EVALUATION OF A PROTOTYPE CLL RISK MODEL

FOR POTENTIAL INCLUSION IN THE COMPUTER PROGRAM NIOSH-IREP

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INTRODUCTION

Trabalka and Apostoaei present an important and well-organized report *(1)* that provides a background, back-up data and rationale for a methodology to develop a prototype risk model for chronic lymphocytic leukemia (CLL) to be used with the NIOSH-IREP computer program. The following review of this report is broken down into two categories. First, the key points of the model development are addressed, technical questions regarding the specific elements of the model are raised and tentative solutions offered which may help refine the CLL risk model. Second, minor editorial changes/ suggestions are introduced.

KEY POINTS OF THE CLL MODEL DEVELOPMENT

A starting point for CLL risk model development described in the Trabalka and Apostoaei report *(1)* was a model currently in use by the Veteran's Administration (VA). In the VA model, risk of CLL is thought to be similar to the risk estimated for a lymphoma and multiple myeloma grouping. The highest of the reconstructed doses to the red bone marrow, spleen or thymus are used to estimate the probability of causation of CLL occurring in military personnel exposed to radiation.

In their report, Trabalka and Apostoaei went through several steps to develop a CLL risk model.

1. Review of the latest epidemiological, molecular and clinical literature on radiation-related risks of CLL.
2. Analysis of incidence rates of CLL in the U.S. and in Japan as a whole and for Hiroshima and Nagasaki separately.
3. Evaluation of the NIOSH model for lymphoma and multiple myeloma in terms of its relevance to the proposed CLL risk model.
4. Creation of a "Version 1" prototype model based on Land et al. 2003 *(2)* by extending a latency period for CLL.

These steps are reviewed in more detail below.

1. Review of the latest epidemiological, molecular and clinical literature on radiation-related risks of CLL.

Trabalka and Apostoaei *(1)* have thoroughly reviewed the key papers from the NIOSH Annotated Bibliography for CLL from 2004, as well as additional papers cited by several reviewers of the arguments advanced by the EEOICPA stakeholders. Sections 3.0 and 4.0 of the report contain a wide review of the recent developments in CLL research. In particular, some of the issues raised are as follows:

- Developmental characteristics of CLL as a form of NHL.
- Description of radiation target organs for CLL.
- Use of historical ICD codes for CLL and potential implications for research.
- New areas of CLL research, including genetic and molecular studies.

The report under review was issued in January 2009 *(1)*. In this reviewer's opinion, it would be essential to augment it with several recent references, which potentially could have an effect on the CLL risk model development. It is understood that recent attempts at developing radiation risk models *(2-4)* necessarily had to rely on the data from the Life Span Study (LSS) of survivors of atomic bombings in Japan to develop various radiation cancer risk models. While the data from the studies of occupationally exposed nuclear workers *(5)* were considered important to predict risks from low-dose low dose-rate exposures, it could not be used for quantitative risk assessment "principally because of the imprecision of the risk estimates obtained" (p. 268, *(4)*). However, since the publication of the NIOSH-CDC *(2)*, UNSCEAR 2000 *(3)*, and BEIR-VII *(4)* reports, the results of a much larger pooled analysis of mortality of more than 400,000 nuclear workers have been published *(6)*. Several reports based on this study provide much more precise estimates of cancer and non-cancer risks due to radiation exposure with narrower confidence intervals compared to the pooled study of nuclear workers *(5)* available at the time the three reports discussed above were issued.

The following recent references are considered particularly important for the development of a CLL risk model:

- Vrijheid et al. 2008 *(7)* analysis of mortality from CLL in a pooled cohort of 295,963 nuclear workers from 15 countries. After an average lifetime cumulative dose of 15 mSv, the study found little evidence of radiation-related risks of mortality from CLL. Small number of deaths in the cohort ascribed to CLL (n cases=65), high probability of

misclassification of CLL on death certificates, and low doses decreased the power of the study. NHL mortality in this cohort (n cases=248), however, was increased with an ERR=0.44 per Gy, 90% CI: <0, 4.78.

