Director’s response to the Nutrition and Metabolism (NME) Branch Review

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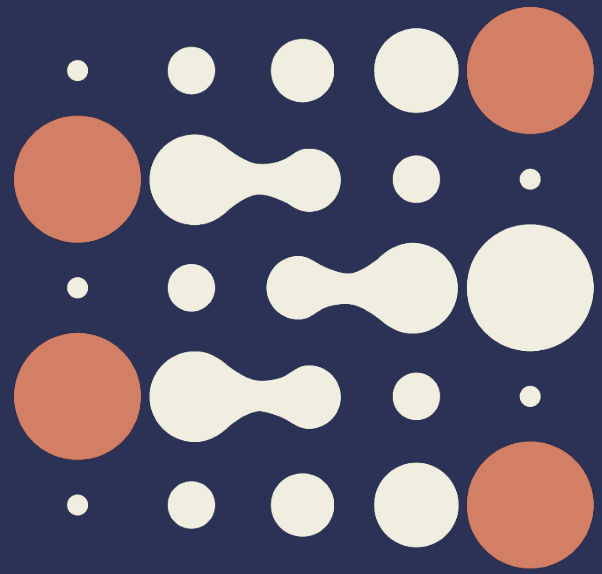
International Agency for Research on Cancer
World Health Organization



OVERALL RECOMMENDATIONS FOR NME

The RP is immensely impressed by NME's innovative and productive research programmes, the state-of-the-art laboratory facilities and statistical methods, and collaborative and supportive research environment. It strongly supports NME's exceptional molecular and nutrition epidemiologic research integrating metabolomics, hormone measurements and genomics within population studies.

Response:

- We thank the RP for their constructive and supportive comments.
- No response required.

Review panel scientific recommendations

1. The RP strongly supports NME's continued leadership role in maintaining and upgrading the research infrastructure for population-based studies, especially the centralization of EPIC data on diet, lifestyle, and cancer and other disease endpoints as well as sample replenishment for cancer cases where the biosamples have been depleted in a timely manner.

The RP recommends the continued collection and centralization of repeated measures of diet and lifestyle factors during the long-term follow-up and the use of repeated measures to correct for measurement errors in self-reported and biological variables.

Review panel scientific recommendations

Response recommendation 1:

- Substantial progress with the signature of Collaborative Research Agreements (CRA) with various EPIC centers.
- Several essential data transfers foreseen in the next months, including:

(i) the centralization of cancer endpoints and vital status (initiated in the second half of 2023),

(ii) the centralization of dietary assessments collected during follow-up,

(iii) the continuous centralization of lifestyle measurements,

(iv) the replenishment of samples for the EPIC biological bank, in collaboration with the Laboratory Services and Biobank (LSB) group

Review panel scientific recommendations

2. The RP strongly supports NME's ongoing projects on metabolomics and other omics (proteomics), nutrition, and cancer risk. This line of research is in the early stage and many of the findings are yet to be replicated. Thus, the RP recommends that the Branch carefully consider appropriate study designs, enlarging sample sizes especially for rare cancers, the inclusion of both internal and external replication samples, and application of the state-of-the-art high-dimensional data analytic techniques.

The current in-house metabolomics platform has been instrumental for the Branch's research programmes. The RP recommends the Branch to evaluate the long-term sustainability of the in-house metabolomics platform. The metabolomics laboratory is currently extremely well-funded and very well operated. However, in the long run, the Branch needs to explore how to best fund the acquisition of new equipment and the operation of an in-house metabolomics platform and consider the possibility, in the future, of partnering with outside metabolomics facilities to conduct metabolomics analysis of stored biospecimen. It is important to weigh the pros and cons of maintaining the in-house metabolomics platform vs outsourcing samples to a core facility in terms of costs and scientific values. It is also important to note that this work in-house is funded through external funds and therefore outsourcing would not affect the Agency's regular budget.

Review panel scientific recommendations

Response recommendation 2:

- NME has further strengthened a long-term strategy for projects on metabolomics:

❑ Enhancement of collaborations for the provision of research resources, including data and biospecimens from comparable study designs to enhance statistical power, particularly for rarer cancers

❑ Investment in NME laboratories has been instrumental to build strong collaborative networks:

➢ Acquisition of metabolomics profiles from large numbers of study samples from international collaborations,

➢ Reinforcement of NME-led research on metabolomics and cancer:

✓ A cohort consortium-based collaboration on the etiology of biliary tract cancers

✓ The DISCERN study to understand the causes of renal, pancreatic, and colorectal cancers in Europe (including replication samples)

