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Is the "largest study ever conducted" on nuclear industry workers really the largest?

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ABSTRACT **The 15-country study on cancer mortality among nuclear radiation workers, coordinated by the International Agency for Research on Cancer is repeatedly cited as "the largest study ever conducted on the subject". This article shows that, despite the very large number of included subjects, this cohort study is less informative that two previous studies including a smaller number of persons. Moreover the statistical significance of the excess relative risk of cancer (except leukaemia) per Sievert, considered as an argument supporting the Linear No Threshold relation, is shown to be a consequence of some aspects of the design and of the lack of robustness of the method of analysis for the evaluation of the lower dose effect. After taking into account these weakness of the design, this important epidemiological study must continued since it is one of the few ways to obtain information on the effect of low dose at low dose rate on human subjects.**

RÉSUMÉ **« La plus grande étude jamais conduite sur les travailleurs de l'industrie nucléaire » est-elle réellement la plus grande ?**

L'étude des 15 pays sur la mortalité par cancer des travailleurs de l'industrie nucléaire coordonnée par le Centre international de recherche sur le cancer est régulièrement citée comme « la plus grande étude jamais réalisée sur le sujet ». Cet article montre, qu'en dépit du très grand nombre de sujets inclus dans l'étude, celle-ci est moins informative que deux études précédentes ayant inclus un plus petit nombre de personnes. De plus on montre que la signification statistique de l'excès de risque relatif de cancer (sauf leucémie) par Sievert, considérée comme un argument en faveur de la relation linéaire sans seuil est la conséquence de certains aspects du protocole et du manque de robustesse de la méthode d'analyse pour évaluer l'effet des plus faibles doses. Après prise en compte de ces faiblesses du protocole, cette importante étude épidémiologique doit continuer car c'est l'une des rares façons d'obtenir, chez l'homme, de l'information sur l'effet des faibles doses, délivrées à faible débit.

Keywords: epidemiology / nuclear workers

In 2005 the *British medical Journal of cancer* published the 15-country study on the risk of cancer of nuclear industry worker (Cardis *et al.,* 2005). The authors claimed that it was "the largest study of nuclear worker ever conducted". In the framed statement untitled "What this study adds?" the journal editor wrote: "*a small excess risk of cancer exists even at the low doses typically received by*

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nuclear industry workers in this study". According to him and to the authors, who went up to calculate the number of cases attributable to exposure to ionising radiation in the cohort, these conclusions were supported by the statistical significance of the estimated slope of the dose effect relationship. This statement was in line with the BEIR VII report (NRC, 2006) that stated "*the risk of cancer proceed in a linear fashion at lower doses without a threshold and the smallest dose has the potential to cause a small increase in risk to humans*". This latter report devoted an appendix to the 15-country study, considering that (i) it brings a strong epidemiological evidence to support the previous statement. (ii) This study updates and supersedes the previous studies on the same subject. The purpose of the present article is to discuss the "*bien fondé*" of these latter two statements.

My purpose is *not* to discuss the likelihood of the linear no-threshold relationship even if my personal conviction is that, neither the biology nor the epidemiology bring decisive arguments in favour of this relation, which for some researchers passed recently from the status of a pragmatic tool for safe radioprotection to that of a scientific truth. See for example two of the recent discussions that appeared in the scientific literature to understand the background of the controversy (Brenner and Sachs, 2006; Tubiana *et al.,* 2006).

1. What have we obtained and what can we further expect from epidemiological studies?

It is well-known that in cancer research epidemiological evidence eventually provides the decisive argument for classifying an exposure as carcinogenic, because the generalisation from animal or cell to human is not safe and also because an exposure can be highly carcinogenic in human and hardly so in animal (*e.g.:* alcohol drinking).

This has been so for many years as long as the public health administration needed only a qualitative statement about the carcinogenic status of an exposure. The mission became almost impossible when epidemiology had to make quantitative statements on exposure with minute effect in order to define "safe exposure". Given its methodology this discipline is unable to detect an effect, which is of the order of magnitude of the random fluctuation of the background level. Some people may well consider that, in this situation, deciding whether the effect exists is an academic question and that such exposure may be considered as safe for practical purpose. We are probably close to this situation for ionising radiation. To understand it we have to summarize the available epidemiological evidence.

