REACH

Innovations under REACH and Challenges for Toxicological Sciences

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REACH is needed to protect man and environment from damage .....

? Chemical Safety before REACH

What will continue ?

? Concept of REACH

What is the strategy for changes ?

? Key elements within REACH

Where is the power to save time and resources ?

? Responsibilities

What is rearranged ?

before REACH		under REACH
	Registration	
New notified Substances Special Chemicals	of Chemical Substances	all Substances >1 t / a Test data
	↓	
	Evaluation	
Classification: Chem/physical Hazards Toxicity CMR	of Dangerous Properties	Classification plus Risk Evaluation
	↓	
	Authorisation	
Pharmaceuticals *Pesticides,* *Substances for* *Cosmetics*	of Production and Use with/without restrictions	All chemical Substances with very dangerous properties
CMR Compounds Persistent organic Substances	of CHemicals	Also EINECS listed substances >1 t / a

Table 3

Experience on data available for Existing Chemical Substances compared with data sets required for notified new substances

	ECS 79/831/EEC		**NNS 7th Amendment 67/548**				
			VII C	VII B	VII A	VIII	
	LPV	**HPV**	"Base set"			Level 1	Level 2
4. Toxicological studies							
4.3 Acute toxicity	**x**	**x**			**x**		
Administered orally	**x**	**x**	**x**	**x**	**x**		
Administered by inhalation		**(x)**	**x**	**x**	**x**		
Administered cutaneously		**x**		**x**	**x**		
Skin irritation		**x**		**x**	**x**		
Eye irritation		**x**		**x**	**x**		
Skin sensitization		**(x)**		**x**	**x**		
Additional tests to investigate organ or system toxicity						**o**	**o**
4.2 Repeated dose toxicity (28 days)		**x**			**x**		
Sub-chronic toxicity study		**(x)**				**o**	
Chronic toxicity study							**o**
4.3 Other effects							
Mutagenicity	**x**	**x**		**x**	**x**		
Screening for toxicity related to reproduction		**x**			**x**		
Assessment of the toxicokinetic behaviour					**x**		
Additional mutagenesis studies		**x**				**o**	
screening study(ies) for carcinogenesis						**o**	
Carcinogenicity study		**(x)**					**o**
Fertility study (one generation).		**(x)**				**o**	
Fertility study (e.g. three-generation study)							**o**
Developmental toxicity study on peri- and postnatal effects							**o**
Teratology study (one species)		**(x)**				**o**	**o**
Teratology study (species not employed in the respective level 1)		**??**					**o**
Basic toxicokinetic information.						**o**	
Toxicokinetic studies which cover biotransformation, pharmacokinetics							**o**

Notification of Chemical Substances

Notified New Chemical Substances (NNS) 1981 - 2006

Year	production volume exceeding t/a			
	1	10	100	1000
Data	base set	level 1	level 1	level 2
EU	3835	394	155	27
DE	1559	312	118	10

ECS Existing Chemical Substances

EINECS Inventory of Substances produced between 1/1971 - 9/1981

More that 100 206 entries - about 30 000 entries will be relevant for REACH

..... the deficits with chemical safety .....

High number of non evaluated existing chemical substances

Generate an information platform without imbalance

Existing procedures cannot accelerate the evaluation process

Omit time consuming discussion on minor risks

The power to regulate is not sufficient for dangerous substances

- dangerous properties
- persistence
- impact on environment

Generate an overview on production chains

Complex distribution across the production chain

Establish a new (open) platform for information

..... *What is the expected workload ?* .....

Registration of
2700 Substances > 1000 t/a
in 3 years

ICCA/OECD 400 Substances in 7 a
1000 Substances in 12 a expected
BUA 300 + 220 Substances in 20 a
EU 120 von 140 Substances in 12 a
MAK 1000 Subst, BG-Chemie 447 Substances

Registration of
4200 Substances 100 – 1000 t/a
in 6 years

29.7 % also belong to the higher production volume

Registration of
7200 Substances 10 – 100 t/a
in 11 years

33.7 % also belong to the higher production volume

Registration of
17 500 Substances 1 – 10 t/a
in 11 years

unknown overlap in production volumes

Plan, how to overcome the deficits under REACH

... continue co-operative chemical policy between manufacturers and regulators, but

- rearrange the responsibilities
- kick out time consuming discussions on minor risks
- focus on key points according to priorities

Registration Evaluation Authorisation of CHemicals

Manufacturers/Importers

ECHA *
* only part

Commission ** +
CA Member States **

** optionally supported by Scientific Commissions

Registration Evaluation Authorisation of CHemicals

Substances produced / imported

Dangerous properties; Exposure

Production / use with or without restrictions

about 30.000 EINECS listed Chemicals, Notified new chemical substances

- classification concerning hazards
- technical use & risks of chemicals
  - health risks for consumers
  - risk for environment

General Adaptation

1. Use of existing data, weight of evidence, QSAR, in vitro methods

2. Testing technically not possible

>1 t plus Annex VII	≥10 t plus Annex VII, VIII	≥100 t plus Annex VII, VIII, Annex IX	≥1000 t plus Annex VII, VIII, Annex IX, X

General Adaptation

3. Substance-tailored exposure-driven testing

Registration of Chemical Substances under REACH

All substances ≥ 1 t/a per Manufacturer or Importer — June 1, 2007

Agency
pre-registration
- compiles and publishes lists of pre-registered substances
- time line for registration
- production or import may continue
- Substance Information Exchange Forum

Existing Substances
EINECS list
+ other substances

Manufacturer/Importer
- information on registrant
- identity of substance (CAS)

PRE-REGISTRATION

June 1 - Dec 1, 2008

PHASE-IN

Time lines for registration
>1000 t : Dec 1, 2010
CMR (1&2): Dec 1, 2010
PBT, vPvB: Dec 1, 2010
100 -1000 t: June 1, 2013
1 - 100 t: June 1, 2018

