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THE HEALTHY WORKER EFFECT AND NUCLEAR INDUSTRY WORKERS

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□ The linear no-threshold (LNT) dose-effect relationship has been consistently used by most radiation epidemiologists to estimate cancer mortality risk. The large scattering of data by International Agency for Research on Cancer, IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007), interpreted in accordance with LNT, has been previously demonstrated (Fornalski and Dobrzyński 2009). Using conventional and Bayesian methods the present paper demonstrates that the standard mortality ratios (SMRs), lower in the IARC cohort of exposed nuclear workers than in the non exposed group, should be considered as a hormetic effect, rather than a healthy worker effect (HWE) as claimed by the IARC group.

Keywords: nuclear industry workers, healthy worker effect, dose-response, Bayesian analysis, hormesis, low radiation

1. INTRODUCTION

Studies of the influence of ionizing radiation on the mortality of nuclear industry workers have been presented in several papers (Fornalski and Dobrzyński 2009; Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007; Luckey 1991, 2008a; Matanoski *et al.* 1991, 2008; Sponsler and Cameron 2005; Berrington *et al.* 2001; McGeoghegan and Binks 2000a, 2000b, 2000c; Ritz *et al.* 2000; Cardis *et al.* 1995; UNSCEAR 1994). It is well known that very large cohorts are required to demonstrate significant effects of low doses of radiation. Control reference groups generally need to be at least as large or larger than the cohort of interest. The referent group should also exhibit similar distributions of age, sex, habits, socio-economic conditions, and exposures to other confounding factors. This is important since differences between "exposed" and "unexposed" groups may be very small. The details of data collection and analysis are important. Final conclusions depend heavily on the careful collection and analysis

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of data. Selection of appropriate control groups is particularly important in studies of ionizing radiation. Perfect control groups are impossible since all people are exposed to a potentially wide range of natural radiation (mean 2.5 mSv/year) and radiation from medical procedures (global mean 0.9 mSv/year). Natural radiation varies with location by up to three orders of magnitude (0.7 to 700 mSv/y). People have lived at high levels of natural radiation for millenia (Luckey 1991) in many areas of the world; for example in some districts of China (HBRRG 1981), Brasil (Guarapari) and Iran (Ramsar). Annual doses in Ramsar can exceed 600 mSv (UNSCEAR 1994; Luckey 2007; Luckey 2008b). High level radiation areas also exist in Europe, e.g. in Scandinavia, France and Russia (UNSCEAR 1994, 2000). However, no increase in mortality or decrease in longevity of people have ever been observed in these regions. In Taiwan (Chen *et al.* 2004, Hwang *et al.* 2008), where a group of people lived for approximately 20 years in houses contaminated by radioactive cobalt and received doses of 120 to 4000 mSv (range 6-200 mSv/y), the cancer mortality among the residents was significantly less than in the referent group. By comparison, the maximal annual dose of 5.3 mSv in nuclear industry workers studied by International Agency for Research on Cancer, IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) is rather small.

The relationship of cancer mortality with radiation dose received by the exposed group is of prime importance. For example, the results from 250,000 nuclear workers was summarized by Luckey (2008b). The average mortality of nuclear workers (67 ± 13%), was substantially lower than in control groups. A meta-analysis of mortality vs lifetime dose showed a lower cancer mortality for nuclear workers who received lifetime doses below 100 mSv (Luckey 2007). The control groups in Luckey's studies were chosen so as to minimize the Healthy Worker Effect (HWE). Minimizing the HWE had been previously recommended (IDSP 1988; Wen *et al.* 1983). The epidemiological findings of Luckey were similar to those presented in the UNSCEAR Report (1994).

A critique of the Linear No-Threshold (LNT) hypothesis (Luckey 2007, 2000b) was supported by the nuclear shipyard worker study which eliminated or minimized the HWE (Rockwell and Muckerheide 2008; Sponsler and Cameron 2005). The earlier shipyard worker study (Matanoski 1991) has recently been reanalyzed by Matanoski *et al.* (2008) who now claims a small, non-significant increase in mortality for a few cancers. A recent, case-control study of indoor radon showed a large decrease rather than increase in lung cancer mortality (Thompson *et al.* 2008), similar to what had been observed in Taiwan. The HWE was not involved in both studies. Further discussions on cancer mortality and low dose radiation were provided by Pollycove (2009). Decreased cancer mortality was also observed in radiotherapy patients (Luckey 2008b; Sakamoto 2004) which clearly cannot be related to the HWE.

Healthy worker effect

The HWE is often offered as an explanation for significantly lower standardized mortality ratios (SMR) among nuclear workers, as well as workers in other industries involving health risks. The HWE assumes better medical care and stricter medical requirements for nuclear workers than for others, resulting in healthier workers. Socio-economic conditions are also important factors, in that better-educated people are assumed to take better care of their health, and receive better nourishment. In theory, typical pre-employment health controls may contribute to the HWE by eliminating potential cancer patients. This fact, if real, should be reflected in a lower SMR ratio in early years of employment. Such an effect was not observed (Figure 1) by IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007). In fact the data tended to support the opposite conclusion. Dependence of the HWE on duration of employment, as well as on the period of follow-up, has been extensively discussed (McMichael 1976).

For interpretation of observations of a decreased mortality a quantitative approach is needed. In order to obtain a reliable description of mortality, it is important to eliminate or minimize the HWE (Wen *et al.* 1983). This can be accomplished by choosing control groups with the same or similar health levels as in study groups. The time variation of mortality in a control population is a difficult factor in analyses. For example, global cancer mortality has been increasing over several decades (GUS 2007) but varying according to country. The SMR value is lowered when mortality incidence is missed. A lower mortality is often attributed to the HWE, even when studies involve a control cohort very closely resembling the study cohort (McGeoghegan and Binks 2000a, 2000b, 2000c; McGeoghegan 2001; McGeoghegan 2002; Skelcher 2001; Wen *et al.* 1983; Kendall *et al.* 1992).

The HWE can influence the study of many diseases, though its attribution of cancer rates and genetic illnesses has been questioned. Routine pre-employment medical examinations do not eliminate cancer-susceptible individuals, as no genetic tests are carried out. "*No healthy worker effect on cancer is found*" by these medical exams (Kojiro 1999). No current or previous medical tests are able to detect signals of future cancer to eliminate cancer-prone individuals.

