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This is a copy of the original comment from UNSCEAR experts. Comment number is inserted for reference to Authors' response'.

Comments on Kato and Yamada paper 'Individual Dose Response and Radiation Origin of Childhood and Adolescent Thyroid Cancer in Fukushima, Japan'

The paper authors claimed that "Childhood and adolescent thyroid cancer in Fukushima was associated with individual external dose estimated in FHMS basic survey. Increased childhood and adolescent thyroid cancer in Fukushima could most probably be attributed to radiation exposure from the nuclear accident." Another point they claimed is determination of the risk coefficient for thyroid cancer based on partial incidence statistics and group assessment of thyroid doses published by UNSCEAR in its 2020/2021 Report, Annex B (see www.unscear.org). UNSCEAR experts have some substantial comments relevant both to dosimetry and epidemiological parts of the paper under consideration.

1. Dosimetry

Comment 1. The authors have taken the estimated external doses of 108,980 participants in the FHMS screening programme whose external doses in the first 4 months were estimated by FHMS (Akahane et al 2013) and correlated them with the thyroid doses for a 10-y old child estimated in the UNSCEAR 2020/2021 Report, annex B for the relevant municipality. They have then used the regression formula derived from this correlation to estimate thyroid doses corresponding to external dose ranges into which they have grouped 36 cases of cancer among the 108,980 participants (Table 1).

The methods and assumptions used in extracting doses from UNSCEAR 2020/2021 Report, annex B have resulted in significant differences between the thyroid doses presented in the paper as being UNSCEAR 2020/2021 Report doses and those actually presented in the UNSCEAR 2020/2021 report. For the non-evacuated municipalities, three in UNSCEAR 2020/2021 Report had average absorbed doses to the thyroid for a 10-y old child over 10 mGy and none were over 20 mGy. For the evacuation scenarios, the average absorbed dose to the thyroid for a 10-y old child is above 20 mGy in one scenario and above 10 mGy in 12 scenarios. The thyroid doses shown in Figure 1B of Kato et al (which are attributed to the UNSCEAR 2020/2021 report) indicate 8 cases where the thyroid dose is greater than 10 mGy and one where it is greater than 20 mGy. **The relationship between the doses presented in the UNSCEAR 2020/2021 Report and those shown in Figure 1B of the paper is not clear and needs to be clarified and justified.**

The authors refer to 59 municipalities in Fukushima prefecture. In the UNSCEAR 2020/2021 Report, doses were presented as population-weighted averages for 50 municipalities which were not evacuated and for 40 evacuation scenarios for 14 localities that were evacuated. The doses were also presented for the first year after the accident. **The general methods used by Kato et al to manipulate the doses presented in the UNSCEAR 2020/2021 report are not clear, and, in particular, how/if they have estimated doses for the municipalities that were evacuated from those presented for the 40 evacuation scenarios.**

The methods and assumptions used to obtain doses from those presented in the UNSCEAR 2020/2021 Report are likely to affect the regression formula the authors derive to estimate thyroid doses for the external dose groups into which they have divided the 36 cancer cases and 108,944 non-cancer cases and any conclusions subsequently made from Table 1. **The dashed lines in Figure 1A seem to represent the confidence intervals on relative risk (although they are not explained and seem to be absent from the <1 mSv dose group).**

C2 From a dosimetry viewpoint, the findings of Kato et al seem to be compromised by the following:

C21- apparent discrepancies in the data presented in Fig 1B (ostensibly derived from UNSCEAR 2020/2021 Report) and those in UNSCEAR 2020/2021 Report itself;

C22- there are large uncertainties associated with thyroid dose estimation, in particular at lower doses where according to UNSCEAR the largest contribution is from ingestion and the assumption is that the whole of Fukushima Prefecture received the same dose. Not clear if the uncertainties in dose have been taken account of in confidence limits of risk estimates;

C23- under Table 1 there is an arbitrary assumption that "The mean doses of the first two groups (<1 mSv and 1–2 mSv) were assumed to be 0.5 mSv and 1.5 mSv..." without any justification of those numbers;

C24- the ratio used for conversion of external dose to thyroid dose did not account for substantial age dependence of thyroid dose, which is another uncertainty factor.

