors in inhalation studies

Interspecies uncertainty factor: 5
- Differences in modeled erythrocyte acetylcholinesterase activity inhibition in humans and rats following oral dosing

Intraspecies uncertainty factor: 3.05
- Comparative brain acetylcholinesterase activity inhibition in post-natal-day 11 rats and adult rats following oral dosing

Total uncertainty factor: 15

Time-scaling
- No time-scaling information

Data for Derivation of AEGL-1
Not recommended??
Ta'naka 1987
4-hour study
male Wistar rats exposed to 9.9 mg/m^3
endpoint of plasma and erythrocyte cholinesterase activity inhibition
questionable measurements

4-hour 9.9 mg/m^3 value divided by 15 and time-scaled using default values of n = 3 and 1 for shorter and longer exposure durations, respectively.

AEGL-1 Values for Methomyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
1.9 mg/m^3	1.3 mg/m^3	1.1 mg/m^3	0.66 mg/m^3	0.33 mg/m^3

Data for Derivation of AEGL-2
DuPont 1966a
4-hour study
exposure to 36 or 44 mg/m^3
36 mg/m^3: clinical signs in one of six rats
44 mg/m^3: clinical signs in six of six rats
clinical signs included slight salivation, lacrimation, mild dyspnea

36 mg/m^3:

AEGL-2 Values for Methomyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
6.9 mg/m^3	4.8 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.2 mg/m^3

44 mg/m^3:

AEGL-2 Values for Methomyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
8.5 mg/m^3	5.9 mg/m^3	4.7 mg/m^3	2.9 mg/m^3	1.5 mg/m^3

Data for Derivation of AEGL-3
Well-conducted study of DuPont 1991
4-hour study
male and female rats exposed to 0, 137, 181, 182, 232, or 326 mg/m^3
endpoint of lethality: 0/10, 0/10, 0/10, 1/10, 6/10, 7/10 rats

Calculated 4-hour $BMCL_{05}$ of 129.45 mg/m^3:

4-hour 129.45 mg/m^3 value divided by 15 and time-scaled using default values.

AEGL-3 Values for Methomyl				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
25 mg/m^3	17 mg/m^3	14 mg/m^3	8.6 mg/m^3	4.3 mg/m^3

Proposed AEGL Values for Methomyl					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	NR 1.9 mg/m^3	NR 1.3 mg/m^3	NR 1.1 mg/m^3	NR 0.66 mg/m^3	NR 0.33 mg/m^3
AEGL-2 (36) AEGL-2 (44)	6.9 mg/m^3 8.5 mg/m^3	4.8 mg/m^3 5.9 mg/m^3	3.8 mg/m^3 4.7 mg/m^3	2.4 mg/m^3 2.9 mg/m^3	1.2 mg/m^3 1.5 mg/m^3
AEGL-3	25 mg/m^3	17 mg/m^3	14 mg/m^3	8.6 mg/m^3	4.3 mg/m^3

AEGL-1: slight acetylcholinesterase activity inhibition in rats, 9.9 mg/m^3, 4 hours. Interspecies and intraspecies uncertainty factors of 5 and 3.05, respectively, for a total of 15 were applied.
AEGL-2: slight clinical signs indicating acetylcholinesterase activity inhibition in one of six rats (or six of six rats).
AEGL-3: based on threshold for lethality (4-hour $BMCL_{05}$ of 129.45 mg/m^3). Inter- and intraspecies uncertainty factors of 5 and 3.05, respectively, for a total of 15 were applied.

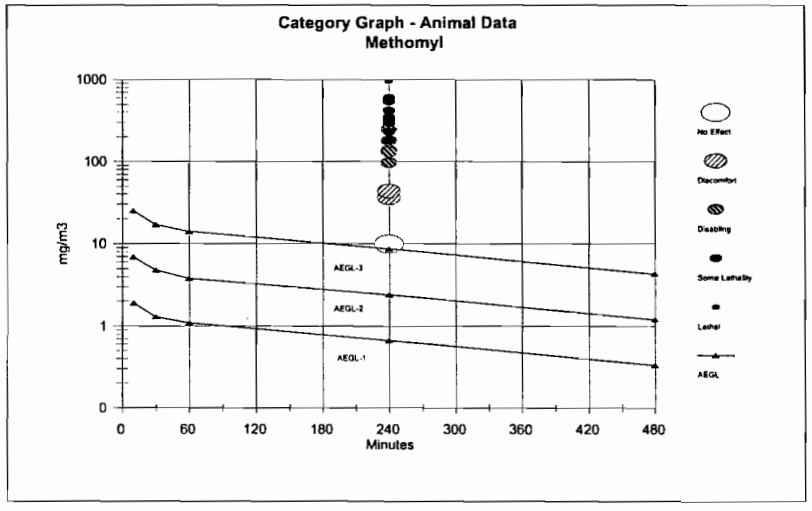
METHOMYL

Human Oral Data.....
19 healthy male subjects, ages 18-40
Groups of 5; 4 controls
Doses of 0, 0.1, 0.2, or 0.3, mg a.i./kg
Clinical signs and symptoms and plasma and erythrocyte cholinesterase measured pre-dose and at set times post-dose
Clinical sign of increased saliva in 0.3 mg/kg dose group
Erythrocyte acetylcholinesterase activity inhibition:
peak effect at 45-90 minutes; recovery by 6 hours post-dose
0.1 mg/kg: 2-19%
0.2 mg/kg: 19-28%
0.3 mg/kg: -35%

Inhalation calculation:
0.3 mg/kg x 70 kg adult = 21 mg
Look at 4-hour value: 21 mg/(20 m^3/24 hours)(4 hours)($1_{absorption}$) = 6.3 mg/m^3
Divide by intraspecies UF of 15: (6.3 mg/m^3)/15 = 0.42 mg/m^3
(10-minute value would be 10 mg/m^3)

METHOMYL

Category graph of toxicity data and AEGL values



ACUTE EXPOSURE GUIDELINE LEVELS FOR ALDICARB

National Advisory Committee for AEGLs Meeting 48
Alexandria, VA
April 14-16, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Paul Tobin

Chemical Reviewers:
Henry Anderson
Daniel Sudakin

Properties

N-methyl carbamate pesticide
Crystalline solid with a low vapor pressure

Data Base

Human oral dosing study
Acute studies with rats
- saturated vapor, 8 hours – no mortality (Risher et al. 1987)
- dust study: 6.7 mg/m^3 mortality of 0/6 rats at 15 minutes, 6/6 at 30 minutes
- aerosol study (UCC 1985)

Repeat-exposure study with aldicarb sulfone (UCC 1977) – lacked details
Oral developmental/reproductive toxicity studies with rats and rabbits
Genotoxicity studies
Oral carcinogenicity studies with rats and mice

Mode of Action

Cholinesterase activity inhibition
- Erythrocyte acetylcholinesterase activity inhibition biomarker
- Sustained action of neurotransmitter acetylcholine

Plasma cholinesterase is butyl or pseudocholinesterase
Inhibition is reversible

Signs and symptoms of acetylcholinesterase activity inhibition (Paul 1987)
- miosis, lacrimation, salivation, tremors, convulsions....
- acetylcholinesterase depression is measured in relation to individual's baseline
- 0-15% = statistical error
- 25-35% slight poisoning
  - 30% activity inhibition from baseline = ACGIH-BEI
- 35-50% = severe poisoning

Uncertainty Factors

Taken from human and rat oral dosing studies with aldicarb
N-methyl carbamate pesticides do not have a port of entry effect, are expected to be rapidly absorbed and do not require activation. Therefore species differences and juvenile-adult differences in sensitivity in oral studies can be used as interspecies and intraspecies uncertainty factors in inhalation studies

Interspecies uncertainty factor: 2
- Differences in modeled erythrocyte acetylcholinesterase activity inhibition in humans and rats following oral dosing

Intraspecies uncertainty factor: 2
- Comparative brain acetylcholinesterase activity inhibition in post-natal-day 17 rats and adult rats following oral dosing

Total uncertainty factor: 4

Time-scaling

No time-scaling information

Data for Derivation of AEGL-1
No data available
AEGL-1 values not recommended

AEGL-1 Values for Aldicarb				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
NR	MR	NR	NR	NR

Data for Derivation of AEGL-2
No data available
Based on steep concentration-response curve, divide AEGL-3 values by 3

AEGL-2 Values for Aldicarb				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
0.21 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.07 mg/m^3	0.04 mg/m^3

Data for Derivation of AEGL-3
Aerosol in dichloromethane (dichloromethane LC_{50} 52,000 mg/m^3, rat, several hours)
4 hour study with rats (UCC 1985)
male and female rats exposed to 0, 0.82, 2.0, 6.0, 8.7, 46.3 mg/m^3
endpoint of lethality: 0/10, 0/10, 1/10, 5/10, 10/10, 10/10 rats

Calculated 4-hour LC_{50} of 3.9 mg/m^3
Calculated 4-hour $BMCL_{05}$ of 0.88 mg/m^3:

4-hour 0.88 mg/m^3 value divided inter- and intraspecies uncertainty factors of 2 and 2, respectively, for a total of 4 and time-scaled using default values of n = 3 and 1 for shorter and longer exposure durations, respectively.

AEGL-3 Values for Aldicarb				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
0.64 mg/m^3	0.44 mg/m^3	0.35 mg/m^3	0.22 mg/m^3	0.11 mg/m^3

Proposed AEGL Values for Aldicarb					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.21 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.07 mg/m^3	0.04 mg/m^3
AEGL-3	0.64 mg/m^3	0.44 mg/m^3	0.35 mg/m^3	0.22 mg/m^3	0.11 mg/m^3

AEGL-1: In absence of suitable data, AEGL-1 values are not recommended.
AEGL-2: Based on steep concentration-response curve, the AEGL-2 values were derived by dividing the AEGL-3 values by 3.
AEGL-3: based on threshold for lethality (4-hour $BMCL_{05}$ of 0.88 mg/m^3). Inter- and intraspecies uncertainty factors of 2 and 2, respectively, for a total of 4 were applied. Time scaling used default values of n = 3 and 1 for shorter and longer exposure durations, respectively.

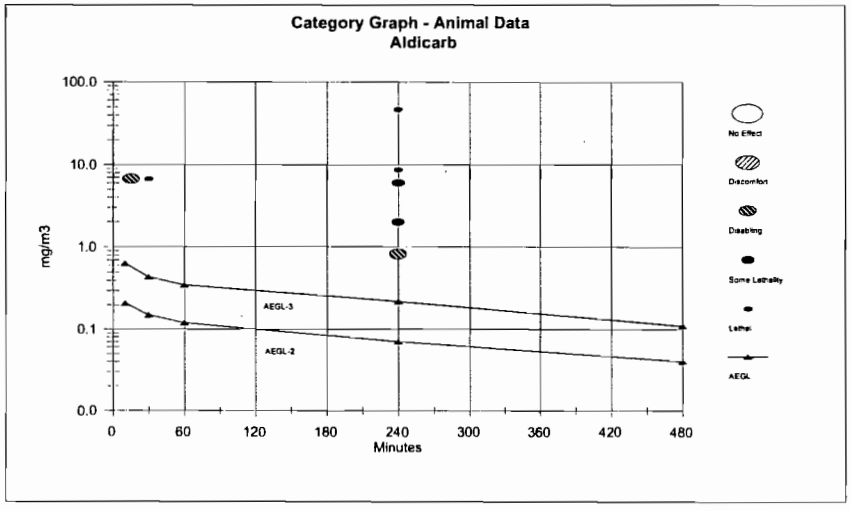
ALDICARB

Human Oral Data….. (Wyld et al. 1991)
47 healthy male and female subjects
Groups of 4-8
Males: doses of 0, 0.01, 0.025, 0.05, 0.06 (one subjects) or 0.0.075, mg a.i./kg
Females: 0, 0.025, 0.05
Clinical signs and symptoms and plasma and erythrocyte cholinesterase measured pre-dose and at set times post-dose
Clinical signs consistent with cholinesterase activity inhibition in males but not females
Erythrocyte acetylcholinesterase activity inhibition:
peak effect at 60 minutes
Males, AChE activity inhibition: 3.8, 12, 29, 38%
Females, AChE activity inhibition: 20, 36%

Inhalation calculation:
0.075 mg/kg x 70 kg adult = 5.25 mg
Look at 4-hour value: 5.25 mg/(20 m^3/24 hours)(4 hours)($1_{absorption}$) = 1.58 mg/m^3
Divide by intraspecies UF of 2: (1.58 mg/m^3)/2 = 0.79 mg/m^3

ALDICARB

Category graph of toxicity data and AEGL values



Perchloryl Fluoride

NAC/AEGL meeting
April 14th-16th, 2009
Washington DC

Perchloryl Fluoride

- CAS Reg. No. 7616-94-6
- Acyl fluoride of perchloric acid- stable compound
- Colorless gas
- Vapor pressure: 8943.9 mm Hg @ 25 °C
- Melting pt: -146 °C; Boiling pt: -46.8 °C
- Flammability limits: substance will not burn but can support combustion
- Production values not found

2

Toxicity Effects

- Strong oxidizer- strong irritant of the eyes, mucous membranes and lungs.
- Systemic effects- induction of methemoglobinemia
- Odor- characteristic sweet odor
- Greene et al. (1960)- 50% of human volunteers detected odor at 41 ppm. Described as sweet/musty. Little to no details on how this was obtained.

3

Summary of Data Available

- Very limited data
- No human data- only anecdotal information
- Animal data- dogs, rats, mice and guinea pigs exposed in acute lethality studies and up to 26 weeks but all from one laboratory and one reported study (Greene et al. 1960). Limited in study details.

4

Acute Data

- 2.5 hr and 4 hr study (Greene et al. 1960)
  - Dogs- 2/concentration
    - 622 ppm for 2.5 hrs: 1/2 dogs died; other treated with methylene blue and survived. Severe cyanosis, convulsions, hyperpnea
    - 451 ppm for 4 hrs: 1/2 dogs moribund upon removal from chamber; other treated with methylene blue and survived. Severe cyanosis, convulsions
    - 425 ppm for 4 hrs: both dogs survive; severe cyanosis, hyperpnea, emesis
    - 224 ppm for 4 hrs: both dogs survive; moderate cyanosis and hyperpnea

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Acute Data (cont'd)

- LC_{50} for rat: 385 ppm
- LC_{50} for mouse: 630 ppm.
- No other values provided (10 rats and 20 mice)
  - Rodents dying had labored breathing, cyanosis and convulsions
  - Moderate discoloration of lungs, pulmonary congestion

6

Acute Data (cont'd)

- Dost et al. (1974)
  - Study actually for chlorine trifluoride, but did expose to perchloryl fluoride also (breaks down to perchloryl fluoride)
  - Used male Sprague-Dawley rats
  - Not provided: # rats used, chamber conditions, effects observed; no values/data provided except for below
  - All rats died: 5000 ppm x 15 min and 2000 ppm x 40 min (all had methemoglobinemia)
  - All rats survive: 2000 ppm x 25 min and 1000 ppm x 60 min
  - Didn't use in derivations due to lack of details

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Acute lethality studies (Greene et al. 1960)			
Species	**Concentration (ppm)**	**Exposure time**	**Effect**
dog	224	4 hrs	Moderate cyanosis, hyperpnea
dog	224	4 hrs	Moderate cyanosis, hyperpnea
dog	425	4 hrs	Severe cyanosis, hyperpnea, emesis
dog	425	4 hrs	Severe cyanosis, hyperpnea, emesis
dog	451	4 hrs	Severe cyanosis, hyperpnea, motor instability, convulsions; dog treated with methylene blue and survived
dog	451	4 hrs	Severe cyanosis, hyperpnea, motor instability, convulsions, moribund in chamber and dog died
dog	622	2.5 hrs	Severe cyanosis, convulsions, death
dog	622	2.5 hrs	Severe cyanosis, hyperpnea, salivation, motor instability; dog treated with methylene blue and dog survived
rat	385	4 hrs	LC_{50}
mouse	630	4 hrs	LC_{50}

8

Repeat Exposure Data

- rats/mice/guinea pigs- 5 days/wk, 6 hrs/day x 7 weeks to 0 or 185 ppm (Greene et al. 1960)
  - 10/10 guinea pigs died after 3 days exposure
  - 18/20 rats and 20/39 mice died after 35 days
  - All had dypsnea, cyanosis and rats had 23% increase in methemoglobin after 1 week
  - Histopath: pulmonary irritation (alveolar edema at first then bronchopneumonia)

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Repeat Exposure Data (cont'd)

- Also exposed rats and guinea pigs to 0 or 104 ppm x 5 days/wk, 6 hrs/day x 5 weeks
  - 1/20 rats and 10/10 guinea pigs died after 25 days
  - Cyanosis observed
  - Similar findings to that at 185 ppm but less severe

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Repeat Exposure (cont'd)

- 10 rats/3 dogs/30 guinea pigs exposed to 0 or 24 ppm, 6 hrs/day, 5 days/wk x 26 wks (Greene et al. 1960)
  - Guinea pigs had underlying respiratory infection; 14/30 died in treated group
  - All dogs and rats survived with no clinical signs
  - ↑ fluoride in bones at end of study

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Repeat exposure studies* (Greene et al. 1960)

Species	Concentration (ppm)	Exposure time	Effect*
dog	0 or 24	6 hrs/d, 5 d/wk for 26 wks	All survived; no clinical signs; ↑ fluoride in femur after 6 months
rat	0, 104 or 185	6 hrs/d, 5 d/wk for 5 wks (104 ppm) or 7 wks (185) ppm	104 ppm: 1/20 died (> 25 exposure days) cyanosis, ↑ methemoglobin, ↓ hemoglobin, histopathological changes (liver, spleen, kidney) 185 ppm: 18/20 died (> 35 exposure days), dypsnea, same effects as 104 ppm but more severe
rat	0 or 24	6 hrs/d, 5 d/wk for 26 wks	All survived no clinical signs; ↑ fluoride in femur after 6 months
mouse	0 or 185	6 hrs/d, 5 d/wk for 7 wks	185 ppm: 20/39 died (after 35 exposure days) dypsnea and cyanosis
guinea pig	0, 104 or 185	6 hrs/d, 5 d/wk for 5 wks (104 ppm) or 7 wks (185) ppm	104 ppm: 10/10 died (> 25 exposure days) cyanosis 185 ppm: 10/10 died (> 3 exposure days) dypsnea and cyanosis
guinea pig	0 or 24	6 hrs/d, 5d/wk for 26 wks	1/30 control and 14/30 treated died* ↑ fluoride in bone, lung lesions*

* In all repeat exposure studies, there were no effects observed in the controls unless otherwise stated
*The high mortality and lung data are questionable as both the control and treated guinea pigs had *Bordetella bronchoseptica* isolated from them

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AEGL-1 Derivation

- POD= 24 ppm;
  - Rats and dogs exposed 6 hrs/day, 5 days/wk for 26 weeks
  - All survived; no clinical signs. Only effect was ↑ deposition of fluoride in femur after 6 months.
- Would be no-effect level after just 8 hrs
- Death occurred in guinea pigs at this concentration but had upper respiratory infection (*B. bronchoseptica*).

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AEGL-1 Derivation (cont'd)

- No time-scaling applied- no effects observed in animals
- Total UF= 30
  - Interspecies UF- 3, there was less than a 2-fold difference in the concentration at which dogs, rats and mice either were moribund or died. All species exhibit similar effects.
  - Intraspecies UF- 10, systemic absorption does occur with exposure; possible increased sensitivity of some of the human population for development of methemoglobinemia

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AEGL-1 Derivation (cont'd)

- Modifying factor (MF)= 2, applied due to the sparse data set; data exist for several species, but studies all performed by one laboratory and raw data and details were limited
- Total factors applied = 60

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AEGL-1 using POD of 24 ppm with no time-scaling; Total UF of 60

10-minute	30-minute	1-hour	4-hour	8-hour
0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/m³)

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AEGL-2 Derivation

- AEGL-2 = 1/3rd of AEGL-3 value
- According to the AEGL SOP (2001), when little data are available and steep dose curve, 1/3rd of the AEGL-3 value can be used for AEGL-2.
- 4-hour acute inhalation dog study:
  - 425 ppm- 2 dogs had severe cyanosis and hyperpnea but survived
  - 451 ppm- 1 of the 2 dogs was found moribund.

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AEGL-2 values derived by taking 1/3rd of AEGL-3 values

10-minute	30-minute	1-hour	4-hour	8-hour
2.4 ppm (10 mg/m³)	2.4 ppm (10 mg/m³)	1.9 ppm (8.0 mg/m³)	1.2 ppm (5.0 mg/m³)	0.77 ppm (3.2 mg/m³)

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AEGL-3 Derivation

- POD = 185 ppm, cyanosis and dypsnea but no deaths at less than 3 days in rats, mice and guinea pigs; no deaths in dogs exposed 4 hrs to 224 ppm
- Dog values show threshold of lethality at higher concentration but these are above rat LC_{50}.
- Time-scaling= Performed using $C^n \times t = k$ where n values range from 0.8 to 3.5 (ten Berge et al. 1986). Due to limited data available, scaling was performed using n=3 for extrapolating to the 30-minute, 1 and 4 hrs and n = 1 for extrapolating to 8 hours (NRC, 2001).

19

AEGL-3 Derivation (cont'd)

- Total UF= 30
  - Interspecies UF- 3, there was less than a 2-fold difference in the concentration at which dogs, rats and mice either were moribund or died. All species exhibit similar effects.
  - Intraspecies UF-10, systemic absorption does occur with exposure; possible increased sensitivity of some of the human population for development of methemoglobinemia

20

AEGL-3 Derivation (cont'd)

- Modifying factor (MF)= 2, applied due to the sparse data set; data exist for several species, but all performed by one laboratory and raw data and details were limited
- Total factors applied = 60
- 10-minute value will be same as 30-min.

21

AEGL-3 values derived by using 185 ppm as POD

10-minute	30-minute	1-hour	4-hour	8-hour
7.1 ppm (30 mg/m³)	7.1 ppm (30 mg/m³)	5.6 ppm (24 mg/m³)	3.5 ppm (15 mg/m³)	2.3 ppm (9.7 mg/m³)

22

AEGL Numbers for Perchloryl Fluoride

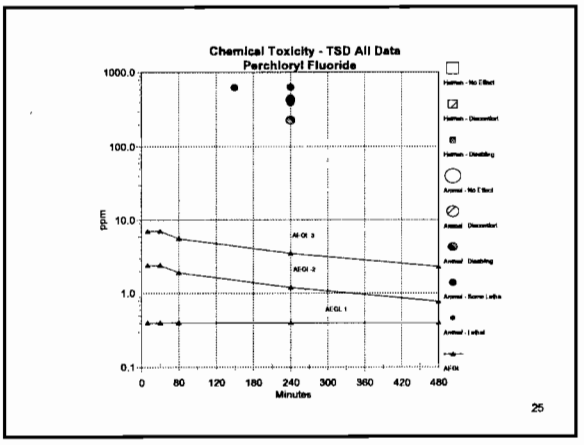
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/ m³)	0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/m³)	0.40 ppm (1.7 mg/m³)
AEGL-2 (Disabling)	2.4 ppm (10 mg/m³)	2.4 ppm (10 mg/m³)	1.9 ppm (8.0 mg/m³)	1.2 ppm (5.0 mg/m³)	0.77 ppm (3.2 mg/m³)
AEGL-3 (Lethal)	7.1 ppm (30 mg/m³)	7.1 ppm (30 mg/m³)	5.6 ppm (24 mg/m³)	3.5 ppm (15 mg/m³)	2.3 ppm (9.7 mg/m³)

23

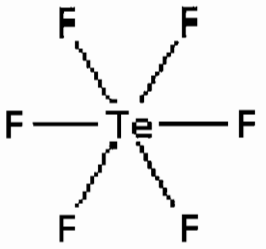
Standard Regulations/Guidelines

- ACGIH TLV-TWA and OSHA PEL-TWA: 3 ppm; Derived from Greene et al. (1960) study; value was approximately 1/10th of the 24 ppm concentration administered in experimental animals over repeated exposures (26 weeks).
- NIOSH IDLH: 100 ppm; Based on Greene's LC_{50} for rats of 385 ppm in an 4-hour acute inhalation toxicity study.

24


Chemical Toxicity - TSD All Data
Perchloryl Fluoride
1000.0
100.0
10.0
1.0
0.1
ppm
0
80
120
180
240
300
360
420
480
Minutes
AEGL 3
AEGL 2
AEGL 1
25

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
TELLURIUM HEXAFLUORIDE
CAS Reg. No. 7783-80-4



NAC/AEGL
April 14-16, 2009
Alexandria, VA

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Roberta Grant

Chemical Reviewers: George Woodall and Lynn Beasley

Hydrolyzes slowly into hydrogen fluoride and tellurium ion or telluric acid

Effects are consistent with severe irritation/corrosivity

One mole of tellurium hexafluoride may decompose in the moist atmospheres to form up to 6 moles of hydrogen fluoride.

However, the limited data set suggests that tellurium is much more than 6-times as toxic as hydrogen fluoride.

