

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

COC workshops follow up – proposal for new guidance statement

1. The COC held two workshops in November 2022 and November 2023, to consider making progress in the way in which risk assessment for carcinogenicity of chemicals is undertaken.
2. To capture the discussions from these workshops and show that COC is keen to see developments in the area, a new guidance statement “A case for change – developing a better approach to assessing risk of cancer from chemicals” is proposed; this is outlined in Annex A.
3. Draft workshop summaries are presented in Annexes B and C to support the consideration of the proposed new guidance statement.

Questions for the Committee

4. Members are asked to consider proposed new guidance statement and in particular:
 - i. Does the Committee agree the new guidance statement should be progressed?
 - ii. Are there any comments on the structure and contents of the new guidance statement?

**Secretariat
March 2024**

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

COC workshops follow up – proposal for new guidance statement

Initial draft outline of proposed new guidance statement

This paper is attached. It will be made publicly available when it has been further developed or on publication.

Secretariat
March 2024



Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)

COC Guidance Statement G11 – draft 0.a

A case for change

Developing a better approach to assessing risk of
cancer from chemicals

<https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc>

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

A case for change – developing a better approach to assessing risk of cancer from chemicals

Introduction

1. The COC recognises many ongoing activities to improve risk assessment of chemicals including assessment of potential carcinogenicity. With these developments, the COC considers that current guidance, and for some sectors regulatory requirements, on assessing risks of cancer focusing on using long-term animal carcinogenicity studies should no longer be considered a ‘gold standard’.

Concerns regarding status quo

2. A lot of work conducted on chemicals with respect to cancer focusses on classification of whether a substance is a carcinogen or not, which is often governed by regulatory requirements, e.g. carcinogens cannot be used in certain product types, or for product labelling e.g. under CLP. In itself, this does not inform on the potential risk of cancer following exposure to a specific chemical, which is the more relevant aspect to consider in protecting human health. Assessing such potential risk, or lack of risk, may be a proactive process, e.g. as an ingredient or impurity in a product, or it may be reactive, e.g. following an accident or contamination incident.

3. There are a number of published papers indicating the limitations of long-term animal carcinogenicity assays both for classification and risk assessment of chemicals. Limitations include that some of the findings are not relevant to human health risk, a significant number of animals are used and that potential for carcinogenicity can be identified from data available before a long-term study is conducted.

4. With new approach methodologies (NAMs) as well as significant projects undertaken using existing data from other evidence, there is general agreement that there are better tools for assessing potential for risk of cancer from chemicals.

5. The COC is aware that there are challenges to regulators in changing the approach in dealing with risk of cancer from chemicals. There is a need to ensure that any change in approach is demonstrated to still ensure protection of health is maintained, as public perception may be that risk assessment of substances will be less rigorous if testing is reduced. It is also likely to be difficult to change from a dichotomous “carcinogen” or not classification approach, and as a consequence communication around cancer risk may be more challenging.

6. Wider barriers to changing how potential risk of cancer from chemicals is assessed include current regulatory requirements which might prevent some industry partners in exploring alternatives; interested industry sectors invite parallel submissions of conventional data along with data from other approaches for regulatory approval, but this is not a requirement and there may be hesitation from industry in supplying such data. Skills and expertise both within industry and regulators to assess data from other approaches may be lacking resulting in uncertainty if conventional information is not supplied.

Lessons from 2 workshops

7. The COC hosted two workshops to discuss how progress can be made in assessing the risk of cancer from chemicals. The first explored the issues from the perspective of the pesticides sector, where use of animal data including the long-term rodent carcinogenicity assay is a regulatory requirement. The second focussed on the cosmetics and personal care industry where use of substances tested on animals for the purposes of cosmetic use after 2013 has been banned, so no new animal data are being used for risk assessments.

8. Across the two workshops it was clear that activities are ongoing to improve carcinogenic risk assessment and move away from the long-term animal carcinogenicity study. In the pesticide sector, programs like the “Rethinking carcinogenicity assessment for agrochemicals project (ReCAAP)” are demonstrating how other data including from shorter animal studies can sufficiently address the potential for cancer risk. This also follows work by ICH¹ in the pharmaceuticals sector which has moved away from requirements for carcinogenicity testing as part of the standard package of data for pharmaceuticals.

9. Some challenges in the cosmetics and personal care sectors specifically were highlighted in the second workshop, where it was noted that few ingredients are in use that have been developed following the animal testing ban. Work is continuing in the area and as exploration is made of alternative approaches for testing for other complex endpoints there will likely be learning with respect to carcinogenicity.

