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Control of Mutagenic Impurities in Drug Substances and Products

- Methods and issues of mutagenicity and carcinogenicity evaluation of pharmaceutical impurities based on ICH M7 guideline

-From the viewpoints of practices for pharmaceutical businesses

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(Ph*i*AS)

Research career (biography since 1987) : Tsukasa Kikuno

- -Manager and Senior Researcher, Chemicals Evaluation and Research Institute, Japan (CERI)
- -Study Director of mutagenicity tests and general toxicity tests (GLP and Guidelines (Chemicals, Pharmaceuticals, Pesticides)) in Bio-testing Laboratory of CERI.
- -Research of international and domestic regulations of chemicals (EU REACH, China, Thailand, Philippines)
- -GHS classification of chemicals (mutagenicity, carcinogenicity, repeated toxicity, reproductive toxicity etc.) and safety data sheet.
- -Genotoxicity and general toxicity research and evaluation of chemicals.
- -Research in NIHS (in 1991): Molecular biological research for detection of mutagens (collaboration with Dr. M. Honma, NIHS)
- -Technical transfer and lecture of mutagenicity to SIRIM, Malaysia (in 1998-2002): Researcher of JICA-Malaysia project of chemicals risk management.
- -Temporary lecturer of mutagenicity and ICH M7 in Ochanomizu University and Meiji University (CERI donation course business).
- -ICH M7, Q3C and Q3D supports and surveys for pharmaceutical companies and academia in Japan:
- -Book writings: ICH M7 (published in 2015), ICH Q3C and Q3D (published in 2017), Science and Techno
  Risk assessment of chemicals (Maruzen Co., Ltd.), etc.
- -Many research reports of QSAR and ICH M7 for pharmaceutical companies and academia.
- -Assessed more than 1,000 pharmaceutical impurities complying with ICH M7, Q3C and Q3D in the last 7
- President and CEO, PhiAS

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Company Profile

- Company name: Pharmaceutical Impurities Safety Assessment Research Institute, Co., Ltd. (PhiAS)
  (株式会社医薬品不純物安全性評価研究所)

- Address: 7-21, 3-15-6 Nishigotanda, Shinagawa-ku, Tokyo 141-0031, Japan
- TEL&FAX: (+81)3-3495-1272
- E-mail: phiaskikuno@gmail.com
- President and CEO: Tsukasa Kikuno (菊野　秩)
- Established in February 1, 2019

Achievements for ICH M7, Q3C and Q3D

- Public lectures for customers of Eighteen times by Tsukasa Kikuno
- On-site seminars and briefing sessions for customers
- Co-authored book “Evaluation, management and application / CTD description method for ICH M7 mutagenic impurities from the development stage” (in Japanese) (Science & Technology Co. Ltd.)
- Co-authored book “Tolerable limit value/ test method setting and appropriate management method of ICH Q3D elemental impurity / Q3C residual solvent” (in Japanese) (Science & Technology Co. Ltd.)
- A number of ICH M7 / QSAR evaluation reports for pharmaceutical customers

Our Core Business

- Contract research and consultation support of ICH M7/QSAR for pharmaceutical companies and academia.
  - Selection of Pharmaceutical impurities
  - Existing information survey of mutagenicity and carcinogenicity of impurities
  - QSAR prediction of mutagenicity of impurities
  - QSAR expert review and judgement
  - Assessment of mutagenicity and carcinogenicity of impurities and ICH M7 Classification
- Contract research and consultation support of ICH Q3C (solvent compounds) and ICH Q3D (elements and element compounds)
  - Toxicity investigation of pharmaceutical impurities from international information sources and toxicity assessment (NOAEL etc.)
  - Calculation and decision of Permitted Daily Exposure (PDE)
  - ICH Q3C and Q3D classification

Our Core Business (continued)

- Toxicity assessment for pharmaceuticals, pesticides and chemicals.
  - Reporting of toxicity assessment of chemicals
- Preparation and maintenance of SDS (Safety Data Sheet) for companies.
  - Reporting of SDS (for domestic purpose)
- Risk assessment for chemicals.
  - Reporting of chemical risk assessment

Mutagenicity of impurities in pharmaceuticals -History and background-

ICH guideline： Q3A（for impurities in drug substance）
Q3B（for impurities in drug product）

- **The manufacturing process has not been clarified at the stage of clinical trials.**
- **If impurities are genetically toxic and carcinogenic, sufficient safety cannot be guaranteed for volunteers in clinical trials.**

The issues of the ICH guidelines have been highlighted.

