Strahlenschutzkommission

Geschäftsstelle der
Strahlenschutzkommission
Postfach 12 06 29
D-53048 Bonn

http://www.ssk.de

Low-dose Extrapolation of Radiation-Related Cancer Risk

Statement of the German Commission on Radiological Protection concerning the ICRP Committee 1 Task Group Report, Draft 12/421/04

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1 Introduction

The ICRP Committee 1 Task Group Report *Low-dose extrapolation of radiation-related cancer risk* reviews

- cancer risks in human populations with low-LET radiation exposures,
- radiation induced DNA damage, repair, and cellular consequences,
- animal experiments on cancer induction and life shorting due to radiation exposures.

The review is supplemented by an uncertainty analysis for risk estimations taking into account probabilities for the existence of a threshold, below which radiation exposure does not cause cancer. The Task Group Report is of high quality and covers many topics which are of importance for the understanding of radiation effects on all levels: molecules, cells and organisms. Nevertheless, several important issues, which are of importance for the evaluation of cancer risks after exposures of ionizing radiation with low/moderate doses have not been mentioned, or are not discussed in sufficient detail.

A main problem in low-dose extrapolation of radiation related cancer risk is the combination of epidemiological and radiobiological data. The Task Group Report remains here on the level of describing epidemiological and radiobiological results separately. Instead, the Task Group Report should encourage future research on integrating low-dose radiobiological results in analyses of epidemiological and animal experimental data. Carcinogenesis is a very complex process, and radiation effects may influence the process on various stages. Radiation may cause, e.g. mutations, epigenetic events, genomic instability, apoptosis, or influence the control of initiated cells. A radiobiological effect on one type of these events does not necessarily imply that cancer risk has the same dose dependence as the effect.

Possible consequences of radiobiological effects on cancer risk estimates can be explored with models of carcinogenesis. An example of such work is the analysis of lung cancer incidence among the atomic bomb survivors with the two-step clonal expansion (TSCE) model of carcinogenesis taking account of low-dose hypersensitivity (Jacob and Jacob 2004). Low-dose hypersensitivity is a main possible radiobiological effect for acute doses of low-LET radiation, which is the exposure mode of the survivors. In the analysis, initiated cells were allowed to express a) low-dose hypersensitivity in cell inactivation, and b) an increased division rate, either due to a replacement of inactivated healthy cells or due to a decrease of the control by neighboring cells. In the preferred model, increasing the division rate is a stronger effect on the clonal growth of initiated cells than the inactivation of initiated cells. For low doses, the resulting estimate of the excess relative risk is in comparison to a linear model comparable for ages-at-exposure of 20 and larger for older ages at exposure.

2 Epidemiological considerations

The chapter provides a useful overview of current knowledge in radio-epidemiology. Issues with regard to dose-response curves are summarized, and factors that are important with respect to their interpretation (such as modifications due to age and sex, lifestyle, radiation quality, transfer to other populations) are discussed.

2.1 Dependence of cancer risk on radiation dose (Section 2.2 of the Task Group Report)

While the SSK fully supports the statements made in this section, one additional point needs to be mentioned. There is some evidence that the data for the atomic bomb survivors may be described using higher neutron weighting factors than 10, as it is done in the standard analyses (Kellerer and Walsh 2001, Walsh et al. 2004a, b). A higher neutron weighting factor decreases the risk estimates for gamma radiation, especially for the least shielded organs such as the breast, bladder and oesophagus. With an assumed weighting factor of 35, which is in line with results on low neutron doses in major past studies on rodents and which corresponds approximately to the current ICRP radiation weighting factor for neutrons, the neutrons contribute about 40 % to the observed excess cancer risk in the breast.

