化学物質毒性ビッグデータベースと、インシリコによる毒性予測

-Ames変異原性試験データベースと、インシリコによる変異原性予測-
Global Management of Chemical Substances

1974
Chemical Substances Control Law (CSCL) Kashinhou

1977
TSCA

1981
EEC

1988
1991
CEPA
CEPA

1991
TCCCA

2003
C-NCSN

2004
REACH

2015
KREACH

2010
C-REACH
Annual Transition of Number of New Chemical Substances Subjected to “Kashinho”

High Volume (>10t/year)

Low Volume (>1t/year)

Small Volume (<1t/year)
### Assessment for New Chemicals in “Kashinhou”

<table>
<thead>
<tr>
<th>New Chemicals (2016)</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High Volume; 325 Chemicals (&gt;10 t/year)</td>
<td>◆ Biodegradability and Bioaccumulation (METI)</td>
</tr>
<tr>
<td></td>
<td>◆ Ecological Effect (ME)</td>
</tr>
<tr>
<td></td>
<td>◆ Human Health Effect (MHLW)</td>
</tr>
<tr>
<td></td>
<td>➢ Ames test (Mutagenicity)</td>
</tr>
<tr>
<td></td>
<td>➢ Chromosomal aberration test</td>
</tr>
<tr>
<td></td>
<td>➢ 28-days repeated dose study</td>
</tr>
<tr>
<td>• Low Volume; 1,677 Chemicals (&gt;1 t/year)</td>
<td>◆ Biodegradability and Bioaccumulation (METI)</td>
</tr>
<tr>
<td>• Small Volume; 35,848 Chemicals (&lt;1 t/year)</td>
<td>◆ Nothing</td>
</tr>
</tbody>
</table>
## QSAR Tools Used in “Kashinhou” in Japan

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>QSAR Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biodegradation</strong></td>
<td>BIOWIN5</td>
</tr>
<tr>
<td></td>
<td>BIOWIN6</td>
</tr>
<tr>
<td></td>
<td>CATABOL</td>
</tr>
<tr>
<td><strong>Bioaccumulation</strong></td>
<td>BCFWIN</td>
</tr>
<tr>
<td></td>
<td>CERI Model</td>
</tr>
<tr>
<td></td>
<td>Baseline Model</td>
</tr>
<tr>
<td><strong>Ecological Effect</strong></td>
<td>TIMES</td>
</tr>
<tr>
<td></td>
<td>ECOSAR</td>
</tr>
<tr>
<td></td>
<td>KATE</td>
</tr>
<tr>
<td><strong>Human Health Effect</strong></td>
<td>DEREK Nexus (Rule)</td>
</tr>
<tr>
<td></td>
<td>CASE Ultra (Stat.)</td>
</tr>
<tr>
<td></td>
<td>TIMES (Hybrid)</td>
</tr>
<tr>
<td><strong>Ministry of Economy, Trade and Industry (METI)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ministry of the Environment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ministry of Health, Labour and Welfare (MHLW)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Great advantage of QSAR Approach for Toxicological Assessment

- 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
QSAR Used in Development of Pharmaceuticals
Genotoxicity and Carcinogenicity Tests in Development of Pharmaceuticals

**Genotoxicity studies:**
- QSAR prediction
- HTP tools (e.g., Mini-Ames)
- GLP in vitro
  - Ames test
  - Mammalian cell
- GLP in vivo
  - Rodent MN study
- Follow-up to bioassay findings

**Carcinogenicity studies:**
- "Screening"
  - Lead compound selection
- Non-clinical development
  - Animal & cell culture studies
- Clinical development
  - Phase I
  - Phase II
  - Phase III
- Rodent 2-year bioassay
Synthetic Route of Drug Substances
(Byproducts)

Degradation from Drug Substances
(Degradants)

Impurities

Mutagenic or non-mutagenic?
医薬品自主回収のお知らせ（クラスⅠ）

（販売名：バルサルタン錠20mg・40mg・80mg・160mg「AA」）

本日、東京都より、別紙のとおり、あずか製薬株式会社が下記の医薬品の自主回収に着手した旨の情報提供がなされましたので、お知らせ致します。

記

販売名：バルサルタン錠20mg・40mg・80mg・160mg「AA」

開発製造販売に関する資料 [PDF形式：106KB]（拡大）

開発製造販売に関する資料 [PDF形式：229KB]（拡大）
Two QSAR 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 QSAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and no further testing is recommended.
What Is Ames Test?