2006年：Position Paper of PhRMA

Paper on Regulatory Toxicology and Pharmacology (2006)　　Dr. Lutz Muller (Roche)

Genotoxicity was hazard identification → Changes to risk assessment

In 2006：EMEA guideline

Roche Viracept problem occurred (2007)

In 2008：US FDA draft guidance

In June 2010：ICH Steering Committee Approves Development of Guidelines for Mutagenic Impurities

In June 2014：ICH M7 Step 4 draft guidelines published

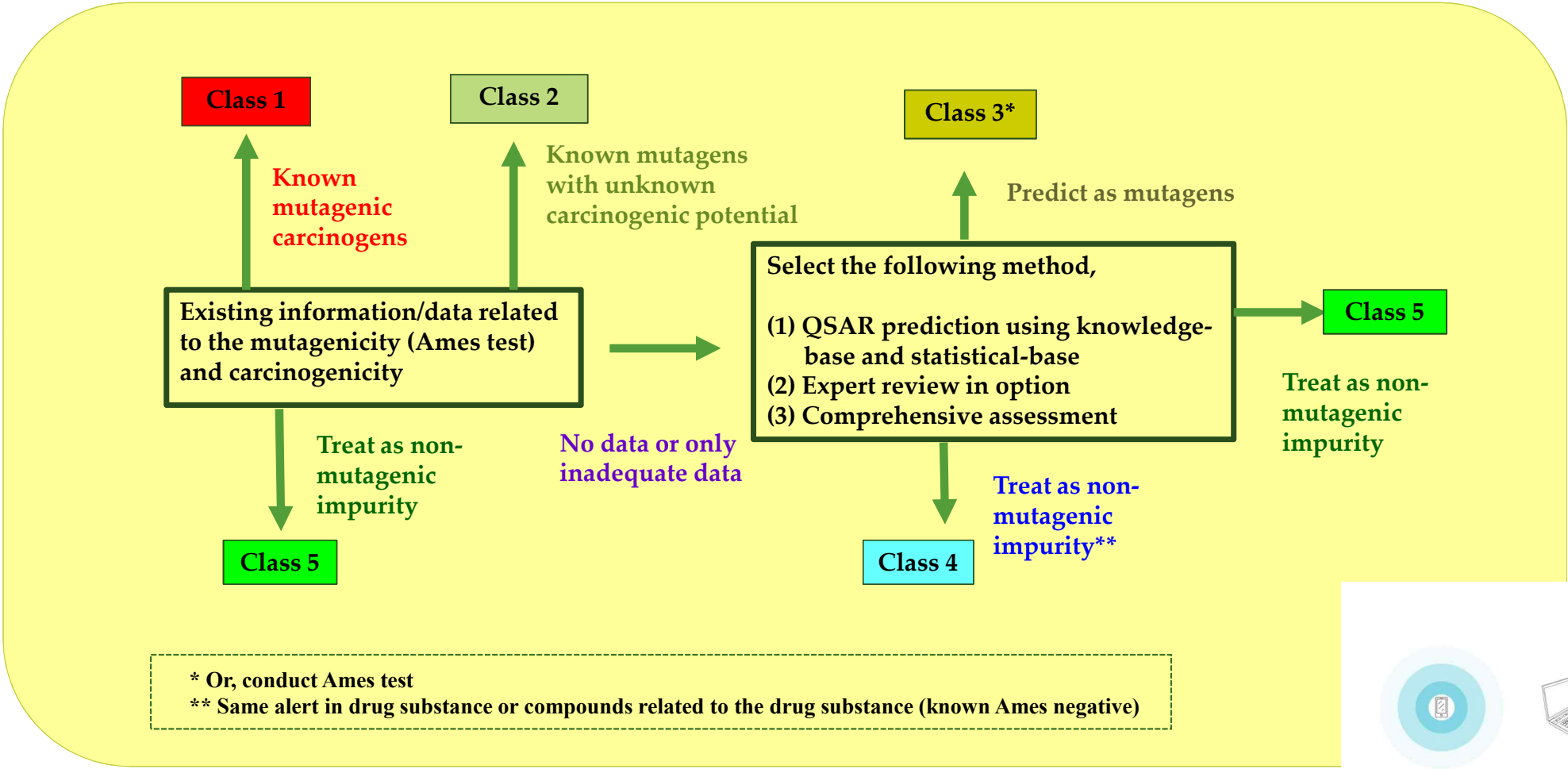
In January 2016：ICH M7 comes into effect in Japan

Mutagenic carcinogens have been detected in multiple drugs even after M7 came into effect, which has become an international issue.

