AOP 272 - Nuclear Energy Agency Committee of Radiological Protection and Public Health (NEA CRPPH) Review (31 August – 30 September 2022) and responses from AOP author:

COMMENT: For me, one of the major interests of the AOP approach is to integrate the results of biology and epidemiology. But for this, it seems to me that it would have been good to include an epidemiologist specialised in ionising radiation and lung cancer in the group. I think that this would have allowed a better consideration of the epidemiological aspects in the document. This should certainly help the acceptance of the AO results in the end by the epidemiological community.

RESPONSE: Within the Strategy section of the overall assessment (pg 14), we have now added the following statement to reflect the above concern:

The current version of this AOP was developed by a team of researchers with backgrounds primarily in AOP development, carcinogenesis, radiobiology, radiation physics and biomolecular epidemiology. However, due to the importance of radiation epidemiology in the international radiological protection system and its underlying assumptions, it seems essential to strengthen the epidemiological aspects of this AOP, a specific area of future improvement.

COMMENT: As I have already said, I think that the context for the development of AO in the field of radiation is very different from that of chemicals, in that many results from epidemiology are available. This is particularly true for lung cancer. The epidemiological literature on the subject is very rich, both for external exposures and for internal contamination. The literature on external exposures is not limited to the cohort of survivors of the Japanese atomic bombings. Results from cohorts of workers exposed to external or internal radiation (for example contamination by plutonium) exist. And for internal exposure to radon, many studies have been carried out on cohorts of miners, in addition to studies in the general population. The review seems to have been focused on general population data in this document, but this choice excludes a whole part of the literature which nevertheless provides relevant evidence for the risk of radiation-induced lung cancer. I don't think we can say, as stated on page 25, that "all relevant publications were considered". Also, several major reports in the field could have been considered (e.g. ICRP Pub 115 2010, UNSCEAR 2019...).

RESPONSE: The KER MIE to AO provides evidence of literature on risk of radiation induced lung cancer. In this section, we have highlighted studies using in vitro, in vivo and human cohorts including biologically based models. Nonetheless, we have now added ICRP 2010 and UNSCEAR, 2019 to the list of references supporting the MIE to AO KER as follows pg 178:

“There is a vast number of reviews that provide evidence of this association (Axelson 1995; Jostes 1996; NRC 1999; Kendall and Smith 2002; Al-Zoughool and Krewski 2009; Robertson et al. 2013; Sheen et al. 2016; Chadwick, 2017; ICRP 2010; UNSCEAR 2019).

We have also revised the sentence of concern related to relevant publications to read “For each of the KERs listed above, all relevant publications **from those used to support the AOP** were considered for quantification.” Pg 26

COMMENT: The calculation of the lung dose from alpha emitters is subject to large uncertainties. Most epidemiological analyses of lung cancer risk and radon have used exposure indicators that are generally

expressed in terms of concentration (Bq/m3) or exposure (WLM). Comparison of these results with those of external exposure in mGy, as done in this report, do not take into account the biological effectiveness of alpha emitters, and must be considered very cautiously.

RESPONSE: To clarify this concern we have added the following sentence to the overall assessment pg 26: "The quantification of these four key event relationships (KERs) from this AOP has been completed as detailed in Stainforth et al., 2020. (Robert Stainforth, Jan Schuemann, Aimee L. McNamara, Ruth C. Wilkins & Vinita Chauhan (2021) Challenges in the quantification approach to a radiation relevant adverse outcome pathway for lung cancer, International Journal of Radiation Biology, 97:1, 85-101, DOI: 10.1080/09553002.2020.1820096)

Briefly, the dose in Gy for epidemiological studies were derived as follows: *Values of equivalent dose (Sv) were converted to absorbed dose (Gy) using the relevant radiation weighting factors defined by the International Commission of Radiological Protection (ICRP 2007). Radon exposure of the lungs reported in units of working level months (WLM) were converted to estimates of absorbed dose by using the recommended ICRP effective dose coefficient for mine and general indoor environments (=10 mSv/WLM; ICRP 2017), tissue weighting factor (=0.12 for the lungs), and radiation weighting factor (=20 for alpha-particles; ICRP 2007). Studies contributing to the WoE of NAd-KER7 were predominantly from occupational cohorts of miners that only provide a summary on the average career-span of a worker, and any lag-period, if any, following the end of employment for which a RR of lung cancer was assessed. In these cases, missing values of the dose rate were estimated as the ratio of the average dose and career-span. The exposure was therefore assumed chronic and constant. The time after exposure was estimated as the average career-span in addition to any lag-period following employment. Missing dose rate values for studies contributing to the upstream KEs forAd-KER1, NAd-KER1, and NAd-KER2 could not be estimated using the same assumption as the nature of the radiation exposure in these studies was often acute.*

COMMENT: The global formalisation of the steps between the MIE and the AO retained in this AO appears to be relatively simple (as illustrated on page 11), and ultimately quite similar to that of the mechanistic models developed for lung cancer (in particular the TSCE models). But it seems to me that the consideration of these mechanistic models, which have been the subject of numerous publications in the literature, could have been more important. Indeed, many articles do not seem to have been considered in this report (see for example Zaballa 2016, Xu 2013, Eidemuller 2012, Foy 2012, Heidenreich 2012, Jacob 2007, Hazelton 2006, Brugmans 2004, Heidenreich 2000…).