HF 1-hr mouse LC_{50} values: 342-501 ppm (NRC 2004)

If the acute inhalation toxicity of tellurium hexafluoride was due only to the hydrogen fluoride hydrolysis products, then approximate 1-hr LC_{50} values for tellurium hexafluoride would range from 57-84 ppm for mice.

However, 4/4 mice died when exposed to only 5 ppm tellurium hexafluoride for 1-hr (Kimmerle 1960).

The increased relative toxicity of tellurium hexafluoride may be due to the tellurium moiety and the slow hydrolysis rate of tellurium hexafluoride.

BOTTOM LINE: AEGL values for tellurium hexafluoride cannot be derived by analogy to hydrogen fluoride.

Kimmerle, 1960

Single Exposure
4-hr exposures followed by 3-wk observation period

Rabbit (1/group)
Guinea pig (1/group)
Rats (2/group)
Mice (4/group)

1 ppm: Respiratory dysfunction, pulmonary edema

5, 10, 25, 50, 100 ppm: 100% mortality

Time to Death (min) for Animals Exposed to Tellurium Hexafluoride for 4-hr

	1 ppm	5 ppm	10 ppm	25 ppm	50 ppm	100 ppm
Rabbit	-	480	140	80	60	15
Guinea Pig	-	360	120	100	70	30
Rat-1	-	1440	100	85	70	25
Rat-2	-	1440	115	60	55	20
Mouse-1	-	960	130	75	50	10
Mouse-2	-	240	130	90	70	15
Mouse-3	-	1440	120	110	45	30
Mouse-4	-	1440	110	110	60	25

Little species variability

Time-to death generally concentration-dependent

Kimmerle, 1960

Rabbit (1/group)
Guinea pig (1/group)
Rats (2/group)
Mice (4/group)

Single Exposure
1-hr exposure followed by 3-week observation period

1 ppm: Increased hyperpnea in all animals

5 ppm: Severe damage to respiratory organs in all animals, very slow recovery, 100% mortality in mice (death between 24 and 36 hours)

Repeat Exposure

1-hr/day exposure for 5 days, followed by 3-wk observation period

1 ppm: No visible effects in the test animals observed, no liver damage in rabbits

AEGL-1 Values: Tellurium Hexafluoride				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
NR	NR	NR	NR	NR

NR =AEGL-1 values are not recommended due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

AEGL-2 Values: Tellurium Hexafluoride				
10-minute	30-minute	1-hour	4-hour	8-hour
0.022 ppm ($0.22 mg/m^3$)	0.022 ppm ($0.22 mg/m^3$)	0.018 ppm ($0.18 mg/m^3$)	0.011 ppm ($0.11 mg/m^3$)	0.0057 ppm ($0.056 mg/m^3$)

Endpoint: 3-fold reduction of AEGL-3 values

Reference: Kimmerle, 1960. [Comparative studies on the inhalation toxicity of sulfur-selenium-, and tellurium –hexafluoride]. Arch. Toxikol. 18: 140-144.

Justified based on the steep exposure response curve:

<u>Rabbit, guinea pig, rat, and mouse 4-hr exposure</u>

1 ppm: Respiratory dysfunction, pulmonary edema

5, 10, 25, 50, 100 ppm: 100% mortality

<u>Rabbit, guinea pig, rat, and mouse 1-hr exposure</u>

1 ppm: Increased hyperpnea in all animals

5 ppm: Severe damage to respiratory organs in all animals, very slow recovery, 100% mortality in mice (death between 24 and 36 hours)

AEGL-3 Values: Tellurium Hexafluoride				
10-minute	30-minute	1-hour	4-hour	8-hour
0.067 ppm (0.66 mg/m^3)	0.067 ppm (0.66 mg/m^3)	0.053 ppm (0.52 mg/m^3)	0.033 ppm (0.33 mg/m^3)	0.017 ppm (0.17 mg/m^3)

Species: Rabbit (1/group); Guinea pig (1/group); Rats (2/group); Mice (4/group)
Concentration: 1 ppm
Time: 4-hr
Endpoint: Highest concentration causing no mortality
Reference: Kimmerle, 1960. [Comparative studies on the inhalation toxicity of sulfur-selenium-, and tellurium –hexafluoride]. Arch. Toxikol. 18: 140-144.

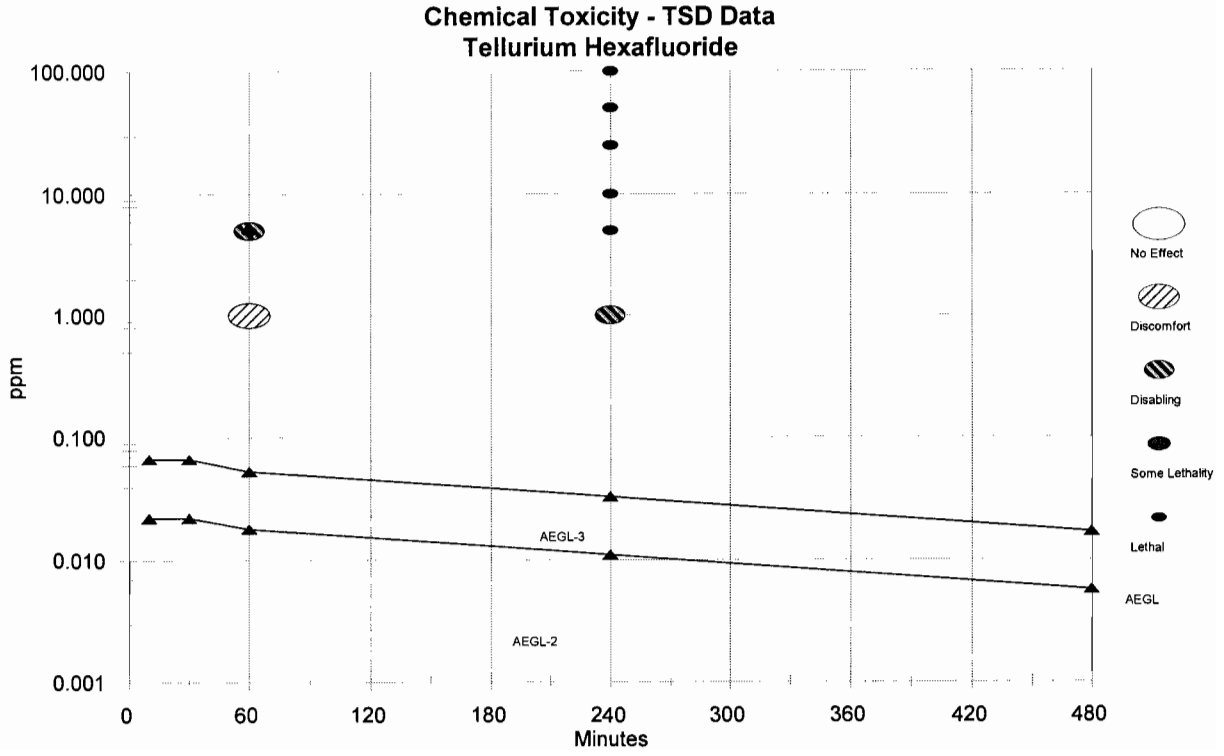
Time Scaling: $C^n \times t = k$, where n=3 for the 30 and 60 min time periods and n = 1 for the 8-hr time period. The 30-min AEGL-3 value was adopted as the 10-min AEGL-3 value.

Uncertainty Factors:
Interspecies = 1
Highly irritating and corrosive. Much of the toxicity is likely caused by a direct chemical effect on the tissues: this type of port-of-entry effects is not expected to vary greatly between species. Limited data suggest that the rabbit, guinea pig, rat, and mouse are similarly sensitive to the acute effects of tellurium hexafluoride.

Intraspecies = 3
Highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly among individuals. The steep concentration-response curve implies limited intra-individual variability.

Modifying Factor = 10
Account for sparse database and potential effects of tellurium

Tellurium Hexafluoride					
Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.022 ppm	0.022 ppm	0.018 ppm	0.011 ppm	0.0057 ppm
AEGL-3	0.067 ppm	0.067 ppm	0.053 ppm	0.033 ppm	0.017 ppm
Selenium hexafluoride					
AEGL-1	0.067 ppm	0.067 ppm	0.053 ppm	0.033 ppm	0.017 ppm
AEGL-2	0.11 ppm	0.11 ppm	0.087 ppm	0.057 pm	0.028 ppm
AEGL-3	0.33 ppm	0.33 ppm	0.26 ppm	0.17 ppm	0.083 ppm
PEL-TWA (OSHA)					0.02 ppm
IDLH (NIOSH)		1 ppm			
REL-TWA (NIOSH)					0.02 ppm
TLV-TWA (ACGIH)					0.02 ppm
MAC- (The Netherlands)					0.02 ppm


Chemical Toxicity - TSD Data
Tellurium Hexafluoride
100.000
10.000
1.000
0.100
0.010
0.001
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
No Effect
Discomfort
Disabling
Some Lethality
Lethal
AEGL

energy API

Gasoline: Composition and Toxicology

Russell White
American Petroleum Institute
April 15, 2009

Outline of Talk

Gasoline Composition

- Past
  - 1990 Industry Average Gasoline (per Clean Air Act)
  - Oxygenates and RBOB
- Present
  - 10% Ethanol In Gasoline (E10)
- Future
  - 2007 Energy Act

Outline of Talk

Gasoline Toxicology

- Past
  - 1978 Toxic Substances Control Act (TSCA)
  - API Testing Programs
- Present
  - Clean Air Act Section 211(b) Requirements
  - High Production Volume (HPV) Challenge
- Future
  - EPA Programs

- Exposure Data Summary

Gasoline Composition

Automotive Gasoline = Unleaded

Aviation Gasoline = Very Different Hydrocarbon Composition + Lead

1990 Industry Average Automotive Gasoline

40 CFR 79.55(b)	**Specifications**
Reid Vapor Pressure	8.7±0.3 psi
Benzene Content, Vol%	1.53±0.3
Distillation, F	T10 123-133F T90 325-335F
Hydrocarbon Type, Vol%	Aromatics 32±2.7 Olefins 9.2±2.5 Saturates 58.8±2.0
Detergent Additive Package	Several But Non-volatile

Gasoline Composition

- Typical Retail Gasoline Contains 200 – 300 Compounds
- Blended To Meet Regional or State Specifications
- Refinery Blending Streams
  - Straight-run Naphtha (Likely Hydrotreated)
  - Catalytically Cracked Naphtha
  - Alkylation Naphtha
  - Isomerization Naphtha
  - Catalytically Reformed Naphtha

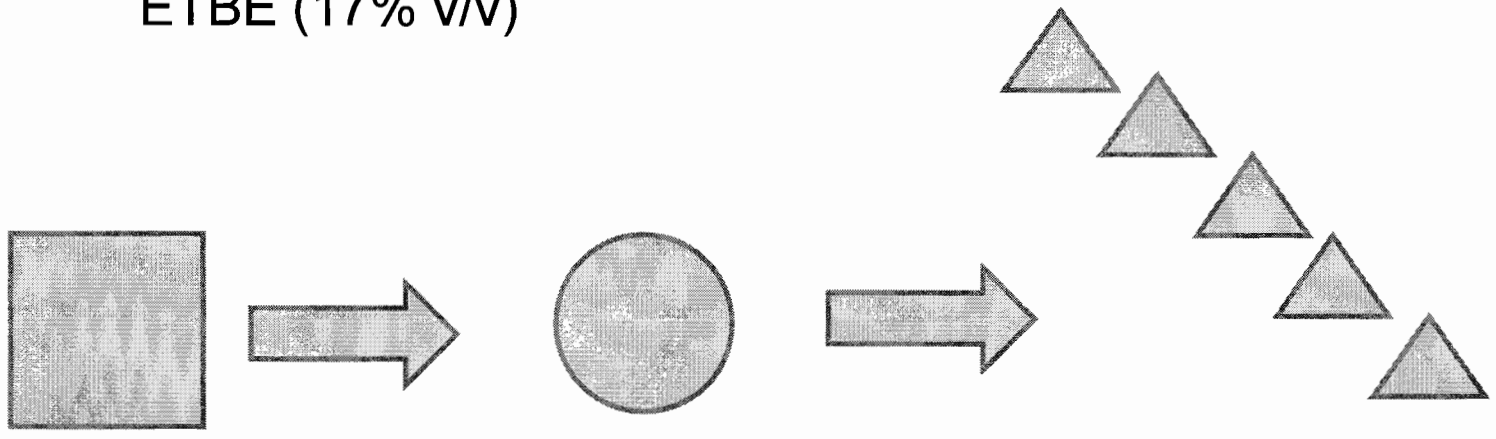
Gasoline Composition

1990 Clean Air Act Required Increased Oxygen Content In Gasoline

Reformulated Blendstock for Oxygenate Blending (RBOB)

Oxygenates

- Ethanol (10% v/v)
- MTBE (15% v/v)
- ETBE (17% v/v)



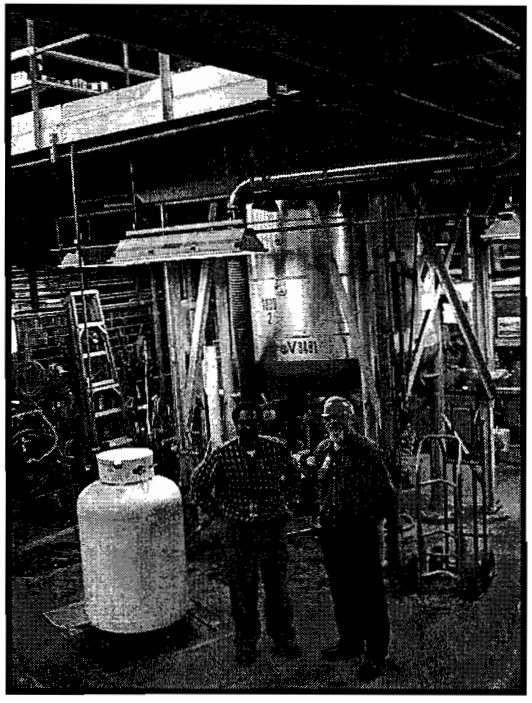
Gasoline Vapor

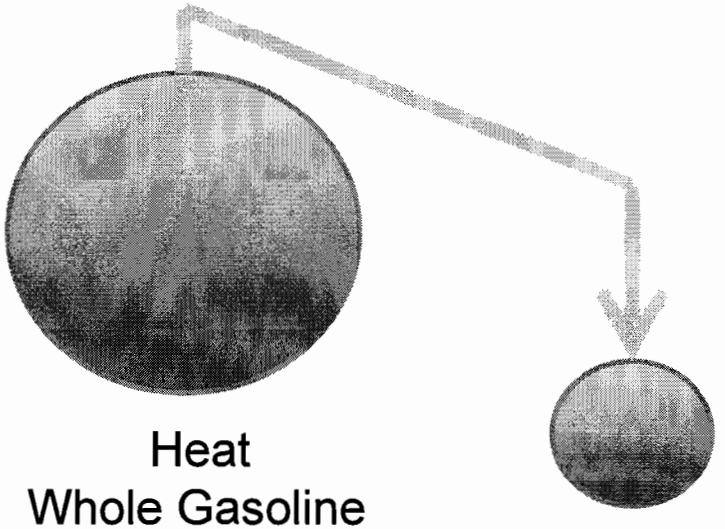
SAMPLE	API 94-02 (liquid)	API 94-02 (vapor)
Carbon Number (Volume %)		
4	5.1	18.9
5	16.8	46.4
6	18.6	23.6
7	19.4	7.8
8	20.7	3.1
9	11.0	0.2
10	5.2	0.0
11	2.1	0.0
12+	1.0	0.0

E10 Vapor

COMPOUNDS % GC Area	Gasoline VC	E10 VC
Isobutane	2.8	2.2
n-butane	13.1	11.6
Isopentane	34.8	34
n-pentane	13.7	10.2
trans-2-pentene	2.6	2.1
2-methylpentane	6.8	5.1
n-hexane	3.1	2.4
Benzene	2.2	1.6
3-methylhexane	1.4	1.2
Isooctane	1.5	1.3
Toluene	3.3	2.4
Ethanol	0.0	13.3

Vapor Condensate Generation





Future Gasoline

More Ethanol!

- Possibly E20
- Increased Use Of E85?
- Cellulosic Ethanol

Gasoline Toxicology

- 1978 Toxic Substances Control Act (TSCA)
  - Gasoline Is A Mixture, Not On TSCA Inventory
  - CAS 86290-81-5

  - API Refinery Streams Program
    - Building Blocks Of Gasoline

  - Acute Battery on Whole Gasoline Liquid
  - Chronic Study On Whole Gasoline Vapor
  - Developmental Study On Whole Gasoline Vapor
  - Dominant-Lethal Study On Whole Gasoline Vapor

Ongoing Gasoline Studies

- CAA Section 211(b) Fuel And Fuel Additive Registration
  - Inhalation Studies
  - Gasoline Vapor Condensate
  - Gasoline + 6 Oxygenates Vapor Condensate

  - 90-Subchronic Study w/Neurotox
  - Immunotoxicity
  - Genotoxicity (Micronucleus and SCE)
  - Developmental Toxicity
  - Reproductive Toxicity
  - Chronic Toxicity (Gasoline and Gasoline w/MTBE)

211b Studies

Rat Studies	Gasoline VC	E10 VC
Subchronic	NOAEL > 10,000 mg/m3	NOAEL > 10,000 mg/m3
Neurotox	Negative	Equivocal
Immunotox	Negative	Positive
Micronucleus	Negative	Negative
Developmental	NOAEL > 20,000 mg/m3	NOAEL > 20,000 mg/m3
Reproductive	NOAEL > 20,000 mg/m3	NOAEL > 20,000 mg/m3
Chronic	In progress	Not Done

High Production Volume (HPV) Challenge Program

- Gasoline Blending Streams Category
  http://www.petroleumhpv.org/index.html

- Screening Information Data Set (SIDS) +
  - Physical Chemical Data
  - Environmental Fate Data
  - Environmental Toxicity Data
  - Mammalian Toxicity Data
    - Acute
    - Repeat Dose
    - Developmental
    - Reproduction
    - In vitro and In vivo Gentox

Future Toxicity Data

- CAA Section 221(b) Requirements
  - Tier 1 – Literature Search And Exhaust Testing
  - Tier 2 – Testing Of Vapor Condensates
  - Tier 3 - No Rulemaking Yet

- HPV Risk-based Prioritization By EPA
  - 2200 HPV Chemicals To Be Reviewed And Prioritized By 2012
  - Follow-up Testing Or Exposure Studies

Gasoline Exposure

Type of Exposure or Study	PPM of Total Hydrocarbon Vapor	Health Effects
Typical gas station perimeter (4 hour average)	0.26	None Expected
Self service fill-up (2 minutes)	10 - 100	None Expected
Refueling attendants (15 minutes)	0.5 - 48	None Expected
(6 hours)	0.1 - 31	None Expected
Mechanics (15 minutes)	0.4 - 138	None Expected
(6 hours)	0.1 - 17	None Expected

Gasoline Exposure

Type of Exposure or Study	PPM of Total Hydrocarbon Vapor	Health Effects
Human volunteers exposed to gasoline		
(30 minutes)	200	Slight eye irritation
	500	Eye irritation
	1000	Eye irritation
CDC Medical Management Guidelines		
for gasoline	>200	Eye irritation
Medical Literature for gasoline exposure		
(8 hours)	160 - 270	Eye irritation
(1 hour)	500 - 900	Eye and throat irritation, dizziness.
(1 hour)	2000	Mild anesthesia

Gasoline Exposure

Summary of gasoline exposure data from literature and in-house sources. CONCAWE Report 97/52

http://www.concawe.be

Thank You

Any Questions?

AEGL -Phosgene

Jürgen Pauluhn
Washington D.C., April 15, 2009

Bayer HealthCare
Bayer Schering Pharma

Outline

1. Phosgene toxicology: past, presence, and future
2. Animal models and wealth of data
3. Rodents vs. non-rodents and relevance to humans
4. $C^n \times t = const.$
5. Consistency with subchronic data (Kodavanti et al., 1997)
6. Derivation of acute reference concentrations based on new data

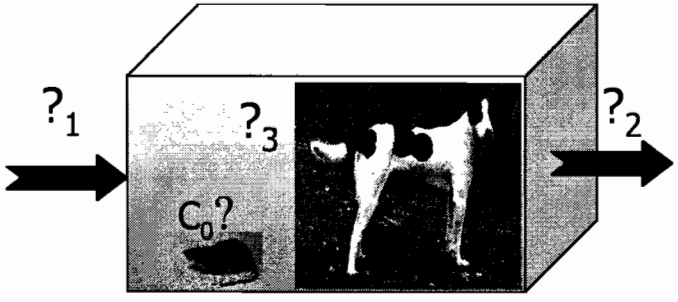
Past, Presence, Future

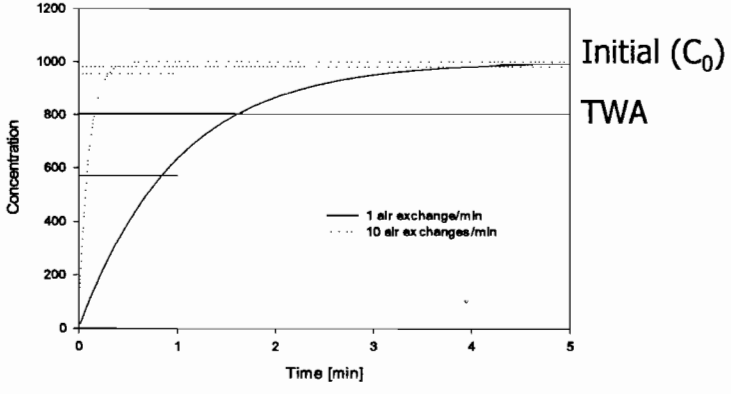
- Past → Presence
  - Impurities of phosgene due to impurities from chlorine production (e.g. HCl)
  - Many processes changed from liquid-phase to gas-phase
  - On demand consumption, no storage, de-emphasis on transportation
  - Specific analytical methods and reference standards available
- Presence → Future
  - Residue-/by-product-free intermediate not dependent on fossil fuels and solvents. The demand of phosgene will increase in the future.