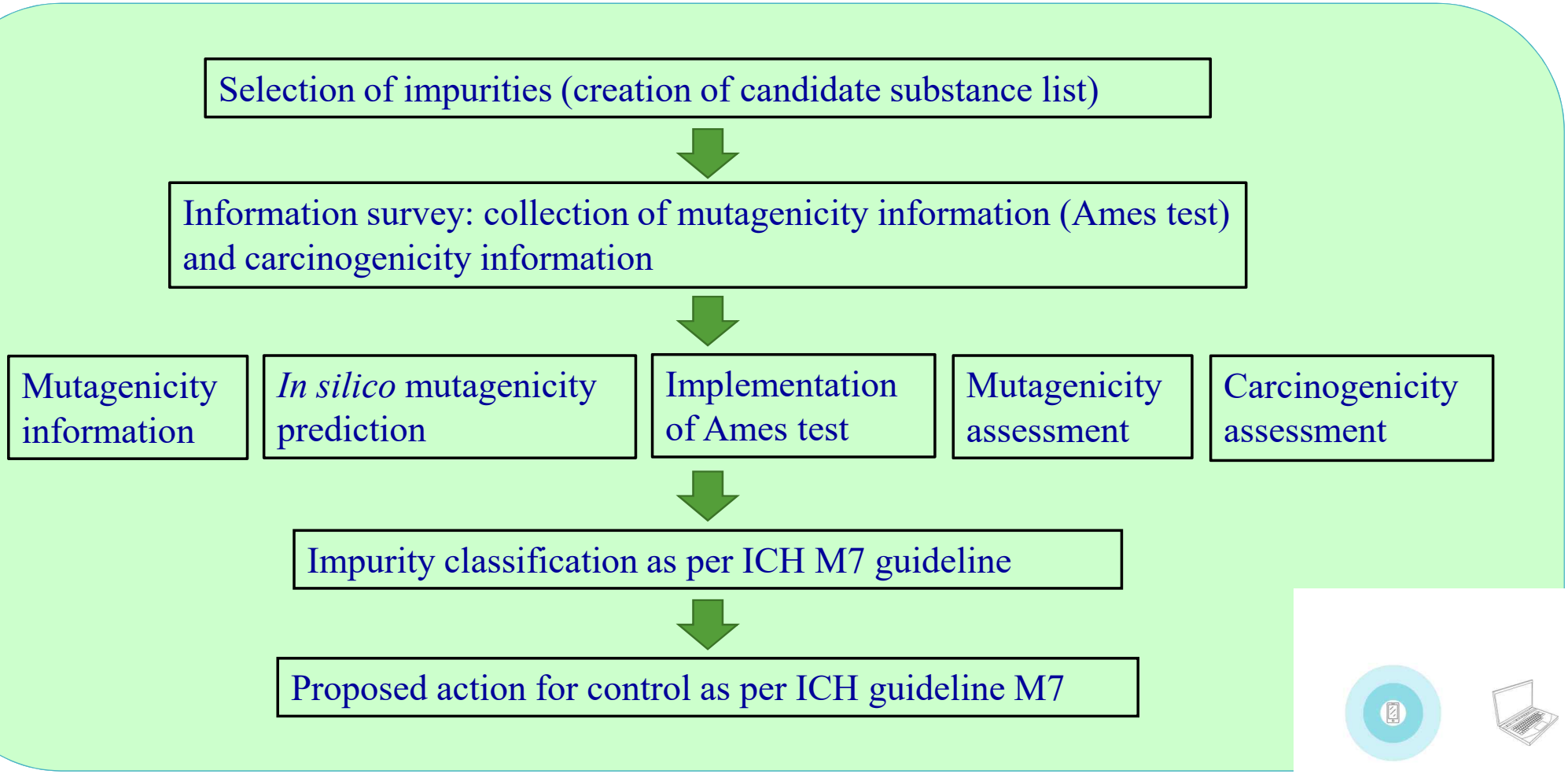
Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions in ICH M7 guideline

	Class	Definition	Proposed action for control
Information survey	1	Known mutagenic carcinogens	Control at or below compound specific acceptable limit
Information survey	2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
***In silico* prediction**	3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
	4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are nonmutagenic	Treat as non-mutagenic impur
	5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impur

Flow chart for hazard classification in ICH M7 guideline (Modified Amberg et al., 2016)



