COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Item for Matters Arising: UK New Approach Methodologies Roadmap

1. Advances in biology, computer science and other related fields are paving the way for major improvements in how we evaluate environmental and public health risks posed by potentially toxic chemicals. The combined advances in discovery and clinical sciences, data science and technology have resulted in toxicity testing which has reached a pivotal transformation point known as the 4th industrial revolution (4IR)[1]. One of the major recent scientific advancements is the development of New Approach Methodologies (NAMs[2]) including high throughput screening (HTS)[3], omics[4] and *in silico*[5] computer modelling strategies (*e.g.* Artificial Intelligence (AI) and machine learning) for the evaluation of hazard and exposure. This also advocates the Replacement, Reduction and Refinement (3Rs) approach (Hartung, 2010[6]).

2. NAMs are gaining traction as a systematic approach to support informed decision making in chemical risk assessment.

3. The Food Standards Agency (FSA) responds to food incidents[7] and it is important that robust risk assessments on the safety of a chemical can be provided. However, sometimes there is very little, or no, toxicological information for a given chemical.

4. For such chemicals, the use of NAMs could provide a more indicative level of risk and therefore greater confidence can be provided for them as well as less uncertainty that individual compounds can be assessed. In addition, the NAMs roadmap is about making use of the best science available, and therefore, integration of these technologies as part of the FSA chemical risk assessment process will be fundamental in the future in the future of human safety assessments to protect consumers.

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[1] The Fourth Industrial Revolution (4IR) is the fourth major industrial era since the initial Industrial Revolution of the 18th century. It is characterized by a fusion of technologies that is blurring the lines between the physical, digital and biological spheres, collectively referred to as cyber-physical systems

[2] New approach methodologies has been emerged as a descriptive reference to any non-animal-based approaches that can be used to provide information in the context of chemical hazard and risk assessment.

[3] High-throughput screening (HTS) is a method for scientific experimentation especially used in drug discovery and relevant to the fields of biology and chemistry. Using robotics, data processing/control software, liquid handling devices, and sensitive detectors, high-throughput screening allows a researcher to quickly conduct millions of chemical, genetic, or pharmacological tests. Through this process one can rapidly identify active compounds, antibodies, or genes that modulate a particular biomolecular pathway. The results of these experiments provide starting points for drug design and for understanding the noninteraction or role of a particular location

[4] Omics are various disciplines in biology whose names end in the suffix -omics, such as genomics, proteomics, metabolomics, metagenomics and transcriptomics.

[5] *In silico:* one performed on computer or via computer simulation.

[6] Hartung, T., 2010. Lessons learned from alternative methods and their validation for a new toxicology in the 21st century. Journal of Toxicology and Environmental Health, Part B, 13(2-4), pp.277-290.

[7] https://www.food.gov.uk/business-guidance/food-incidents-product-withdrawals-and-recalls

5. The future of the safety assessment of chemicals in food depends on adaptability and flexibility in utilising the best scientific methodologies and strategies available to respond to the accelerating developments in science and technology. In order to achieve this, the FSA and Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) have developed a UK roadmap towards acceptance and integration of these NAMs including predictive toxicology methods using computer modelling into safety and risk assessments for regulatory decision making. The FSA are planning to organise a further workshop around this later this year.

Members are asked to note the recent draft version of roadmap attached at ANNEX A and endorse the planned workshop.

This paper is presented largely for information, but Members are welcome to contact the Secretariat if they have any detailed comments. An updated draft will be available prior to the workshop.

Secretariat

June 2021

ANNEX A to TOX/2021/31

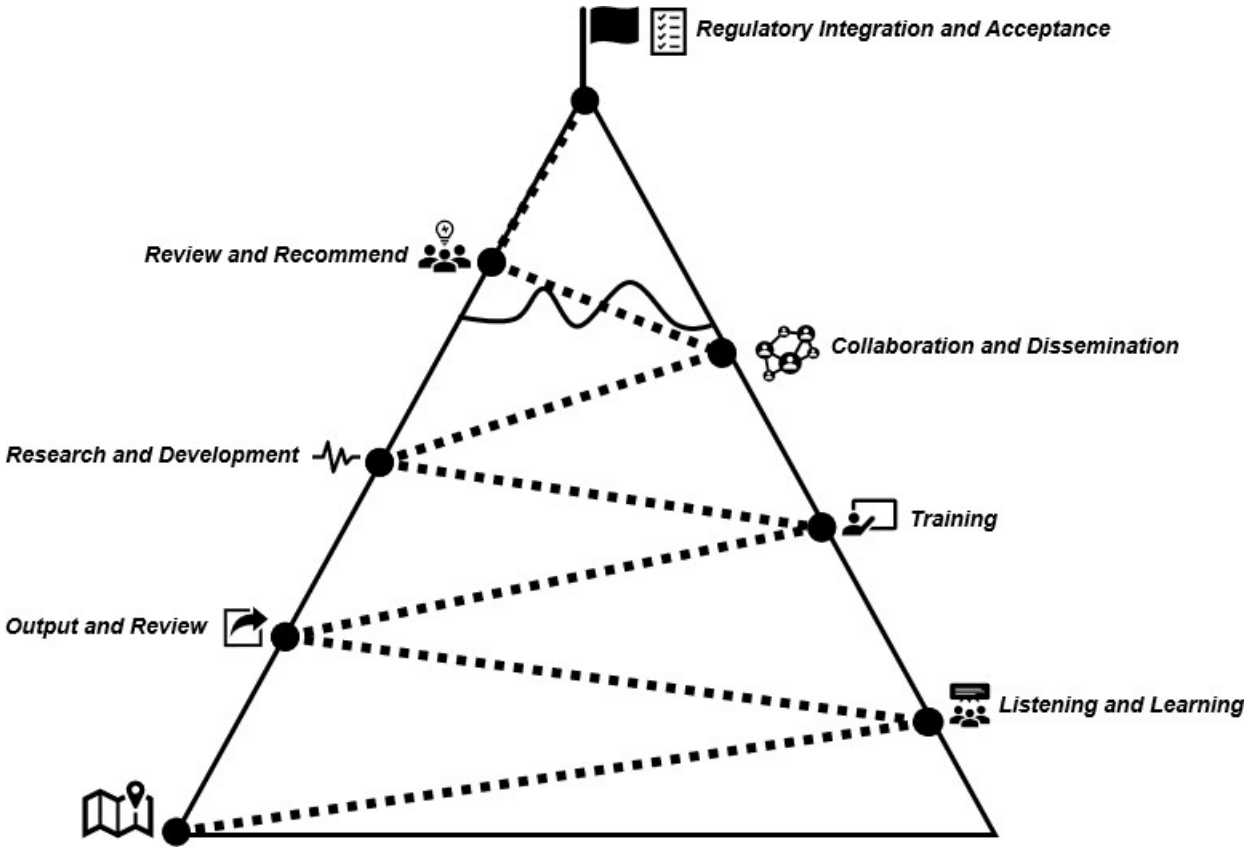
COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