Dormant, subclinical malignant tumors, which are not clinically detectable, are common in the population (Akslen and Naumov 2008; Weinberg 2008). This is exemplified by occult thyroid cancer, the incidence of which varies from 9.0% in Poland to 35.6% in Finland (Harach *et al.* 1985; Moosa and Mazzaferri 1997). Some dormant cancers can be detected with molecular tumor markers (ACS 2009). However, such methods were not in use for pre-employment health exams at the time when the IARC data (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) were generated. Such methods are not included in procedures for

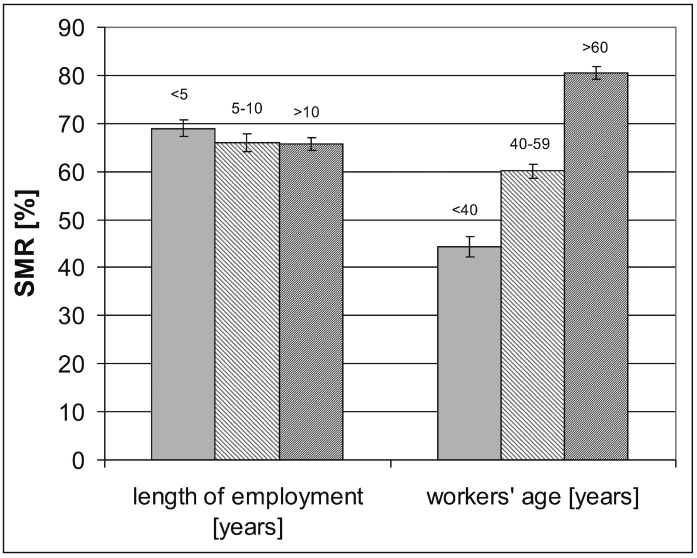

FIGURE 1. Weighted averages of all causes SMRs as a function of the duration of employment (on the left) and the age at death (on the right).

pre-employment health control even today, and are not recommended in protocols of the International Commission on Radiological Protection (ICRP). They are also not given in directives of the European Union Council, or in International Basic Safety standards of the International Atomic Energy Agency (IAEA).

The conclusions of several recent reviews (Luckey 2007, 2008b; Chen *et al.* 2004; Hwang *et al.* 2008; Rockwell and Muckerheide 2008; Sponsler and Cameron 2005; Thompson *et al.* 2008) are opposite from those of IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007). Two alternative methods, a conventional least-square method and a Bayesian approach, were used to re-analyze data compiled by IARC in this paper.

2. IARC DATA AND THE HEALTHY WORKER EFFECT

IARC group (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) summarized information from approximately 400,000 nuclear industry workers from 15 countries, with analyses of all cause and all cancer mortality rates. The main results of this study (Vrijheid *et al.* 2007) are presented in Figures 1 and 2. A decrease in all cause mortality in the nuclear workers cohort is shown in Fig. 2 (data was taken from Table 7 in (Vrijheid *et al.* 2007)). The standardized cancer mortality ratio was 19% (Table 7 in Vrijheid *et al.* 2007). SMRs calculated as a function of worker age and duration of employment should not be arithmetically averaged over results coming from all 15 countries (Fornalski and Dobrzyński

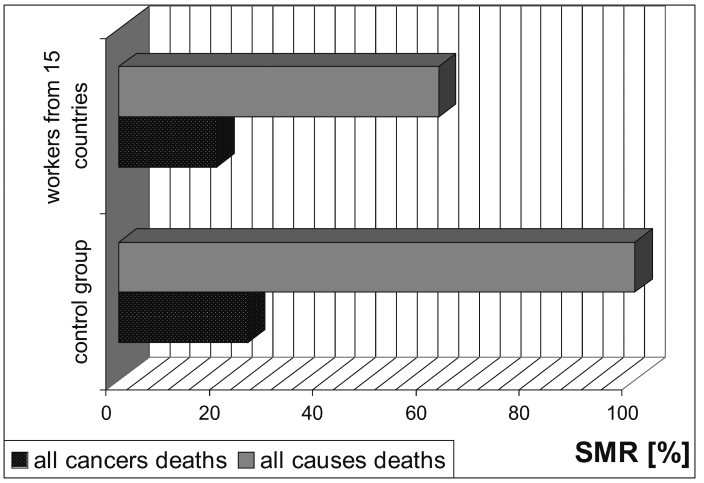

FIGURE 2. The SMR for all cancers (two black bars) and all causes (two grey bars) in two cases: control group of the general population and nuclear industry workers from 15 countries.

2009). A weighted average is more appropriate, because of highly variable uncertainties in the data, with some scatterings of points extending much further than several standard deviations. The SMR is weakly dependent on the duration of employment (Figure 1), as opposed to the conclusions expressed in IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007), who attributed the data to the HWSE (Healthy Worker Survivor Effect). It follows from Fig. 1 that collective dose is not a critical factor in the health of nuclear industry workers. The collective dose data does not describe spatial-temporal dose-distribution patterns, which can be of major importance for estimating cancer risk in humans (Jaworowski 1999). Therefore, the average dose per year, rather than the collective dose, is used in the present analysis.

The latency time for cancer formation in most cases exceeds 10 years. Because the average follow-up time in the IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) studies was less than 13 years, the effect of increased radiation induced cancer mortality would be expected to be rather small or non-existent. The SMR for cancer mortality, as registered in IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007), was 19%. However, the cancer mortality relative to the all deaths in the exposed cohort was 31%. This should be compared with a figure of about 25% which is typical for unexposed cohorts (GUS 2007). This increased cancer death rate should not, however, necessarily be interpreted in terms of increased cancer risk, as opposed to decreased mortality from all other causes. The observed average mortality from all causes, as a function of worker age (Figure 1), seems natural and is not attributed to the influence of ionizing radiation.

Cancer incidence markedly increases with increasing age. However, a 100 years of observation of British radiologists (Berrington *et al.* 2001) has shown that the SMR for cancer decreases with observation time. Even cancers with long latency periods are lower than expected from referent groups. This effect is not connected with the Healthy Worker Effect since "*a standardized mortality ratio of 0.71 for all cancers and 0.68 for all deaths compared with other medical practitioners (who presumably also registered with professional bodies) effectively excludes a healthy worker effect in this group*"; this also indicates "*a highly significant beneficial effect of radiation at moderate doses*" and implies that Berrington *et al.* (2001) were involved in excessive "*thinking only of harmful effects of radiation*". The HWE "*is used irrespective of the extent or degree of benefit obtained within the workplace, to avoid invoking the other scientific conclusion*", and "*when we look at the entry for all cancers as a cause of death (…) we see that our standardized mortality is a meager 0.46 (…). When this is corrected for socioeconomic class the figure becomes 0.61, and when it is compared with all male medical practitioners it is 0.71 (…). The authors attribute this low death rate, at least in part, to the healthy worker effect*" (Cameron and Daunt 2002). And in fact an SMR equal 1 or greater than 1 was obtained by Berrington *et al.* (2001)!

