Accelerating the Pace of Chemical Risk Assessments Workshop
September 14–15, 2016
US Environmental Protection Agency
Washington, DC

Responses to Request for Regulatory Information

California Environmental Protection Agency (CalEPA), USA 2

Consumer Product Safety Commission (CPSC), USA 3

European Chemicals Agency (ECHA), European Union 5

European Food Safety Authority (EFSA), European Union 6

Health Canada, Canada 8

National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia 10

National Institute for Industrial Environment and Risks (INERIS), France 10

National Institute for Public Health and the Environment (RIVM), The Netherlands 11

National Institute of Technology and Evaluation (NITE), Japan 13

Organisation for Economic Co-operation and Development (OECD), Health and Safety Programme 13

Safety and Health Technology Center (SAHTECH), Taiwan 15

US Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP), Environmental Fate and Effects Division (EFED), USA 16

US Environmental Protection Agency (EPA), Endocrine Disruptor Screening Program (EDSP), USA 17

California Environmental Protection Agency (CalEPA), USA

Legislative Drivers

Numerous, including the following:[1]

- Birth Defects Prevention Act, 1984. SB 950: Chapter 2; Article 14, Sections 13121 -13133, California Food and Agriculture Code.
- Food Safety Act, 1989. AB 2161: Chapter 2; Article 14, Sections: 13134 –13135, California Food and Agriculture Code.
- Toxic Air Contaminants Act, 1983. AB 1807 (Tanner): Chapter 3.5, Sections 39650 -39675, California Health and Safety Code.
- Green Chemistry Laws, 2008 ("Safer Consumer Products"). AB 1879 (Feuer); SB 509 (Simitian): Sections 25252 and 25253, California Health and Safety Code.
- Biomonitoring California, 2006. SB 1379 (Perata): Chapter 8, Section 105440, California Health and Safety Code.
- Safe Drinking Water and Toxic Enforcement Act, 1986 ("Proposition 65"). Chapter 6.6, Sections 25249.5 - 25249.13, California Health and Safety Code.
- Oil and Gas: Well Stimulation, 2013. SB 4 (Pavley): Chapter 1, Division 3, California Public Resources Code.

Chemical Universe Covered

(1) Pesticide risk assessment and pesticide regulation/mitigation
(2) Selection of chemicals in consumer products for mandated alternatives analysis
(3) Chemical designation and prioritization for biomonitoring
(4) Other risk assessment needs including for toxic air contaminants, drinking water contaminants
(5) Identification of chemicals as carcinogens or reproductive toxicants under Proposition 65
(6) Hydraulic fracturing and other oil and gas chemical evaluation

Timelines For Action

Ongoing efforts and data needs in each of the above programs. No sunset date. No timelines in statute or regulation.

Expected Outcomes

(1) Incorporation of NAM data as an adjunct to animal data in risk assessments for pesticides, toxic air contaminants, and drinking water contaminants to inform weight of evidence determinations and support point of departure selection, where appropriate.
(2) Use of NAM toxicology data to support hazard trait identification in biomonitoring and Safer Consumer Products priority product selection, and for screening hazard evaluation of hydraulic fracturing chemicals.
(3) Use of NAM exposure tools for biomonitoring and Safer Consumer Products priority product selection and for pesticide risk assessments.
(4) Creation of NAM-supported structural - functional chemical groups for evaluation under Biomonitoring California and other existing statutory authorities.
(5) Use of read-across methods for dose-response evaluation of data poor chemicals.

[1] Note: None of the California legislative drivers explicitly or implicitly requires the use of alternative methods or data.

ED_001449_00000011

(6) Contribution to understanding community risks associated with oil and gas production, distribution and processing.
(7) Continued use of case studies to assess the potential to use NAM data for mode of action clarification, hazard identification and dose-response in risk assessment.

STATUS OF ACTIVITIES (PRIORITIZATION VS QUANTITATIVE ASSESSMENT)

(1) Active efforts to evaluate the strength of existing NAM data for all of our data needs and to advocate for improvements in NAM data to address gaps and identify deficiencies.
(2) Ongoing development of subject matter expertise within our Agency.
(3) Current incorporation of a review of NAM toxicology data in pesticide risk assessments, other risk assessments, and Prop 65 hazard identification documents.
(4) Routine consultation of ToxCast and Tox21 data for evaluations of data-poor chemicals, including in a recent evaluation of a groundwater contaminant associated with a waste site.
(5) Urgent need for improved chemical use and product exposure estimation tools for our Safer Consumer Products program's product selection activities.
(6) Current project on alternatives to Bisphenol A in food can linings that includes a review of available NAM data.
(7) Routine use of more well-established methods such as BMD and PBPK modeling and exposure modeling in all of our risk assessments.

ACCEPTANCE STATUS OF NEW ALTERNATIVE METHODS (NAMS)

California has a very high level of interest in NAMs, and is closely watching the development of these methods. There is extensive support for any effort to fill data gaps on the hazards of previously untested chemicals. There is also a lot of support for additional information on mode of action and to provide better understanding of dose response, especially at low doses, for well-tested agents such as pesticides.

To date, however, our evaluations have identified some significant gaps and deficiencies in the available NAM toxicity data. For example, our case study on pesticides found that the NAMs failed to identify critical endpoints for the chemicals studied, including acetylcholinesterase inhibition, GABA inhibition, and neurotoxicity signals. Our case study on phthalates found that NAM methods failed to identify known modes of action for well-studied phthalates, or to group phthalates according to known hazard traits such as androgen inhibition and carcinogenicity. For these reasons, California is currently not using NAM data alone to draw any conclusions about the absence of an effect, either for prioritization or for risk evaluation. We will continue to evaluate the methods and work collaboratively with EPA to strengthen them. EPA has been highly responsive to user community feedback, and we are optimistic that NAM data will be increasingly useful for numerous purposes in the fairly near future.