New substances
June 1, 2008

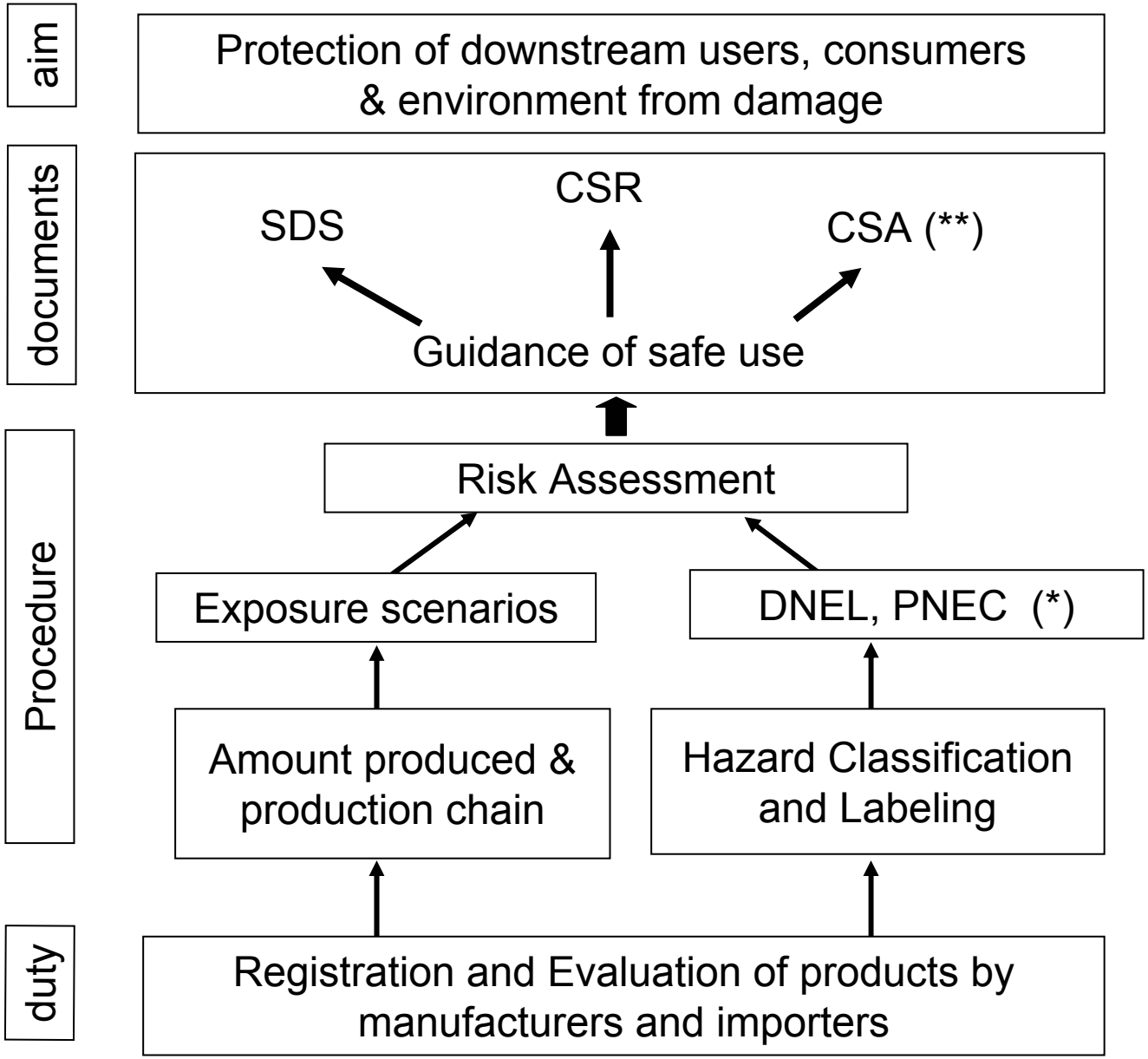
New Notified Substance
ELINCS list
(Dec 1, 2008)

REGISTRATION

Agency
registration
- registration number for New Notified Substances
- technical evaluation of dossiers
- substance evaluation

Manufacturer / Importer
Classification, labeling,
Safety data sheet (SDS),
Chemical safety report (CSR)
Chemical safety assessment (CSA)

Submission of dossiers
Proposal for test on vertebrates
Time line for gathering missing data


aim
Protection of downstream users, consumers & environment from damage
documents
SDS
CSR
CSA (**)
Guidance of safe use
Procedure
Risk Assessment
Exposure scenarios
DNEL, PNEC (*)
Amount produced & production chain
Hazard Classification and Labeling
duty
Registration and Evaluation of products by manufacturers and importers

Registration documents include

General Information

1. **Registrant Information**
2. **Identification of substance**
3. **Information on manufacture and use(s)**
4. **Classification**
5. **Guidance on safe use**
6. **Information on exposure / use categories**

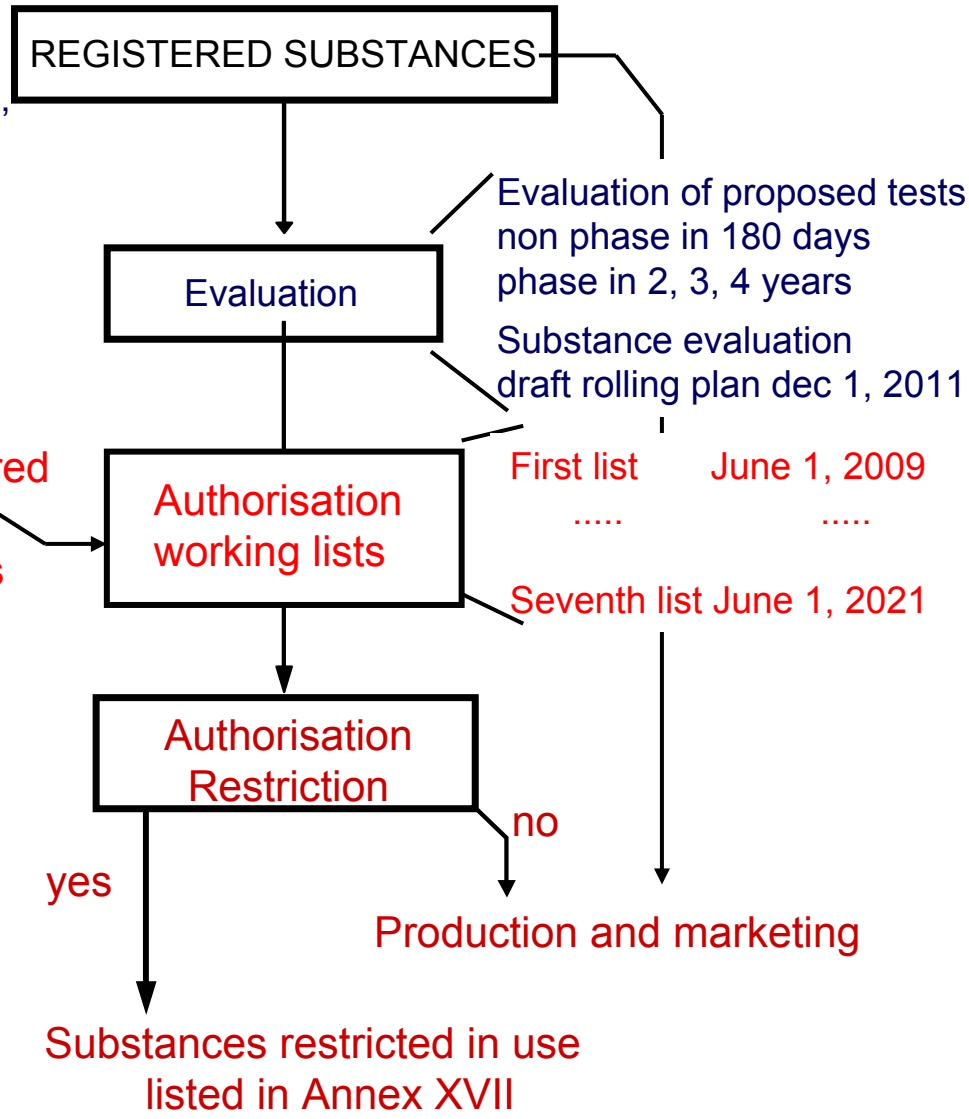
Safety Data Sheet (SDS)	classification, labeling safety measures, ..
Chemical Safety Report (CSR)	summary of data Risks for human and environment exposure during use(s) *
Chemical Safety Assessment (CSA)	(for internal use) overview on all available information (incl uncertainties)