There is a significant problem with the definition and calculation of the Healthy Worker Effect (IDSP 1988; Choi 1992). The lower value of SMR can not be shown to be connected to the HWE, when SMR values vary by a large amount, e.g., from 40% to 110%, as found in IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007). The HWE depends on the cohort under study (Carpenter 1987), and, as was also stated in the section 1**,** "*the HWE is not a problem for cancer mortality*" because of non-existing cancer and genetic testing system at the time of accepting people for work. The HWE has been estimated according to the degree of the disagreement of their data with expectations in several papers. When the SMR = 90%, the HWE is said to be 10%, when SMR = 80%, the HWE = 20%, and so on. When the results show that the SMR = 100% or more, it is said that HWE does not appear in the study group (Gridley *et al.* 1999; Meijers *et al.* 1989). One might then ask why one should not assert an "unhealthy worker effect" (Brooks *et al.* 2007) in such cases? SMR results differ greatly for different lines of work, material status, age and even sex (Chen and Seaton 1996; McMichael 1976). In conclusion one must pose the difficult question of whether there is any serious evaluation of the HWE, or whether the HWE is in effect a "*Zombie Science*", not supported by medical evidence but dogmatically used (Charlton 2008)?

IARC study (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) explains the reduced SMR values as due to the HWE. If this is true, then IARC SMR results should be significantly lower than SMR values published in earlier studies (Luckey 2008b; Wen *et al.* 1983; Hwang *et al.*

2008; Sponsler and Cameron 2005; Raman *et al.* 1987) in which HWE was eliminated. However, SMR values shown in IARC are larger. Therefore, the attribution of low SMRs in IARC to HWE might be considered a biased assumption, supported less by facts than by preconceptions. This problem was discussed by Wagner (2003) who stated that "*the healthy worker selection bias argument could go either way, depending on which way one wants it to go*".

SMR values depend strictly on the choice of control group, and can vary a great deal when the group characteristics vary with time. When the hazard of interest (here the level of ionizing radiation) in the control group is not much lower than in the studied cohort, the impact of all preconceptions on the interpretation of results can become quite high. This can make related epidemiological studies more uncertain as sources of information. A number of papers contain the claim that HWE should not be invoked in epidemiological studies (Li and Sung 1999; Monson 1986; Cohen 2002). "*HWE is of little or no consequence in interpreting data on cancer mortality*" and "*the healthy worker effect is relatively weak in comparison to causal excesses that can be detected in epidemiologic data*" (Li and Sung 1999). Explanations, other than the HWE, must be considered for observed decreases of SMR values among nuclear industry workers.

3. STANDARDIZED MORTALITY RATIO (SMR)

SMRs for all cause and all cancer mortality among nuclear workers are presented in Fig. 3, which presents data (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) as a function of the annual dose received by a person rather than the collective dose, since the collective dose is not a good parameter for description of SMR. The error bars in Fig. 3 reflect two standard deviations (95% confidence intervals) and are derived from Vrijheid *et al.* (2007).

A very large scattering of experimental points (between 35-100% of SMR), larger than those indicated by original error bars is seen in Fig. 3. In addition, the data is quite inhomogeneously distributed along the dose axis. This makes it very difficult to fit and validate any trend line drawn from these points. In fact, this lends doubt to the accuracy of any function fitted to these data. The most sensible solution would be to use a weighted average of data points. In order to verify this, an analysis of the simplest possible dose-effect dependences was carried out. Two models were tested: one which treats SMR and relative risk of contracting lethal cancer as independent of dose (in the range of low doses received by nuclear workers), and one which posits a linear dose-effect relationship. A similar analysis has been carried out (Fornalski and Dobrzyński 2009), in which error bars were symmetrized, the range of studied doses somewhat limited, and the uncertainty of the doses neglected.

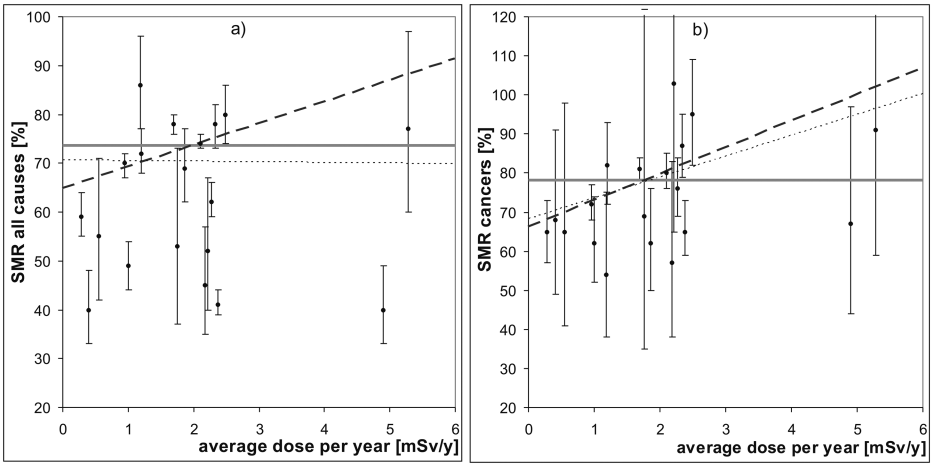

FIGURE 3. SMR [%] for a) deaths from all causes, b) cancer deaths vs average dose per year [mSv/y]; the grey horizontal line is an average obtained following Bayesian analysis, the dashed line is a Bayesian fit ("Bayes2") and the dotted line is a standard least squares (χ^2) fit. All uncertainties are taken from IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007).

3.1. Data analysis methods

Two approaches were used in the analyses: a standard statistical analysis (minimization of χ^2 value) and a Bayesian analysis (Sivia 1996; Sivia and Skilling 2006). The standard statistical approach involves evaluation of standard deviations as an approach to characterizing the accuracy of data. The resulting fitted regression line minimizes the function

$$\chi^2 = \sum_i (D_i - T_i)^2 / \sigma_i^2 ,$$

where $\{D_i\}$ denote measured values, $\{\sigma_i\}$ their uncertainties and $\{T_i\}$-expected values calculated for parameters that are fitted to the measured data.