Past Inhalation Toxicology Studies: How to put into Perspective?

$$C_t = C_0\left(1 - e^{-\frac{F}{V}t}\right)$$

$$t_{95}\ (\text{min}) = 3\times\left(\frac{\textit{chamber volume}}{\textit{chamber airflow}}\right) = \frac{3\times 1}{10\,to\,1} = 0.3 - 3\,\text{min}$$





?1: Generation

- Dissolution and evaporation
- Dispersion in solvents (@-40°C)
- Evaporation of neat phosgene

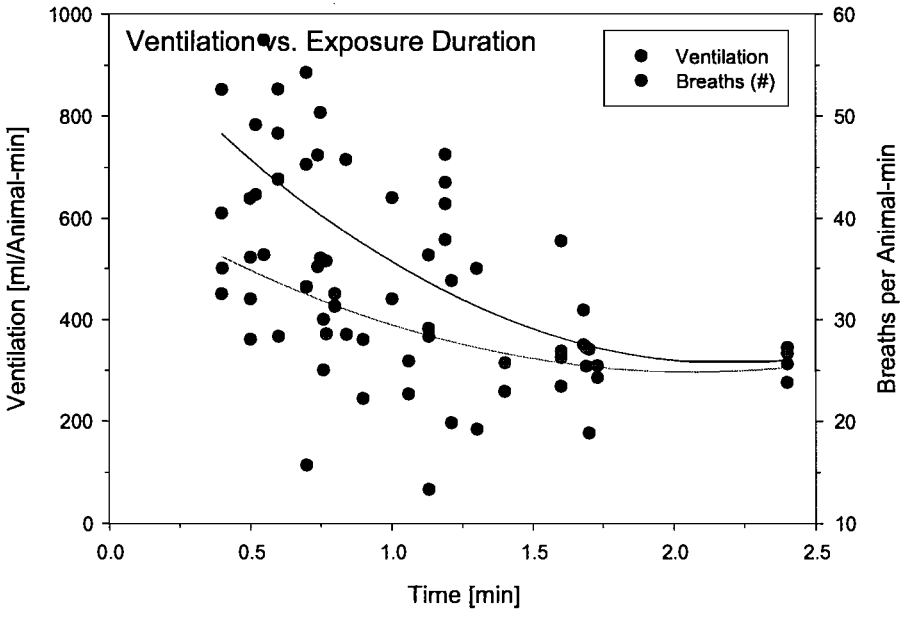
?2: Characterization

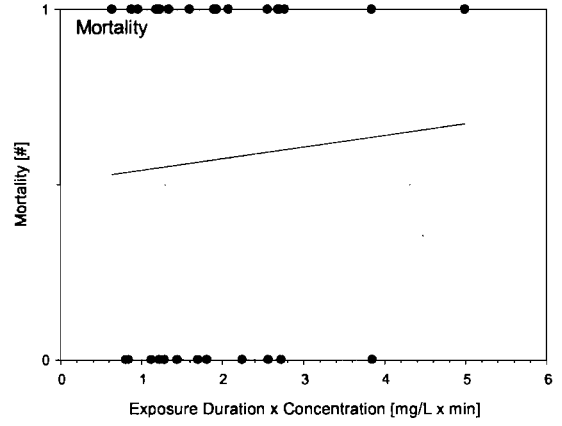
- Time-Weighted-Average (no profile)
- Trapping agent (aqueous/alcohol mixtures)
- Analyte: Cl^- not intact phosgene

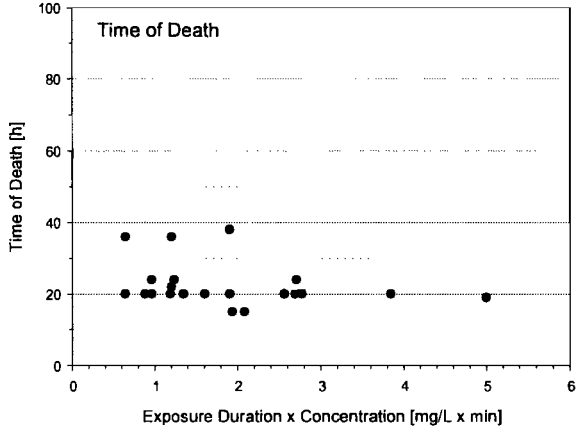
?3: Exposure (chambers/specialized)

- Breathing zone concentrations?
- Non-homogeneity of atmospheres (δ=3.5)
- when t_{95} is not attained then TWA#C_0
- Instable breathing patterns
- Masks/nostril tubes/intubation (larger species)

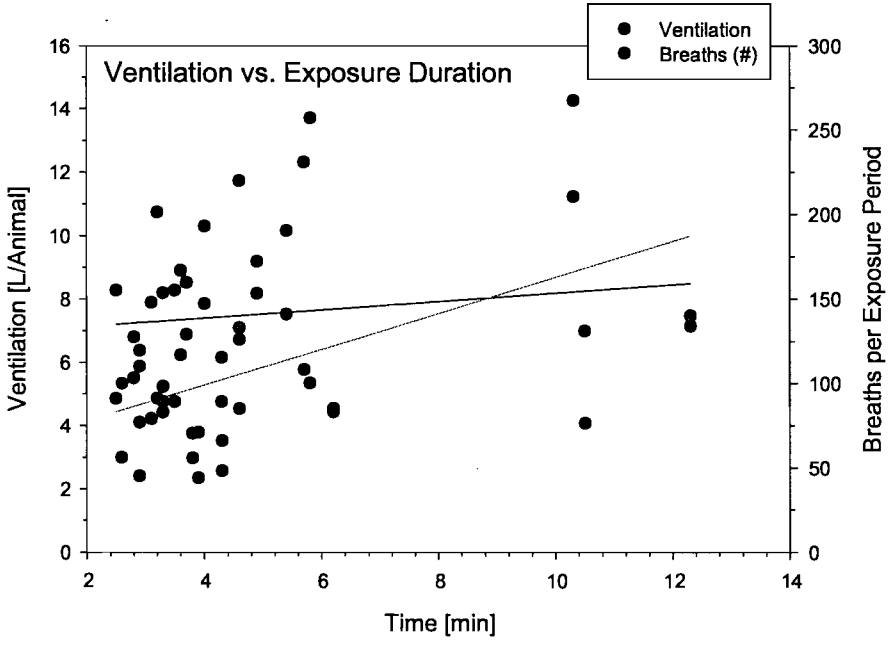
Macaca Mulatta (≈1944)

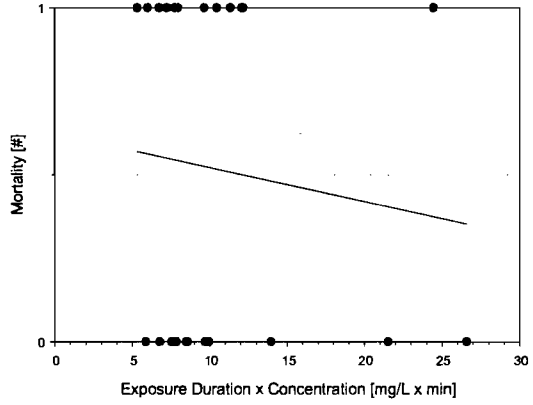


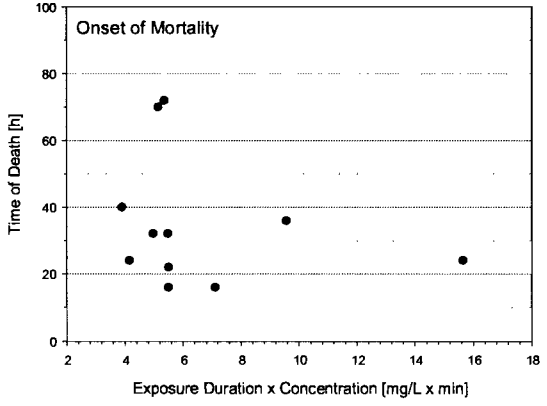




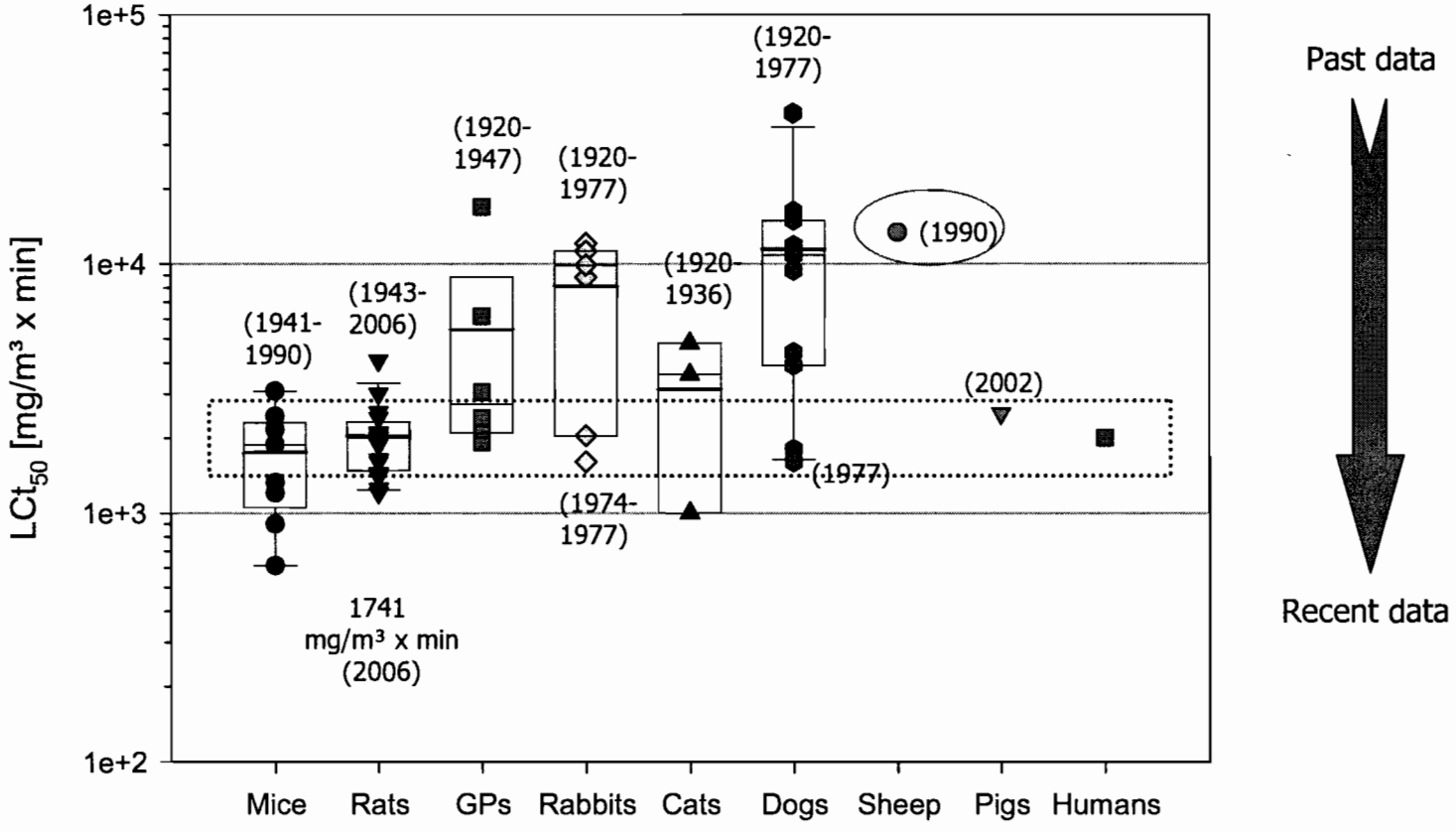
Mongrel-Dog (≈1944)







Critical Comparison of past LCt_{50} - Data



Studies with exposures <10 min excluded

Past Human Evidence

- Phosgene of the past (<1980) differs from ‚modern' phosgene.
- Current situation:
  - Clean chlorine (no HCl)
  - Gas-phase reactions generally preferred (no hydrolysis), no liquid spills
  - On-site production & use (no transport or storage)
  - Double-wall technology with sensing technologies in the void space flushed with N_2 („the global phosgene handbook")

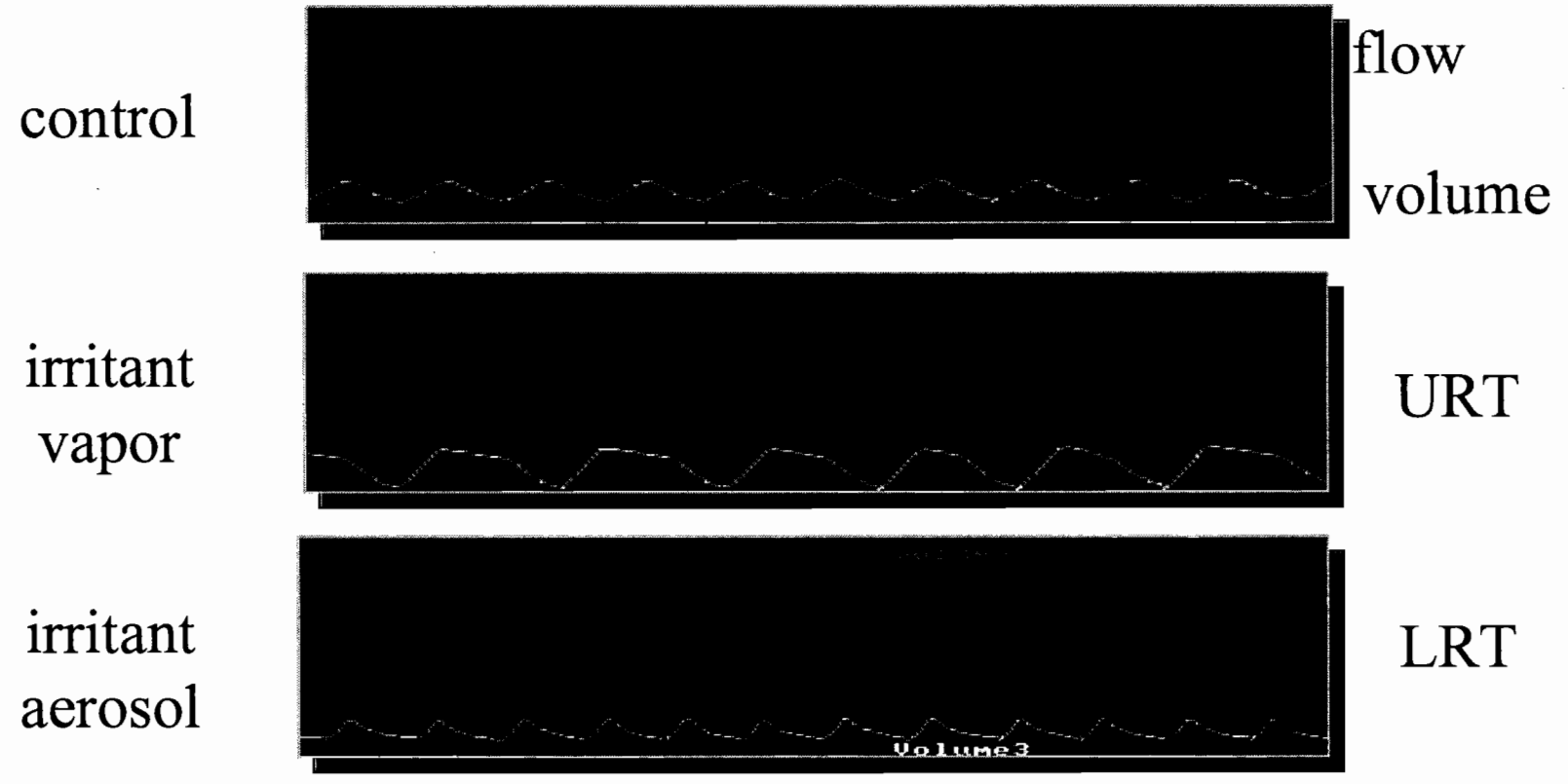
Focus of New Studies

- Nose-only exposure of rats and dogs
- Principal mechanism of toxicity and role of HCl (*acylation vs. hydrolysis*)
- Purpose-driven design of studies to verify / refute inhalation studies of the past
- Focus on lethal and non-lethal endpoints
- Focus on most sensitive endpoints which are indicative of pulmonary fluid imbalance
- Long-term sequelae of high-level, short-term exposures

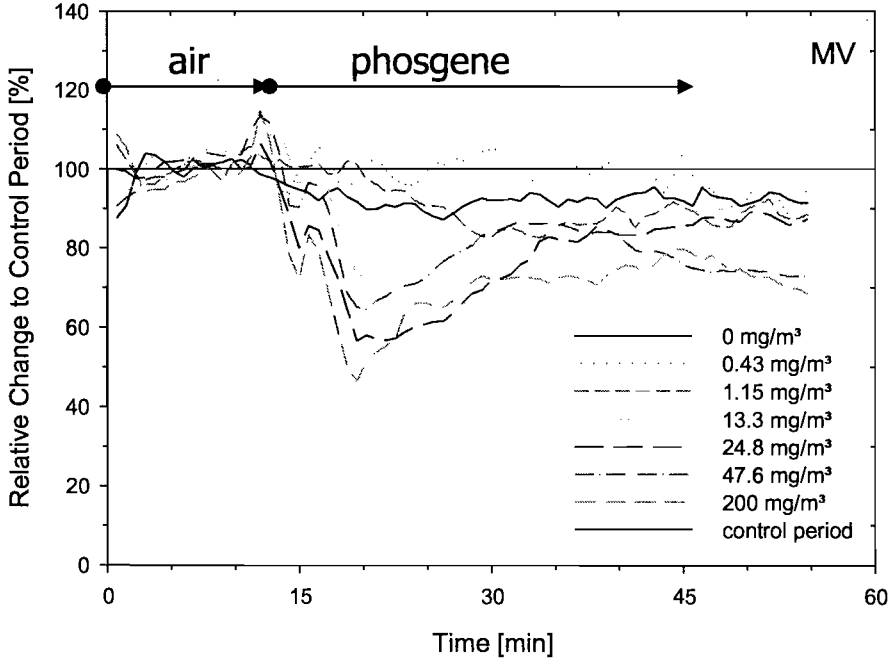
Why Non-Rodents (Dogs)?

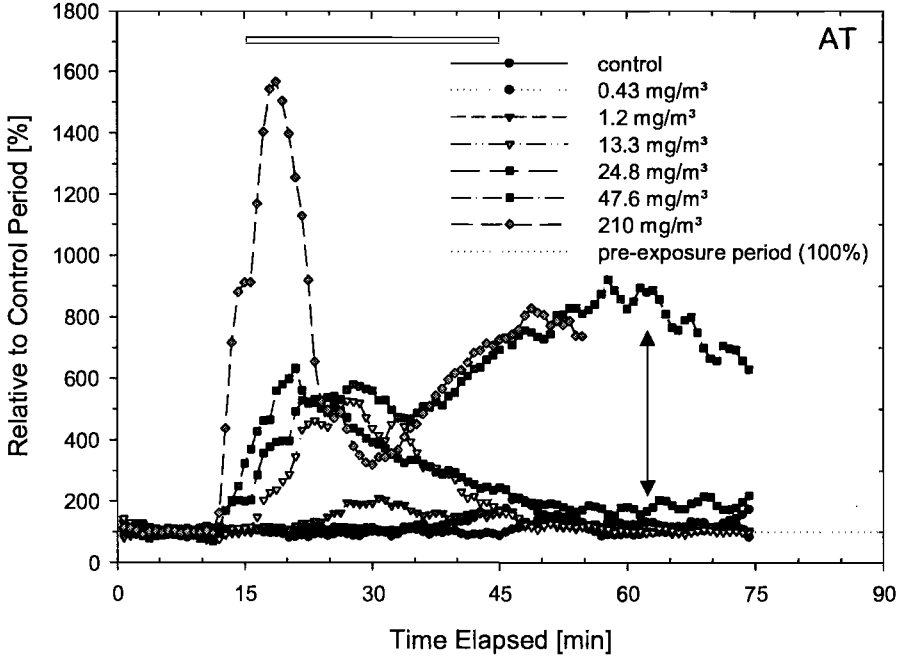
- Species of choice for inhalation pharmaceuticals (validated technology, enormous data base, high human relevance).
- Oronasal breathing pattern and physiology more similar to humans.
- Lung morphology and innervation more similar to humans, e.g. respiratory bronchioli, relative abundance of mucus goblet cells, less pronounced reflex-mediated mucosal defense.
- Arterial blood easier to collect (compared to rats).

Vagal Stimulation by Phosgene: *Kretschmar vs. Paintal Reflex*



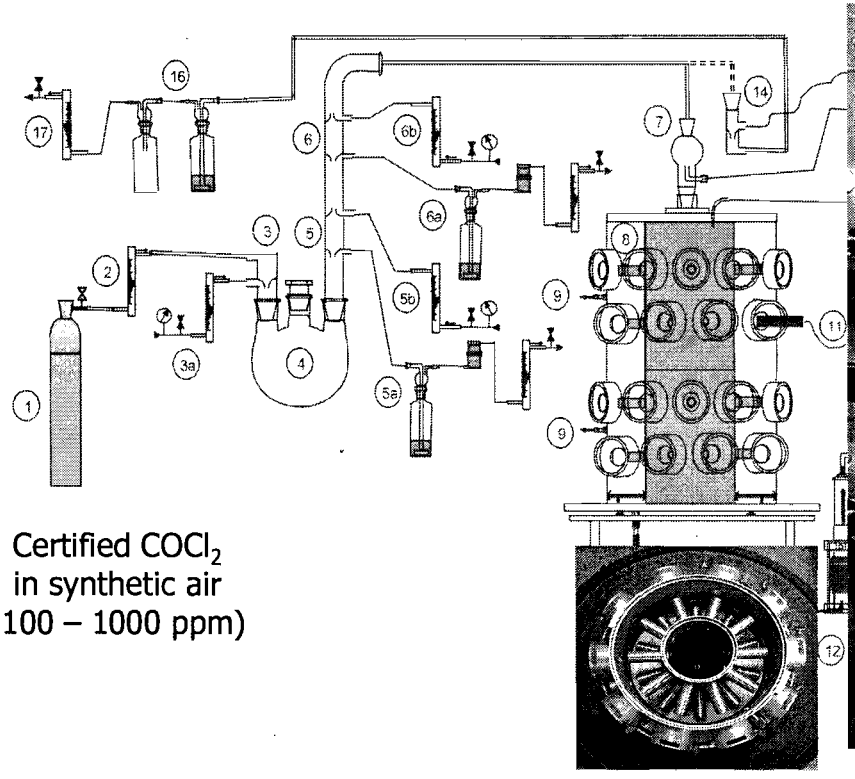
Analysis of Respiratory Reflexes in Phosgene-exposed Rats



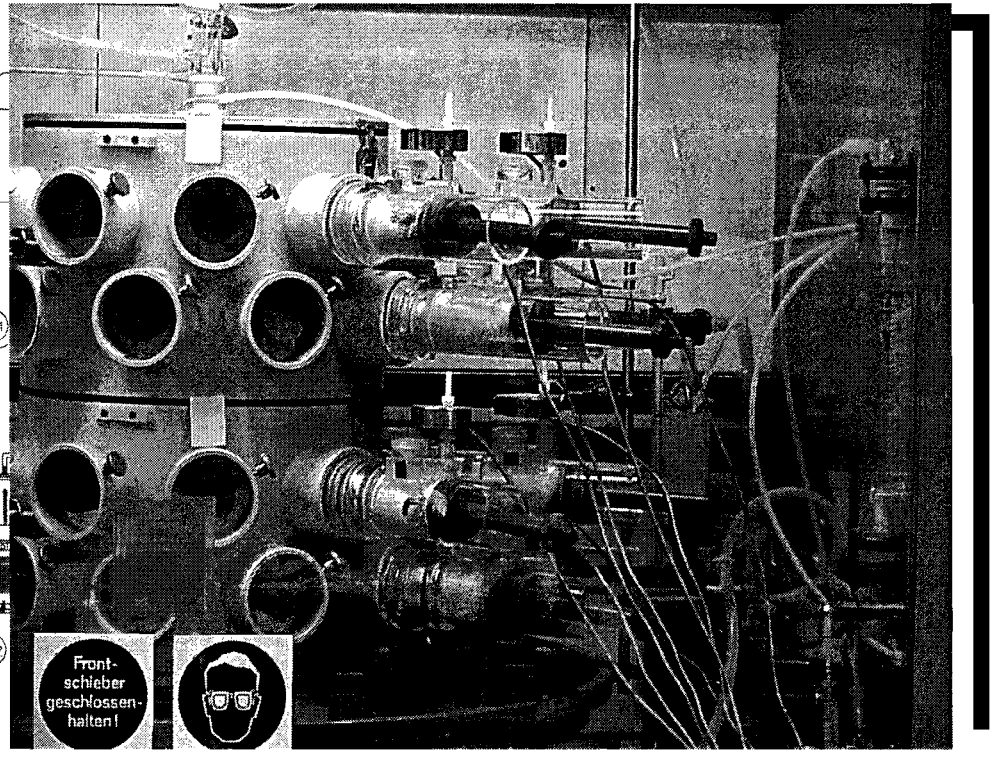


- Changes in respiratory patterns indicative of lower respiratory tract irritation
- Exposure shorter than 15-min may produce false negative data
- Cxt extrapolations from t_{long} to t_{short} are most conservative

Directed-flow Nose only Exposure of Rats (Phosgene)



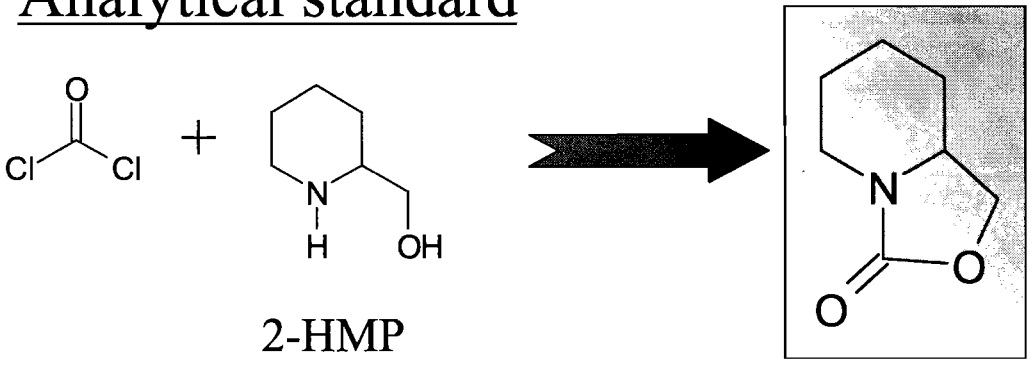
Certified $COCl_2$
in synthetic air
(100 – 1000 ppm)



Nominal Concentration = Actual Concentration (3 different methods)