¹ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

10. Both workshops suggested a need for demonstration of effectiveness of alternative approaches to aid regulatory change; recognised barriers to uptake including a lack of international harmonization and legislation; and acknowledged the need for courage to submit dossiers with supplementary non-conventional data or without drawing on historical conventional data to lead the way and provide assurance to others in the same or different sectors that effective cancer risk assessment can be undertaken without (long-term) animal data.

11. Alongside scientific developments, the workshops flagged the importance of clear communication of developments in the field recognising the sensitivity around cancer risk compared to some other types of toxicity, as public risk perception will be an important consideration for risk management.

Call to Action

12. The COC is keen to encourage continued exploration of different scientifically robust approaches to assessing cancer risks from chemicals.

13. It is acknowledged that this will require up front effort and investment from industry colleagues, but with a long-term goal to improve risk assessment and with potential to change the assessment requirements for chemicals.

14. The Committee will keep an active watch on peer-reviewed literature in the area, including exploring how these papers address some of the barriers to progress. Interested parties are invited to contact the Secretariat with information on activities in the area.

Summary / Conclusions

15. TBC

COC Guidance Statement G11 draft v0.a
Date TBC

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References

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

**COC workshops follow up – proposal for new guidance
statement**

Draft summary of November 2022 workshop

This paper is attached. It will not be made publicly available until the presenters have had opportunity to review the summary of their presentations.

Secretariat

March 2024

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

COC Workshop November 17th, 2022 – Draft summary

Changing the paradigm: How should we assess cancer risk in the UK?

1. This paper presents a summary of the presentations made at the COC workshop held in November 2022 along with notes of the plenary and breakout group discussions, which have been collated for individual questions, for Members to consider next steps and further activities.
2. The principal aim of the workshop was to determine what definitive steps can be undertaken to make progress towards improvement of the chemical risk assessment process and regulatory requirements for carcinogenicity, based on research undertaken over the last 10-20 years.
3. The workshop considered the issues in the context of pesticides, but further discussion of different regulatory areas is planned for the future, and it is anticipated that discussion will build from this first workshop.
4. A draft summary of the presentations and discussions is provided at Annex A.

Questions for the Committee

5. Members are asked to consider Annex A and in particular:
 - i. Comment on the themes coming from the discussions
 - ii. Consider potential next steps, in terms of future COC discussion topics or further workshops or other activities

IEH Consulting under contract supporting the UKHSA COC Secretariat

March 2023

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CC/2023/03 Annex A

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

COC Workshop November 17th, 2022 – Draft summary

Changing the paradigm: How should we assess cancer risk in the UK?

Draft summary

This Annex is attached. It is not being made public as it contains summaries of speaker presentations to be checked with the individuals concerned. The output from the workshop will be available on the COC website in due course.

IEH Consulting under contract supporting the UKHSA COC Secretariat

March 2023

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Changing the paradigm: How should we assess cancer risk in the UK?

Aims and objectives of the workshop.

The principal aim of the workshop was to determine what definitive steps can be undertaken to make progress towards improvement of the chemical risk assessment process and regulatory requirements for carcinogenicity, based on research undertaken over the last 1020 years. The workshop considered the issues in the context of pesticides, with a plan for further discussion of different regulatory areas in the future.

Summary of presentations

Risk assessment of carcinogens in plant protection products - Dr Susy Brescia, Chemicals Regulation Division, HSE

This talk addressed the status quo of the cancer assessment of pesticide active substances, identifying the limitations of the current paradigm and exploring some of the new approaches that are being developed.

- Pesticides are regulated under the retained GB Regulation 1107/2009. In relation to carcinogenicity, OECD guideline-compliant cancer bioassays in rats and mice have to be submitted by applicants. For existing pesticides, epidemiological data may also be available and should be evaluated alongside the animal studies.
- Hazard identification and classification (under the retained GB CLP Regulation) is the first step in the assessment of carcinogenicity. If treatment-related tumours are observed, the substance will be regarded a carcinogen and classification for carcinogenicity will be warranted, i.e. with classification as Category 1A, 1B or 2.
- If the substance is classified as Category 1 under the GB CLP Regulation, it cannot be approved on the basis of its hazard properties and no further assessment is required. If the substance is classified as Category 2, approval is possible, with the assessment proceeding to the hazard characterisation step, unless mode of action (MoA) information is generated showing that the

