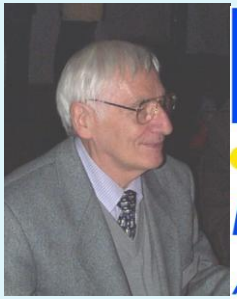
Der Landestierschutzbeaufragte



EUSAAT

European Society for Alternatives to Animal Testing

EUSAAT2013 - Linz (Austria)
15-18 September 2013

Willi Halle Memorial Lecture

Dr. med. Horst Spielmann
Professor for Regulatory Toxicology, FU Berlin
& Sate Animal Welfare Commissioner, Berlin

Topics

I. Bjorn Ekwall & Willi Halle: concept of “basal cytotoxicity”
II. The history of cellular pathology
III. Willi Halle as an isolated scientist in East Germany
IV. Society for Cell and Tissue Culture (GZG)
V. 1985 patent on “method for predicting LD-50“ from cytotoxicity data
VI. The Register for cytotoxicity RG – US, OECD & EURL ECVAM
VII. National and international recognition of the RC
VIII. Honorary membership GZG & MEGAT/EUSAAT

History of Cytotoxicity Testing

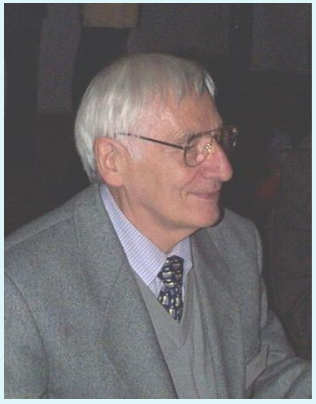
Two pioneers have in the 1980ies proposed the concept of "basal cytotoxicity" for *in vitro* prediction of *in vivo* toxicity

Björn Eckwall

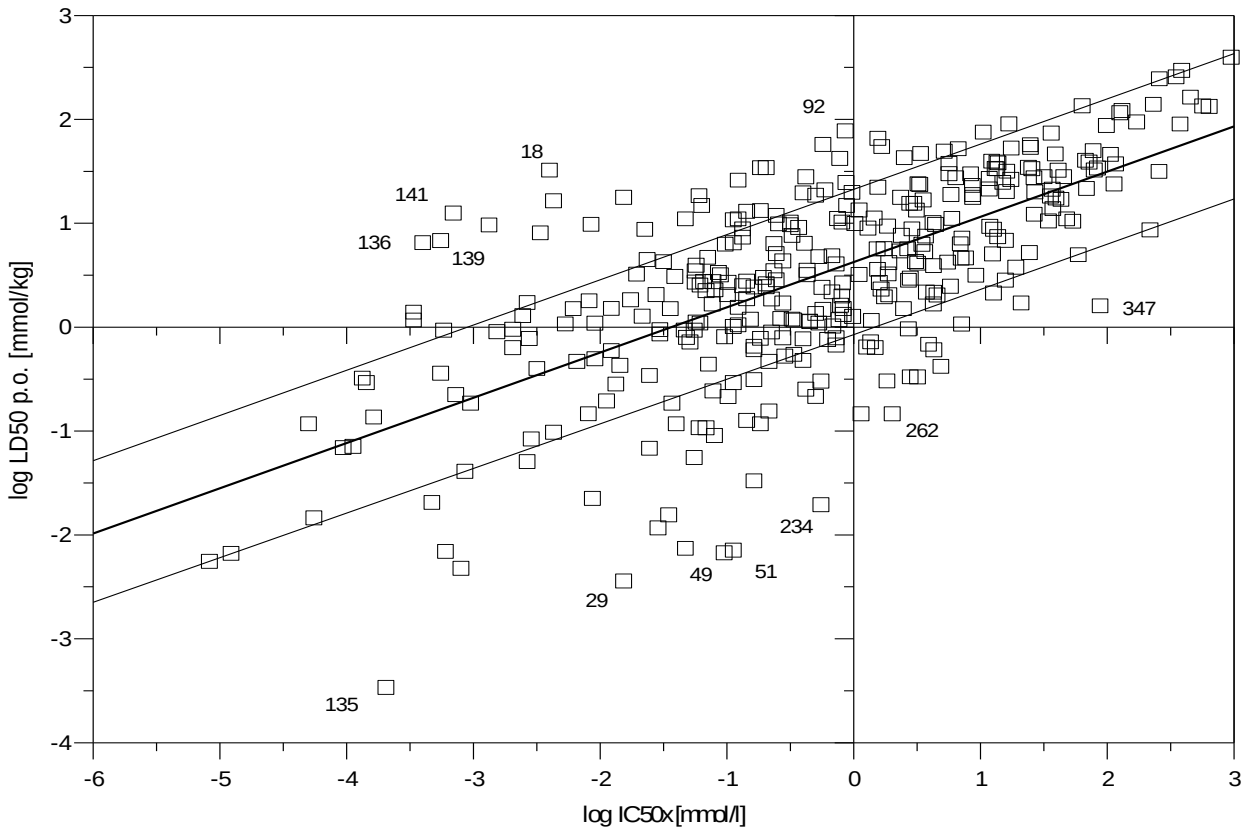
(The MEIC Program

Willi Halle

(The Register of Cytotoxicity)



RC 1,2: Linear Regression



$\log (LD_{50}) = 0.435 \times \log (IC_{50x}) + 0.625$ (n = 347 data pairs)

Today Cytotoxicity is the basis of in vitro toxicology
Who has laid the foundations for this concept of modern toxicology ??

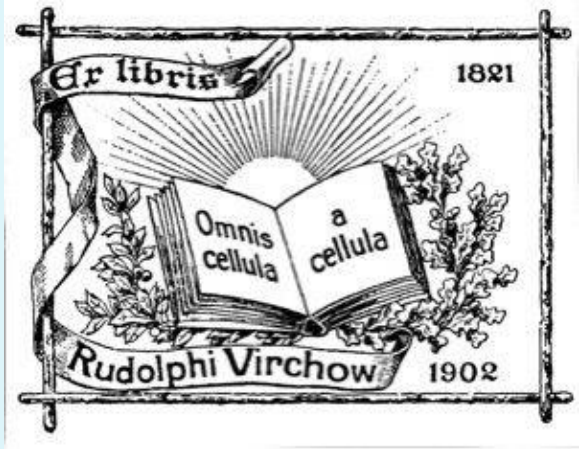
Rudolf Carl Virchow

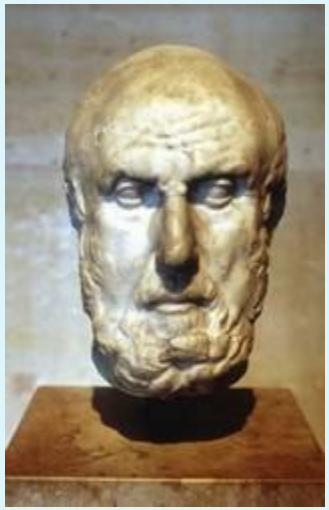
In 1858 Rudolf Virchow established the science of ***cellular pathology*** *"Zellularpathology"* when he published the epigram

Omnis cellula e cellula

"every cell originates from a cell"

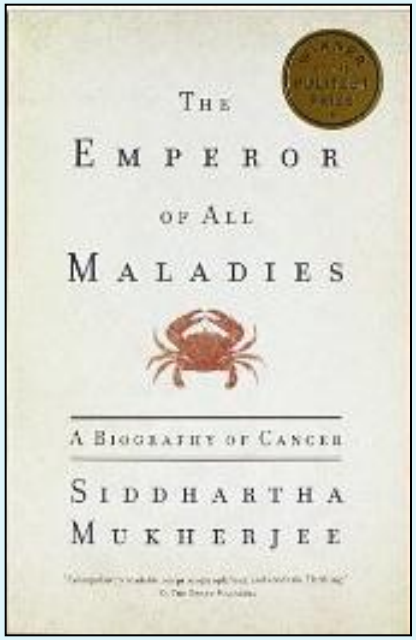
In a series of 20 brilliant consecutive lectures covering the pathophysiology of disease that formed the basis of his book, ***Cellular Pathology – one of the greatest medical texts of all time.***





Hippocratic Method and the Four Humors in Medicine

The body of man has in itself blood, phlegm, yellow bile and black bile; these make up the nature of his body, and through these he feels pain or enjoys health. Now he enjoys the most perfect health when these elements are duly proportioned to one another in respect of compounding, power and bulk, and when they are perfectly mingled.



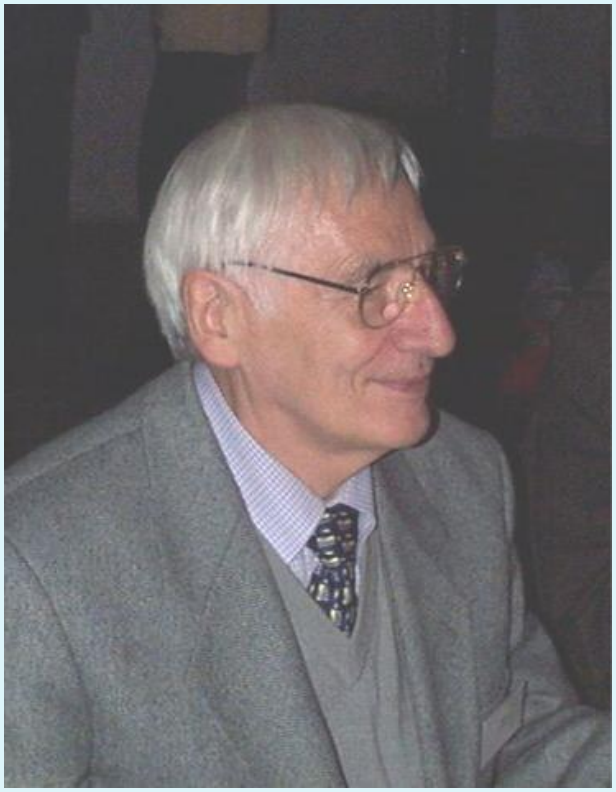
2011

Hippocrates: Cancer could not be treated by surgery, since if you cut off a tumor the black bile is still in the rest of the body and not eliminated.

Virchow could not find any evicence of „black bile“ in the body. His tumor theory is based on cellular pathology (1858):
Omnis cellula e cellula "every cell originates from a cell”
A single cancer cell will divide continously and give rise to malignant tumor cells spreading throughout the body.

The modern stem cell concept (ESC & iPS) is also based on Virchow‘s concept ***„Omnis cellula e cellula ("every cell originates from a cell”)***

Who is Willi Halle ?



- born 30 October 1928
  in Erfurt (Thuringia)
- 1949-1956 study (Biology)
  at the University of Jena
- since 1956 married, 2 children
- 1956 - 1993 scientific work in two Institutes of the East German "Akademie der Wissenschaften"
  - 1956-1971 Institute for Cardiological Research, Berlin
  - 1971 - 1993 Institute for Drug Research ("Institut für Wirkstofforschung, IWF"), Berlin

- 1963 promotion (Dr.rer.nat.) on spontaneously contracting cardiomyocytes
- 1969 habilitation at the Humboldt University of Berlin on the model character of spontaneously contracting cells (heart and amnion)

Who is Willi Halle ?

