



# **Analysis of the Correlation Between In Vitro Cytotoxicity Data and Acute Toxic Effects in Humans**

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# Acute Systemic Toxicity Testing

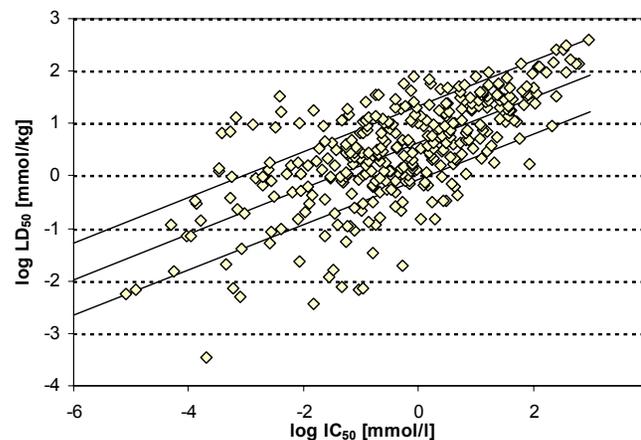


- Establish hazard to human health
- Classify chemicals



**MEIC study** correlation of a battery of three human cell line in vitro assays with peak human lethal blood concentration

**Register of Cytotoxicity**

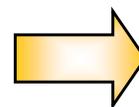




# The NICEATM-ECVAM Joint Validation Study on In Vitro Methods for Assessing Acute Systemic Toxicity

## In vitro methods:

- BALB/c 3T3 Neutral Red Uptake (NRU)
- Normal Human Keratinocyte (NHK) NRU



**72 chemicals  
tested in 3  
labs**

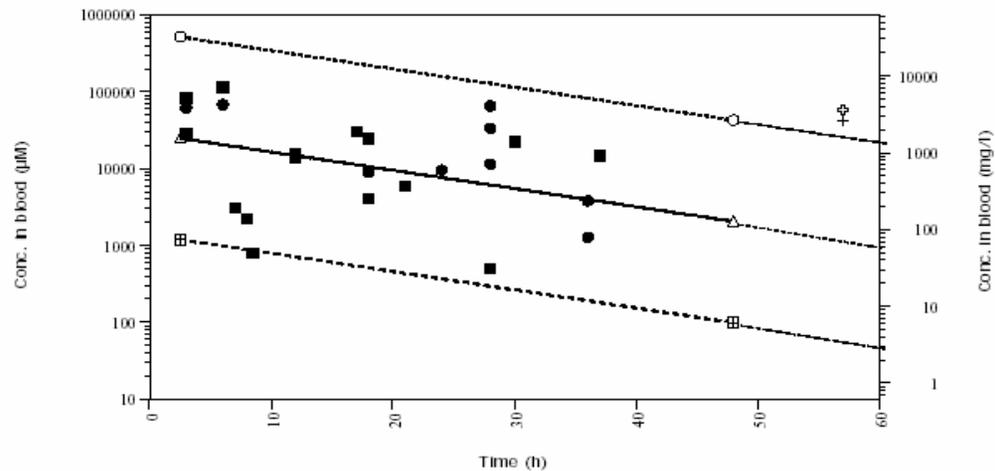
## Study objectives:

- Extent to which dose selection based on in vitro data can reduce the number of animals in acute toxicity studies
- Correlation with:
  - Human lethal concentrations
  - Rodent oral LD<sub>50</sub> values across the six GHS hazard categories
- Generate a high quality in vitro database to support development of additional methods to be included in a testing strategy

# In Vivo Data: The MEMO Monographs

<http://www.cctoxconsulting.a.se/database.htm>

Figure 1B. Human cases with lethal blood concentrations of Ethylene glycol



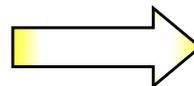
- Sub-lethal blood concentrations plotted versus time to derive an  $LC_{100}$  curve (upper limit for survival)
- Lethal concentrations plotted versus time to derive an  $LC_0$  curve (lower limit for lethality)
- An  $LC_{50}$  curve calculated as the average of the  $LC_{100}$  and  $LC_0$  curve
- Peak serum concentrations derived from  $LC_{50}$  curves