The cohort of survivors of the Hiroshima and Nagasaki bombing (SHN) has been extensively studied and provided the essential of our knowledge of radiation effect at low to moderate doses. Contrary to what is often stated this study *is not* a high dose study since 80% of the survivors have been exposed to less than 100 mSv and 99% to less than *200 mSv*, this latter subjects receiving on average *116 mSv* (Preston *et al.*, 2004) This study has also the advantage of including a large number of persons of all ages and both sexes followed up in incidence and mortality for many years. Despite some limitations, the success of the SHN cohort study, due in part to its careful quantitative analysis, may have prevented the use of other data to complete the assessment of epidemiological evidence.

Because ionising radiation is both useful and dangerous it exists many other opportunities of following persons exposed to low or moderate doses of radiation in order to measure the qualitative and quantitative consequence of this exposure on the health of the population. Up to now the main studies with measured radiation doses have been about subjects receiving radiation therapy or being exposed for medical diagnostic purposes. These studies benefit from high quality dosage and satisfactory follow-up but suffer from studying subjects not representative of the general population.

Despite the specific and peculiar aspects of the cohorts that have been followed up, the results are reasonably consistent, both qualitatively and quantitatively and suggest that the use of the SHN study have been an acceptable basis for the radioprotection policy.

It was clear however that the above studies were not adequate for assessing the risk of subjects receiving mainly fractionated doses, as it is the cases for the general population subject to environmental exposure, repeated medical screening or diagnostic procedures. In the absence of other evidence, the results of animal experiments have been used, and as a pragmatic approach, the effect observed in high dose rate studies was halved to obtain an estimate of low dose rate effect.

In the 1990's, at the occasion of the revision of the dose limit by ICRP (1991) there was a general feeling that the validity of the above method to quantify the risk of ionising radiation for the most common circumstances of exposure, should be re-assessed. The nuclear industry workers provided the population that was the easiest to study because of a good monitoring of the exposure and a complete follow-up, which was facilitated by the collaboration of the industry. The International Agency for Research on Cancer (IARC) set up such a study and published the first results in 1994 (Cardis *et al.,* 1994), this study superseded the numerous cohort studies of nuclear workers that were too small, by at least an order of magnitude, to provide meaningful results. In its first publication the IARC was able to gather the data from USA, UK and Canada. This three-country study showed that the observed effect of radiation exposure at low dose rate was consistent with the extrapolation from high dose rate study but was still too small to provide a definitive answer (Cardis *et al.*, 1994, 1995; Estève, 1995). The upper limit of the confidence interval of the ERR/Sv for all cancer except leukaemia was quasi equal to the ERR/Sv obtained from the SHN study. Therefore there was no evidence of a reduced risk for low dose rate. At that stage it would have been essential to decide in which way a refinement of this result could be obtained from further epidemiological investigations. The answer of IARC has been to include as many nuclear workers as possible in the cohort in the hope of increasing the precision of the estimate. As we shall see below this did not happen and it could have been predicted.

2. What is a large cohort study?

A cohort study may be large, when considering the number of included subjects, but in reality very small when considering the precision of the estimate of the parameter of interest, in this case the ERR/Sv. It is well-known that the precision of a cohort study depends on the number of expected deaths and not on the number of subjects included in the cohort: the greater the number of expected deaths, the smaller the random variability of the number of observed deaths; and greater is the chance of demonstrating an excess deaths due to exposure, if the latter is large enough to produce an effect substantially larger than this random variability. If the objective is in addition to measure the slope of a dose effect relationship the range of exposure should be as large as possible within the interval of linearity of the relation. Therefore the cohort subjects should be old enough and have been exposed to a large range of radiation doses within the "*0–200 mSv*" interval.