- **1962 Willi Halle founded East German “Society for Cell- and Tissue Culture (GZG)” which first was a Section of the “Society of Experimental Medicine”.**
- **From 1964 Willi Halle was for several years President of the GZG and until 1991 member of the presidium**
- **In 1991, after German unification, the GZG formed the core Society when the West and East German Cell Culture Societies were merged.**

13 August 1961: East- and West-Germany separated by a tight border & Berlin by the “Berlin Wall”

The East German "Isolation" Policy...

... severely affected Willi Halle's scientific development and career:

While

- **in 1961 a 3 month scientific fellowship at the marine zoological station of the University of Naples was possible**
- **attending two international Congresses in Stockholm (1961) and Brussels (1968) was possible**

Willi Halle was not allowed

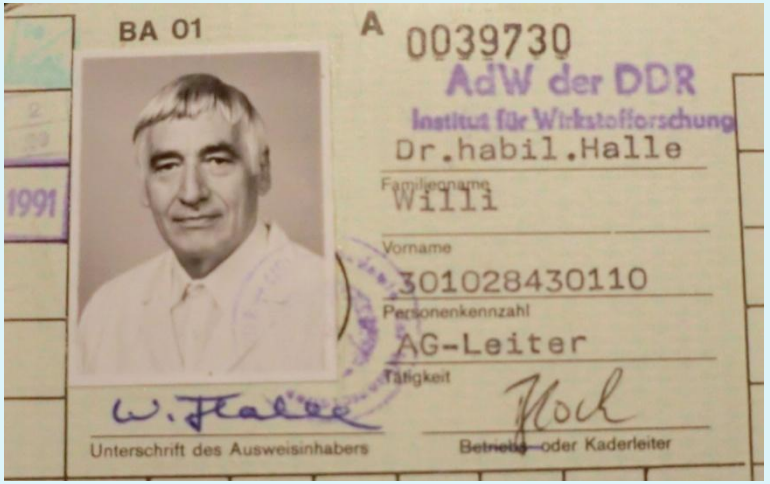
- **in 1965, to accept a 1-year Riker-Fellowship for a stay in the USA awarded to him by the International Union of Pharmacology**
- **after the "reform" of the Academy of Science in 1969, to accept any invitation to western countries, among them the most prominent by his colleagues Michael Balls and Björn Eckwall**

As a free-minded Scientist...

Willi Halle did not accept these politically driven restrictions

As a consequence, at the “Institut für Wirkstoffforschung” Willi was degraded from his position as Group-Leader and Deputy Head of a Department (1971) to become head of a small cell culture laboratory (1989).

Moreover, after publication of his first “Register of Cytotoxicity (RC)” in 1988, he was forced to stop further work on the RC, and to do other, non-promising work instead.



On 9 November 1989, Willi Halle's scientific working conditions changed over night

The Berlin Wall fell ...

...and already 3 days later, on 12 November 1989, Willi Halle had an appointment with Horst Spielmann, head of the new institution ZEBET at the (Federal Health Office, BGA) in West Berlin.

For Willi Halle, this political development was just to good to be true, and his scientific scepticism made him not believe his eyes and ears...so he wanted to rescue the RC for the scientific community before it was too late.

Prof. Wollenberger

Willi Halle

Prof. Wollenberger‘s cardiovascular research team 1963

Laboratorium für Zellzüchtung. 1962
Dr Willi Halle, Fr-Schieweck, Fr. Claus

Inst. for cardio-vasculsr research 1963

Vorder- und Hinterfront des "Laborgebäudes
der Arbeitsstelle für Kreislaufforschung"

November 1963

GESELLSCHAFT

ZUR VERBREITUNG

WISSENSCHAFTLICHER

KENNTNISSE

KREISVORSTAND MITTE

BERLIN C 2, NEUE KÖNIGSTR. 65

TELEFON: 51 03 91

APPARAT 216

Dalmatinische Reise

Strahlende Sonne, blaues Meer – ist meist alles, was wir von diesem Himmelsstrich wissen.
Herr Dipl. Geogr. **Hans-Ulrich Pews** schildert Ihnen mit schönen Farblichtbildern Land und Leute.

Am 5. Juni 1963

Die Kultivierung lebender Zellen und Gewebe

Herr Dipl. Biol. **W. Halle,** Arbeitsstelle für Kreislaufforschung in Berlin-Buch, beantwortet Ihnen die Frage, ob Zellen außerhalb des Organismus weiterleben können und berichtet von der Bedeutung, die sich für den erkrankten Menschen daraus ergibt. (Lichtbilder)

Am 12. Juni 1963

Australien – Traum und Wirklichkeit

Herr Dr. **Ernst Adler** macht diesen fernen Erdteil in Farblichtbildern für Sie lebendig und zeigt Ihnen Licht und Schatten.

Am 19. Juni 1963

Diese Vorträge beginnen pünktlich 18.45 Uhr im Museum für Naturkunde, Invalidenstr. 43. Eintritt: DM 1,- / Studenten: DM 0,50. Für Mitglieder freier Eintritt! Das Museum ist bereits ab 15 Uhr für die Besichtigung geöffnet.

(304) VEB Graph. Werkst. Bln., Werk III/2 Ag 056/63 03 0793

Willi Halle 1963
Mesuring the effect of digoxin on the contractivity of cultured heart cells

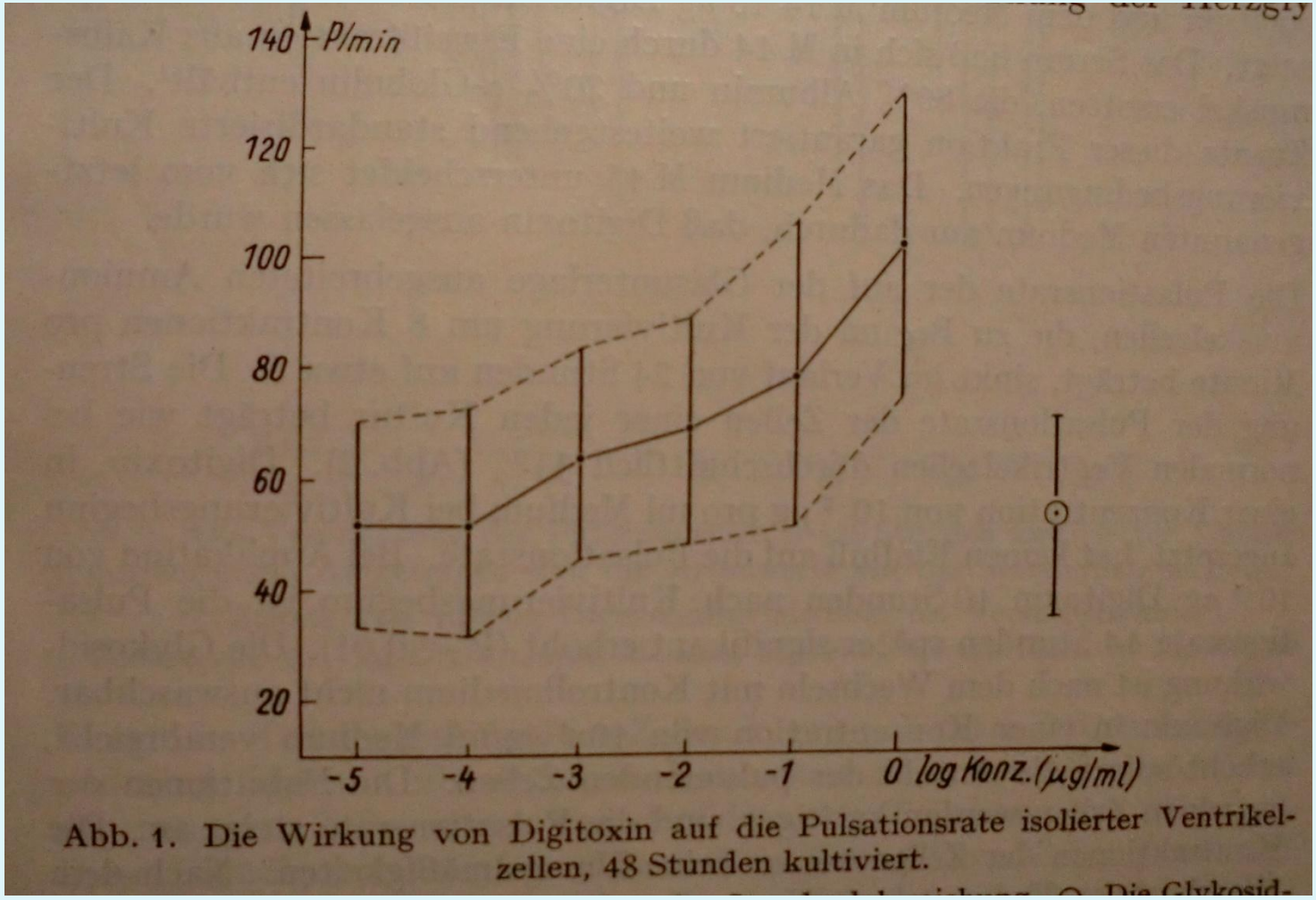
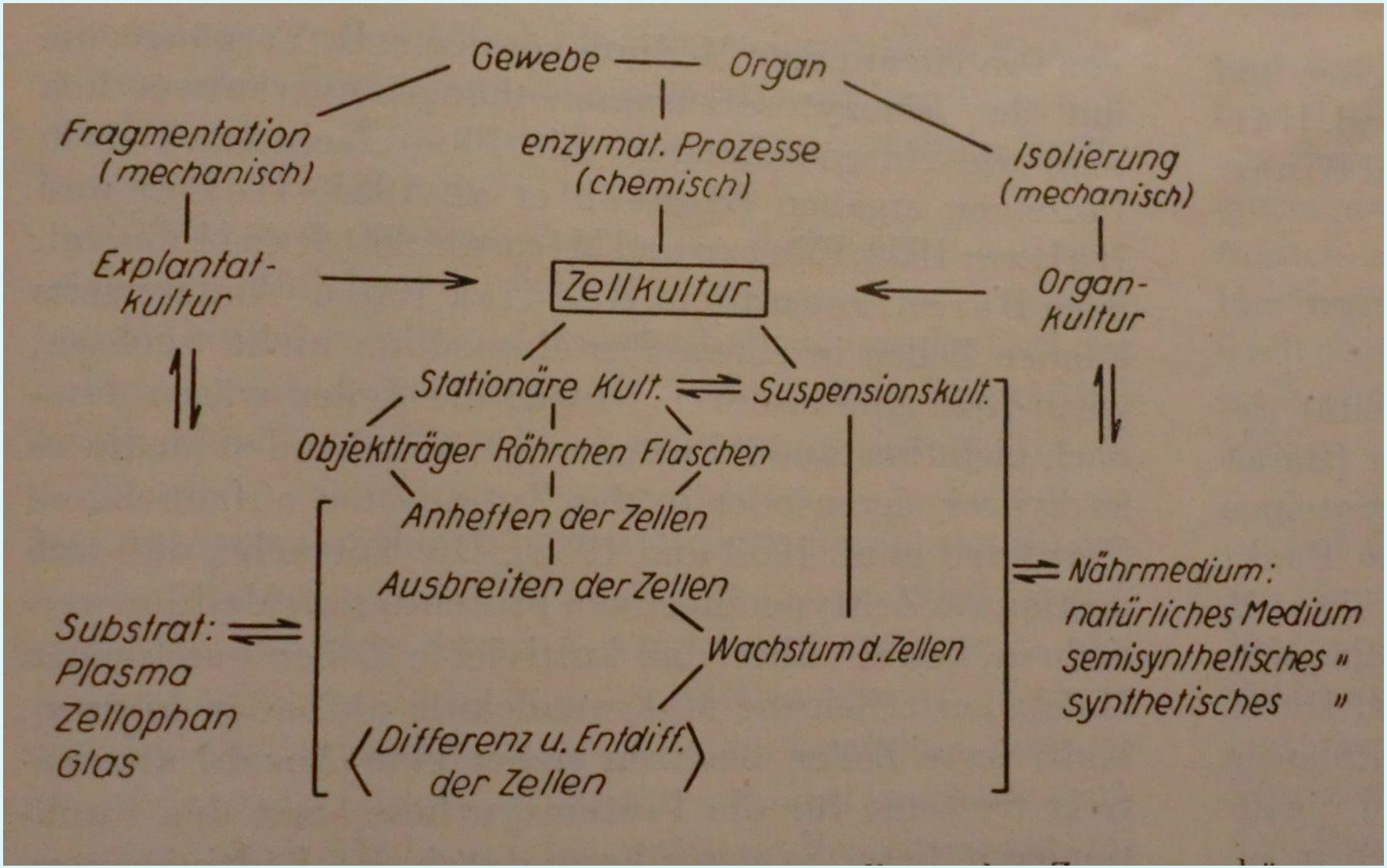