Evaluation and Authorisation of Substances under REACH

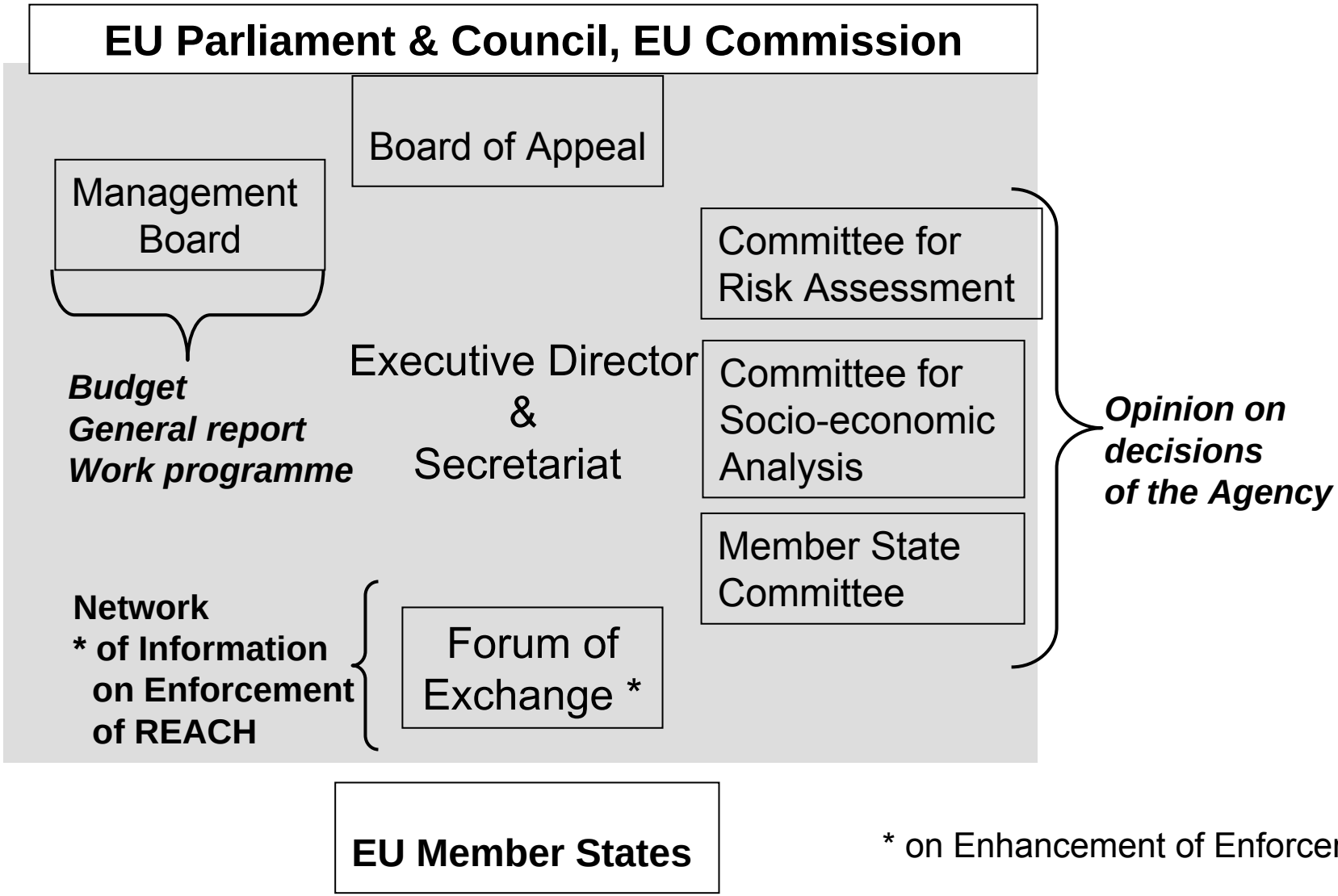
Evaluation

- Dossier evaluation by ECHA
  compliance check (5% of any dossiers),
  evaluation of tests on vertebrates
  (all > 100 t/a substances)
  evaluation of overall testing protocol