Work flow for mutagenicity and carcinogenicity evaluation

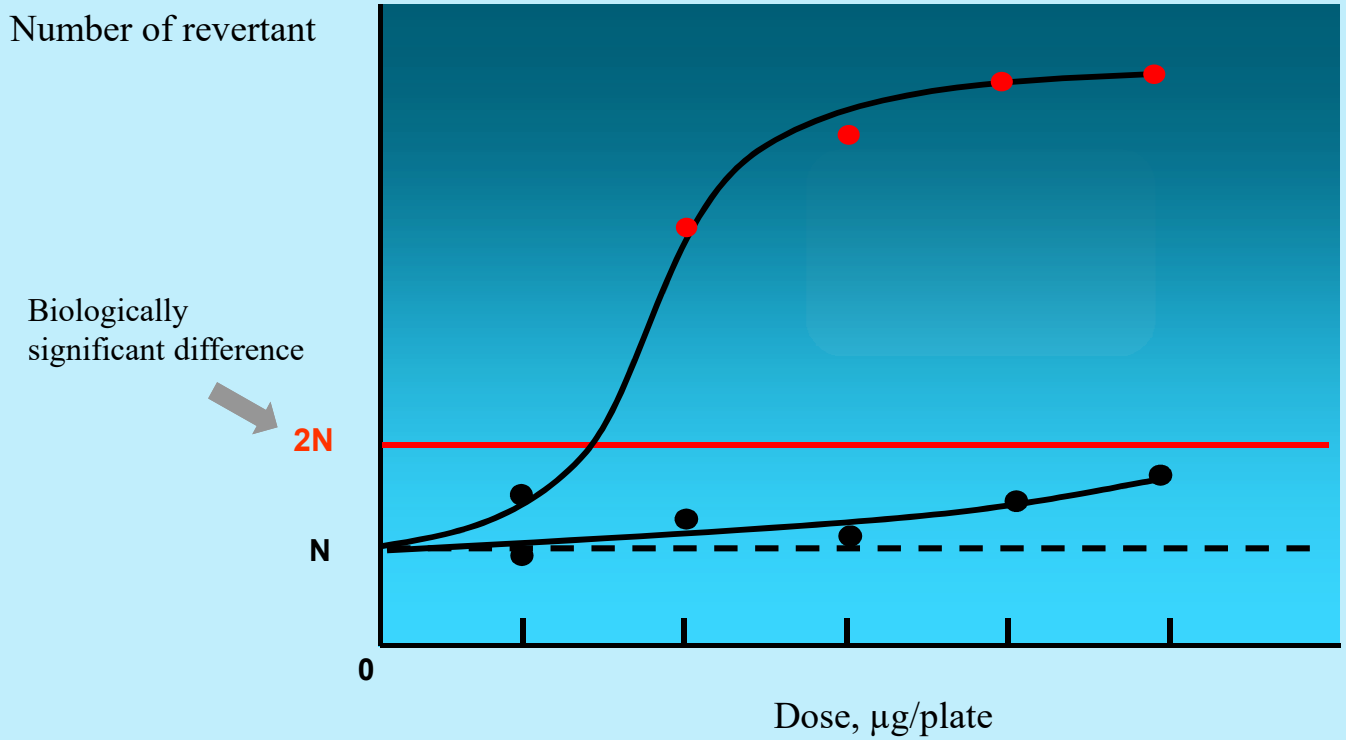


Positioning of the Ames test in genotoxicity/mutagenicity tests

Genotoxicity test/ mutagenicity test (examples)		Test method		
		DNA damage	Gene mutation	Chromosome aberration
In vitro (bacteria)		・DNA damage or repair test ・*umu* test	・Reverse mutation assay (Ames test) (*S. typhimirium* or *E. coli*)	–
In vitro (cultures cells)		・UDS test ・DNA adduct formation test ・Comet assay	・Mouse lymphoma test ・HPRT test	・Chromosome aberration test ・Micronucleus test
In vivo (experimental animals)	Somatic cells	・Liver UDS test ・DNA adduct formation test ・Comet assay	・Mouse spot test ・Gene mutation assay with transgenic animals ・*Pig-A* test	・Bone marrow chromosome aberration test ・Micronucleus test using red blood cells ・Sister chromatid exchange test using bone marrow
	Germ cells	・UDS test using testicular cells ・DNA adduct formation test	・Specific locus test in mice	・Heritable translocation test in rodents ・Dominant lethal test in rodents ・Spermatogonia chromosomal aberration test in rodents ・Sperm micronucleus test in rodents ・Sister chromatid exchange test with sperm

Major bacterial strains of Ames test: *Salmonella typhimurium* TA100, TA98, TA1535, TA1537, TA102, *Escherichia coli* WP
WP2 *uvrA*/pKM101, etc.

