

Enhancing safety and quality of life
through scientific research



***In Silico* Approaches in Genetic Toxicology -Progress and Future-**

Masamitsu Honma, Ph.D.

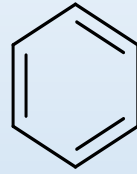
**Division of Genetics and Mutagenesis,
National Institute of Health Sciences,
Tokyo, JAPAN**

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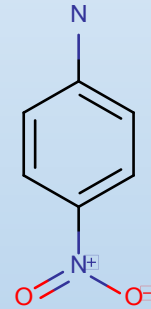
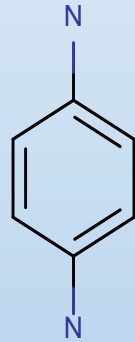
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Mutagenicity?



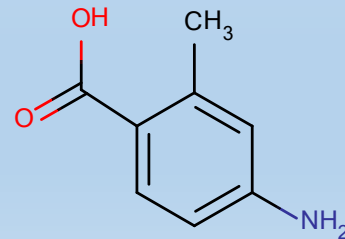
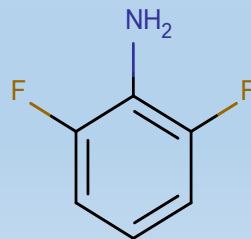
Non-Mutagenic
(Ames -ve)

Carcinogen



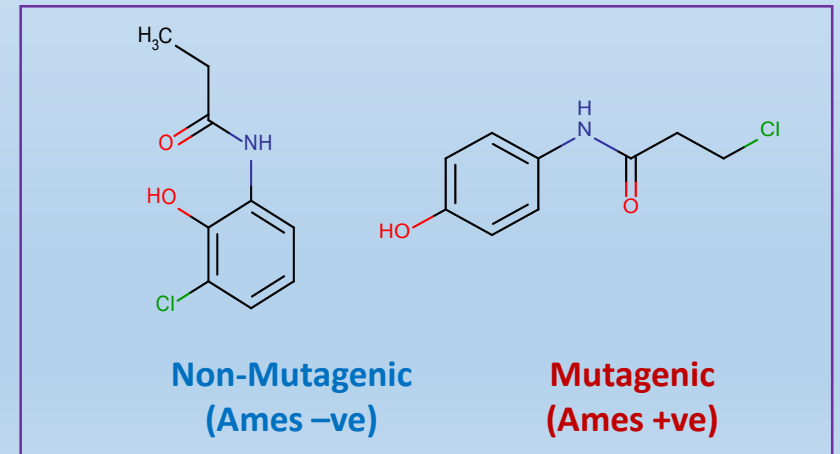
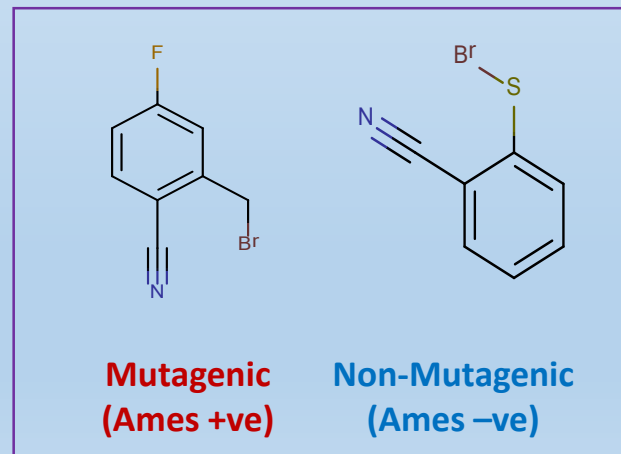
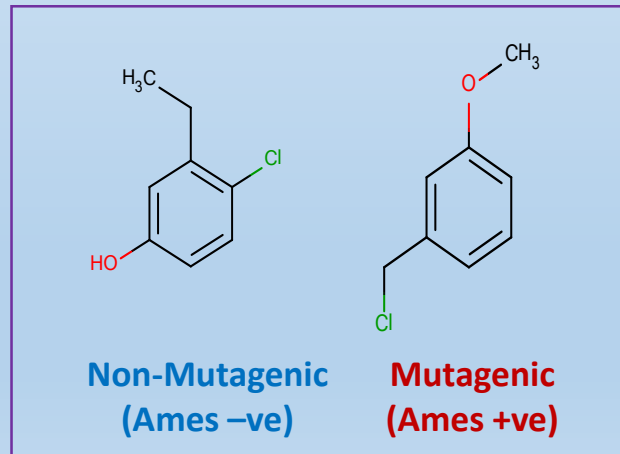
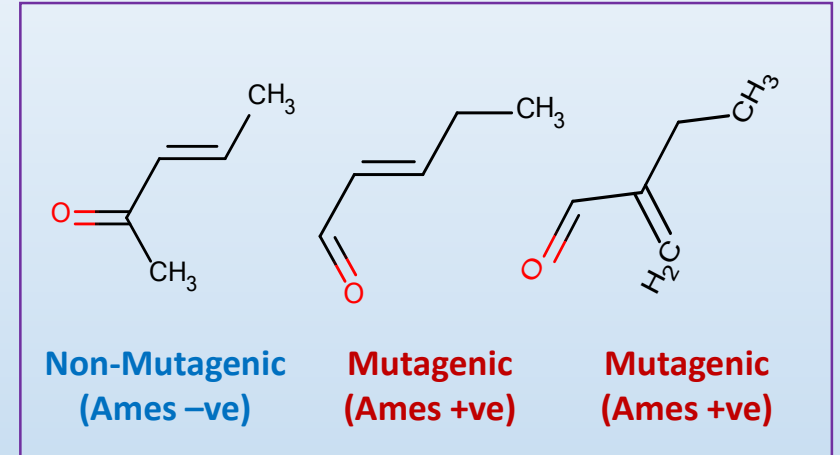
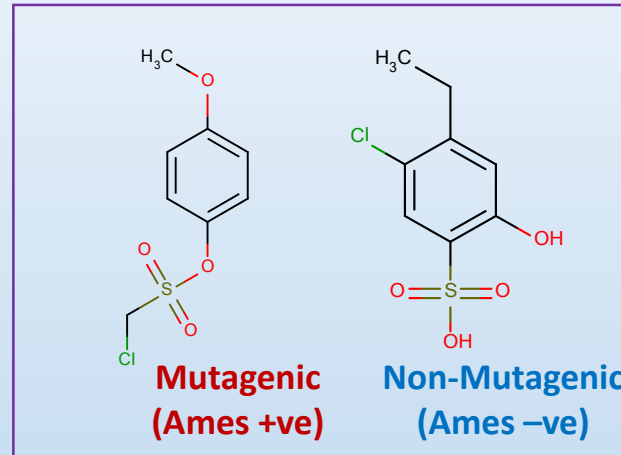
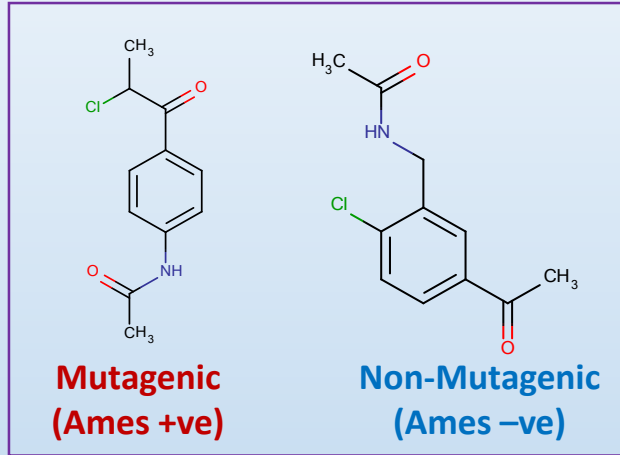
Mutagenic
(Ames +ve)

Non-carcinogen

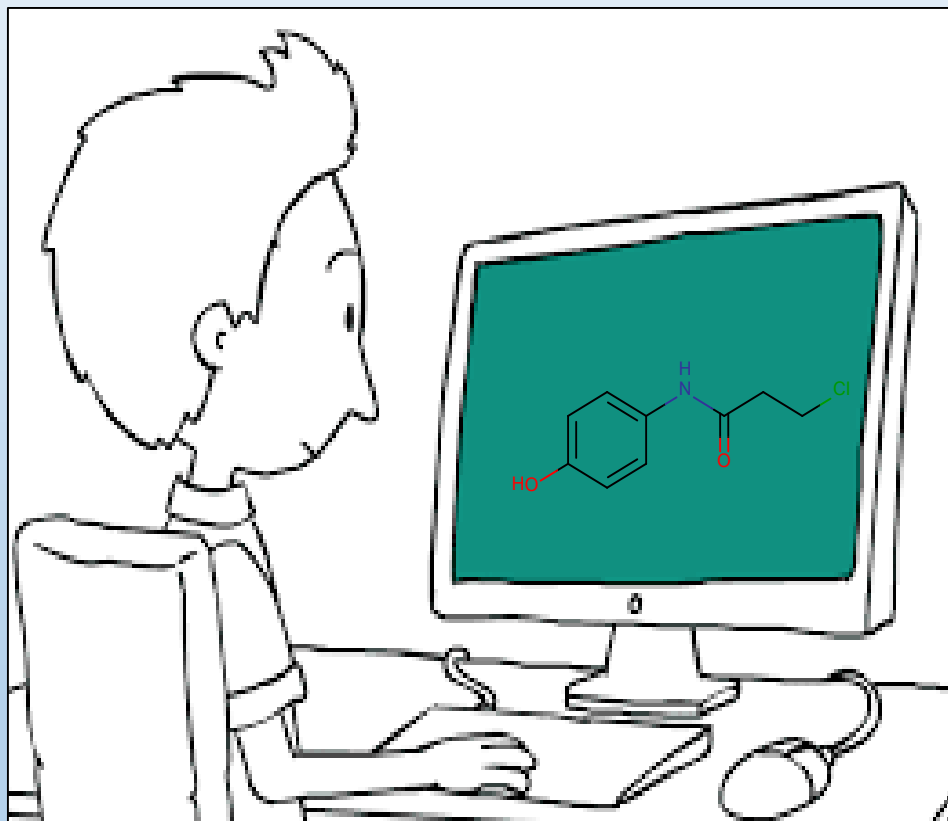


Non-Mutagenic
(Ames -ve)

Mutagenicity?