In the Bayesian approach, the analysis starts with the algorithm described by Sivia (1996) and Sivia and Skilling (2006). A primary motivation behind this approach is the assumption that estimated standard deviations of experimental points may underestimate actual uncertainties. The plausibility for this is shown in Figure 3, given the substantial scattering of experimental points. The Bayesian analysis is then assumed to be sensitive to patterns through assignment of larger uncertainties to potential 'outliers'.

A strength of Bayesian analysis is reflected in Fig. 4. Following the example of Sivia and Skilling (2006), a set of data containing intentional outliers is simulated. The solid lines follow the Bayesian analysis and accurately describe the intended linear function, while the dotted lines are direct χ^2 fits; reasonable results are obtained even with outliers.

Healthy worker effect

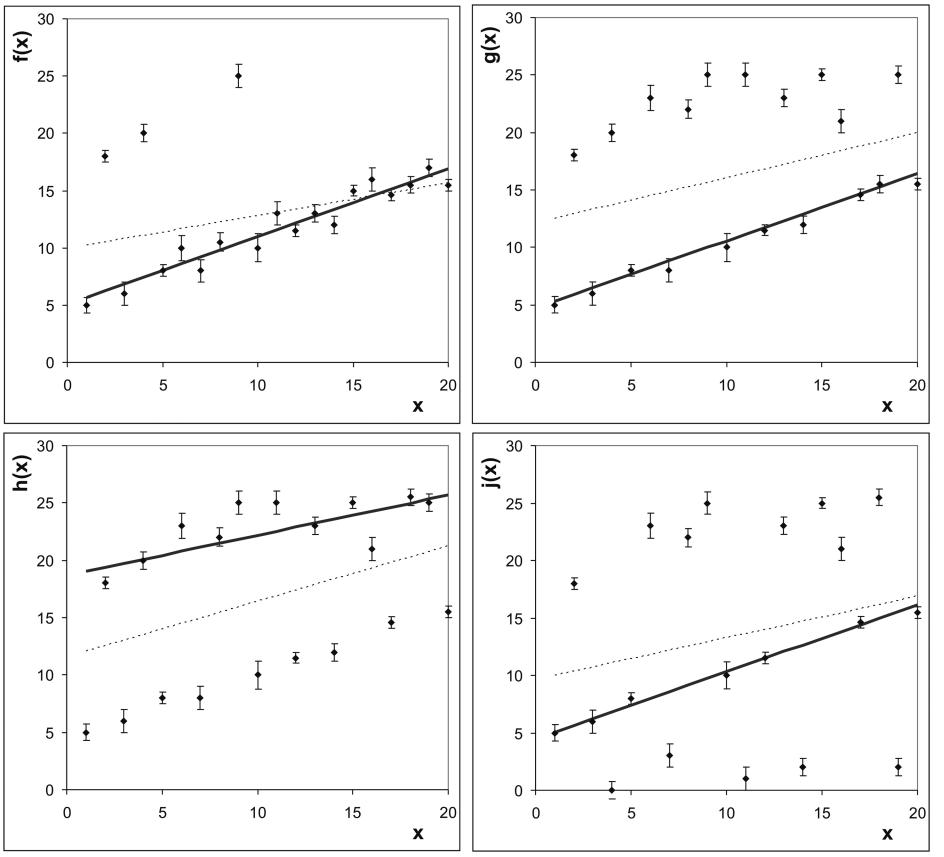

FIGURE 4. Examples of Bayesian analysis fitting (solid lines) to simulated points containing intentional outliers. The dotted lines are obtained from minimizing χ^2 function (least squares) – poor fit is seen. The function *f(x)* shows the fitting with only 3 outliers. The *g(x)* contains many more outliers, but Bayesian analysis (solid line) still works well. In the example of *h(x)*, where the number of outliers is higher than correct data, the Bayesian approach cannot help: there are more points showing another trend than the intended one. However, when number of outliers is high and they lie above and below the main trend, the Bayesian analysis still works (see *j(x)*).

The Bayesian analysis begins with the probability of observing an experimental value E when T is expected,

$$P\left(E\middle|\sigma,o\right)=\frac{1}{\sqrt{2\pi}\sigma}\exp\left\{-(T-E)^2/(2\sigma^2)\right\}p(\sigma), \tag{1}$$

where $p(\sigma)$ is a probability of uncertainty σ in the experimental data E. The parameter o stems from other parameters representing the problem. When this is unknown, the so-called Jeffrey's prior (Sivia and Skilling 2006) defines:

$$p(\sigma)=\frac{1}{\ln(\sigma_{\max}/\sigma_{\min})}\cdot\frac{1}{\sigma} \tag{2}$$

where σ_{max} and σ_{min} are the upper and lower limits of uncertainty σ. Such values can be difficult to assign, and one can also use another prior (Sivia and Skilling 2006),

$$p(\sigma) = \frac{\sigma_0}{\sigma^2} \tag{3}$$

where σ_0 is an uncertainty assigned to the given point *E*. Given a set $\{E_i,T_i\}$, with, for example, $T_i = aD_i + b$, (with *a* and *b* fitting parameters), the logarithm of the total probability of data $\{E_i\}$ is:

$$L = \sum_{i=1}^{N} \ln L_i = \sum_{i=1}^{N} \ln \int \frac{1}{\sqrt{2\pi}\sigma_i} \exp\left\{-(T_i - E_i)^2 / (2\sigma_i^2)\right\} p(\sigma_i) d\sigma_i \tag{4}$$

Parameters *a* and *b* are obtained from maximizing (4), i.e., setting *dP/da* and *dP/db* to zero:

$$\sum_{i=1}^{N} g_i (T_i - E_i) \frac{dT_i}{d\alpha_n} \equiv \sum_{i=1}^{N} g_i R_i \frac{dT_i}{d\alpha_n} = 0 \tag{5}$$

where the weights g_i depend on residuals $R_i = T_i - E_i$, with $\{T_i\}$ functions of n = 1, .., N_p parameters. For example, with the prior (3) the weights are:

$$g_i = \frac{1}{R_i^2} \cdot \left\{ 2 - \frac{R_i^2}{\sigma_{0i}^2} \cdot \frac{1}{\exp(R_i^2 / 2\sigma_{0i}^2) - 1} \right\} \tag{6}$$

Solving (5) numerically yields *a* and *b*. Finally, the Hessian is calculated to estimate uncertainty of the parameters. More detailed information is given in Fornalski and Dobrzyński (2009).