- Muirhead at al. 2009 *(8)* presented the results of an extended follow-up of the cohort of 174,541 workers from the National Registry for Radiation Workers in the U.K. After an average cumulative dose of 25 mSv, no increased risk of CLL incidence (n cases=128) or mortality (n cases=69) was observed, although confidence intervals were wide and were compatible with risks estimated for other types of leukemia. In contrast, incidence risk of NHL was border-line significant with an ERR=1.28 per Sv, 95% CI: -0.38, 4.06, p one-sided=0.081 (n cases=305). A similar, albeit smaller and non-significant, increasing trend of death from NHL with dose was observed.

- Richardson et al. 2009 *(9)* recently reported a positive significant association between ionizing radiation and NHL in a cohort of U.S. nuclear workers from the Savannah River Site (SRS), significantly larger in size than the one observed in the age- and sex-comparable LSS cohort (ERRs of 7.62 and 1.12 per Sv, respectively). The analysis was based on 51 deaths from NHL in a cohort of 20,940 SRS workers exposed to comparatively high average cumulative doses of 44 mSv *(10)*. An earlier study *(11)* did not find any increase in risk for CLL based on 22 deaths.

- Two additional recent incidence-based studies of radiation workers have shown an association between CLL and occupational radiation exposure *(12, 13)*, with one study *(12)* reporting a significant increase in CLL among Czech uranium miners presumably due to a gamma-radiation component of exposure in the mines and the other study *(13)* reporting an elevated risk among radiologic technologists who worked during the early years, when occupational doses were presumably high.

- Finally, two case-control studies of leukemia among Chornobyl (Chernobyl) clean-up workers have been published recently. Kesminiene et al. 2009 *(14)* reported on the incidence of hematological malignancies among clean-up workers from Belarus, Russia

and Baltic countries. The majority of workers were from Belarus and had little exposure to actual clean-up work. Nevertheless, doses experienced by the clean-up workers (median 13 mGy) were comparable to the doses received by the occupationally exposed nuclear power industry workers from the recent 15-country study (mean=19 mSv) *(6)*. Radiation-related risk of CLL was similar to that of non-CLL leukemia, ERR=4.7 and 5.0 per Gy, respectively. However, the dose-response was not statistically significant, in no small part due to a small number of cases (40 cases of leukemia, including 19 CLL).

A second case-control study of Chornobyl cleanup workers from Ukraine utilized essentially the same method to estimate radiation doses from detailed dosimetric questionnaires, but used a much more rigorous case ascertainment protocol and case verification and confirmation procedures *(15)*. The study was based on leukemia cases confirmed by the International Hematology and Pathology Panel *(15, 16)*. As a disclosure, I am a senior and corresponding author of this study *(17)* and have performed all data analyses for the publication.

In Romanenko et al. 2008 *(17)*, workers were exposed to relatively high doses, although still in the low-dose range (mean dose=76 mGy). A significant dose-response was reported for all leukemia with an ERR=3.44 per Gy, 95% CI: 0.47, 9.78. There was no significant difference in risk of CLL (n cases=39) and non-CLL (n cases=32) leukemia (p=0.75) and the risk of CLL was estimated at 4.09 per Gy, 95% CI: <0, 14.41. To further clarify these issues, the study has been extended to ascertain cases for another 6 years (2001–2006) and its results are expected at the end of 2010.

In summary, a new evidence that came into light in the year since the report has been issued, provides evidence for the hypothesis advocated by Trabalka and Apostoaei *(1)* that CLL may be radiogenic and that its risk profile may be similar to that previously observed for other types of leukemia and/ or NHL. These studies are of particular importance because they provide evidence from the low-dose studies, a dose range of primary interest for occupationally exposed workers in the U.S.

2. Analysis of incidence rates of CLL in the U.S. and in Japan as a whole and for Hiroshima and Nagasaki separately

Trabalka and Apostoaei used 2005 SEER database *(18)* to estimate sex- and age-specific incidence rates of CLL in the United States. This database contains information on new cancers diagnosed in the 13 U.S. metropolitan cancer registries in 1992-2002. The methodology used to estimate the rates in Table A.1 and Figure A.1 is not entirely clear and should be explained in more detail. It should also be noted that a much more detailed and up-to-date information about incidence rates in the U.S. population has been quoted in a recent article by Dores et al. 2007 *(19)*. Relevant to the current report, the article provides incidence rates of CLL and small lymphocytic lymphoma (SLL), a type of NHL closely related to CLL, estimated from the SEER database for 1993-2004 *(20)*. Dores et al. 2007 *(19)* showed that there were significant delays in reporting of CLL but not SLL in SEER. They estimated underreporting of CLL to be as high as 24% and suggested that 9-12 years were needed to capture delayed reporting. Zent et al. 2001 *(21)* suggested that, due to the rather indolent nature of CLL, tumor registries may be missing as much as 38% of CLL compared with the incidence of CLL detected using sophisticated measures such as flow cytometric immunophenotypic analysis.