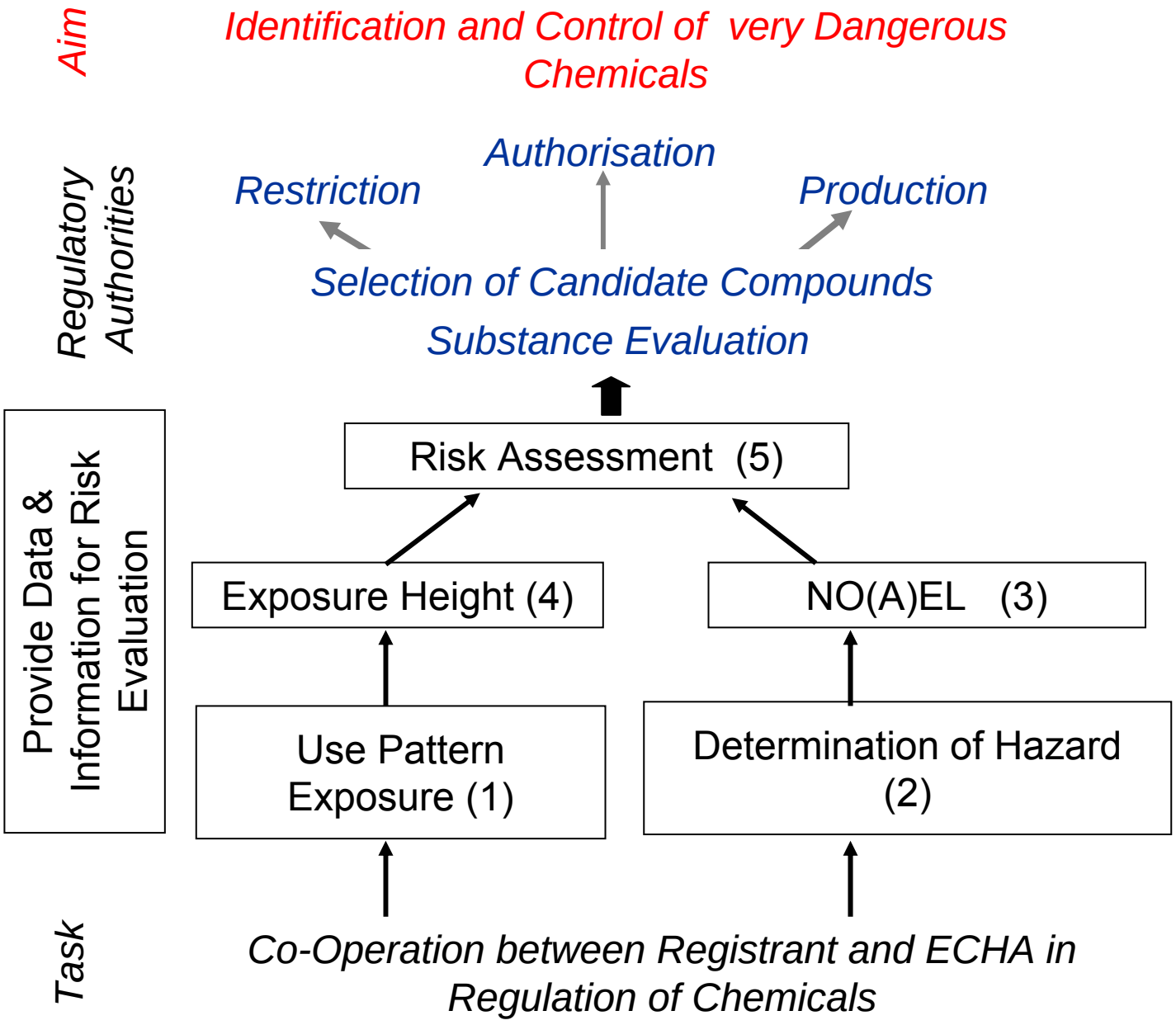
- Substance evaluation
  (risk based priority, > 100 t/a substances
  ECHA and CA MS



European Chemicals Agency



* on Enhancement of Enforcement


Aim
Identification and Control of very Dangerous Chemicals
Regulatory Authorities
Authorisation
Restriction
Production
Selection of Candidate Compounds
Substance Evaluation
Provide Data & Information for Risk Evaluation
Risk Assessment (5)
Exposure Height (4)
NO(A)EL (3)
Use Pattern Exposure (1)
Determination of Hazard (2)
Task
Co-Operation between Registrant and ECHA in Regulation of Chemicals

Candidates for Registration from Inventory of Existing Chemicals under REACH

Volumes of production or import , per enterprise	> 1000 t/a	100 - 1000 t/a	10 -100 t/a	> 1 t/a
Time for pre-registration	June 1, 2008 Nov 30, 2008	June 1, 2008 Nov 30, 2008	June 1, 2008 Nov 30, 2008	June 1, 2008 Nov 30, 2008
Dead line for registration	Nov 30, 2010	May 31, 2013	May 31, 2018	May 31, 2018
Number of substances which are candidates for registration under REACH	2 693	4 152	7 335	17 500
substances with highest production volume in this band, % of the total number in this band	100 %	70,3 %	66,3 %	**(a)** unknown
Substance which have also higher production volumes, % of the total number in this band	**(b)**	29,7 %	33,7 %	**(a)** unknown
Number of registrations, calculated from number of competitors	14 545	7 668	13 513	**(a)** unknown
Mean number of competitors / substance	5,4	1,8	1,8	**(c)** < 1,8
% substances with one producer / importer	40 %	61 %	61 %	
% substances with less than 3 producers / importers	67 %	92 %	91 %	**(c)** > 90 %
Number of substances with more than 30 competitors	77	3	3	**(c)** 0

Article 75 of the Regulation

1) A European Chemicals Agency is established for the purposes of managing and in some cases carrying out the technical, scientific and administrative aspects of this Regulation and to ensure consistency at Community level in relation to these aspects.

2) The Agency shall be subject to a review by 1 June 2012.

Duties of ECHA

before 06/2008	TGD‘s, justification Criteria for adaption, ...
07-11/2008	Lists of pre-registered substances, SIEF
Registration 12/2010	NNS, since 06/2008 all new Substances (Evaluation of registration dossiers) until 12/2012 1. Group; 06/2016 2. Group; 06/2022 3. Group
Authorisation 06/2009	7 Working list of Candidate compounds for authorisation, support of EU bodies; Scientific advice upon request,....

..... *Expectations on REACH* .....

High number of non evaluated chemical substances

Generate an information platform without embalance

Existing regulations on chemicals are highly developed but cannot gain speed

Omit time consuming dicussion on minor risks

The power to regulate is not sufficient for some circumstances

- dispersive use of chemicals with dangerous properties
- persistence of often used chemicals
- impact on environment

Obtain an overview on downstream use

Complex distribution across the production chain

Establish a new platform of information

Standard Testing under REACH

8.1	skin irritation	beyond 10 t/a **
8.2	eye irritiation	beyond 10 t/a **
8.3	Sensitisation	beyond 1 t/a
8.4	Mutagenicity	beyond 10 t/a**
8.5	Acute Toxicity	beyond 1 t/a (exemptions)
8.6.1	repeated dose toxicity (28 d)	beyond 10 t/a
8.6.2	repeated dose toxicity (90 d)	beyond 100 t/a beyond 10 t/a case-by-case
8.7.1	reproductive toxicity	beyond 10 t/a
8.7.2	developmental toxicity	beyond 100 t/a
8.7.3	two generation toxicity study **	beyond 100 t/a
8.8	*Toxicokinetics*	*beyond 10 t/a (exemptions)*
8.9	Carcinogenicity study	beyond 1000 t/a

Adaptation of Standard Test Regime (Annex XI)

General Information for all Substances > 1 t / year

1. Registrant Information
2. Identification of substance
3. Information on manufacture and use(s)
4. Classification
5. Guidance on safe use
6. Information on exposure / use categories

General Adaptation

1. Use of existing data, weight of evidence, QSAR, in vitro methods
2. Testing technically not possible

>1 t plus Annex VII	≥10 t plus Annex VII, VIII	≥100 t plus Annex VII, VIII, Annex IX	≥1000 t plus Annex VII, VIII, Annex IX, X

Specific exemptions from test regimes are given in Column 2 of Annexes

General Adaptation

3. Substance-tailored exposure-driven testing

New approaches within REACH for Evaluation of Industrial Chemicals

Before REACH

- Specialised commissions
  - for classification of hazards and labelling
  - for evaluation of chemicals with risk for worker's health and classification of carcino-genic, mutagenic and reprotoxic properties including setting of standards and justification

