RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

IRSN
INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

INFORMATION NOTE

30/08/2024

Publication of new results from the INWORKS epidemiological study on the risk of leukemia, lymphoma, and multiple myeloma among nuclear industry workers

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 study protocol, which is based on the standardization of 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 B. 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 with 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?

The results of the INWORKS study published on August 30, 2024 on *The Lancet Haematology* website present an updated analysis of the associations between radiation dose and mortality from haematological malignancies in INWORKS, with worker follow-up extended by 10 years (Leuraud et al., Lancet Haematol 2023). An updated analysis of the risk of death from solid cancer was published in 2023 (Richardson et al., British Med J 2023). Compared with previous analyses, this extension of the follow-up period 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 was 16 milligray (mGy)[1] accumulated over the duration of their working life. A total of 103,553 deaths were recorded in the cohort, including 771 from leukemia (excluding chronic lymphocytic leukemia), 1,146 from non-Hodgkin's lymphoma, 122 from Hodgkin lymphoma, and 527 from multiple myeloma.

The results show that the risk of leukemia (excluding chronic lymphocytic leukemia) **increases in proportion to the dose received, by around 26.8% (90% confidence interval: 11.3 to 45.5%) for an increase in the cumulative dose absorbed at the red bone marrow of 100 mGy.** These results confirm those already obtained in 2015 (29.6%; 90% confidence interval: 11.7 to 52.1%) (Leuraud et al., Lancet Haematol 2015), with a gain in the precision of the risk estimate, as evidenced by the reduced amplitude of the confidence interval.

This dose-dependent increase in the risk of leukemia (excluding chronic lymphocytic leukemia) **remains significant when the analysis is restricted to cumulative doses below 300 mGy**, but is no longer significant when the analysis is restricted to doses between 0 and 200 mGy.

As in the previous study published in 2015 (Leuraud et al., Lancet Haematol 2015), the analyses revealed no significant associations for non-Hodgkin or Hodgkin lymphomas. In contrast, a dose-response relationship was observed for multiple myeloma, with an increase of 16.2% (90% confidence interval: 0.6 to 36.4%) for a 100 mGy increase in cumulative bone marrow dose.

What can you learn from INWORKS?

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

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.

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 dose-risk relationship for leukemia 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.).

Quantifying the impact of radiation at low doses and dose rates

From the dose-risk relationship estimated in INWORKS, the proportion of the risk of death from leukemia (excluding chronic lymphocytic leukemia) attributable to exposure to ionizing radiation can be calculated.

According to this calculation, among 10,000 workers with the average characteristics of INWORKS workers (in terms of period of activity, cumulative dose, sex, age, and duration of follow-up), 3,341 deaths are expected, including 25 from leukemia (excluding chronic lymphocytic leukemia). Of these 25 deaths, 1.3 would be attributable to exposure to ionizing radiation.

Publication reference

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, Richardson DB. Leukaemia, lymphoma, and multiple myeloma mortality after low-level exposure to ionising radiation in nuclear workers (INWORKS): updated findings from an international cohort study. Lancet Haematol. 2024 (https://www.thelancet.com/journals/lanhae/home)

For further information

Websites

IRSN. INWORKS. https://www.irsn.fr/recherche/letude-inworks

IARC. INWORKS. https://www.iarc.who.int/

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.

Bilan 2022 des expositions professionnelles aux rayonnements ionisants en France : une exposition qui augmente mais reste inférieure à la période pré-Covid | IRSN

Ionizing Radiation Epidemiology Laboratory (LEPID)

French cohort of nuclear workers SELTINE

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

Other publications from INWORKS

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

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. Lancet (thelancet.com)

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 lowdose -radiation exposure: comparison of results between the INWORKS nuclear workers study and the -Abomb 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

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

Richardson DB, Laurier D, Leuraud K, Gillies M, Haylock R, Kelly-Reif K, Bertke S, Daniels RD, Thierry-Chef I, Moissonnier M, Kesminiene A, Schubauer-Berigan MK. Site-specific cancer mortality after low-level exposure to ionizing radiation: Findings from an update of the International Nuclear Workers Study (INWORKS). **Am J Epidemiol.** 2024. https://doi.org/10.1093/aje/kwae256.

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