The incidence rates of combined CLL/SLL in Dores et al. 2007 *(19)* are twice as high as those reported by Trabalka and Apostoaei in Table A.1 *(1)*, 7.04 and 3.72 per 100,000 per year for males and females, respectively. Approximately twenty-five percent of cases are attributed to SLL. Thus, there is still a big discrepancy between the numbers in Table A.1 and the numbers cited in Dores et al. 2007 *(19)*. The discrepancy is important because it provides evidence about incidence rates of CLL in the U.S. population in the absence of occupational radiation exposures.

Tables A.2 and A.3 present estimates of incidence rates of CLL in the Japanese population and for the Hiroshima and Nagasaki population separately. Trabalka and Apostoaei used IARC Publication No. 143 to estimate these rates *(22)*. It should be noted that a more recent edition of the Cancer Incidence on Five Continents (CI5) is now available (detailed CI5-VIII *(23)* and CI5-IX *(24)*). In addition, Table A.2 does not specify the years that were used to estimate incidence rates. Finally, incidence rates of CLL in Nagasaki are very unstable due to a small number of observed cases. For example, upon quick review of the detailed CI5-VIII *(23)*, this reviewer

observed that incidence rates of CLL varied widely from year to year in 1973-1997 in the Nagasaki Tumor Registry, with the majority of annual rates being zero, but some rates being as high as 0.93 and 0.81 per 100,000 per year for males and females, respectively. Thus, the calculation of expected number of CLL cases on page 5 is subject to great uncertainty.

In summary, this section would benefit from a more detailed description of the methods used to estimate average incidence rates of CLL in the U.S. and in the Japanese population. Provisions should be made to account for delayed reporting of CLL cases in the SEER database. In view of the main argument of this report that CLL and SLL are the same diagnostic entity, efforts should be made to include SLL incidence rates in the calculations. The more up-to-date datasets should be used in the calculations. Caution should be exercised while predicting an expected number of CLL cases in the absence of radiation in the Japanese population due to high variability of incidence rates of CLL in this population.

3. Evaluation of the NIOSH model for lymphoma and multiple myeloma in terms of its relevance to the proposed CLL risk model.

Trabalka and Apostoaei *(1)* reviewed a lymphoma model developed for the previous iteration of NIH Radioepidemiological tables and presented a justification for its use in predicting radiation-related risks of CLL. It is hard to agree with their argument to use a risk model for a combined grouping including multiple myeloma cases simply because 'it too is a disease of old age' (p.15, *(1)*). So far, there are very few studies which have explicitly evaluated the biological processes underlying radiation-related multiple myeloma and its origins. CLL and multiple myeloma are both B-cell hematological malignancies, but are entirely "distinct lymphoproliferative neoplasms with different clinical presentations and clinical courses" (p.561, *(25)*). In addition, keeping a combined group estimate would necessarily lower the risk estimate to be used for CLL. In fact, average excess relative risk estimate for multiple myeloma among men in the LSS study is 0.17 per 1 Sv, i.e. five-fold lower than a risk estimate for NHL among men, ERR=0.91 per Sv. Since The Principles & Practice of Oncology textbook by DeVita et al. *(26)* notes that 25% of CLL are SLL cases, it makes sense to use the higher estimate for NHL cases in the new CLL risk model.

Another argument advanced to use a combined estimate for NHL, multiple myeloma and Hodgkin's lymphoma is that NHL may include both indolent lymphomas (of which CLL/SLL is a part) and more aggressive lymphomas. The notion of CLL being indolent has been disputed recently. Several studies have demonstrated marked differences in the clinical course and morphological features of CLL diagnosed in Chornobyl cleanup workers exposed to gamma radiation and the general population *(27-29)*. Chornobyl-associated CLL cases were characterized by younger age, more advanced stage of disease at presentation, and faster progression. Cleanup workers with comparatively large radiation doses had CLL characterized by high mutation rates in several genes associated with poor disease prognosis *(27, 28)*. Thus, it is possible that CLL among workers occupationally exposed to radiation could differ from the CLL in the general population unexposed to radiation.