2.2 Extrapolation to low doses and dose rates (Section 2.4.4 of the Task Group Report)

Whereas in the past it has been reported that linear dose-response relationships describe the data for solid cancer among the atomic bomb survivors best, there are two recent papers, in which a linear-quadratic dose response is preferred. Walsh et al. (2004a) improved standard analyses of all solid cancers combined by using organ-specific doses instead of colon doses. A linear-quadratic dose response was found for the follow-up 1950-1997. The SSK recommends mentioning this paper in the Task Group Report. Preston et al. (2004) found as well a significant upward curvature in the data on all solid cancers combined using a follow-up 1950-2000. The SSK supports the recommendation of Preston et al. not using the linear-quadratic model to estimate low-dose risk. The reason is the result of a non-parametric analysis, which does not show a decreased risk per dose at low doses. The SSK recommends supplementing dose-response analyses in the low-dose range by using non-parametric methods. In the non-parametric method of Chomentowski et al. (2000), a series of analyses of excess risks in dose intervals is performed, which makes results independent of the choice of the intervals and gives a parameter-free visualization of the dose dependence of the excess risk estimate and its uncertainty.

The SSK agrees with the statements in the Task Group Report that for the atomic bomb survivors

- solid cancer data do not consistently support that the risk at low doses is by a factor of 2 lower than the risk derived from the 0-2 Sv data,
- leukemia data do support the risk at low doses being lower than the risk derived from the 0-2 Sv data.

Considering that excess deaths due to leukemia constitute less than 20 % of the excess deaths due to solid cancer, the SSK supports the general conclusion that the data for the atomic bomb survivors do not give strong arguments for reduced risks per unit dose at low doses. As stated earlier, the SSK is not aware of sufficiently strong scientific arguments to keep the concept of a DDREF. A possible underestimation of the risk at low doses does not confer with the principle of precaution.

3 Low-dose risk – Biology

The Chapter *Low-dose risk – Biology* of the Task Group Report summarizes biological considerations for low dose risk. An emphasis is placed on recent mechanistic and molecular aspects of DNA damage response mechanisms and their potential impact on risk assessment. This represents a suitable and up-to-date survey of the various processes, which should assist in the development of a more generalized picture of our current knowledge about low dose risk assessment.

The central importance of DNA lesions for radiation-related risk is stated several times. The Task Group Report deals, however, only with effects caused by hits in the cell nucleus. The SSK recommends mentioning that also radiation exposure of the cell plasma may cause mutations. Wu et al. (1999) irradiated the cytoplasm of human-hamster hybrid (A_L) cells with a microbeam of α-particles. A significant increase in mutations at the CD59 (S_1) nuclear gene locus was observed. Cytoplasmic irradiation with a single α-particle doubled the spontaneous mutation frequency, while a two- to threefold increase was observed after four cytoplasmic traversals. The mutational spectrum was similar to the spontaneous mutation spectrum, but it was different from that observed after targeted nuclear irradiation. The possible importance of targeted cytoplasmic irradiation is further supported by new findings, which show that cytoplasmic microbeam irradiation ($^3He^{2+}$) of glioma cells induces micronuclei in co-cultured neighboring nonirradiated human fibroblasts. Nitric oxide (NO) was shown to be responsible for this bystander effect (Shao et al. 2004).

3.1 Damage caused by radiation (Section 3.2 of the Task Group Report)

In addition to clustered DSBs and breaks associated with base damage, radiation-induced clustered base damages (also called "localized denatured regions" or "S1 nuclease-sensitive sites", short "S1 sites") need to be considered. These damages are approximately twice as frequent as DSBs, and they can be detected and quantified by use of S1 endonuclease in γ-irradiated phages, bacteria, yeast and mammalian cells (Geigl and Eckardt-Schupp 1990, 1991, Gulston et al. 2002, Lomax et al. 2002). The repair kinetics of S1 sites in yeast are similar to those of DSBs suggesting similar repair processes (probably homologous recombination) for both types of damage. Clustered DNA damage induced by densely ionizing radiation leads to complex genetic changes (visible as chromosomal rearrangements) which are likely to contribute significantly to the carcinogenic properties of densely ionizing radiation (Singleton et al. 2002).