Determination of Phosgene in Exposure Atmospheres

Analytical standard



2-HMP

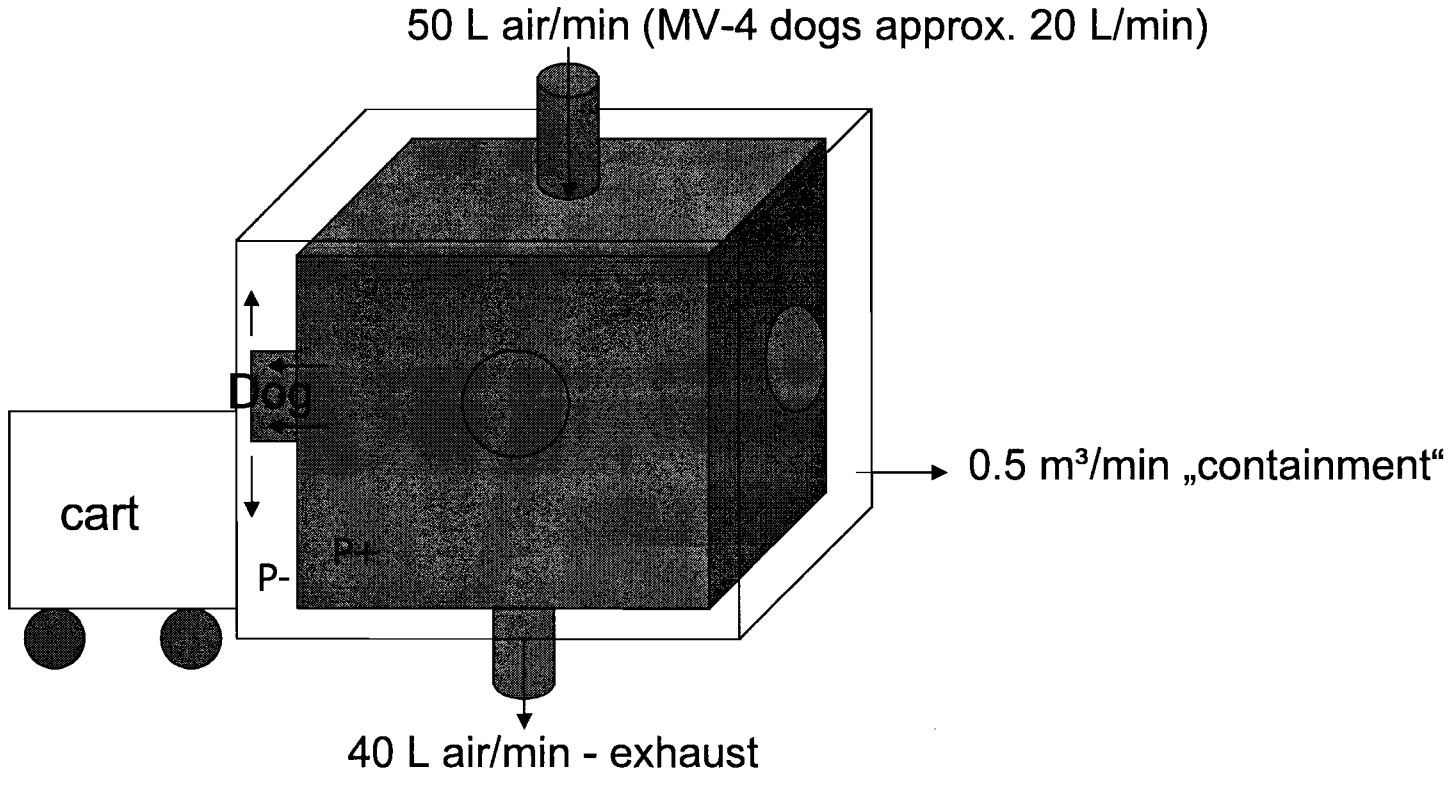
stable derivative as final analyte

Analytical Methods:

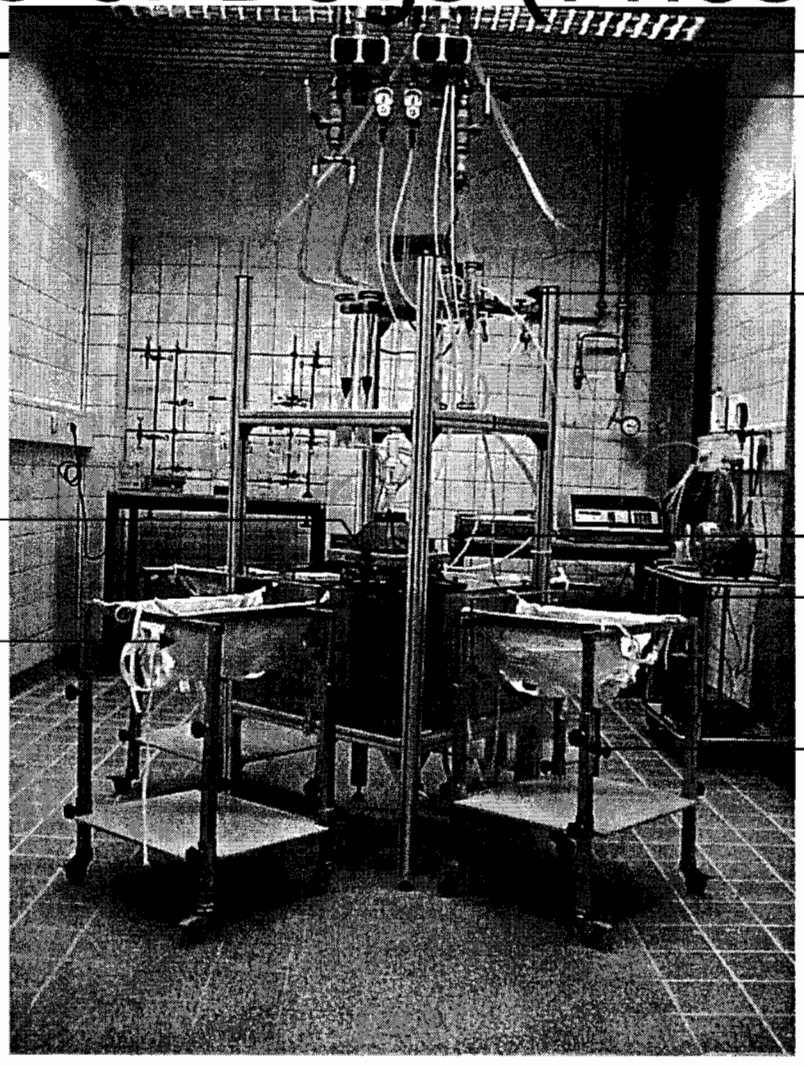
- Nominal concentrations
- 2-HMP - GC
- Binos real-time monitoring
- Paper tape real-time

Despite different principles, all methods delivered the same outcome

Directed-flow Nose only Exposure of Dogs (Phosgene)



Directed-flow Nose only Exposure of Dogs (Phosgene)



Room ventilation - top

Electricity / pressurized air / vacuum

Mixing of pressurized air / dilution air / phosgene gas

Exposure characterization

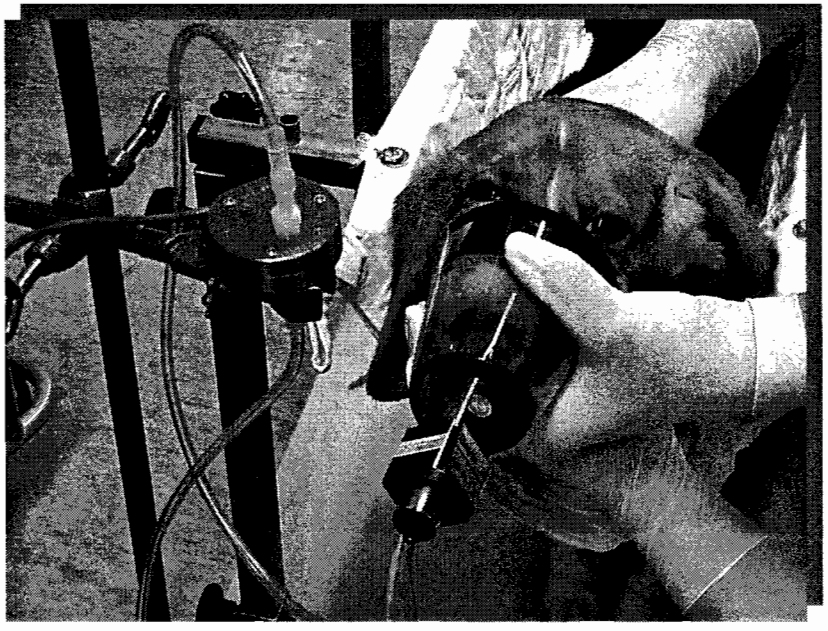
Chamber in scaffold

Animal endpoints

Room ventilation - floor

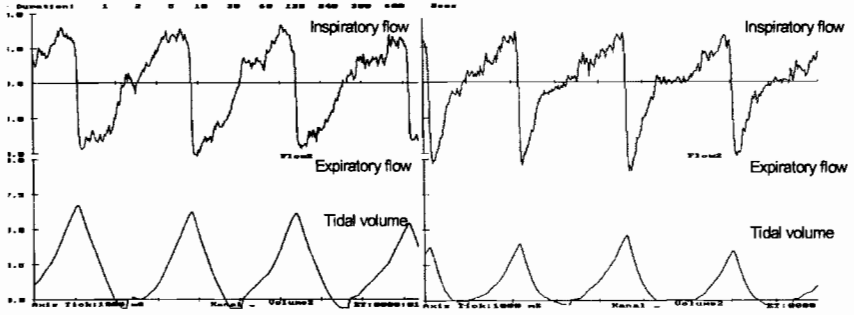
Cart for individual dogs in slings

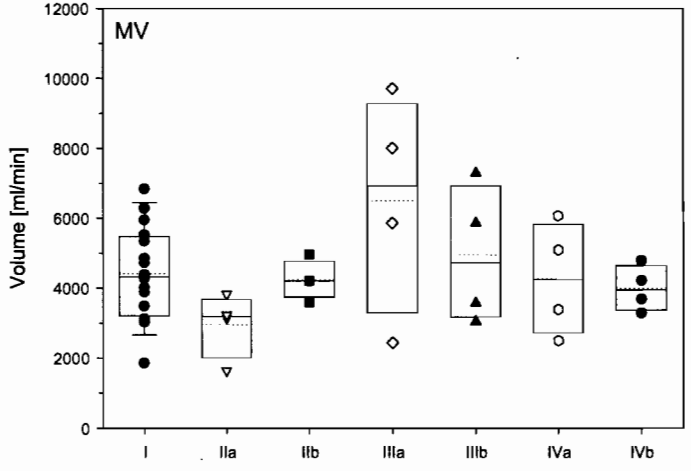
Beagle Dogs (Lung Function)



Lung Function Measurements

Prior to exposure: **After exposure:**



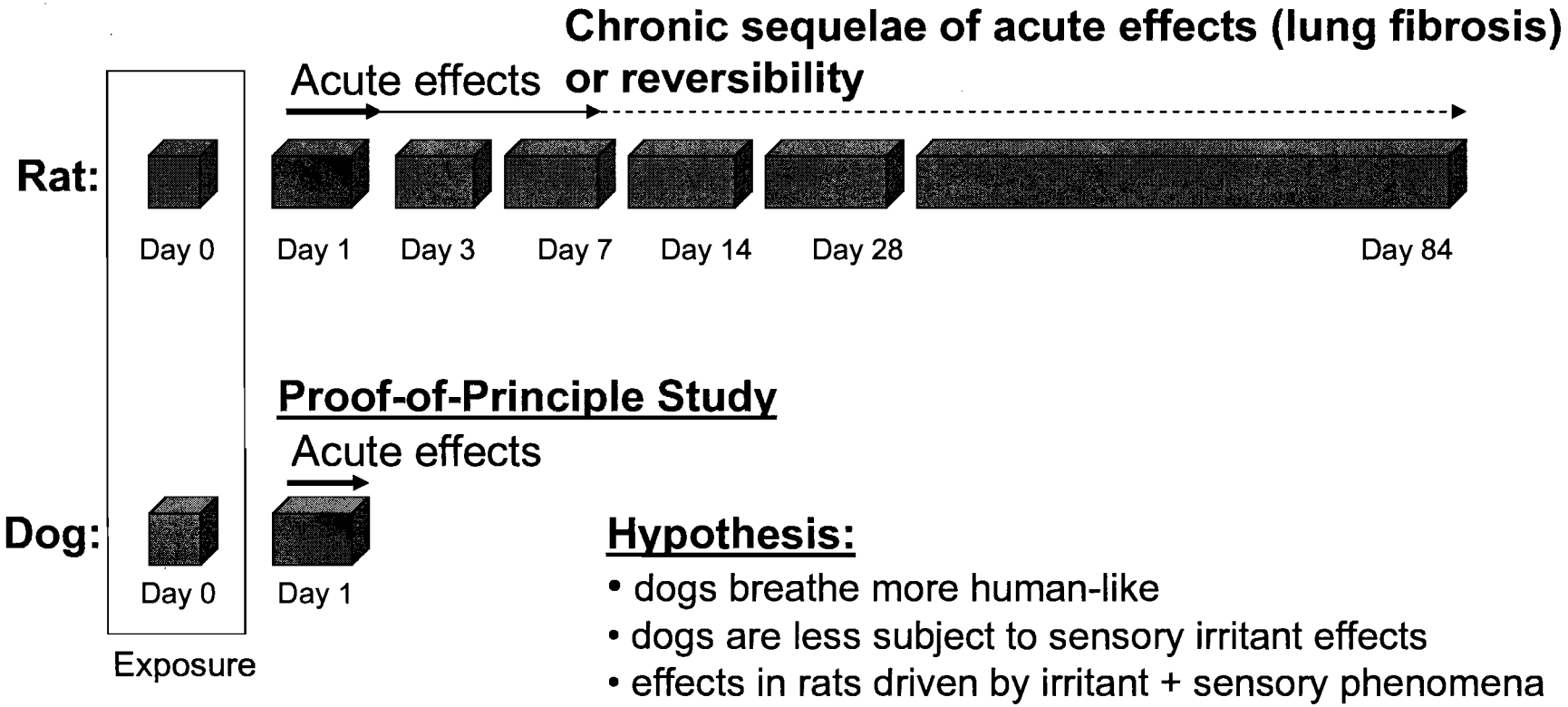


Summary I

- Instant change in breathing reflexes in rats, although transient in nature.
- Ventilation becomes stable after approx. 15 min exposure duration.
- No evidence of bradypneic periods (trigeminal stimulation in the upper airways).
- Dogs did not show marked changes in reflexes.

Non-Lethal Toxic Potency – Study Design

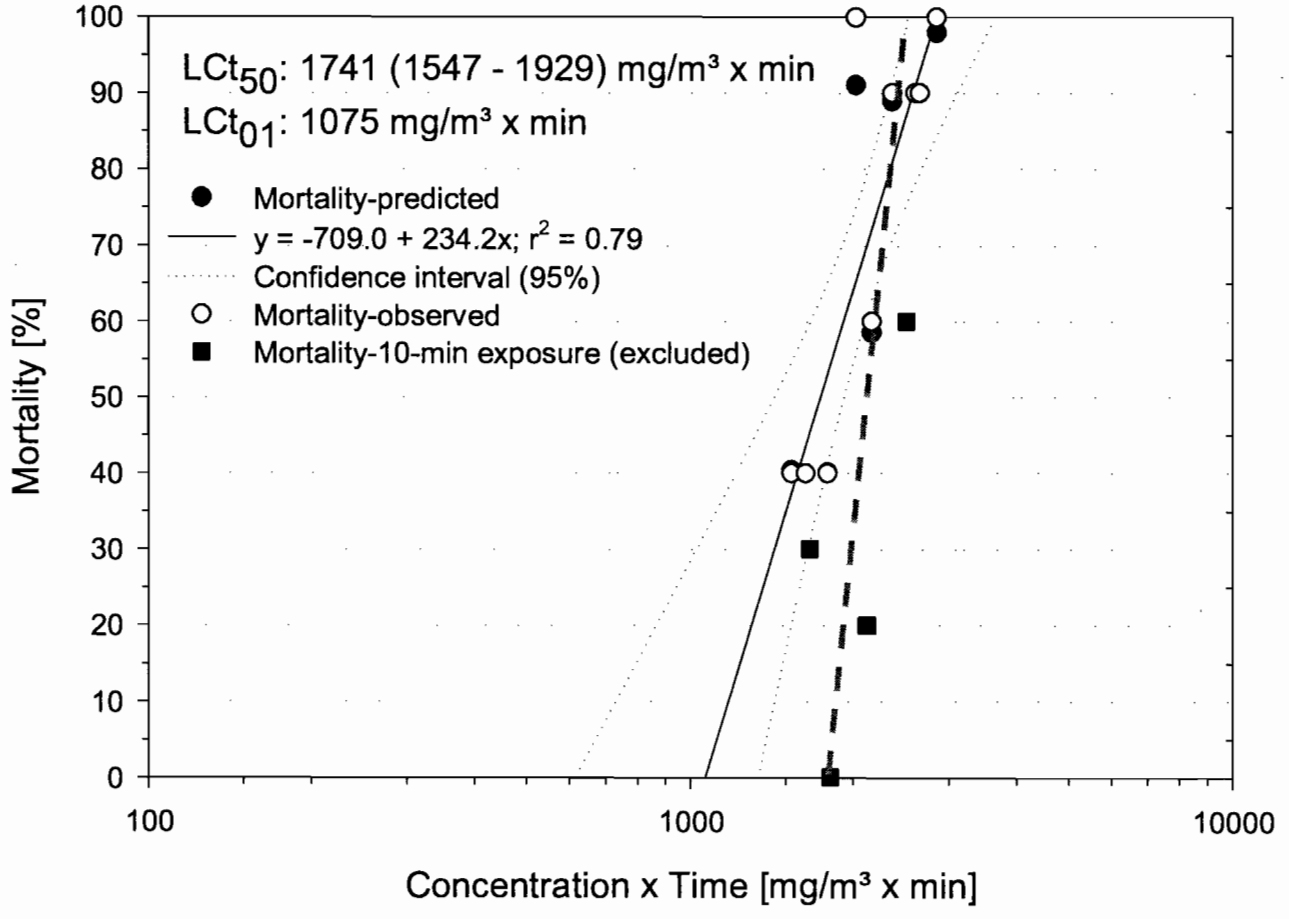
Dose-Time-Response Study



Hypothesis:

- dogs breathe more human-like
- dogs are less subject to sensory irritant effects
- effects in rats driven by irritant + sensory phenomena

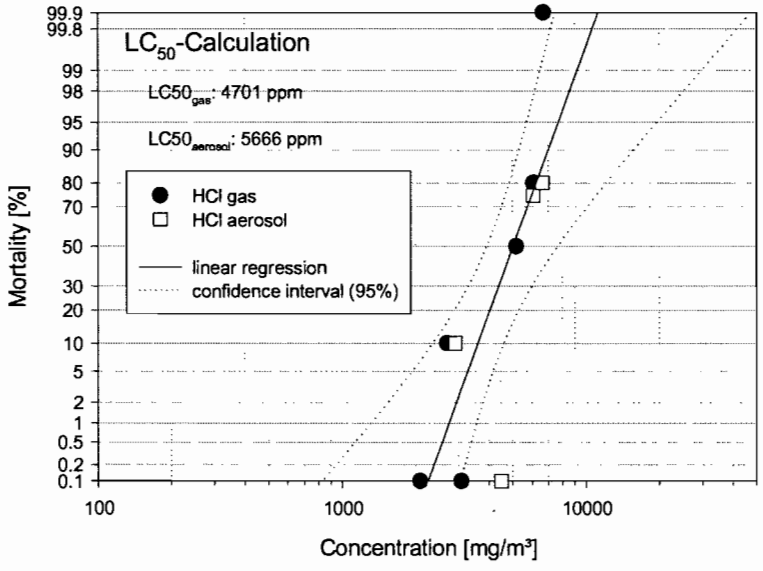
Acute Lethal Toxic Potency of Phosgene in Rats

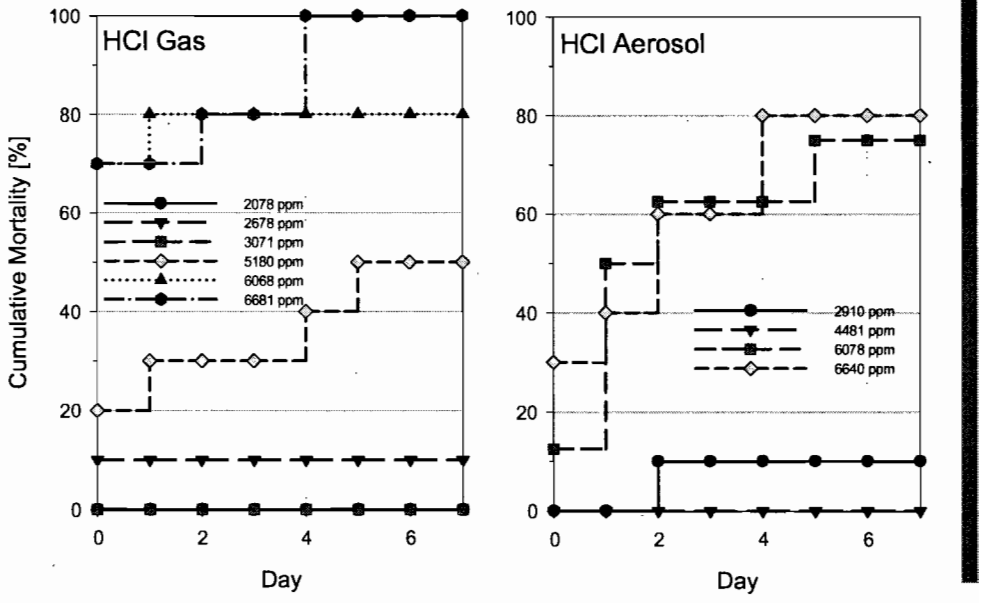


Onset of mortality <24 hr postexposure

Hydrogen Chloride Vapor/Aerosol (*1 x 30-min Exposure of Rats*)

Data duplicated from Darmer et al., 1974

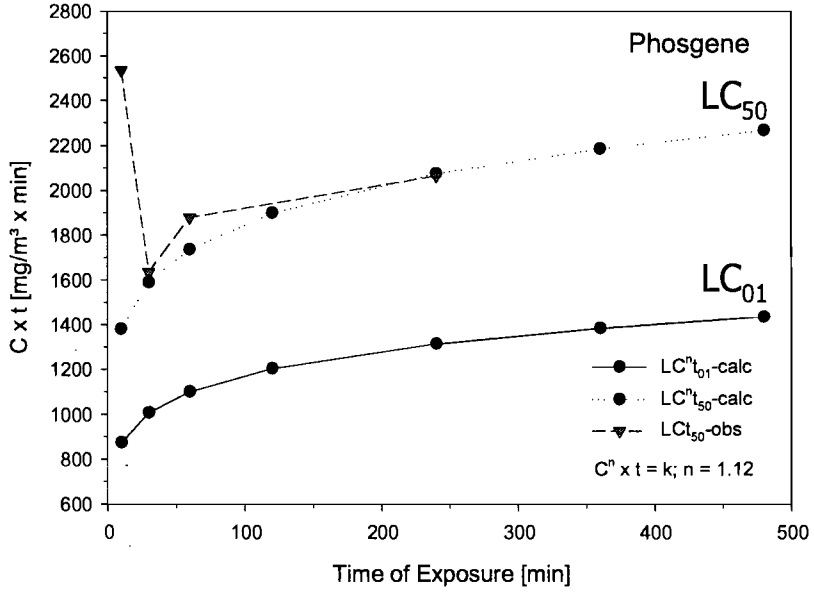


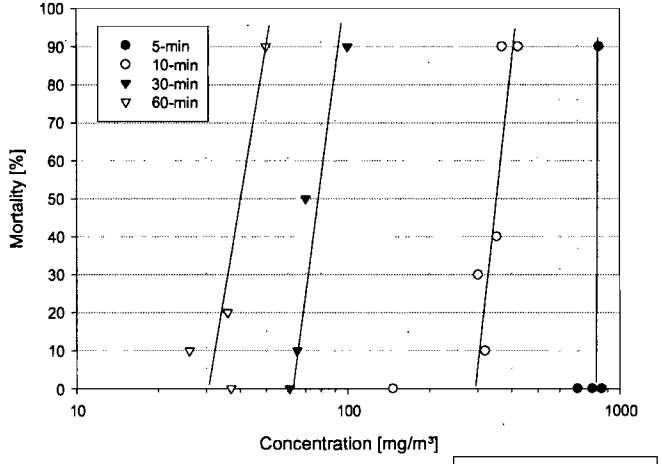


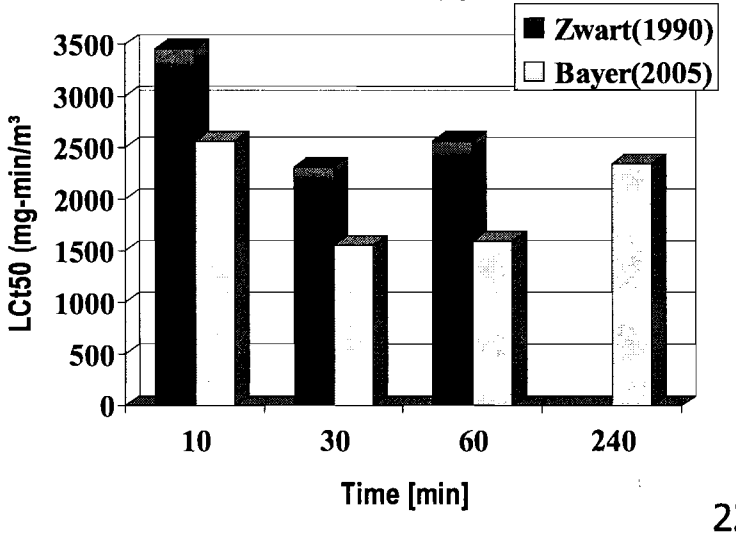
Delayed-onset effects typical for HCl but not Phosgene