# In Vivo Data

41 of 72 chemicals selected for the NICEATM-ECVAM study are MEMO chemicals

Contract made to Expertrådet for the collection of data for:

- Aminopterin (no data found)
- Sodium selenate anhydrous
- Cadmium II chloride
- Acetonitrile



44 chemicals with reliable human data

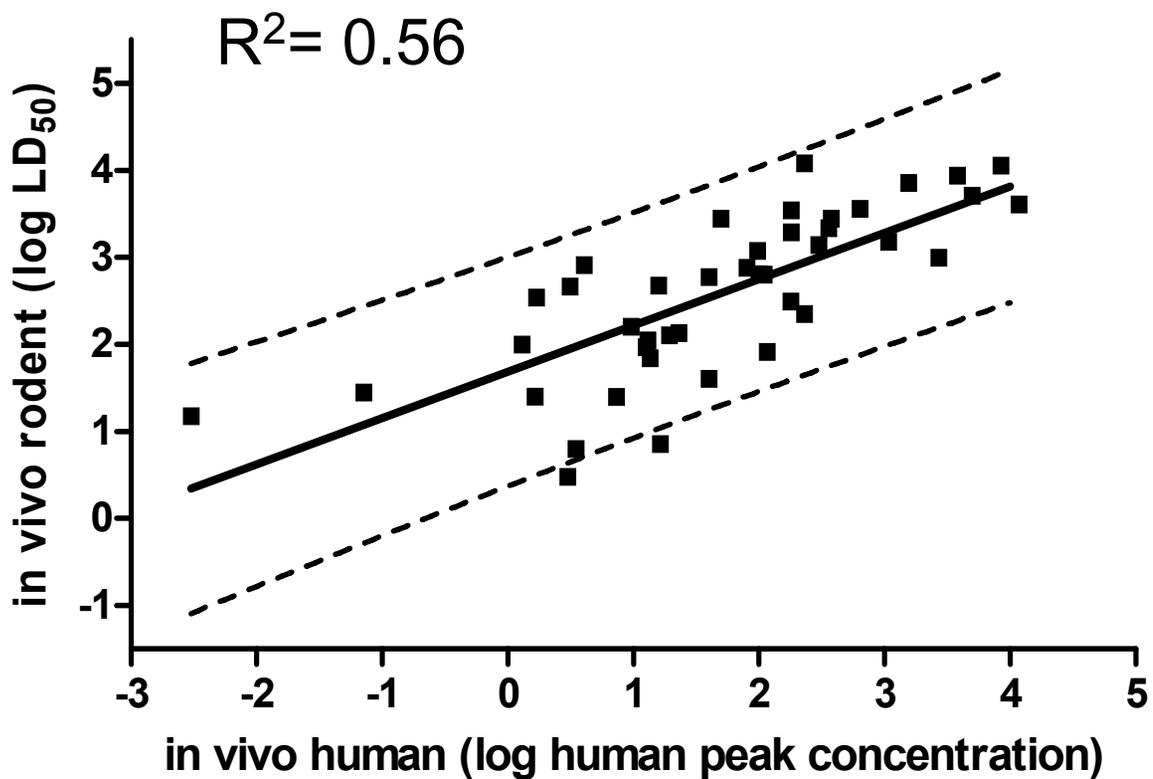
- 24 Handbooks and clinical & forensic medicine tabulations
- **Databases:** Medline Toxnet HSDB IRIS ITER Toxline, TRI and ChemIDplus, POISINDEX and Thomes, Micromedex, 2003, RTECS, NIOSH
- 20 Poison Information Centres