Genotoxic/mutagenic chemicals

DNA Damage

Mutation → Cancer

Ames Test

rat liver extract

possible mutagen

Salmonella strain (requires histidine)

media with minimal histidine

plate

incubate

a high number of revertants (his- to his+) suggests the mutagen causes mutations

control plate (natural revertants)

plate

incubate

Mutants

Wild-Type
Why Ames/QSAR?

• 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 model for Ames mutagenicity  
  • Rule-Based Models  
  • Statistical-Based Models
### Performance of Four QSAR Models for Predicting Ames Mutagenicity

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

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

<table>
<thead>
<tr>
<th>Database (name )</th>
<th>Information</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benchmark Data Set for <em>In Silico</em> Prediction of Ames Mutagenicity (Hansen et. al., 2009)</td>
<td>Ames mutagenicity database for 6,500 compounds</td>
<td><a href="http://doc.ml.tu-berlin.de/toxbenchmark/">http://doc.ml.tu-berlin.de/toxbenchmark/</a></td>
</tr>
<tr>
<td>National Toxicology Program (NTP) database</td>
<td>2,163 chemicals in genetic toxicity studies</td>
<td><a href="">ftp://157.98.192.110/ntp-cebs/datatype</a></td>
</tr>
<tr>
<td>Toxicity Reference Database (ToxRefDB)</td>
<td>Studies on 330 chemicals, many of which are active ingredients of pesticides</td>
<td><a href="http://actor.epa.gov/toxrefdb/faces/SearchByEndpoint.jsp">http://actor.epa.gov/toxrefdb/faces/SearchByEndpoint.jsp</a></td>
</tr>
</tbody>
</table>
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.

Masamitsu HONMA, Ph.D.
Director, Division of Genetics & Mutagenesis
National Institute of Health Sciences
1-18-1 Kamiyoga, Setagaya-ku,
Tokyo 158-8501, Japan
E-mail: honma@nihs.go.jp
## Participants in Ames/QSAR Project

<table>
<thead>
<tr>
<th>QSAR Vender</th>
<th>QSAR Tool</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lhasa Limited (UK)</td>
<td>a. Derek Nexus</td>
<td>Rule</td>
</tr>
<tr>
<td></td>
<td>b. Sarah Nexus</td>
<td>Statistical</td>
</tr>
<tr>
<td>2. MultiCASE Inc (USA)</td>
<td>c. CASE Ultra statistical-based</td>
<td>Statistical</td>
</tr>
<tr>
<td></td>
<td>d. CASE Ultra rule-based</td>
<td>Rule</td>
</tr>
<tr>
<td>3. Leadscope Inc (USA)</td>
<td>e. Leadscope statistical-based</td>
<td>Statistical</td>
</tr>
<tr>
<td></td>
<td>f. Leadscope rule-based</td>
<td>Rule</td>
</tr>
<tr>
<td>4. Istituto di Ricerche Farmacologiche Mario Negri (Italy)</td>
<td>g. CAESAR</td>
<td>Statistical</td>
</tr>
<tr>
<td></td>
<td>h. SARPY</td>
<td>Rule</td>
</tr>
<tr>
<td></td>
<td>i. KNN</td>
<td>Statistical</td>
</tr>
<tr>
<td>5. LMC - Bourgas University (Bulgaria)</td>
<td>j. TIMES_AMES</td>
<td>Rule</td>
</tr>
<tr>
<td>6. Istituto Superiore di Sanita (Italy)</td>
<td>k. Toxtree</td>
<td>Rule</td>
</tr>
<tr>
<td>7. Prous Institute (Spain)</td>
<td>l. Symmetry</td>
<td>Statistical</td>
</tr>
<tr>
<td>8. Swedish Toxicology Science Research Center (Sweden)</td>
<td>m. AZAMES</td>
<td>Statistical</td>
</tr>
<tr>
<td>9. FUJITSU KYUSHU SYSTEMS LIMITED (Japan)</td>
<td>n. ADMEWORKS</td>
<td>Statistical</td>
</tr>
<tr>
<td>10. IdeaConsult Ltd. (Bulgaria)</td>
<td>o. AMBIT</td>
<td>Statistical</td>
</tr>
<tr>
<td>11. Molecular Networks GmbH and Altamira LLC (USA)</td>
<td>p. ChemTune•ToxGPS</td>
<td>Statistical</td>
</tr>
<tr>
<td>12. Simulations Plus, Inc (USA)</td>
<td>q. MUT_Risk</td>
<td>Statistical</td>
</tr>
</tbody>
</table>
Ames/QSAR Project (Phase I-III) Challenged Chemicals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>556 (14.5%)</td>
<td>562 (14.7%)</td>
<td>629 (14.3%)</td>
<td>1757 (14.4%)</td>
</tr>
<tr>
<td>Negative</td>
<td>3,336 (85.5%)</td>
<td>3,267 (85.3%)</td>
<td>3,780 (85.7%)</td>
<td>10,383 (85.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>3,902</td>
<td>3,829</td>
<td>4,409</td>
<td>12,140</td>
</tr>
</tbody>
</table>
## ROC Graphs for Challenged QSAR Models’ Validation