UK New Approach Methodologies Roadmap

Secretariat
2021

Paving the way for a UK Roadmap:

Development, Validation and Regulatory Acceptance of New Approach Methodologies (NAMs) in Chemical Risk Assessment



2021

Food Standards Agency

Executive summary

Advances in biology, computer science and other related fields are paving the way for major improvements in how we evaluate environmental and public health risks posed by potentially toxic chemicals. The combined advances in discovery and clinical sciences, data science and technology have resulted in toxicity testing which has reached a pivotal transformation point known as the 4th industrial revolution (4IR). One of the major recent scientific advancements is the development of new approach methodologies including computer modelling strategies for the evaluation of hazard and exposure whilst championing the Replacement, Reduction and Refinement (3Rs) approach.

The volume of data produced in the world is growing ever more rapidly, from 33 zettabytes in 2018 to an expected 175 zettabytes in 2025 (IDC, 2018) (Food Systems[1]). The Department for Business, Energy and Industrial Strategy (BEIS) white paper on Regulation for the Fourth Industrial Revolution notes that changes in technology are occurring at a "*scale, speed and complexity that is unprecedented*"[2]. The use of such technologies can help improve regulatory processes in several ways such as to improve the efficiency of data collection and to exploit data already held by agencies to support better analysis and risk assessment (BEIS Report-The use of emerging technologies for regulation)[3].

The future of food safety assessment of chemicals depends on our adaptability and flexibility whilst using the best scientific methodologies and strategies available in order to respond to the accelerating developments in science and technology.

For regulatory agencies to incorporate and implement these new predictive capabilities brings both challenges and opportunities. Moving from research to risk assessment to regulatory setting and *beyond* there must be suitable validation and acceptance of these new and emerging technologies.

Innovative technologies should be reviewed and evaluated once developed to be able to integrate them into the risk assessment strategies for chemical testing for human health and the environment. Using a validation process via an evidence driven approach to address the data gaps in the risk assessment process will facilitate the acceptance and validity of these NAMs as well as pave the way for alternative methods testing strategies. Integration of these technologies as part of the risk assessment process will be fundamental in the future of human and environmental safety.

In order to achieve this, the Food Standards Agency (FSA) and Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) have developed a UK roadmap towards acceptance and integration of these new approach methodologies including predictive toxicology methods using computer modelling into safety and risk assessments for regulatory decision making.

[1] https://ec.europa.eu/info/sites/info/files/research_and_innovation/research_by_area/documents/2020.2082_en_04.pdf
[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/807792/regulation-fourth-industrial-strategy-white-paper-web.pdf
[3] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/926585/emerging-technologies-for-regulation.pdf

Introduction & Background

Chemical Landscape

"The Toxicity Data Landscape for Chemicals" paper (Judson ,2009[4]) reported that 28 million chemicals had been discovered. Only three million had been tested on animals and some of these also tested in human studies. Approximately, a further one million had some *in vitro*/*in silico* screening assay data only. By 2020, over 350,000 chemicals and mixtures of chemicals had been registered for production and use worldwide. The identities of many chemicals remain publicly unknown because they are claimed as confidential (over 50,000) or ambiguously described (up to 70,000) (Wang *et al*., 2020[5]).

It is understandable that with those numbers, finding an accurate and optimized model poses a big challenge, not least for example whereby some of the environmental chemicals that don't necessarily come with a toxicological package. However, by combining data from traditional methodologies with data from these new emerging technologies we will be able to predictive risk more rapidly and efficiently.

Hopefully this will be an opportunity to engage cross cutting themes and tap into other projects *e.g*., Genome UK[6] and Accelerating the Pace of Chemical Risk Assessment (APCRA)[7] as well as trans collaborations across academia, industry and beyond.

Current Chemical Challenges

- Too many chemicals to test
- Traditional methods can be slow and costly
- Adopting the principles of the 3Rs (*i.e.* Replacement, Reduction and Refinement of animal experiments)
- Not enough data on compound/compounds assessing

Opportunities

Adopt new approach methodologies (NAMs) to predict risk more rapidly, accurately, and efficiently.

