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INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

INFORMATION NOTE

Publication of new results from the INWORKS epidemiological study of cancer risk among nuclear industry workers

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What is the INWORKS study?

INWORKS is a large-scale epidemiological study designed to quantify the health risks potentially associated with repeated exposure to low doses of ionizing radiation. Its creation was initiated in the late 2000s and the first results were published in 2015.

INWORKS investigates the effects of low-dose exposure to ionizing radiation on the health of workers in the nuclear industry. This epidemiological study brings together cohorts of French, American, and British workers employed in the nuclear industry (fuel preparation, research, power generation, reprocessing of irradiated fuel) and monitored for external exposure to ionizing radiation by personal dosimeters. The population studied in INWORKS includes almost 310,000 male and female workers employed from the mid-1940s onwards.

The strength of INWORKS lies in its protocol, which is based on standardized inclusion criteria for the three cohorts, the duration of follow-up (an average of almost 35 years), verification of data homogeneity and quality, and verification of the stability of results through sensitivity analyses (Hamra et al., Int J Epidemiol 2015). The method for reconstructing individual dosimetric history has been the subject of a specific publication (Thierry-Chef et al., Radiat Res 2015).

Who carried out the INWORKS study?

The INWORKS study is coordinated by the International Agency for Research on Cancer (IARC, www.iarc.fr) and Prof. David Richardson of the University of California-Irvine (UCI, https://uci.edu/). The French, American and British cohorts were set up respectively by the Institut de Radioprotection et de Sûreté Nucléaire (IRSN, www.irsn.fr), the National Institute for Occupational Safety and Health (NIOSH, www.cdc.gov/niosh/) and the UK Health Security Agency (UKHSA, https://www.gov.uk/government/organisations/uk-health-security-agency). The *Barcelona Institute for Global Health* (ISGlobal, https://www.isglobal.org/en/) is also part of the consortium. Analyses were carried out by all partners.

What is the purpose of the INWORKS study?

The aim of INWORKS is to verify the validity of the assumptions underlying the current system of radiation protection for workers, which is based in particular on extrapolating knowledge of radiation-induced risks from the epidemiological follow-up of survivors of the Hiroshima and Nagasaki bombings. Questions persist as to the validity of using information derived from studies of populations exposed to acute doses of ionizing radiation (delivered all at once at a high dose rate), as were the bombing survivors, to ensure the protection of populations repeatedly exposed to low doses and low dose rates of external exposure, as are certain nuclear workers.

What is IRSN's contribution to the INWORKS study?

IRSN has been an active contributor to the INWORKS study since its inception. IRSN participates in INWORKS analyses and coordinates the French cohort included in INWORKS.

The French cohort included in the INWORKS study comprises over 59,000 workers from CEA, EDF and Orano. The results of the latest analyses of the French cohort were published in 2022 (Laurent et al., Cancers 2023). These results would not have been possible without over 35 years of cohort-building work, and the collaboration of nuclear operators. Further details can be found at www.irsn.fr/seltine.

What do the new INWORKS study results show?

Results from the INWORKS study published on August 17, 2023 on the *British Medical Journal* website present an updated analysis of associations between radiation dose and mortality from solid cancers in INWORKS, with worker follow-up extended by 10 years (Richardson et al., BMJ 2023). Compared with previous analyses, this extension of follow-up time has strengthened the study's ability to detect risks at low dose levels.

The 309,932 workers included in the INWORKS study were monitored for an average of 35 years over the period 1944-2016. At the end of the follow-up, their average age was 66. The average dose received by workers is 18 mGy accumulated over the duration of their working life. A total of 103,553 deaths were recorded in the cohort, including 28,089 from solid cancers.

The results show that the risk of solid cancers increases in proportion to the dose received, by around 5.2% (90%-IC confidence interval: 2.7 to 7.7%) for an increase in the cumulative absorbed dose to the colon of 100 milliGray[1]**.** These results confirm those already obtained in 2015 (4.7%; 90%-IC: 1.8 to 7.9%) (Richardson et al., 2015), with a gain of almost 20% in the precision of the risk estimate, as evidenced by the reduced amplitude of the confidence interval.

Further INWORKS results on other causes of death will be published shortly.