(since 1981)

- Obligation to notify New Chemicals including classification of dangerous properties and risk assessment
- Inventory of Existing Chemicals and risk assessment for a selected substances

Pre-registration
6 - 12 / 2008
phase-in status

↓

Registration
6/ 2008
phase-in
12 / 2010
6 / 2013
6 / 2018

↓

Evaluation
Dossier evaluation
Substance Evaluation

↓

Authorisation
Annex XIV

Annex XV
Annex XVII

under REACH

Close information gaps for industrial chemicals („no data – no market")
- full responsibility of producer for identification of dangerous properties
- incentives for cooperation between competitors (SIEF)

Approaches to gain speed
- grouping of substances
- predictive tools (QSAR)
- adaptation of test regimes

Need for justification of test on vertebrates
- proposal for planned tests before doing
- publication of the identity of the substance(s) and hazard(s) planned to be checked
- 45 day period to comment by interested parties
- incentives to use alternative methods

Authorization of dangerous chemicals
- restriction in use pattern
- justification for/against substitution
- periodically recheck by reports on new data

alternative Methods

(RRR: reduction, refinement, replacement)

Acute toxic class method

➡ pattern-based methods (...omics)

read across, chemical categories

➡ in silico

➡ in vitro

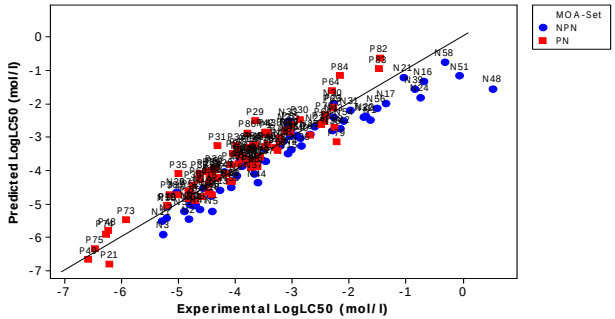
ITS: intelligent (integrated) test strategies

W. Lilienblum · W. Dekant · H. Foth · T. Gebel · J. G. Hengstler · R. Kahl · P.-J. Kramer · H. Schweinfurth · K.-M. Wollin. Alternative methods to safety studies in experimental animals: role in the risk assessment of chemicals under the new European Chemicals Legislation (REACH) Archives of Toxicology 82, 211-236 (DOI 10.1007/s00204-008-0279-9)

In silico-Methods: Computational modelling of Structure-Activity-Relationship

SAR
Expertensystems
→ yes / no type of information

QSAR
statistical correlation



There is hope, if

The basic mechanism relies on easy to get physico-chemical properties of compounds

The unknown substance belong to the group of training data set (domain of applicability)

The endpoint of action is not complex

The mechanisms of action is known

? The mechanisms of action are modelled by separate subsets ?

Options for strategies using new technologies for testing

Gene Array

Exposure with model compounds
- *in vivo*
- *in vitro*

⇩

f.i. Clusteranalysis or PCA

Identification of gene cluster/signatures associated with specific toxic mechanisms