Cxt Relationships of Phosgene and HCl are markedly different

$$Y_{\mathrm{Pr}obit} = b_0 + b_1 \log(C) + b_2 \log(t);\ n = b_1 / b_2$$



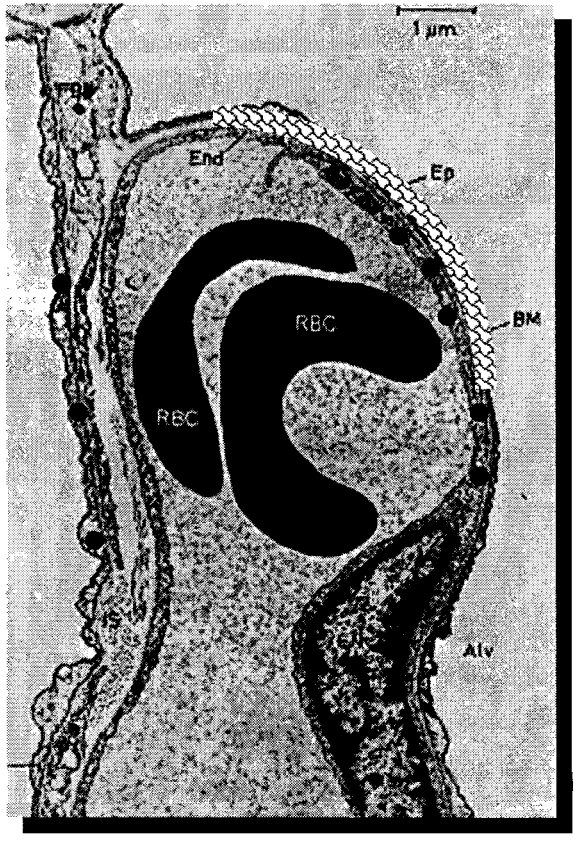


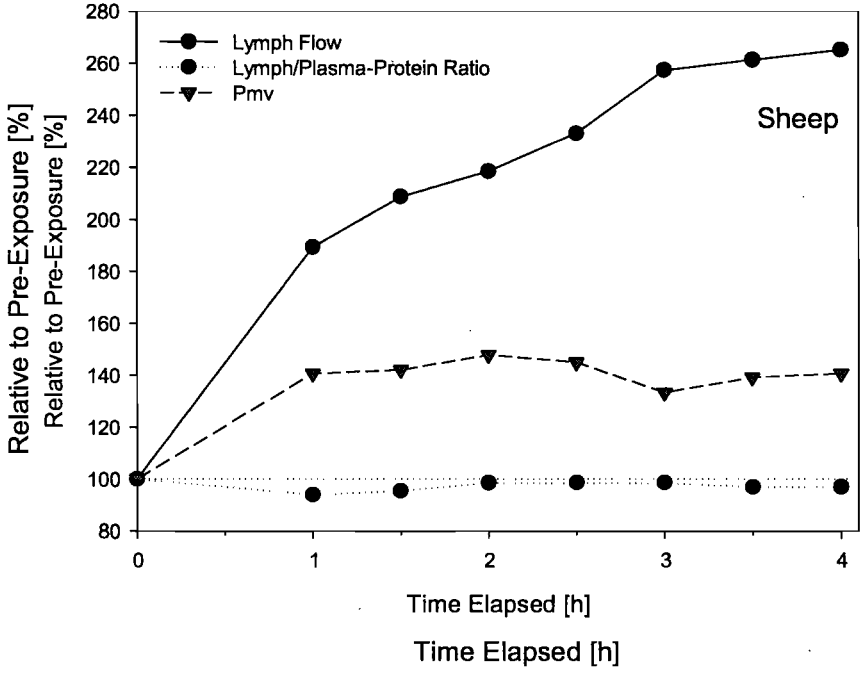


Summary II

- HCl does not appear to play any modulatory role in acute toxicity.
- Short-term exposures should preferentially rely on exposure periods ≥30 min.
- Toxicity is determined by the retention of gas in the pulmonary region.
- Measurements in bronchoalveolar lavage are most sensitive to detect damage.
- Dose-response curves very steep, i.e., a highly controlled exposure technology with short t_{95} is required.

Time-Course of Edema Formation

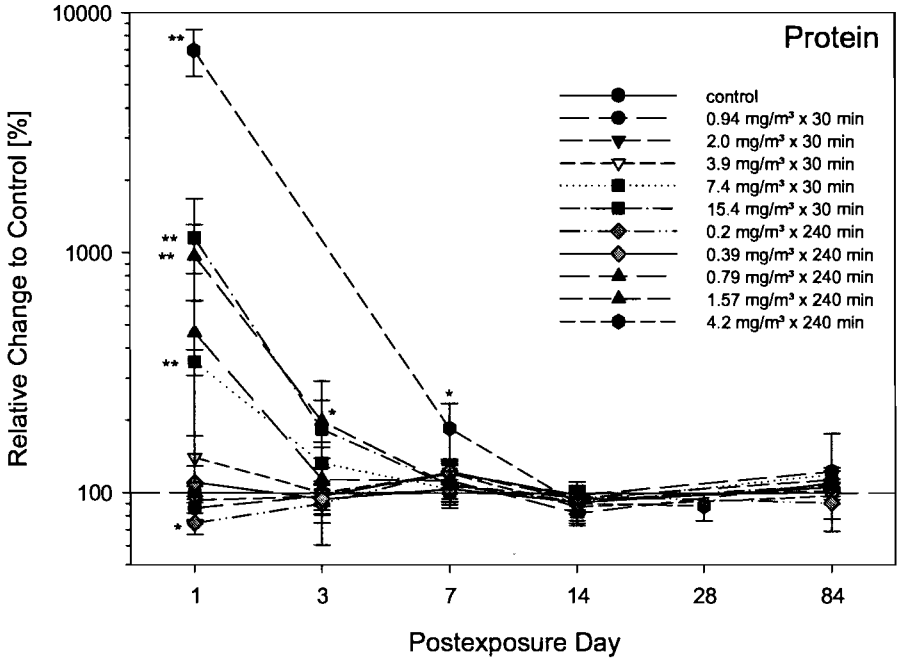


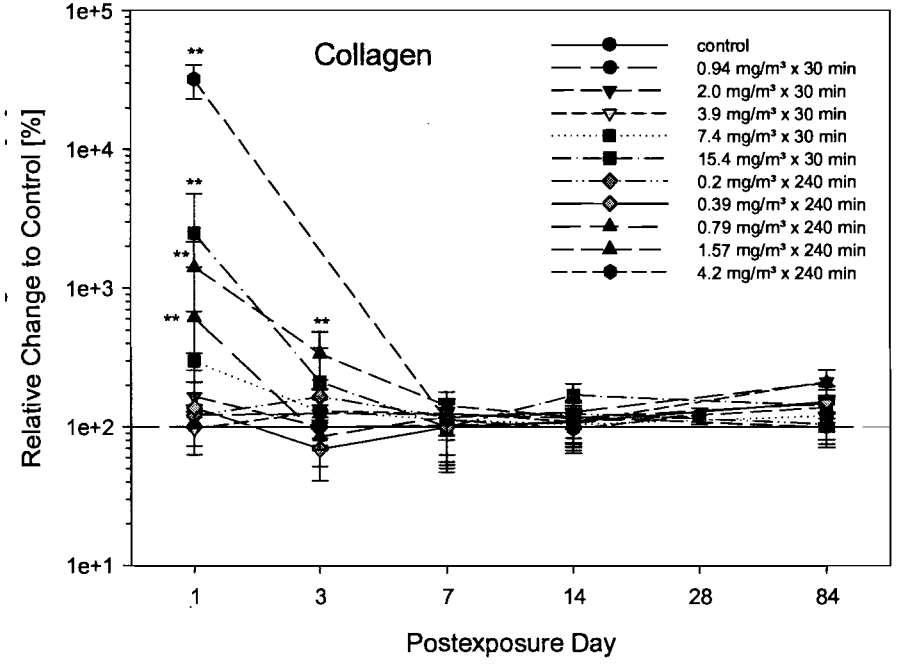


Exposure intensity: approx. 2443 mg/m³ x min (expos. 10 min)
data from Brown et al. (2002), Keeler (1990).

Phosgene: Time-Course Studies do not show Evidence of Chronicity

Sircol Assay for Soluble Collagen





Measurements in bronchoalveolar lavage fluid (rats)

Histopathology – 3 Months Postexposure

Histopathology findings of rats exposed nose-only to phosgene. Animals were sacrificed at end of the 4 or 12 week postexposure period. With the exception of the 4.2 mg/m³ x 240 min group (postexposure period 4 weeks) all rats were sacrificed on postexposure day 84.

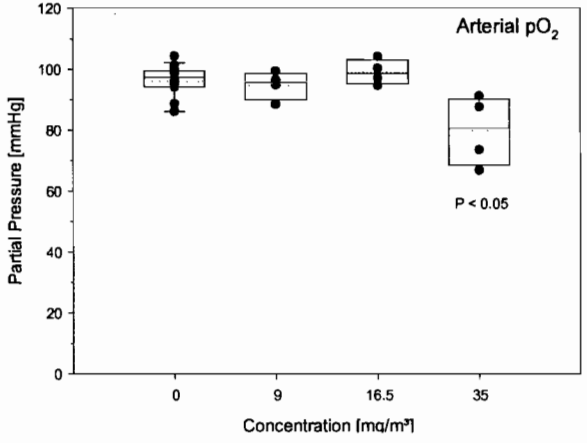
Parameter	Exposure: 1 x 30 minutes						Exposure: 1 x 240 minutes				
	Concentration [mg phosgene/m³]										
	0	1	2	4	8	16	0.2	0.4	0.8	1.6	4.2
Focal inflammatory infiltrations	2/6	1/6	1/6	1/6	2/6	2/6	1/6	1/6	1/6	1/6	0/6
Focal septal thickening	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/6	0/6	1/6
Septal fibrosis	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/6	0/6	0/6
Pleural fibrosis	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/6	1/6	0/6	0/6
Hypercellularity/term. bronchi	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	5/6

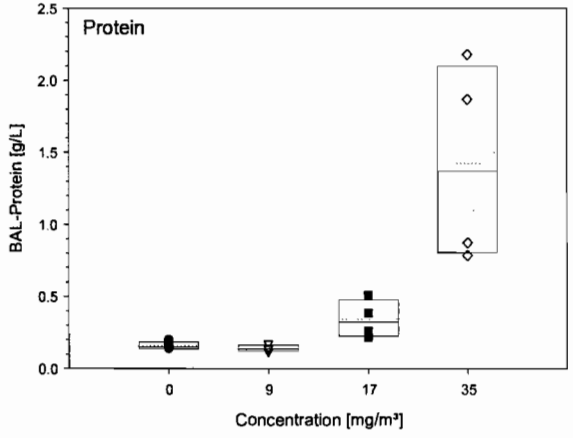
Grading: all findings were scored at the lowest grade 1, i.e. minimal (1 of 5 rats of the 4.2 x 240 mg/m³ x min showed a grade 2 hypercellularity of the terminal bronchioles), #/#: number of animals with findings/ number of animals examined.

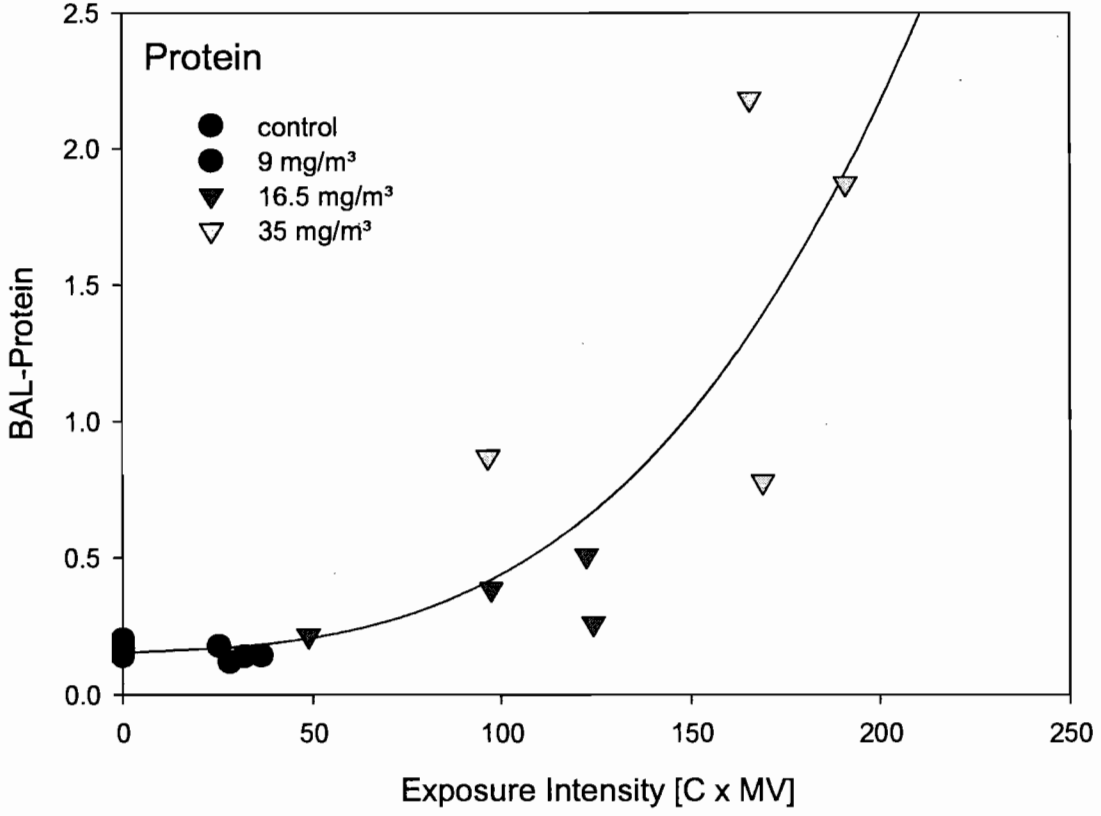
Summary III

- **Cxt-products of 1008 mg/m³ x min caused a BAL-protein elevation ~70-times the control.**
- This LCt_{01} dose was tolerated without mortality.
- No evidence of fibrosis or other long lasting, potentially irreversible effects at concentrations cytotoxic to alveolar cells.

Non-Lethal Toxic Potency – Acute Dog Inhalation Study





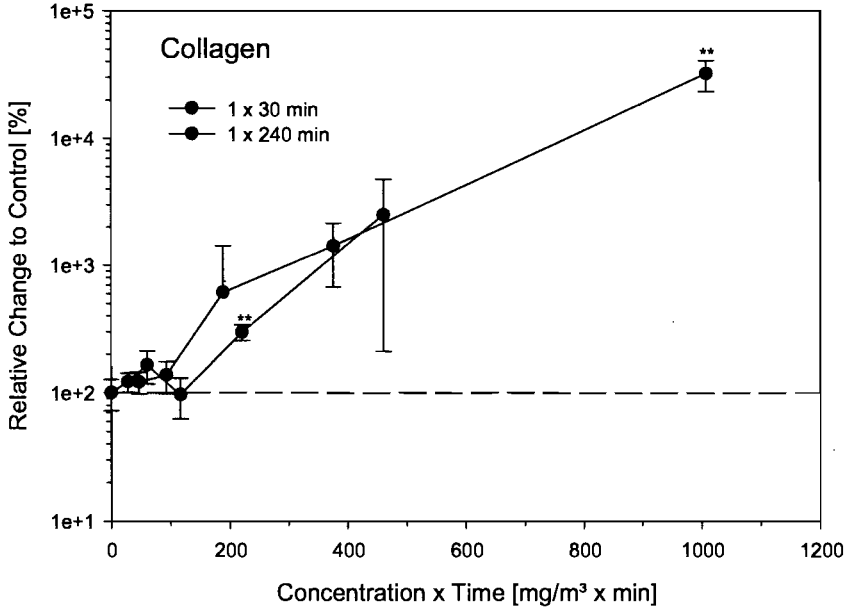


Cxt: 270 510 1050 mg/m³ x min
≈ 68 128 263 ppm x min

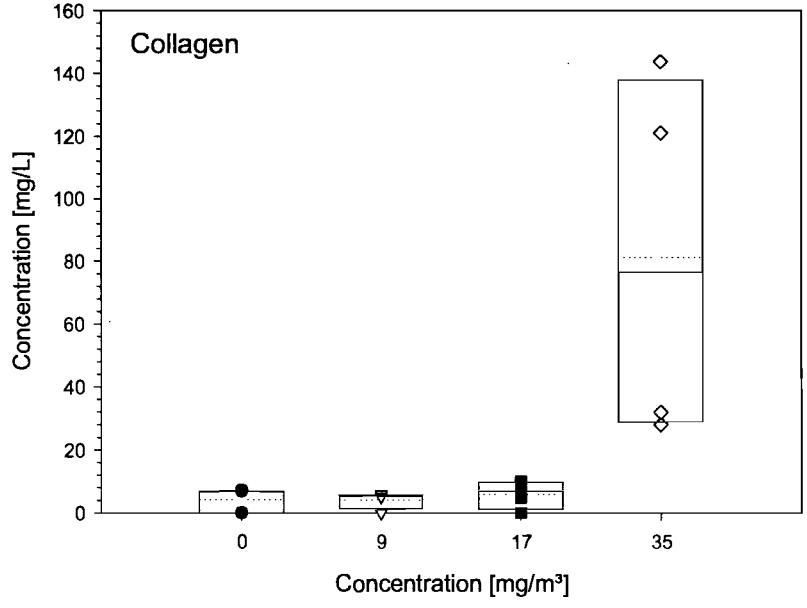
Exposure: 1 x 30 minutes

Increased Collagen in BAL-fluid: What does this mean?

Rat



Dog



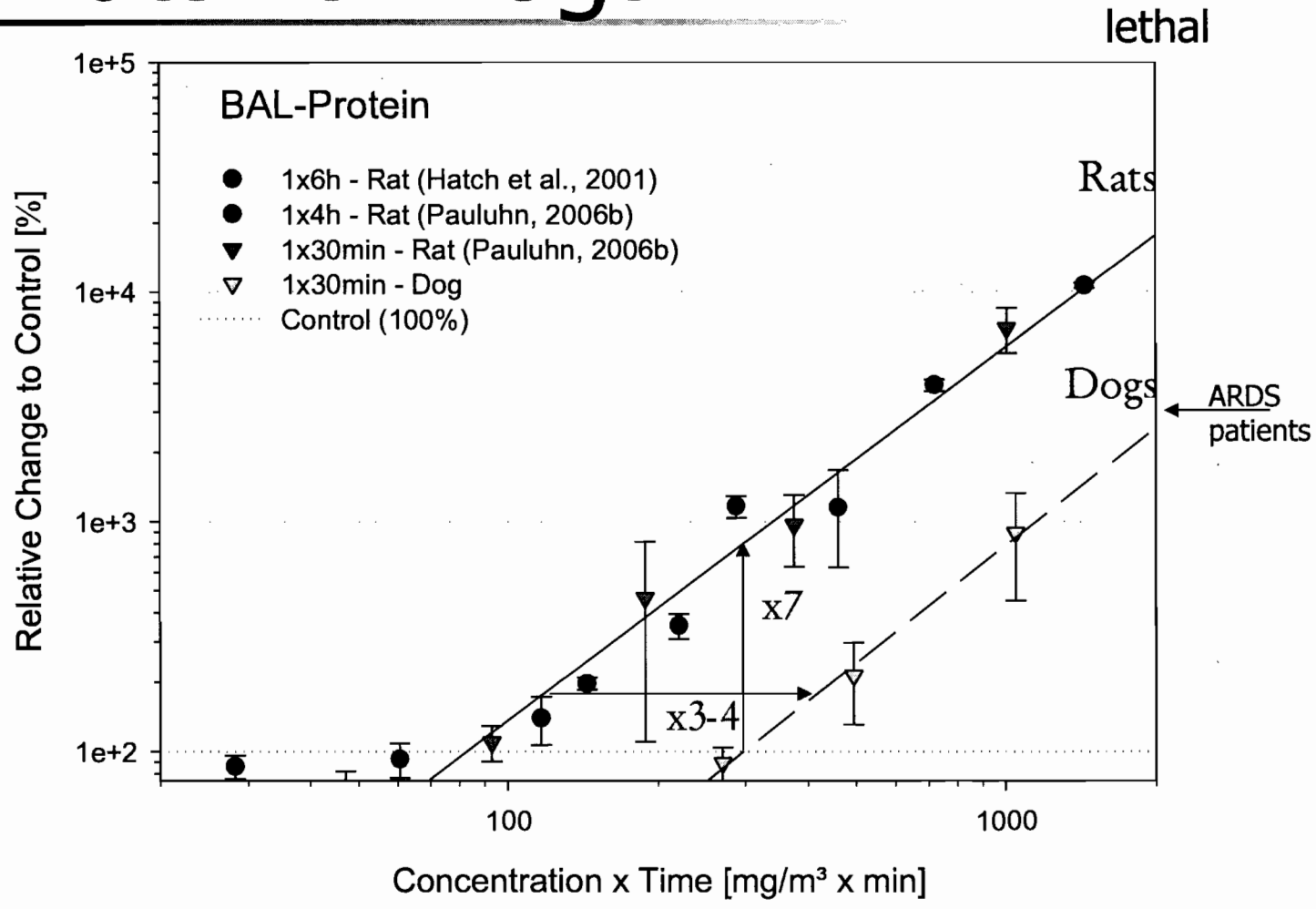
Cxt: 270 510 1050 mg/m³ x min
≈ 68 128 263 ppm x min

The source of increased alveolar collagen is serum rather than a product from fibrocytes (myofibroblasts).