A careful consideration should be given to existing risk models for development of a new CLL risk model. For example, recent studies showed that risks of incident CLL among Chornobyl clean-up workers are comparable to the risks of non-CLL leukemia. Both studies *(14, 17)* showed that CLL risks are at the level of risks observed for leukemia in the LSS study, i.e. average excess relative risk of 3.91 at 1 Sv for men *(3)*. These studies, thus, show that further consideration should be given to using current leukemia models to predict risks of CLL.

This reviewer understands that the most recent updates of leukemia and lymphoma incidence in the LSS cohort based on DS02 have not been published, but would strongly advocate waiting for them and asking Dr. Land to develop a new CLL risk model based on the combination of NHL and CLL cases along with careful consideration of the recently published Chornobyl studies. If this choice is entirely not possible, then the NHL-alone model is more appropriate than a combined lymphoma and multiple myeloma risk model.

4. Creation of a "Version 1" prototype model based on Land et al. by extending the latency period for CLL.

The three most important assumptions of the new prototype model proposed by Trabalka and Apostoaei *(1)* are as follows:

- A latency period for CLL has a point estimate of 15 years

- Bone marrow is not an appropriate target organ for CLL risk estimation
- A dose and dose-rate effectiveness factor (DDREF) should be used for fractionated exposures
- A multiplicative model, in which an excess relative risk per unit of dose multiplies the background risk, is not appropriate for CLL

A choice of a 15-year lag in the incident CLL risk model is not completely justified as it is based on neither real observational studies nor biological models, but solely on the mathematical projections. At the time when all solid cancers are assigned a 10-year latency period, it is hard to defend a notion that CLL is somehow different from other cancers. A strategy of separating CLL from other radiation-related leukemias has been challenged recently and one should be cautious about introducing new 'exceptional' approaches to modeling CLL risks. A quick review of the most recent CLL/NHL studies showed that a 10-year lag has become a standard in the last decade. Richardson et al. 2009 *(9)* found significant increases in risk of NHL mortality in the SRS cohort both under 5-year and 10-year lag assumptions. In our study of Chornobyl clean-up workers *(17)*, we assessed lag time in 1-year increments between 0 and 10 years. The deviance, was minimized for both CLL and non-CLL analyses when we the lag interval was set to 2 years.

A discussion regarding target organs for CLL on page 18 is not entirely clear to this reviewer. The great majority of occupationally exposed workers in the U.S. would have been exposed to external gamma radiation. Their exposures are usually recorded as whole-body doses and stored either by employing facilities, the Nuclear Regulatory Commission or the Department of Energy. The majority of recent studies of U.S. nuclear workers used whole-body or bone marrow doses for analysis of leukemia, CLL, NHL or combination thereof *(9, 30, 31)*. A proposal to develop a "surrogate for a whole-body dose … {*by way of}* combination of the esophageal, colon, and bone marrow doses" as described on p. 18 is, therefore, questionable.

Land et al. 2003 *(2)* report applied the DDREF factor to all chronic exposures. However, a notion that the risk per unit dose decreases with decreasing dose and dose-rate is not supported in any of the low-dose low-dose-rate studies published in the last decade. The 15-country study *(6)* showed that the risk of solid cancer among occupational exposed workers was similar or higher

per unit of dose exposure compared to the LSS study. Thus, a continued use of the DDREF factor should be carefully evaluated.

An argument about handling of risk transport between population advanced in paragraph 2 on page 19 is not convincing. The reason that so far we have limited data about CLL risks from epidemiological studies of radiation workers and medically exposed groups is not because the interaction between CLL and radiation is not multiplicative but because most occupational studies to date were based on mortality rather than incidence and mortality data usually underestimate, possibly substantially, the occurrence of CLL. Case in point is a recent study from the U.K. by Muirhead et al. 2009 *(8)* which showed that approximately 50% of CLL incident cases did not have a corresponding death from CLL. Not surprisingly then, recent mortality studies that evaluated dose response for CLL separately had either negative findings *(6, 32)* or positive findings with a negative dose–response trend *(31, 33, 34)*. In view of this underreporting of deaths from CLL, more attention should be paid to the recent results with respect to radiation-related risks of NHL. As mentioned on page 2 of this report, Muirhead et al. 2009 *(8)* reported a border-line significant risk of incident NHL in their study.