Judgment of Ames test results



Information sources (examples) of mutagenicity (Ames test) and carcinogenicity for existing information surveys using at PhiAS

GHS Classification Results by GHS Relevant Ministries (Sourced from: MHLW Site for Occupational Safety)
Initial Risk Assessment Report/Chemical Substances Hazard Assessment Report, Chemicals Evaluation and Research Institute, Japan (CERI)/National Institute of Technology and Evaluation (NITE)
Japan Existing Chemical Data Base (JECDB), NIHS
NITE Toxicity and Eco-toxicity Test Results
Ministry of Economy, Trade and Industry (METI) Safety Test Results
Public Notice on the Guidelines for Preventing the Impairment of Workers' Health Pursuant to the Provisions in Paragraph 3 of Article 28 of the Industrial Safety and Health Act, MHLW
Results of Carcinogenicity Studies Commissioned by MHLW, Japan Bioassay Research Center (JBRC)
Environmental Risk Initial Assessment of Chemicals, MOE, Japan
Recommendations for Working Environment Allowable Concentrations, Japan Society of Occupational Health (JSOH)
OECD SIDS report (SIDS Initial Assessment Report)
Environmental Health Criteria (EHC), IPCS (International Program on Chemical Safety)
Concise International Chemical Assessment Document (CICAD), IPCS (International Program on Chemical Safety

Information sources (examples) of mutagenicity (Ames test) and carcinogenicity for existing information surveys using at PhiAS (continued)

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, International Agency for Research on Cancer (IARC)
FAO/WHO Joint Expert Committee on Food Additives – Monographs (JECFA Monographs)
Risk Assessment Report, EU
American Conference of Industrial Hygienists (ACGIH)
Integrated Risk Information System (IRIS), U.S. EPA
NTP Database
NTP Report on Carcinogens (RoC)
NTP Technical Report (NTP TR)
Toxicological Profile, Agency for Toxic Substances and Disease Registry (ATSDR)
Priority Substances List Assessment Report, Canadian Environmental Protection Act (CEPA), Environment Canada, Health Canada
Australian Department of Health and Aging: Priority Existing Chemical Assessment Report, National Industrial Chem Notification and Assessment Scheme (NICNAS)
Pesticides “Reregistration Eligibility Decision”, U.S. Environmental Protection Agency (EPA)
Mutagenicity Test Results, "Shokubanoannzennsaito", MHLW

Information sources (examples) of mutagenicity (Ames test) and carcinogenicity for existing information surveys using at PhiAS (continued)

Hazardous Substance Data Bank (HSDB)
Carcinogenicity Potential Database (CPDB)
Test Data of Agricultural Chemicals, Food and Agricultural Materials Inspection Center (FAMIC)
Pesticide Safety Information, Japan Crop Protection Association
Risk Assessment Reports, Food Safety Commission of Japan
Study on the Review of Safety of Existing Food Additives, Ministry of Health, Labour and Welfare (MHLW)
NITE CHRIP
REACH Registered Substances Information, European Chemicals Agency (ECHA)
European Commission, Scientific Committee on Food
European Medicines Agency, Public statement
The EFSA Journal
PubChem CCRIS
PubMed
PubChem

Information sources (examples) of mutagenicity (Ames test) and carcinogenicity for existing information surveys using at PhiAS (continued)

DEFGOT, MAK Collection for Occupational Health and Safety, MAK Values Documentations, List of MAK and BAT values
Patty’s Toxicology, Patty's Industrial Hygiene and Toxicology
Initial assessment of environmental risks of chemical substances (MOE, Japan)
WHO/FAO Pesticide Data Sheets（PDSs）
BUA Report (BUA), German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance
Chemical fact sheet (MOE, Japan)
AIST Risk Assessment Document, National Institute of Advanced Industrial Science and Technology (AIST)
Hazardous Substance Fact Sheet (New Jersey Department of Health and Senior Services)
US HPV Challenge Program (HPV-IS)
FAO/WHO Joint Meeting on Pesticide Residues - Monographs of toxicological evaluations
RTECS (Registry of Toxic Effects of Chemical Substances)
EU C&L Inventory, ECHA
BIA: GESTIS-database on hazardous substances

QSAR Prediction

- Evaluate comprehensively for mutagenicity of impurities using two types of (Q) SAR (knowledge-base, statistical-base)
- Following the principles of OECD QSAR model validation
- Knowledge-base QSAR: DEREK, CASE Ultra GT_EXPERT, LeadScope, Toxtree, Oncologic, HazardExpert, OECD QSAR Toolbox, etc.
- Statistical-base QSAR: CASE Ultra GT1_BMUT, LeadScope, SciQSAR (MDL-QSAR), Sarah, TOPKAT, ADMEWORKS, etc.
- Expert review (judgment) for QSAR prediction results

Recent information for ICH M7/QSAR

Scientific paper for ICH M7/QSAR Expert Review

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

- This paper can be used as the main reference material as an SOP (information from US M7 experts)

Overseas-information collection results for ICH M7/QSAR (Sept.-Oct., 2019)

- USA: Hearing from US M7 experts for current situation and recognition for M7/QSAR.
- Canada: As in EU and US, M7 compliance of new drug substances, new drug products, and generic drugs has already been applied.
- Taiwan: M7 is already known to pharmaceutical companies. M7 has been introduced to the guidelines to be followed. M7 legislation is near.