What is *In Silico* and QSAR?



- *In silico* toxicology is a type of toxicity assessment that uses computational methods to predict the toxicity of chemicals.
- A QSAR (Quantitative Structure-Activity Relationship) is a mathematical relationship between a biological activity of a chemical and its structures and characteristics.
- QSAR/ *in silico* toxicology attempts to find consistent relationship between toxicity and molecular properties, so that these “rules” can be used to evaluate the toxicity of new compounds.

Why Ames Assay?

- The electrophilic theory of chemical carcinogenesis was developed by James and Elizabeth Miller in the 1970s.
- Bruce Ames developed the Ames assay in 1972. It has a high positive predictivity for DNA-reactive chemical carcinogens based on the electrophilic theory. The Ames assay is an *in vitro* model of chemical carcinogenicity.
- Other reasons to develop QSAR models -----
 - Highly reproducible results among laboratories
 - Large number of data set
 - Binary results (positive or negative)

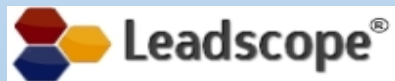


QSAR Models

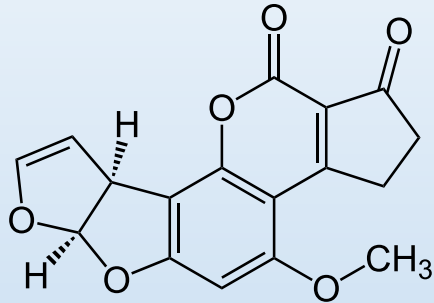
1. Rule-Based Models

2. Statistical-Based Models

3. Hybrid Models



Statistical-Based QSAR



$$\text{Activity} = F(\text{descriptors})$$

Results

Topological
Geometric
Electronic
Physicochemical

Calculation of
molecular descriptor

Internal and
external validation

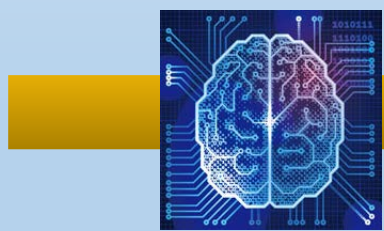
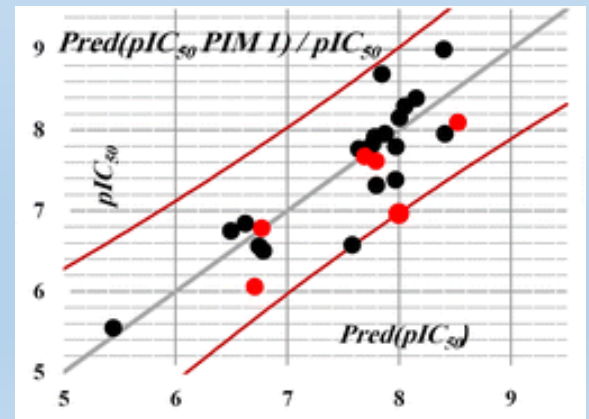
Statistical analysis

Machine Learning

Training set (thiadiazol)								pIC_{50}
N°	% N	μ	ω	NHA	NHD	MTI	...	Obs.
1	14.330	4.752	5.141	3	2	8205	...	2.533
2	13.080	4.353	5.023	3	2	10835	...	2.204
4	10.070	4.124	4.469	3	2	25571	...	0.634
7	8.800	0.805	4.167	5	2	35529	...	0.681
8	7.820	0.141	3.989	7	2	45907	...	1.207
...
...
...
...
62	8.310	3.311	4.511	5	2	39911	...	1.797

Molecular descriptor

Activity



Artificial neural net
k-nearest neighbors
Random forest
Decision tree
Support vector machine

Rule-Based vs. Statistical-Based

Rule-Based

- Rules are suggested by experts.
- **Mechanism is known or suggested.**
- Validation sets are available for every rule.
- Longer development cycle.
- Can not extrapolate prediction new chemotypes.

Statistical-Based

- Alerts can be mined automatically from a training set of chemicals with known toxicity labels.
- The training data usually consists of positive and negative examples.
- Different machine learning approaches can be used.
- **Extremely data dependent.**

QSAR Approach for Toxicological Assessment



Great advantage

- High throughput screening for huge number of chemicals without cost and labor
- Test for unavailable chemicals (e.g., impurity, intermediates, flavoring chemicals)
- Strongly contribute to animal welfare

But-----

- Can be applied to practical assessment?
- Is the QSAR prediction correct and reliable?

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1 3 4, 2 3 1, 8 2 5

ORGANIC AND INORGANIC
SUBSTANCES
TO DATE

A global team of scientists is continually adding substance information from the world's disclosed chemistry to the CAS REGISTRYSM, the gold standard for chemical substance information.

Latest News

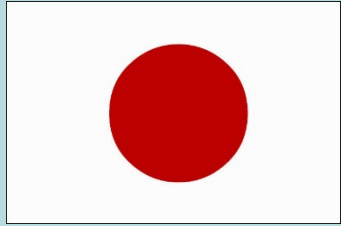
[CAS Brings the Brightest Early-Career Researchers from Around the Globe Together for the 2017 SciFinder® Future Leaders Program](#)

July 10th, -2017-

[Wiley and CAS Announce Collaboration to Deliver Advanced Predictive Cheminformatics Capabilities to](#)

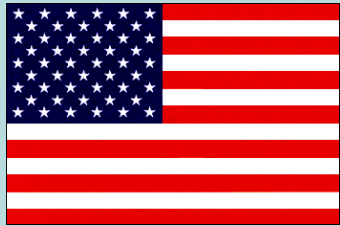
Global Management on Chemical Substances

1974



Chemical
Substances Control
Law (**CSCL**)
Kashinhou

1977



TSCA

1981



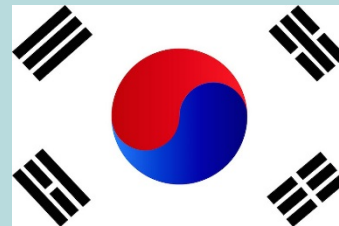
EEC

1988



CEPA

1991



TCCA

2003



C-NCSN

2004

REACH

2015

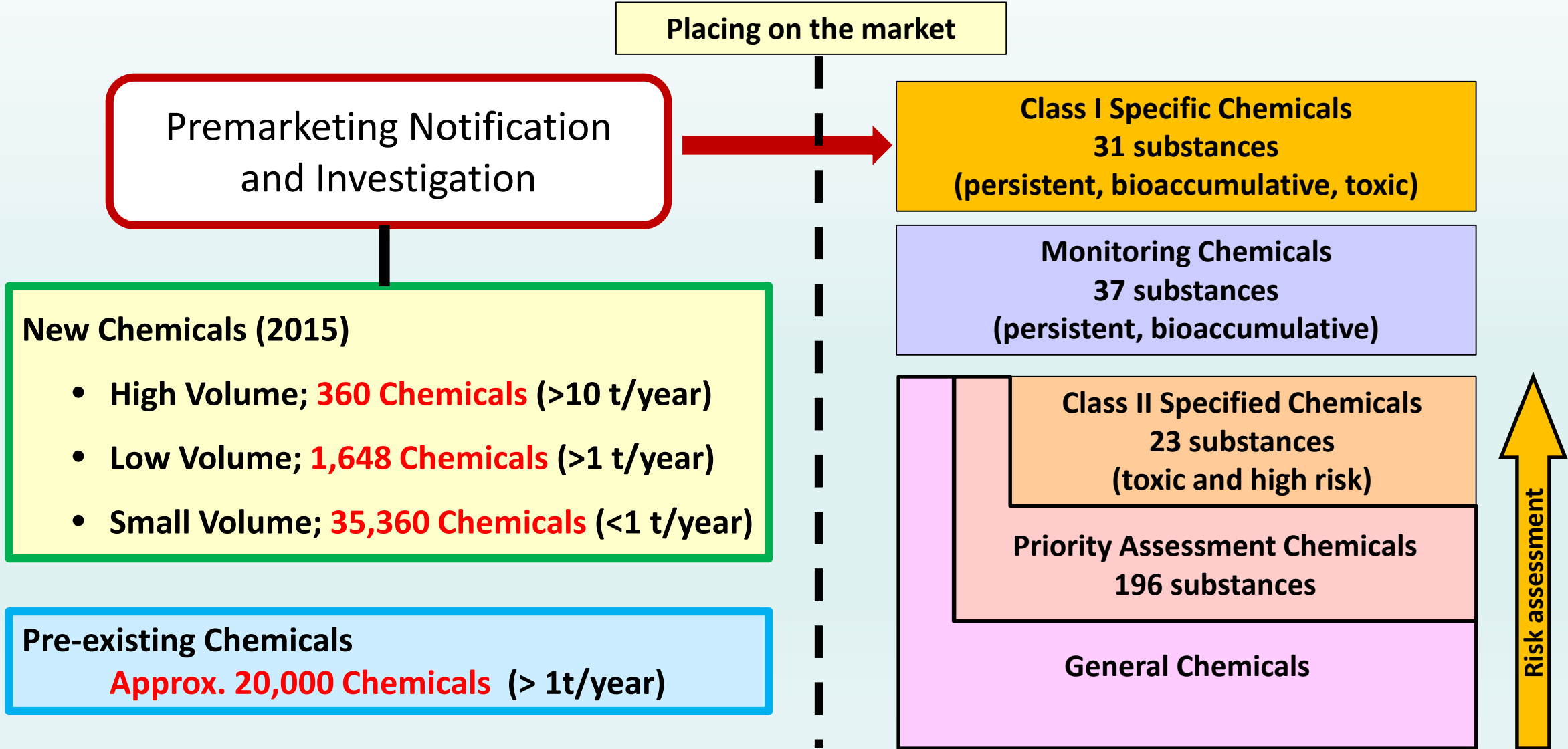
KREACH

2010

C-REACH



Overview of “Kashinhou” for New Chemicals



Evaluation for New Chemicals in “Kashinhou”