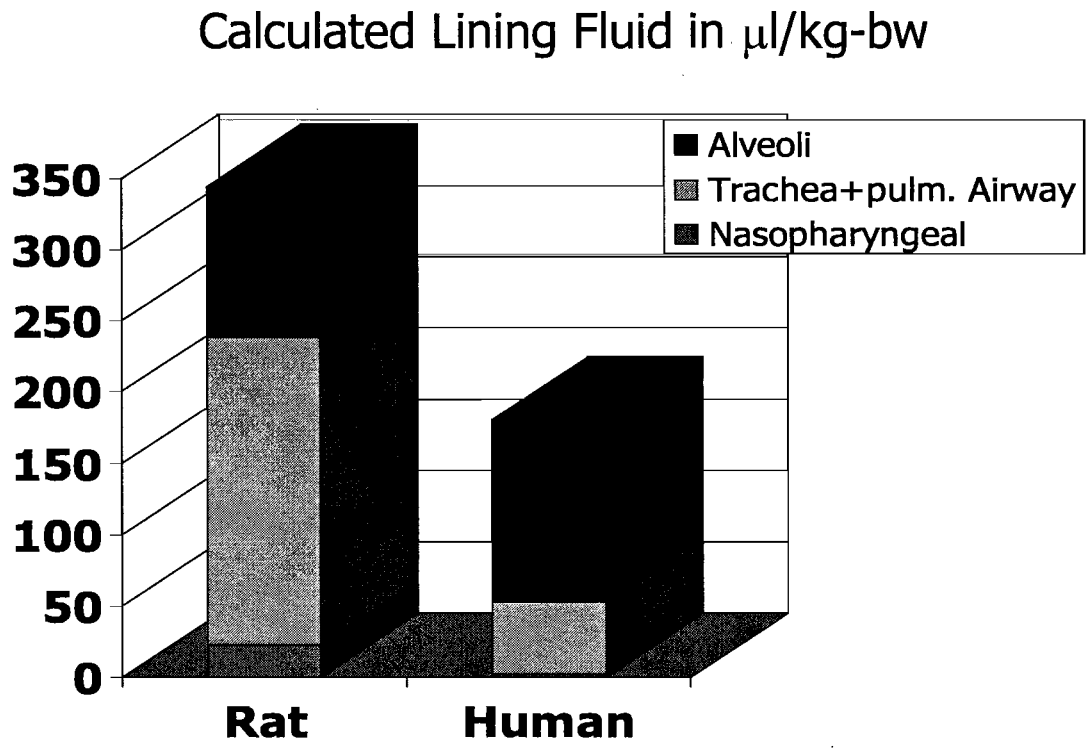
- No lobar differences in susceptibility (only one lobe lavaged)
- BAL-protein more sensitive than histopathology

	NOAEL					LOAEL							
	0 mg/m³	9 mg/m³				16.5 mg/m³				35 mg/m³			
Dog-no.	5 dogs	5748	5750	5756	5762	801	838	822	853	814	825	876	877
Sex	(1 m + 4 f)	m	m	m	m	m	m	f	f	m	m	f	f
BW (kg)	12.2±2.6	14.5	14.4	13.6	12.4	14.2	11.8	10.8	11.2	11.9	11.8	10.7	10.6
Lung-BW ratio	0.76±0.09	0.81	0.76	0.80	0.84	0.85	0.80	0.97	0.97	1.65	1.95	1.1	1.1
Edema	-	-	-	-	-	-	-	-	-	+	+	+	-
		Grades of Bronchoalveolar Necrosis / Hypercellularity[a]											
Cranial right	0	0	0	0	0	3	1	2	0	2	0	3	2
Medial right	0	0	0	0	0	1	1	2	1	0	2	2	0
Caudal right	0	0	0	0	0	3	0	2	1	0	0	3	3
Access.right	0	0	0	0	0	2	1	2	1	0	0	2	2
Caudal left	0	0	0	0	0	2	1	3	1	0	0	3	3
Cranial left	0	0	0	0	0	3	1	3	1	0	0	2	0
Mean	0	0	0	0	0	2.3	0.8	2.3	0.8	0.3	0.3	2.5	1.7
		Grades of Fibrinous Inflammation[a]											
Cranial right	0	0	0	0	0	0	0	0	0	0	2	0	0
Medial right	0	0	0	0	0	0	0	0	0	3	0	0	2
Caudal right	0	0	0	0	0	0	0	0	0	3	2	0	0
Access.right	0	0	0	0	0	0	0	0	0	2	1	0	0
Caudal left	0	0	0	0	0	0	0	0	0	2	2	0	0
Cranial left	0	0	0	0	0	0	0	0	0	2	3	0	4
Mean	0	0	0	0	0	0	0	0	0	2.0	1.7	0	1.0
		Respiratory Minute Volume											
MV_1 (L/min)	4.2±1.6	4.3	4.0	3.1	3.9	6.8	5.3	5.9	3.5	4.4	4.8	6.3	3.0
MV_2 (L/min)	(not	3.8	1.6	3.1	3.2	8.0	9.7	5.9	2.4	5.1	6.1	3.4	2.5
MV_3 (L/min)	exposed)	5.0	4.2	4.2	3.6	5.9	7.2	3.0	3.6	3.7	4.8	3.3	4.2
		Bronchoalveolar Lavage and Arterial Blood Gases											
BAL-Prot(g/L)	0.16±0.026	0.14	0.18	0.12	0.14	0.51	0.26	0.39	0.21	2.18	1.87	0.78	0.87
BAL-PMN (%)	0.27±0.28	1.3	1.3	1.3	2.3	3.0	3.0	3.7	1.0	6.3	8.3	5.7	6.0
apO_2 (mmHg)	96.0±5.3	88.3	94.8	96.4	99.3	100.2	94.6	97.1	104.0	73.4	66.7	87.3	91.1

Non-Lethal Toxic Potency Rats vs. Dogs



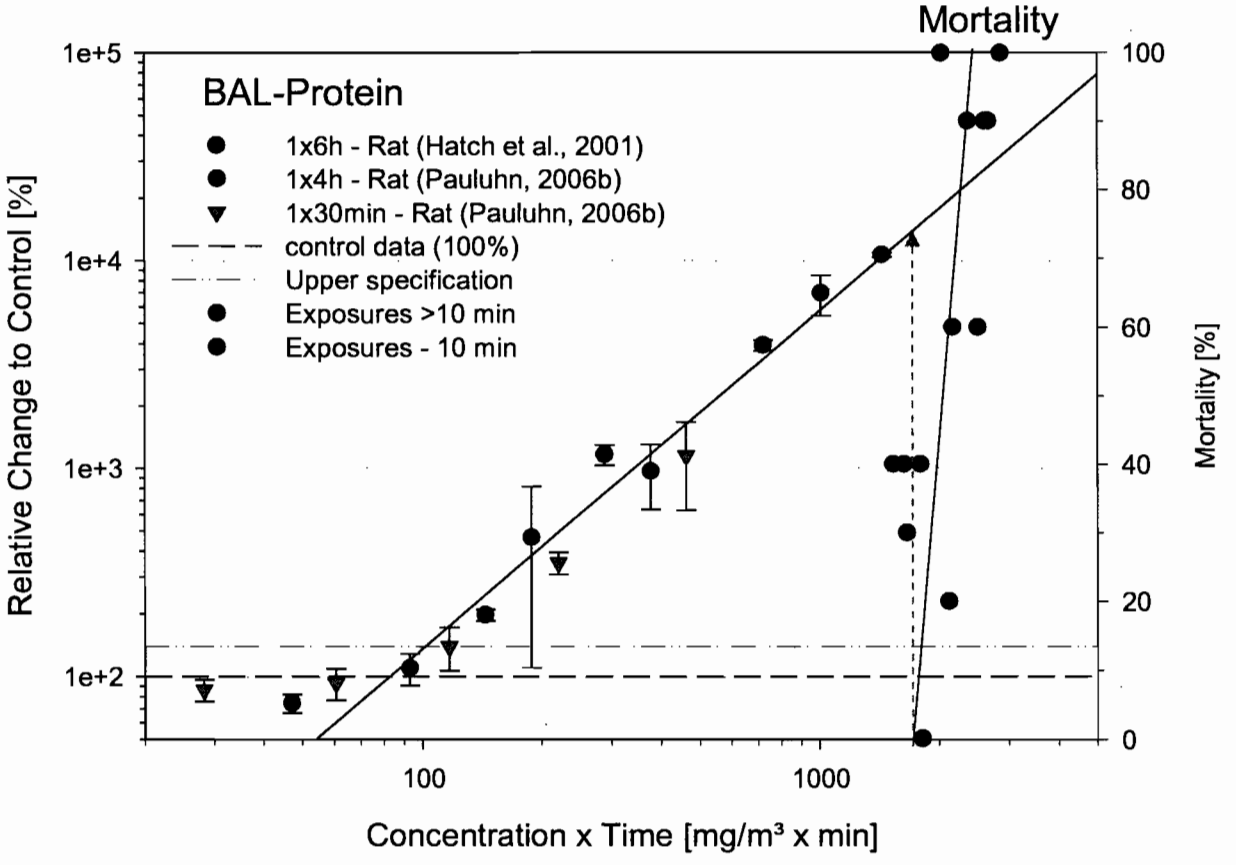
Interspecies Extrapolation of Substances Interacting with Surfactant



Total LF in lungs: human 20-40 ml→ **0.43 mg/kg**; rat: 0.09 ml → **0.36 mg/kg**

Data from: R.A. Parent, Treatise on Pulmonary Toxicology (1991)

Phosgene: Mortality vs. BAL-Protein

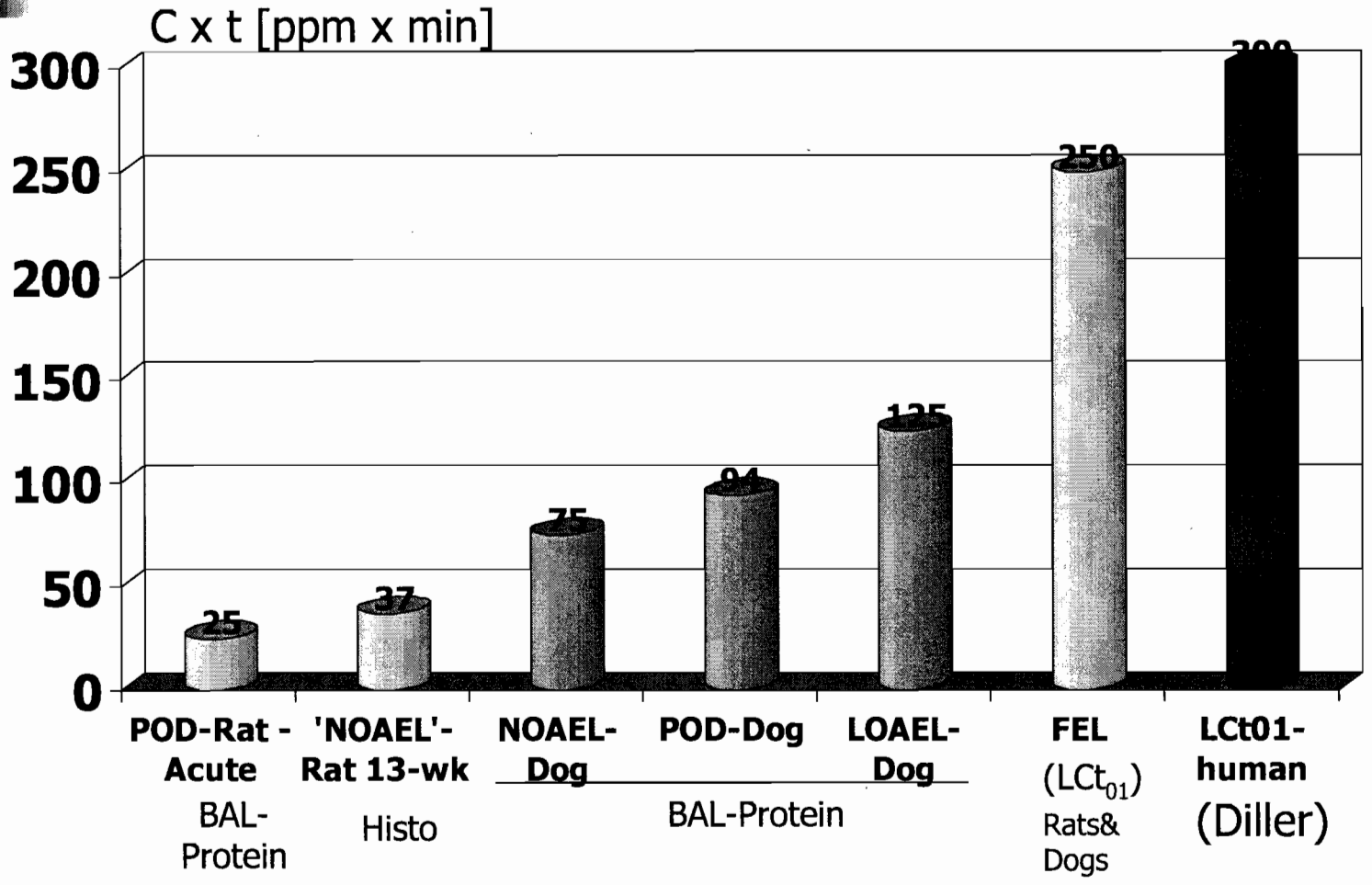


Mortality occurs up to the first postexposure day **(no delayed effects)**

Summary IV

- Dogs breathe more human-like than rats.
- Acinary structure of dogs more human-like than rats.
- Reflexively-induced effects are less pronounced in dogs. BAL-fluid not (or less) contaminated by proteins from airway secretions.

Comparison of Key Data

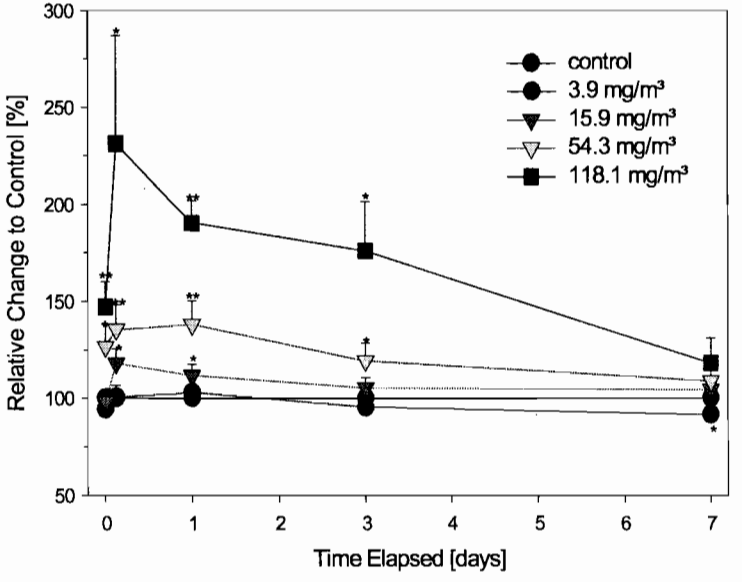


Assessment Factors – Weight of Evidence Based?

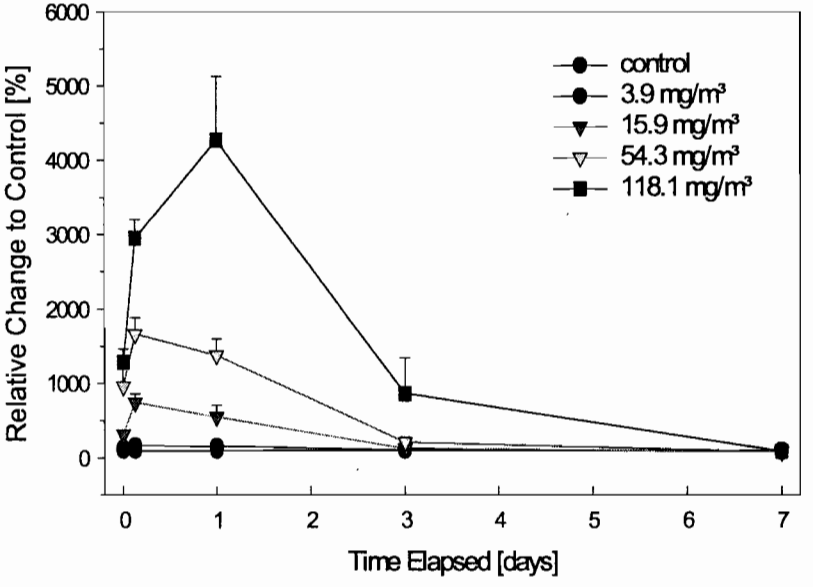
- Endpoints can be integrating, target organ-specific or mode-of-action specific. Each level produces its own POD.
- Hence, endpoints to probe critical effects differ markedly in sensitivity.
- Effect quality, human relevance, and use-fulness as biomarker of exposure & effect need to be considered.

Lung Weights vs. BAL-Protein

Lung weights



Protein in BALF



Exposure: Polyisocyanate aerosol 1 x 6-h (rats)

Assessment Factors

- **Mode of action:** High-surface tension lung edema due to surfactant depletion and Type I cell injury. Direct mode of action at the initial site of deposition.
- **Interspecies** dosimetric/morphometric adjustments: Alveolar ventilation, acinary anatomy, physiology: $(V_E/SA_P)_A$: $(V_E/SA_P)_H$ = 0.25/0.39 : 25/89 >2 [L-min / m^2]. Vol-LF_A/Vol-LF_H <1. Acute rat data based on BAL are implicitly conservative ($NOAEL_{acute}$ < $NOAEL_{13\text{-}wk}$).
- **Intraspecies** variables: Related to local dose (MV) and pre-existing pneumonitis (diminished reserve capacity of lung).

Derivation of AEGL-3

- Rat: species of choice, nose-only with phosgene-specific characterization of atmospheres. Exposure durations 10- to 240 min. GLP-compliant.
- LC_{01} (based on 30 to 240 min exposures): 1075 mg/m³ (269 ppm); LC_{50}:LC_{01} = 1.6.
- Toxicity depends solely on pulmonary dose. $C^1 \times t$ = const.. Rats inherently more susceptible than humans.
- LCt_{01} of rats not different to those reported for humans (and dogs). Hence, an AF-Interspecies factor does not appear to be justified. AF-Intraspecies factor of 3 seems to be defensible.

LC_{01} / 3 - Implicit interspecies AF: MV human : rat ≈1:3 and V_e: SA ≈2. Explicit intraspecies AF: 3. Toxicity target-site specific and direct. Confirmatory human evidence.

	10-min	30-min	60-min	4-hours	8-hours
AEGL - 1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL - 2 (Disabling)	**0.6**	**0.6**	**0.3**	0.08	0.04
AEGL - 3 (Lethal)	**3.6 → 9.0**	**1.5 → 3.0**	**0.75 → 1.5**	0.20 → **0.35**	0.09 → **0.2**
ERPG - 1 (Nondisabling)	--	--	NR	--	--
ERPG -2 (Disabling)	--	--	0.2 → 0.5	--	--
ERPG - 3 (Lethal)	--	--	1.0 →1.5	--	--

All concentrations in ppm

Derivation of AEGL-2: Gross et al. Study (1965)

- Phosgene dissolved in kerosene and stripped-off for inhalation exposure studies.
- Exposure profile unknown, particle concentration unknown ("carrier effect"), methodological details lacking, indirect analytical method, nominal estimates lacking, virus infection of rats (hypothesized by the authors themselves).

Derivation of AEGL-2: Rat Data

- $NOAEL_{acute}$ BAL-Protein < $NOAEL_{13\text{-}wks}$ histopathology (i.e., not all protein may be reflective of alveolar instability).
- NOAEL follows the $C^1 \times t = const.$ concept. Effects observed at 4-hrs consistently more pronounced than at 0.5 hrs.
- Rats have a rodent-specific, reflex-triggered mucosal defense system (to prevent plugging of lower airways).
- NOAEL based on endpoints probing mechanism-based injury at the target organ level.
- Changes rapidly reversible and without long-term sequelae (even at the LC_{01} range). Increased BAL-protein occurs at $\approx LC_{01}/10$.

Derivation of AEGL-2: Dog Data

- Dog 30-min Inhalation Study:
  - Identical exposure method of dogs and rats
  - BAL-endpoints (smallest lobe), arterial blood gases, lung function, histopathology (time point: maximum response, i.e. approx. 24-hrs postexposure).
- Dose-response curve parallel to rat study.
- $NOAEL_{0.5\text{-}h}$- BAL-protein: 75 ppm x min; POD: 94 ppm x min.
- $LOAEL_{0.5\text{-}h}$- BAL-protein: 125 ppm x min in dogs.
- Susceptibility of dogs not different to that of humans. Hence, an AF-interspecies factor does not appear to be justified. An AF-intraspecies factor of 3 is considered adequate.

$POD_{BAL\text{-}Protein}$ / 3 - Explicit intraspecies AF: 3. Toxicity target-site specific and direct. Confirmatory human evidence.

	10-min	30-min	60-min	4-hours	8-hours
AEGL - 1 (Nondisabling)	NA	NA	NA	NA	NA
AEGL - 2 (Disabling)	**0.6 → 3.0**	**0.6 → 1.0**	**0.3 → 0.5**	0.08→ **0.15**	0.04→ **0.07**
AEGL - 3 (Lethal)	**3.6 → 9.0**	**1.5 → 3.0**	**0.75 → 1.5**	0.20 → **0.35**	0.09 **→ 0.2**
ERPG - 1 (Nondisabling)	--	--	NR	--	--
ERPG -2 (Disabling)	--	--	0.2 → 0.5	--	--
ERPG - 3 (Lethal)	--	--	1.0 →1.5	--	--

All concentrations in ppm

Analysis of Plausibility

- AEGL-3 (1-hour):
  - **1.5 ppm** (steep dose-response relationship; nose-only)
  - LC_{01}-human x AFs ≈ 300/(3 x 60) **≈1.7 ppm** (*plausibility test passed*)
- AEGL-2 (1-hour):
  - **0.5 ppm** (MV and size of dog similar to those of children; AFs adjusts for preexisting alveolar disease; no physiological changes at 2.1 ppm-60 min (time-adjusted); no evidence of potential long-term sequelae)
  - TLV 0.1 ppm x 480 min → **0.8 ppm-h** (*plausibility test passed*)

EU and OELs – Impact of New Data

- MAK 0.02 ppm → 0.1 ppm (TWA)
  - Ceiling 0.04 ppm → 0.2 ppm (STEL)
- Multiple EU-countries followed
- SCOEL: to be discussed in June 2009.

Rationale: $NOAEL_{Dog}$ BAL-protein = 300 mg/m³ x min or 75 ppm x min → 75 ppm x min/480 min = 0.15 ppm → 0.1 ppm. No AFs necessary based on species selection (dog) and direct mode of actions.

Results published 3 publications and 1 workshop summary.

Development of Acute Exposure Guideline Limits Using Oral Data

George M. Rusch,

April, 2009

Factors Influencing Dose

Oral

- Chemical reactivity
- Uptake from Gut
- Chemical Changes in the Gut (acidic vs. lung slightly basic)

• Inhalation

- Chemical reactivity
- Solubility
- Volatility
- Uptake from upper respiratory pathways
- Uptake from lung
- Deposition in lung
- Particle size

• Gavage

- Can not be compared to inhalation (Bolus vs Integrated)

Oral Dose (mg/kg)

Oral dose = ρ * dose /body wt. (kg)

ρ = percent taken into the body

dose = amount administered (mg)

Inhalation Dose

$$\text{Inhalation dose} = \frac{\alpha * \text{exposure level} * \text{min. vol.} * \text{length of exp.}}{\text{body wt. (kg)}}$$

- α = amount retained in entire respiratory system
- Exposure level = mg/m^3 (can be in other units e.g. mg/L)
- Min. vol. = amount of air inhaled per min. (m^3)
- Length of exposure = total minutes (e.g. 6 hrs. = 360 min.)

Units must be consistent

If exposure level is mg/m^3 ;min. vol. must be in m^3

If exposure level is mg/L; min. vol. must be in L

Comparison: Oral to Inhalation

Oral dose = ρ * dose /body wt. (kg)

$$\textbf{Inhalation dose} = \frac{\alpha * \text{exposure level} * \text{min. vol.} * \text{lgth of exp.}}{\text{body wt. (kg)}}$$

Assume ρ = 1

- **Then:**

$$\textbf{Dose(mg)/body wt.(kg)} = \frac{\alpha * \text{exp. level} * \text{min. vol.} * \text{lgth of exp.}}{\text{body wt. (kg)}}$$

E.g. Exp.level = mg/m3; min vol. = m3/min; lgth. of exp. = min

Example: Oral to Inhalation

Oxamyl : Oral LD_{50} male rats = 2.5 mg/kg

Estimate 4-hr LC_{50}

Assume: $\alpha = 0.9$ (i.e. 90%)

Rat body weight is 0.300 kg (i.e. 300 gm.)

Rat min. vol. = 160 mL or 0.00016 m^3

$$\text{dose /body wt. (kg)} = \frac{\alpha * \text{exp. level} * \text{min. vol.} * \text{lgth of exp.}}{\text{body wt. (kg)}}$$

$$2.5 \text{ mg/kg} = \frac{0.9 * \text{exp. Level} * 0.00016 \text{ m}^3\text{/min} * 240 \text{ min.}}{0.3 \text{ kg}}$$

$$\text{Exp. Level} = \frac{2.5 \text{ mg/kg} * 0.3 \text{ kg}}{0.9 * 0.00016 \text{ m}^3\text{/min} * 240 \text{ min}}$$

$$\text{Exp. Level} = 21.7 \text{ mg/m}^3$$

Example: Inhalation to Oral

Oxamyl : 4-hr Inhalation LC50 male rats = 64 mg/m^3

Estimate Oral LD50 for male rats

Assume: $\alpha = 0.9$ (i.e. 90%)

Rat body weight is 0.300 kg (i.e. 300 gm.)

Rat min. vol. = 160 mL or 0.00016 m3

$$\text{dose /body wt. (kg)} = \frac{\alpha * \text{exp. level} * \text{min. vol.} * \text{lgth of exp.}}{\text{body wt. (kg)}}$$

$$\text{Dose} = \frac{0.9 * 64\ \text{mg/m}^3 * 0.00016\ \text{m}^3/\text{min} * 240\ \text{min.}}{0.3\ \text{kg}}$$

Dose = 7.37 mg/kg

Comparison: Inhalation to Oral

For an oral dose of 2.5 mg/kg the estimated 4-hr Inhalation LC50 is 21.7

For a 4-hr inhalation LC_{50} of 64 mg/kg the estimated oral LD_{50} is 7.37 mg/kg.

