Session V

In this guide

Paving the way for the paradigm shift The UK Roadmap

Dr Camilla Alexander White presented on “Next generation risk assessment (NGRA) of systemic toxicity effects”.

142. There is increased interest from the UK on fundamental principles and paradigms of future regulations since EU exit and there is more discussion on the interpretation of the precautionary principle.

143. The UK chemical strategy was last published in 1999. In 2021, The Royal Society of Chemistry published Drivers and scope for a UK chemicals framework.

144. Controversy remains around the hazards vs risk paradigm and different codified hazards. However, there will be more controversy regarding the use of NAMs.

145. Endocrine disrupting chemicals for example were reviewed towards the end of 2019. There was a unanimous vote that a risk-based approach would be the most appropriate for endocrine disrupting chemicals.

146. Should there be a move into risk-based regulation? Therefore, the centre of decision making should be a “protection not prediction” philosophy. These decisions should be transparent and open to scrutiny. Science advisory groups/Committees are fundamental to some of this shift in culture (such as reviewing new content in future dossiers using NAMs and NGRA). Risk is a function of hazard and exposure and is still a function of NAMs.

147. The principles of NGRA were discussed. These principles underpin the use of new methodologies in the risk assessment of cosmetic ingredients.

148. There are 9 principles in cosmetics with the goal of human safety were discussed. The 9 principles of NGRA for cosmetics regulation (ICCR, 2018) could be drawn as a parallel for the principles of all NAMs:

1. Overall goal human safety assessment.
2. Assessment is exposure-led.
3. Assessment is hypothesis driven.
4. Assessment is designed to prevent harm.
5. Assessment follows an appropriate appraisal of all existing information.
6. Assessment uses a tiered and iterative approach.
7. Assessment uses robust and relevant methods and strategies.
8. Sources of uncertainty should be characterised and documented.
9. The logic of the approach should be transparently and explicitly documented.

149. A tiered framework for exposure assessment: deterministic, probable, and specific models (refinement to include biomonitoring) should be used.

150. Levels of confidence and uncertainty are also defined amongst the principles (ICCR-2018).

151. There is a 10-step framework and the use of read-across in NGRA. Caffeine has been used as a model substance. There is three times more work involved

compared to a standard risk assessment or dossier. The framework starts with exposure and uses deterministic exposure assessment using the tiered exposure assessment.

Different types of tiers include:

- Tier 1 Scenario A Deterministic.
- Tier 2+ Scenario A Probabilistic.
- Tier 1 Scenario B Deterministic.
- Tier 2+ Scenario B Probabilistic.

152. The higher tiers are used to assess biological activity using gene profiling and/or oestrogen receptor activity.

153. For the UK Roadmap, one of today's challenges can be solved by developing new relevant skills of the next generation of scientists. More investment will be needed, upscaling and new research, particularly in the fields in exposure assessment if the UK were to be world leaders in risk-based regulations, in particular NGRA. There needs to be investment in NAMs technologies for NGRA (i.e., Characterise relevant hazard potencies). More case studies should be developed and collate the data to see how they are working. Social science will play a role, in terms of risk communication that will need to be considered. A global open-source data should be created. Would there need to be a new agency with a research arm. The UK roadmap is important for cross-department wide, but it's more important for the broader perspectives than just FSA/COT. It should be used to collaborate globally.

154. Finally, develop a framework to protect not predict.

Professor Robert Lee presented on "Regulatory law issues in human health and environment".

155. Professor Lee outlined the functions of the FSA as outlined in the Food Standards Act, including to protect public health from risks; establish advisory committees; develop policy; provide advice, information or assistance to other agencies such as local authorities; and to monitor developments in science, technology and other areas. But the FSA also has objectives, which Professor Lee described as soft law elements rather than hard law, which include providing guidance and the minuted decisions of advisory committees.

156. The objectives are written into strategic programmes. The FSA aims to define and bring on stream programmes of work on date and new technologies.

Failing to meet objectives can be subject to judicial review.

157. The FSA also has powers but has to take into account the nature and magnitude of risks to public health and has to also take into account uncertainty, the advice of scientific advisory committees and to consider costs versus benefits.

158. There is little in hard law that stops the development of NAMs. The soft laws could be aligned with NAMs.

159. The advantages of NAMs appear to be that they are faster, cheaper, ethical, mechanistic, and protective to some degree. They look better placed to address data gaps, yet their formal adoption in regulations is limited.

160. Professor Lee moved on to discuss socio-technical barriers. The “N” in NAMs stands for new, so how many scientists in regulatory agencies will have had an involvement in NAMs if they were in higher education more than 20 years ago? In regulatory cultures there is stasis. Making errors costs, which engenders caution. However, if we do not begin to adopt NAMs then the barriers will remain as there won’t be the development, validation, and acceptance in regulations.