■ High Volume; >10 t/year (360 Chemicals in 2015)

- Biodegradability and Bioaccumulation (Ministry of Economy, Trade, and Industry)
- Ecological Effect (Ministry of the Environment)
- Human Health Effect (Ministry of Health, Labor and Welfare)
 - Ames assay
 - Chromosomal aberration test or mouse lymphoma assay
 - 28-days repeated dose study

■ Low Volume; >1 t/year (1,648 Chemicals in 2015)

- Biodegradability and Bioaccumulation (Ministry of Economy, Trade, and Industry)

■ Small Volume; <1 t/year (35,360 Chemicals in 2015)

- No evaluation

QSAR Tools Used in “Kashinhou” in Japan

	Endpoints	QSAR Tools
Ministry of Economy, Trade and Industry (METI)	Biodegradation	BIOWIN5 BIOWIN6 CATABOL
	Bioaccumulation	BCFWIN CERI Model Baseline Model
Ministry of the Environment	Ecological Effect	TIMES ECOSAR KATE
Ministry of Health, Labour and Welfare (MHLW)	Human Health Effect (Ames Mutagenicity)	DEREK (Rule) MCASE (Stat.) AWORKS (Stat.)

Performance of 3 QSAR Tools for Ames Mutagenicity in “Kashinhou”

	Performance (%)	Existing 206 Chemicals (Hayashi et al, 2005)*	New 616 Chemicals (~2011)
DEREK	Concordance	86.4	89.3
	Sensitivity	73.1	50.0
	Specificity	88.3	91.9
MCASE	Concordance	88.0	89.3
	Sensitivity	65.0	39.6
	Specificity	91.1	95.3
AWORKS	Concordance	70.1	89.3
	Sensitivity	73.1	44.6
	Specificity	69.7	88.6

*Hayashi et al., *In silico* assessment of chemical mutagenesis in comparison with results of Salmonella microsome assay on 909 chemicals, *Mutat Res.*, 588, 129–135, 2005

[> Testing of chemicals](#)[> Assessment of chemicals](#)[> Risk management of chemicals](#)[> Chemical accident prevention, preparedness and response](#)[> Pollutant release and transfer register](#)[> Safety of manufactured nanomaterials](#)[> Agricultural pesticides and biocides](#)[> Biosafety - BioTrack](#)

OECD Quantitative Structure-Activity Relationships Project [(Q)SARs]

(Quantitative) Structure-Activity Relationships [(Q)SARs] are methods for estimating properties of a chemical from its molecular structure and have the potential to provide information on hazards of chemicals, while reducing time, monetary cost and animal testing currently needed.

To facilitate practical application of (Q)SAR approaches in regulatory contexts by governments and industry and to improve their regulatory acceptance, the [OECD \(Q\) SAR project](#) has developed various outcomes such as the principles for the validation of (Q)SAR models, guidance documents as well as the QSAR Toolbox. The OECD (Q)SAR Project is carried out with the financial assistance of the European Union.

The information on the project and its products are available from the following links:

The Project

[History](#)[Introduction to \(Q\)SARs](#)[Grouping of Chemicals](#)[Validation of \(Q\)SAR Models](#)

The Products

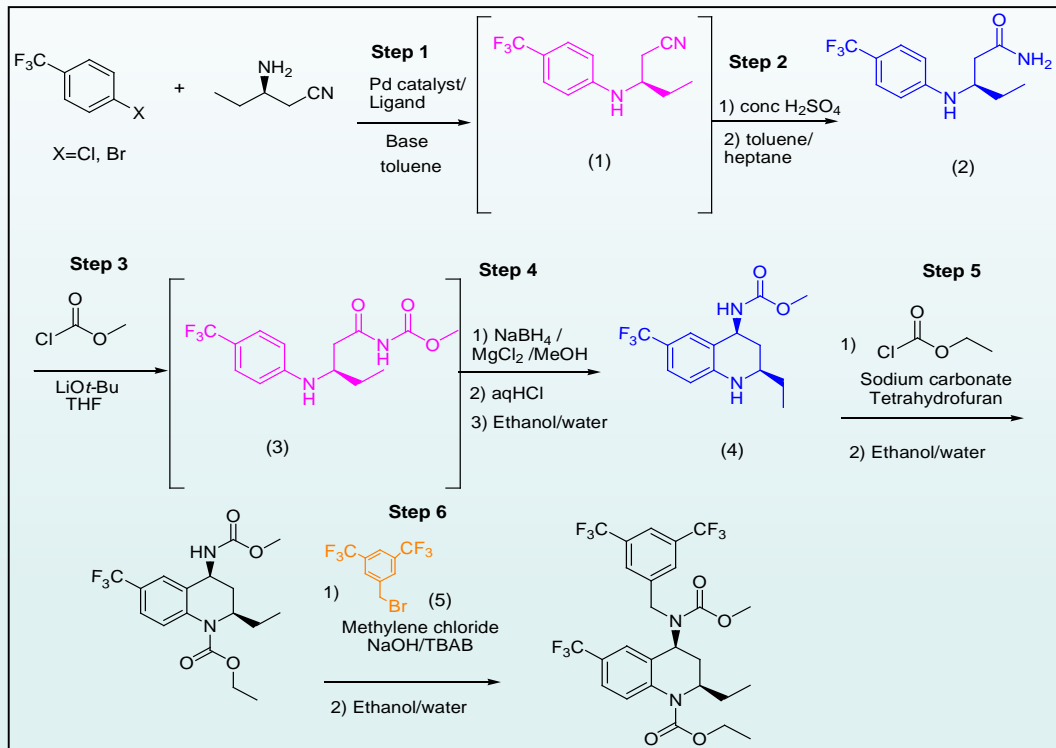
[OECD \(Q\)SAR Toolbox](#)[QSAR Toolbox: FAQs](#)[OECD Guidance Documents and Report](#)[Donators to the Toolbox](#)[OECD QSAR Toolbox: Discussion Forum](#)

LINKS

[> Animal welfare](#)[> Hazard Assessment](#)

QSAR Used for Assessing Mutagenicity of Impurities in Pharmaceuticals





**Synthetic Route of Drug Substances
 (Byproducts)**

**Degradation from Drug Substances
 (Degradants)**

Impurities

Mutagenic or non-mutagenic?

Major Points of ICH-M7 Guideline for Assessment of Genotoxic Impurities

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC)
IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL
CARCINOGENIC RISK

M7

Current Step 4 version
dated 23 June 2014

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

- The focus of this guideline is on DNA reactive substances which can be detected by the Ames assay
- Evaluation of mutagenicity of impurities using the **QSAR**
- Application of a Threshold of Toxicological Concern (TTC) to control genotoxic impurities

(Q) SAR Analysis in ICH-M7

- **Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be **expert rule based** and the second methodology should be **statistical based**.**
- **The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and **no further testing is recommended**.**

Performance of Four QSAR Models for Predicting Ames Mutagenicity

Data Source	QSAR Type	QSAR Tool	Sensitivity (%)	Specificity (%)	Concordance (%)
Hansen (Industrial chemicals) 2,647 compounds (67% positive)	Rule	DEREK	80.9	59.1	73.7
		Toxtree	85.2	53.1	74.6
	Statistical	Mcase	74.6	74.0	74.4
		LSMA	67.8	63.8	66.4
Roche (Pharmaceuticals) 2,335 compounds (13% positive)	Rule	DEREK	43.4	91.6	85.5
		Toxtree	42.9	77.5	73.1
	Statistical	Mcase	30.6	85.8	78.9
		LSMA	17.4	93.9	83.6

Hillebrecht A et al., Comparative Evaluation of *in Silico* Systems for Ames Test Mutagenicity Prediction: Scope and Limitations., *Chem Res Toxicol*, 24, 843–853, 2011)

How to Improve QSAR Prediction ?

◆ New QSAR Algorithm/ Model

- AI, Deep-learning ?