# In Vitro Data

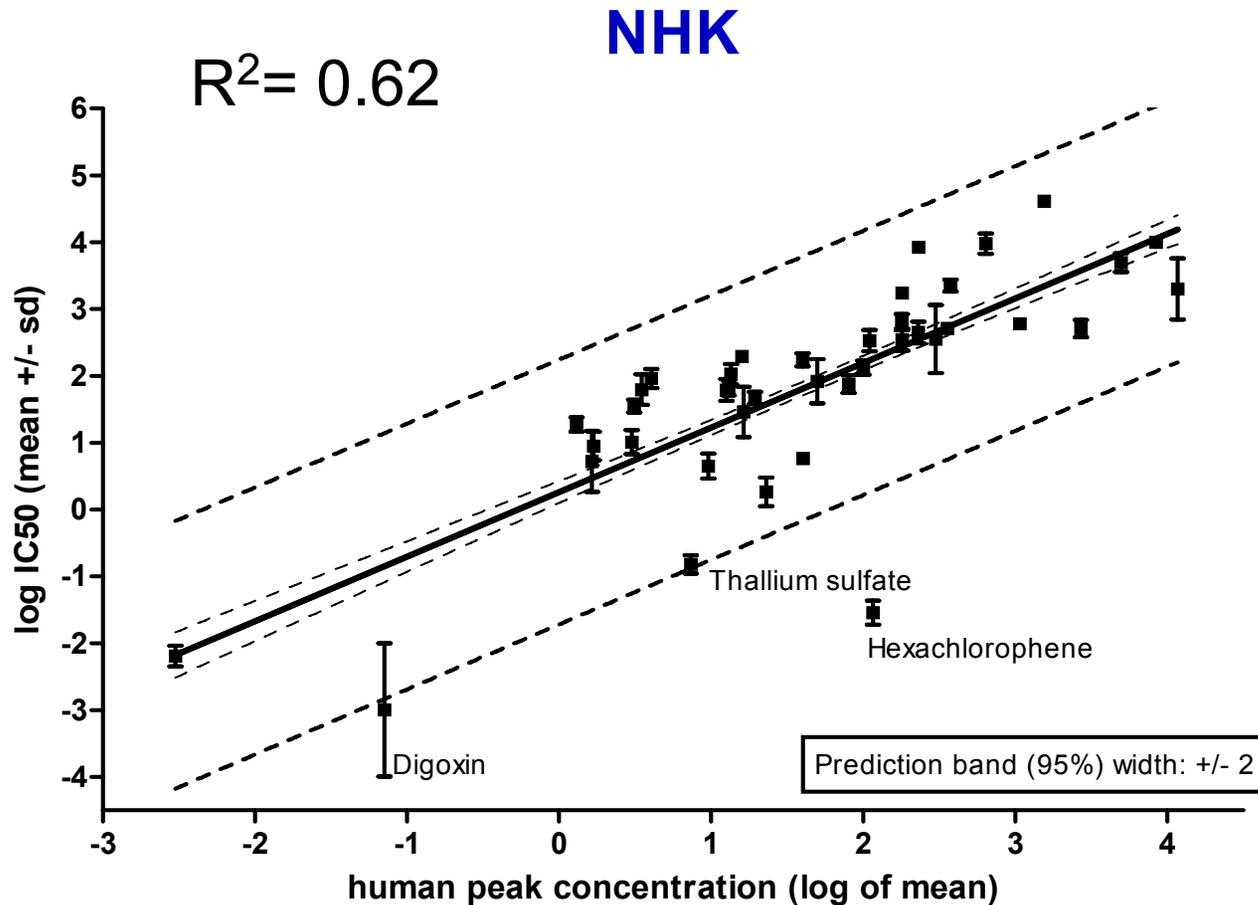
- **IC<sub>50</sub> values obtained in the different labs for each chemical**
- **At least 4 IC<sub>50s</sub> from two different labs and consistent results**

<b>3T3</b>	<b>NHK</b>
Excluded chemicals	Excluded chemicals
<b>Carbon tetrachloride</b> (1 IC <sub>50</sub> value from one lab)	<b>Carbon tetrachloride</b> (1 IC <sub>50</sub> value from one lab)
<b>Xylene</b> (4 IC <sub>50</sub> values - two different labs but inconsistent data)	<b>Xylene</b> (3 IC <sub>50</sub> values from one lab)
<b>Methanol</b> (no IC <sub>50</sub> values)	
<b>Lithium Carbonate</b> (3 IC <sub>50</sub> values -one lab)	
<b>Tot: 40 chemicals</b>	<b>Tot: 42 chemicals</b>