Abb. 1. Die Wirkung von Digitoxin auf die Pulsationsrate isolierter Ventrikelzellen, 48 Stunden kultiviert.

Willi Halle‘s cell culture scheme in 1963



BOOK Cell & Tissiue Culture 1966

Probleme der Zell- und Gewebezüchtung

unter besonderer Berücksichtigung der Struktur
und Funktion der Zelle

1. Arbeitstagung
der Arbeitsgruppe Zell- und Gewebezüchtung
Berlin, am 22. und 23. Mai 1964

Redaktion
Dr. rer. nat. W. Halle
Vorsitzender der Arbeitsgruppe Zell- und Gewebezüchtung

Mit 36 Abbildungen im Text
und 46 Abbildungen auf 16 Tafeln

VERLAG THEODOR STEINKOPFF
DRESDEN UND LEIPZIG
1966

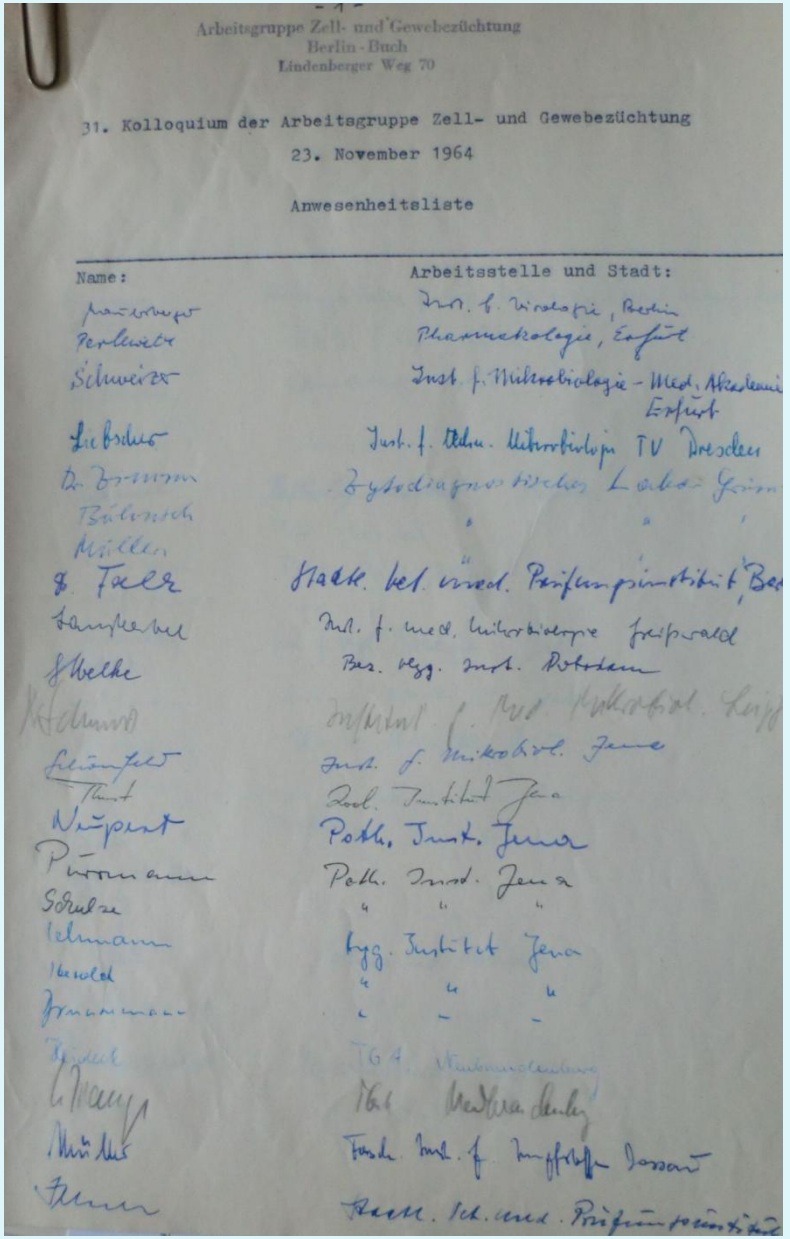
Establishing GZG in 1964

GRÜNDUNGSPROTOKOLL

für den Verein
Gesellschaft für Zell- und Gewebezüchtung e. V.

Mit dem heutigen Tage, dem um Uhr gründen die Unterzeichnenden den Verein "Gesellschaft für Zell- und Gewebezüchtung e. V." mit Sitz in Berlin. Der Verein soll der Förderung der Wissenschaft und Forschung dienen und in das Vereinsregister eingetragen werden.

Die Gründungsversammlung findet statt in



Arbeitsgruppe Zell- und Gewebezüchtung
Berlin-Buch
Lindenberger Weg 70

31. Kolloquium der Arbeitsgruppe Zell- und Gewebezüchtung

23. November 1964

Anwesenheitsliste

Name:	Arbeitsstelle und Stadt:
[illegible]	Inst. f. Virologie, Berlin
Perlewitz	Pharmakologie, Erfurt
Schweizer	Inst. f. Mikrobiologie - Med. Akademie Erfurt
Liebscher	Inst. f. theor. Veterinärbiologie TU Dresden
Dr. Brown	Zytodiagnostisches Labor Jena
Bülowius	" " "
Müller	" " "
G. Fischer	Stadt. bet. med. Prüfungsinstitut, Berlin
Kampschulte	Inst. f. med. Mikrobiologie Greifswald
Helke	Bez. hygg. Inst. Potsdam
[illegible]	[illegible]
Lindner	Inst. f. Mikrobiol. Jena
[illegible]	Zool. Institut Jena
Wüpper	Polikl. Inst. Jena
Pörtzmann	Polikl. Inst. Jena
Schulze	" " "
Lehmann	hygg. Institut Jena
Herold	" " "
[illegible]	" " "
[illegible]	TGA Naturwissenschaften
[illegible]	TGA Medizin Berlin
[illegible]	Forsch. Inst. f. Impfstoffe Dessau
[illegible]	Staatl. bet. med. Prüfungsinstitut

(19) **BUNDESREPUBLIK DEUTSCHLAND**

PATENTSCHRIFT

(12) **Wirtschaftspatent**

(11) **DD 241 750 B1**

Teilweise bestätigt gemäß § 18
Absatz 1 Patentgesetz der DDR
vom 27.10.1983
in Übereinstimmung mit den entsprechenden
Festlegungen im Einigungsvertrag

5(51) **G 01 N 33/15**
C 12 N 5/06

DEUTSCHES PATENTAMT

German Patent 1985

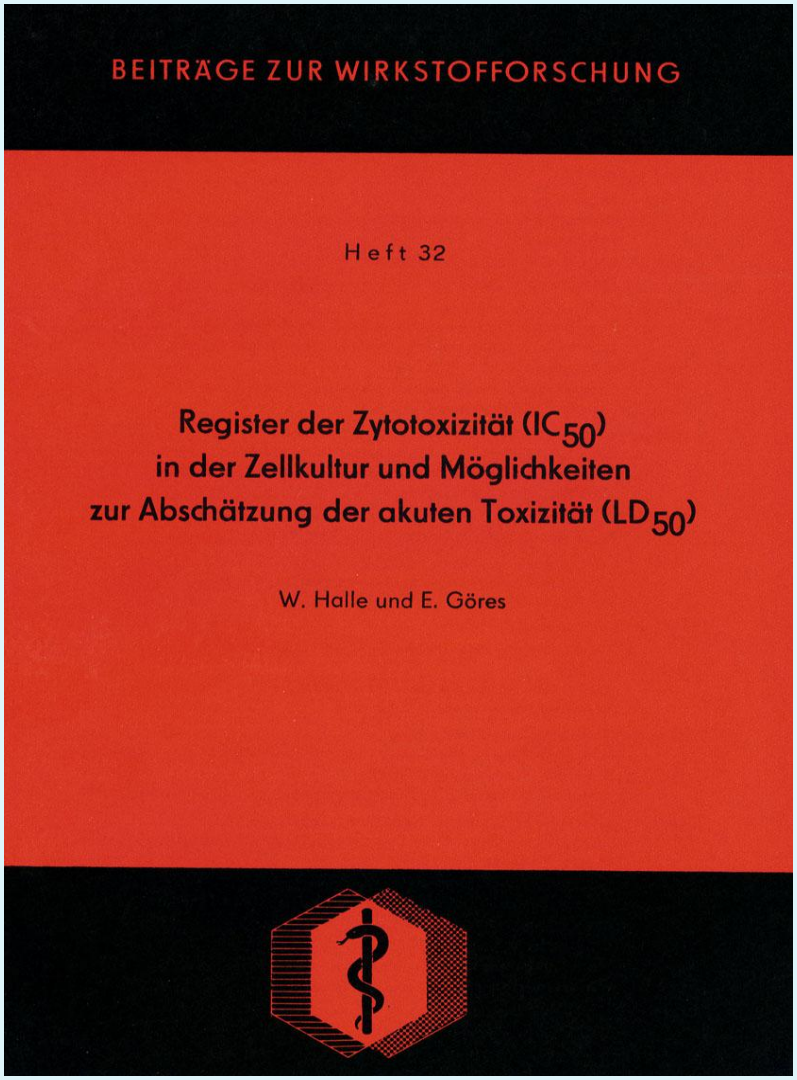
(21)	DD G 01 N / 281 743 3	(22)	15.10.85	(45)	11.06.92
				(45)	17.10.90
				(45)	11.11.87
				(44)	24.12.86

(71) siehe (73)
(72) Halle, Willi, Dr. rer. nat. habil. Dipl.-Biol.; Göres, Erhard, MR Prof. Dr. med. habil.; Janowski, Klaus, Dr. med., DE
(73) Akademie der Wissenschaften der DDR, Otto-Nuschke-Straße 22/23, O - 1086 Berlin, DE

(54) **Verfahren zur quantitativen Bestimmung der LD_{50}**

Method for determining the LD50

How it started: Willi Halle's Register of Cytotoxicity (RC)



The first Registrer, RC1

<u>Content</u>:
117 chemicals

<u>Per each chemical</u>:

- **several published IC_{50} values**
- **one LD50 value per species (mouse / rat) per administration route (oral / intravenious), taken from the *Registry of Toxic Effects of Chemical Substances (RTECS)***

... published 1988 by the "Institut für Wirkstofforschung (IWF)" in Berlin

The whole RC1 was created on a typewriter...