[4] Judson, R., Richard, A., Dix, D.J., Houck, K., Martin, M., Kavlock, R., Dellarco, V., Henry, T., Holderman, T., Sayre, P. and Tan, S., 2009. The toxicity data landscape for environmental chemicals. *Environmental health perspectives*, *117*(5), pp.685-695.
[5] Wang, Z., Walker, G.W., Muir, D.C. and Nagatani-Yoshida, K., 2020. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environmental science & technology*, *54*(5), pp.2575-2584.
[6] https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare
[7] https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra

What are NAMs and why is there a drive in the regulatory context?

Advances in biology, computer science and other related fields are paving the way for major improvements in how we evaluate environmental and public health risks posed by potentially toxic chemicals. The combined advances in discovery and clinical sciences, data science and technology have resulted in toxicity testing which has reached a pivotal transformation point known as the 4th industrial revolution (4IR)[8]. One of the major recent scientific advancements is the development of NAMs including high throughput screening[9], omics[10] and *in silico*[11] computer modelling strategies (*e.g.* Artificial Intelligence (AI) and machine learning) for the evaluation of hazard and exposure. This also advocates the Replacement, Reduction and Refinement (3Rs) approach (Hartung, 2010[12]) proposed 50 years ago by Russell and Burch (1959)[13].

What is being done?

To keep pace with the digital evolution, we are using the latest technology and best available scientific methodologies to incorporate additional tools into our regulatory risk assessment process to evaluate safety in food, consumer products and environment more efficiently without compromising quality.

Why?

Improved risk assessments of chemicals for which there are currently no, or very few data and therefore improved consumer safety.

Who are the UK FSA and the COT?

The UK FSA[14] is an independent Government department working across England, Wales, and Northern Ireland to protect public dietary health and consumers' wider interests in food. The FSA uses expertise and influence so that people can trust that the food they consume is safe and is what it says it is. The Science, Evidence and Research Division (SERD) of the FSA provides strategic analysis, insight, and evidence across the FSA's remit to underpin the development of policies, guidance, and advice on food safety.

[8] The Fourth Industrial Revolution (4IR) is the fourth major industrial era since the initial Industrial Revolution of the 18th century. It is characterized by a fusion of technologies that is blurring the lines between the physical, digital and biological spheres, collectively referred to as cyber-physical systems

[9] High-throughput screening (HTS) is a method for scientific experimentation especially used in drug discovery and relevant to the fields of biology and chemistry. Using robotics, data processing/control software, liquid handling devices, and sensitive detectors, high-throughput screening allows a researcher to quickly conduct millions of chemical, genetic, or pharmacological tests. Through this process one can rapidly identify active compounds, antibodies, or genes that modulate a particular biomolecular pathway. The results of these experiments provide starting points for drug design and for understanding the noninteraction or role of a particular location

[10] Omics are various disciplines in biology whose names end in the suffix -omics, such as genomics, proteomics, metabolomics, metagenomics and transcriptomics.

[11] *In silico:* one performed on computer or via computer simulation.

[12] Hartung, T., 2010. Lessons learned from alternative methods and their validation for a new toxicology in the 21st century. Journal of Toxicology and Environmental Health, Part B, 13(2-4), pp.277-290.

[13] https://www.nc3rs.org.uk/the-3rs

[14] https://www.food.gov.uk/

The COT[15] assesses chemicals for their potential to harm human health. Scientific evaluations are carried out at the request of the FSA, Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA)[16], and other government departments and regulatory authorities.

Why are the FSA and COT taking a lead on this?

The FSA responds to food incidents[17] and it is imperative that risk assessments on the safety of a chemical are provided. The data used can only be what is available and sometimes there is very little, or no, toxicological information for a given chemical.

For these chemicals, the use of NAMs will provide a more indicative level of risk and therefore greater confidence in risk assessments that individual compounds can be assessed. This will be fundamental in risk assessment scenarios where limited to no information is available on the toxicity of a chemical.

The FSA and COT have been reviewing the use of NAMs to scope what methods are out there, in order for the best methodologies to be used in risk assessment and understand how these can be incorporated in a regulatory context.

There is a need for integration of several methodologies which will form part of the integrated approaches to testing and assessment (IATAs)[18].

FSA Digital Vision

In the FSA Chief Scientist data science report (2017)[19], it stated that "*Big data and data science bring relatively new tools and techniques to Government analytics*".

In the Science Council[20] Working Group on Data Usage and Digital Technology Final Report to the FSA it stated in one of the recommendations: "*Encourage the development of data capabilities and skills across the FSA staff base[21] therefore, we want to embrace the new technologies and enhance capabilities for our staff*."

[15] https://cot.food.gov.uk/
[16] Formerly Public Health England.
[17] https://www.food.gov.uk/business-guidance/food-incidents-product-withdrawals-and-recalls
[18] Integrated approaches to testing and assessment (IATAs) provide a means by which all relevant and reliable information about a chemical is used to answer a defined hazard characterization question. Information considered can include toxicity data, computational model predictions, exposure routes, use cases, and production volumes. This information is used to characterize outcomes that can inform regulatory decision-making. (https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-its/its.html)
[19] https://www.food.gov.uk/sites/default/files/media/document/chiefscientificadviserssciencereport%20%281%29.pdf
[20] https://science-council.food.gov.uk/
[21] https://science-council.food.gov.uk/sites/default/files/2020-08/finrepscwgondatausageanddigtech.pdf

What have the FSA / COT done so far?