⇩

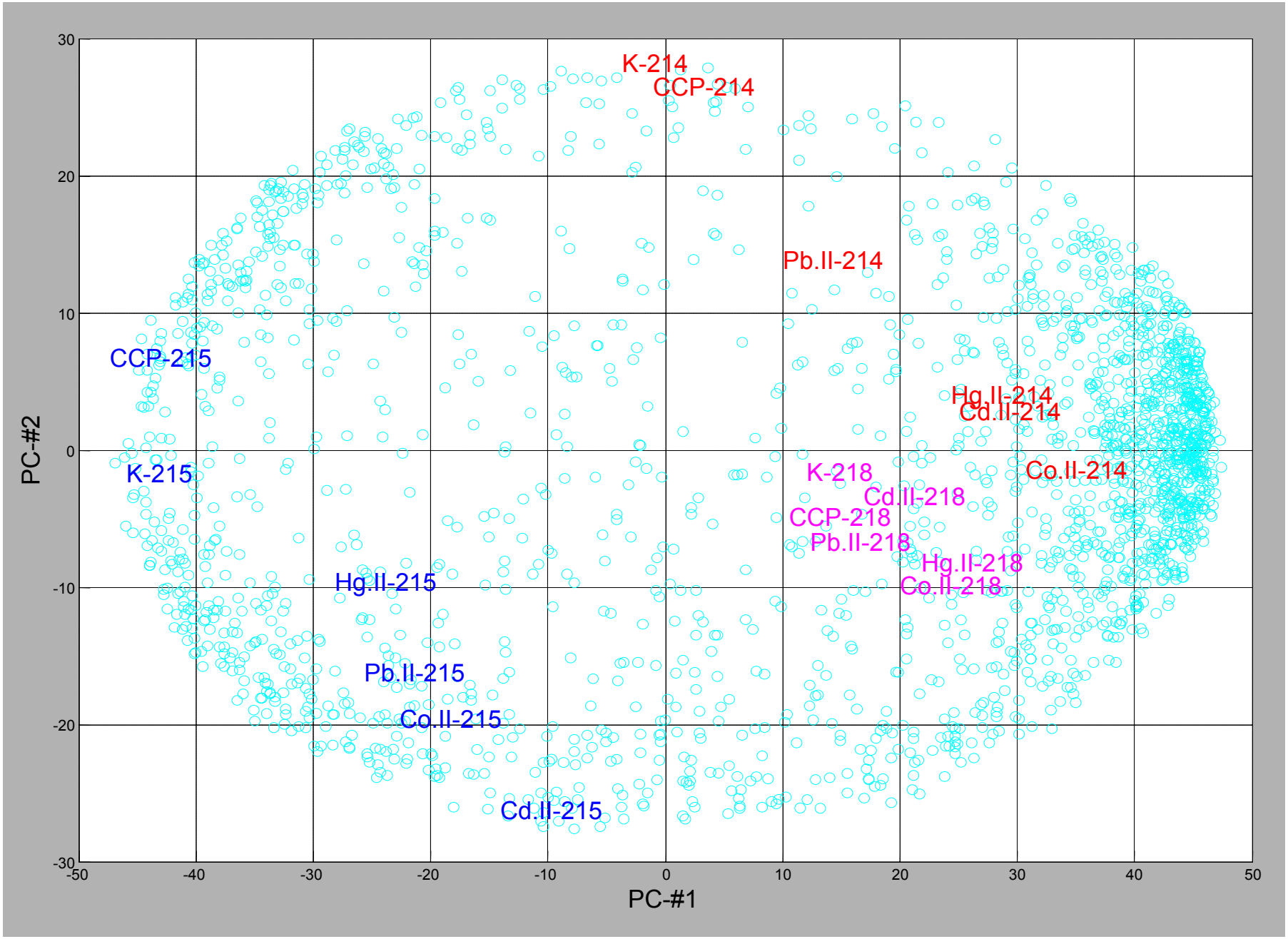
Reduction of complexity

Identification of minimal information needed for prediction of toxic mechanisms

⇩

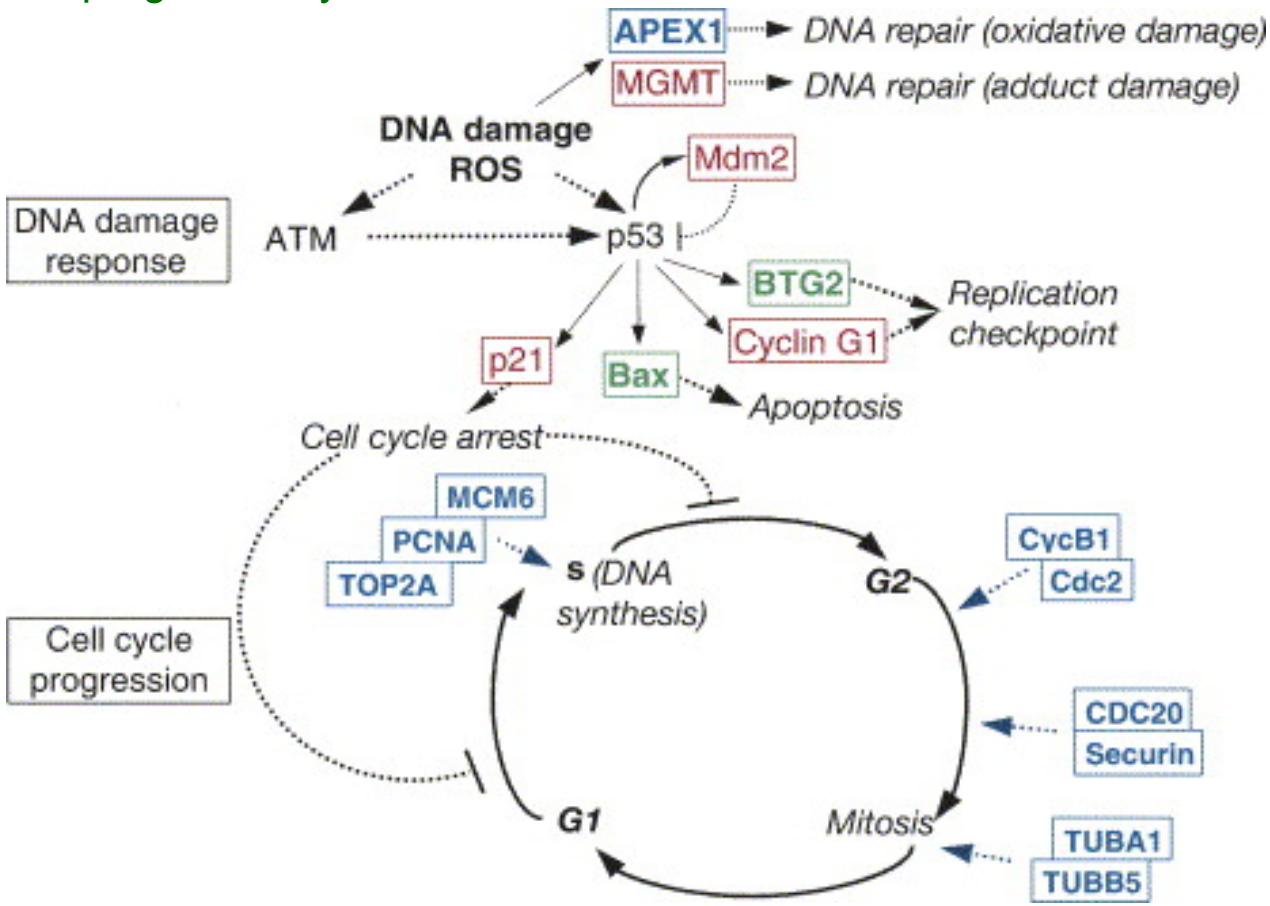
f.i. TaqMan or LightCycler

Compilation of lists with minimal needed genes; assessment of gene expression with quantitative assays


K-214
CCP-214
Pb.II-214
CCP-215
Hg.II-214
Cd.II-214
K-215
K-218
Co.II-214
Cd.II-218
CCP-218
Pb.II-218
Hg.II-218
Co.II-218
Hg.II-215
Pb.II-215
Co.II-215
Cd.II-215
PC-#2
PC-#1
30
20
10
0
-10
-20
-30
-50
-40
-30
-20
-10
0
10
20
30
40
50

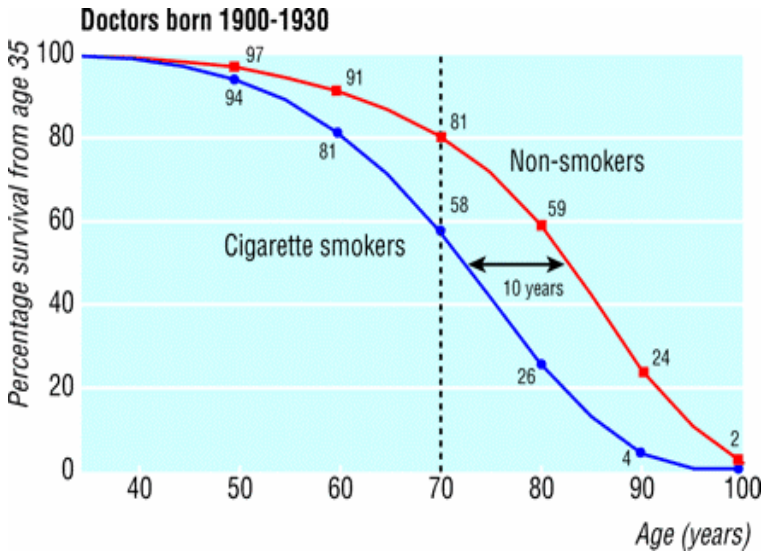
- upregulated by 2-nitrofluorene, dimethylnitrosamine, NNK, aflatoxin B (genotoxic carcinogen)
- upregulated by methapyrilene, diethylstilbestrol, Wy-14643, piperonylbutoxide (non genotoxic carcinogen)
- upregulated by both