### Table of Results

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity (%)</strong></td>
<td>56.7 (38.6-70.0)</td>
<td>58.0 (41.6-72.1)</td>
<td>57.1 (31.7-67.6)</td>
</tr>
<tr>
<td><strong>Specificity (%)</strong></td>
<td>77.7 (62.5-91.5)</td>
<td>84.2 (64.9-92.8)</td>
<td>79.9 (60.7-93.0)</td>
</tr>
<tr>
<td><strong>Accuracy (%)</strong></td>
<td>74.7 (63.6-83.9)</td>
<td>80.3 (65.8-87.7)</td>
<td>76.7 (68.0-87.3)</td>
</tr>
</tbody>
</table>
国立医薬品食品衛生研究所インハウス研究
化学物質安全性ビッグデータベースの構築と人工知能を用いた医薬品・食品・生活化学物質のヒト安全性予測基盤技術の開発研究

1. Data収集
   - 公共データベース
     - OECD Toolbox
     - ToxRef, OpenFoodTox
     - PubMed
     - AOP Wiki
   - 化学構造データ
     - AMES DB (遺伝毒性DB)
     - HESS DB (一般毒性DB)
     - Perceollome DB (遺伝子発現DB)
     - 前臨床安全性試験データ集

2. データの共有と統合
   - 新規の学習用データ
     - 国衛研のデータ集
       - 構造
       - 分子量
       - 物性
       - 用途
       - 暴露シナリオ
       - 他の既知データ

3. データ解析・リスク予測モデル開発
   - AIを活用したヒト安全性予測システムプラットフォームのプロトタイプ構築
   - 検証用
   - 新規の学習用データ
   - 事前リスクの入力
   - ベット試験データの入力

AIを活用したヒト安全性予測プラットフォームのプロトタイプ構築研究

リスク予測値の実利用（検証）研究
- 食品・生活化学物質の毒性発現予測
- 創薬候補分子の毒性発現予測
- 医薬品等の未知又は薬物副作用発現予測
- バイオ後続品の市販後安全性の検証
- その他医薬品・食品等リスク予測に係る個別課題

データの取得
- 創薬候補分子の毒性発現予測
- 医薬品等の未知又は薬物副作用発現予測
- バイオ後続品の市販後安全性の検証

事業効果
- 信頼性の高い安全性評価基準の設定
- "中毒・過剰摂取の回避、長期暴露の回避"
Development of Deep Learning Models for Predicting Ames Mutagenicity

(A) Convolutional Neural Network (CNN) From SMILES TEXT

**SMILES**

OC3=C(N=NC1=CC=C(C=C1)[N+](\[O-\])=O)C2=C(C=CC=C2)C=C3

(B) Graph Convolutional Neural Network (GCCN) From Chemical Structure
# Performance of CNN Deep Learning Model for Predicting Ames Mutagenicity

**Training data:** 1,6651 Chemicals  
**Validation data:** 2,000 Chemicals

<table>
<thead>
<tr>
<th>Ames Results</th>
<th>+</th>
<th>-</th>
<th>Total</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNN Prediction</td>
<td>+</td>
<td>161</td>
<td>336</td>
<td>497</td>
<td>55%</td>
<td>80%</td>
</tr>
<tr>
<td>-</td>
<td>133</td>
<td>1370</td>
<td>1503</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>294</td>
<td>1706</td>
<td>2000</td>
<td></td>
<td></td>
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</tbody>
</table>
Where is our goal?