Review panel scientific recommendations

Response recommendation 2:

- ❑ Added value of an in-house metabolomics laboratory (rising costs of outsourcing laboratory analysis, issues related to shipping biological samples biobanked at IARC): **efficient and cost-effective pilot studies performed**
- ❑ Regular assessment of the pros and cons of maintaining a competitive in-house metabolomics platform vs. outsourcing

- Medium- to long-term perspectives:

- ❑ Identify priority research areas, enrich collaborative networks, and build complementary expertise
- ❑ Continue to monitor the long-term sustainability of the lab (major external funding, competitiveness of its metabolomics platforms)
- ❑ Ensure to meet the large profiling work:
- ➢ Technical staff: P1 scientist position and LY4 research assistant are currently being recruited; One research assistant (RB) fully working on untargeted metabolomics

Review panel scientific recommendations

3. The RP supports NME's new large-scale initiative on proteomics of cancer through collaboration with an industrial partner (Somalogic). The RP encourages the Branch to seek other industrial partners for other biomarker analyses including metabolomics, lipidomics, genomics and epigenetics (complying with IARC's policies around engaging with the private sector).

Review panel scientific recommendations

Response recommendation 3:

- ❑ Acquisition of an increasing volume of molecular data remains a priority for NME.
- ❑ Seeking future opportunities to generate additional molecular data for EPIC, in accordance with IARC policies on engagement with the private sector and with other EPIC collaborating Institutes.
- ❑ Setting up of an NME Olink machine for proteomics analyses, allowing for more comprehensive studies of the exposome and its role in cancer etiology, within and beyond the EPIC study.

Review panel scientific recommendations

4. The RP supports NME's leadership role in multiple international consortia of diet, metabolomics, and cancer risk (including the NCI cohort consortium; Diet and Cancer Pooling Project at Harvard; COnsortium of METabolomics Studies (COMETS)). These consortia are especially important for the studies of rare cancer endpoints such as early-onset colorectal cancer, liver cancer, and triple negative breast cancer. The RP recommends the Branch to take more leadership roles in individual cancer endpoints and carefully consider sufficient sample sizes and statistical power for multiple omics analyses, gene-diet interactions, MR analyses, and subgroup analyses by age and tumour subtypes.

Review panel scientific recommendations

Response recommendation 4:

- ❑ NME actively involved in consortia, leveraging sufficient large sample size for appropriate statistical power
- ❑ Leading role in the NCI Cohort Consortium: alcohol and cancer and early-onset colorectal cancer (leaders Drs. P. Ferrari and N. Murphy)
- ❑ Partners in various consortia:
- ✓ Biliary Tract Cancer Pooling Project (BiTCaPP)
- ✓ COMETS
- ✓ "EULAT Eradicate GBC" project
- ✓ Pooling Project on Diet and Cancer
- ✓ Premenopausal Breast Cancer Collaboration
- ✓ Asia Cohort Consortium https://www.asiacohort.org/

Review panel scientific recommendations

5. The RP supports NME's current projects on diet, lifestyle, and cancer survival in EPIC and other large cohorts. Because few consortia for cancer survivors are existing, the RP recommends the Branch to participate or initiate consortia for cancer survivors, similar to the consortia for cancer incidence.

Review panel scientific recommendations

Response recommendation 5:

- ❑ Ongoing design of such cancer survival studies in collaboration with the National Cancer Center Japan, in which prospective data from European (i.e., EPIC, UK Biobank) and Japanese (i.e., the Japan Public Health Center-based prospective study, JPHC and JPHC-NEXT studies) will be leveraged.
- ❑ Seeking external funding to initiate these promising studies.

Review panel scientific recommendations

6. The RP supports the research on multimorbidity and cardiometabolic comorbidities and recommends the NME to expand studies by taking advantage of already existing resources and real-world databases elsewhere. The RP recommends that NME carefully consider the complexities of conducting this line of research including reverse causation, influence by treatments, survival bias, and missing data in real-word databases.

Review panel scientific recommendations

Response recommendation 6:

- ❑ Enhancement of the NME strategic vision on multimorbidity by expanding the research network to integrate additional existing resources and real-world databases.
- ❑ Discussions initiated with scientists from the Republic of Korea to establish a collaboration involving the use of a Korean real-world database.
- ❑ To address the challenges of conducting multimorbidity research, a methodological investment will be made to address potential issues in analyses of cancer survival related to survival bias, lack of cancer treatment, and missing data.
- ❑ Successful implementation of a multilevel time raster multiple imputation approach to BMI:
  - ➢ Longer duration, greater degree, and younger age of onset of overweight and obesity during early adulthood positively associated with the risk of 18 cancers in a real-world database of 2.6 million Catalan adults https://www.nature.com/articles/s41467-023-39282-y#Sec5

Review panel scientific recommendations

7. The RP recommends that NME carefully evaluate whether conducting lifestyle intervention trials is a high priority research area for the Branch given the high cost and complexity of conducting these trials especially in the context of cancer prevention. Given the limited financial and professional resources and high burden of the NME research staff, the RP considers this line of research a lower priority compared to other lines of research within the Branch.