This dose-dependent increase in the risk of solid cancers remains significant when the analysis is restricted to low cumulative doses below 100 mGy.

Analyses conducted on restricted dose intervals suggest that the slope of the dose-risk relationship may be steeper for doses below 100 mGy (i.e., the dose-risk relationship may be supra-linear), but these new results need to be corroborated by risk analysis at low doses in other populations exposed under comparable conditions. For example, this trend appears in the American cohort contributing to INWORKS (Kelly-Reif et al., Int J Epidemiol 2023), but not in the French cohort (Laurent et al., Cancers 2023).

To assess the existence of a potential bias in these results due to the absence of individual data on tobacco consumption, lung cancers were excluded from the analysis. This exclusion had very little impact on the risk estimate. This result rejects the possibility of a significant smoking bias.

What can you learn from INWORKS?

The benefits of international research collaborations

The INWORKS study is based on the merger of three pre-existing cohorts. This international collaboration has made it possible to verify and consolidate the results previously suggested by each of these three studies. Combining the data from these three cohorts in a single study provides the analytical power needed to detect risks at low dose levels (to detect a small increase in cancer frequency, a very large population size is essential). This joint database also makes it possible to analyze heterogeneities between cohorts.

[1] The milliGray (mGy) is the unit of absorbed dose, representing the energy deposited by ionizing radiation per unit mass, in this case in the colon.

Effects of radiation at low dose rates

The current radiation protection system is based in particular on extrapolating knowledge of radiation-induced risks from the epidemiological follow-up of survivors of the Hiroshima and Nagasaki bombings, who were exposed to acute doses of ionizing radiation (delivered all at once at a high dose rate).

The INWORKS study provides an estimate of the solid cancer dose-risk relationship for cumulative exposures over time, with results consistent with those derived from survivors of the atomic bombings of Hiroshima and Nagasaki. These results therefore provide a very important addition to the consolidation of the assumptions underlying the radiation protection system. In particular, they support the justification for radiological protection of populations exposed to low doses of ionizing radiation (nuclear industry workers, medical staff, diagnostic medical exposure, etc.).

Effects of low-dose radiation

The INWORKS results show that the dose-risk relationship for solid cancers persists when the analysis is restricted to cumulative doses below 100 mGy. This is consistent with the underlying assumption of the radiation protection system that there is no dose threshold. On the basis of INWORKS results, a dose threshold, if it existed, could not be higher than a few tens of mGy. The corollary of this result is that, for low doses, the increase in cancer risk is low.

Analyses carried out on restricted dose intervals suggest that the slope of the dose-risk relationship may be stronger for doses below 100 mGy. Nevertheless, the estimate of the slope of the dose-risk relationship is framed by a wide confidence interval. This means that the uncertainty associated with the value of the slope is significant, and that this result should be treated with caution. These results contribute to the discussion of the validity of applying a risk reduction factor to low doses and dose rates, as incorporated in the construction of the current radiation protection system.

Quantifying the impact of low-dose radiation and dose rates

Based on the dose-risk relationship estimated in INWORKS, and assuming that this relationship is causal, we can calculate the proportion of the risk of death from solid cancers attributable to exposure to ionizing radiation.

According to this calculation, among 1,000 workers with the average characteristics of INWORKS workers (in terms of period of activity, cumulative dose, gender, age, and duration of follow-up), 334 deaths are expected, 91 of them from cancer, and of these 91 cancer deaths, 1 would be attributable to exposure to ionizing radiation. The proportion of deaths from solid cancers attributable to external radiation exposure in the INWORKS population is therefore of the order of 1%.