106 Acetylsalicylsäure — V0 0700 000 — Mm 180,17

Syn.: Aspirin

LD_{50}	: R p.o.	5,55	mmol
	M p.o.	4,52	mmol
IC_{50}	: 6.	9,9 -1	mM
	10.	4,2	mM
	13.	2,0	mM
		2,3 -1	mM
	14.	2,58	mM
	20.	2,03	mM
	22.	1,05	mM
		1,05	mM
	24.	6,55	mM
	34.	2,33	mM
	44.	2,05	mM
$IC_{50\bar{x}}$	:	1,70	mM
F_s		5,34	

107 Tolbutamid — YS 4550 000 — Mm 270,38

LD_{50}	: M p.o.	9,62	mmol
IC_{50}	: 6.	1,49	mM
	67.	2,20	mM
$IC_{50\bar{x}}$	:	1,81	mM
F_s		1,22	

2.5. Datenschlüssel

1. Zl: P-815 = Mastocytom, Maus
   IC_{50}: Zellproliferation: Zellzahl (sb: 001, 010, 0
   AbK, $t_E \geq 18$ h, Suspensionskultur

2. Zl: Ehrlich-Ascitestumor, Maus
   IC_{50}: Zellproliferation: Zellzahl
   AbK, t_E 22 h, Suspensionskultur

3. Zl: Diploide Fibroblasten, menschliche embryonale
   IC_{50}: Zellzahl, sb
   AnK, t_E 4 d

4. Zl: KB
   IC_{50}: Zellproliferation: Proteingehalt
   AbK, t_E 72 h (s. 86)

5. Zl: HeLa
   KB
   J-111 = Leukämie, Mensch
   C = Conjunctiva, Mensch
   G = Darmepithel, Mensch
   S-180 = Sarcom, Maus
   IC_{50}: Zellproliferation: Proteingehalt
   AnK, t_E 4 - 7 d mit mehrmaligem Wechseln des Versuchsmediums

6. Zl: HeLa
   IC_{50}: Stoffwechselhemmtest: pH-Änderung des Nährme
   Abk, t_E 7 d

7. Zl: HeLa-S3
   IC_{50}: Zellzahl: Optische Dichte
   AnK, t_E 72 h

... by Willi Halle's wife Siegrid

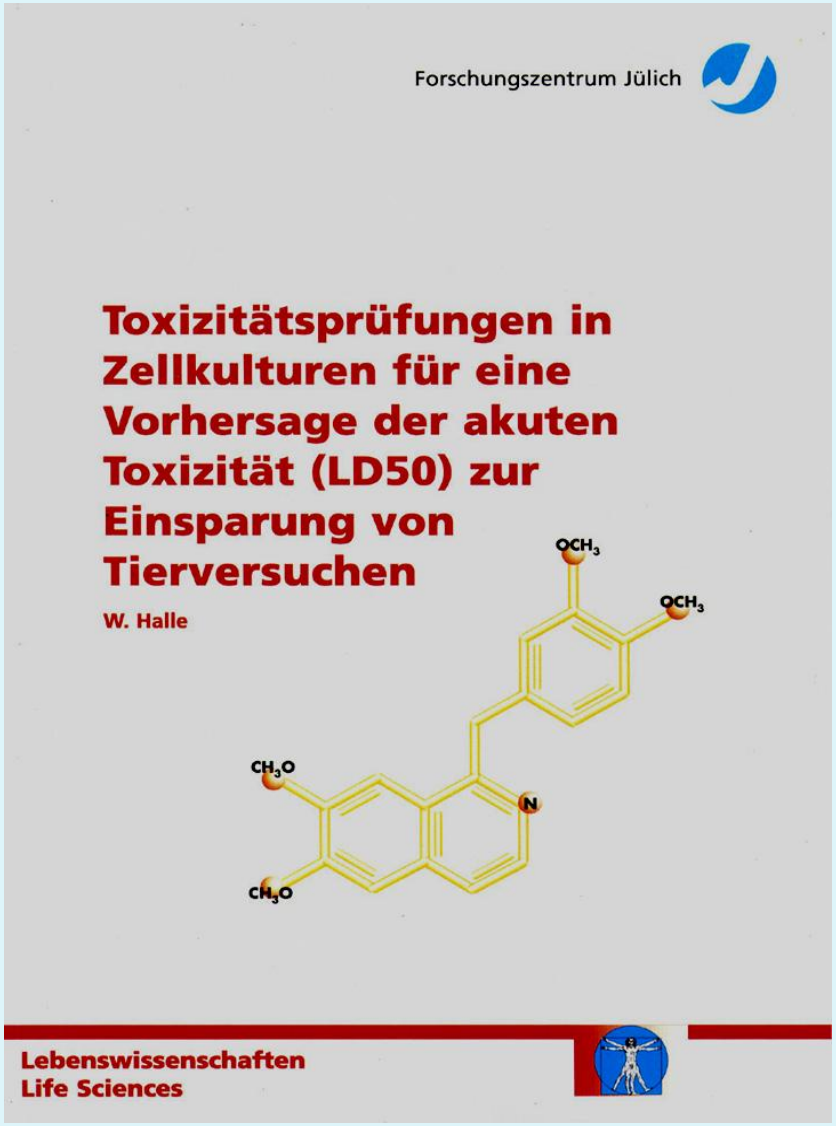
Willi Halle was sceptical about changes in East Berlin after the "wall fell" in 1989

he was punished at the IWF because of his contact to ZEBET, and only signs of solidarity, like a personal invitation by the President of the BGA, did improve his position at the IWF.

However, from January 1990 on

- **a continuous collaboration with ZEBET started**
- **Willi Halle received funding by the Ministry for Education, Science and Research (BMBF) to upgrade his RC**
- **Willi Halle was able to travel and stay for a month with Björn Eckwall and Eric Walum, Directors of the MEIC Programme**
- **Willi Halle became the best known guest in all scientific libraries in Berlin, in particular the library of the Schering AG**
- **Willi Halle became honouree member of several Scientific Societies, e.g. the SSCT and MEGAT**
- **after retirement (1993), Willi worked as an associated scientist at ZEBET on transferring the RC into a PC data base system.**

1998: Publication of the RC 1+2



347 chemicals

funded by the German Ministry for Education, Science and Research (BMBF 1998)

Halle‘s Register RC1,2 translated (ATLA 2003)

ATLA 31, 89–198, 2003

The Registry of Cytotoxicity: Toxicity Testing in Cell Cultures to Predict Acute Toxicity (LD50) and to Reduce Testing in Animals[1]

Willi Halle

c/o ZEBET at the BfR, Diedersdorfer Weg 1, 12277 Berlin, Germany

Translated by Marlies Halder,[2] Andrew Worth,[2,3] and Elke Genschow[4]

[2]European Centre for the Validation of Alternative Methods (ECVAM), Institute for Health & Consumer Protection, European Commission Joint Research Centre, 21020 Ispra (VA), Italy; [4]ZEBET at the BfR, Diedersdorfer Weg 1, 12277 Berlin, Germany

...in 1927 the physiologist John W. Trevan

...to estimate the relative poisoning potency of drugs and medicines because the use of death as a (quantal) toxicological endpoint allowed for comparisons between substances that poison the body in different ways.

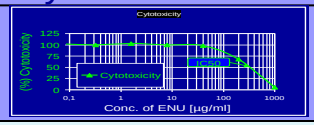
The LD_{50} gives a measure of the immediate or acute toxicity of a chemical in the strain, sex, and age group of a particular animal species being tested.

Primarily, the LD_{50} concept was not developed for predicting human lethal doses. However, it was used for this purpose lacking of other measures.

The concept of the RC

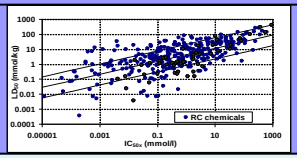
LD_{50} Data (NIOSH/RTECS)

Cytotoxicity Data from Literature

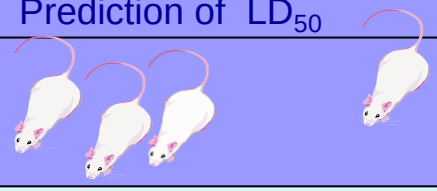


Data base

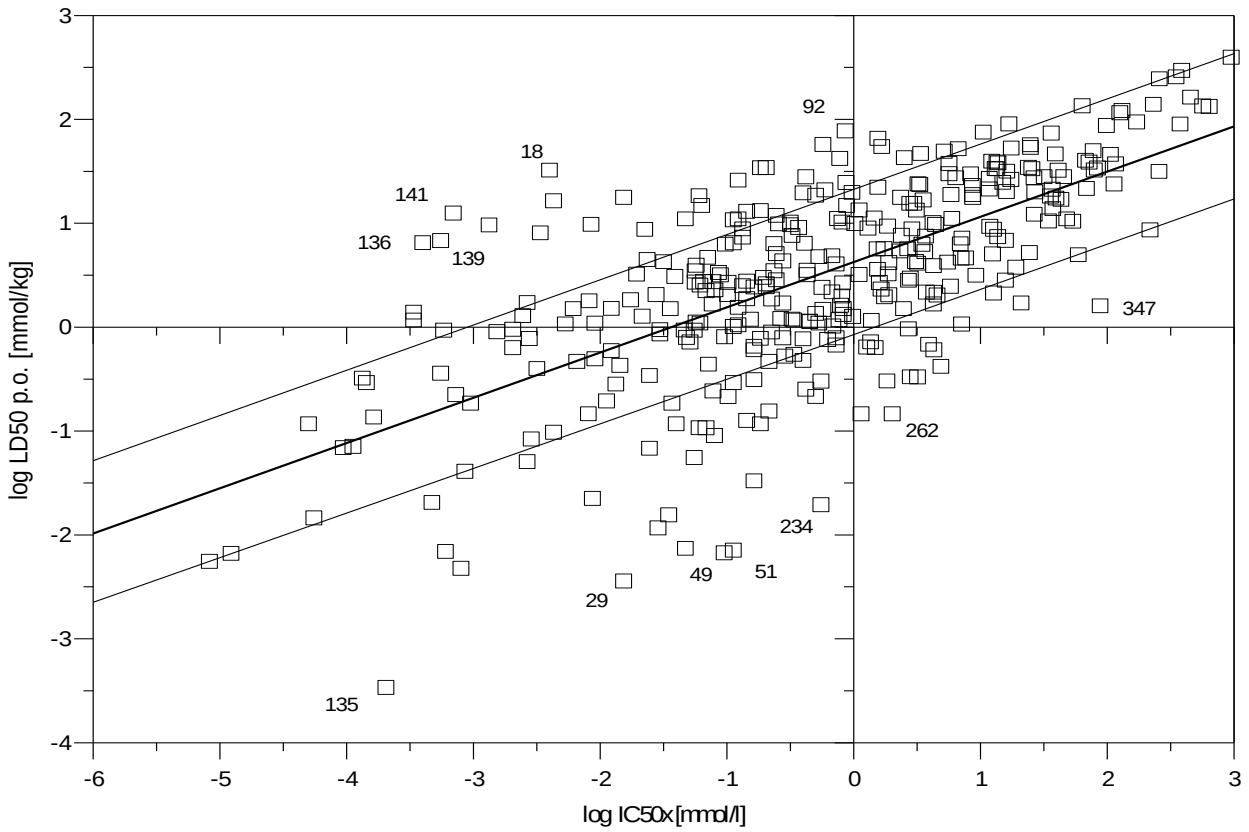
Linear Regression



Prediction of LD_{50}



RC 1,2: Linear Regression



$\log (LD_{50}) = 0.435 \times \log (IC_{50x}) + 0.625$ (n = 347 data pairs)