A Bayesian statistical approach to model selection is discussed in Sivia and Skilling (2006). Here it is necessary to find the posterior ratio of two likelihood functions of the candidate models, say *A* and *B*:

$$posterior\_ratio = \frac{prob(A \mid D,I)}{prob(B \mid D,I)} \tag{7}$$

where *D* denotes original data and *I* the knowledge from the pre-experimental information. The posterior probabilities for *A* and *B* are then products of probabilities for all data points. Using Bayes' theorem:

$$\begin{aligned} prob(A \mid D,I) &= prob(D \mid A,I) \times prob(A \mid I) \,/\, prob(D \mid I) \\ prob(B \mid D,I) &= prob(D \mid B,I) \times prob(B \mid I) \,/\, prob(D \mid I) \end{aligned} \tag{8}$$

The terms *prob(A|I)* and *prob(B|I)* cancel when neither *A* nor *B* is preferred initially. The terms *prob(D|I)* are set in both equations to the same constant value. For a model *B* with an adjustable parameter λ, the term *prob(D|B,I)* are expressed as:

$$prob(D \mid B,I) = \int prob(D \mid \lambda,B,I) \times prob(\lambda \mid B,I) d\lambda \tag{9}$$

The value *prob(D|λ,B,I)*, where λ is given, is a standard likelihood function. When λ is assumed to lie between λ_{min} and λ_{max}, a prior within this range is written as:

$$prob(\lambda \mid B,I) = \frac{1}{\lambda_{max} - \lambda_{min}} \text{ for } \lambda_{min} \le \lambda \le \lambda_{max} \tag{10}$$

Let λ_0 denote the value of λ which yields the closest agreement with the measurements, so the probability *prob(D|λ$_0$,B,I)* maximizes *B*'s likelihood function. This is represented using a Gaussian function:

$$prob(D \mid \lambda,B,I) = prob(D \mid \lambda_0,B,I) \times \exp\left(-\frac{(\lambda - \lambda_0)^2}{2\delta\lambda^2}\right) \tag{11}$$

We can calculate (9) using both (10) and (11). Putting the result into (8) yields the final form of (7):

$$\frac{prob(A \mid D,I)}{prob(B \mid D,I)} = \frac{prob(A \mid I)}{prob(B \mid I)} \times \frac{prob(D \mid A,I)}{prob(D \mid \lambda_0,B,I)} \times \frac{\lambda_{max} - \lambda_{min}}{\delta\lambda\sqrt{2\pi}} \tag{12}$$

The first term on the right reflects relative prior preference for alternative theories. As stated earlier, these probabilities can be the same, so that the first term is 1. The second term involves the primary estimation of the models' agreement with data. The last term is a so called "Ockham's factor", preventing use of over-complicated models (Sivia and Skilling 2006).

3.2 Fitting linear dose-effect relations to SMR

Two independent models were tested in order to describe SMR data. The first (denoted as M1) assumes that the standardized mortality ratio (SMR) is independent of annual dose, so that the fitted function is y = const. The second model (M2) assumes SMR = a<D> + b, where <D> is the average annual dose. *A priori* it is difficult to decide between M1 or M2, so both models are assigned the same probability of acceptance. The analyzed data are contained in Tables 5 and 7 in (Vrijheid *et al.* 2007).

Implementation of model M1 involves calculation of standard weighted averages. The uncertainties are presented originally in terms of two standard deviations. In the case of SMR for all cause mortality, one obtains SMR = (67.8 ± 14.7)% with χ^2 = 226.5, and in the case of SMR for all cancer mortality, one obtains SMR = (76.5 ± 13.0)% with χ^2 = 18.7. The values of χ^2 and large uncertainties show that the deviations of points from their averages are much larger than claimed uncertainties permit. One might conclude that M2 better describes the data. The two parameters were obtained by least-squares; parameters obtained for the M2 model are shown in Table 1. The SMRs are shown as functions of annual doses. Cumulative doses are found in Table 1 for comparison with other studies.

TABLE 1. Parameters of straight lines fitted[a] to the SMR data presented in Tables 5 and 7 of IARC[b] (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007).

Subject of SMR	a	b	χ^2
All causes vs cumulative average dose[c]	-0.26 ± 0.06	0.727 ± 0.013	888.7
All causes vs average annual dose[c]	-2.34 ± 0.62	0.719 ± 0.012	891.7
All causes vs average annual dose[d]	- 0.11 ± 0.41	0.706 ± 0.009	193.1
Cancers vs cumulative average dose[c]	0.35 ± 0.13	0.701 ± 0.026	68.2
Cancers vs average annual dose[c]	4.75 ± 1.39	0.685 ± 0.025	63.2
Cancers vs average annual dose[d]	5.35 ± 0.92	0.682 ± 0.018	13.7

[a]A standard least-squares fit was used.

[b]All doses are given in mSv.

[c]Symmetric uncertainties (one standard deviation).

[d]Original asymmetric uncertainties from the IARC papers (Vrijheid *et al.*, 2007; Therry-Chef *et al.*, 2007; Cardis *et al.*, 2007), see Fig. 3 (thin lines). Note that these uncertainties are twice as high as the standard deviations. Therefore χ^2 is lower by the factor of 4 with respect to that calculated when single standard deviations are used.

The analysis shows (also reflected in Table 1) that parameter *b* is well defined, and is close to 0.70 (i.e. the SMR is at a level of 70%). A different conclusion is appropriate for the slope parameter *a*. Its value is strongly dependent on how calculations are carried out (in fact its sign also depends on this). This is a consequence of the scattering of points. The high values of χ^2 show that model M2 cannot be treated as an improvement over model M1. Although the values of χ^2 are smaller for M2, one should note that M2 contains a larger number of fitted parameters than M1. The lower χ^2 values consistently follow from larger uncertainties in the data on cancer mortality, and the larger uncertainties result from much lower statistics (smaller data sets). The reliability of these data is not high.

The negative and positive values of slope parameter, *a*, may cause some confusion. It would be expected that better understanding of the data follows from Bayesian analysis, where all uncertainties can be treated as dubious and usually underestimated. The calculations are given in section 3.1.