Ratios: 21.7/2.5 = 8.68 and 64/7.37 = 8.68

Limitations: Oral to Inhalation

- **Often do not know α or ρ**
- **Toxicity of chemical can alter minute volume during exposure (e.g. irritants and CNS depressants will lower minute volume, therefore the dose will be lower)**
- **Uptake in upper respiratory system will lead to different distribution than in lung**
- **For poorly soluble particles, poor clearance from lung can lead to higher dose**
- **For poorly soluble particles poor uptake from digestive system can lead to lower dose.**
- **Oral uptake initially entrohepatic circulation**
- **Inhalation uptake is into systemic circulation**
- **Oral dosing often underestimates the toxicity by inhalation**

ATTACHMENT 16

Route-to Route Extrapolations

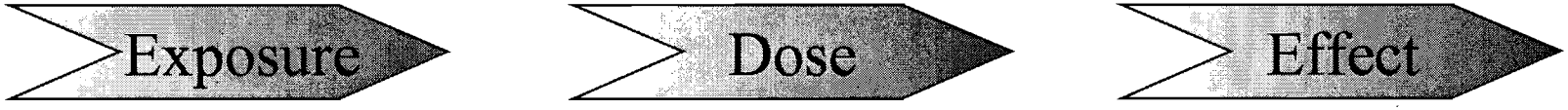
Jürgen Pauluhn

Bayer HealthCare
Wuppertal, Germany

Extrapolation Oral to Inhalation

- Absorption profile: AUC vs. C_{max}
- Metabolism: Toxification vs. Detoxification
- Toxicophoresis: GI vs. Lung
- (Neuro-)Physiological responses specific to the respiratory tract, reflex-induced changes in thermoregulation, acid-base status

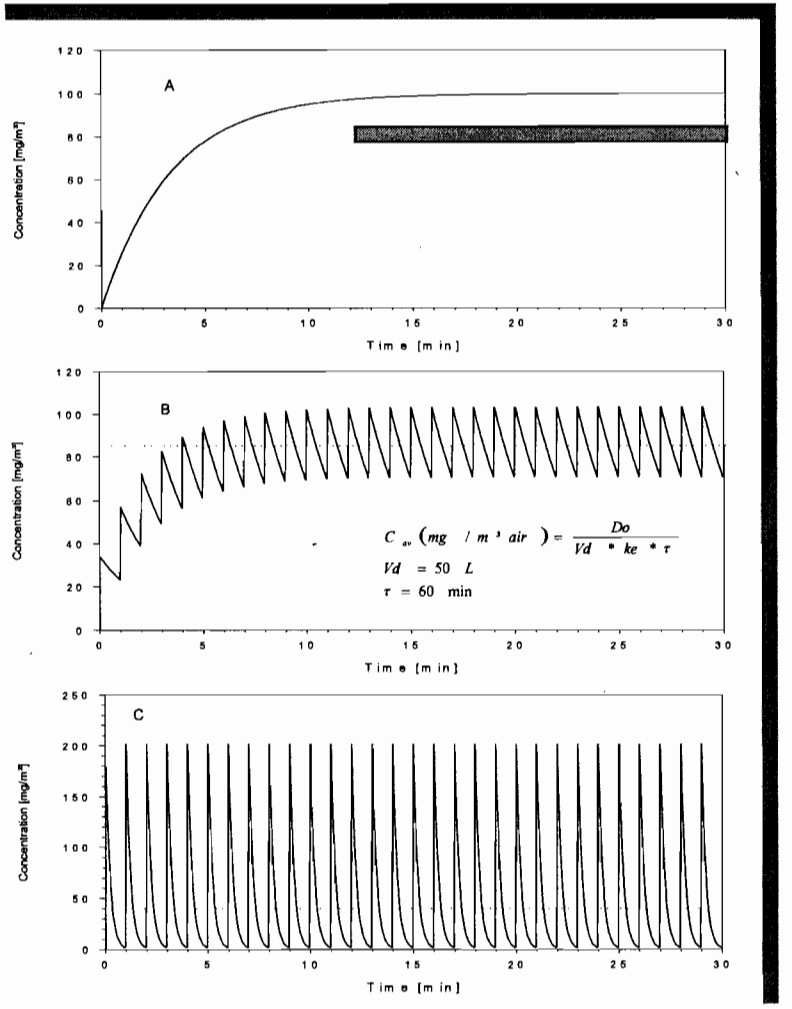
Dosimetry and Test Design



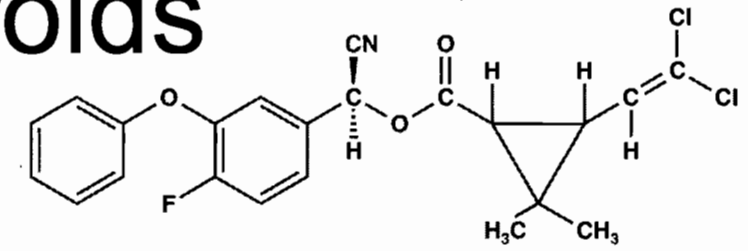
- Equivalence of exposure regimens
- Dose generated equal the dose delivered?
- Variables affecting absorption # variables affecting deposition & retention
- Portal-of-entry effects, regional deposition and systemic effects

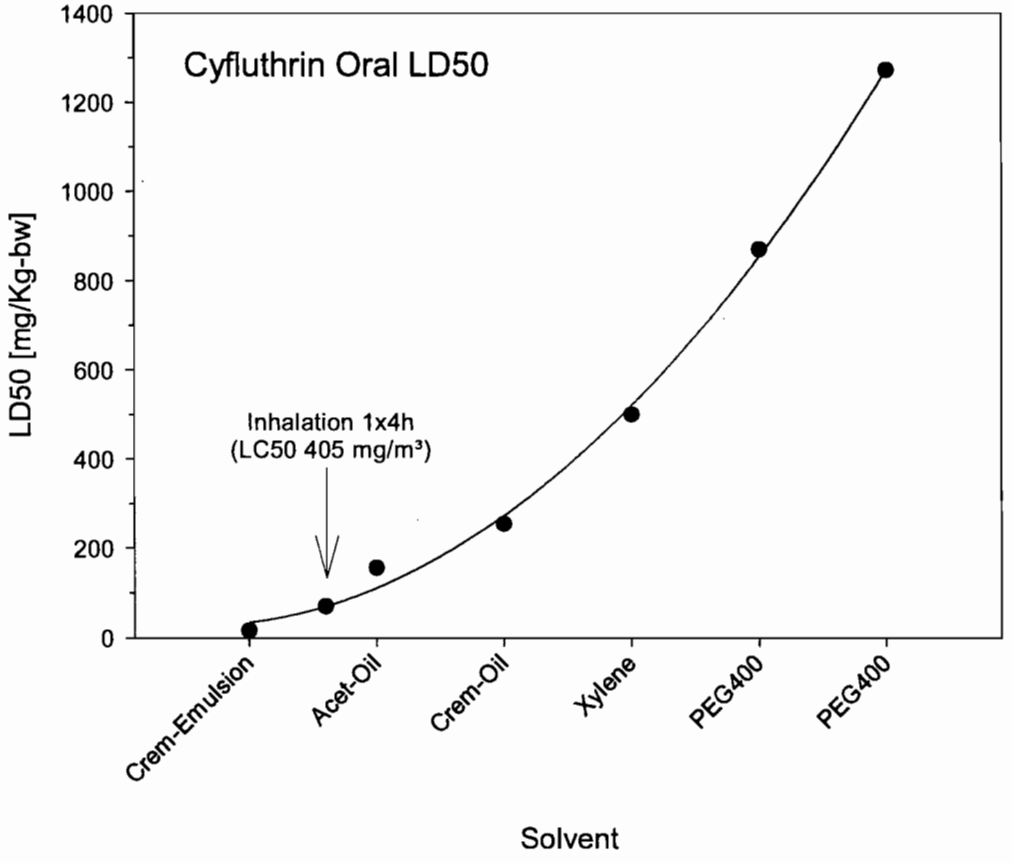
Exposure Regimen

- Fixed-time - variable exposure concentrations protocol / continuous generation
- Fixed-time - variable exposure concentrations protocol / discontinuous generation
- Fixed concentration - variable exposure-time protocol

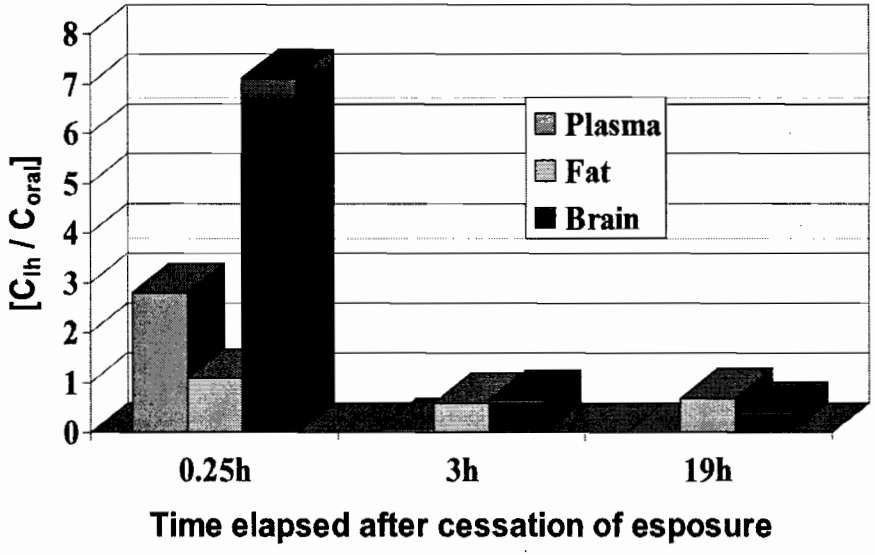


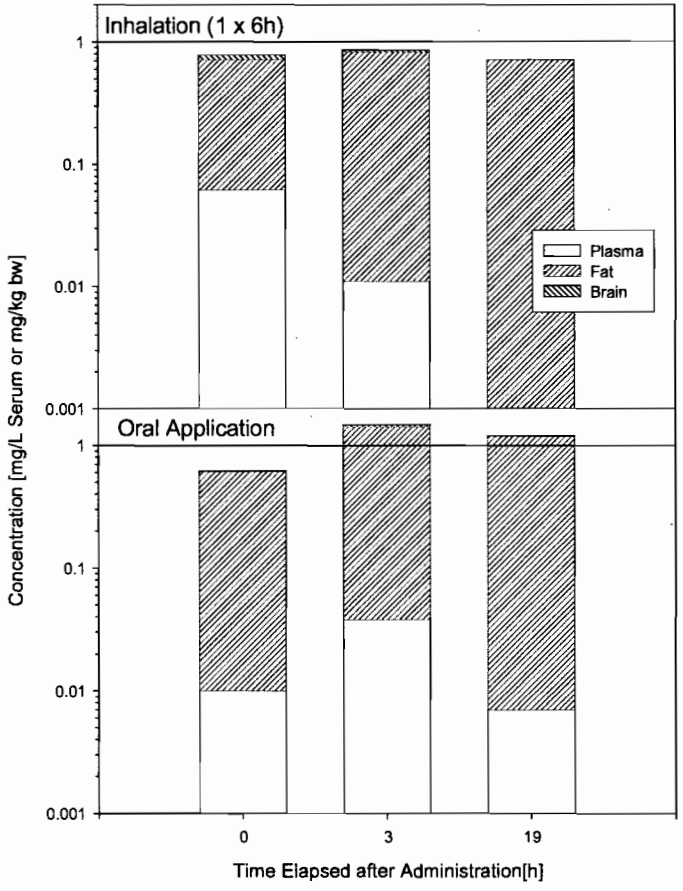
Type II Pyrethroids





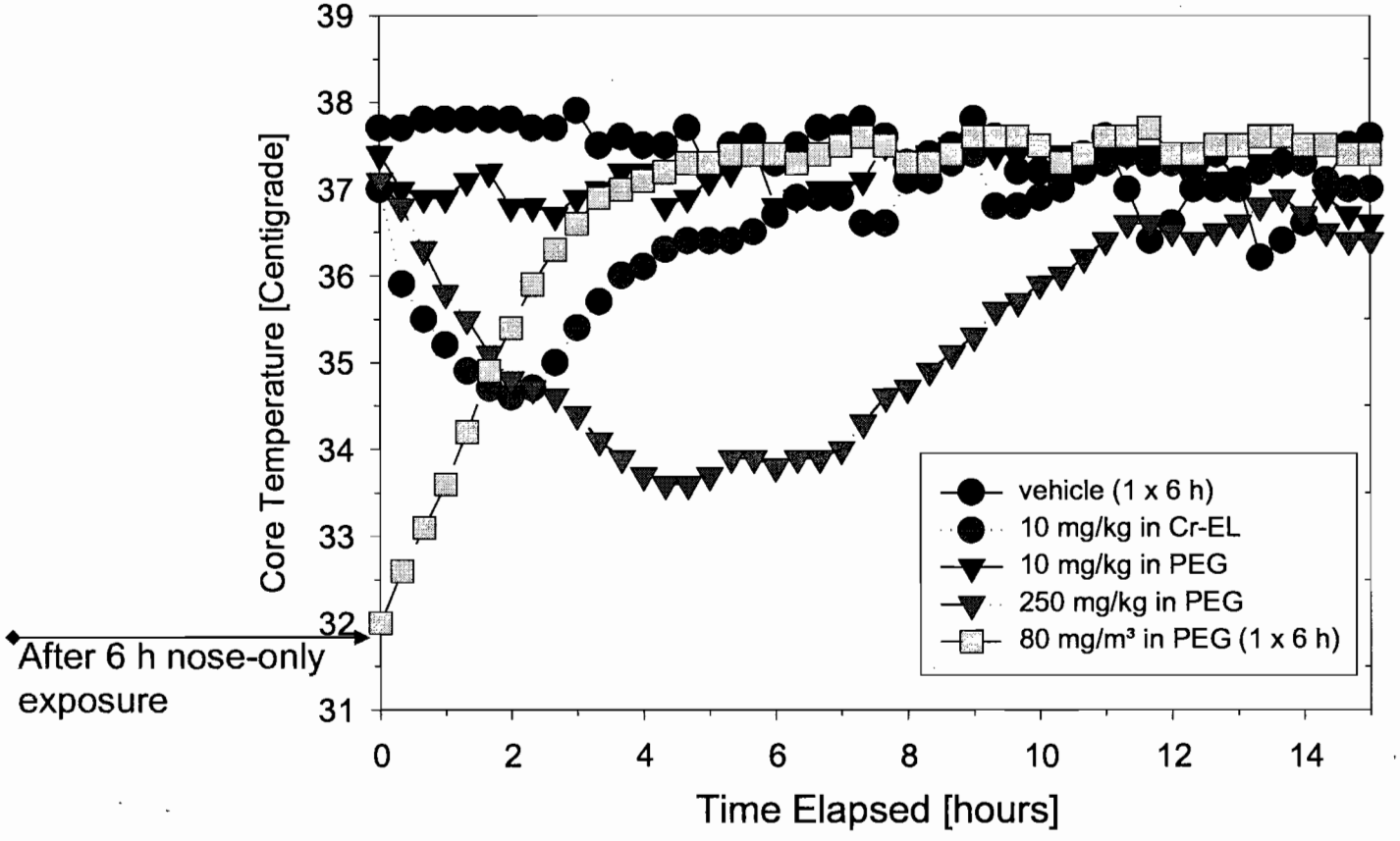
Route-to-Route Extrapolation – Compartmentalization





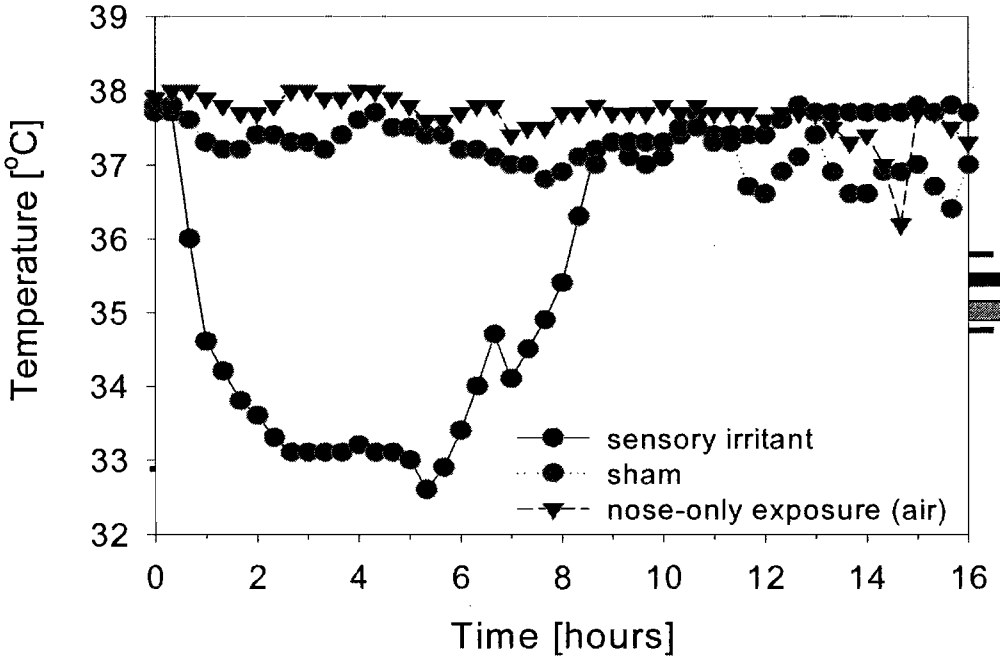
Dosimetrically adjusted exposure: oral = inhalation

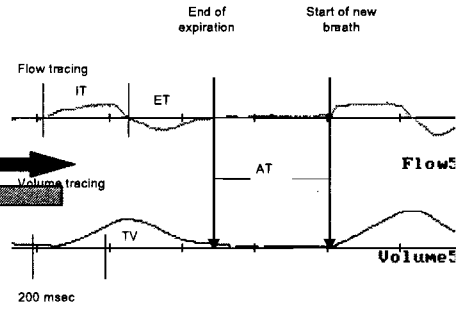
Impact of Route of Exposure (Type II Pyrethroids)



PEG: Polyethylene glycol E 400

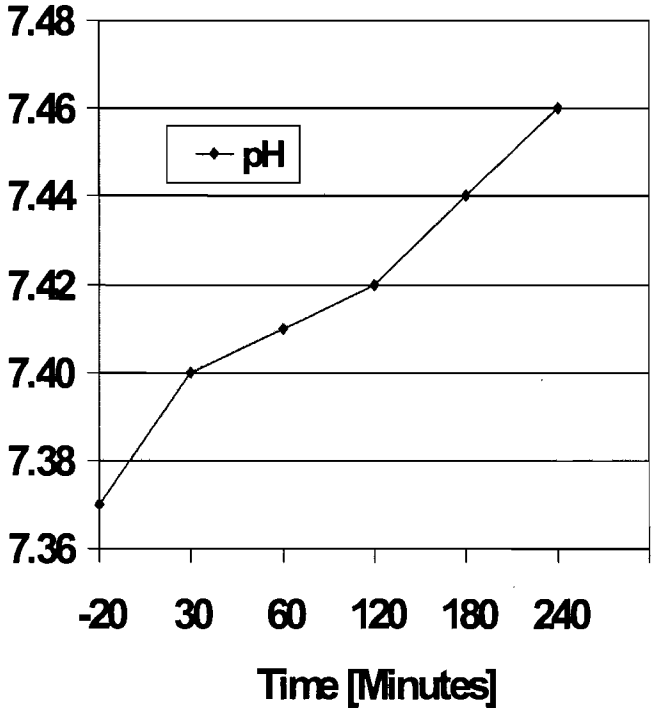
Respiration & Body Temperature

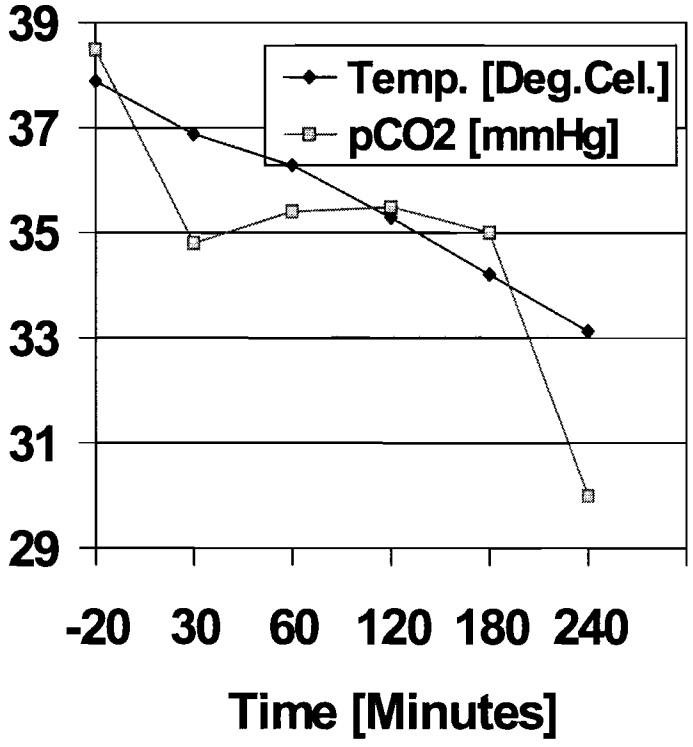




Response to toxicants ⟷ Heat dissipation & metabolism ⟷ Respiration & dosimetry

Type II Pyrethroids: Arterial Blood-Gases / Acid-Base-Status

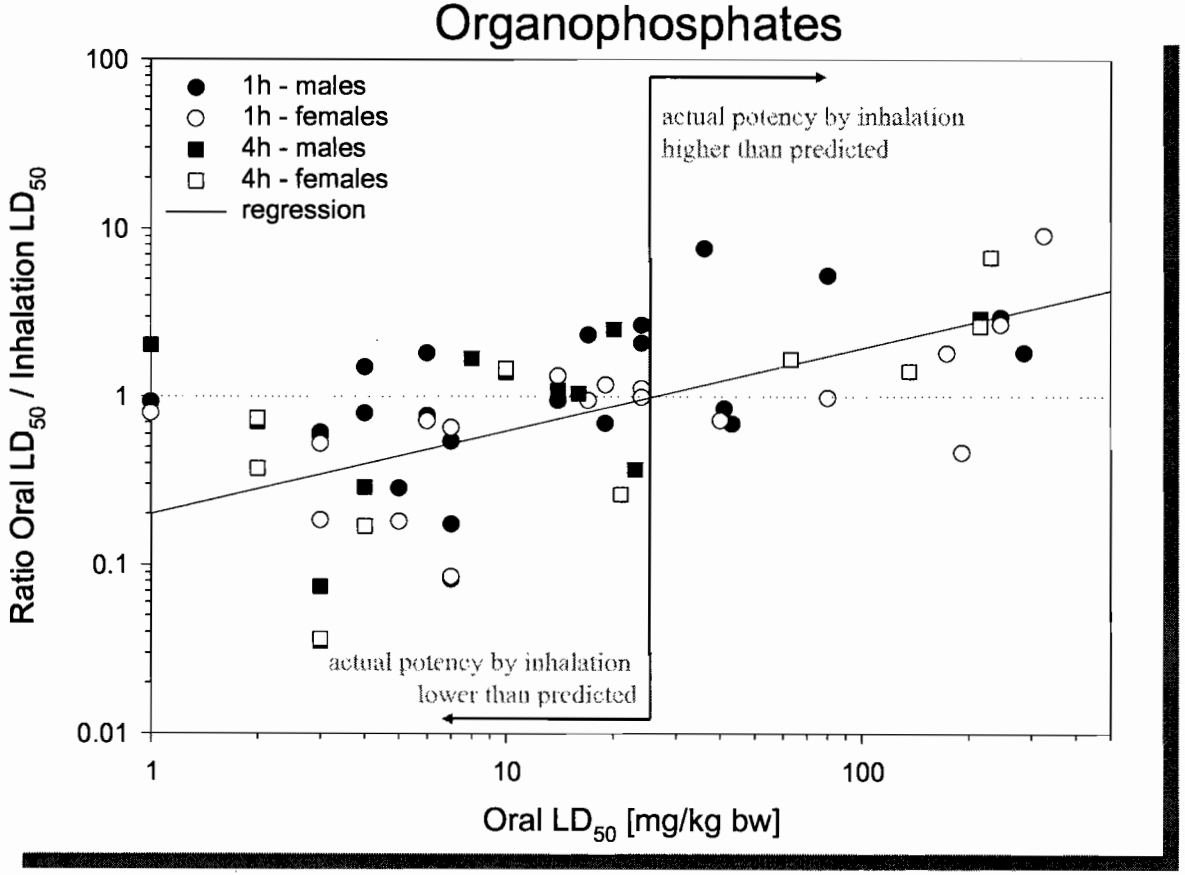




Pyrethroids

- Quality of extrapolations oral → inhalation requires knowledge about the PK profiles for either route.
- Compartmentalization oral # inhalation
- CNS-toxicity superimposed by reflex-mediated physiological responses.
- Most critical endpoint in humans: Excitatory local toxicity (paresthesias)

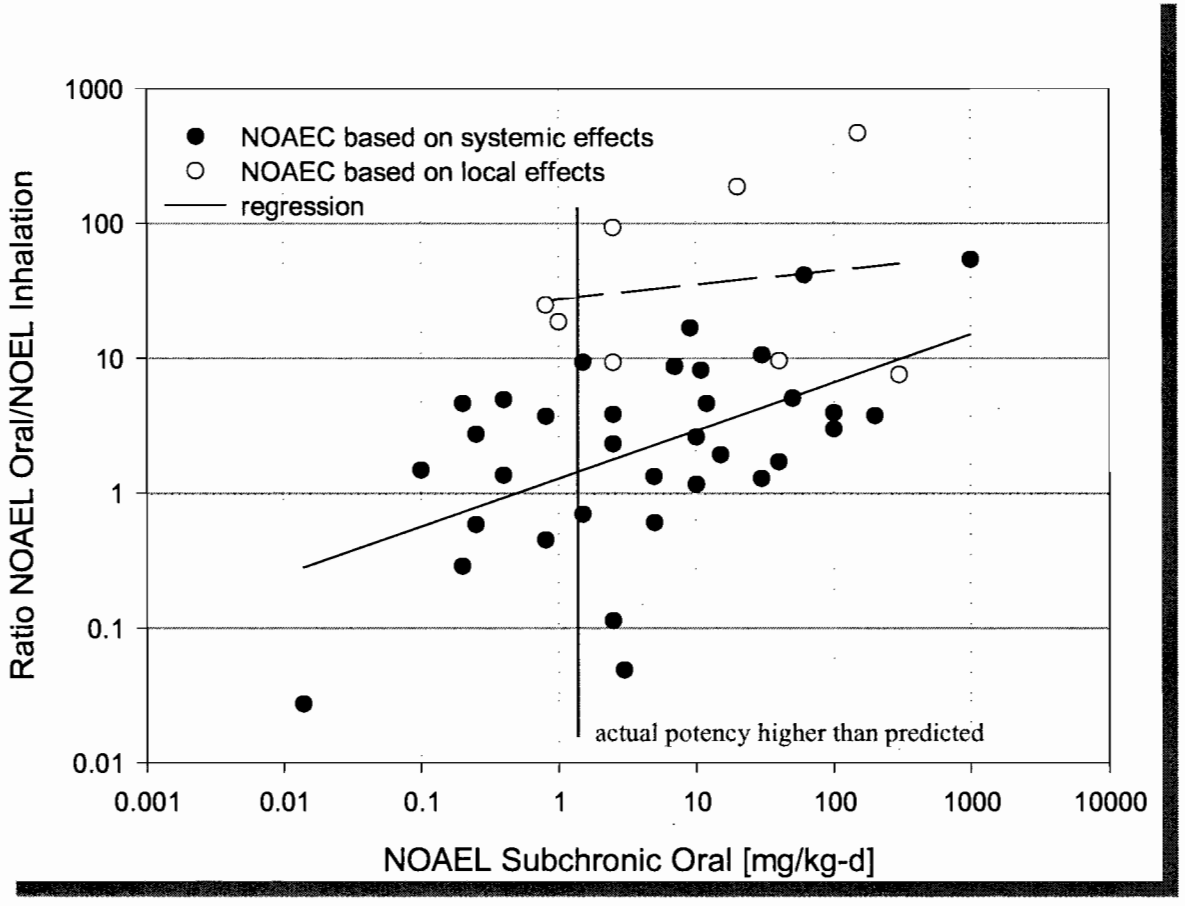
LD_{50}-Gavage/LC_{50}-Inhalation: Dispositional Factors



Range: ±10 too high / too low

Data from: J.E. Storm, K.K. Rozman, and J. Doull, Toxicology **150**, 1-29 (2000).