Halle's acceptance criteria for basal cytotoxicity data

- ➔ only mammalia cells (or cell lines)
- ➔ no hepatocytes (basal cytotoxicity!)
- ➔ incubation time with chemical ≥ 16 h
- ➔ at least 2 different IC_{50} values per chemical, derived...
  - from different labs
  - from one lab, but different cells /cell lines
  - from one lab, from one cell /cell line but different endpoints

- ➔ cell-proliferation markers
  - cell number
  - cell protein
  - DNA content,
  - DNA synthesis
  - colony formation
- ➔ metabolic markers
  - MIT-24 test
  - MTT
  - MTS
  - XTT
- ➔ membrane-markers
  - Neutral Red Uptake
  - Trypan-blue exclusion
  - Cell attachment /detachment
- ➔ differntiation markers

RC-N	Chemical	IC 50x	LD50 p.c	LD50 p.	LD50 i.	LD50 i.	Mol. Weigh	log P	FS	n IC50s	LD 50
1	Trenimon	0,0000033			0,0022		231,28		3,32	2	
2	Actinomycin D	0,0000081	0,0057	0,01	0,00037	0,0008	1255,6	3,21	64,5	13	0,0057
3	Aminopterin	0,000012		0,0068			440,47		45,6	8	0,0068
4	Vincristine sulfa	0,000019			0,0011	0,0018	923,14	2,82	20	21	
5	K-Strophantin	0,000044			0,021	0,0035	710,9		1,58	2	
6	Colchicine	0,000054		0,015	0,004	0,0043	399,48	1,03	469	13	0,015
7	Ouabain	0,000072			0,024		584,73		8,79	6	
8	Digitoxin	0,00011	0,073		0,012	0,0065	765,05	1,76	4,16	3	0,073
9	Amethopterin	0,00015	0,3	0,32	0,031	0,14	454,5	-1,85	48,1	18	0,3
10	Emetine	0,00016	0,14				480,71	3,24	2,71	3	0,14
11	Doxorubicin H	0,00033		1,2		0,036	580,03	1,27	49,2	8	1,2
12	Puromycin	0,00033		1,43			471,58	0,03	5,05	6	1,43
13	Cycloheximide	0,00059	0,0071	0,47	0,0089	0,53	281,39	0,55	44,4	32	0,0071
14	Mitomycin C	0,00084	0,042	0,051	0,009	0,015	334,37	-0,38	13,7	5	0,042
15	8-Azaguanine	0,0013		9,86		0,2	152,14	-0,71	4,8	4	9,86
16	Azaserine	0,002	0,98	0,87		0,36	173,15		6,67	9	0,98
17	5-Fluorouracil	0,0026	1,77	0,88	3,84	0,62	130,09	-0,89	22,4	15	1,77
18	Captan	0,0039	33,3	23,3	21		300,59	2,35	3,16	3	33,3
19	Cytochalasin B	0,005			1,64		479,67		2,39	2	
20	Cadmium II chl	0,0064	0,48	0,95			183,3		13,3	14	0,48
21	6-Mercaptopuri	0,008		1,84		0,53	152,19		55,2	12	1,84
22	Digoxin	0,008		0,023	0,032	0,0098	781,05	1,26	1790	10	0,023
23	Daraprim	0,0089		0,51			248,74	2,69	2,5	6	0,51
24	Ethylenediamin	0,01					292,28		3,07	3	
25	Thio-TEPA	0,011		0,2	0,079		189,24	0,53	2,49	8	0,2
26	Kelthane	0,012	1,55	1,13			370,48		5,31	2	1,55
27	Chlorpromazine	0,014	0,44	0,82	0,094	0,05	318,89	5,35	2,13	5	0,44
28	Aldosterone	0,014					360,44	1,08	40,1	3	
29	Mercury II chlor	0,015	0,0037	0,37	0,011	0,029	271,49		17,8	19	0,0037
30	Sodium arsena	0,015					185,91		4,21	4	
31	Chloroquine dip	0,017	1,88	0,97			515,92	4,63	18,7	10	1,88
32	Hydrocortisone	0,022					362,51	1,61	56,9	6	
33	p-Chloromercur	0,024		0,07			357,16		4,84	18	0,07
34	Diethylstilbestr	0,025				1,12	268,38	5,07	18,2	17	
35	Flufenamic acid	0,029	0,97	2,54	0,35	0,56	281,25	2,08	3,36	5	0,97

Validation of the RC

register	number of chemicals	r	a	b	$F_G \leq \log 5$ (%)
old	102	0.644	0.598	0.471	73.5
I	**117**	**0.667**	**0.637**	**0.477**	**73.5**
II	**230**	**0.666**	**0.634**	**0.414**	**72.6**
I & II	347	0.672	0.625	0.435	72.6

$LD_{50} = a + b \times \log IC_{50x}$

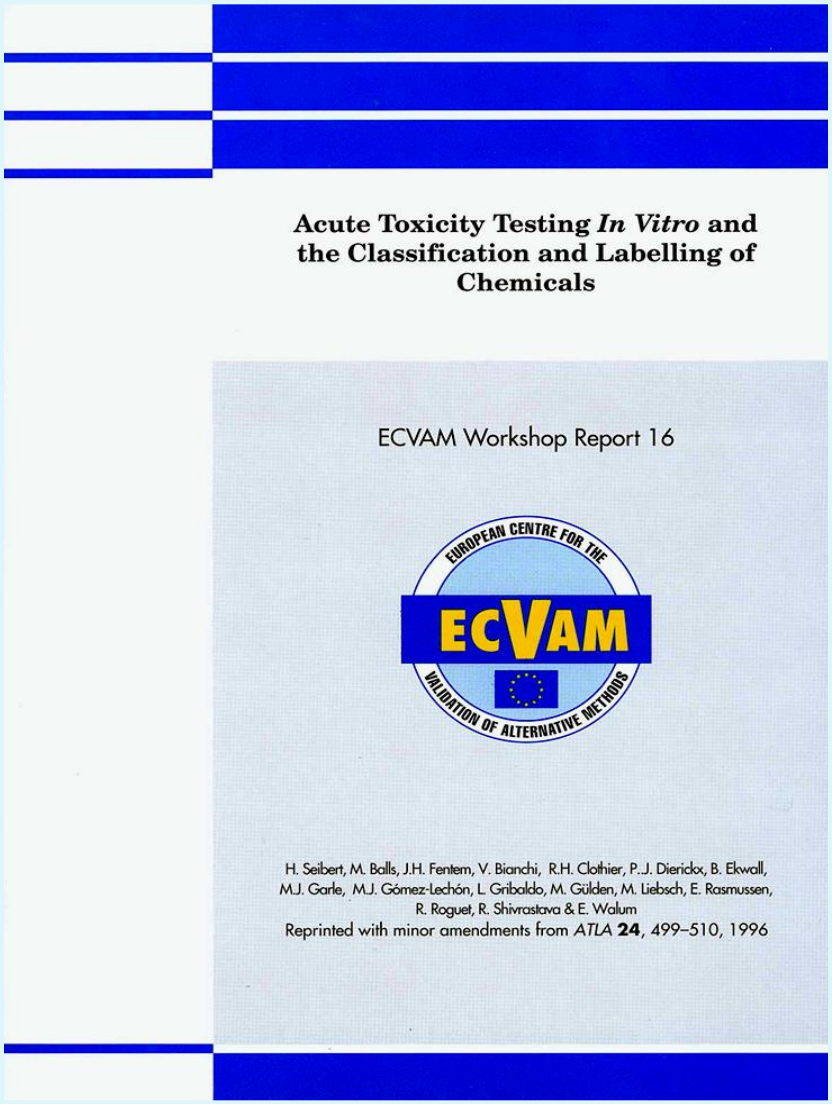
a = intercept

b = regression coefficient

r = correlation coefficient

Cell line	No. of chemicals	r	a	b	$F_G \leq \log 5$ (%)
BCL-D1	22	0.72	0.536	0.633	77
3T3-L1	91	0.72	0.631	0.427	74
RC: several cell lines	347	0.67	0.625	0.435	73

3R's step-by-step: The "starting dose approach"



In vitro **methods ....could, however, be used in a tier testing scheme to reduce the number of animals used...**

...in the new sequential dosing methods such as the acute toxic class (ATC) and up-and-down procedures (UDP).

In these *in vivo* tests, use of the minimum number of animals possible depends upon the correct choice of the starting dose.