◆ Training data set

- New
- Many
- Reliable

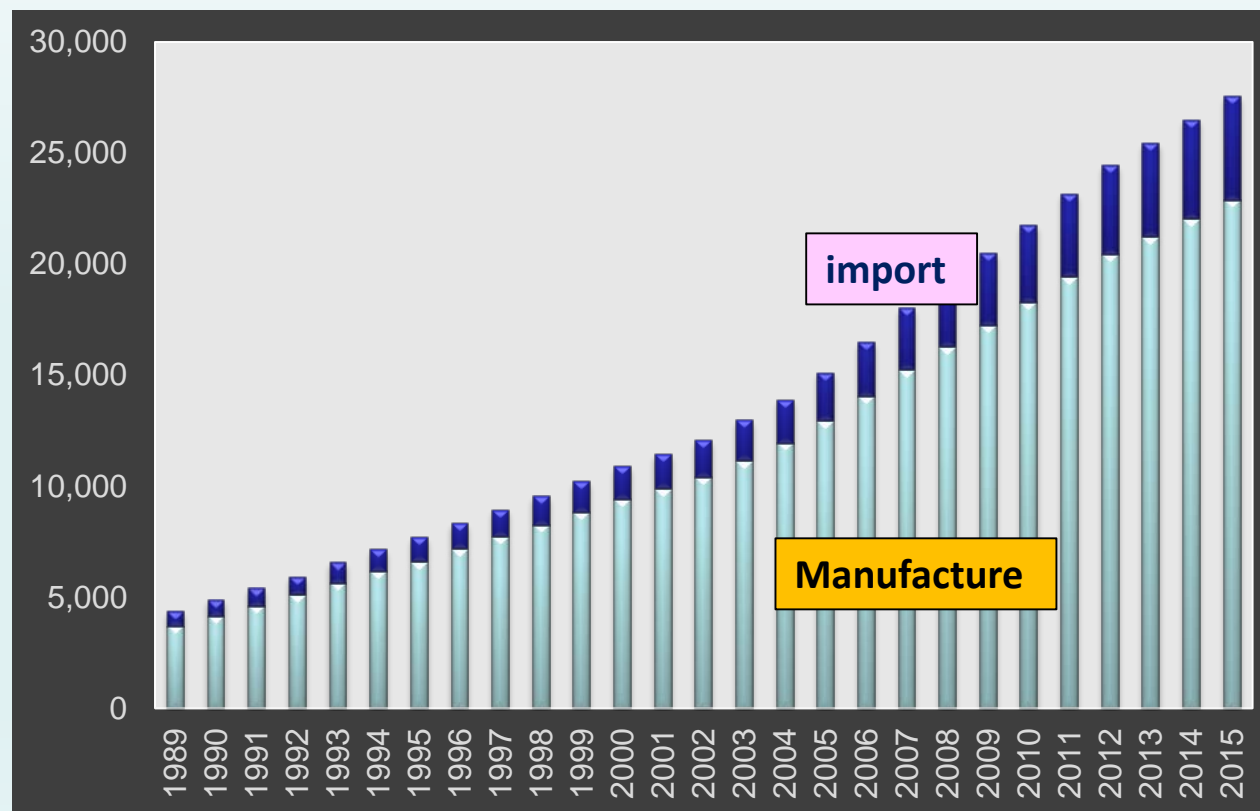


Ames Mutagenicity Data Sources in Major Public Domain

Database (name)	Information	Link
Benchmark Data Set for <i>In Silico</i> Prediction of Ames Mutagenicity (Hansen et. al., 2009)	Ames mutagenicity database for 6,500 compounds	http://doc.ml.tu-berlin.de/toxbenchmark/
Carcinogenic Potency Database (CPDB)	1,547 chemicals	http://toxnet.nlm.nih.gov/cpdb/cpdb.html
GAP – Genetic Activity Profile Database by US EPA and IARC (Latest update in 2000)	Data on approx. 300 chemicals from volumes 1-50 of the IARC Monographs and on 115	http://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=44472&CFID=726518&CFTOKEN=15601022
Existing Chemicals Examination (EXCHEM) database (Japan)	Ames mutagenicity for more than 360 HPV chemicals	http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
Istituto superiore di Sanità database (ISSCAN)	More than 1,150 chemical compounds tested with the long-term carcinogenicity bioassay on rodents, mutagenicity data.	http://www.iss.it/meca/index.php?lang=1&anno=2013&tipo=25
National Toxicology Program (NTP) database	2,163 chemicals in genetic toxicity studies	ftp://157.98.192.110/ntp-cebs/datatype
Toxicity Reference Database (ToxRefDB)	Studies on 330 chemicals, many of which are active ingredients of pesticides	http://actor.epa.gov/toxrefdb/faces/SearchByEndpoint.jsp
TOXNET database : Carcinogenesis Research Information System database (CCRIS) and the Genetic Toxicology Databank (GENE-TOX)	CCRIS: over 9,000 chemical records with animal carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition test results. GENE-TOX: on over 3,000 chemicals, from expert peer review of the open scientific literature.	http://toxnet.nlm.nih.gov/

Industrial Safety and Health Law “An-eihou” in Japan

Chemicals newly manufacturing produced or imported more than 100kg/year must be assessed its mutagenicity by Ames assay.



The permission of the use of the Ames data to improve QSAR models by Chemical Hazards Control Division, Industrial Safety and Health Department, Labor Standards Bureau in MHLW

**Proposal of International
Collaborative Studies to Improve
Ames/QSAR models
(QSAR2014, Milan, Italy, June 2014)**



To QSAR Builders

-1st Circular for Ames (Q)SAR Collaborative Study-

June, 2014

Ministry of Health, Labour and Welfare in Japan has collected and evaluated new Ames mutagenicity results. The National Institute of Health Sciences has the results of approximately 12,000 new chemicals. The Ames assays were conducted under GLP according to Industrial Safety and Health Act in Japan. We can now provide the Ames data to improve the reliability and applicability of your QSAR models for predicting Ames mutagenicity.

We first provide a list of 4,021 chemicals without the results of Ames mutagenicity assay (Excel and SD files). After calculating the Ames mutagenicity by your QSAR tools, you return the excel file with the results (positive, negative, and others). We evaluate the performance of your QSAR tool (sensitivity, specificity, and others). Then, we disclose the Ames results. You can integrate the Ames results into your QSAR model as learning sets. Next, we provide another 4,000 chemicals list. According to this procedure, we provide 12,000 chemical data totally, and you can integrate these Ames mutagenicity results into your QSAR model. We believe that this project strongly contributes to improve the QSAR models as well as to promote QSAR studies.

If you are interested in this project, please contact with me.

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Director, Division of Genetics & Mutagenesis
National Institute of Health Sciences
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Tokyo 158-8501, Japan
E-mail: honma@nihs.go.jp

Participants in Ames/QSAR Project

QSAR Vendors

QSAR Model

-
- | | |
|--|---|
| 1. Lhasa Limited (UK) | DEREK Nexus, SARAH |
| 2. MultiCASE Inc (USA) | CASE Ultra rule-, statistical-based |
| 3. Leadscope Inc (USA) | Leadscope rule-, statistical-based |
| 4. Prous Institute (Spain) | Symmetry |
| 5. Bourgas University (Bulgaria) | OASIS TIMES |
| 6. Istituto Superiore di Sanita (Italy) | Toxtree |
| 7. Istituto di Ricerche Farmacologiche Mario Negri (Italy) | SARpy + VEGA + CAESER (consensus model) |
| 8. Swedish Toxicology Science Research Center (Sweden) | AZAMES |
| 9. FUJITSU KYUSHU SYSTEMS (Japan) | ADMEWORKS |
| 10. IdeaConsult Ltd. (Bulgaria) | AMBIT |
| 11. Molecular Networks GmbH and Altamira LLC (USA) | ChemiTunes |
| 12. Sumilation Plus (USA) | Mut_Risk-0 |
-

Ames Mutagenicity of Challenging Chemicals

Class A : Strongly positive, in which the chemical generally induces more than 1,000 colonies/mg in at least one Ames strains in the presence or absence of rat S9.

Class B : Positive, in which the chemical induces colonies more than 2-fold of the negative control at least one Ames strains in the presence or absence of rat S9, but not in class A.

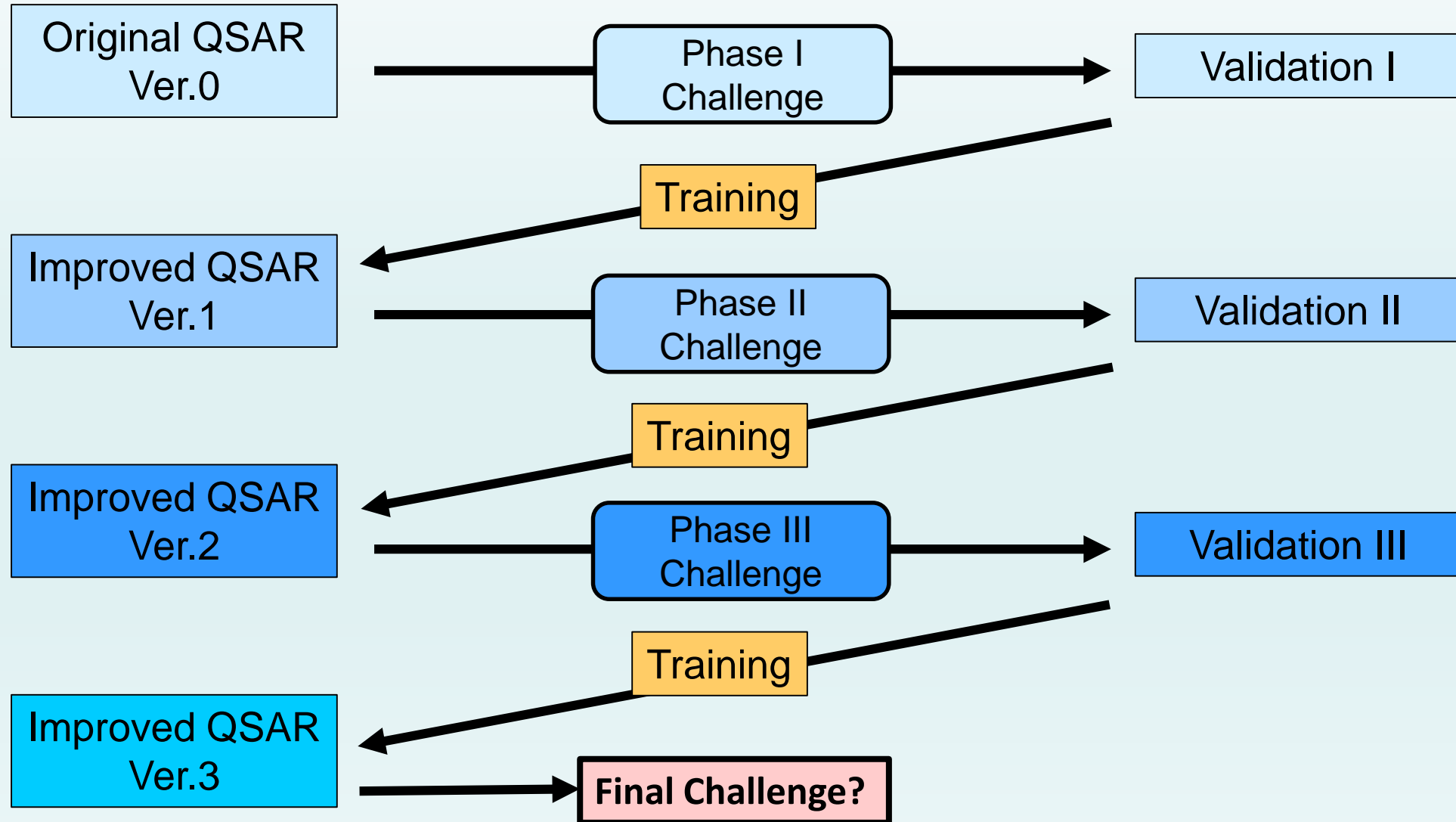
Class C : Negative, which is neither class A nor B.