Can we perfectly predict Ames mutagenicity by QSAR or Deep Leaning?
Inter-Laboratory Reproducibility of Ames Mutagenicity

<table>
<thead>
<tr>
<th>Databases</th>
<th>Intersections</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTP/NCI; TA 100</td>
<td>20 chemicals</td>
<td>85%</td>
</tr>
<tr>
<td>GTP/NTP; TA 100</td>
<td>39 chemicals</td>
<td>79%</td>
</tr>
<tr>
<td>GTP/NCI; TA 98</td>
<td>18 chemicals</td>
<td>88%</td>
</tr>
<tr>
<td>GTP/NTP; TA 98</td>
<td>21 chemicals</td>
<td>92%</td>
</tr>
</tbody>
</table>

**-S9**

<table>
<thead>
<tr>
<th>Databases</th>
<th>Intersections</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTP/NCI; TA 100</td>
<td>15 chemicals</td>
<td>80%</td>
</tr>
<tr>
<td>GTP/NTP; TA 100</td>
<td>14 chemicals</td>
<td>(21%)*</td>
</tr>
<tr>
<td>GTP/NCI; TA 98</td>
<td>13 chemicals</td>
<td>90%</td>
</tr>
<tr>
<td>GTP/NTP; TA 98</td>
<td>23 chemicals</td>
<td>65%</td>
</tr>
</tbody>
</table>

82%

*excluded for calculation

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

Analyzed Dr. Mekenyan in Bourgas "Prof. As. Zlatarov" University
Is this Ames Positive?

-Example A-

<table>
<thead>
<tr>
<th>QSAR Tools</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derek NX</td>
<td>PLAUSIBLE</td>
</tr>
<tr>
<td>CASE Ultra</td>
<td>Positive</td>
</tr>
<tr>
<td>PHARM_SALM</td>
<td></td>
</tr>
</tbody>
</table>

**Alert: 352 Aromatic amine or amide (from KB: Derek KB 2015 2.0)**

R1, R4 = polysubstituted benzene ring
R2, R3 = H, CH3, CH2OH, CH2OH=CH2, CH2CH2CH
R5 = H, *(C(=O)R)2(=O)R
R6, R7 = H, F
R8 = any atom
Is this Ames Positive?
-Example B-

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

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

<table>
<thead>
<tr>
<th>QSAR Tools</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derek NX</td>
<td>INACTIVE</td>
</tr>
<tr>
<td>CASE Ultra</td>
<td>Negative</td>
</tr>
<tr>
<td>PHARM_SALM</td>
<td></td>
</tr>
</tbody>
</table>
Build Robust QSAR and AI Model

Re-building Ames data base

An-eihou data: 15,000 Chemicals X 5 Ames strain X 2 conditions (+/-S9) X 2 studies X 6 doses = 1,800,000 data
Other existing data: 10,000 Chemicals X 5 Ames strain X 2 conditions (+/-S9) X 2 studies X 6 doses = 1,500,000 data
AI/QSAR Based Mutagenicity (Toxicity) Evaluation

Negative

Positive

Alert ID 7: c-N3H2

Alert ID 27: c: c (c:H) - N3H2
Extrapolation to Human Hazard and Human Risk

- Hazard in human
- Risk in human
数多くの化学物質、入手困難な化学物質の毒性評価にはQSAR/AI等のインシリコ技術が重要である。

QSAR/AIによる化学物質の毒性予測の向上のためには、信頼性の高いビッグデータベースの構築が必須である。

生物学的な毒性試験には常に生物学的なばらつきや不確実性が存在する。QSAR/AIは従来の毒性試験結果を超えた評価を可能にするかもしれない。

QSAR/AIは化学物質の毒性を予測するツールではなく、化学構造から毒性を科学的判断が可能な評価系として将来利用できる日が来るかもしれない。
Web-Site and Outcomes of the Challenge Project

AME/SQAR 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/NIH 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).
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