- tumours are not relevant to humans and the therefore the substance is not carcinogenic in humans.
- Categorisation based on hazard criteria alone was considered by the speaker to be outdated and misleading as no consideration is given to the carcinogenic potency of the substance, nor the potential for exposure. A law-change would be needed, however, for the UK to adopt a risk-based approach.
- For hazard classification purposes, in the case of negative results in cancer bioassays, the Maximum Tolerated Dose (MTD) needs to have been reached. It was emphasised that if the MTD is not reached, this can give inconclusive evidence of carcinogenicity. With our increased understanding of cancer biology and the stochastic nature of carcinogenesis, it is becoming clearer that the rodent bioassay is of questionable predictiveness; it is also time consuming and very animal-intensive.
- The speaker outlined some approaches that have been applied for assessing genotoxic carcinogens in recent years, including a full threshold approach for aneugens, a practical threshold methodology for indirect genotoxicants, a margin of exposure approach, and in some cases (e.g. pesticide metabolites) the genotoxicity Threshold of Toxicological Concern (TTC). At present there is no clear guidance on the extent to which non-linear kinetics can be applied to dose-response carcinogenicity data to evaluate hazard at the low doses of exposure that are relevant to humans.
- With the recent analytical advances and the development of new approach methodologies (NAMs), it may be possible to use a battery of in vitro tests addressing the hallmarks of cancer (receptor activation, cell proliferation, cell transformation, gap junction, intercellular communication, cytochrome p 450 (CYP) induction, oxidative stress induction, immunosuppression/immune evasion, induction of cell signalling pathways, increased resistance to apoptotic cell death, pathogenic angiogenesis, genetic instability, cellular senescence/telomerase, tissue invasion and metastasis) in an integrated approach to testing and assessment (IATA) methodology.

ReCAAP: Rethinking Carcinogenicity Assessment for Agrochemicals Project – Dr Phil Botham, Syngenta Product Safety

- For the past 40 years, questions have been raised about the relevance and regulatory utility of rodent cancer bioassays in human health risk assessment.

- As a result, a working group of (mainly US) experts has established the Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) to propose a weight of evidence approach for waiving rodent cancer bioassays for the registration of food-use pesticides.
- The following hypothesis was generated by ReCAAP; 'The long-term rodent bioassay is not required to evaluate the potential for carcinogenicity in humans and confidently protect human health from cancer risk'.
- To move away from the bioassay, more modern techniques could be utilised, with a 90-day study providing a de minimus data set needed for most carcinogenic evaluations, including human relevance. One possible flaw in the approach is that rare cancers (e.g., eye tumours, pancreatic tumours) and cancers with a long latency period may not be picked up. In addition, it is possible that the approach may identify too many end points.
- A weight of evidence (WoE) approach was recommended which includes readacross data from similar chemicals. This approach was tested with 15 pesticides with a range of cancer classifications, types and MoA.
- The project performed a retrospective analysis of publicly available human safety data on a range of pesticides to determine if sufficient information would have been available to provide both a carcinogenicity assessment and a health-protective chronic risk assessment without conducting rodent cancer bioassays. Information used included exposure, mode-of-action, physicochemical, metabolism, and toxicological data, together with read across data on pesticides with the same MoA.

In vitro and shorter-term *in vivo* assays can be used to evaluate carcinogenic potential through identification of primary effects that lead to DNA changes, DNA damage, or increased cell division.

- Through this approach it is possible to protect health by setting exposure limits that prevent the primary toxicities, that could result in long term effects such as cancer. The approach can also provide appropriate information needed for hazard-based classification.
- The case studies developed by ReCAPP have provided a potential WoE approach that could be used to reduce or eventually eliminate the need for

- rodent cancer bioassays. Feedback from regulatory authorities has been supportive while also highlighting a number of important challenges around having a small base for read across chemicals, missing data for MoA key events and application to chronic exposure risk assessment; these are now being addressed.
- Work to do to obtain more confidence in the proposed approach includes submission of the approach for specific chemicals as an OECD IATA. This may bring in more global insight with respect to whether to continue use of the rodent cancer bioassay.

What can the carcinogenicity assessment of pesticides learn from the new approaches taken for pharmaceuticals: a pathologist's perspective – Dr Richard Haworth, Toxicological Pathologist, COC member

- Since the publication of the original S1B guideline on carcinogenicity testing of pharmaceuticals in 1998, the International Council for Harmonisation (ICH) has recognised that “scientific advances toward elucidation of mechanisms of carcinogenicity, greater understanding of the limitations of rodent models, and several retrospective analyses of pharmaceutical datasets indicate that 2-year rat carcinogenicity studies might not add value to human carcinogenicity risk assessment in some cases and the carcinogenic potential could have been assessed adequately based on a comprehensive assessment of all available pharmacological, biological, and toxicological data”.
- The resulting S1B(R1) addendum encourages an integrated science-based, WoE approach to inform whether a 2-year rat study is likely to add value to a human carcinogenicity risk assessment. The carcinogenic potential of a pharmaceutical in humans is assigned into one of three categories:
 - likely, such that a 2-year rat carcinogenicity study would not add value;
 - unlikely, such that a 2-year rat study would not add value;
 - uncertain, such that a 2-year rat carcinogenicity study would add value to human risk assessment.
- The five types of data that are considered useful for the WoE approach include: drug target biology and the primary pharmacologic mechanism of the