Furthermore, the reason that high-dose studies of populations treated with radiotherapy for a first primary cancer showed no increase in the incidence of CLL, whereas a significant increase was demonstrated for all other types of leukemia *(35, 36)*, is because of the short follow-up after radiation treatment and young age of cancer survivors.

In summary, the four main assumptions used to develop a prototype CLL risk model are questioned by this reviewer. A model assuming a standard 10-year latency period based on the whole-body doses seems the most appropriate at this time. Further analysis of the LSS incidence data and its comparison with the recent studies of incident CLL in occupationally exposed workers *(14, 17)* should shed light on the appropriateness of the DDREF at low doses.

MINOR EDITORIAL CHANGES/ SUGGESTIONS.

- A statement on page 5 that "If the estimated number of CLL cases in the absence of radiation exposure had been greater than 4, then we might have been able to conclude that the dose-response for CLL in the LSS cohort should be negative" is incorrect. The relationship between expected and observed cases of CLL is not related to the dose-response due to radiation.
- There are several mistakes in referencing various tables on pages 14-15:
    - Tables 18, 19 and 20 in UNSCEAR 2000 *(3)*
    - Table IV.C.2 in Land et al. 2003 *(2)*
- Several direct quotes from Land et al. 2003 *(2)* on p.15 are not properly referenced
- Section 5.0 would benefit from a more structured approach with separate subtitles for separate topics
- Figure 1 is missing Boivin et al. 1986 *(36)* with 166 CLL cases
- A discussion of the application of weights to different target organs on p.18 is highly speculative and should be carefully re-evaluated
- In view of the recently published studies, this reviewer disagrees with a statement on page 19 about 'week radiogenicity' of CLL. Improved study methods and diagnostic procedures in recent studies provide substantial evidence of radiation-related risks of CLL

REFERENCES

1. J. R. Trabalka and A. I. Apostoaei, *Development of a CLL Risk Model for NIOSH-IREP*. SENES Oak Ridge, Inc.: Oak Ridge, TN, 2009.
2. C. E. Land, E. Gilbert, J. M. Smith, F. O. Hoffman, A. I. Apostoaei, B. Thomas and D. C. Kocher, *Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables.* NIH Publication No. 03-5387. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute: Bethesda, MD, 2003.
3. UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation), *2000 Report to the General Assembly, with Scientific Annexes. Volume II: Effects.*, United Nations: New York, 2000.
4. BEIR VII-phase II, *Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation.* National Academy Press: Washington, DC, 2005.
5. E. Cardis, E. S. Gilbert, L. Carpenter, G. Howe, I. Kato, B. K. Armstrong, V. Beral, G. Cowper, A. Douglas, J. Fix and et al., Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res* **142** (2), 117-32. (1995).
6. E. Cardis, M. Vrijheid, M. Blettner, E. Gilbert, M. Hakama, C. Hill, G. Howe, J. Kaldor, C. R. Muirhead, M. Schubauer-Berigan, T. Yoshimura, F. Bermann, G. Cowper, J. Fix, C. Hacker, B. Heinmiller, M. Marshall, I. Thierry-Chef, D. Utterback, Y. O. Ahn, E. Amoros, P. Ashmore, A. Auvinen, J. M. Bae, J. Bernar, A. Biau, E. Combalot, P. Deboodt, A. Diez Sacristan, M. Eklof, H. Engels, G. Engholm, G. Gulis, R. R. Habib, K. Holan, H. Hyvonen, A. Kerekes, J. Kurtinaitis, H. Malker, M. Martuzzi, A. Mastauskas, A. Monnet, M. Moser, M. S. Pearce, D. B. Richardson, F. Rodriguez-Artalejo, A. Rogel, H. Tardy, M. Telle-Lamberton, I. Turai, M. Usel and K. Veress, The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. *Radiat Res* **167** (4), 396-416 (2007).
7. M. Vrijheid, E. Cardis, P. Ashmore, A. Auvinen, E. Gilbert, R. R. Habib, H. Malker, C. R. Muirhead, D. B. Richardson, A. Rogel, M. Schubauer-Berigan, H. Tardy and M.

Telle-Lamberton, Ionizing radiation and risk of chronic lymphocytic leukemia in the 15-country study of nuclear industry workers. *Radiat Res* **170** (5), 661-5 (2008).