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

Summary of in domain predictions generated for the two (Q)SAR methodologies.

Statistic-based result	Expert rule-based result	Count[a]	Percentage of results that were experimentally identified Ames mutagens
Positive	Positive	1253	59.7%
Negative	Positive	499	37.5%
Positive	Negative	353	24.7%
Negative	Negative	7978	8.1%

[a] Out of 15,886 compounds tested.

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

Summary of analysis where at least one of the methods generates an out-of-domain result.

Statistic-based result	Expert rule-based result	Count	Percentage of results that were experimentally identified Ames mutagens
Out-of-domain	Positive	296	36.2%
Out-of-domain	Indeterminate	78	28.2%
Out-of-domain	Out-of-domain	1558	11.8%
Out-of-domain	Negative	2027	11.8%

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

Different scenarios that include an indeterminate call from one or both of the methodologies.

Statistic-based result	Expert rule-based result	Count	Percentage of results that were experimentally identified Ames mutagens
Indeterminate	Positive	516	50.6%
Out-of-domain	Indeterminate	78	28.2%
Positive	Indeterminate	155	27.7%
Indeterminate	Negative	668	23.2%
Indeterminate	Indeterminate	93	20.4%
Negative	Indeterminate	314	11.8%

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

To quantify the actions resulting from such a review, the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) between May 2016 and April 2017 analyzed 519 impurities for bacterial mutation using software from **Leadscope (2017), Lhasa Limitec (Lhasa, 2017), and MultiCASE (MultiCASE, 2017). (Kruhlak et al., 2017)** The expert-reviewed predictions were concordant with the consensus (Q)SAR results 87% of the time with:

- 2.1% of the negative consensus predictions changed to positive after the expert review
- 4.2% of the positive consensus predictions changed to negative after the expert review
- 61% of the indeterminate consensus predictions changed to negative after the expert review
- 11% of the indeterminate consensus predictions changed to positive after the expert review
- 28% of the indeterminate consensus predictions were not changed

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

Statistic-based results	Expert rule-based results	Count
Negative	Negative	7,978
Out-of-domain	Negative	2,027
Out-of-domain	Out-of-domain	1,558
Positive	Positive	1,253
Indeterminate	Negative	668
Indeterminate	Positive	516
Negative	Positive	499
Positive	Negative	353
Negative	Indeterminate	314
Out-of-domain	Positive	296
Positive	Indeterminate	155
Indeterminate	Indeterminate	93
Out-of-domain	Indeterminate	78

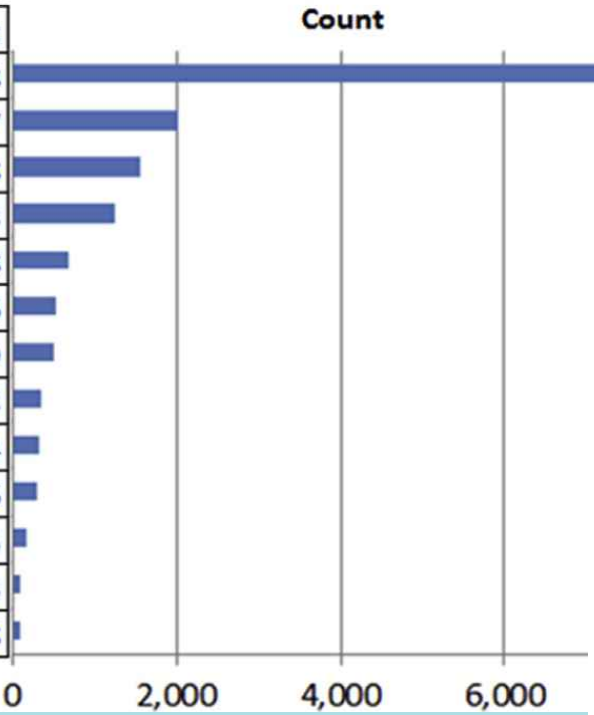
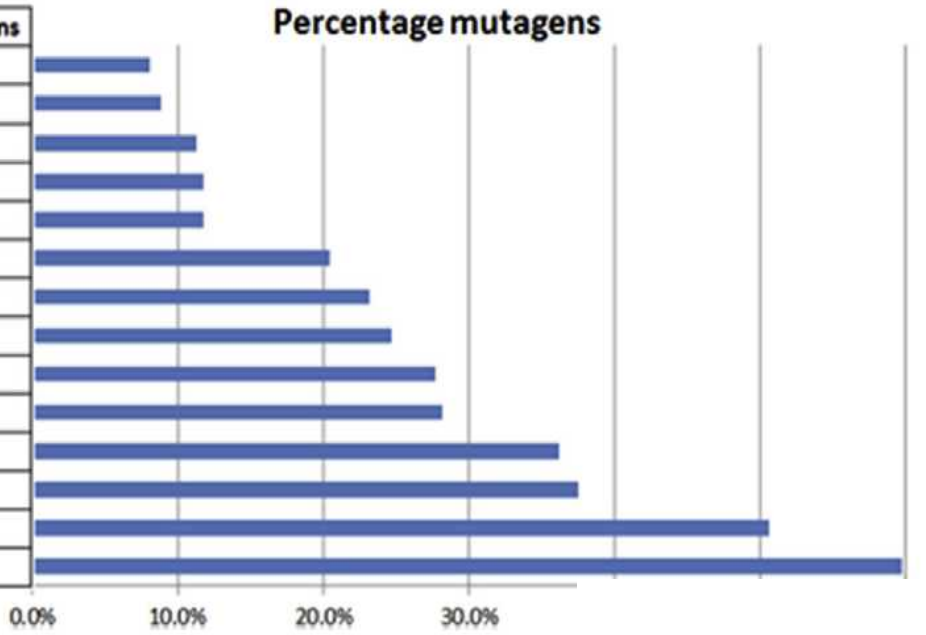