- parent compound and major human metabolites; secondary pharmacology screens for the parent compound and major metabolites; hormonal perturbation; genetic toxicology study data; and immune modulation.

The pathway leading up to this change in regulation started with devising a strategy to bring about regulatory change through industry working with regulators. Data relevant to the WoE evaluation was collected for 48 chemicals, including historic and prospective testing and dossiers prepared. These were evaluated by the S1 Expert Working Group and completed in June 2021.

- The driving force behind the addendum has been to reduce animal usage and use data that are better in terms of predictive human risk than information obtained from the 2-year rodent bioassay.

Plenary Discussion

The following points were raised during discussion of the presentations:

- Is route of exposure considered? Some degree of extrapolation needed as standard bioassay is oral not inhalation.
- BMDL10 is good predictor of threshold – can be used as a surrogate.
- If UK was to adopt the US approach this would allow consideration of thresholds.
- To change the law might be possible with UK REACH but there are political pressures not to do this.
- Some legislative changes are coming into EU REACH (in 2027) which may include the acceptance of the use of new approaches.
- Care needs to be taken about yes/no genotoxicity assessment – more chemicals are now equivocal. Could a WoE approach be applied to genotoxicity data to get over this?
- Companies sell globally and have to deal with regulators worldwide – e.g. European Chemical Agency (ECHA).

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- What happens with data that have already been generated vs data for new products?
- How long will the 'end game' take for carcinogenicity assays?
- Where do epidemiology data sit?
- Would an ICH-type approach for agrochemicals or chemicals be feasible?
Would this be politically difficult?

Discussion group questions and themes.

Overarching theme questions:

1. What opportunities are there to improve carcinogenic risk assessment in the UK?
2. What is the future of the 2-year / lifetime bioassay?

Discussion group questions:

3. Should carcinogens still be a special case for risk assessment?
4. How do we assess the level of risk of cancer associated with exposure to a chemical?
5. How common are weak carcinogens? How should carcinogenic risk assessment be adapted for low-level exposures?
6. How do we use new approach methodologies to improve cancer risk assessment?
7. What opportunities does UK REACH and other specific sector regulations offer for the evolution of carcinogenic risk assessment in the UK?

Questions for all groups:

8. What barriers are there for changing carcinogenic risk assessment in the UK?
9. What concrete next steps can be taken?
10. What is expected from COC to facilitate future evolution of carcinogenic risk assessment for the UK?

The following section captures responses from the breakout groups to each of the questions posed.

Question 3. Should carcinogens still be a special case for risk assessment?

- Yes. People are concerned about cancer. Latency period and irreversibility of changes are key reasons to regard it as a special case.
- Politically it would be very difficult to say we are not worried about the risk of cancer.

Question 4. How do we assess the level of risk of cancer associated with exposure to a chemical?

The following points were discussed:

Exposure:

- What is exposure and how it can be measured? Does exposure mean from the environment or tissue exposure?

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

- Models from food diaries are often used to evaluate exposure. Dietary studies are sometimes old and unreliable.
- Assumptions for exposure are conservative. Using biomarkers of exposure may be a better way of assessing exposure and are useful for existing chemicals. The human biomonitoring for Europe (HMB4EU) project is a useful initiative on biomarkers of exposure.
- Few exposure data or biomarker data are available for new chemicals. Exposure to new chemicals could be assumed based on exposure to similar chemicals.

Comparison of exposure to toxicity values:

- Exposure models are set and outputs are compared with health-based guidance values (HBGV) (acceptable/tolerable daily intakes/benchmark doses (ADI/TDI/BMDL)), which don't relate to a level of risk but rather are regulatory levels indicating minimal risk.
- This approach is binary, i.e. lower or higher than the HBGV indicates no risk or a potentially increased risk, respectively, unless epidemiology data are used to quantify the level of risk. If HBGVs are used, then the level of risk may be overestimated.
- HBGVs can be based on one critical study which is a conservative approach and there is a risk of bias assessment. However, the study is usually identified as part of a WoE approach using all available evidence with judgement made as to what is appropriate .
- EFSA and other authoritative bodies use margin of exposure (MOE) approaches to compare exposure with toxicity levels if a HBGV cannot be calculated for a contaminant, for example if there are insufficient data. The use of such an approach for regulated chemicals such as pesticides, where data are required for approval, may be subjected to greater societal judgment.
- Non-genotoxic and genotoxic (DNA reactive) carcinogens should be considered differently.