Publication reference

Richardson DB, Leuraud K, Laurier D, Gillies M, Haylock R, Kelly-Reif K, Bertke S, Daniels RD, Thierry-Chef I, Moissonnier M, Kesminiene A, Schubauer-Berigan MK. Low dose exposure to ionizing radiation and cancer: Updated findings from the International Nuclear Workers Study (INWORKS). **British Med J.** 2023; 382:e074520. https://www.bmj.com/content/382/bmj-2022-074520

For further information

Hamra GB, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan J, Haylock R, Laurier D, Leuraud K, Moissonnier M, Schubauer-Berigan M, Thierry-Chef I, Kesminiene A. The International Nuclear Workers Study (INWORKS). **Int J Epidemiol**. 2015 Jul 6. pii: dyv122. doi: 10.1093/ije/dyv122. http://ije.oxfordjournals.org/content/early/2015/07/06/ije.dyv122

Daniels RD, Bertke SJ, Richardson DB, Cardis E, Gillies M, O'Hagan JA, Haylock R, Laurier D, Leuraud K, Moissonnier M, Thierry-Chef I, Kesminiene A, Schubauer-Berigan MK. Examining temporal effects on cancer risk in the International Nuclear Workers' Study (INWORKS). **Int J Cancer** 2017; 140:1260-1269. https://onlinelibrary.wiley.com/doi/10.1002/ijc.30544

Gillies M, Richardson DB, Cardis E, Daniels RD, O'Hagan JA, Haylock R, Laurier D, Leuraud K, Moissonnier M, Schubauer-Berigan MK, Thierry-Chef I, Kesminiene A. Mortality from circulatory diseases and other non-cancer outcomes among nuclear workers in France, the United Kingdom, and the United States (INWORKS). **Radiat Res.** 2017; 188(3):276-90. https://bioone.org/journals/radiation-research/volume-188/issue-3/RR14608.1/Mortality-from-Circulatory-Diseases-and-other-Non-Cancer-Outcomes-among/10.1667/RR14608.1.short

IRSN. La radioprotection des travailleurs. Occupational exposure to ionizing radiation in France: 2022 assessment. Pôle Santé Environnement. IRSN Report No. 2023-00387. Fontenay-aux-Roses, 2023.

Kelly-Reif K, Bertke SJ, Daniels RD, Richardson DB, Schubauer-Berigan MK. Ionizing radiation and solid cancer mortality among US nuclear facility workers. Int J Epidemiol. 2023. https://doi.org/10.1093/ije/dyad075

Laurent O, Samson E, Caër-Lorho S, Fournier L, Laurier D, Leuraud K. Updated Mortality Analysis of SELTINE, the French Cohort of Nuclear Workers, 1968-2014. **Cancers** 2023; 15:79. https://doi.org/10.3390/cancers15010079

Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GA, Haylock R, Laurier D, Moissonnier M, Schubauer-Berigan MK, Thierry-Chef I, Kesminiene A. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. **Lancet Haematol.** 2015 July; 2: e276-e281. www.thelancet.com/haematology http://dx.doi.org/10.1016/S2352-3026(15)00094-0.

Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, Haylock R, Moissonnier M, Schubauer-Berigan M, Thierry-Chef I, Kesminiene A, Laurier D. Risk of cancer associated with low-dose radiation exposure: comparison of results between the INWORKS nuclear workers study and the A-bomb survivors study. **Radiat Environ Biophy.** 2021; 60:23-39. https://link.springer.com/article/10.1007/s00411-020-00890-7

Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GA, Haylock R, Laurier D, Leuraud K, Moissonnier M, Schubauer-Berigan MK, Thierry-Chef I, Kesminiene A. Risk of cancer from exposure to ionizing radiation: a retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). **British Med J** 2015. http://www.bmj.com/cgi/doi/10.1136/bmj.h5359

Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Haylock R, Leuraud K, Laurier D, Moissonnier M, Schubauer-Berigan MK, Thierry-Chef I, Kesminiene A. Site-specific cancers following exposure to ionizing radiation: a retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). **Epidemiol.** 2018; 29(1):31-40. https://journals.lww.com/epidem/Fulltext/2018/01000/Site_specific_Solid_Cancer_Mortality_After.5.aspx

Thierry-Chef I, Richardson DB, Daniels RD, M. Gillies M, Hamra GA, Haylock R, Kesminiene A, Laurier D, Leuraud K, Moissonnier M, O'Hagan JA, Schubauer-Berigan MK, E. Cardis, on Behalf of the INWORKS Consortium. Dose estimation for a study of nuclear workers in France, the United Kingdom and the United States of America: methods for the International Nuclear Workers Study (INWORKS). **Radiat Res.** 2015; 183(6):632-42. http://www.rrjournal.org/doi/abs/10.1667/RR14006.1