Illustration of the number of times different (Q)SAR results are encountered.

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses

(Amberg, A. et al., 2019: Regulatory Toxicology and Pharmacology 102, 53-64.)

Statistic-based results	Expert rule-based results	Count	Percentage mutagens
Negative	Negative	7,978	8.1%
Out-of-domain with probability of being positive < 0.2	Negative	1,415	8.8%
Out-of-domain	Negative	2,027	11.3%
Negative	Indeterminate	314	11.8%
Out-of-domain	Out-of-domain	1,558	11.8%
Indeterminate	Indeterminate	93	20.4%
Indeterminate	Negative	668	23.2%
Positive	Negative	353	24.6%
Positive	Indeterminate	155	27.7%
Out-of-domain	Indeterminate	78	28.2%
Out-of-domain	Positive	296	36.1%
Negative	Positive	499	37.5%
Indeterminate	Positive	516	50.6%
Positive	Positive	1,253	59.7%



Summary of the likelihood of misclassifying a mutagenic impurity as non-mutagenic for different combinations of results.

Overseas-information collection results for ICH M7/QSAR

- USA: Information from ICH M7/QSAR experts from the US
- Canada: Information from Health Canada ICH M7 expert sources
- Taiwan: Information from Taiwan ICH M7 sources

- Information obtained on September-October, 2019
- All questions from M7 customers in Japan
- Q & A, discussion: USA, Taiwan
  Writing Q & A: Canada

Overseas-information collection results for ICH M7/QSAR*

*The Q&A presented here is part of the overall discussion.

*Private communication by experts from Taiwan and USA. Therefore, please note that this information is not necessarily finalized.

- What is the approximate number of pharmaceutical-related companies in your country, including companies involved with research and development of bulk drugs, new drug substances, new formulations, generic drugs, and drug products?

(USA) There are approx. 100 large pharmaceutical companies and approx. 5000 middle or small-sized pharmaceutical companies in USA.

(Taiwan) Approximately 168 pharmaceutical companies (as GMP pharmaceutical factories)

Overseas-information collection results for ICH M7/QSAR

- Progress is being made with globalization of drug development and business transactions. In relation to the drug development and manufacture by domestic pharmaceutical companies or imports into your country by foreign pharmaceutical companies, do your country‘s competent authorities request compliance with ICH M7 to these companies?

(Canada) Whether a pharmaceutical company has assessed and controlled their API and/or drug product in compliance with ICH M7 is determined at the time a drug submission is reviewed. At the drug review stage, Health Canada follows the recommendations outline in ICH M7 and would expect pharmaceutical sponsors to also follow the M7 guideline.

(USA) For existing pharmaceutical products, M7 is required for drugs whose manufacturing method has been changed. All other drugs (new drug substances, new drug products, generic products) are basically subject to M7 in USA.
In countries other than ICH, India, for example, is also required to support M7.