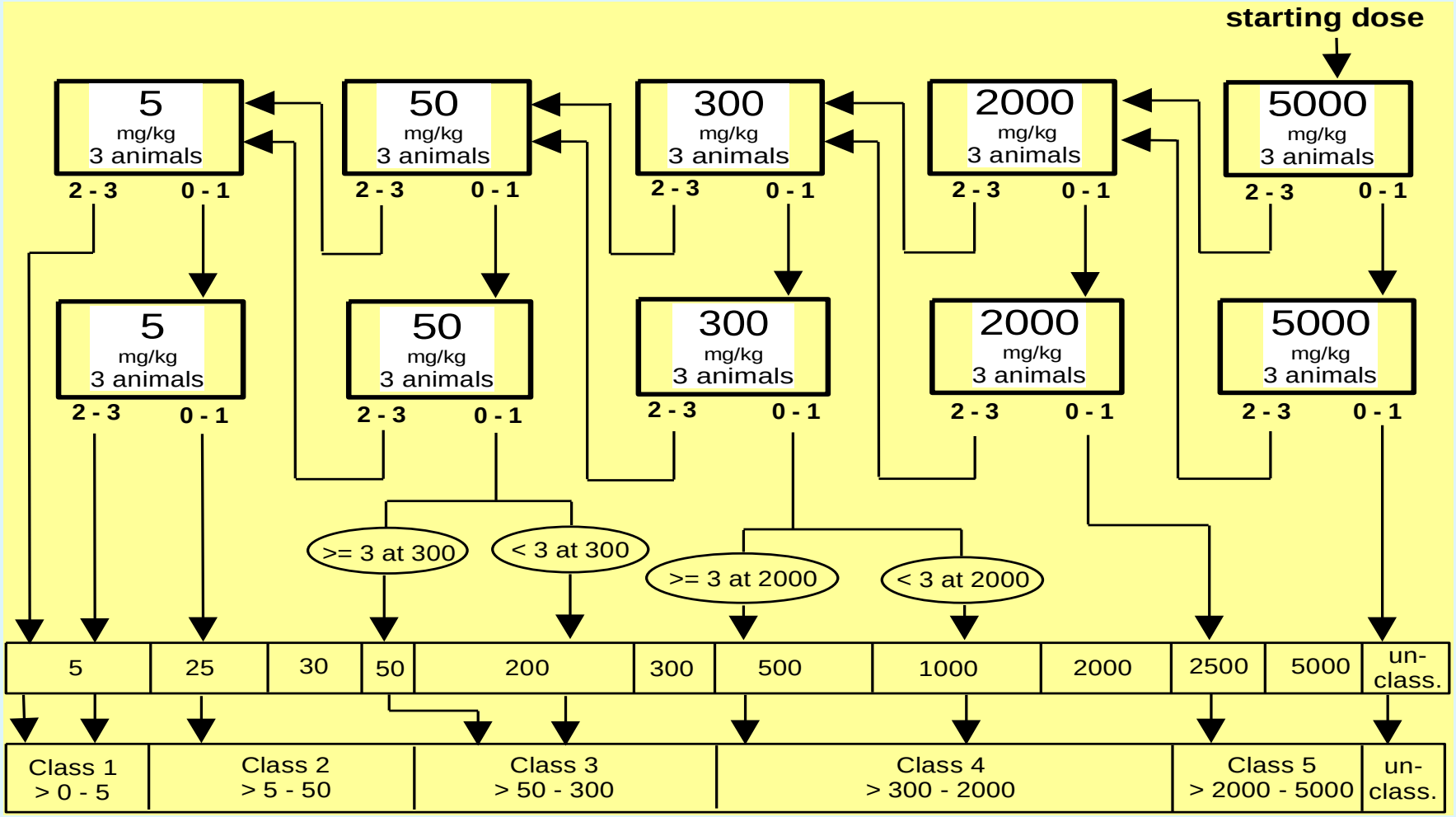
ATLA 27, 957–966, 1999

Determination of the Starting Dose for Acute Oral Toxicity (LD50) Testing in the Up and Down Procedure (UDP) From Cytotoxicity Data

Horst Spielmann, Elke Genschow, Manfred Liebsch and Willi Halle

ZEBET, BgVV, Diedersdorfer Weg 1, 12277 Berlin, Germany

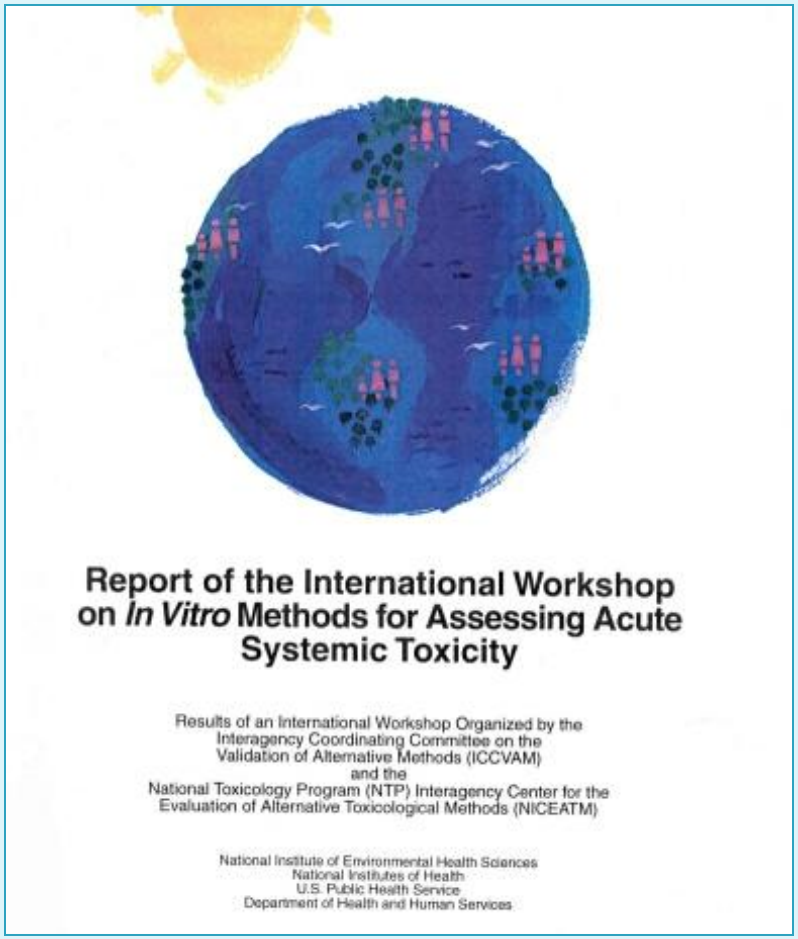
The ATC Method (OECD TG 423)



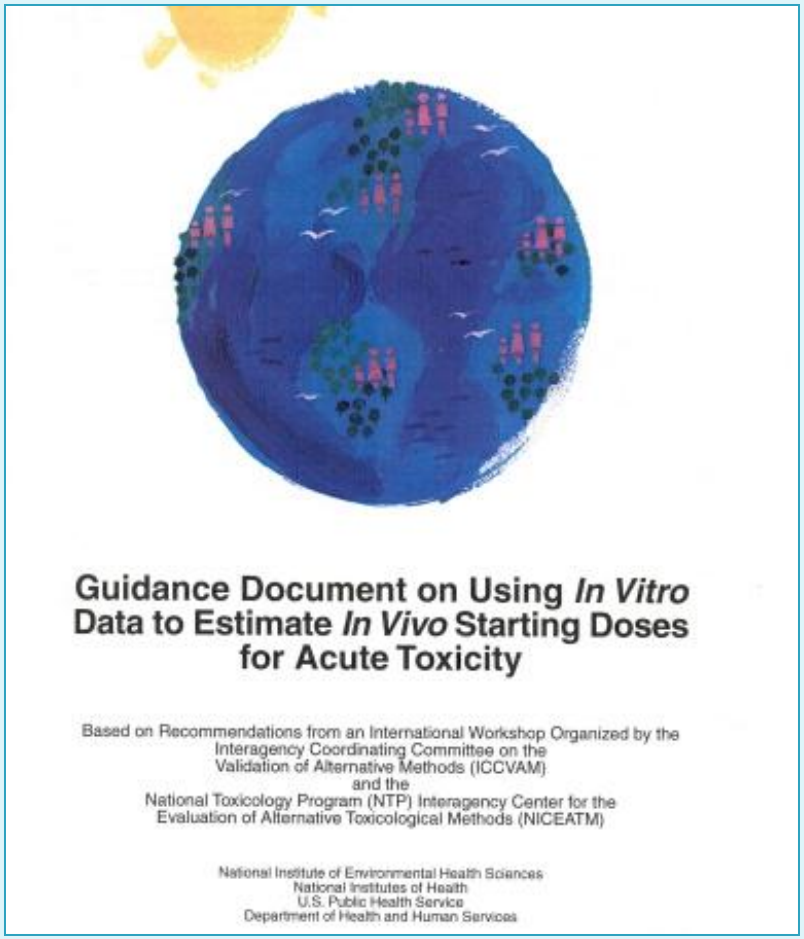
ATC Method: influence of the starting dose on numbers of animals dying in acute oral toxicity testing (LD-50)

$\beta = 2$	Starting dose in mg/kg body weight					
	25		200		2000	
true LD_{50}	used	dead	used	dead	used	dead
1	3.0	3.0	6.0	6.0	9.0	9.0
2	3.0	3.0	6.0	6.0	9.0	9.0
5	3.1	2.8	6.1	5.8	9.1	8.8
10	3.4	2.7	6.4	5.6	9.4	8.6
20	4.6	2.8	7.2	5.3	10.2	8.3
50	7.5	3.3	8.6	4.2	11.6	7.2
100	9.3	3.2	9.3	3.3	12.2	6.2
200	11.2	3.2	9.7	3.1	12.0	5.3
500	14.0	3.3	9.3	3.3	10.0	3.9
1000	14.9	2.6	9.1	2.6	9.2	2,7
2000	15.4	1.8	9.4	1.8	9.3	1.8
5000	16.5	1.0	10.5	1.0	9.0	1.0
10000	17.3	0.4	11.3	0.4	7.7	0.4
20000	17.8	0.1	11.8	0.1	6.6	0.1
50000	18.0	0.0	12.0	0.0	6.1	0.0
100000	18.0	0.0	12.0	0.0	6.0	0.0

ICCVAM Workshop (2000) and publications (2001)