Consumer Product Safety Commission (CPSC), USA[2]

LEGISLATIVE DRIVERS

- ☐ Federal Hazardous Substances Act (FHSA)
- ☐ Consumer Product Safety Act (CPSA)
- ☐ Consumer Product Safety Improvement Act of 2008 (CPSIA)

[2] This report was prepared by the CPSC staff; it has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

ED_001449_00000011

Chemical Universe Covered

In general, CPSC's jurisdiction includes products used in and around the home, schools, and recreational settings, except where the product is regulated by another federal agency, for example: food, drugs, cosmetics, medical devices, radiation, pesticides, or automobiles. CPSC also has jurisdiction over special (child-resistant) packaging for drugs, cosmetics, household chemicals, and liquid nicotine.

Current chemical activities include: phthalates, engineered nanomaterials (ENM), flame-retardant chemicals (FRs), playground surfaces made from recycled rubber, phthalate substitutes, VOCs, indoor air quality, lead, and other metals.

Timelines For Action

- Phthalates: Final Rule is in development.
- Playground surfaces: Risk Assessment (RA) within 2 years.
- FRs, ENMs, and phthalate substitutes are multiyear projects.

Expected Outcomes

- Phthalates: Final rule.
- FRs: (a) Staff briefing package recommending whether Commission should grant or deny a petition to ban organohalogen FRs in furniture, mattresses, electronics, and children's products; (b) RAs of FRs in children's products.
- ENMs (a) Research on exposure from ENM in consumer products; (b) Development of nanoparticle specific indoor air models to predict nanomaterial release and consumer exposure; (c) Nano prioritization tool development.
- Playground surfaces: Multiroute, multichemical RA.
- Phthalates substitutes: Prioritization, identifying data needs. There is a lack of toxicity data for some substitutes.

Status of Activities (prioritization vs quantitative assessment)

- Phthalates: Quantitative risk assessment (QRA) is complete.
- Playground surfaces: QRA
- FRs: QRAs
- ENMs: Prioritization; quantitative assessment for selected ENMs
- Phthalate substitutes: Prioritization

Acceptance Status of NAMs

CPSC is active in the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), including the development of an integrated testing strategy for skin sensitization and alternative acute toxicity tests, and the validation and acceptance of specific methods for regulatory use. Manufacturers may use specified alternative test methods to determine whether their products are skin or eye irritants. See the CPSC animal testing page at *http://www.cpsc.gov/library/animaltesting.html*. If a manufacturer or other entity performs a hazard test that has not been previously approved by the Commission, CPSC staff will consider the data on a case-by-case basis.

CPSC issued Chronic Hazard Guidelines (RA guidelines) and a supplemental definition of "chronic toxicity," to address carcinogenicity, neurotoxicity, reproductive/developmental effects, and other chronic hazards (http://www.cpsc.gov/pagefiles/132280/chronichazardguidelines.pdf). Under the guidelines, a substance may be considered "probably toxic to humans" regarding chronic hazards only if there is as least "sufficient evidence" in animals or "limited evidence" in humans. In the guidelines, *in vitro* studies or other alternative

ED_001449_00000011

methods are considered as supplemental data providing additional support for determining whether a substance is "toxic," as defined in the guidelines. Therefore, in the absence of animal or epidemiological data, it would be difficult or impossible for CPSC to issue a mandatory regulation to address chronic hazards, such as carcinogenicity, neurotoxicity, or developmental/reproductive toxicity.

European Chemicals Agency (ECHA), European Union

Legislative Drivers

REACH is a regulation of the European Union, adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals, while enhancing the competitiveness of the European Union (EU) chemicals industry. It also promotes alternative methods for the hazard assessment of substances in order to reduce the number of tests on animals.

The classification, labelling and packaging (CLP) Regulation (EU implementation of the Globally Harmonized System of Classification and Labeling of Chemicals) ensures that the hazards presented by chemicals are clearly communicated to workers and consumers in the EU through classification and labelling of chemicals

ECHA also administers the Biocidal Product Regulation and the Prior Informed Consent Regulation (PIC). In the context of this workshop, we will focus on REACH and CLP.

Chemical Universe Covered

For REACH and CLP all chemicals, manufactured or placed on the market either on their own, in mixtures or in articles are in principle considered. All types of chemistry are included.

Substances are defined as a chemical element and its compounds in the natural state or obtained by any manufacturing process. A substance has one or multiple compositions, including impurities and additives that need to be taken into account for hazard and risk assessment.

Specifically for REACH some (partial) exemptions apply. Examples are radioactive substances, intermediates, food and feed related chemicals, medicinal products for human or veterinary use, cosmetic products.

Timelines For Action

From the REACH legal text: "Pursuant to the implementation plan adopted on 4 September 2002 at the Johannesburg World Summit on sustainable development, the European Union is aiming to achieve that, by 2020, chemicals are produced and used in ways that lead to the minimisation of significant adverse effects on human health and the environment."

Import or manufacture of a chemical above 1 metric tonne per annum per company (legal entity) requires registration. There is no distinction anymore between old and new chemicals. Previous 'new chemicals' are regarded as already registered. Previous 'existing chemicals' are phased in. The last deadline for phase-in chemicals is 2018.