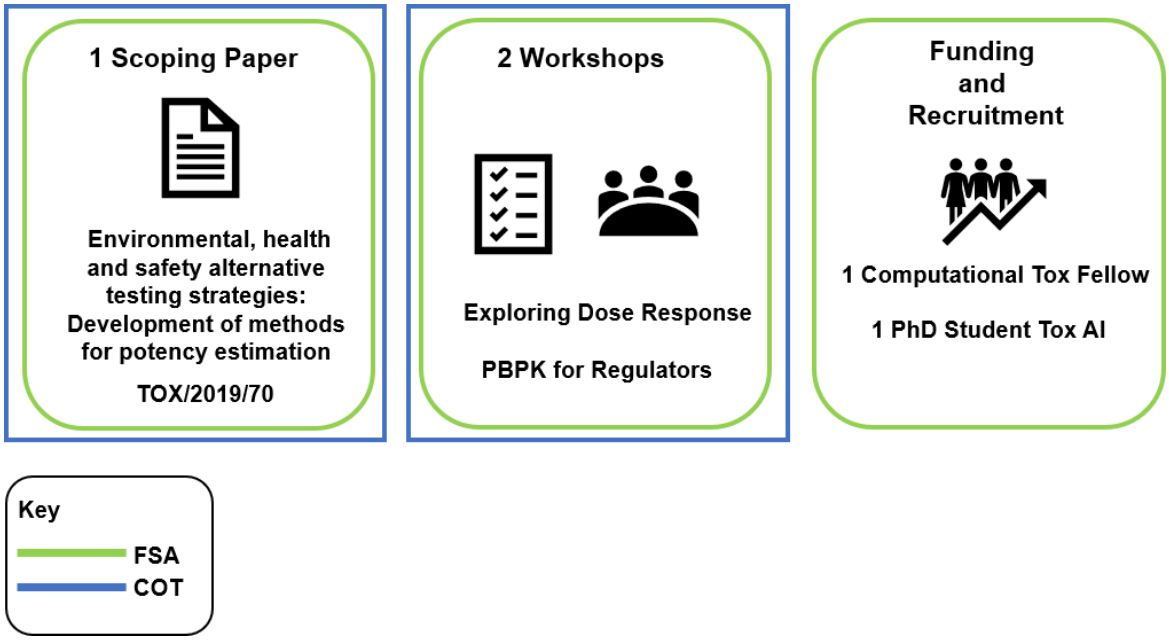


Figure 1. Diagram of what the FSA/ COT have done so far in the NAMs space.

The scoping paper "*Environmental, health and safety alternative testing strategies: Development of methods for potency estimation*" (TOX/2019/70[22]) and the full workshop reports will be made available through the COT website (currently under reserved business).

Exploring Dose Response (EDR) Workshop Summary

The UK FSA and the COT held an "*Exploring Dose Response*" workshop (March 2020) in a multidisciplinary setting inviting regulatory agencies, government bodies, academia and industry[23]. The workshop provided a platform from which to address and enable expert discussions on the latest *in silico* prediction models, new approach methodologies (NAMs), physiologically based pharmacokinetics (PBPK), future methodologies, integrated approaches to testing and assessment (IATA) as well as methodology validation. Through case studies (including plastic particles, polymers, tropane alkaloids, selective androgen receptor modulators), the workshop outlined and explored an approach that is fit for purpose applied to human health risk assessment in the context of future food safety assessment. Furthermore, possible future research, to establish points of departure (PODs) using non-animal alternative models and to improve the use of exposure metrics in risk assessment, was discussed.

Overall conclusions were as follows:

a) The use of pragmatic guidelines/framework for incorporating these models into risk assessment. Using case studies such as those outlined in the workshop should be used towards applicability and confidence in the models.

[22] https://cot.food.gov.uk/sites/default/files/2021-01/COT%20Final%20Minutes%20December%202019.pdf
[23] https://cot.food.gov.uk/sites/default/files/2020-08/tox202030edrworrkshopforwebreserved_0_tobeuploaded.pdf

b) Human biomonitoring data will be key to identify realistic snapshots of exposure scenarios as well as big data which need to be linked to human clinical data.

c) Exposure data and exposure science will be key in developing *in silico* models in risk assessment and to explore the use of exposomics.

d) There should be transparency throughout the process i.e. consumer facing engagement on NAMs.

e) There should be planning to take these new methods forward using social sciences research and technical research for integration

Ultimately, it was collectively agreed that integration of these new technologies as part of our risk assessment methodologies, with a validation process throughout, will be key in the acceptance of the models (by regulatory bodies) and will be fundamental in the future of human and environmental safety (Figure 2).

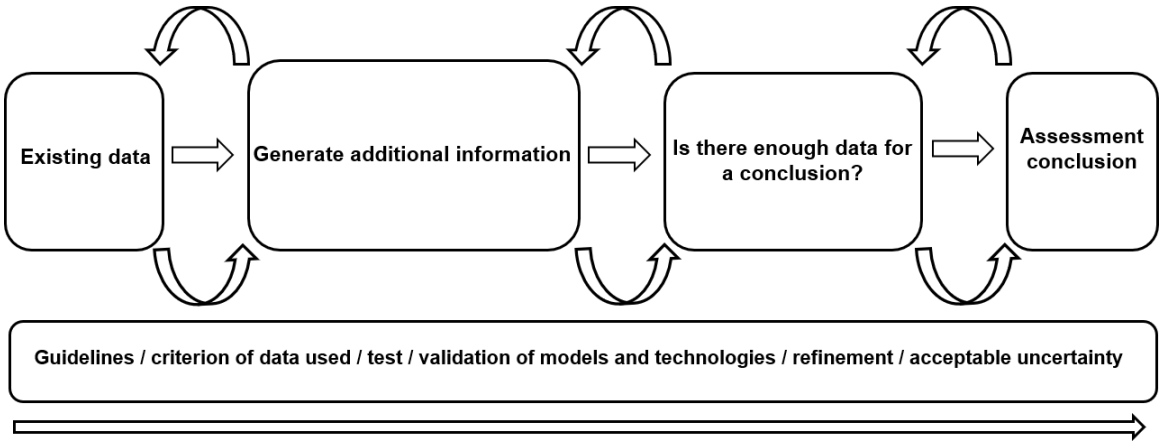


Figure 2. Concluding workflow for integration of NAMs in regulatory risk assessment from the EDR workshop.