Question 5. How common are weak carcinogens? How should carcinogenic risk assessment be adapted for low-level exposures?

- A definition of 'weak carcinogen' is needed, as strict definitions would remove subjectivity and misinterpretation.
- 'Weak' could mean a small effect or that a high dose is needed before an effect is seen.

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

- The framework for risk assessment of carcinogens should not be adapted to consider weak carcinogens. It is important that a standard approach is followed for all potential carcinogens.
- Weak carcinogens are common.
- Potency is important but it's unclear what is meant by terminology such as 'weak carcinogen'. Need to qualify assessments of potency so the level of risk is a function of the degree of exposure.
- What is the importance of knowing if the tumour is aggressive or not, in terms of risk? This is not considered currently.
- Potency has already been assessed and there is a Lhasa database available. Decisions on how to best use those data better are required.

Question 6. How do we use new approach methodologies to improve cancer risk assessment?

- A definition is needed for 'new approach methodologies' (NAMs) as it can be taken to mean those that do not use animals, or alternatively those that are different from the traditional testing paradigm.
- Some of the methodologies classified as 'new' have been being developed or available for many years.
- The NAMs should be used alongside current testing strategies, including *in vivo* studies, as these will be required by some regulators for some time, both globally and in the UK.
- Validation, reproducibility and scientific justification are key so that they can contribute to a WoE approach.
- Validation may be problematic as many of the NAMs are not directly linked to the development of cancer. There can be several steps between receptor activation and cancer development.
- A definition of 'validation' is needed as this is often misrepresented in the literature with terms such as 'light touch validation'. Only assays performed to OECD guidelines will be used under the 'mutual acceptance of data' (MAD) system.
- Data from 'non-validated' assays can be used, but must be weighted accordingly in the risk assessment. Work is ongoing by OECD in conjunction with ECHA and the FDA to identify which NAMs are most suitable for validation to develop an IATA.
- NAMs might be used to test hypotheses which can be used to direct traditional testing to those hypotheses that are most relevant. Currently, it is uncertain whether NAMs can/will replace the traditional bioassay, but they can be used to support 90day and shorter length *in vivo* studies.

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

- Incentives could be provided to industry to encourage running NAMs alongside traditional assays?
- The capability of regulators to assess NAMs data is uncertain.

Question 7. What opportunities do UK REACH and other specific sector regulations offer for the evolution of carcinogenic risk assessment in the UK?

- UK REACH was transposed from EU REACH and amended to refer to UK specific bodies such as the UK Chemicals Agency that sits within the Health and Safety Executive (HSE), rather than ECHA.
- DEFRA is carrying out an assessment of UK REACH and how it can be improved/streamlined, etc. the Chairs of COM, COC and COT have provided input into this.
- UK is developing a UK Chemicals Strategy that will be in place until 2040 and stakeholders are being asked to contribute. This may move towards a risk-based approach rather than the current hazard-based methodology. COC will be kept informed on any opportunities to comment on drafts and may need to advise on what is the best approach to carcinogen risk assessment based on the available science.
 - o The use of NAMs will play a key role in the Chemicals Strategy. Case studies are needed to illustrate the use of NAMs and compare outcomes to traditional data.
- How much of a leader does the UK want to be? COC can help to justify to the UK Government why a certain approach should be taken. UK may end up isolated if the approach is not adopted globally. Strategic thinking is key.
- COC guidance applies to REACH and other legislation that runs alongside in different sectors.
- Regulators could play a greater part by attending meetings. Being able to ask questions of Committee members would be of benefit for both.
- A cross-government group, such as Interdepartmental Group on Health Risks from Chemicals (IGHRC), may be ideal to discuss these issues.
- ECHA's approach to carcinogenic risk assessment is too conservative, and they are too fearful of uncertainty. It is perceived that ECHA always considers the worst case as the likely case, which is unhelpful some of the time. This was not considered a barrier to changing the carcinogenic risk assessment in the UK, but an opportunity for UK to move away from this and focus on risk instead.

Question 8: What barriers are there for changing carcinogenic risk assessment in the UK?

- Harmonisation across markets for industry.