To prioritise substances of potential interest an annual screening round is performed. This "feeds" the regulatory processes: compliance check, substance evaluation, risk management and classification and labelling. The compliance check is aimed at creating a level playing field, while (substance) evaluation is aimed at generating additional information required to decide on the need for risk management measures. Under REACH all dossiers are verified for completeness, but not all are verified for compliance.

ED_001449_00000011

Expected Outcomes

Under REACH and CLP, the 'Burden of proof' is on industry: REACH/CLP make transparent their efforts to ensure safe use of chemicals. This should ensure risk management at the company level. This should be an ongoing process. ECHA, Member States and European Commission scrutinise substances:

- where regulatory risk management is needed and;
- to ensure a level playing field.

Status of Activities (prioritization vs quantitative assessment)

Industry has done quantitative assessments for previously "exisiting" substances which are manufactured or imported >100 tonne per year. Industry has classified and labelled (and notified to ECHA) all substances. Industry has done quantitative assessments for all 'new' substances manufactured or imported >1 tonne per year.

ECHA has used this information to prioritise and conclude on substances. Around 180 substances are manually screened per year since 2014. In terms of results, ECHA has recently published a report giving a status of activities (https://echa.europa.eu/documents/10162/13634/operation_reach_clp_2016_en.pdf).

Some highlights:

- ECHA's website has information on more than 120 000 chemicals
- 31 of the 168 substances of very high concern have been placed on the authorisation list – they cannot be used without a specific authorization
- 20 restrictions made under REACH limit the use and reduce risks of hazardous chemicals
- 200 opinions on harmonised classification and labelling trigger further risk management actions
- ECHA has published on its website more than 54 000 registration dossiers for 14 000 substances
- Nearly 10 000 companies have registered chemicals
- Over 10 000 companies have informed ECHA of their substance's classification
- Hundreds of companies have directly or indirectly applied for authorisation to use a substance of very high concern.

Acceptance Status of NAMs

ECHA has (very) limited experience in using NAM for prioritisation purposes. NAM are not used for quantitative assessment. Not by industry, nor by authorities. ECHA hosted a Scientific Workshop early 2016 to review the use of NAM, for prioritisation but also in support of Read-Across.

European Food Safety Authority (EFSA), European Union

Legislative Drivers

For horizontal issues and methodological development at EFSA, the legislative framework is the EFSA founding regulation (EC) No 178/2002: "The Scientific Committee shall be responsible for the general coordination necessary to ensure the consistency of the scientific opinion procedure, in particular with regard to the adoption of working procedures and harmonisation of working methods. It shall provide opinions on multi-sectoral issues falling within the competence of more than one Scientific Panel, and on issues which do not fall within the competence of any of the Scientific Panels."

ED_001449_00000011

Pesticides: Regulation (EC) 1107/2009 requires pre-marketing authorization and regular renewals of active substances used in Plant Protection Products and sets a negative list for co-formulants. Regulation (EC) 396/2005 stablished Maximum Residue Limits for pesticides in food and feed.

For other regulated compounds (feed and food additives, vitamins and minerals) and contaminants coming of anthropogenic or natural sources, specific regulation/legislation exist.

Chemical Universe Covered

The Scientific Committee would covers all the chemical space with regards to food and feed safety compounds particularly with regards to compounds that may be assessed by more than one EFSA panel.

Pesticides: Mostly pesticides active substances and their metabolites. New work on other chemicals and mixtures used as co-formulants is expected soon.

For other panels, the chemical space is defined by the legislation covering the remit of each EFSA panel dealing with chemical risk assessment (feed additives, food contact materials, food additives etc.).

Timelines For Action

Pesticides: We conduct ca. 150 assessments per year plus an Annual report on residues monitoring at EU level. The selection of the substances is based on: regulatory deadlines, new proposals from industry, or ad-hoc requests (e.g. triggered by new information).

The Scientific Committee develops guidance documents (GD) of horizontal nature; the timeline to develop a GD varies between 1–2 years on average. The GD with respect to methodologies would have an impact on all EFSA panels (e.g., weight of evidence, chemical mixtures, benchmark dose, and new methods in risk assessment). In addition, research contracts to develop new methods and tools are ongoing on a yearly basis and have a large part of the focus dedicated to new methods in risk assessment and alternatives to animal testing.

Expected Outcomes

Scientific Committee: to bring new working methods and tools for the scientific panels dealing with chemical risk assessment. These include the development of case studies to illustrate the applicability of the approaches, guidance documents, scientific reports and open access tools, software and training courses for staff and experts.

Pesticides: Better understanding of the current or planned use of NAS for the assessment of pesticides in the U.S. and other jurisdictions. In addition discussion on the use of pesticides as data-rich and high-concern substances for further exploring the use validation/assessment of NAS.

Status of Activities (prioritization vs quantitative assessment)

Scientific Committee: a number of activities are ongoing in the area of NAMs for both prioritization and quantitative assessment and include the development of TKL tools, hazard databases, the identification of emerging chemical risks, prioritization and assessment of chemical mixtures.

Pesticides: quantitative assessment; prioritization is not relevant for pesticides as risk assessment prior to authorization is mandatory.

ED_001449_00000011

ACCEPTANCE STATUS OF NAMS

Scientific Committee: a number of activities are ongoing in the area of acceptance of NAMs and case studies, covering EFSA's chemical space are under developments to increase acceptance (e.g., case studies on regulated chemicals and contaminants to test the applicability of generic toxicokinetic (TK) models and tools (single chemicals and mixtures), hazard database, *in vitro* methods for metabolism and TK combined with probabilistic distributions for human metabolism and TK processes (EFSA, 2014) "Modern methodologies and tools for human hazard assessment of chemicals" http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3638/full.