PBPK for Regulators Workshop Summary

The UK FSA and the COT held a "*PBPK for Regulators*" workshop[24] (December 2020) in a multidisciplinary setting with delegates from regulatory agencies, government bodies, academia and industry. The workshop provided a platform to enable expert discussions and presentations on the application of PBPK to human health risk assessment in a regulatory context as well as potential future research.

Main overarching conclusions of PBPK workshop:

a) PBPK modelling tools are applicable in the explored areas of use, and there is some expertise available for their utilisation.

b) PBPK modelling offers opportunities from which to address questions for compounds that are otherwise not solvable.

c) Widespread acceptance amongst regulatory bodies appears to be limited by lack of available in-house expertise.

d) Familiarisation using real world case studies would help in developing more

[24] https://cot.food.gov.uk/sites/default/files/2021-03/TOX-2021-06_PBPK%20for%20Regulators%20Report_Cover%20page_final.pdf

experts in the field and increasing acceptance.

e) In a regulatory context, establishing fitness for purpose for the use of PBPK models require multi-partite discussion and harmonised guidance.

f) Finally, PBPK modelling is part of the wider "new approach methodologies" for risk assessment.

Regulatory Acceptance of NAMs

NAMs and IATAs are rarely accepted by regulatory bodies, however it is now at a pivotal point in the paradigm shift that incorporation and integration will be fundamental in more efficient and rapid risk assessment. The key question is how these approaches can be facilitated in a regulatory setting using the supporting technology available. The use of these methods through various case studies as a 'proof of principle' concept is becoming apparent.

Worldwide perspectives on emerging technologies

The focus of the 7th annual Global Summit on Regulatory Science (GSRS17) was Emerging Technologies for Food and Drug Safety[25] and the summit publication stated that "*Moving forward toward greater integration of emerging data and novel methodologies for chemicals risk assessment will need continuous efforts on capacity building*."[26]

Furthermore, in the recent EU Farm to Fork strategy and the EU Green Deal Food 2030 Pathways for Action (Food systems and data[27]) it states: "*to valorise emerging technologies, tools, standards and infrastructure for use in food systems*".

The future direction of safety assessment science will depend heavily on the evolution of the regulatory landscape. A key challenge, though, is whether the regulatory framework can keep pace with the increasing speed of scientific and technological developments (Worth *et al.*, 2019[28]).

Food authorities should strive to incorporate the best scientific methods available (Kavlock *et al*., 2018[29]) into chemical risk assessment. The future of food safety assessment depends on adaptability, flexibility and revolutionary principles in order to respond to the accelerating developments in science and technology.

This implies close collaboration between chemists, toxicologists, informaticians, risk assessors and others to develop, maintain and utilise appropriate models. Not only must the different disciplines come together, but also those scientists from industry, academia and regulatory agencies must recognise the commonalities (Cronin *et al*.,

[25] https://www.fda.gov/about-fda/science-research-nctr/global-summit-regulatory-science-brasilia-brazil-09182017-09202017
[26] Slikker Jr, W., de Souza Lima, T.A., Archella, D., de Silva Junior, J.B., Barton-Maclaren, T., Bo, L., Buvinich, D., Chaudhry, Q., Chuan, P., Deluyker, H. and Domselaar, G., 2018. Emerging technologies for food and drug safety. Regulatory Toxicology and Pharmacology, 98, pp.115-128.
[27] https://ec.europa.eu/info/sites/info/files/research_and_innovation/research_by_area/documents/2020.2082_en_04.pdf
[28] Worth, A.P., 2019. The future of in silico chemical safety… and beyond. Computational Toxicology, (10) pp 60-62
[29] Kavlock, R., Chandler, K., Houck, K., Hunter, S., Judson, R., Kleinstreuer, N., Knudsen, T., Martin, M., Padilla, S., Reif, D. and Richard, A., 2012. Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. Chemical research in toxicology, 25(7), pp.1287-1302.

2019[30]). The challenge is to respond to the growing need for adaptable, flexible and even bespoke computational workflows that meet the demands of industry and regulators, by exploiting the emerging methodologies of Tox21[31] and risk assessment.

UK Government on data and emerging technologies

The volume of data produced in the world is growing ever more rapidly, from 33 zettabytes[32] in 2018 to an expected 175 zettabytes in 2025 (IDC, 2018) (Food Systems[33]). The Department for Business, Energy and Industrial Strategy (BEIS) white paper on Regulation for the Fourth Industrial Revolution notes that changes in technology are occurring at a "*scale, speed and complexity that is unprecedented*".[34] The use of such technologies can help improve regulatory processes in several ways such as to improve the efficiency of data collection and to exploit data already held by agencies to support better analysis and risk assessment[35].

In the 'Rebuilding a Resilient Britain'[36] programme[37] one of the departmental Areas of Research Interest (ARIs) marked as a priority was "data science and digital technologies" in the "Changing Systems" theme[38].

Furthermore, incorporating NAMs into the regulatory context compliments Defra's research program on systems thinking approach[39] which includes Food systems.