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

- Emotive subject for the general population.
- Risk appetite from government perspective.
- The benefits of industrial chemicals are harder to get across to the general public compared with, for example, pharmaceuticals.
- Possible conflicts between industry and regulators.
- Legal challenges to not using a hazard based approach to risk assessment.
- Need to increase engagement with regulators as they play a pivotal role.
- Need to increase education of regulators, i.e. increase knowledge about how assays are performed, and the uncertainties and variability related to the assays.
- Poorly conducted studies are being published – this is an issue with all journals.
- Regulators need educating in terms of new assays such as transcriptomics and how they can be used in risk assessment.
- Noted that some regulators are willing to be more flexible and accept new science.
- The Innovative Licensing and Access Pathway (ILAP) from the Medicines and Healthcare products Regulatory Agency (MHRA) was noted as a useful tool.
- Overall, there is a need to increase training, education and engagement of the regulator.
- The biggest barrier is the law; COC is supposed to advise on approaches to inform legislation. However, the Committee has no influence over ECHA, which is an issue. The suggestion of forming another global partner chemicals agency would definitely help overcome this, as establishing a common approach, global partners would prompt ECHA to alter their regulations to match what is happening globally. COC would not implement new tests, but advise on a new approach and specifically new guidance on the weight of evidence approach. Global harmonisation on this approach would afford the UK influence over ECHA's legislation for fear of falling behind.
- Barriers are regulatory. There is also a lack of harmonisation both globally and within the UK on how risk assessment is carried out, which can lead to different conclusions being drawn.
- A harmonised scheme would help industry as currently there are a number of different submissions to handle. Constructive discussions are vital.
- Barriers may be exaggerated, as the UK has the chance to look at carcinogenic risk assessment from a fresh perspective.

Question 9. What concrete next steps can be taken?

- Move to risk-based type approach in small steps to help with acceptance.
- Collect data from shorter-term assays alongside that from the 2-year bioassay, so that an evidence base is built up.
- Better quantitative exposure information is needed.
- Better absorption, distribution, metabolism and excretion (ADME) information would be of benefit as physiologically based pharmacokinetic (PBPK) modelling is not a trivial undertaking.
- Communication to the general public across all areas should be transparent and understandable. This includes narrative labelling/carcinogen classification.
- There is a need to define the 'problem statement' i.e., what are we trying to achieve? This may be different between sectors, so involvement of COM and COT would be beneficial.
- Could COC take a lead in facilitating discussions between different contributors to define what the best science is and identify resources required?

Key concerns around WoE, validation, communication, and knowing what we have available were identified across all breakout groups.

Consideration of over-arching theme questions

What opportunities are there to improve carcinogenic risk assessment in the UK?

- It was considered that there is an opportunity to improve the way in which chemicals are assessed for carcinogenic risk in the UK.
- Better communication to the public about risk assessment is needed, potentially with more relatable analogies for conveying risk.
- An internationally agreed definition of what we mean by WoE is key. This could be an OECD document.

What is the future of the 2-year / lifetime rodent bioassay?

- We can do better, but can't replace it until we have something else in place.

Next Steps

- COC will address how a new approach can be adopted and deployed and the resources needed for this.

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

- The discussion will continue through the British Toxicology Society (BTS) to help engage young toxicologists.
- Engagement with bodies such as People for the Ethical Treatment of Animals (PETA), as animal use will be key in supporting the argument to move away from the 2-year bioassay.
- Engagement with COM in the first instance to keep the focus on carcinogenicity and then COT.
- Find out what is happening internationally to see if it may complement any new approaches from the UK.

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

CC/2024/01 Annex C

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

**COC workshops follow up – proposal for new guidance
statement**

Draft summary of November 2023 workshop

This paper will be attached. It will not be made publicly available until the presenters have had opportunity to review the summary of their presentations.

Secretariat

March 2024

COC Workshop 16th November 2023 – draft summary

If we can't use animal data, what can we do?

How is carcinogenicity assessed in the cosmetics and personal care industry?

Aims and Objectives

This was a second workshop to further consider and determine what definitive steps can be undertaken to make progress that could support improvement to the chemical risk assessment process and regulatory requirements for carcinogenicity, based on research undertaken over the last 10-20 years.

This workshop follows workshop 1 held in November 2022 which considered these issues in the context of pesticides; this session focussed on the advances in risk assessment in the context of cosmetics and personal care industry.

Presentations

Key take-aways from Workshop #1: November 2022 – Ruth Dempsey, COC and Science Speaks

Ruth Dempsey summarised the key points from the first workshop focussing on pesticides which included: noting the opportunities with development of UK REACH, the likely need for a stepwise approach as new methodologies are available to be applied and ensuring public confidence, and recognising the need for international harmonisation for weight of evidence.