Pesticides - Route-Dependence of NOAELs

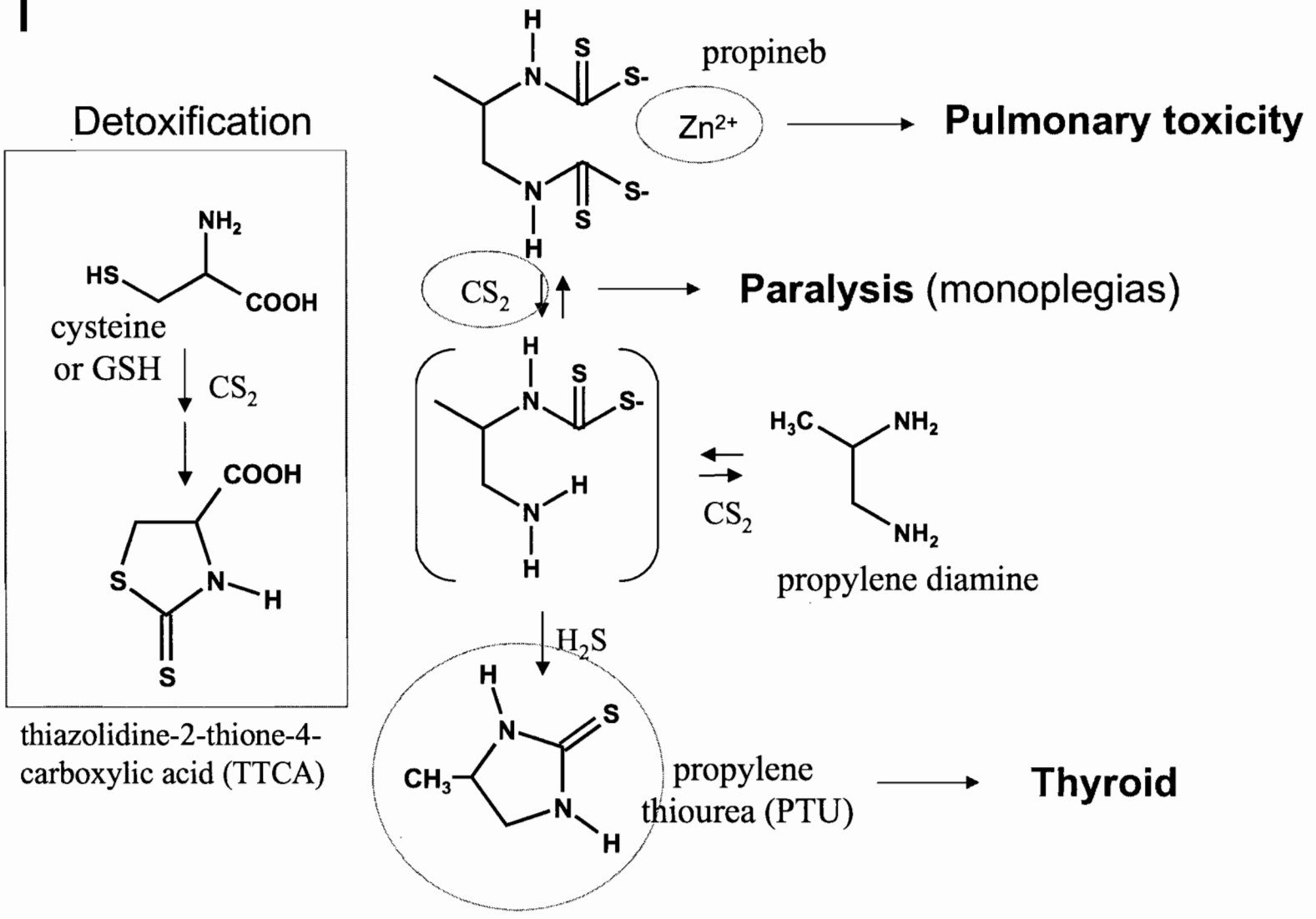


Basis: Inhalation studies 3-4 wks and 4-wk feeding or gavage: 71%, ≥13-wk dietary studies: 29% (n = 42)

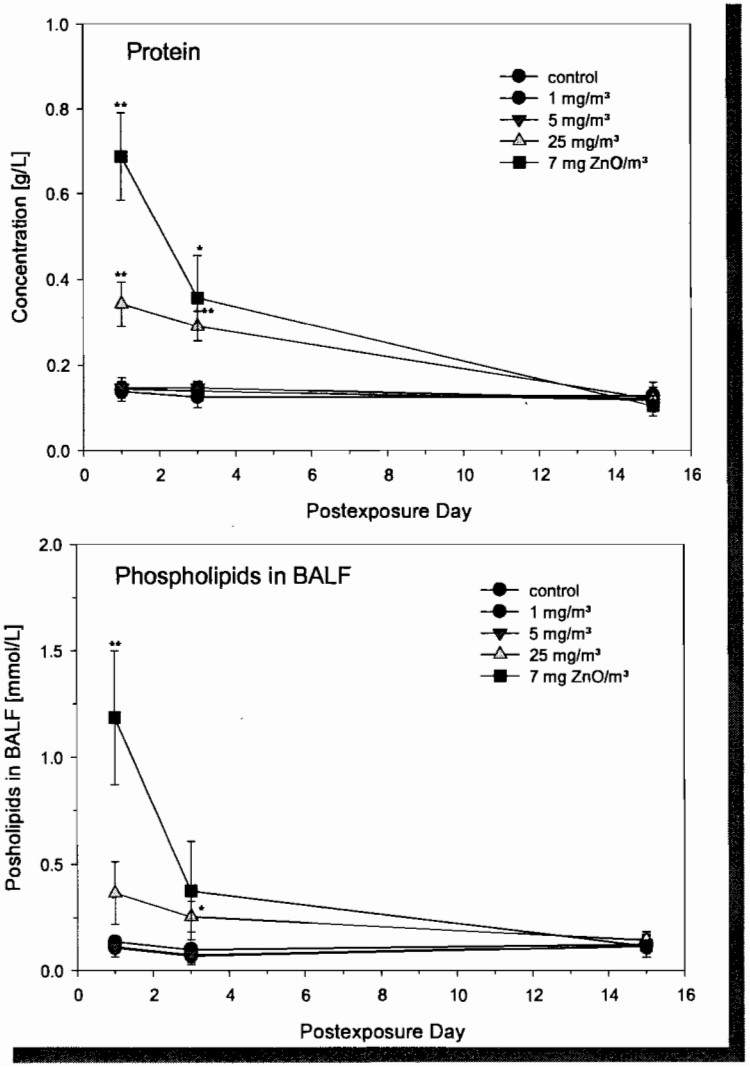
Summary I

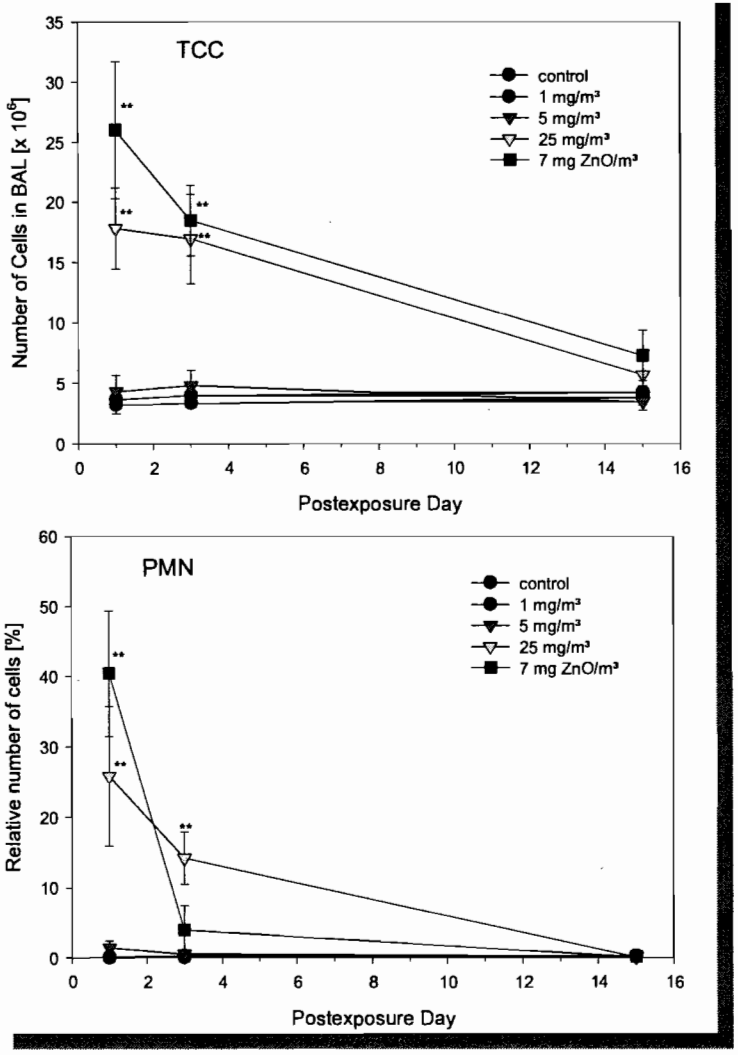
- For simple, systemically acting pesticides (primary acute mode of action CNS) extrapolated values differ from the correct value by range of 1-100.
- For subchronic studies for systemically and locally acting substances the range was <1-10 and 10-700, respectively.
- General tendency: Toxicity by inhalation is underestimated by oral data.

GI-Tract Related Toxicophoresis



Disposition and Response
(1-wk Inhalation Exposure-Rats)





Inhalation vs. GI-Tract

NOAEL's in Rats: Oral vs. Inhalation

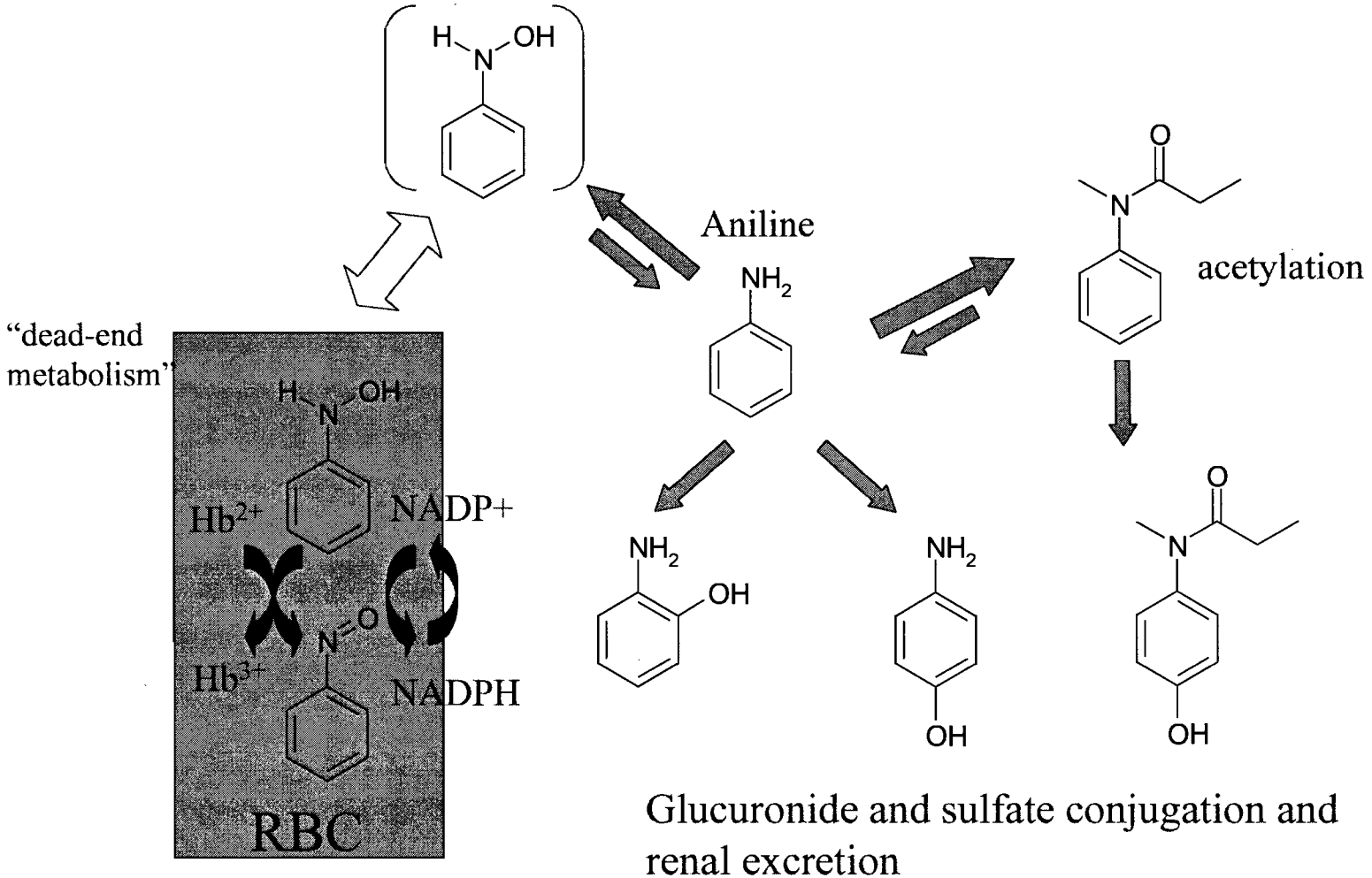
	Gavage (90-day)	Feeding (2-yrs)	Inhalation 1-4 wks
Neuro-muscular	< 5	5	1.4
Thyroid	5	0.5	>28
Lung	-	-	≈1.4 (4 mg/m³)

Units: mg x kg^{-1} x day^{-1}

Summary II

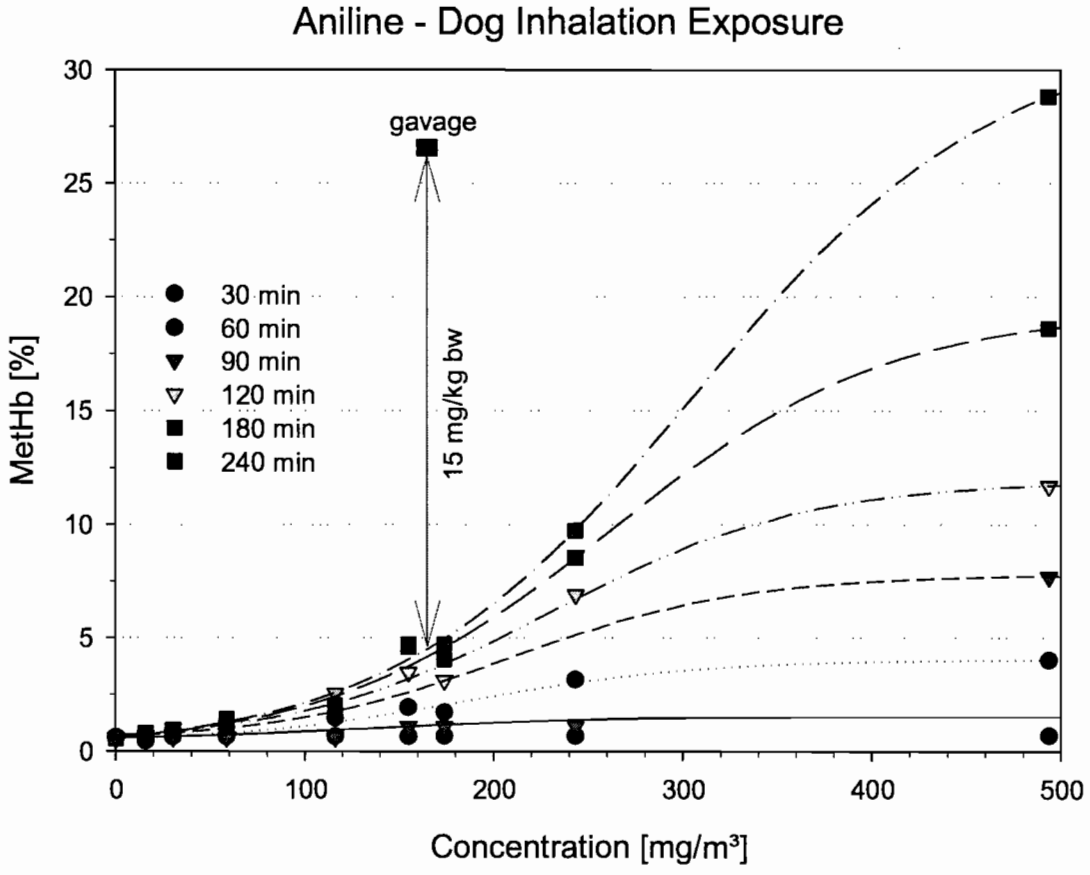
- Substances undergoing route-specific toxicophoresis may not be subjected to route-to-route extrapolation.
- Toxic profile changes with route and regimen.
- NOAELs change with route and regimen.

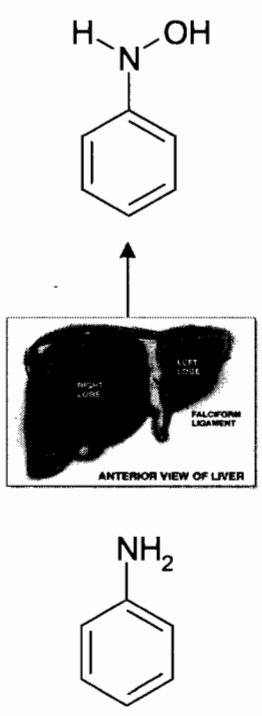
Hematotoxicity of Arylamines



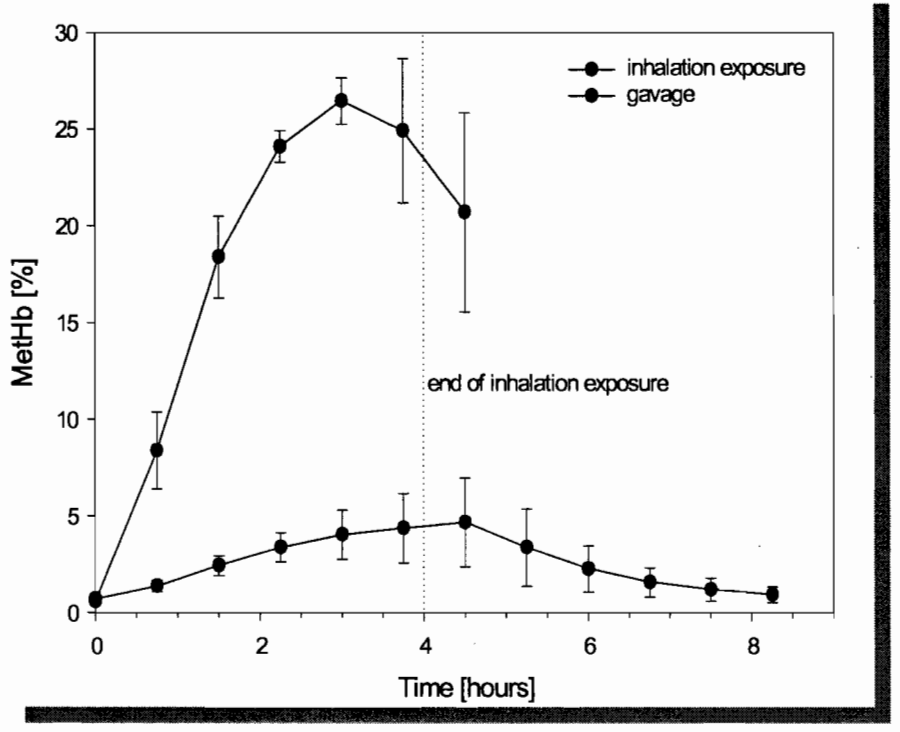
Glucuronide and sulfate conjugation and renal excretion

Aniline – Route & Time Dependence of MetHb-Formation



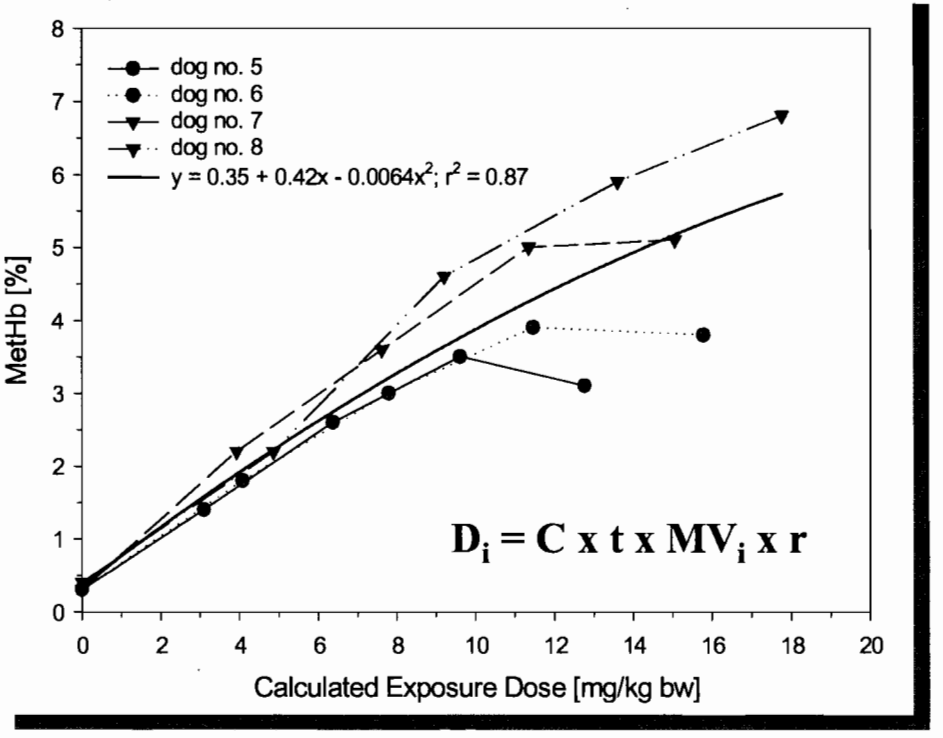


Aniline - MetHb-Formation following equal Doses after Inhalation & Gavage



Exposure profile more important than total dose

Exposure profiles need to be identical to compare dose



Conclusion

- GI-tract dosing due to particles deposited in the extra-thoracic region have to be considered.
- Non-inhalation routes do not necessarily predict what happens following inhalation.
- In the absence of PK-data and knowledge about the critical toxic mechanisms do not extrapolate from oral to inhalation or, alternatively, apply an AF of at least 25.