RESPONSE: Biologically based pathways were considered in the AOP, there are relevant papers highlighted within the report as follows:

Pg 177"Biologically based mechanistic models of carcinogenesis have been developed that describe the complex process of maliginancy (Ruhme et al.2017, Luebeck et al. 1999). We also cite the Gilbert and al review (2009) which discusses the three cellular steps to cancer: initiation, promotion and progression. In addition to these we have now added the suggested studies, however, the addition of these papers will not change the overall WOE call for our quantitative understanding of the AOP.

We have added the above papers as follows:

Biologically based mechanistic models of carcinogenesis have been developed that describe the complex process of maliginancy (Ruhme et al.2017; Luebeck et al. 1999; Zaballa 2016, Eidemuller 2012; Heidenreich 2012; Jacob 2007, Hazelton 2006; Brugmans 2004 and Heidenreich 2000)

COMMENT: The evidence used in the analysis of the relationship between MIE and AO is exclusively from epidemiology (except for "evidence for biological plausibility"), and mainly from radon exposures. Given the wealth of epidemiological literature on the subject, I am surprised that "evidence for empirical support" and "evidence for quantitative understanding" are considered to be only "moderate".

RESPONSE: Pg 179 the "Dose and Incidence" section of the MIE to AO KER there is evidence presented from in vitro studies, animal rat studies, simulation models and studies using non radon radiation stressors. In addition to these studies, we also provide evidence from human studies (indoor radon exposures and outdoor radon exposures) and cite a large systematic review (Rodriques-Martinez e al, 2018). These and other studies can be found in the annex and pgs 177-180.

The evidence for quantitative understanding is weighted moderate as there still remain considerable inconsistencies in findings as highlighted in the "inconsistency" section of the AOP MIE to AO KER. Overall, the change in lung cancer incidence cannot be ***precisely predicted*** based on a relevant measure of deposition of energy. There remains uncertainty in the quantitative prediction. Known modulating factors and feedback/feedforward mechanisms are not accounted for in the quantitative description, as availability of data is limited. Therefore, despite the wealth of epidemiological data our quantitative understanding of this relationship is moderate.

COMMENT: Some aspects such as the interaction with tobacco, the differences of risk estimates between males and females, or the variations in risk according to the histological type of the tumour would deserve more attention.

RESPONSE: We agree the highlighted interactions are important factors for consideration, as we expand the AOP in the future, appropriate evidence can be added. However, at the time of building the AOP, we noted limited evidence to suggest a strong sex-specific response to lung cancer. The following studies have been added to the modulating section of MIE to AO (pg 184).

- Kim et al., 2016: Proportion of lung cancer deaths induced by radon was slightly higher in females but after stratifying for smoking, the attributable risk of lung cancer death was similar between genders
- Narendran et al., 2019: Review analyzes sex differences of radiation response and generally found that radiosensitivity is higher in females. Also notably mentions that the excess relative risk for lung cancer was higher in females than males when workers were exposed to plutonium at the Mayak nuclear facility.
- Cahoon et al., 2017: Higher excess relative risk for lung cancer in females after Japanese atomic bomb exposure
- Ozasa et al., 2012: Also reports higher excess relative risk in females compared to males when analyzing atomic bomb survivors

Where appropriate, the relevance of data presented was also discussed in the context of histological type tumors, for example in the mutation to lung cancer section of the AOP, we highlight that mutational signatures can be identified to lung cancer sub-types and some of these signatures are shared. The availability of evidence to support delineations in mechanisms in the context of our proposed pathway for lung cancer subtypes is not clear.

In terms of tobacco smoke, this is a different class of stressor, with a different molecular initiating event from radiation and hence for any of the MIE to KEs relationships, studies using tobacco smoke are not considered. However, for other KERs, smoking is highlighted as a confounding/modulating factor (i.e smoking can influence double strand break fidelity, tobacco smoke can increase mutations, TP53 mutations are not associated with smoking, G to T conversions are more common in smokers, chromosomal aberrations in minors are not due to smoking status). Future AOPs can be developed specifically to consider the interactions of tobacco smoke with Radon.