Review panel scientific recommendations

Response recommendation 7:

- ❑ Intervention studies are of lower priority within NME due to their high cost and complexity
- ❑ NME will continue to develop and leverage the LIFE-SCREEN intervention study (funded by the French INCa):
  - ➢ Low cost
  - ➢ Useful information on patients' implementing lifestyle changes
- ❑ NME will rely on existing collaborations with Institutes that developed *ad hoc* expertise in the field.
  - ➢ the Women Alcohol Study (replication of our biomarker discovery study on alcohol intake).

Review panel scientific recommendations

8. The RP recommends the NME to integrate the Precision Nutrition framework within its ongoing and future projects, in line with the framework that has been embraced by NIH and many academic institutions worldwide. The goals of precision nutrition are to improve dietary assessment methods, develop omics biomarkers for diet and disease risk, and develop computer algorithms for personalized nutrition strategies to improve diet quality and health outcomes.

Review panel scientific recommendations

Response recommendation 8:

- Several ongoing projects led by NME scientists, including MeDiCa (WCRF, 2022) and DISCERN (EU, 2022), target the identification of metabolic biomarkers and signatures of dietary exposures
- NME objectives:
  - to use data from dietary intervention studies to further assess individual metabolic responses to changes in their diet
  - to assess the relevance of our results for precision nutrition.
  - To optimize dietary assessment methods to be used in epidemiological studies, accounting for the level of detail required for precision nutrition.
- Development of a pilot study to evaluate food frequency questionnaires to assess dietary intakes among children with cancer on a global scale. The questionnaires were standardized and allowed some tailoring to local contexts for the identification of food specificities.

Review panel scientific recommendations

9. The RP recommends that NME enhance its efforts to conduct validation studies of novel dietary indices such as NOVA classifications of processed foods, food diversity, planetary impact of dietary patterns, and various dietary quality indices. The Agency should consider providing pilot grants to support the validation studies.

Review panel scientific recommendations

Response recommendation 9:

❑ Validation of dietary assessment methods and novel dietary indices through comparison with reference methods and biological markers:

- Stronger correlations between dietary and plasma phospholipid for n-3 PUFA (r= 0.41 for 22:6n-3, DHA) and for industrial *trans* fatty acids (r= 0.479 for 18:1n-9 *trans*, elaidic acid)[1]
- The UPF pattern, as defined based on the NOVA classification (group 4;% kcal/day) positively associated with blood levels of industrial elaidic acid (r=0.54) and 4-methyl syringol sulfate (r = 0.43).
- Associations for the other 3 Nova groups with these food processing biomarkers were either inverse or non-significant[2].
- Unfortunately, resource mobilization for this type of validation work can be challenging

[1]https://pubmed.ncbi.nlm.nih.gov/37686727/; [2]https://pubmed.ncbi.nlm.nih.gov/36590209/

Review panel scientific recommendations

10. The RP strongly supports NME's efforts to develop new statistical methods for metabolomics data harmonization and multi-omics analyses. More work is needed to improve methods for MR analyses of dietary and lifestyle factors where genetic instruments are relatively weak, mediational analyses of complex biological pathways, measurement error analyses of self-reported diets, and high-dimensional data analyses that integrating diet and lifestyle factors with multi-omics data.

Review panel scientific recommendations

Response recommendation 10:

- ❑ New approaches for the pre-processing and statistical analysis of omics data (epigenetic, GWAS, metabolomics, proteomics, etc.) for their use in cancer epidemiology studies.
- ❑ New approaches using cutting-edge machine learning algorithms, such as a new method based on ‘optimal transport’ for the automatic alignment of untargeted metabolomics data acquired in different studies and methods
  - ➢ The technique is based on the data shared lasso to conduct pan-cancer analyses of pre-diagnostic metabolite blood levels
- ❑ Enhanced collaboration with worldwide experts of machine learning and artificial intelligence, Mendelian Randomization and causal inference to maintain a state-of-the-art toolbox of statistical methods

Review panel scientific recommendations

11. NME is to be commended for its work in LMICs. Given its independent and impartial authority on carcinogenicity, IARC is uniquely positioned to initiate and conduct research, and contribute to capacity building in these countries. The RP recognizes the challenges in securing funding for large-scale studies in these countries. The case-control studies conducted to date, while being small and subject to biases, can nevertheless provide useful preliminary data which are essential to secure funding for prospective studies. They are also valuable for understanding the logistics for the successful implementation of projects in those areas. Ideally, LMIC-based studies would be coordinated and funded at the Agency level.