Pesticides: several *in vitro* methods are currently accepted see list http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013XC0403(02)&from=EN; currently EFSA is supporting EC in updating this list; other methods can be proposed and accepted case-by-case. In addition, the new EFSA guidance on residue definition includes several non-testing approaches for the assessment of metabolites.

Health Canada, Canada

LEGISLATIVE DRIVERS

Canada's Chemicals Management Plan (CMP) conducts risk assessments under CEPA. The federal role and approach includes the following:

- The *Canadian Environmental Protection Act 1999* (CEPA) is the main federal law that protects the environment and human health from pollution.
- CEPA sets out a pre-market assessment regime for substances that are *new to Canada*, and one for targeted post-market assessment of *existing substances* already in Canada that are on the Domestic Substances List (DSL).
- Some authorities related to chemicals management are shared by the Minister of the Environment and the Minister of Health (e.g. assessment, risk conclusions, risk management regulations). Others are administered solely by the Minister of the Environment (e.g. enforcement, pollution prevention).
- CEPA provides tools to prevent risks from new substances (e.g., conditions, prohibition) and to manage risks from harmful existing substances (e.g., regulations, pollution prevention plans, codes of practice).
- CEPA requires that CEPA risk management tools be used, but instruments under Health Canada (HC) Acts (e.g. *Canada Consumer Product Safety Act, Food and Drugs Act, Pest Control Products Act)* have also been used.

CHEMICAL UNIVERSE COVERED

- CEPA required that the approximately 23,000 Domestic Substance List (DSL) substances already in Canada before its new substances regime was implemented be "categorized" for potential health and environmental risks.
- This process, completed in Fall 2006, identified about 4,300 "priority existing substances" needing to be addressed by 2020 to determine if they are harmful and need to be risk managed.
- The Government of Canada is looking to expand the risk assessment programme beyond this subset of Categorized chemicals post-2020.

ED_001449_00000011

Timelines For Action

- The Government of Canada is currently in the 10th year of the CMP which was launched in 2006.
- A key objective is to address the 4,300 existing substances identified as priorities following Categorization by 2020 in three phases.
  - Phase 1 – The Challenge Initiative (2006-2011; 1064 substances)
  - Phase 2 – Substance Grouping Initiative (2011-2016; 1700 substances)
  - Phase 3 – Remaining Priorities (2016-2020; 1500 substances)
- Next Steps moving forward in preparation for post-2020 risk assessment activities will include the development and implementation of approaches for the identification and screening of new priorities for risk assessment.

Expected Outcomes

- Expected completion of current CMP commitments by 2020-2021 and broad acceptance of the use of read-across and *in silico* approaches for risk assessment.
- Expect that there will be a continued need to increase the use of NAMs to address a large number of substances that have limited or no toxicity data.
- Expect that there will be a need to increase awareness and communication with stakeholders of the advancing risk assessment methodologies and approaches used to support decision making.

Status of Activities (prioritization vs quantitative assessment)

- Quantitative Assessment:
  - Read-across and in silico methods ((Q)SAR) used to address hazard data gaps in current CMP risk assessments.
  - Read-across case studies were submitted and endorsed under the OECD IATA Case Studies project (Yr 1, 2015-16).
  - Data generated from NAMs used to support formation of substance groups / categories when available.
- Screening/Prioritization:
  - Exploring the use of NAMs for lower-tier assessments (e.g. HTS / toxicogenomics data as provisional point(s) of departure) and potential tiered approach for data generation.
  - Exploring the use of NAMS (e.g. EDSP AUC models) as a hazard metric to support the request for updated exposure related information through Inventory Update Surveys to industry.

Acceptance Status of NAMs

- There has been a progressive increase in the use of NAMs within the CMP since 2011 with *in silico* and computational toxicology and grouping approaches being the most used.
- Read-across has been an integral element of the risk assessment program for existing substances since 2011 as well and has been well accepted to support risk assessment conclusions and recommendations.
- ESRAB's early work in the area of integrating NAMs to support risk assessment activities moving forward has been supported by the CMP Science Committee and the Health Canada Science Advisory Board.

ED_001449_00000011

National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia

Legislative Drivers

NICNAS is established by the Industrial Chemicals (Notification and Assessment) Act 1989.

NICNAS's high-throughput framework for assessing previously unassessed industrial chemicals that are already in use, known as IMAP, is not directly authorised by legislation – it was instituted by Ministerial agreement. On completion of IMAP Stage 1 (assessing 3000 chemicals over 4 years), the Minister approved proceeding to IMAP Stage 2.

Chemical Universe Covered

Industrial chemicals in Australia are defined by exclusion (ie all chemicals with uses other than as pesticides, veterinary medicines, therapeutic goods, and foods, or radioactive chemicals). Therefore, NICNAS regulates ingredients in formulated cosmetics and tattoo inks as well as chemicals used in industrial processes.

Timelines For Action

IMAP Stage 2 will operate until the new legislation to implement reforms to the scheme commences operation (anticipated to be in 2018).

Expected Outcomes

Similarly to IMAP Stage 1, Stage 2 will focus on identifying chemicals that require additional risk mitigation, in conjunction with a greater emphasis on deprioritisation of groups of low risk chemicals.

Status of Activities (prioritization vs quantitative assessment)

IMAP Stage 2 is currently at the prioritization/deprioritisation stage, augmented by semi-quantitative or quantitative assessment as needed to justify relevant risk management outcomes.