[30] Cronin, M.T., Madden, J.C., Yang, C. and Worth, A.P., 2019. Unlocking the potential of in silico chemical safety assessment–A report on a cross-sector symposium on current opportunities and future challenges. Computational Toxicology, 10, pp.38-43.
[31] 21st century toxicology' (Tox 21) refers to 'the transformation underway in the tools and approaches used to evaluate chemical substances for possible effects on human health'. National Research Council, 2007. Toxicity testing in the 21st century: a vision and a strategy. National Academies Press.
[32]Zettabytes are 1,000,000,000,000,000,000,000 bytes. Zettabyte is approximately equal to a thousand Exabytes, a billion Terabytes, or a trillion Gigabytes
[33] https://ec.europa.eu/info/sites/info/files/research_and_innovation/research_by_area/documents/2020.2082_en_04.pdf
[34] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/807792/regulation-fourth-industrial-strategy-white-paper-web.pdf
[35] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/926585/emerging-technologies-for-regulation.pdf
[36] https://www.gov.uk/government/collections/rebuilding-a-resilient-britain
[37] The 'Rebuilding a Resilient Britain' programme builds on work to develop government science capability and the external evidence base to support policy development. This report sets out more analysis relating to data and evaluation. It examines existing questions to identify cross-cutting themes, and to provide a platform for engagement between government departments and academics to consider medium and long-term questions.
[38]https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/964759/Data_and_Evaluation_ARI_summary_paper.pdf
[39] https://www.gov.uk/government/news/science-research-programme-launched-to-inform-defra-policy-making

How does the FSA plan to integrate NAMs in the regulatory space?

↓

Formulating the problem space

It has been well known that designing and structuring your problem space (Goel and Pirolli[40]) will be fundamental in its outputs (Newell et al., 1993) [41] and success (Goel and Pirolli 1989[42]). The science of design consists of the efficient computational techniques that are available for actually finding optimum courses of action in real situations, or reasonable approximations to real situations (Simon, 1981[43]).

The FSA plans to do problem exploration techniques which includes interactive sessions to risk assessment and define the questions that need answering.

Figure 3. Formulating the problem space for project outputs.

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Breaking Down the Silos: Drivers and Obstacles

In the Malloy *et al* (2017)[44] paper it recommended to support trans-sector and transdisciplinary efforts to integrate predictive toxicology "*Use existing efforts to bring together regulators, industry, civil society, and academics to agree on testing protocols for nanotechnologies as a model that then could be adopted in other fields*".

[40] Goel, V. and Pirolli, P., 1992. The structure of design problem spaces. Cognitive science, 16(3), pp.395-429.
[41] Newell, A., Yost, G.R., Laird, J.E., Rosenbloom, P.S. and Altmann, E., 1993. Formulating the problem space computational model. In The Soar papers (vol. II) research on integrated intelligence (pp. 1321-1359).
[42] Goel, V. and Pirolli, P., 1989. Motivating the notion of generic design within information-processing theory: The design problem space. AI magazine, 10(1), pp.19-19.
[43] Simon, H.A., 2019. *The sciences of the artificial*. MIT press.
[44] Malloy, T., Zaunbrecher, V., Beryt, E., Judson, R., Tice, R., Allard, P., Blake, A., Cote, I., Godwin, H., Heine, L. and Kerzic, P., 2017. Advancing alternatives analysis: the role of predictive toxicology in selecting safer chemical products and processes. *Integrated environmental assessment and management*, *13*(5), pp.915-925.

Despite advances, the scope and pace of adoption of NAMs, including toxicogenomics tools and data sets in chemical risk assessment, have generally, not met the ambitious expectations of their proponents (Pain *et al*., 2020)[45].

Regulatory uptake has been hesitant to adopt NAMs and despite notable improvements and new applications some of the major obstacles remain, such as compatibility knowledge barriers.

Incorporation | Adopters of change | Data to Deployment

The incorporation and implementation of these new predictive capabilities by regulatory agencies brings both challenges and opportunities.

Moving from research to risk assessment to regulatory setting and beyond the validation and leverage acceptance of these new emerging technologies must be ensured. The FSA plan to learn from other regulatory agencies and other conceptual frameworks (*e.g.* IPBES Conceptual Framework[46] *i.e*. to structure the syntheses that will inform policy, and to improve comparability across various assessments carried out at different spatial scales, on different themes, and in different regions) in different settings.

NAMs are gaining traction as a systematic method to support the informed decision on chemical risk assessment. Adapting how we assess risk will be and has always been a challenge, but *big switches* have, and can, occur through innovation attributes that facilitate and accelerate adaptation (Rogers, 2003).[47] In Attwell's 1992 paper[48], it was concluded that a sensible way, was to treat a knowledge barrier approach to technology diffusion, as a distinct theory in its own right. The diffusion of technology is reconceptualized in terms of organizational learning, skill development, and knowledge barriers. As knowledge barriers are lowered, diffusion speeds up, and one observes a transition from an early pattern in which the new technology is typically obtained as a service to a later pattern of in-house provision of the technology.