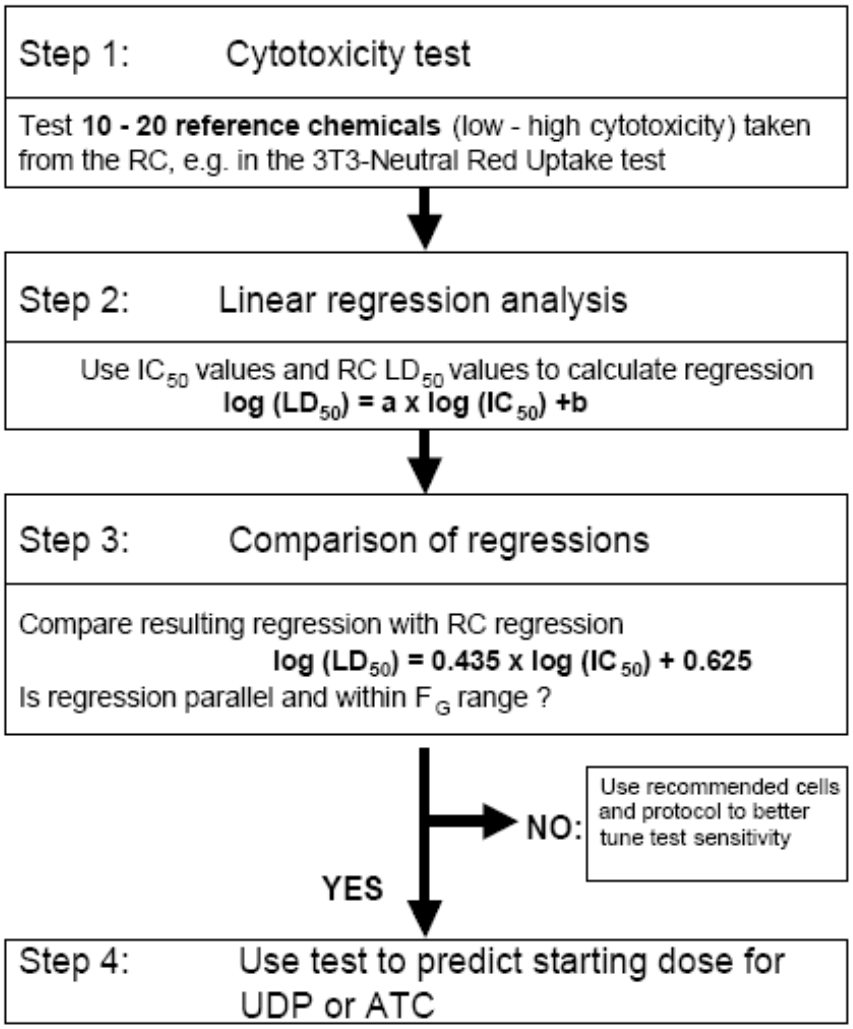
NIH Publikation No: 01-4499



NIH Publikation No: 01-4500

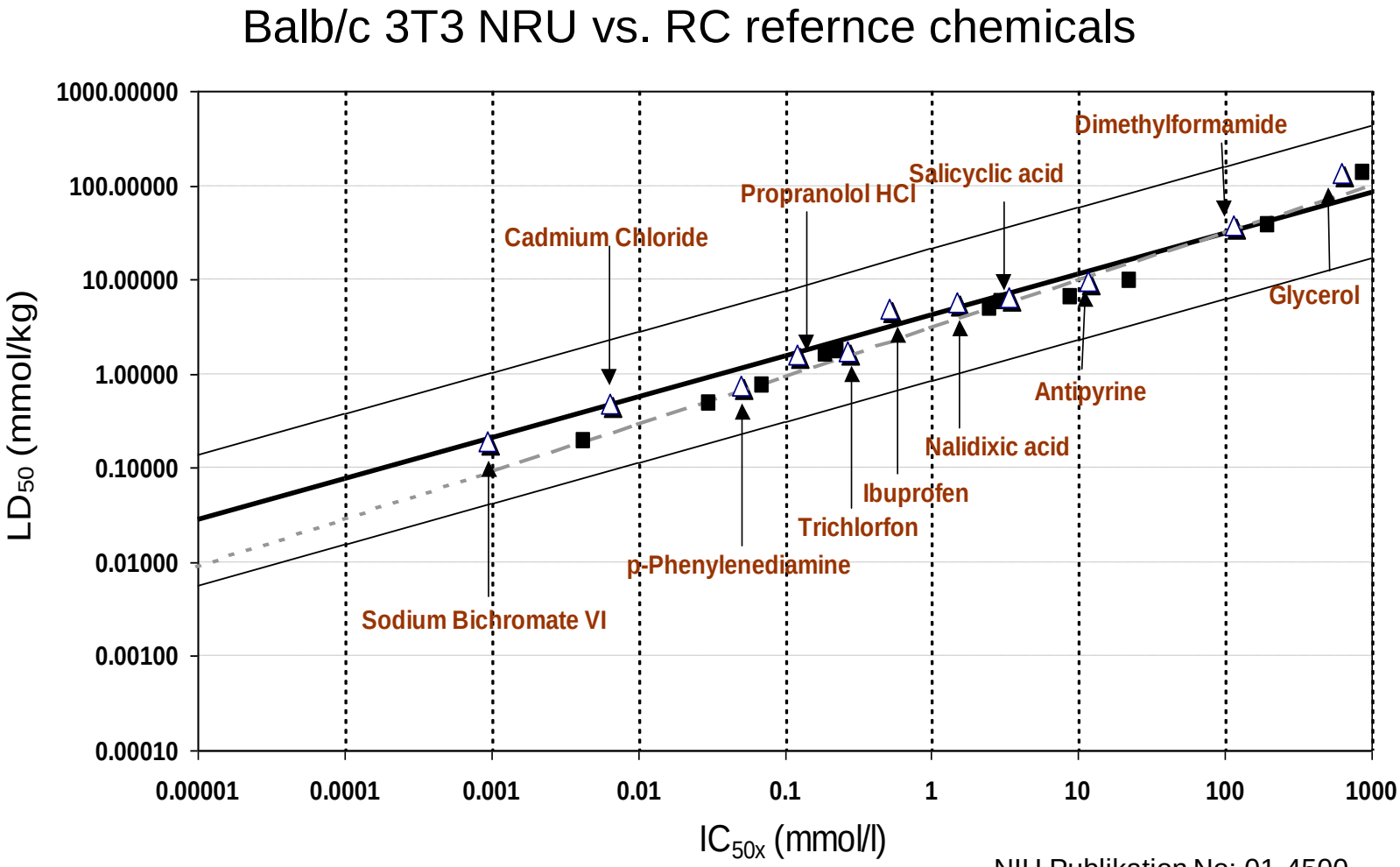
http://iccvam.niehs.nih.gov/

Check of any basal cytotoxicity assay if it can make use of Willi Halle's Prediction Model

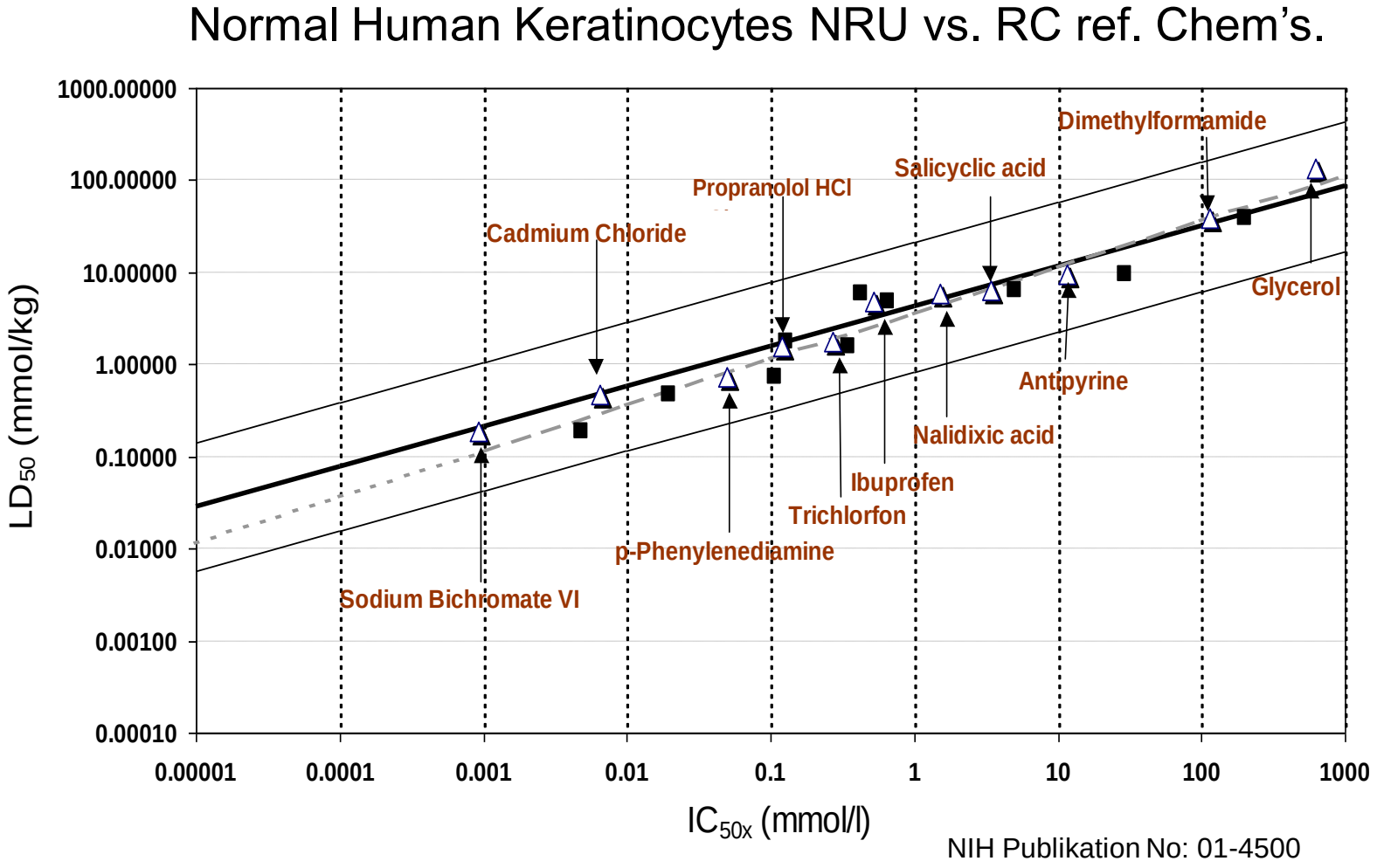


NIH Publikation No: 01-4500

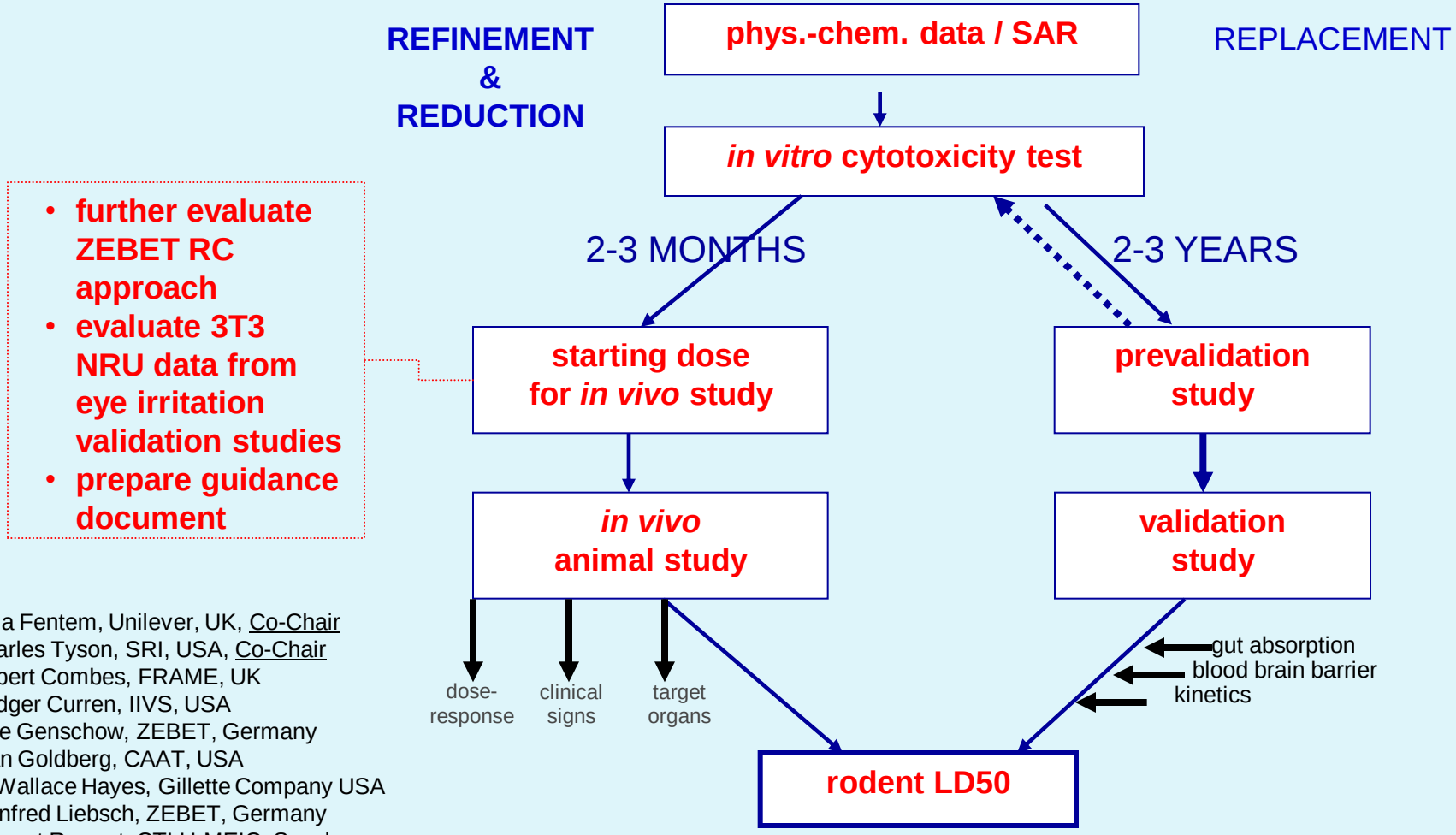
RC-Regression: confirmed in permanent mouse cell line