14 days rat in vivo



From: Ellinger-Ziegelbauer et al., Mutation Research, 575, 2005

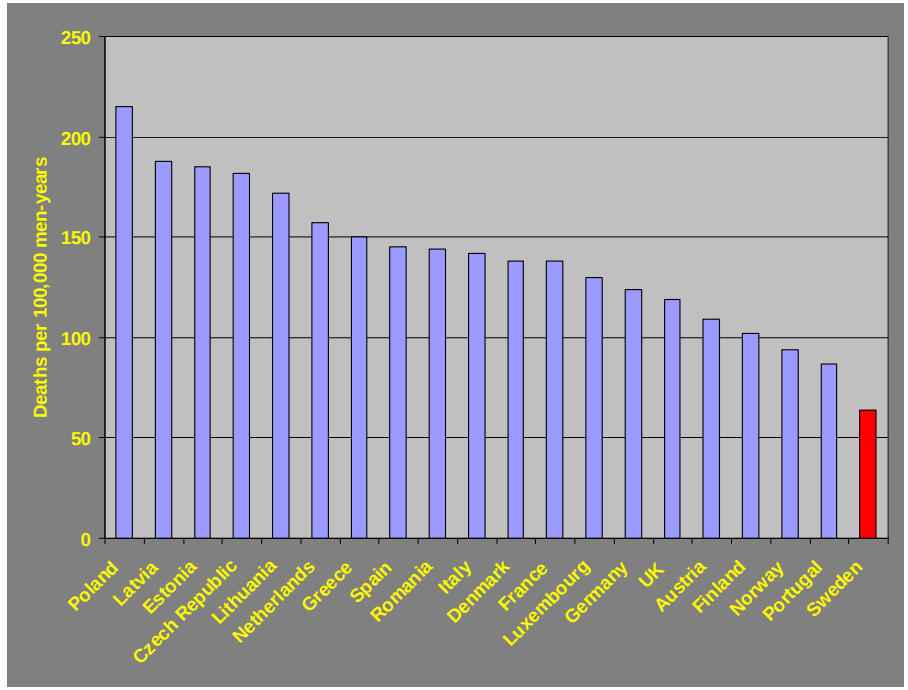
Time to effect



Loss of life expectancy
in cigarette smokers
British Doctor Study
borne between 1900-1930

Source
Doll, Peto, Boreham, Sutherland.
BMJ 2004

„The European experience“



Lung Cancer Deaths, Men Age 40+,
Europe 2001
WHO-IARC Worldwide Cancer Mortality Database

Source
Prof. Brad Rodu
University of Louisville, Kentucky USA

Lessons learned from Tobacco example

Exposure is decisive	? Pack years, Disposition in lung
Crucial components	Complex mixture(s), large variety of effects
Time to effect	Decades for tumor; short for irritation, inflammation
Target Organs	Specific pattern, port of entry may be (less) decisive
Interplay of cells	large variety of supportive events cell to cell communication (immune system)
Responses within Cells	Metabolic activation; balance between phase I and II enzymes plus transporter DNA repair DNA methylation epigenetic control (of apoptosis) gene silencing (of tumor suppressor) cell cycle arrest for DNA repair complex co-operation & co-ordination large difference between periods of time for effect

? Screening by „..Omics“ ?

Overview on methods, accepted for regulatory purposes

Toxicological endpoint	(No. der OECD Test Guideline)	
Genotoxicity/ mutagenicity	**In vivo**	**In vitro**
	Mammalian erythrocyte micronucleus test 474	Bacterial reverse mutation test 471
	Mammalian bone marrow Chromosmal aberration test 475	*Saccharomyces cervisiae* Gene mutation assay 480
	Sex-linked recessive lethal test in drosophila 477	Mammalian chromosme aberration test 476
	Rodent dominant lethal test 478	Mammalian cell gene mutation test 478
	Mammalian spermatogonial	Micronucleus test 487
	Chromosomal aberration test 483	Mouse spot test 484
	Mouse spot test 484	Sister chromatid exchange assay in mammalian cells 479
	Mouse heritable translocation assay 485	DNA damage and repair (UDS) in mammalian cells 482
	Unscheduled DNA synthesis (UDS) test (mammalian liver) 486	

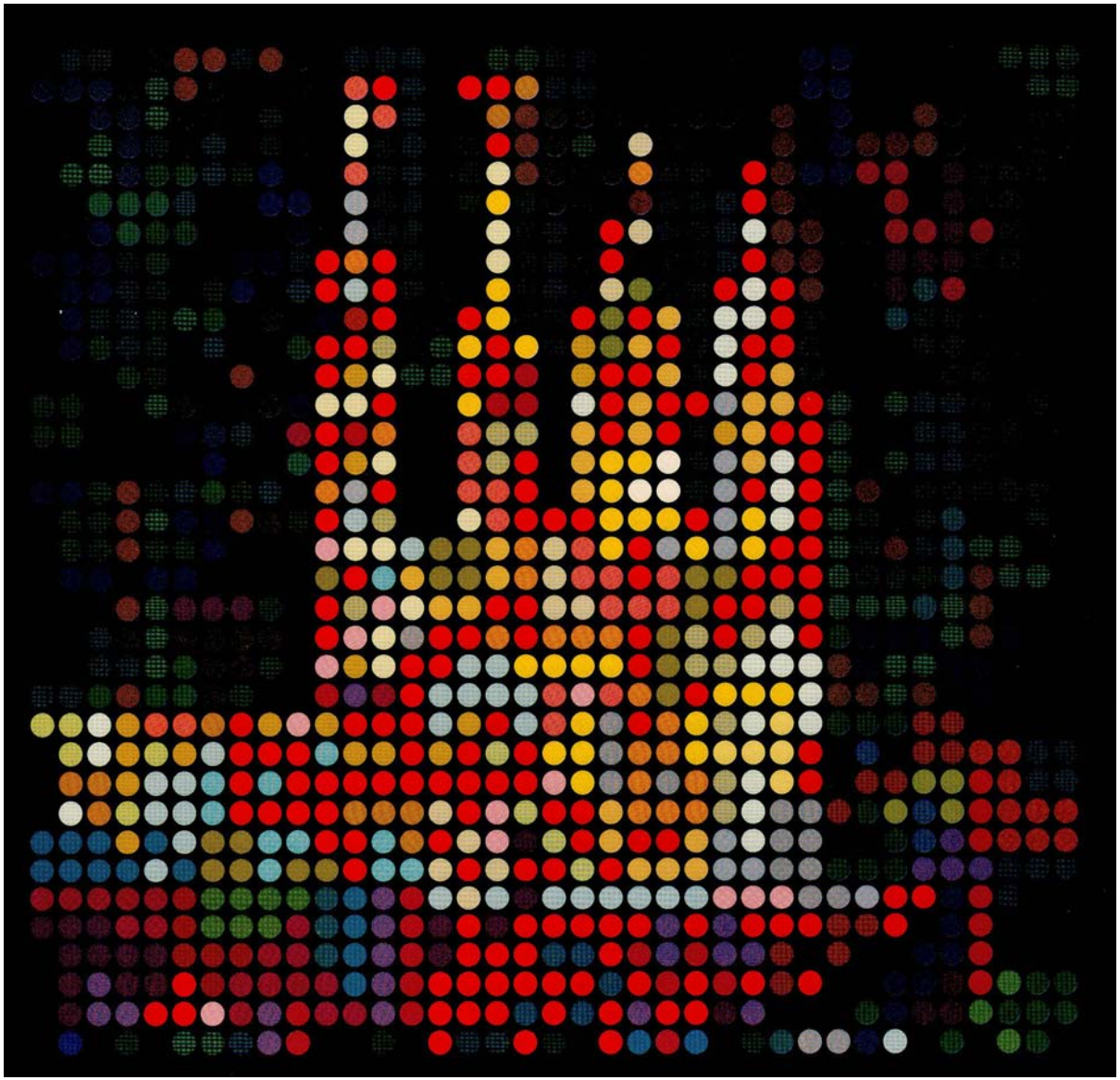
Overview on methods, accepted for regulatory purposes