Ames/QSAR Project (Phase I-III) Challenged Chemicals

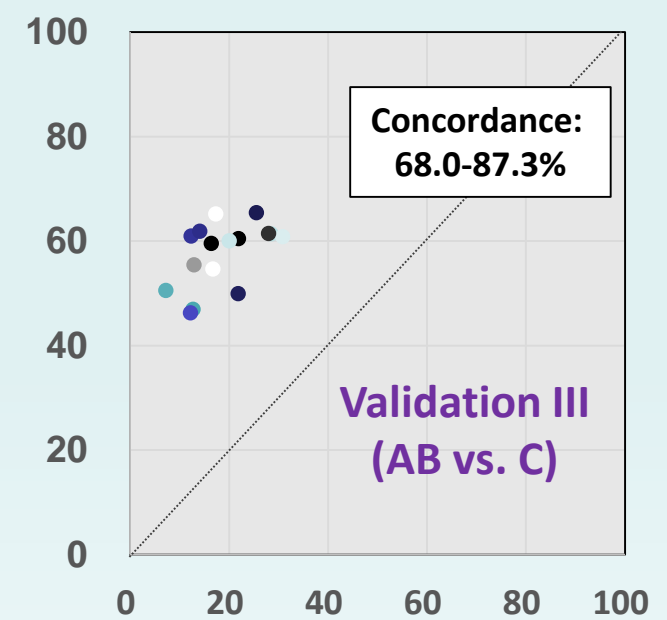
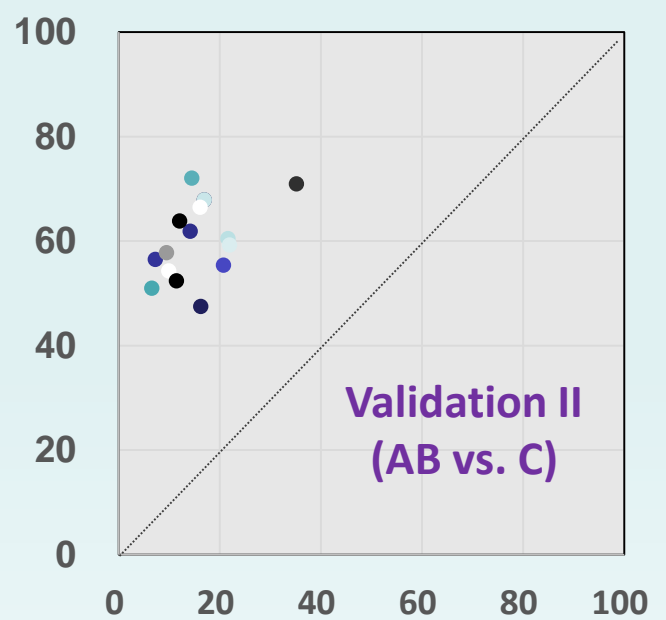
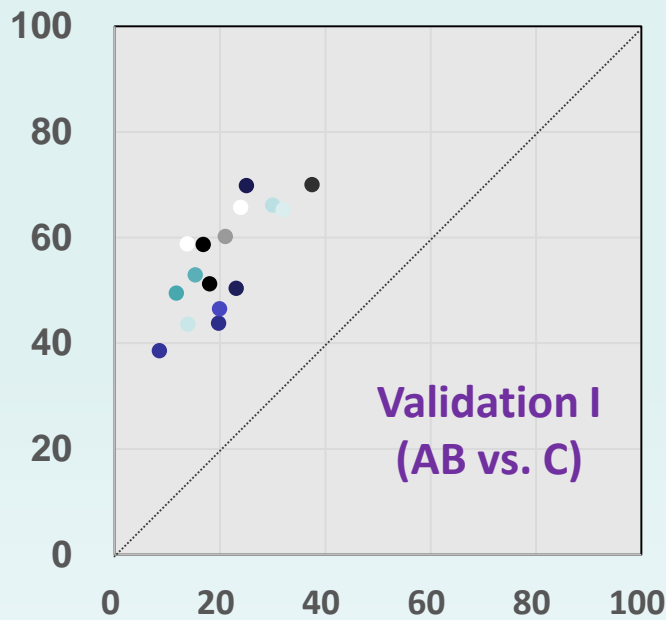
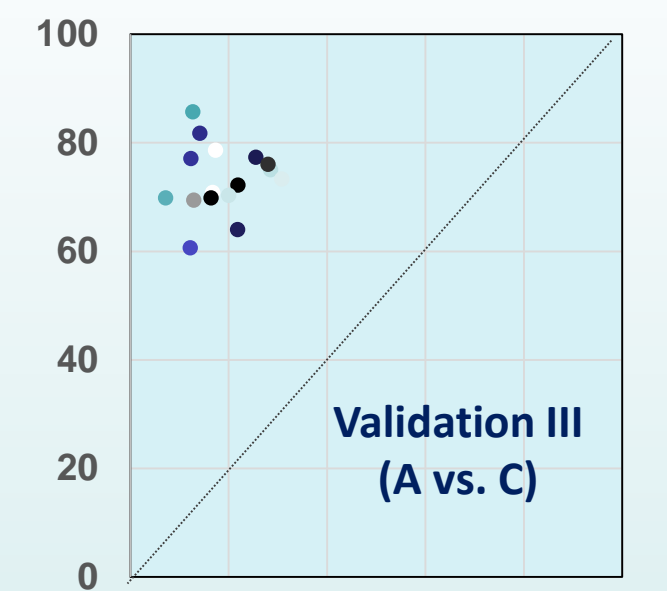
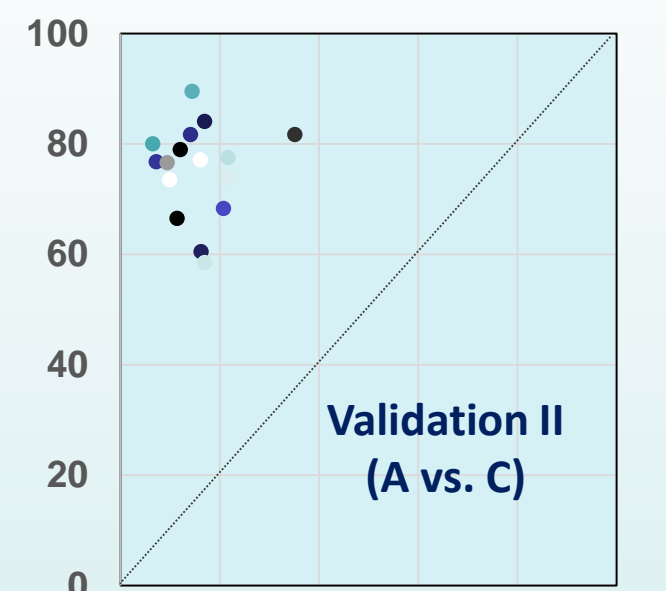
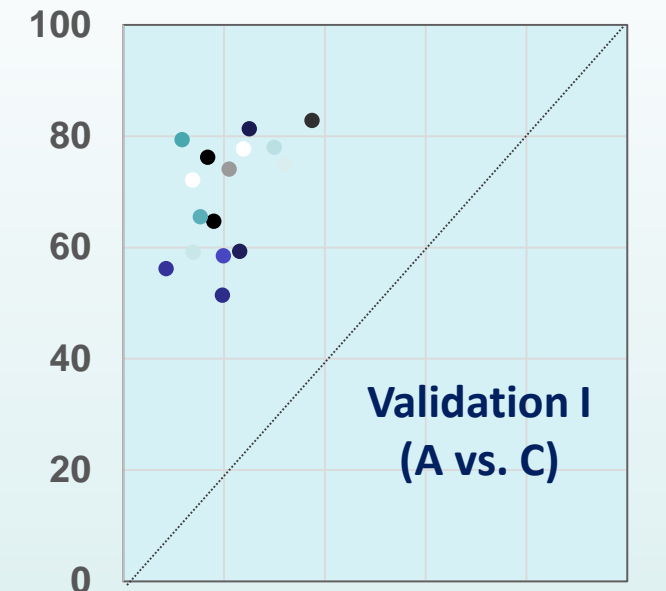
Category	Phase I (2014-2015)	Phase II (2015-2016)	Phase III (2016-2017)	Total (2014-2017)
Class A	183 (4.7%)	253 (6.6%)	236 (5.4%)	672 (5.5%)
Class B	383 (9.8%)	309 (8.1%)	393 (8.9%)	1,085 (8.9%)
Class C	3,336 (85.5%)	3,267 (85.3%)	3,780 (85.7%)	10,383 (85.6%)
Total	3,902	3,829	4,409	12,140