8. C. R. Muirhead, J. A. O'Hagan, R. G. Haylock, M. A. Phillipson, T. Willcock, G. L. Berridge and W. Zhang, Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer* **100** (1), 206-12 (2009).
9. D. B. Richardson, H. Sugiyama, S. Wing, R. Sakata, E. Grant, Y. Shimizu, N. Nishi, S. Geyer, M. Soda, A. Suyama, F. Kasagi and K. Kodama, Positive associations between ionizing radiation and lymphoma mortality among men. *Am J Epidemiol* **169** (8), 969-76 (2009).
10. D. B. Richardson, S. Wing and S. Wolf, Mortality among workers at the Savannah River Site. *Am J Ind Med* **50** (12), 881-91 (2007).
11. D. B. Richardson and S. Wing, Leukemia mortality among workers at the Savannah River Site. *Am J Epidemiol* **166** (9), 1015-22 (2007).
12. V. Rericha, M. Kulich, R. Rericha, D. L. Shore and D. P. Sandler, Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. *Environ Health Perspect* **114** (6), 818-22 (2006).
13. M. S. Linet, D. M. Freedman, A. K. Mohan, M. M. Doody, E. Ron, K. Mabuchi, B. H. Alexander, A. Sigurdson and M. Hauptmann, Incidence of haematopoietic malignancies in US radiologic technologists. *Occup Environ Med* **62** (12), 861-7 (2005).
14. A. Kesminiene, A. S. Evrard, V. K. Ivanov, I. V. Malakhova, J. Kurtinaitis, A. Stengrevics, M. Tekkel, L. R. Anspaugh, A. Bouville, S. Chekin, V. V. Chumak, V. Drozdovitch, V. Gapanovich, I. Golovanov, P. Hubert, S. V. Illichev, S. E. Khait, V. P. Kryuchkov, E. Maceika, M. Maksyoutov, A. K. Mirkhaidarov, S. Polyakov, N. Shchukina, V. Tenet, T. I. Tserakhovich, A. Tsykalo, A. R. Tukov and E. Cardis, Risk of hematological malignancies among Chernobyl liquidators. *Radiat Res* **170** (6), 721-35 (2008).
15. A. Romanenko, V. Bebeshko, M. Hatch, D. Bazyka, S. Finch, I. Dyagil, R. Reiss, V. Chumak, A. Bouville, N. Gudzenko, L. Zablotska, M. Pilinskaya, T. Lyubarets, E. Bakhanova, N. Babkina, N. Trotsiuk, B. Ledoschuk, Y. Belayev, S. S. Dybsky, E. Ron and G. Howe, The Ukrainian-American study of leukemia and related disorders among

Chornobyl cleanup workers from Ukraine: I. Study methods. *Radiat Res* **170** (6), 691-7 (2008).

16. I. Dyagil, M. Adam, G. W. Beebe, J. D. Burch, S. N. Gaidukova, D. Gluzman, N. Gudzenko, V. Klimenko, L. Peterson, R. F. Reiss and S. C. Finch, Histologic verification of leukemia, myelodysplasia, and multiple myeloma diagnoses in patients in Ukraine, 1987-1998. *Int J Hematol* **76** (1), 55-60 (2002).
17. A. Y. Romanenko, S. C. Finch, M. Hatch, J. H. Lubin, V. G. Bebeshko, D. A. Bazyka, N. Gudzenko, I. S. Dyagil, R. F. Reiss, A. Bouville, V. V. Chumak, N. K. Trotsiuk, N. G. Babkina, Y. Belyayev, I. Masnyk, E. Ron, G. R. Howe and L. B. Zablotska, The Ukrainian-American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: III. Radiation risks. *Radiat Res* **170** (6), 711-20 (2008).
18. SEER-13, Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1992-2002), National Cancer Institute, CDDPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission. 2005, www.seer.cancer.gov
19. G. M. Dores, W. F. Anderson, R. E. Curtis, O. Landgren, E. Ostroumova, E. C. Bluhm, C. S. Rabkin, S. S. Devesa and M. S. Linet, Chronic lymphocytic leukaemia and small lymphocytic lymphoma: overview of the descriptive epidemiology. *Br J Haematol* **139** (5), 809-19 (2007).
20. SEER-13, Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1992-2004), National Cancer Institute, CDDPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission. 2007, www.seer.cancer.gov
21. C. S. Zent, M. J. Kyasa, R. Evans and S. A. Schichman, Chronic lymphocytic leukemia incidence is substantially higher than estimated from tumor registry data. *Cancer* **92** (5), 1325-30 (2001).
22. Parkin DM, Whelan SL, Ferlay J, Raymond L and Y. J, *Cancer Incidence in Five Continents Vol. VII*. IARC Scientific Publications, No. 143: Lyon, 1998.
23. Parkin DM , Whelan SL , Ferlay J , Teppo L and Thomas DB *Cancer Incidence in Five Continents: Vol. VIII*. IARC Scientific Publications, No. 155: Lyon, 2003.