Acceptance Status of NAMs

NICNAS considers negative outcomes to be useful in deprioritisation, and positive outcomes are useful to inform decisions regarding read-across and to prioritise chemicals for assessment. However, many of these methodologies have yet to be validated to support explicit regulatory action to mitigate identified risk.

National Institute for Industrial Environment and Risks (INERIS), France[3]

Legislative Drivers

At the national level in the EU, drivers are linked to the role of member states within EU regulations or directives (e.g., REACH, biocides…). The interaction between national and EU legislative drivers is therefore complex. For example, a member state is in position to advocate for "restrictions" and has therefore to build up a case to submit to European agencies. Doing so it must build up a strong case. Hence, there is a need to prioritize the efforts.

Very often, there is a national concern, which induces member state to take national actions that have (or not, depending on the legal context) to be defended at the EU levels. Indeed, other drivers must be taken into account, associated with public debates (e.g. phthalates, BPA, glyphosate). A member state may wish to have a proactive policy to foster EU action (e.g. nanomaterials).

[3] As INERIS does not represent the French authorities, and is not a regulatory agency the description of the legislative drivers may be uncomplete or biased. It reflects what can impact the research and expertise activities in the institute.

ED_001449_00000011

The case of pollutants, which are not covered by regulations based in the "no data no market" philosophy, implies often national actions, and in any case national decisions (e.g. regulations on emissions from traffic or specific industrial releases, or selection of the substances which are country specific in the Water Framework Directive). The knowledge of the toxicity and ecotoxicity of metabolites (e.g., in water), requires more hazard assessment, in contrast with the decision on the limitation of releases, or soil content, that requires more risk assessment.

Chemical Universe Covered, Timelines For Action, and Expected Outcomes

The following description relates to French national efforts that are related to INERIS actions (including non INERIS actions that are connected to subjects we are dealing with. There is no specific limitations in the scope. At present, pesticides, and among them pyrethroids, are especially under study, with two concerns: knowledge of exposure (the share of intakes through residues, airborne exposure, biocides, veterinary medicines is not well characterized), knowledge of the effect of mixtures. Traditional but more often Computational toxicology is involved, traditional exposure assessment studies and biomonitoring are also involved, epidemiological surveys are developed.

The case of nanos is also under scrutiny, although the above mentioned approaches are not quite developed. The effort is more on developing new tools (e.g. artificial multicellular systems), on grouping. On endocrine disruption, the present R&D activities are centered on developing assays (e.g. zebra fish), which cannot actually be described as high throughput. However, the search for more efficient biomarkers should be mentioned, as well as the ecotoxicological concern. Meanwhile, expert bodies (ANSES, ANSM) are assessing about ten substances a year.

Actions are conducted on substances whose hazards are quite well known (e.g., Chromium, lead …PAH) but on which there is an issue in exposures and especially on environmental justice. Fast mapping tools have been developed.

Issues are dealt with at the European level with H2020 programs such as EUOMIX, NANREG, EUTOXRISK. It is generally in this context that NAMs are developed or validated (qAOP, tools for mixture prediction, QSAR predictive power, air Liquid interface biological models). However some NAMS are not part of those programs (fast environmental justice mapping, some biomarkers).

Status of Activities (prioritization vs quantitative assessment)

Assessment is, at INERIS, the most usual status. Assessment can be hazard assessment, with the development of screening tools (e.g. QSAR, read across) but more often risk assessment (from qAOP to basic exposure assessment).

National Institute for Public Health and the Environment (RIVM), The Netherlands

Legislative Drivers

RIVM is the Netherlands' main public sector knowledge institute in the field of public health, nutrition, safety and environmental management. It conducts research and has a number of practical tasks, which are intended to promote public health and ensure a clean and safe environment. Risk assessment and risk management are key concepts underpinning RIVM's activities, with a focus on human health, safety and the quality of ecosystems. A further key concept is the integration of knowledge.

RIVM produces practical, reliable and impartial information for the benefit of government authorities at all levels, thus helping them to develop and implement appropriate policy. In addition, RIVM has a number of practical and supervisory responsibilities in the areas of public health and environmental management. The different roles that RIVM plays range from performing applied scientific research, to providing policy

ED_001449_00000011

advice, participating in national and international committees, in some cases even with a mandate from the Dutch ministries, to answering questions from the general public or giving advice to the general public or stakeholders. These different roles sometimes results in dilemmas among RIVM's staff or causes misunderstandings outside RIVM. RIVM's main target groups are government authorities at all levels, the professional field and the general public.

Chemical Universe Covered

- ☐ industrial substances
- ☐ pesticides
- ☐ biocides
- ☐ nanomaterials
- ☐ genetically modified organisms

Expected Outcomes

- ☐ Better understanding how the CAs implement use of NAM into regulatory framework.
- ☐ Cooperation on the compilation of the master list of chemicals of concern and case studies.

Status of Activities (prioritization vs quantitative assessment)

Both prioritization and quantitative assessment.

Acceptance Status of NAMs

For the assessment of risks of chemical substances for man and environment, animal studies are commonly performed. Alternatives for these studies may only be applied if the legal frameworks for the assessments explicitly offer a possibility for them. RIVM has analyzed ten of such European frameworks for assessment of chemical substances whether such a possibility is present. In nine of the ten frameworks, reference is made to the possibility to use alternative methods for animal tests and thus pose no barriers for them. In the tenth framework, for the acceptance of veterinary medicinal products, it is not clear: the Directive does not mention this possibility, but in the underlying, mandatory (but nog legally binding) guideline alternative methods are suggested. This makes the legal status of the possibility to use alternative methods unclear in this framework.