Review panel scientific recommendations

Response recommendation 11:

- ❑ Successful setting up of epidemiological studies in Africa, Latin America and in Asia
  - ➢ Recruitment of subjects still on-going for the PRECAMA study in Latin America, and new recruitment centres will soon be joining (eg. new centres in Brazil),
  - ➢ Fourteen manuscripts already published from all our studies in LMICs
- ❑ Progress in strengthening collaboration with the Confluence project:
  - ➢ Large world-wide international consortium on breast cancer coordinated by the NCI
  - ➢ Participation of samples from Brazil and Morocco, making substantial contributions for future genetic studies in under-represented populations.
- ❑ Analysis of the NICHE pilot data
- ❑ Launch of the global childhood cancer cohort with IIPAN
- ❑ NICHE foresees gradual scaling-up in additional LMICs in the coming 5 years

Review panel managerial recommendations

1. The RP considers that it is critical that the senior scientist position becoming vacant following the departure of Dr Gunter (Branch Head) in January 2023 (or that of Dr Ferrari if he takes on this position after the interim) be maintained through IARC core funding. The search process for hiring a new senior scientist should be initiated in a timely fashion to fill the upcoming vacancy. It is essential that the transition does not result in a net loss of a senior position within NME, whose outstanding leadership relies significantly but not only on its capacity to attract external funding.

Review panel managerial recommendations

Response recommendation 1:

- ❑ The position of NME Branch Head has been advertised in August (Dr P. Ferrari Acting Branch Head)
  - ➢ The recruitment process is currently ongoing
- ❑ NME leadership is counting on the fact that senior positions within NME will not be lost

Review panel managerial recommendations

2. The RP is deeply concerned about the loss of 4 professional staff (including 2 senior scientists) during the review period. To maintain NME's cutting-edge research in the field of nutrition and omics, the RP recommends that IARC maintain the expertise in metabolomics and high-dimensional data analyses to keep the high quality of research in the Branch.

Review panel managerial recommendations

Response recommendation 2:

- ❑ NME able to move one laboratory research assistant to the IARC regular budget
- ❑ New scientist position at the P1 level on metabolomics (external budget), with funding visibility for two years

Review panel managerial recommendations

3. Funding uncertainties has put a serious strain on Branch personnel. The RP suggests that, if possible, the Agency provides a portion of hard money support (e.g. 10% or more) for the Team leaders or PIs who are spending substantial amount of time writing grants. This is common practice in other leading institutions.

Review panel managerial recommendations

Response recommendation 3:

- ❑ Four team leaders at the P2 level currently have 100% of their position covered by external funds, mostly through obtention of competitive grants
- ❑ This process is clearly not efficient and time consuming
- ❑ Should any regular budget funds become available within the 2024-2025 biennium, financial support to these positions will be a priority

Review panel managerial recommendations

4. The RP recommends that students and postdoctoral fellows be given the opportunity to develop abilities in grant writing, mentoring and teaching in preparation for their future careers.

Review panel managerial recommendations

Response recommendation 4:

- ❑ Opportunities to contribute to the writing of grant applications and to participate in the mentoring of junior colleagues, such as term Masters' level students
- ❑ The IARC Research Training and Fellowship Programme's Postdoctoral Charter: (https://www.iarc.who.int/news-events/launch-of-the-iarc-postdoctoral-fellowship-charter/)
  - ➢ promotes early career scientists to be involved in teaching opportunities ranging from assisting in the IARC Epidemiology Summer School to external teaching, lecturing activities (may even be renumerated)
- ❑ NME will continue to actively encourage these activities by early career scientists

Review panels managerial recommendations

5. The RP encourages NME to maintain gender diversity in the leading positions in the Branch.

Review panel managerial recommendations

Response recommendation 5:

- ❑ NME firmly committed to all the principles of Equity, Diversity and Inclusion at IARC (https://www.iarc.who.int/equity-diversity-and-inclusion-at-iarc/)
- ❑ NME will make every effort to maintain and promote diversity, including gender diversity, in its leadership and general composition

Thank you

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