In the Bayesian analysis of SMR data, both above-mentioned priors, the Jeffrey's prior $[\propto 1/\sigma]$ (2) and the alternative prior $[\propto 1/\sigma^2]$ (3), were used. The results for the latter are described as "Bayes2". The results obtained for the model M1 are presented in Table 2 for both cases: all cause mortality and all cancer mortality. The results, SMR = (73.3 ± 1.3)% for all cause mortality, and SMR = (76.1 ± 6.5)% for all cancer mortality, obtained with prior (3), appear stable and are reasonably based on results presented in Figures 1-3. Taking original asymmetric uncertainties from (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007), one obtains an SMR for all cause mortality of 73.7 ± 0.8 % and an SMR for all cancer mortality of 78.3 ± 3.8 %. These values are found in Fig. 3 as horizontal lines.

Healthy worker effect

TABLE 2. SMR results of the Bayesian analysis for model M1 with Jeffrey's prior and the Bayes2 prior[a]. In the case of the Jeffrey's prior, the values of constant SMR were calculated by allowing the declared uncertainties to be raised by the multiplicative factor, *mult*, which is shown in the 2[d] column.

Subject	Mult	Constant	χ^2
SMR all causes vs cumulative average dose [mSv]	1.1	0.677 ± 0.005	768.0
	5.0	0.694 ± 0.016	60.0
	20.0	0.730 ± 0.019	20.8
	100.0	0.734 ± 0.016	15.8
	Bayes2	0.733 ± 0.013	29.2
SMR cancers vs cumulative average dose [mSv]	1.1	0.765 ± 0.009	67.6
	5.0	0.764 ± 0.037	17.1
	20.0	0.755 ± 0.011	12.1
	100.0	0.743 ± 0.070	10.9
	Bayes2	0.761 ± 0.065	20.1

[a]Symmetric uncertainties and one standard deviation were taken into account

Using the Jeffrey's prior in (2) of section 3.1 requires using the factor *mult*, which gives a range of uncertainties from $\sigma_{min} = \sigma_o$ to $\sigma_{max} = \text{mult} \cdot \sigma_o$. The symbol σ_o denotes initial uncertainty. Table 2 contains results for different *mult*. Going beyond *mult* = 20 is not necessary, since the expected value of χ^2 for this factor is about 19, which equals the number of data points. This value of *mult* is relatively high and indicates that the uncertainties in data from different sources are greatly underestimated. A possible alternative explanation of these data is that they can be treated as independent, so that no common function would apply to them.

The values of SMR in Table 2 are close to those obtained previously by weighted averaging. However, differences in the uncertainties show that the Bayesian method can improve on conventional least-squares.

Fitting an SMR which is independent of dose appears to give reasonable results. However, for completeness and comparison with Table 1, linear models (model M2) were fitted to the same data. The line parameters obtained with the Jeffrey's prior and various multiplication factors are shown in Table 3. Table 4 presents results obtained with the second prior

TABLE 3. SMR for all causes vs the cumulative average as obtained for various multiplication factors in the Bayesian analysis using Jeffrey's prior – model M2 (with symmetric uncertainties and one standard deviation).

Mult.	a	b	χ^2
1.1	-0.25 ± 0.07	0.725 ± 0.014	753.9
5.0	-0.04 ± 0.21	0.699 ± 0.034	59.4
20.0	0.27 ± 0.17	0.674 ± 0.036	19.7
100.0	0.27 ± 0.18	0.673 ± 0.037	14.9

TABLE 4. Parameters of the linear dose-effect dependence of SMR obtained within the Bayes2 approach – model M2 (with symmetric uncertainties and one standard deviation)[a].

Subject (SMR)	a	b	χ^2
All causes vs average cumulative dose	0.28 ± 0.15	0.672 ± 0.031	27.6
All causes vs average annual dose	4.31 ± 1.81	0.651 ± 0.035	25.8
Cancers vs average cumulative dose	0.55 ± 0.24	0.671 ± 0.043	16.4
Cancers vs average annual dose	6.51 ± 2.59	0.662 ± 0.042	16.1

[a]All doses [in mSv] are individual cumulative ones.

(proportional to $1/\sigma^2$ – the "Bayes2"). The latter are very similar to those obtained with the Jeffrey's prior and *mult* at 20 or more.

Two significant observations are implied by Tables 3 and 4:

- a negative slope, *a,* for all cause mortality when the *mult* for Jeffrey's prior is small. This indicates acceptance of uncertainties as originally given. This trend changes when *mult* increases and approaches the results of the 'Bayes2' model. The change in slope is the result of the extensive scattering of data points.
- The second observation relates to cancer mortality. The slope, *a,* is consistently positive, since the related data exhibit less scattering. In addition, the fitted lines are only weakly dependent on the way the data are analyzed.

The results in Tables 3 and 4 were obtained using symmetric uncertainties (one standard deviation). Assuming initially asymmetric uncertainties (two standard deviations) from the IARC data (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007), the results do not significantly change. An SMR = (4.44 ± 0.93) <D> + (64.9 ± 2.2) [%] was obtained for all cause mortality, and an SMR = (6.77 ± 1.46) <D> + (66.2 ± 2.7) [%] for all cancer mortality. Here <D> is the average annual dose (in mSv) received by one person. The related graphs are shown in Fig. 3. For <D> = 0, the SMR values for all cancer and for all cause mortality are very similar, but the increase with dose is about 1.5 times higher for all cancers.

Assuming a non-zero slope, the SMR for deaths from all cause and for all cancer mortality increases with dose (Table 4 and Figure 3). However, the starting level of SMR is more than ~30% below normal. The parameters obtained in Table 4 are very close to those obtained by using the Jeffrey's prior and *mult* values above 20 (Table 3). Note, however, that two data points corresponding to the highest doses generally lie below the straight lines of Fig. 3. This is contrary to what would be expected: the highest slope is obtained from the data at lowest doses. Thus, in spite of the consistency of the results of fits, the estimated slopes cannot reflect actual values. This supports the conclusion that model M1 is more reliable than M2.

There are two other factors which favor model M1 over M2. The first is the fact that the increase of SMR with dose (Table 4) is rapid; for example the slope for cancer in annual doses is 6.5. With this information and a standard interpretation of cumulative dose, one would expect that after 10 years of exposure one would have SMR=130%, and after 20 an SMR=200%. This in fact would be for an annual dose of only 1 mSv! This type of mortality increase is implausible and has not been seen. This would imply that model M2 cannot be fully correct, since it predicts implausibly high mortalities.

The second factor involves a more mathematical analysis: through a Bayesian approach, one finds that model M1 for all causes of death is two times more likely than M2. This is obtained from dividing two likelihood functions for all input points by a factor containing parameter ranges (the Ockham factor) – see "model selection" in Sivia and Skilling (2006) and section 3.1.