The investigation also shows that it's mostly practical barriers that obstruct the use of alternatives for animal tests, and not so much legal barriers. There is, for example, a lack of alternatives for some animal tests, or they are not sufficiently suitable or validated.

The study notices two other points of attention. The first concerns the use of results from alternative methods in the risk assessments for calamities and for the determination of industrial locations with hazardous substances. Specific animal test results are often of high importance there. The results of alternative methods do no directly fit into the calculation methodologies applied by some countries for these risk assessments.

Secondly, the classification, labelling and packaging (CLP) of chemical substances needs attention. The framework REACH, which is leading and for which the data used for CLP are generated, states that alternatives are possible, on the condition that the results of alternative methods are suitable for CLP. For some classifications, however, no alternative test methods are available and the classification criteria limit the use/development of alternative methods. (Heringa 2014).

ED_001449_00000011

National Institute of Technology and Evaluation (NITE), Japan

Legislative Drivers

- Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. (CSCL)

Chemical Universe Covered

- Chemical substances
  Chemical compounds substance created through chemical reactions
- Industrial chemicals
  Chemicals that are subject to other laws such as medicines and pesticides are outside the scope of CSCL

Timelines For Action

- Screening assessment: Every year
- Prioritization of PACS (Risk Assessment I-(i)): Every year
- Detailed risk assessment (Risk Assessment I-(ii)): Until 2019fy, 53 PACS

Expected Outcomes

- Filling data gaps on hazard assessment and exposure assessment
- Validating the reliability of NAMs (QSAR etc.) for regulatory use
- Providing information and knowledge on risk assessment unit

Status of Activities (prioritization vs quantitative assessment)

- Screening assessment: 7678 chemicals in 2015fy
- Prioritization of PACS (Risk Assessment I-(i)): 124 chemicals in 2015fy
- Detailed risk assessment (Risk Assessment I-(ii)) : Completed 13 chemicals

Acceptance Status of NAMs

- Read-across is used for chemical safety assessment of biodegradability and bioaccumulation potential.

Organisation for Economic Co-operation and Development (OECD), Health and Safety Programme

Legislative Drivers

One of the objectives of the OECD Chemicals Management Programme is to "ensure efficiencies and optimal use of resources for governments and industry through harmonization of policies and instruments and by creating mechanisms for sharing work in areas of mutual interest."

In the context of the Decision-Recommendation of the Council on the Co-operative Investigation and Risk Reduction of Existing Chemicals [C(90)163/Final], OECD member countries have committed to co-operatively investigate chemicals in order to identify those which are potentially hazardous to the environment and/or to the health of the general public or workers.

Chemical Universe Covered

The focus of the co-operative investigation of chemicals at the OECD until recently was on high production volume existing industrial chemicals, however the Task Force on Hazard Assessment has been working for a

ED_001449_00000011

number of years on methodologies for assessment of chemicals including application of Integrated Approaches to Testing and Assessment (IATA, see http://webnet.oecd.org/OECDGROUPS/Bodies/ShowBodyView.aspx?BodyID=7369&BodyPID=9816&Lang=en&Book=True).

As of 2014, one focus of the Co-operative Chemicals Assessment Programme is on the application of Integrated Approaches to Testing and Assessment through the review of case studies.

Timelines For Action

The programme has a mandate until 2020 and is subject to renewal every four years by OECD member countries.

Expected Outcomes

Series of case studies and development of guidance for the application of Integrated Approaches to Testing and Assessment. Information from this project will be made publicly available (http://www.oecd.org/env/ehs/risk-assessment/hazard-assessment.htm).

Status of Activities (prioritization vs quantitative assessment)

The cases reviewed focus on hazard identification and characterisation within different regulatory contexts, including for regulatory risk assessment purposes in some countries.

Thus far countries and other stakeholders submitted and reviewed 4 case studies in 2015, and developed a considerations document of the learnings from the case studies. An additional 5 case studies are currently under review in 2016. Submission of case studies for 2017 is encouraged.

2015 Case Studies:

- In Vitro Mutagenicity of 3,3' Dimethoxybenzidine (DMOB) Based Direct Dyes [Canada and United States]
- Repeat Dose Toxicity of Substituted Diphenylamines (SDPA) [Canada]
- Hepatotoxicity of Allyl Ester Category [Japan]
- Bioaccumulation Potential of Biodegradation Products of 4,4'-Bis (chloromethyl)-1,1'-biphenyl [Japan]

2016 Case Studies:

- Repeated-Dose Toxicity of Phenolic Benzotriazoles [Japan]
- Pesticide Cumulative Risk Assessment & Assessment of Lifestage Susceptibility [United States]
- 90-Day Rat Oral Repeated-Dose Toxicity for Selected n-Alkanols: Read-Across [ICAPO]
- 90-Day Rat Oral Repeated-Dose Toxicity for Selected 2-Alkyl-1-alkanols: Read-Across [ICAPO]
- Chemical Safety Assessment Workflow Based on Exposure Considerations and Nonanimal Methods [JRC/BIAC]

Acceptance Status of NAMs

The objective is to increase experience with the use of IATA (including NAMs) and to create common understanding of using novel methodologies and the generation of considerations/guidance stemming from these case studies. It is envisioned that case studies within this project could be used as vehicles for further exploring the application and combination of AOPs, HTS, toxicogenomics and other in vitro/in vivo

data in specific chemical hazard assessments elaborated for regulatory purposes. Many of the cases involve grouping of chemicals and read-across.