Ames/QSAR Project (Phase I-III) Challenge Program



ROC Graphs for Challenged QSAR Models' Validation

Sensitivity (%)

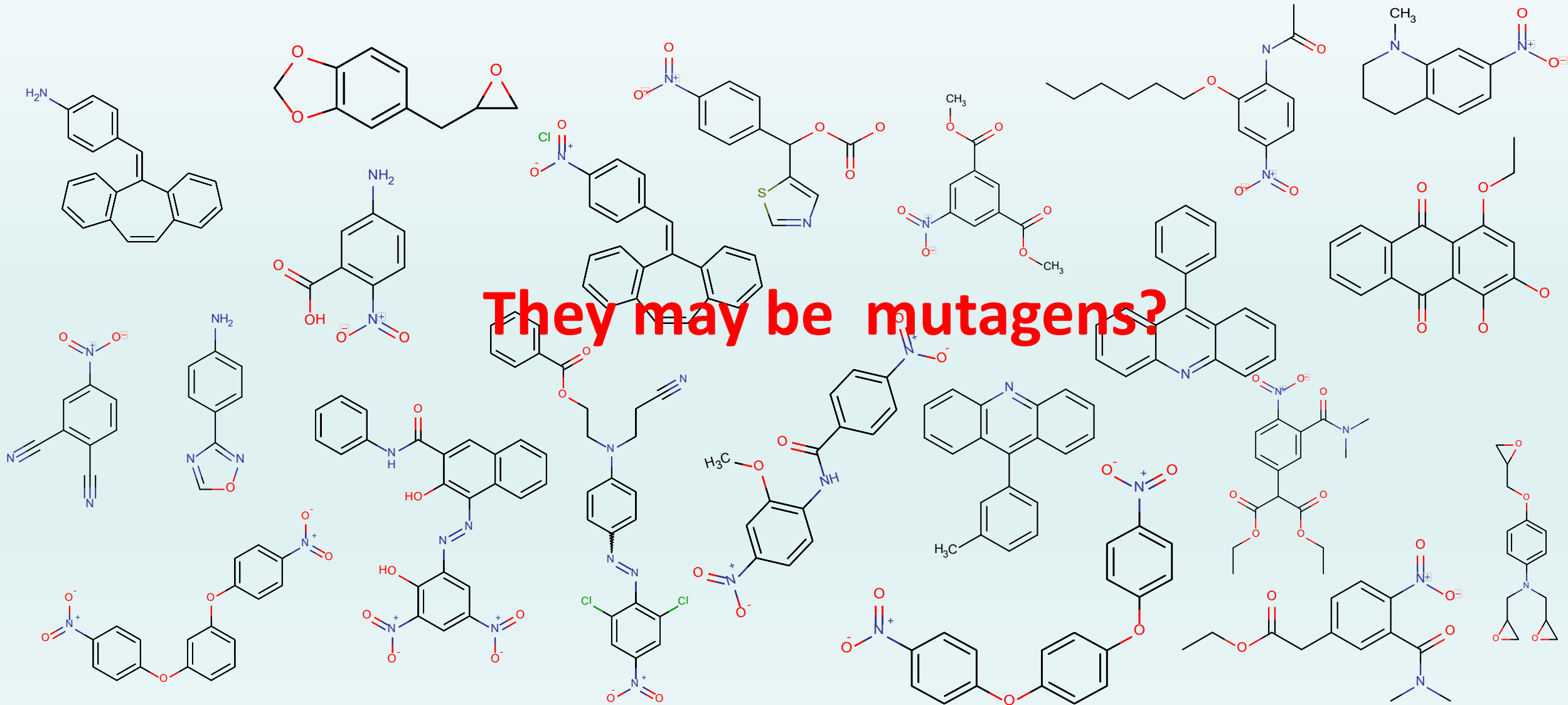


100-Specificity (%)



False Positive

Class C chemicals, but positive call by almost QSAR tools



Web-Site of AMES/QSAR International Collaborative Study



国立医薬品食品衛生研究所 安全性生物試験研究センター 変異遺伝部

DIVISION OF GENETICS AND MUTAGENESIS, NATIONAL INSTITUTE OF HEALTH SCIENCES

AMES/QSAR International Collaborative Study

Robust Quantitative Structure–Activity Relationship (QSAR) models defining toxicological endpoints are desirable to enable regulatory authorities to identify chemicals possibly causing adverse effects without performing actual toxicological studies. Much effort has been invested in the development of QSAR models to predict Ames mutagenicity, among many toxicological endpoints, to exploit the large body of Ames data and the strong correlation between chemical structure and Ames mutagenicity. Ames results are important for decisions on the development of chemical products and pharmaceuticals and the assessment of chemical safety, given that a positive result corresponds to increased cancer risk from exposure to the chemical even at a low level. The ICH-M7 guideline (Assessment and control of DNA-reactive impurities in pharmaceuticals to limit potential carcinogenic risk) currently recommends two QSAR models (expert rule-based and statistical) to predict Ames mutagenicity for initially assessing DNA-reactive impurities in pharmaceuticals. This is the first international guideline addressing the use of QSAR in lieu of an actual toxicological study for human health assessment. Thus, QSAR models for Ames mutagenicity now require much greater prediction power to ensure the safety of chemicals. To increase this prediction power, experimental data sets as training data to build the models are important. Large numbers of highly reliable data sets will allow development and improvement of QSAR models with high predictive power.

The Division of Genetics and Mutagenesis, National Institute of Health Sciences (DGM/NIHS) has Ames mutagenicity data for approximately 12,000 new chemicals. The Ames assays were conducted according to the OECD TG471 guideline and Industrial Safety and Health Act in Japan under GLP-compliant conditions. We now provide these Ames data to QSAR builders/vendors to improve their QSAR models for predicting Ames mutagenicity with the permission of the Industrial Safety and Health Department of the Ministry of Health, Labor and Welfare (MHLW), Japan. The Ames/QSAR international collaborative study led by DGM/NIHS launched on 2014. Because most of the Ames data are confidential, the QSAR builders/vendors participating in the project must execute a confidentiality agreement. Twelve QSAR builders/vendors from USA, UK, Italy, Spain, Bulgaria, Sweden, and Japan are currently participating in this project (Table 1).

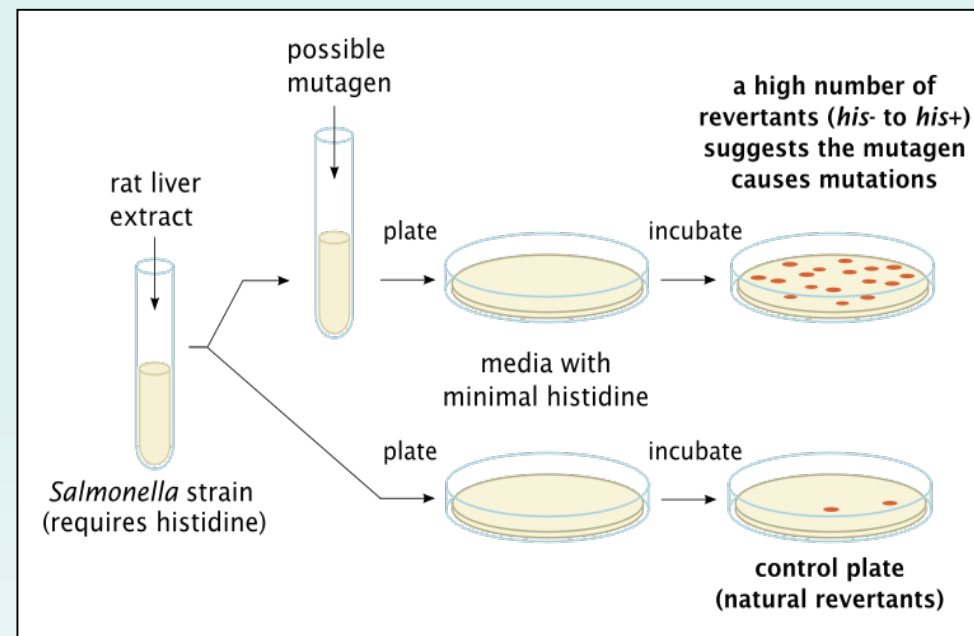
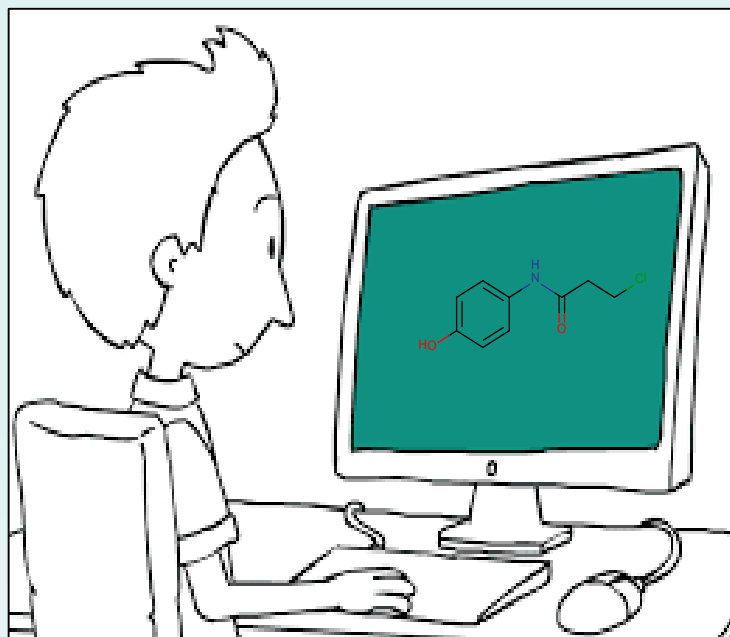
AMES QSAR



The next Ames/QSAR challenge program will start from the middle of 2018. Not only QSAR vendors, but also academia and IT companies are welcome to join the challenge. Hopefully, new QSAR models using AI and deep-learning will challenge.