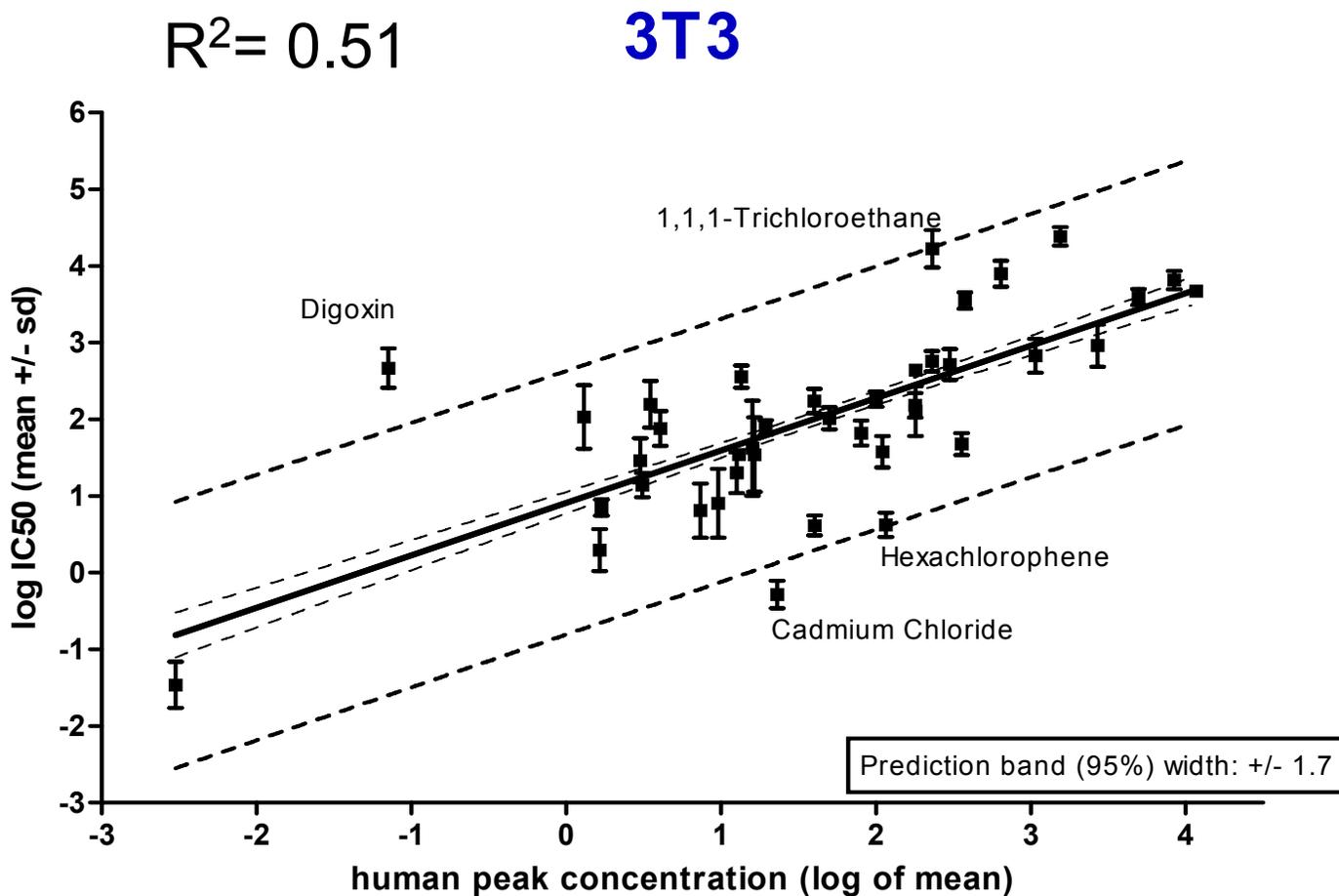
# In Vivo - In Vivo Correlation



# Human In vitro – Human In Vivo correlation



# Mouse In Vitro – Human In Vivo Correlation



# In Vitro-in Vivo correlation

$R^2 = 0.56$

	In vivo human	In vivo rat
In vitro human (NHK)	$R^2 = 0.62$	$R^2 = 0.53$
In vitro mouse (3T3)	$R^2 = 0.51$	$R^2 = 0.44$

# Conclusions

- **Human and mouse in vitro tests predict similarly rodent in vivo results.**
- **The human in vitro test tends to better predict human LC<sub>50</sub>s than the murine one.**
- **The human in vitro test predicts human lethality at least as good as the acute rodent study.**
- **Efforts within the A-Cute-Tox Integrated Project aim to improve this prediction further.**