2. Epidemiology

C3. The paper derives an unbelievable ERR/Gy estimate of 213 (95% CI 129, 297) (top of KY pg. 3) based on only 36 thyroid cancer cases. The implausibility of this estimate is seen by comparison with estimates from high-quality studies of other populations: of Chernobyl studies, an ERR/Gy in Ukraine [Tronko, 2006] of 5.25 (95% CI 1.70, 27.5, n= 45 thyroid cancers) and an ERR/Gy in Belarus [Zablotska, 2011] of 2.15 (95% CI 0.81, 5.47, n= 85 thyroid cancers). A combined study of 9 populations exposed to external radiation at thyroid doses under 100 mGy [Lubin, 2017] yielded an ERR/Gy of 9.6 (95% CI 3.7, 17.0, n=184 thyroid cancers). It is notable that the central estimates of risk were 5.25, 2.15 and 9.6, respectively in these studies, in comparison to the Kato and Yamada's estimate of 213. Furthermore, the upper confidence bounds in these studies were all far below KY's ERR/Gy estimate of risk of 213, and even far below Kato and Yamada's lower confidence bound of 129.

C4. Unfortunately, Kato and Yamada's description of methods provides too little information to fully determine how the authors derived their results. Kato and Yamada indicate they used "linear regression" to estimate risk, but did not state what was meant by "linear regression." In whatever way they conducted the regression analysis, the results are questionable.

C5. Inaccuracies may be especially pronounced because the analysis was based on only a small number of thyroid cancers (e.g., only 5 cases with estimated doses of 2 mSv or more) and low doses. Their estimated confidence bounds (129 and 297) differed from the central estimate of 213) by less than a factor of 2, which lacks plausibility, since the confidence bounds for other major, high-quality studies of radiation and thyroid cancer risk [Tronko 2006; Brenner 2011; Zablotska 2011; Lubin 2017] mostly showed CI that differed from their central estimates by more than a factor of 2, even though the other studies had larger numbers of thyroid cancers and broader ranges of doses. (A study with small number of cancers and a narrow range of low doses would normally have much more uncertainty, that is, a much wider confidence interval on the risk estimate, than one with a larger number of cancers and a broad range of doses.)

C6. The analysis did not take into account uncertainties in the dose estimation, which are attributable to both uncertainties in the modeling of estimated external doses and to further uncertainties in individuals' behaviors that were modeled in estimating thyroid doses. A sound analysis would take into account dose uncertainties and be based on an appropriate analytic method.

C7. Of importance, the Kato and Yamada's estimates were based on only 36 of the 150 thyroid cancer cases they mention in the second screening. There was clearly a substantial potential for bias when only 24% of the cases were included, and when the reasons for the availability of dose information or lack of it for given individuals (which was apparently the criterion for inclusion of individuals) were unknown.

C8. If it was a biased sample of thyroid cancer cases, the Kato and Yamada's results would be inaccurate estimates of risk (e.g., if individual dose information was obtained from a greater proportion of higher-dose thyroid cancer cases than lower-dose ones, this would tend to inflate an estimate of risk). Since their calculated risks were so much higher than those of other major studies, there were probably individual dose-participation biases that inflated the estimated risks. Kato and Yamada's did not adjust for age or sex. As in most studies, the FHMS frequency of thyroid cancer cases was greater among females and especially at older ages. The failure to take age and sex into account may have produced bias in their results.

In part II of their analysis (page 3, left column) they indicate that all-Japan thyroid cancer incidence peaked in 2011, the year of the FDNPS accident. They state this supports a radiation etiology. However, the Chernobyl and other studies of radiation and thyroid cancer clearly indicate that excess thyroid cancer from radiation does not begin to occur until 3-4 years after exposure. It is much more plausible that the peak within a year after the accident was associated with a sharp increase in the frequency of thyroid cancer screening rather than with radiation.

In part III of their results Kato and Yamada's suggest that the Fukushima thyroid cancer rates demonstrate radiation attribution because the number of cases increases with age at exposure, as was also seen in Ukraine and Russia (but not in Belarus) after the Chernobyl accident. However, the finding generally supports an interpretation that thyroid cancer rates increase with age, irrespective of radiation exposure. A radiation interpretation is not supported by the fact that there was essentially no evidence of thyroid cancer after exposure at ages 0-4 in the Fukushima group. Other radiation studies, including those in all three of the named Chernobyl-associated countries, have shown substantial thyroid cancer risk after exposure at ages 0-4, so the lack of it in the Fukushima population is inconsistent with radiation attribution.

All in all, there probably are biases in the inclusion of thyroid cancer cases compared to other individuals in the Kato and Yamada's ill-defined subcohort, as well as errors in the analysis and discrepancies in the interpretation of time and age trends. The study therefore lacks credible evidence that supports the conclusions.

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