Where is our goal?

Can we perfectly predict Ames mutagenicity by QSAR?



Inter-Laboratory Reproducibility of Ames Mutagenicity

-S9

Databases	Intersections	Concordance
GTP/NCI; TA 100	20 chemicals	85%
GTP/NTP; TA 100	39 chemicals	79%
GTP/NCI; TA 98	18 chemicals	88%
GTP/NTP; TA 98	21 chemicals	92%

82%

+S9

Databases	Intersections	Concordance
GTP/NCI; TA 100	15 chemicals	80%
GTP/NTP; TA 100	14 chemicals	(21%)*
GTP/NCI; TA 98	13 chemicals	90%
GTP/NTP; TA 98	23 chemicals	65%

GTP: Report of the U.S. Environmental Protection Agency Gene-Tox Program

NCI: Short-Term Testing Program in the National Cancer Institute (NCI), National Institutes of Health, US Department of Health and Human Services

NTP: NTP Program - P&G Inventory

*excluded for calculation

What means Ames positive?

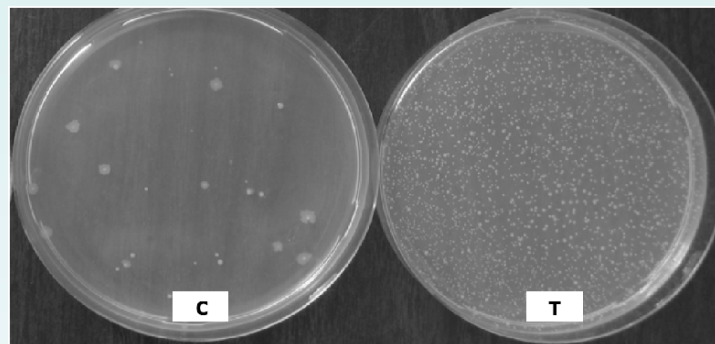
Class A : Strongly positive, in which the chemical generally induces more than 1,000 colonies/mg in at least one Ames strains in the presence or absence of rat S9.

Class B : Positive, in which the chemical induces colonies more than 2-fold of the negative control at least one Ames strains in the presence or absence of rat S9, but not in class A.

Class C : Negative, which is neither class A nor B.

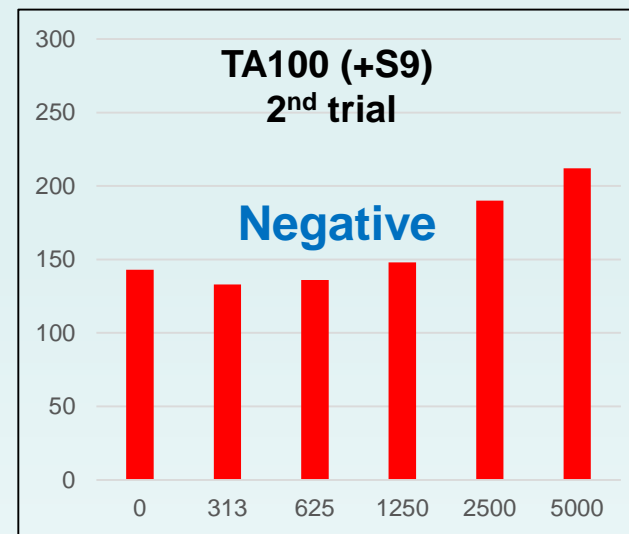
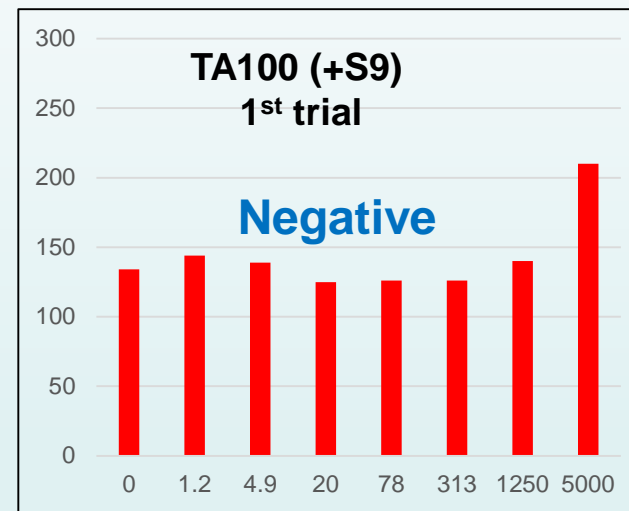
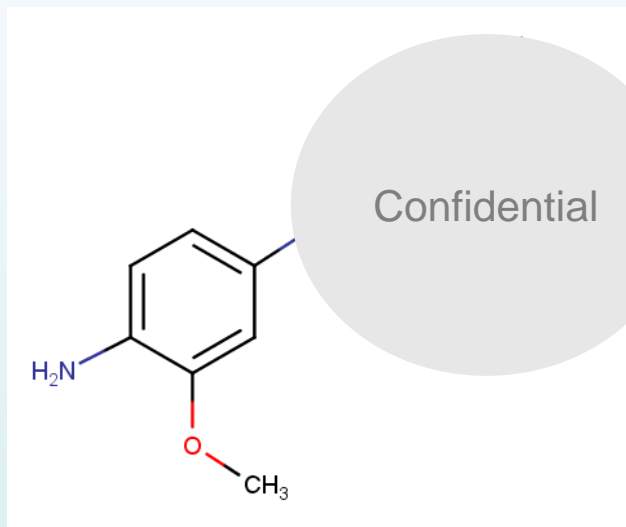
may contain false-positive.

may contain false-negative.



Is this Ames Positive?

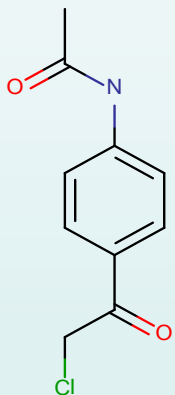
-Example A-



QSAR		Results
Derek NX		PLAUSIBLE
		Alert matched: 352 Aromatic amine or amide
CASE Ultra	PHARM_ECOLI	Negative
	PHARM_SALM	Inconclusive

Is this Ames Positive?

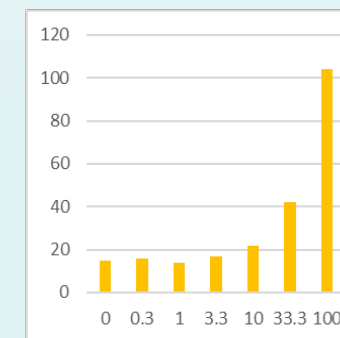
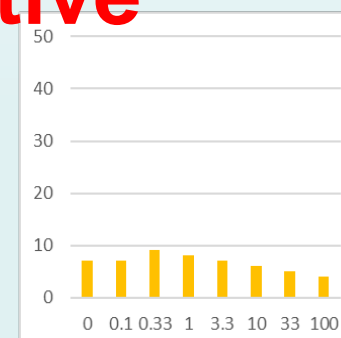
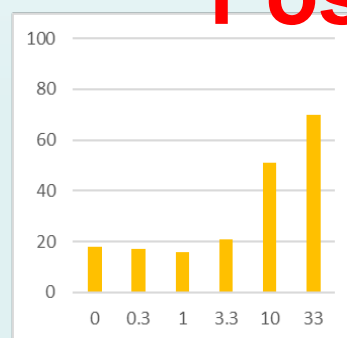
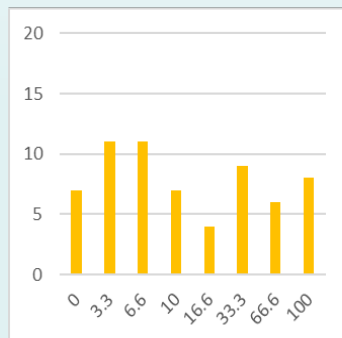
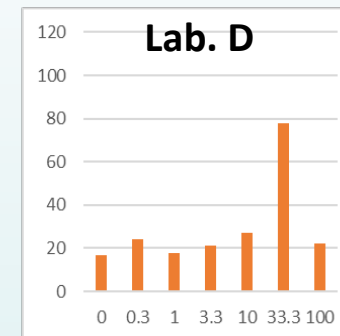
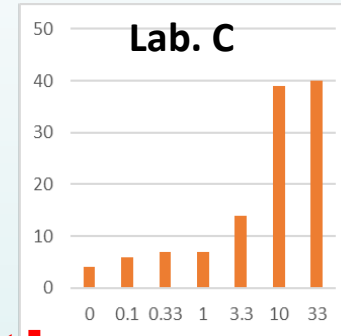
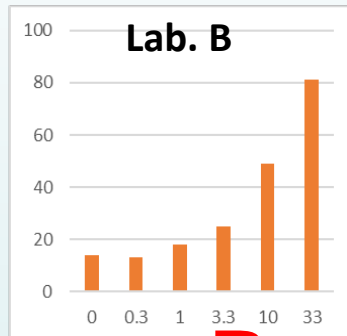
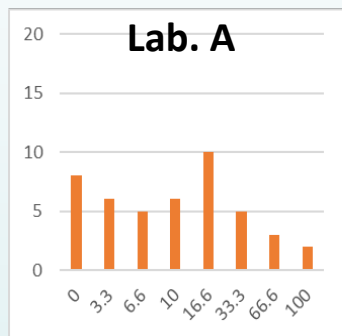
-Example C-



4'-(chloroacetyl)
acaetanilde
(Cas# 140-49-8)