4. RELATIVE RISK (RR) OF CANCER DEATH

In the paper of Cardis *et al.* (2007), the authors present data based on relative mortality ratios, taking workers with lowest doses as a control group. Thus, for the least exposed group, RR was taken as RR=1, with some resulting internal comparisons (Fig. 5). An alternative statistical analysis of these data is presented below. As before, two models (section 3.2): M1, with constant and dose-independent relative risk RR, and M2, with relation RR = a<D> + b were tested, where <D> is the cumulative dose. Two analysis methods were used: classical least-square fit (minimum χ^2) and Bayesian analysis (see section 3.1).

It follows from Table 1 in (Cardis *et al.* 2007) (which contains all the required data), that an increase of RR for leukemia is observed at a cumulative dose as low as 7.5 mSv (Fig. 6). In light of these extensive data, including the data from Hiroshima and Nagasaki (UNSCEAR 1994, 2000), such an increase is not plausible. In addition, this increase, though not very pronounced, occurs also for all causes of death, all cancers, solid cancers, non-cancer causes and many other results. Although hypersensitivity was observed in some colonies of cells in these cases, one cannot expect that this may describe a large population of people. There are in fact at least two ways to explain this phenomenon: one involves systematic errors in data collection. To correct the data in this case, one would need to adjust all of the data points downward, resulting in the value RR=1 at this local maximum, for a dose of 7.5 mSv. The second potential explanation is an unknown cause of deaths, not connected with ionizing radiation.

Two other questions occur when one inspects the data for higher cumulative doses. The first involves the unusually high relative risk obtained for a dose of 175 mSv. For example, considering mortality from

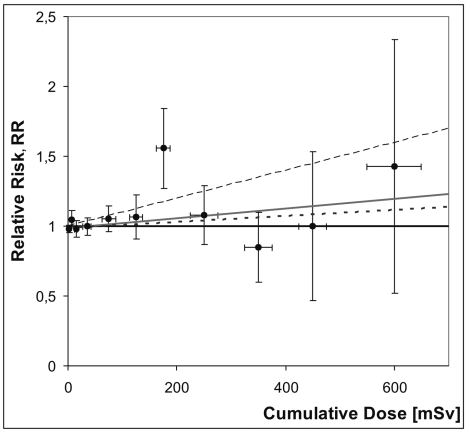

FIGURE 5. Relative Risk (RR) vs cumulative dose [mSv] from all cancers deaths. Solid horizontal line corresponds to RR=1, the highest dashed line is a fit as given by IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007), grey solid line corresponds to the least-squares solution, and dotted line is a Bayesian fit, when the point for 175 mSv is not taken into account.

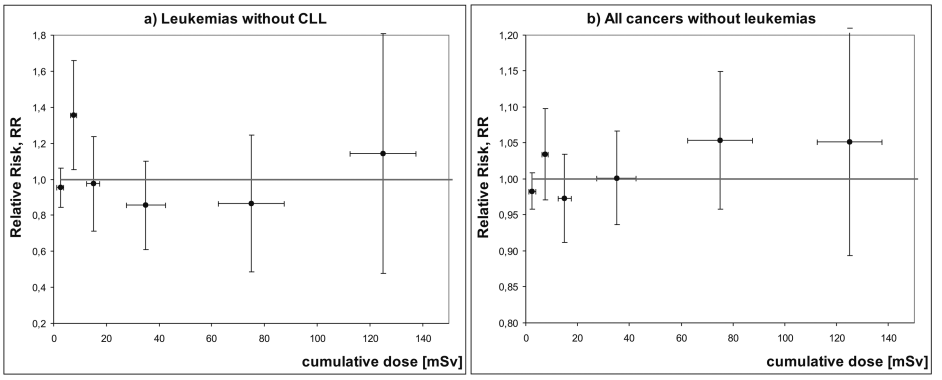

FIGURE 6. The Relative Risk (RR) connected with the cumulative dose for a) the leukemias without CLL, and b) all cancers without leukemias. The local maximum for the 7.5 mSv is clearly seen in both cases.

all cancers (Fig. 5), this data point appears too large. It might be reasonable to consider this point an 'outlier' and, for the moment, neglect it in this part of analysis. The second question involves data above a level of 500 mSv. In this dose range a very small number of deaths is registered, and it is unclear how much weight should be given to this data point, in particular since the dose uncertainty here appears high. Therefore the analysis has been carried out both with and without this point taken into account.

Results of all least-square and Bayesian analyses are shown in Table 5. The data are divided into three groups depending on the number of points. The first shows the results obtained when all 11 points published in (Cardis *et al.* 2007) are included. The next column contains the result

Healthy worker effect

TABLE 5. Results of Relative Risk (RR) based on least-square and Bayesian analysis[a].

	Results		
Subject	All 11 points	Below 500 mSv	without point at 175 mSv
Model M1, least-square method	x	<RR> = 1.001 ± 0.004	<RR> = 0.994 ± 0.005 –[b]
Model M2, least-square method	$a = (3.4 \pm 5.1)\cdot 10^{-4}$ b = 0.990 ± 0.024	$a = (3.1 \pm 4.2)\cdot 10^{-4}$ b = 0.991 ± 0.022	$a = (1.6 \pm 2.4)\cdot 10^{-4}$ b = 0.991 ± 0.008
			$a = (1.2 \pm 4.5)\cdot 10^{-4}$ b = 0.992 ± 0.022 –[b]
Modified[c] model M2, least-square method	$a = (2.74 \pm 2.93)\cdot 10^{-4}$	$a = (2.43 \pm 3.17)\cdot 10^{-4}$	$a = (0.58 \pm 2.17)\cdot 10^{-4}$ –[b]
Model M2, Bayesian method ('Bayes2')	$a = (3.0 \pm 18.1)\cdot 10^{-4}$ b = 0.99 ± 0.25	$a = (2.4 \pm 16.7)\cdot 10^{-4}$ b = 0.99 ± 0.24	$a = (2.1 \pm 3.2)\cdot 10^{-4}$ b = 0.99 ± 0.07

[a]The data were divided into three groups, depending on the number of analyzed points.
[b]Only 9 points: the 175 mSv and above 500 mSv ones were excluded.
[c]Where b=1; function y = ax + 1 was fitted to the data.

of the analysis using the 10 points below 500 mSv. The last column shows the results when only 9 points are taken into account, with the point at 175 mSv considered an 'outlier'.