Safety and Health Technology Center (SAHTECH), Taiwan

Legislative Drivers

Taiwan's Environment Protection Administration (Taiwan EPA) launched Taiwan's "Regulation of New and Existing Chemical Substance Registration" under by Taiwan "Toxic Chemical Substances Control Act." At the same time, Taiwan Ministry of Labor (Tw MOL) also launched "Regulation of Governing Designating and Handling of Priority Management Chemicals" under by Taiwan Occupational Safety and Health Act.

Chemical Universe Covered

The chemicals included are all new and existing chemical substances.

Timelines For Action

EPA

- Registration and submit data for manufacturing, importing for new chemical substance was from December, 2014 to present.
- Phase 1 Registration of Existing Chemical Substances began on September 1, 2015, and ended on March 31, 2016.
- Tier 0 risk assessment screening has been started in March, 2016.
- The draft of high risk chemical substances for standard registration will expect to announce in 2017.

MOL

- To enhance safety for workers, MOL required handlers to report information of Priority Management Chemicals.
- The data collection is an ongoing process.
- First step screening (tier 0) is complete, based on the handling amount and the GHS classification of the Priority Management Chemicals. The tier 1 will be launched after the high risk chemical substance are identified by Tier 0 analysis.
- The first Tier 1 analysis will be performed in third quarter 2016.

Expected Outcomes

- To classify risk categorical of the inventory of existing chemical substances.
- Chemical substances hazard classification and prioritization by risk categories in Taiwan chemical management programs.

Status of Activities (prioritization vs quantitative assessment)

- The Taiwan Chemical Substance Inventory (TCSI) lists have more than 100,000 chemical substances. The results of Phase 1 registration improve regulator to distinguish active existing chemical substances from the inactive one. Based on Phase 1 results, Taiwan EPA has started the tier 0 risk assessment screening, and decided which chemical substances with adequate GHS classification will be assigned to high, moderate, and low risk categories.
- Taiwan MOL were performing the screening step for chemicals' data collected from Priority Management Chemicals reporting process and finished the Tier 0 screening, and the further tier 1

ED_001449_00000011

risk assessment will proceed to determine the different designated chemicals as required for chemical exposure for labors.

Acceptance Status of NAMs

The current acceptance to use NAMs are QSAR in skin corrosive and eye irritation testing. A manufacturer/importer can submit QSAR report to replace the original animal testing defined in new chemical substance regulation act, and EPA will review the materials to decide if theirs report are appropriate for the new chemical substance. At the same time, EPA also looks for other possible alternative testing method to replace the traditional animal testing in other testing, e.g. Read-across combination with *in vitro* testing, including data from HTP or -omics.

US Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP), Environmental Fate and Effects Division (EFED), USA

Legislative Drivers

The primary legislative drivers in EFED are the **Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)** and the **Endangered Species Act (ESA)**. The FIFRA standard is no unreasonable harm to the environment and requires that both risks and benefits to be balanced. The ESA considers risks only and had embedded in it a high level of protection down to the individual level of biological organization. Regulatory actions include ecological risk assessments for new pesticides, new pesticide uses, existing pesticides, emergency uses, and experimental uses. For new pesticides and pesticide uses, the **Pesticide Registration Improvement Act (PRIA)** sets strict timelines for registration decisions to be made.

Chemical Universe Covered

Conventional pesticides (~ 1000+ chemicals), many thousands of pesticide degradation products, formulated products with multiple active ingredients, selected nanoscale pesticides (and nano-scale carriers), pesticide formulation components ("inerts"). Compared to industrial chemical assessments, the pesticides program is often considered "data rich" with respect to toxicity and environmental fate information. However, data on degradation products and formulation components is much less plentiful.

Timelines For Action

Timelines vary from as little as 60 days (emergency uses) to 18–24 months (new pesticides). Longer time periods for Endangered Species Act consultations.

Expected Outcomes

Programmatically, expected outcomes from EFED are ecological risk assessments that are used to inform risk management decisions regarding pesticide registration and risk mitigation measures in the U.S. These can vary from simple "hazard quotient" approaches to complex spatially- and temporally-explicit assessments of ecological risk. The division also performs drinking water exposure modeling to support human health risk assessment.

Status of Activities (prioritization vs quantitative assessment)

Most activity falls into the quantitative risk assessment area, but we do conduct some "read across" and QSAR activities regarding pesticide degradates. Prioritization is occasionally conducted.

Acceptance Status of NAMs

Currently, use of alternate methods of testing in OPP/EFED is relatively limited, but has been done as part of the Endocrine Disruption Screening Program (EDSP). *In-silico* an *In-vitro* methods are considered as

ED_001449_00000011

another line of evidence in risk assessment, but are not commonly used in lieu of traditional chemical testing methods. Lack of (or very limited) cross-validation of alternative test methods with pesticides and associated ecological receptors is one primary obstacle to their adoption in EFED. Establishing quantitative Adverse Outcome Pathways (AOPs) is viewed as a very useful approach for integrating chemical toxicity information across multiple levels of biological organization in the context of ecological risk assessment.

US Environmental Protection Agency (EPA), Endocrine Disruptor Screening Program (EDSP), USA

Legislative Drivers

The US EPA developed the Endocrine Disruptor Screening Program (EDSP) in response to section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA) which requires EPA to *"develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate."*21 U.S.C. 346a(p)(1). In addition, the provision in section 1457 of the Safe Drinking Water Act (SDWA) provides that "*the Administrator may provide for testing under the screening program … any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance*." 42 U.S.C. 300j-17. Based on recommendations from the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC; 1998) and, pursuant to the Administrator's discretionary authority, EPA adopted a two-tiered screening and testing strategy known as the EDSP and expanded the program to include the androgen and thyroid hormonal pathways of the endocrine system and to address ecological effects.