The "*rate of adoption is the relative speed with which an innovation is adopted by members of a social system*" Rogers (2003). Therefore, throughout the process the FSA will strive to be transparent in the process and engage with the public. Techniques for adoption and integration could include spherical cow[49] in order for maximum understanding for all our stakeholders including the consumer. Data

[45] Pain, G., Hickey, G., Mondou, M., Crump, D., Hecker, M., Basu, N. and Maguire, S., 2020. Drivers of and Obstacles to the Adoption of Toxicogenomics for Chemical Risk Assessment: Insights from Social Science Perspectives. Environmental health perspectives, 128(10), p.105002.
[46] Díaz, S., Demissew, S., Carabias, J., Joly, C., Lonsdale, M., Ash, N., Larigauderie, A., Adhikari, J.R., Arico, S., Báldi, A. and Bartuska, A., 2015. The IPBES Conceptual Framework—connecting nature and people. *Current opinion in environmental sustainability*, *14*, pp.1-16.
[47] Rogers, E.M. (2003). Diffusion of innovations, 5th Ed. New York, NY
[48] Attewell, P., 1992. Technology diffusion and organizational learning: The case of business computing. Organization science, 3(1), pp.1-19.
[49] Spherical cow: is a humorous metaphor for highly simplified scientific models of complex real-life phenomena.

visualisation exploration techniques could be applied (*e.g.* Mondrian[50] and Manet[51] (Unwin *et al* 1996[52])) to make use of multidimension data. Incorporating data sets such as Open FoodTox[53] into the latest predictive models will drive the discovery of useful patterns in chemical prints and more decisive tree networks into the architecture of the decision flowchart.

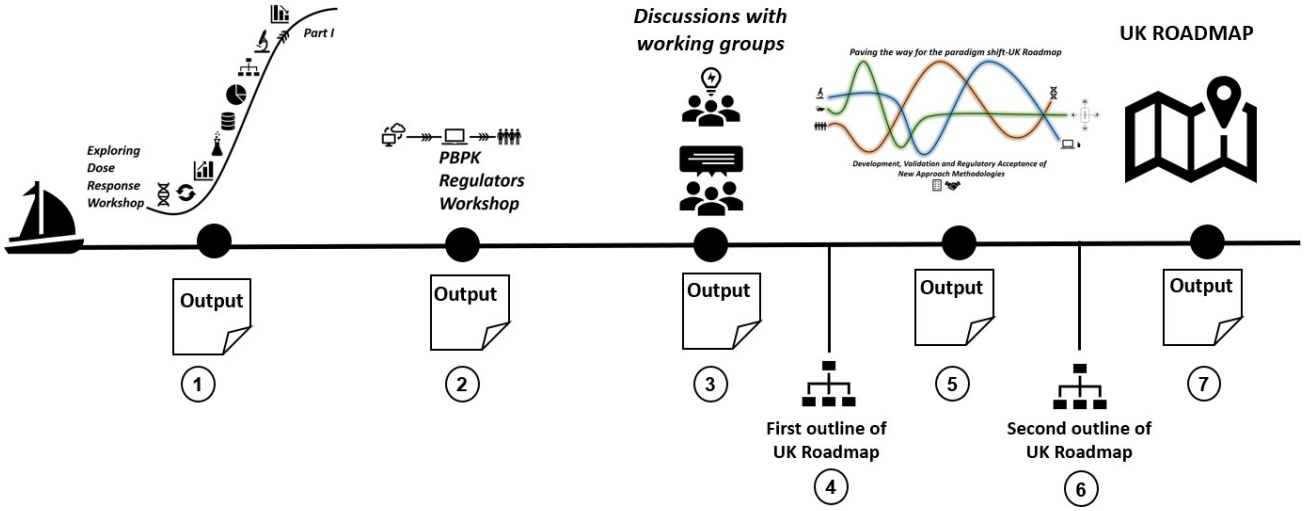
Innovative technologies should be reviewed and evaluated once, prior to integration, as part of the risk assessment strategies for chemical testing for human health and the environment. Using a validation process via an evidence driven approach to address the data gaps in the risk assessment process will facilitate the acceptance and validity of these NAMs as well as pave the way for alternative testing strategies with confidence.

In order to use the best science available, integration of these technologies as part of the FSA chemical risk assessment process will be fundamental in the future of human safety *i.e.* the consumer.

This UK roadmap will pave the way towards acceptance and integration of NAMs into safety and risk assessments from a regulatory perspective and make use of the government R&D Roadmap[54].

[50] Mondrian is a general-purpose statistical data-visualization system.
[51] MANET is for exploring data, whether raw data, transformed data or model residuals. MANET provides a range of graphical tools specially designed for studying multivariate features. MANET useful for gaining insights into the structure and relationships of their data sets.
[52] Unwin, A., Hawkins, G., Hofmann, H. and Siegl, B., 1996. Interactive graphics for data sets with missing values—MANET. Journal of Computational and Graphical Statistics, 5(2), pp.113-122.
[53] https://www.efsa.europa.eu/en/data/chemical-hazards-data
[54] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/896799/UK_Research_and_Development_Roadmap.pdf

Stepping and (Mile)Stones -How the FSA got here



Paving the way for a UK Roadmap Journey-How the FSA got here

1) Output of the Exploring Dose Response Workshop
2) Output of the PBPK Regulators Workshop
3) Output of the discussions with working groups
4) First outline of the UK Roadmap
5) Output of the Paving the way for the paradigm shift-UK Roadmap Development, Validation and Regulatory Acceptance of New Approach Methodologies workshop.
6) Second outline of the UK Roadmap
7) Finalisation of the UK Roadmap