RC-Regression: confirmed in primary human cells



ICCVAM Workshop Recommendations

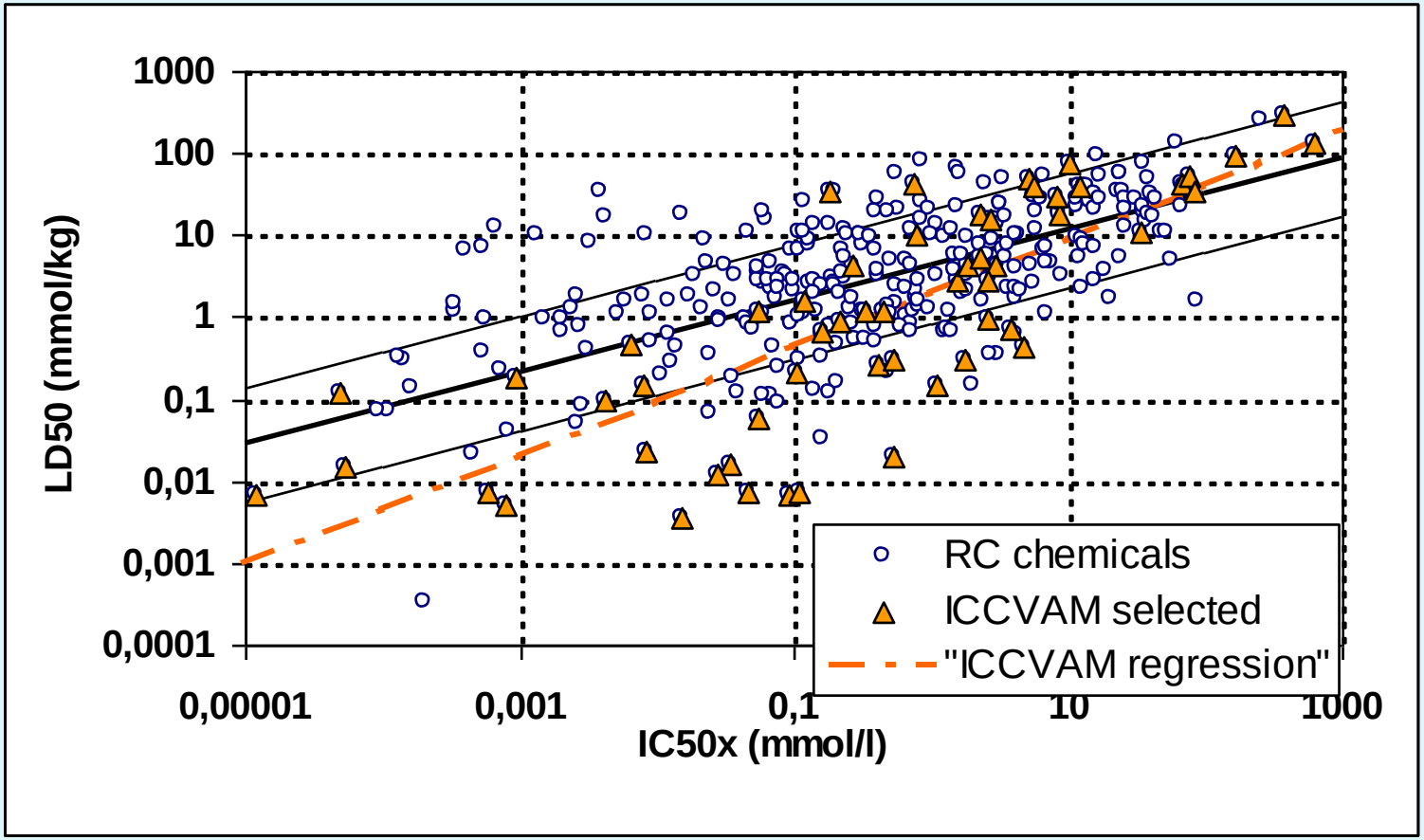


Julia Fentem, Unilever, UK, Co-Chair
Charles Tyson, SRI, USA, Co-Chair
Robert Combes, FRAME, UK
Rodger Curren, IIVS, USA
Elke Genschow, ZEBET, Germany
Alan Goldberg, CAAT, USA
A. Wallace Hayes, Gillette Company USA
Manfred Liebsch, ZEBET, Germany
Lennart Romert, CTLU-MEIC, Sweden
Noriho Tanaka, FDSC, Japan

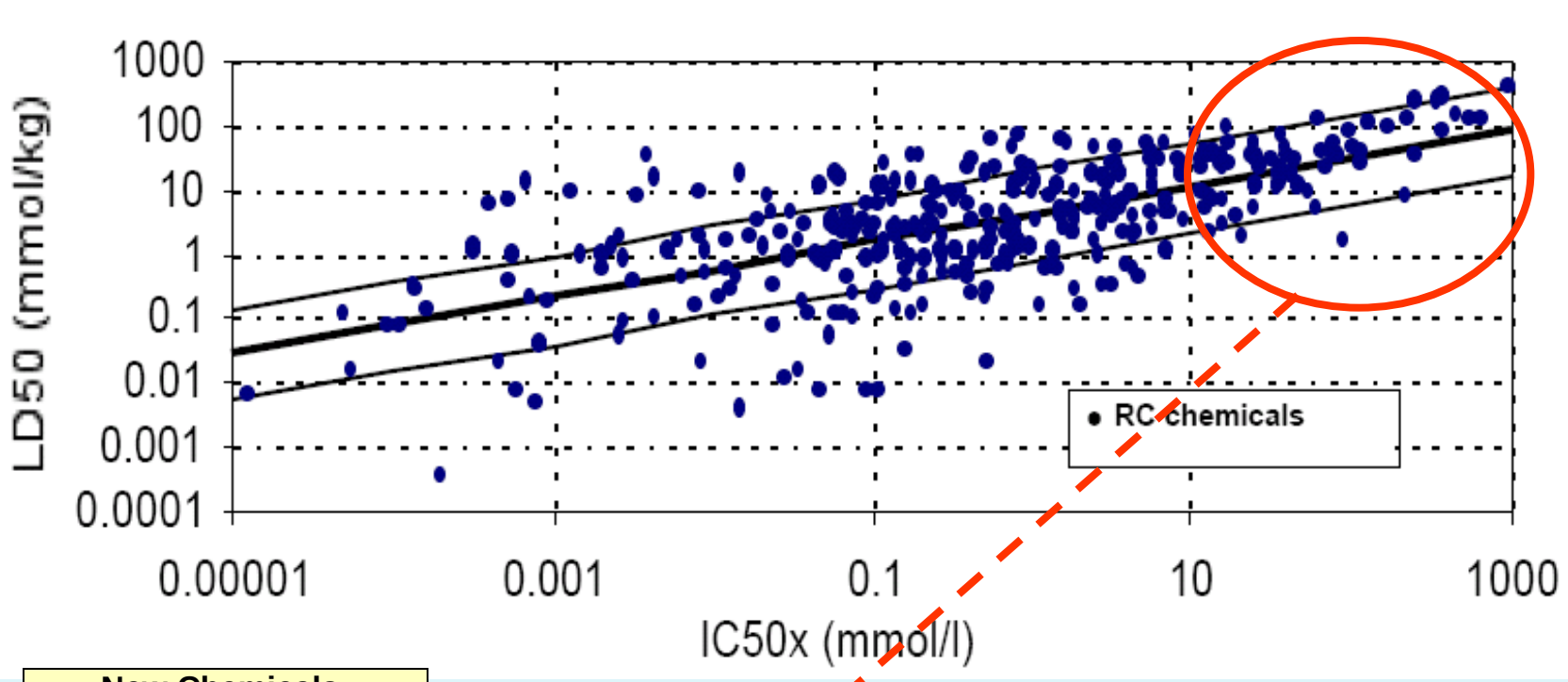
NIH Publikation No: 01-4500

ICCVAM-ECVAM: experimental validation study of Willi Halle's RC Prediction Model

Chemicals from the RC selected for the ICCVAM-ECVAM Validation study

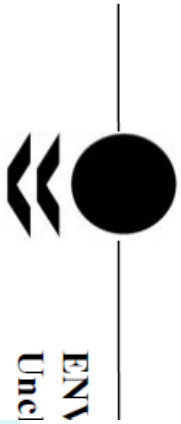


Use under REACH: Halle's RC model for predicting the absence of toxicity



New Chemicals: Oral toxicity distribution	
LD_{50} [mg/kg]	chemicals [%]
≤ 25	0
> 25 - 200	3.1
>200 - 2000	21.1
>2000	75.8

In these 2 classes 97% of all new industrial chemicals



Unclassified

ENV/JM/MONO(2010)20

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

20-Jul-2010

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Series on Testing and Assessment

No. 129

GUIDANCE DOCUMENT ON USING CYTOTOXICITY TESTS TO ESTIMATE STARTING DOSES FOR ACUTE ORAL SYSTEMIC TOXICITY TESTS

JRC SCIENTIFIC AND POLICY REPORTS

April 2012

EURL ECVAM Recommendation on the 3T3 Neutral Red Uptake Cytotoxicity Assay for Acute Oral Toxicity Testing

Both publications make reference to the RC but not to Willi‘s 1985 patent

http://www.charite.de/gzg/GZGEhr

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1981 HONORARY MEMBER of GZG

EUSAAT

European Society for Alternatives to Animal Testing

Willi Halle
HONORARY MEMBER
***30 October 1928**
†26 May 2013

Thank you Willi Halle for your contribution to the basal cellular toxicity concept and for giving a rare example of „the honest scientist“