24. M. P. Curado, B. Edwards, H. R. Shin, H. Storm, Ferlay J , M. Heanue and P. Boyle, *Cancer Incidence in Five Continents: Vol. IX*. IARC Scientific Publications No. 160: Lyon, France, 2007.
25. S. Srinivasan and C. A. Schiffer, Concurrent B-cell chronic lymphocytic leukemia and multiple myeloma treated successfully with lenalidomide. *Leuk Res* **33** (4), 561-4 (2009).
26. V. T. DeVita, T. S. Lawrence, S. A. Rosenberg and R. DePinho, *Cancer: Principles & Practice of Oncology*. Eighth ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2008.
27. I. Abramenko, N. Bilous, A. Chumak, E. Davidova, I. Kryachok, Z. Martina, S. Nechaev, I. Dyagil, D. Bazyka and V. Bebeshko, Chronic lymphocytic leukemia patients exposed to ionizing radiation due to the Chernobyl NPP accident-With focus on immunoglobulin heavy chain gene analysis. *Leuk Res* **32** (4), 535-45 (2008).
28. I. Kryachok, O. Polyshchuk, I. Dyagil, I. Abramenko, D. Bazyka and V. Bebeshko, Comparative analysis of CLL in persons who suffered after Chernobyl accident and in unexposed CLLpatients. *Haematologica* **90** (Supplement), 454A (2005).
29. T. J. Hamblin, Have we been wrong about ionizing radiation and chronic lymphocytic leukemia? *Leuk Res* **32** (4), 523-5 (2008).
30. G. R. Howe, L. B. Zablotska, J. J. Fix, J. Egel and J. Buchanan, Analysis of the Mortality Experience amongst U.S. Nuclear Power Industry Workers after Chronic Low-Dose Exposure to Ionizing Radiation. *Radiation Research* **162** (5), 517-526 (2004).
31. M. K. Schubauer-Berigan, R. D. Daniels, D. A. Fleming, A. M. Markey, J. R. Couch, S. H. Ahrenholz, J. S. Burphy, J. L. Anderson and C. Y. Tseng, Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature. *Br J Haematol* **139** (5), 799-808 (2007).
32. N. S. Shilnikova, D. L. Preston, E. Ron, E. S. Gilbert, E. K. Vassilenko, S. A. Romanov, I. S. Kuznetsova, M. E. Sokolnikov, P. V. Okatenko, V. V. Kreslov and N. A. Koshurnikova, Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat Res* **159** (6), 787-98 (2003).
33. G. M. Matanoski, J. A. Tonascia, A. Correa-Villasenor, K. C. Yates, N. Fink, E. Elliott, B. Sanders and D. Lantry, Cancer risks and low-level radiation in U.S. shipyard workers. *J Radiat Res (Tokyo)* **49** (1), 83-91 (2008).

34. J. D. Boice, S. S. Cohen, M. T. Mumma, E. Dupree Ellis, K. F. Eckerman, R. W. Leggett, B. B. Boecker, A. B. Brill and B. E. Henderson, Mortality among radiation workers at Rocketdyne (Atomics International), 1948-1999. *Radiat Res* **166** (1 Pt 1), 98-115 (2006).
35. R. A. Kleinerman, J. D. Boice, Jr., H. H. Storm, P. Sparen, A. Andersen, E. Pukkala, C. F. Lynch, B. F. Hankey and J. T. Flannery, Second primary cancer after treatment for cervical cancer. An international cancer registries study. *Cancer* **76** (3), 442-52 (1995).
36. J. F. Boivin, G. B. Hutchison, F. B. Evans, K. T. Abou-Daoud and B. Junod, Leukemia after radiotherapy for first primary cancers of various anatomic sites. *Am. J. Epidemiol* **123** (6), 993-1003 (1986).