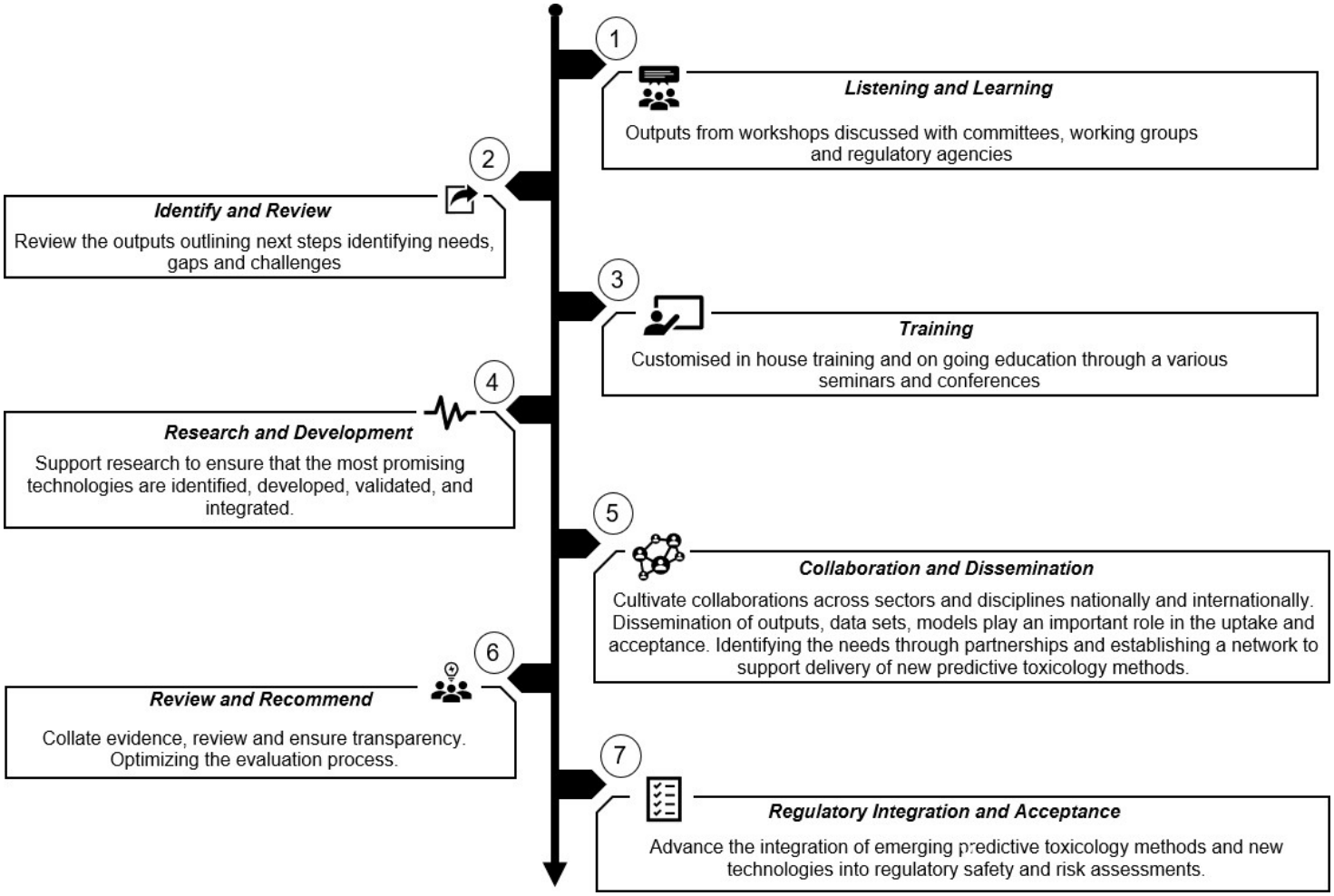


Figure 4. The UK Roadmap

Overall objectives of the roadmap are to:

- identify latest available NAMs for optimal risk assessment
- learn from other regulatory agencies and beyond
- validate through case studies
- build confidence in NAMs in the regulatory setting
- develop skills and training
- implement and integrate NAMs in the regulatory setting

The 7 Steps to Integration & Acceptance

The UK Roadmap

1. Listening and Learning

- *Outputs from workshops organised by the FSA and COT will be discussed with relevant and appropriate committees, working groups and regulatory agencies for opportunity to comment and input.*
- *FSA will review what other regulatory agencies and industry have done and what still needs to be done.*

2. Identify and Review

- *Review the outputs outlining next steps identifying needs, gaps, and challenges. Identify available NAMs and what the pros and cons for each are and where their strengths lie.*
- *Formulate the problem space.*
- *Identify opportunities and challenges.*
- *Throughout the process continue to review internal and external research and development and how that may impact on the Roadmap*

3. Training

- *Customised in-house training and ongoing education through various seminars and conferences*
- *Skill development: building a resilient organization.*
- *From the perspective of FSA and COT we can then suggest that other regulators / cross government would need similar training.*

4. Research and Development

- *Support and initiate research to ensure that the most promising technologies are identified, developed, validated, and integrated.*
- *Assess the list of NAMs and other roadmaps.*
- *Computational Fellow*
- *Tox AI PhD student*

5. Collaboration and Dissemination

- *Cultivate collaborations across sectors and disciplines nationally and internationally. Dissemination of outputs, data sets and models will play an important role in the uptake and acceptance. Identifying the needs through partnerships and establishing a network to support delivery of new predictive toxicology methods.*
- *Network with regulatory agencies and academics in this workspace.*
- *Set up a hub in the FSA and Cross-Government, industry, and academia to disseminate models etc.*
- *Set up a cross Whitehall NAMs working group so we can exchange information in this area.*

6. Review and Recommend

- *Collate evidence, review, and ensure transparency. Optimizing the evaluation process.*
- *Maintain open transparency throughout.*
- *Citizen science/public consultation on how the public feel on alternative testing strategies.*
- *Present work throughout to working groups and scientific advisory committees.*

7. Regulatory Integration and Acceptance

- *Advance the integration of emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments.*
- *Integrate the best possible methodologies in risk assessment.*
- *Virtual laboratories acceptance.*
- *Integration of NAMs in a regulatory setting.*