From the above point of view, most studies of nuclear workers undertaken up to now are unable to produce information on low dose effect at low dose rate. In particular all studies of "national" cohorts of workers of the electricity production, taken alone, are unable at this stage to produce the relevant information; the calculation of an ERR/Sv in these circumstances is irrelevant (Howe *et al.*, 2004; Zablotska *et al.,* 2004). Table I give some examples of cohort studies with their precision and the number of excess deaths, expected on the basis of the ERR/Sv provided by the SHN study. This confirms the expected lack of precision of national study of the nuclear power industry and shows that the 15-country study is less precise than the three-country study and even less precise than the English study based on the National registry of radiation workers (Muirhead *et al.,* 1999). Despite a larger number of cancer deaths, the 15-country study has less expected excess deaths than the three-country study and, even if the number of excess deaths

TABLE I

Precision of nuclear radiation worker studies as a function of the mean exposure dose and of the expected excess deaths (deaths from all cancers except leukaemia).

Comparaison de la précision des différentes études portant sur les travailleurs professionnellement exposés aux rayonnements ionisants, en fonction de la dose moyenne reçue et de l'excès de décès attendu (décès par cancers autres que léucémies).

Study	Number of monitored workers	Number of deaths	Mean dose (mSv)	ERR/Sv (Confidence interval)	CI width	Expected excess	Reference
CIRC 3-country study	95 673	3 830	40.2	-0.07 (-0.39;0.30)	0.69	46	Cardis *et al.*, 1994
CIRC 15-country study	407 391	5 024	19.4	0.97 (0.27;1.80)	1.53	28	Cardis *et al.*, 2005
UK registry of radiation workers	124 743	3 020	30.5	0.086 (-0.28;0.52)	0.80	27	Muirhead *et al.*, 1999
USA, Power Industry	53 698	368[1]	30.7	0.51 (-*2.01*;4.64)	6.65	3	Howe *et al.*, 2004
Canada, Power Industry	45 468	474[1]	13.5	2.80 (-0.038;7.13)	7.17	2	Zablotska *et al.*, 2004

[1]solid cancer.

is about the same as in the English study, the latter is more precise because the dose range is larger and as a consequence the slope is estimated with a greater precision.

Contrary to the assertion of the BEIR VII report the 15-country study does not supersede the previous studies of nuclear workers.

3. Why the largest study ever conducted on nuclear workers is not really the largest?

Since the data of the two studies that are more precise than the 15-country study are included at least partially in the latter we may ask why the last IARC study achieve such a low precision. The answer is found in the second series of publication of the 15-country study (Cardis *et al.,* 2007). The small average exposure, which is responsible for the weak precision, is explained by the exclusion of workers who have been *potentially* exposed to other irradiations than X- or γ-rays. This decision eliminated from the cohort many workers among the more exposed: 60% of deaths occurring among subjects exposed to more than *200 mSv* and included in the three-country study were excluded from the 15-country study. If the objective of a "pure" exposure is in principle legitimate, it is not justified here since this strategy has lower the exposure, showing that these workers were also highly exposed to low-LET radiation. The bias would therefore have been in the direction of possibly over estimating the radiation effect and not hiding it, as it would have been the case if these workers had been exposed to low dose of low-LET radiation.

TABLE II

Comparison of the two IARC studies: Relative risk of dying from cancer other than leukaemia, according to radiation exposure (see Tab. 8 of Cardis *et al.*, 1995).

Comparaison des 2 études du CIRC: Risques relatifs de mortalité par cancers (autres que les leucémies) en fonction des doses reçues (voir Tab. 8 de Cardis *et al.*, 1995).

dose	IARC 15-Country Study					IARC 3-Country Study				
(mSv)	Obs.	Exp.	RR	CI		Obs.	Exp.	RR	CI	
0-	3547	3581.3	**1.00**			2234	2228.0	**1.00**		
10-	1225	1225.2	**1.00**	0.93	1.06	1183	1196.3	**0.99**	0.92	1.06
100-	165	133.3	**1.23**	1.06	1.44	196	190.5	**1.03**	0.89	1.19
200-	87	84.4	**1.03**	0.83	1.27	217	214.8	**1.01**	0.88	1.16

Table II shows the relative risk that are obtained in the two IARC studies using dose intervals, which provided an acceptable precision[2]. Three important facts are evidenced from this table: (i) the number of deaths observed in the 15-country study was only larger in the lower dose interval, where enough information was already available in the 3-country study. (ii) The number of deaths observed in the higher dose intervals is larger in the 3-country study, giving to the latter a better chance to detect a possible effect of ionising radiation. (iii) The two studies agreed on the absence of an effect at dose lower than 100 mSv [3].