Chemical Universe Covered

Based upon FFDCA and SDWA chemical universe covered are pesticide active ingredients, pesticidal inerts, and chemicals contaminants of concern in drinking water. List 1, list 2 and 10K see links attached.

Table 1. The numerical estimates of chemicals associated with each authority.

Citation	Statutory Language	Defined Universe
FFDCA §408(p)(3)(A) (21 U.S.C. 346a(p)(3)(A))	"(3) SUBSTANCES - In carrying out the screening program . . . the Administrator — (A) shall provide for the testing of all pesticide chemicals;"	Pesticide Active Ingredients = ~1000 Chemicals Pesticide Inert Ingredients = ~4000 Chemicals
Citation	**Discretionary Authority**	**Defined Universe**
FFDCA §408(p)(3)(B) (21 U.S.C. 346a(p)(3)(B))	"(3) SUBSTANCES - In carrying out the screening program . . . the Administrator — (B) may provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such substance.	Anticipated to add minimally to the universe over the next 5 years. Will be dependent on case by case determinations regarding cumulative effects and exposure.
SDWA §1457	In addition to the substances referred to in section 408(p)(3)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a(p)(3)(B)) the Administrator may provide for testing . . . of any other substance that may	Regulated Contaminants = ~90 Chemicals Preliminary Universe

ED_001449_00000011

(42 U.S.C. 300j–17)	be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance.	~6000 Chemicals
	Universe of Chemicals for Prioritization and Screening	~10000

[4]See Footnote

Estimates of the universe of chemicals may change over time. The Office of Pesticide Programs (OPP) registers new pesticide active ingredients or approves new inert ingredients for incorporation into product formulations each year.

TIMELINES FOR ACTION

Developed Tier 1 and Tier 2 battery of tests for EDSP and harmonized guidelines with OECD early 2000. The EDSP has been developed over the past 19 years and has demonstrated that the current screening process may take upwards of five years before a Tier 1 decision is available or Tier 2 test orders are issued. In light of recent advances in high-throughput assays and computational models, in addition to predicted advances likely to come in the next two years, EPA is moving to consider new, rapid screening methods. The availability of additional alternative high-throughput assays and computational models in the near term will allow EPA to screen more chemicals in less time, involve fewer animals, and cost less for everyone. Furthermore, reconsideration of the EDSP List 2 chemicals may be appropriate since "ER Model" data are available for many List 2 and other chemicals. Ongoing use of high-throughput screening assays and computational models will address thousands of chemicals in the future.

EXPECTED OUTCOMES

The Agency has built additional experimental and CompTox capacity around ToxCast to enhance the application of its data to the agency's evaluation strategies and to help inform decision-making for EDSP. Assuming current levels of funding, this focus during FY 2016-FY 2019 in a number of ways, to take advantage of the continuing revolution in biomedical research.

STATUS OF ACTIVITIES (PRIORITIZATION VS QUANTITATIVE ASSESSMENT)

Moving forward, the Agency fully recognizes the opportunity to further evolve the CompTox area and broaden its application to agency activities potentially across its diverse regulatory frameworks. These novel applications can add significant efficiency and effectiveness to agency operations, enable it to participate in the Big Data revolution, and enhance the agency's visibility as a High Performing organization. In addition to expanding the chemical screening activities beyond the current 10,000 chemicals in Tox21, opportunities to further accelerate the pace of the revolution in toxicity testing include:

- Exploring how the ToxCast/Tox21 data can be used to develop high-throughput risk assessments, in particular for data poor chemicals (e.g., industrial chemicals);
- In concert with growing international efforts such as the European REACH, incorporating advancements in computational chemistry to allow 'read-across' from chemical structures with known bioactivity to other structures with less data;
- Using the high-throughput hazard and exposure information to prioritize chemicals for assessment and data call-in;

[4] §408(p)(3)(A) and (B) are both subject to the exemptions described at §408(p)(4) EXEMPTION. —Notwithstanding paragraph (3), the Administrator may, by order, exempt from the requirements of this section a biologic substance or other substance if the Administrator determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen.

- Using the high-throughput hazard and exposure information to begin to evaluate cumulative risk of chemical exposures;
- Expanding and extrapolating to novel assays that have relevance to ecological impacts;
- Customizing and uniquely adapting the emerging 'organs-on-a-chip' technologies for specific application to EPA chemical testing and evaluation systems; and
- Integrating computational activities with complementary experimental capacity to enhance synergies, performance, and reliability on the emerging data for endocrine pathways beyond estrogen, androgen, and thyroid endpoints and non-endocrine pathways such as neurodevelopmental toxicity.

ACCEPTANCE STATUS OF NAMS

- Validated test methods, covering a range of mammalian and ecological species, to screen 52 chemicals (list 1) for potential perturbation of the estrogen, androgen, or thyroid pathways.
- First application of ORD CompTox and Tox21 research--Chemical prioritization based on estrogen and androgen bioactivity using high throughput and CompTox methods.
- Introduced the use of high throughput screening and computational models as an alternative to three Tier 1 assays (published June 16, 2015).
- Implementation of high throughput screening and CompTox approaches resulted in our ability to screen 2,000 chemicals for the androgen pathway, and 3,000 chemicals for the estrogen pathway.
- Evaluating partial EDSP List 2 for bioactivity in androgen pathway and estrogen pathway (currently underway).

For more info: https://www.epa.gov/endocrine-disruption

ED_001449_00000011