161. This will require a significant building of networks. The roadmap reflects well-known processes. Training is fundamental for the regulatory community, but the culture needs to be considered too. The place for NAMs is within the soft law areas. Professor Lee suggested starting with a soft law review now and see how well those are aligned to the reception of NAMs as they stand.

Professor Timothy Malloy (University of California Los Angeles) presented on “Advancing alternative testing strategies in regulatory decision making”.

162. Professor Malloy started by discussing the impact of regulatory approaches in adoption of NAMs giving the example of EPA, ECHA and the UK FSA/COT Roadmap.

163. Informal law and formal law were explained with risk context and court interpretation.

164. Risk context is the legal side with different purposes for which NAMs may be used. Risk assessment and risk management need to consider whether quantitative risk assessments should be used or a more qualitative approach. Another context is whether to use NAMs and whether safer design can use alternative assessments for consumer products Malloy and Beryt (2016).

165. Formal law in most settings and existing law are not a barrier and are therefore agnostic. In turn, this encourages and mandates the use of NAMs. TSCA anticipated the use of non-animal testing and built it into statute and assumed that regulators would make great use of NAMs as they were developed. However, this hasn't seemed to be a great driver elsewhere. A recent study on NAMs in REACH in the EU stated that there is some use of QSARs and in vitro assays but that they are not used as widely as they could have been and in fact, are rarely used.

166. For court interpretation, it involves court instances when challenged by industry. Courts are generally quite accepting of NAMs and accept that regulatory agencies must use the best available science, therefore, in theory, courts do not stand in the way of NAMs.

167. In informal law (Agency practices) it is expected that there will be a push based on freedom. Agencies have not taken advantage of the discretion. Social barriers can be quite a big barrier to changes. Different departments within an agency could be at odds.

168. In 2014 there was a survey on decision making of those involved in chemical risk assessment (Zaunbrecher et al., 2017). Other surveys were also done in Canada-with similar conclusions.

169. The survey discussed screening and prioritisation and the viable use of NAMs. There was a fairly sizable number (25%) that were using NAMs to make risk assessment decisions. And at what level of the risk assessment? E.g., screening/prioritisation, comparative risk assessment of alternative chemicals? Weight of Evidence (WoE)? Qualitative risk assessment? Dose finding studies, setting of NOAELs? The most important consideration is how viable is the use of NAMs in said technology and its applied use.

170. What are the barriers to adoption of NAMs for the validation process? Standardisation? social aspects? expected inherent disinclination for change? It is not really all about the science (but there may be a lack of funding, and inadequate facilities also play a role). It is more so with the socio-legal barriers (identified as priority and more common by survey). There is a resistance to change, slow validation process, regulatory acceptance, lack of standardisation. As well as the main ones (less common); legal challenge of results and of authority (not all agencies are going all in yet (so makes it look risky). However, we may need to consider risk/benefit?

171. The drivers of adoption (identified as priority/more common by survey) are the need for toxicology data by reducing test costs; demand by regulatory agencies; and ethical concerns. Less commonly identified drivers were demand by consumers; industry competition; and demand by NGOs. There needs to be recognition that this is a multidisciplinary undertaking with collaboration, outreach, and planning.

172. There needs to be much more proactive work by regulatory agencies to promote the use of NAMs which might make wider acceptance of it easier but there could also be a mandate on the use of NAMs. In summary, legal doesn't stand in the way of NAMs adoption.

Dr Nicole C. Kleinstreuer presented on "Alternative Toxicological Methods and the ICCVAM strategic roadmap".

173. The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is an NTP office focused on the development and evaluation of alternatives to animal use for chemical safety testing. The topics in this section provide information about approaches used to replace, reduce, or refine animal use while ensuring that the toxic potential of the substances is appropriately characterized.

174. The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is a permanent committee of the National Institute of Environmental Health Sciences (NIEHS). ICCVAM is composed of representatives from 17 U.S. federal regulatory and research agencies. These regulatory and research agencies require, use, generate, or disseminate toxicological and safety testing information.

175. In January 2018, "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States" was published. ICCVAM coordinated the development of the strategic roadmap, a resource to guide the U.S. federal agencies and stakeholders seeking to adopt new approaches to safety and risk assessment of substances. The three pillars are: Utilization, Confidence and Technology.

176. There are 4C's to underpin the roadmap: Communication, commitment, collaboration and confidence.

177. Progress has been achieved since the ICCVAM roadmap and consensus of all the ICCVAM agencies. Through the map the work is more efficient, and the

approach is robust.

178. The Integrated chemical environment (ICE) dashboard looks at accessing data resources, quality tools or curated data. ICE provides curated data and tools to support chemical safety testing; Tox21 data are curated using analytical chemistry and assay-specific information; in vitro data are mapped to mechanistic targets and regulatory endpoints; in silico predictions are available for physical chemical and ADME properties; IVIVE tool uses ICE or user data to estimate in vivo exposure levels (Bell et al., 2020).

179. Tox21 and ToxCast screening data QC information flags to remove confidence values. Biological context is provided to the user.