Cosmetics Regulations – A GB perspective – Frances Hill, Office for Product Safety and Standards (OPSS)

Frances Hill gave a summary of the current approach and responsibilities of industry with respect to cosmetic safety assessments. It was noted that much of the UK approach draws on the SCCS (EU Scientific Committee on Consumer Safety) notes of guidance, and that any compound classified as a carcinogen, mutagen or reproductive toxicant under GB-CLP (classification, labelling and packaging legislation) is excluded from use in cosmetic products unless a derogation is granted by the Secretary of State. It was also noted that OPSS is part of a cross-Government group on embedding new approach methodologies (NAMs).

Perspective and learnings from the cosmetics industry – Emma Meredith, Cosmetic, Toiletry and Perfumery Association Limited (CTPA)

Emma Meredith summarised the actions within the industry as animal testing for cosmetic products have been banned in the UK and EU as part of a series of rolling testing and marketing bans since 2004.

Industry has a number of validated alternative methods available for a number of endpoints, however for others including repeated dose and acute inhalation toxicity there is no specific NAM alternative. It is likely that combinations of tests and approaches are required for more complex systemic toxicity endpoints. There also are challenges with respect to regulatory acceptance, refinements and standardisation of methods and education.

A number of solutions were suggested to aid regulatory acceptance, including highlighting that NAMs are not a direct mimic of endpoints from animal studies, promoting a focus on risk and exposure rather than hazard, using case studies and sharing learning to facilitate dialogue between industry and regulators.

Experience of using NGRA for consumer safety decision-making and reflections on carcinogenicity – Dr Carl Westmoreland, Unilever

Carl Westmoreland described approaches adopted to ensure safety without animal testing. These include: using all available data on the ingredient such as clinical or epidemiological data, exposure-based waiving such as threshold of toxicological concern, read across, history of safe use and next generation risk assessment (NGRA). With NGRA there is a paradigm shift to protection of health rather than prediction of adverse effects, and using NAMs to ensure chemical exposures do not cause harm to consumers.

Learnings were also provided from the area of developmental and reproductive endpoints to consider potential biomarkers associated with these endpoints and how NGRA may be used in this area. Given the complex endpoints, there are likely to be similarities with potential for substances to cause carcinogenicity in terms of needs for development in the approaches used.

The last mile: achieving a new paradigm for carcinogenicity assessment – Dr Gina Hilton, PETA Science Consortium International

Gina Hilton explored the need to normalise new approaches in carcinogenicity assessments, flagged work in the Rethinking chronic toxicity and Carcinogenicity Assessment for Agrochemicals Project (ReCAAP), and subsequent development of an integrated approach to testing and assessment (IATA) submitted to the OECD.

A key element of the ReCAAP project was developing risk estimates or points of departure to support risk assessment based on interpretation of the available data on the substance in question.

A number of challenges were presented in regulators consideration of the data packages presented in particular in terms of sufficiency of data, need for further guidance on read across and steps made on this, and in particular continuing exploration of case studies to aid a 'learning by doing' strategy.

Discussion group questions and themes

Overarching theme questions:

1. What opportunities are there to improve carcinogenic risk assessment in the UK?
2. What is the future of carcinogenicity assessment?

Discussion group questions:

3. Should carcinogens still be a special case for risk assessment?
4. How do we assess the level of risk of cancer associated with exposure to a chemical?
5. How can exposure-response concepts and different degrees of carcinogenic risk be more effectively communicated to the public?
6. How do we use new approach methodologies to improve cancer risk assessment?
7. What opportunities do the Cosmetic Regulations offer for the evolution of carcinogenic risk assessment in general in the UK?

Questions for all groups:

8. What barriers are there for changing carcinogenic risk assessment in the UK?
9. What concrete next steps can be taken?
10. What is expected from CoC to facilitate future evolution of carcinogenic risk assessment for the UK?

The following section captures key responses from the breakout groups and plenary discussion to each of the questions posed.

Question 1 – What opportunities are there to improve carcinogenic risk assessment in the UK?

- There is an opportunity to use an existing data package with the carcinogenicity animal testing data removed, followed by re-assessment of the remaining data and an evaluation of whether the same conclusion regarding carcinogenic is reached (i.e. in the absence of the 2 year bioassay).

Question 2 – What is the future of carcinogenicity assessment?

- Need to consider underlying biology resulting in cancer.

This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

- Moving to humanised alternative methods rather than animal testing.
- Animal testing should not be used as a gold standard against which to compare NAMs data – need to disconnect risk from the animal data.
- Important to consider data quality, and whether studies are conducted to appropriate guidelines.