(Taiwan) By 2023, legal compliance of Tier 2 (including M7 compliance) will be required. The i
compliance has already been mandated by domestic pharmaceutical companies as an administrative

Overseas-information collection results for ICH M7/QSAR

- We understand that, in ICH member countries (USA and EU), even apart from new bulk drugs and new formulations, generic drugs and even small parts of commercial products are expected to comply with ICH-M7. In your country, what is the status of ICH-M7 compliance by generic drugs and commercial products?

(Canada) Applications for generic drug products are expected to comply with the ICH M7 guideline.

(USA) In the US, generic drug applications have increased such as approx.5:95 or higher for new drugs versus generics. Conservative response for generic drugs is required.

(Taiwan) Taiwan has the ICH Adoption List including M7.

Overseas-information collection results for ICH M7/QSAR

- What inquiries are frequently come from the authority after clinical trial notification or common technical document is submitted?

(Canada) From the safety perspective, most inquiries are related to lack of information submitted (QSAR analyses, Ames tests, references to available carcinogenicity studies).

- In EU and US generic pharmaceuticals and partial pharmaceutical products in the market have to be assessed and controlled as same method of impurity management and notification to authority as new drug substances and new drug products. How about the actions of generic pharmaceuticals in your country? If there are different between them, tell me what.

(Canada) In regards to ICH M7, generic pharmaceuticals are evaluated in the same manner.

Overseas-information collection results for ICH M7/QSAR

- Has M7 support for existing pharmaceutical products started in your country?

(Canada) This question appears to be more relevant to the pharmaceutical industry. From the regulatory perspective, for existing products, any time there is a 'change' as outlined in ICH M7 sections 4.2, 4.3, a re-evaluation of mutagenic impurity limits is warranted.

(USA) Even in the case of existing pharmaceuticals, if the manufacturing method or others are changed, M7 compliance is covered.

- Is it necessary for the evaluation to cover compounds with which there is a potential of contamination, including compounds that have never actually been chemically detected?

(Canada) The risk assessment or evaluation will depend on the synthesis for the API and proposed control strategy.

(USA) Even if it is a compound that has not been detected, it is better to evaluate it as compounds that may theoretically be mixed.

Overseas-information collection results for ICH M7/QSAR

- In relation to ICH-M7, to what extent is it necessary to detect and analyze small peaks due to impurities chemical analysis, to identify the relevant molecular structures, and to evaluate mutagenicity?

(Canada) For non-mutagenic impurities, impurities above the reporting threshold should be reported in the dossier (refer to ICH Q3A and ICH Q3B). For potentially mutagenic impurities, the recommendation in ICH M7 and Q11 would apply.

(USA) Using chemical analysis methods, it is necessary to analyze impurities including not only large peaks but also smaller peaks, structure identification, and comply with M7 compliance (mutagenicity, carcinogenicity). In the case of Valsartan, it is understood that companies need such a strict response. Therefore, it is necessary to make a conservative evaluation using the possible analytical method(s) even for the smaller peak(s). In addition, there should be no mutagenic impurities in pharm in excess of TTC as a result of risk considerations. It is also important to consider appropri control methods such as purge factor.

Overseas-information collection results for ICH M7/QSAR

- If QSAR prediction is carried out as compliance with ICH-M7, how precise does the expert review or expert judgment have to be? For example, within the range of QSAR prediction output reports, are there any difficulties with making a positive vs. negative decision fundamentally?

(Canada) Expert review is most useful when the predictions are conflicting or inconclusive. In the case where the output of the QSAR analyses are both positive or both negative, and if Health Canada chemists do not identify additional structures of concern, then the QSAR analyses are accepted.

(USA) It is important to judge positive and negative from the QSAR prediction output report. However, when QSAR results are inconclusive and out of domain, an expert review (judgment) is required to make an appropriate predictive evaluation. Amberg et al., 2019 is helpful.

- In ICH M7 transaction, are there any in vivo tests (excluding test guideline methods) accepted in the authority? What is the tests? For example, only pig-A?

(Canada) If the sponsor chooses to evaluate the in vivo relevance of a positive Ames test resu vivo gene mutation assay should be performed. To this end, either the transgenic mutation as the pig-A assay are recommended since these assays evaluate gene mutation.

Overseas-information collection results for ICH M7/QSAR

- Is there a standard for the background (expertise) required of the person who performs expert judgment?

(Canada) If expert judgment is performed at Health Canada, a person with subject matter expertise would be requested to perform the assessment. This could involve both a chemist and a toxicologist.

(USA) There is no specific standard in the background of Expert judgment. For example, in India, people who are not specialized are available. However, there are many specialists in large companies, etc., and more sophisticated expert judgments likely have been established.

Thank you.