180. Other tools like the Curve Surfer tool allows an individual to view and interact with concentration response curves from cHTS. The PBPK tool allows generation of predictions of tissue-specific chemical concentration profiles following a dosing event.

Session V Roundtable discussion

181. The participants welcomed and praised the organisers of the workshop for presenting a legal perspective to the adoption of NAMs.

182. There was discussion over UK law and whether we have the same formal (hard) and informal (soft) law as in the USA.

183. The UK courts do not reject novel techniques although they must be accredited or sufficiently sound, the factors to be considered are: “1. Whether the theory or technique can be or has been tested; 2. Whether the theory or technique has been subject to peer review and publication; 3. The known or potential rate of error or the existence of standards; and 4. Whether the theory or technique used has been generally accepted.” The Crown Prosecution Service, 2019, Prosecution Guidance, Expert Evidence.

184. It might also help to involve the public somehow. It is likely that there is always the risk that people think that using a different approach to EU means "watering down" standards. If demand from consumers for NAMs is low are the ethical concerns driven by scientists?

185. The GM crops issue shows what can happen if public acceptance is missing. Doesn't it depend on how the question is phrased, i.e., "would you prefer to use in vitro tests rather than animals?" as opposed to "what tests would you

prefer to be done to ensure that your vaccine/medicine is safe?"

186. There is a need to demonstrate that standards will not be being lowered just because something different is being done, and indeed should be better using the best state of the art science.

187. People are risk averse, so they tend to focus on losses more than gains. Perhaps NAMs need to be promoted in a way that emphasises what can be lost if there is no encouragement for their use and acceptance, rather than the gains.

188. People are sceptical of anything that benefits industry, there appears to be the assumption that they are not interested in the health of the consumer.

189. Discussions about mRNA vaccines went in the same direction and participants discussed how learnings could be taken from the public reaction to those.

190. There were suggestions that the Scientific Advisory Committees could be bolder in requesting NAMs for mechanistic support and argument on AOPs and MOAs. For example, in regulated products where there are data requirements, data need to be generated by methods that are fit for purpose. There could be benefits if NAMs were to be accepted in this space. Accepted methods help the regulated community as they are pointing to a standard. Would there need to be a standard? Could NAMs be used without having a standard?

191. Generally, courts show deference to regulatory agencies; judges recognised that they are not trained in the roles of the regulatory agencies. The agency is following the science and whether it is fit for purpose for discharging their regulation. However, understandably people feel more comfortable with accepted methods.

192. A participant raised the role of responsibility and where does the responsibility lie? Who needs to be convinced? Is it at the Ministerial level? Is it similar to what the FSA are doing with gene editing? Perhaps statutory legislation should be passed to prescribe what can be used.

193. Participants discussed how the legal perspectives are interesting in terms of different approaches. The EU prescriptive approach to chemical testing (legal safety) and the US flexible approach regulators can use the best science. The argument for a prescriptive approach for legal certainty is not as much of an issue as originally thought, if the courts are understanding of the use of the best available science. The OECD will not dispute or oppose the use of new NAMs.

Given that the UK has now left the EU One option would be for the UK to copy over all of the UK law. Now the UK are charged with making decisions on what they will or will not accept i.e., codified or common law. The EU exit strategy was essentially the UK taking back control which could be seen as great determination on the part of government to offer a lead in science and develop an enterprise in regulatory science.

194. Another participant mentioned the FAO/WHO Pesticides advisory committee with the understanding that the FAO/WHO assess data including NAMs. However, none have been submitted because applicants are concerned about how this would be viewed once in the public domain. There needs to be some thought about parallel assessment as a way to evaluate NAMs.

195. The FSA introduced the law on allergen labelling with wide stakeholder surveys including patient support groups. Perhaps something similar could be done with NAMs.

196. It will be difficult to testify against regulatory adoption of NAMs but who needs to be convinced? Legal certainty of the NAMs isn’t as disagreed with as they used to be or at least that is the perception. The Courts defer to the regulators for their expertise on this.

197. What about international law and integration of NAMs? Does there need to be a strategy for this? There is a need for industry guidance on how this happens in order to define the number of the drivers for the process. There should be learnings from industry on what can and cannot be shown such as what works, early signals, from product pipeline. It could be a topic for the FSA Chair and other Executive Management Team boards at other government departments (OGDs).

198. There needs to be good public engagement with education for the public and good communication.

199. The proportionality of costs needs to be comprehensive. The benefits need to be seen from the public’s perspective and the regulatory interest considered. There should be an open dialogue with the citizen’s jury approach and an education of what the science consists of.

200. There needs to be a link with the precautionary principle and conservatism in standard toxicology approaches.

201. The loss of not taking up NAMs needs to be considered i.e., gains and benefits is fundamental.

202. Funding bodies e.g., research councils should be involved especially with a view to improving engagement and education.

203. Publications in journals to increase confidence and continue working with academia.