Question 3 – Should carcinogens still be a special case for risk assessment?

- From a scientific perspective, carcinogens are not necessarily a special case for risk assessment. All substances go through risk assessment, but challenges with link to carcinogenicity.
- Recognise there is a public perception of concern over cancer, as well as mutagenicity and reproductive toxicity, so there is low tolerance in the risk assessment if there is potential for substances to be considered as having these risks.
- Carcinogenicity, Mutagenicity and Reproductive (CMR) endpoints are important to allow correct labelling of products – but could be challenging to identify with more to other approaches – noted that only CMR2 category chemicals may be used in cosmetics not CMR1A or CMR1B.

Question 4 – How do we assess the level of risk of cancer associated with exposure to a chemical?

- Margin of safety estimates obtained using NAMs data are likely to be the greatest for cosmetic products due to the low level of systemic exposure obtained from applying cosmetics. This may not be as robust a risk estimate for chemicals with higher levels of systemic exposure, such as pesticides.

Question 5 – How can exposure-response concepts and different degrees of carcinogenic risk be more effectively communicated to the public?

- Working together on public communication, between policy makers and scientists.
- Better messaging from regulators, politicians and doctors on assurance of 'safety' and margins of exposure – also consider risk-benefit.
- Considering options for responsible 'influencers' on e.g. safety certification and how much product are they using each day or for food supplements supporting sticking to recommended maximum doses to avoid concern over exceedance.
- Exploring digital labelling, with the option to provide information but recognise that uptake of information may depend on individuals using products.
- Recognise public perception and desire for choice.
- Challenge of binary classification - carcinogenic or not – in practice want to prevent chronic adverse risk.

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- Consider proactive communications on COC guidance and evaluate engagement with relevant media outlets.

Question 6 – How do we use new approach methodologies to improve cancer risk assessment?

- What is meant by 'improve'? It could be taken to mean being more protective rather than predictive, using less or no animals, getting the assay to be more reflective of humans, or being quicker and cheaper to run.
- Tier 1 approach of NAMs gives greater coverage of biological effects and exposure modelling is an important and strong component of this - in contrast to the exposure component of traditional risk assessment which is often weak or missing.
- Many of the biomarkers included in Tier 1 are relevant to carcinogenicity - need to understand if any biomarkers are missing but it is Tier 2 that provides greater focus on specific endpoints. Tier 1 biomarkers need to be broad to give reassurance that key toxicities are not being missed.
- There is a need for the validation of NAMs.
- A new methodology framework would be a weight of evidence approach in an OECD guideline(s) / OECD style guideline, and utilise COT road map.

Question 7 – What opportunities do the Cosmetic Regulations offer for the evolution of carcinogenic risk assessment in general in the UK?

- The cosmetic industry has made substantial changes to testing as a result of regulatory pressure, however, we do not currently know if the new ways of evaluating carcinogenicity are as 'good'.
- Potential to act as a proof of concept for other sectors.
- It was noted that innovation in terms of the use of new ingredients/chemicals in cosmetic products may have been stifled by the inability to carry out animal testing. This may have greater impact on other sectors where chemical innovation is greater.

Question 8 – What barriers are there for changing carcinogenic risk assessment in the UK?

- Regulators need support and training to understand new data.
- Barriers include difficulty in trust of new methods, may be perceived as too complicated, reluctance to change to new assays, reputational damage if key endpoints are missed and lack of funding to ensure applicability of assays.
- Published case studies are important to build confidence in the use of NAMs.
- Challenge of harmonisation and global data requirements for chemicals under different regulatory regimes.

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- Need to bring together people with a range of different specialities to make the assessment especially as we move towards new approaches, and facilitate discussions between groups of people who have different backgrounds especially in new disciplines that supports toxicology.

Question 9 – What concrete next steps can be taken?

- Use of IATA could be key step to help change.
- Definition of the minimal in vitro data set is needed.
- Need to take action rather than continuing discussion.

Question 10 – What is expected from CoC to facilitate future evolution of carcinogenic risk assessment for the UK?

- The COC could drive education, publish guidance, offer training and co-ordination.
- COC could support bring industry and regulators together to make progress.

Other key points

- Challenge with respect to who pays for validation, training and data generation for NAMs.
- Important to learn from activities from across the world
- For risk assessment aim is to derive points of departure to be health protective rather than predicting specific tumours.
- Would be helpful to bring together UK chemical expertise, e.g. committees and Government Departments and Agencies, to make progress.
- Develop milestones and deliverables for next steps.