Therefore, the decision of excluding subjects on the basis of a potential mixed exposure has been inefficient, leading to a loss of precision. The increase in the number of subjects, non-exposed or exposed to a very low dose of radiation, led to a greater heterogeneity of the reference category, which is no longer similar to exposed subjects in term of confounding factors. This has been demonstrated to be true for social-class, for which the confounding effect has been corrected, and also for tobacco consumption, for which it was not possible to correct. This is also likely to be true for other unmeasured factors, casting doubts on the results of the study.

The likelihood of the presence of the above cause of confounding is confirmed by the heterogeneity of the results for the various countries, where the factors may have plaid a role in different directions. The few studies on the association between tobacco smoking and exposure to RI confirmed this idea. Figure 2 of Cardis *et al.* (2005) showed clearly that the ERR/Sv in the Canadian cohort is different from that observed in both the English and US cohorts of the power industry workers

[2] For the relative risk calculation presented in this table, I used the classical approximation (Breslow and Day, 1987) since the detailed data necessary for the Mantel-Haenszel calculation were not available to me. The difference between the two estimates is usually weak.

[3] The larger non-significant value (1.51) for the slope of the linear model for the ERR/Sv is probably explained by the poor precision achieved by this model at low dose and on a narrow range (see Tab. 2 of Cardis *et al.*, 2007).

since their confidence intervals are disjoint. The fact that the heterogeneity test is not significant is just a further demonstration that the tool-kit associated with the linear model for the ERR/Sv is inadequate for low dose study on a narrow range[4].

The 15-country study does not support the existence of a small excess risk of cancer at low dose of ionising radiation such as those received by nuclear radiation workers.

4. What next?

Overall the studies of nuclear workers did not detect a significant risk below 100 mSv. Keeping in mind the remark made in *note 2*, which may change slightly the following assertion, we may state that the excess risk, if it exists at all, is less than 6%. These studies showed, without ambiguity, that the radioprotection rules, based on the extrapolation of the moderate to high doses studies, give a satisfactory protection to workers whose activities imply exposure to low doses of ionising radiation. In other words, the quantitative risk assessment obtained from extrapolating the SHN data and confirmed by the studies of subjects exposed for medical treatment or diagnosis provides a valid reference for an efficient radioprotection. Actually, it is possible that the risk coefficients obtained from this approach are slightly over-estimated, because of the use of the linear no threshold relationship together with the multiplicative model, which over estimate the lifetime risk for the subjects exposed during childhood (de Vathaire *et al.,* 1999).

However, the nuclear radiation worker studies *are still too imprecise* to show that the empirical rule of halving the risk provided by high rate study for estimating the risk after low rate or protracted exposure is justified.

Should we say that, at the light of their results, the nuclear worker studies were useless? The answer is clearly negative. First it brings the reassurance that the risk of ionising radiation is not an order of magnitude larger than anticipated by high rate studies as it has been sometime stated. Second, it is important to realise that the cohorts that has been assembled by IARC are, for most of them, composed of young subjects and should be more informative in a decade or two, an elapsed time that is relatively short for epidemiological cohort studies. Third, there is no other way to gather more information on *human subjects* exposed to low dose at low dose rate.

[4] This tool-kit is essentially the "epicure" software, which was developed for studying the SHN cohort and, which is used as a black box by most epidemiologists.

Therefore, in my opinion it is important to continue this work, but it is necessary that the investigators revised their strategy of inclusion to avoid the follow-up of a large number of subjects, which are hardly exposed to ionising radiation. In addition the use of the multiplicative model and its tool-kit is probably not optimal. Its robustness being unwarranted in this context, the use of a simpler and robust approach should be recommended.

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