It follows from Table 5 that, after removing the point for dose range above 500 mSv, the value of RR, obtained by least-squares applied to model M1, is <RR> = 1.001 ± 0.004, with χ^2= 11.2. If, in addition, the point at 175 mSv is removed as an outlier, <RR> changes to 0.994 ± 0.005 with χ^2= 2.1. The large drop in χ^2 shows that all the poor fits in the previous value <RR> are due to this single point. It is important to note that the remaining points lie almost exactly on the line RR = 1 (this is similar to the problem mentioned earlier, where the value of RR for leukemia at the low dose of 7.5 mSv appears overestimated).

A great increase of RR is consistently found at 175 mSv in all cause mortality, lung cancer deaths, solid cancer deaths, and all cause mortality, excluding leukemia. Generally speaking, the trends (shown in Fig. 6) of RR among all cause mortality, all cancer mortality or cancer deaths, excluding leukemia, are quite similar.

When model M2 is used, the uncertainty in slope (one standard deviation) is approximately the size of the slope itself. Although this does not invalidate the model in itself, it does indicates that the model might have lower credibility. Moreover, using model M2 consistently yields values of *b* lower than 1. Because of the basic assumption that RR at the lowest dose must be one, the function RR = a·x + 1 has also been fitted to the data. Results of these fits are also included in Table 5, though they are not significantly different from previous ones.

One more observation should be noted regarding the M2 model: results in Table 5 show again that the one point at 175 mSv is the main cause of all the uncertainty in the value of the slope, *a*. It is important that when this point is not included, the χ^2 values for the M2 model are not much better than ones for model M1. Thus, use of the additional slope parameter, *a*, does not enhance information on the dose-effect relationship (Sivia and Skilling 2006). The lines given originally by IARC (Cardis *et al.* 2007) are shown in Figure 5.

When the Bayesian approach is used, χ^2 values decrease as expected; however, this is accompanied by an increase in standard deviations of *a* and *b*. This can be expected, since achieving a more representative result (dataset) requires effective increases in data uncertainties. A consequence of this is that for IARC data, the Bayesian approach is less helpful in assigning a dose-effect dependence for RR.

In the above calculations the uncertainties in doses (whose estimates are given by horizontal error bars in Fig. 5) were neglected. When taken into account, the value of the slope parameter decreases by about 1% when all data are included, but as much as by 14% when the data for 175 mSv are excluded.

Thus, we can conclude that the RR data (Cardis *et al.* 2007) does not require an M2 model with non-zero slope. The simpler model of the two, which give similar results is preferred (according to Ockham's razor, *Non sunt multiplicanda entia sine necessitate*). In the present case, this is the M1 model, where RR = const.

5. CONCLUSIONS

The analysis of data published in IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) on the mortality of nuclear industry workers from 15 countries indicate both a decrease in the SMR and an approximate dose-independence of relative risk (RR) for cancer mortality for the range of doses evaluated (Figs 2 and 5). This has frequently been observed in a number of other health studies of nuclear industry workers over the world. Using two alternative statistical methods – the standard least-square test and a Bayesian analysis (Sivia 1996; Sivia and Skilling 2006) – both SMR and RR data have been shown as either independent of dose or having a linear dose-effect relationship known as the LNT. Although the IARC data (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) do not negate the possibility of LNT-type dependence, the present analysis indicates that it is much more likely that no dependence on dose exists. An attempt to see the agreement of the data with the LNT hypothesis might be considered more a matter of prior belief than reasoning based on the data (Oakley *et al.* 2006).

There are few statistically backed facts which would justify the belief that doses received by the studied cohort of workers could be a cause of

cancer mortality. The average annual doses received by the workers in these studies were at a level of 2 mSv, and even in the more extreme case of Switzerland, they did not exceed 5.3 mSv/year. These doses are comparable with average global natural radiation levels, which are about 2.4 mSv, and are much lower than in the study of radiologically contaminated houses in Taiwan (Chen *et al.* 2004; Hwang *et al.* 2008), or in some areas of China (HBRRG 1981), and a number of other countries (UNSCEAR 2000). The data presented by Luckey (2007, 2008b), Thompson *et al.* (2008) and UNSCEAR (1994) are quite similar to those of IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) (Figs 1 and 2) and consistently show substantial decreases of cancer mortality as compared with "unexposed" reference cohorts. There is little reason to believe in an HWSE in the IARC cohort (Fig. 2) (Arrighi and Hertz-Picciotto 1994).

The IARC authors (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) do not consider the possibility that the effects of radiation exposure could be beneficial (Fig. 2) (Luckey 2008b). The potentially therapeutic role of low doses of ionizing radiation is supported by biological arguments and facts (Nowosielska *et al.* 2009; Cohen 2008; Lin 2007; Pollycove 2007; Sakamoto 2004; Hosoi and Sakamoto 1993), in particular using the microdose and adaptive response models (Leonard 2008; Scott *et al.* 2009). To the potential detriment of the study, such facts and possible interpretations were not considered by IARC group (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007).

The HWE was used by IARC (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) as the only explanation of lower than expected mortality; the view is not supported by published data. In fact, there are many who believe that the HWE should not be used in analysis of cancer and in epidemiological studies (Li and Sung 1999; Monson 1986; Cohen 2002; Kojiro 1999; Cameron and Daunt 2002; Carpenter 1987; Sanders 2008). The most prominent deficit in the IARC data is the extremely high data variance. The focus should be on cause of observed differences in SMRs if the HWE were indeed responsible. To learn why SMR levels varied so widely it would be of interest to compare the pre-employment and employment medical routines to which workers were subjected in the 15 countries. This type of study could shed more light on the HWE problem. On the other hand, the analysis of the IARC data (Vrijheid *et al.* 2007; Therry-Chef *et al.* 2007; Cardis *et al.* 2007) treats all reported values of SMR using the same underlying model. The above re-analysis of these data shows primarily that the results of the analysis depend heavily on the way it is carried out. As mentioned before, the SMR data are inconclusive due to the large scattering of points and uneven distribution along the dose axis, while the very sparse RR data may contain at least one outlier. In spite of the strength of the Bayesian method, the present paper shows

that in the case of such inconsistent data there is no reason to use strong mathematical tools, and that a "common sense" approach in such situations can be sufficient. The implication most consistent with the IARC data is that neither SMR nor RR is dependent on dose, while the most solid conclusion concerns their average values.

A review of the data published by IARC and re-analyzed by Fornalski and Dobrzyński (2009) reveals inadequate statistics on all cause and all cancer mortality. It is also very important to examine and analyze morbidity, and not only mortality, in the same cohort of workers.

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