TA1537
(-S9)

TA1537
(+S9)

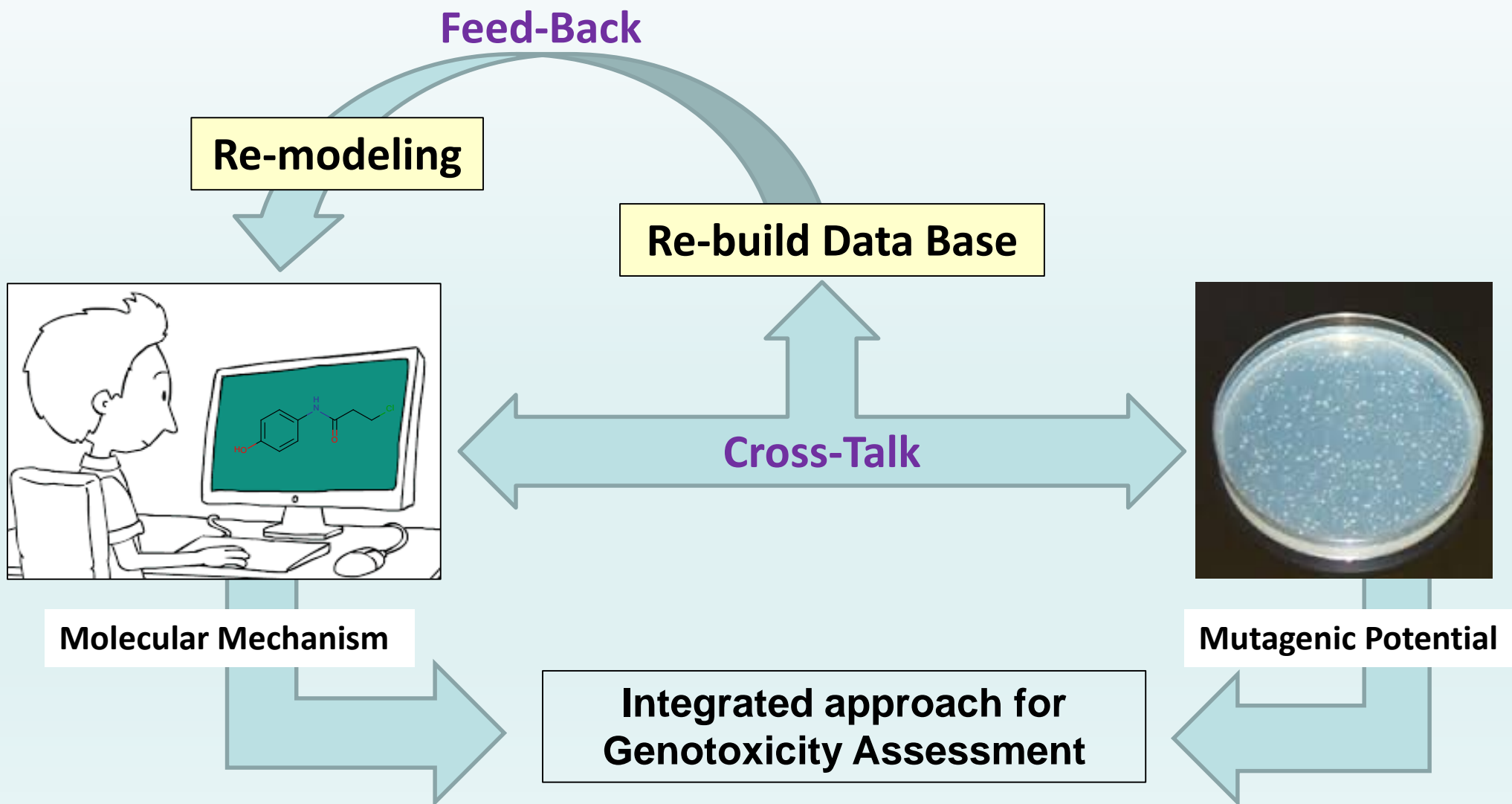


Positive

QSAR		Results
Derek NX		INACTIVE
CASE Ultra	PHARM_ECOLI PHARM_SALM	Negative Negative

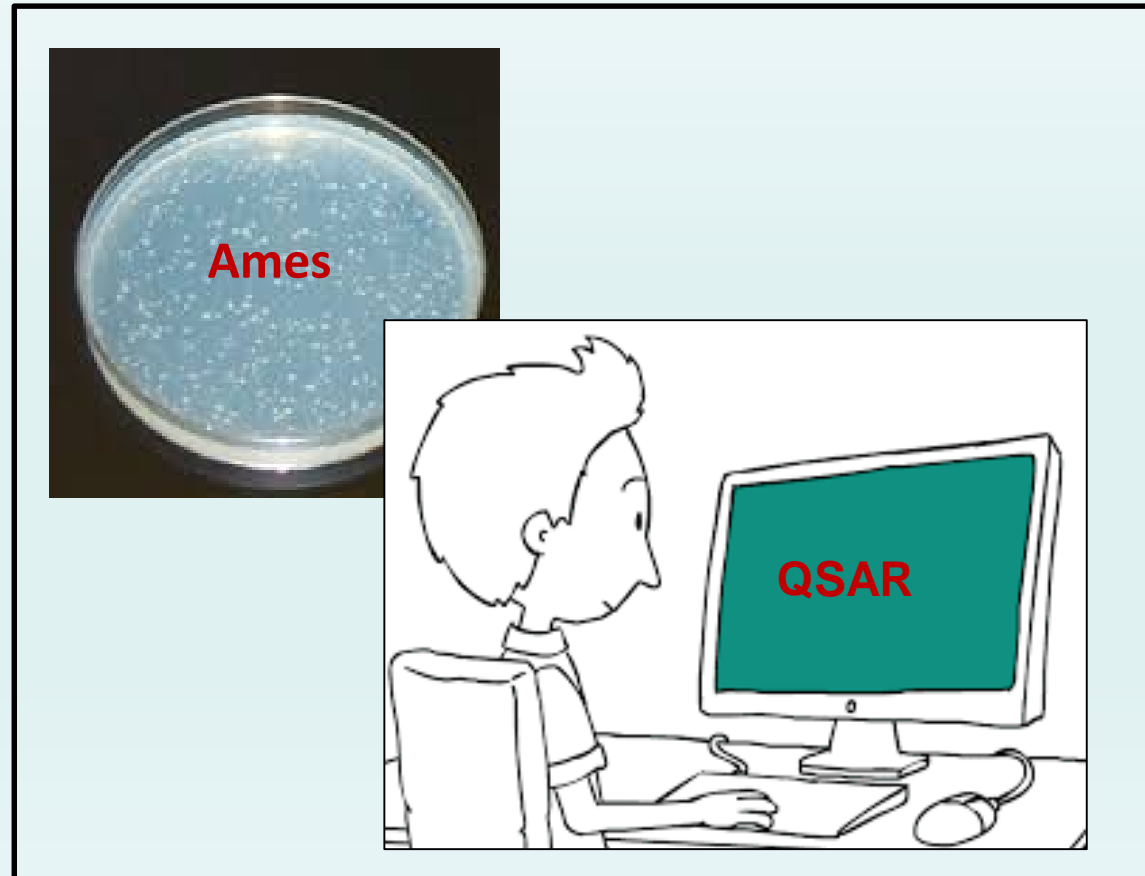
Dunkel et al., Environ Mutagen, 7, Suppl. 5, 1-248 (1985)

QSAR beyond Ames



QSAR is not only a tool for the prediction. It can support to judge the results of actual Ames test.

Use of Integrated Ames/QSAR approach



Genotoxicity vs. Carcinogenicity

Genotoxic Carcinogen

Genotoxicity test: +ve
Carcinogenicity test: +ve

Genotoxic Non-carcinogen

Genotoxicity test: +ve
Carcinogenicity test: -ve

False Positive



False Negative

--but, non-genotoxic carcinogens are possible.

Non-genotoxic Carcinogen

Genotoxicity test: -ve
Carcinogenicity test: +ve

Non-Genotoxic Non-carcinogen

Genotoxicity test: -ve
Carcinogenicity test: -ve



Performance of Genotoxicity Tests for Detecting Rodent Carcinogens (2)

Reports		<i>In vitro</i>		<i>In vivo</i>	Ames +	Ames +	Ames +
		Ames	CA	MN	CA	MN	CA + MN
Morita et al., Mutat. Res. 802, 1, 2016	Sensitivity (%)	59.0	62.8	41.0	74.3	68.7	80.8
	Specificity (%)	73.9	48.5	60.5	37.5	45.3	21.3
Ames /QSAR integrate approach and re-evaluation of Morita's data	Sensitivity (%)	71.3					
	Specificity (%)	84.1					

Battery Tests vs. Integrated Approach

Battery Tests

Ames

+

In Vitro
CA

+

In Vitro
MN

Sensitivity



--but false positive



Specificity



Expert Judgement



Integrated Approach

Ames

+

QSAR

Sensitivity



Specificity



But, should be considered----

- Exposure level
- A class of mutations
- *In vivo* metabolites
- Human metabolites



They will also be predicted by QSAR near future.

Summary



- QSAR is an ideal tool as high throughput screening for huge number of chemicals without costs, labors and animals.
- The ICH-M7 guideline is the first international guideline addressing the use of QSARs for evaluating human health effect.
- A large number of highly reliable data sets are essential to allow the development and improvement of QSAR models.
- The Ames/QSAR international collaborative study is successfully ongoing. Its outcome gives a lot of benefits to QSAR vendors, QSAR users, and regulatory.
- The integrated approach with QSAR results increases the sensitivity and specificity of the Ames assay for predicting rodent carcinogens. It can support to judge the Ames results with molecular mechanism.

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