Toxicological endpoint		**(No. der OECD Test Guideline)**
Carcinogenicity	**In vivo**	**In vitro**
	Carcinogenicity studies 451 Combined chronic toxicity Carcinogenicity Studies 453	Cell transformation assay (SHE, Balb/c 3T3, C3H10T Test listed only in Annex V of Directive 67/548/EEC or accepted by Regulatory authorities of some EU member states

Full Carcinogenicity Studies

Aim: Tumor formation after long treatment

+ genotoxicity	500 animals / substance	limits
- genotoxicity	1 000 000 € and more	sensitivity of species specificity of effect mechanism of effect duration up to 3.5 years



In Toxicology it is better to keep an answer open and to be aware of an continuing problem than to give an early answer and give a wrong feeling for safety or risk

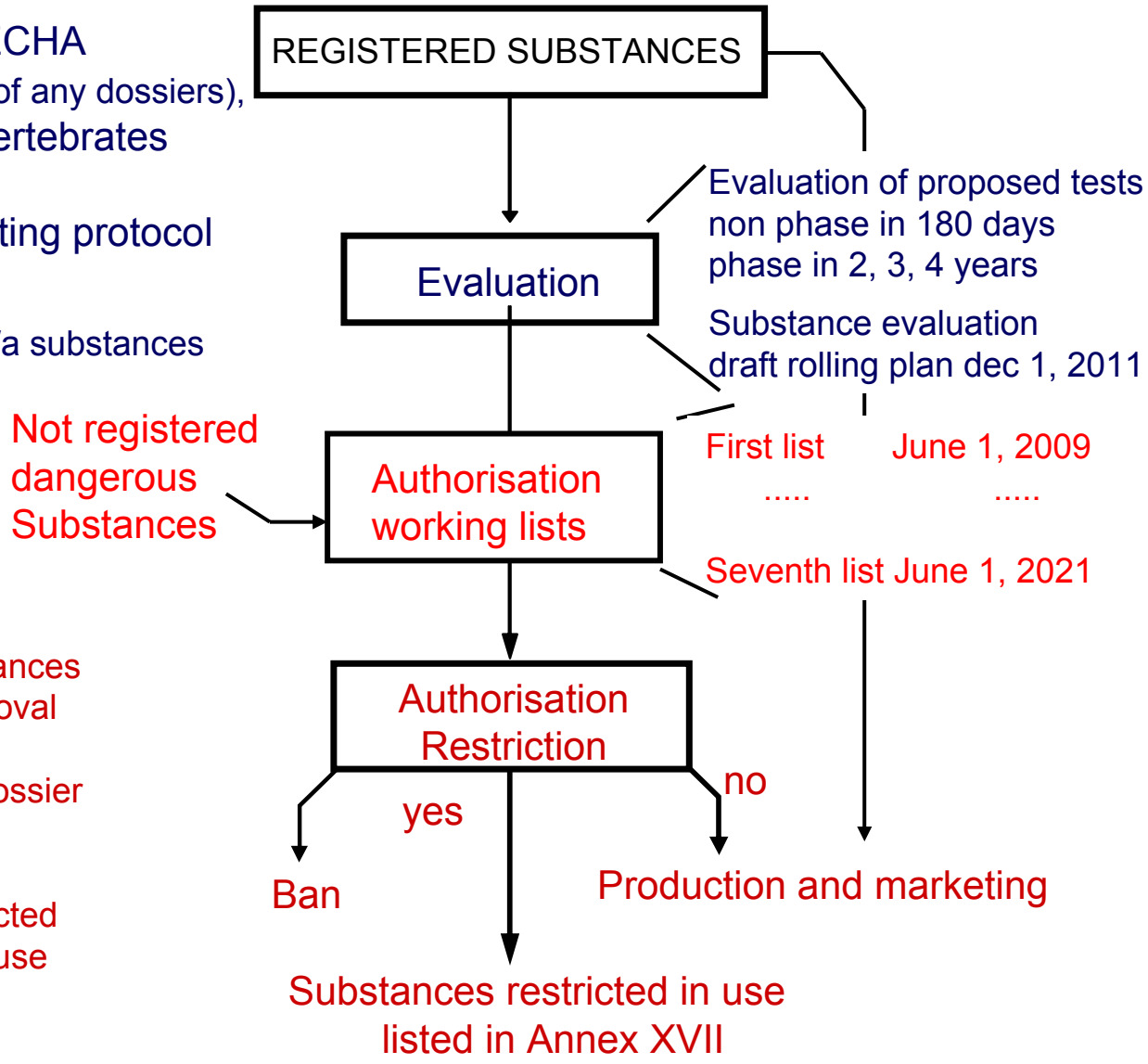
„Gene typing..?“

„Marktkirche“
Halle / Saale
Martin Luther‘s
Church

Evaluation and Authorisation of Substances under REACH

Evaluation

- Dossier evaluation by ECHA
  compliance check (5% of any dossiers),
  evaluation of tests on vertebrates
  (all > 100 t/a substances)
  evaluation of overall testing protocol
- Substance evaluation
  (risk based priority, > 100 t/a substances
  ECHA and CA MS



REACH

It‘s a consequent step to increase chemical safety

- Co operative chemical policy will continue
- Primary responsibilities will be rearranged
- Priorities will be set towards perceived risks and data gabs will be tolerated for other cases
- Very dangerous chemical compounds will be detected and selected for full risk assessment
- A new institution is established on the level of EU Community
- The timelines and requested information are very ambitious

However,

The workload is immense and expertise is needed on all levels

Different perspectives and expectations may turn out to be the main problem of the future

REACH

Where is Academic Toxicology ?

reminder

Is the strategy to decide how to select the right chemical substances in order to make use of them under the right circumstances with appropriate measures for safety and to find the balance between

Protection of man and environment

Academic Toxicology

narrow time frame

development

education, qualification

Management of data

Animal protection

Economy