3.2 Damage response pathways (Section 3.3 of the Task Group Report)

Recently, indications for potential non-linear dose dependence were found for several response mechanisms, and it is suggested to include a discussion of this work in the report. For example, there is some evidence that the ATM-dependent response pathway may not be fully activated after exposure at low dose rate (9.4 cGy/h; Collis et al. 2004) or at doses below 400 mGy delivered at high dose rate (Kitagawa et al. 2004). Also, the pathways leading to ATM activation may differ at lower and higher doses (Mochan et al. 2003). Reduced activation of ATM has been implicated as causing insufficient G2/M arrest (Collis et al. 2004). This is corroborated by the observation that one of the two types of the G2-arrests (Xu et al. 2002), namely the early, ATM-dependent arrests, exhibits similar dose requirements as is seen for ATM activation. Insufficient activation of the ATM-dependent response pathway

has also been implicated as a critical factor determining low dose hypersensitivity (Marples et al. 2004).

Reduced activation of the ATM-dependent response pathway may translate into reduced activation of p53 at low doses (Kitagawa et al. 2004). As a consequence, pro-apoptotic genes appear to be induced only at higher damage densitiy. Dose rate-specific differences in the expression of p53 target genes were also observed in large scale array analyses (Amundson et al. 2003).

3.3 Fidelity of DSB repair (Section 3.4 of the Task Group Report)

There is no doubt that changes in the balance of DSB repair pathways cause an increase in the occurrence of chromosomal aberrations. The role of NHEJ is thoroughly discussed, however, the Task Group Report should also mention deregulation in the use of subpathways of homologous recombination for the repair of radiation-induced DSBs. Generally, non-crossover subpathways like synthesis-dependent strand annealing (SDSA) and BLM/topoIIIα-dependent dissolution of Holliday junctions mediate DSB repair without generation of sister chromatid exchanges (SCE's) and chromosomal rearrangements, whereas the subpathways dependent on RAD51C-XRCC3 and MUS81 that cause crossover lead to SCE's (Liu and West 2004). Several genes are known which suppress crossovers in yeast and mammalian cells, like SRS2, RAD18, and other RecQ helicases. Mutations in these genes cause significant increases in the frequencies of SCE's and chromosomal aberrations (Ira et al. 2003, Tateishi et al. 2003, Hu et al. 2005).

Furthermore, it was early shown that DSB repair processes and ATM-dependent signaling are required for the maintenance of telomeres in yeast and mammalian cells. If the telomere structure is disturbed, chromosomal fusions occur (for a recent review see Iliakis 2004). Additionally, a close correlation between radiosensitivity and telomere maintenance is postulated (Slijepcevic 2004, Slijepcevic and Al-Wahiby 2005).

4 Cellular consequences of radiation-induced damage

This is a very well written, comprehensive summary, based on relevant literature which has been published up to the year 2004. However, the authors of the chapter do not mention at all epigenetic modifications, like e.g. histone-tail phosphorylation, acetylation and methylation, DNA-methylation and nucleosome-remodeling (Jiang et al. 2004, Bird 2002, Jenuwein and Allis 2001, Becker and Hörz 2001, Lund and Lohuizen 2004). These modifications are known to play important roles in chromatin-organization and, therefore, also for damage induction by ionizing radiation and may be even more for DNA (chromatin) repair. It seems therefore very likely that epigenetic modifications will affect "cellular consequences of radiation induced damage" to a high degree.

5 Carcinogenic effects of ionizing radiation

Animal experiments contribute significantly to the understanding of carcinogenic effects of ionizing radiation. There is, however, as stated in the Task Group Report only limited information on radiation-related cancer in the low-dose range. The data on myeloid leukemia show, as the data for atomic bomb survivors, a reduced risk per dose in the low-dose range. Whereas also for lung adenocarcinomas a reduced risk per dose is observed in animal

experiments with low dose, such an effect has not been observed for mammary tumors. In this context, the SSK supports the important statement in the Task Group Report that 'myeloid leukemia is probably more sensitive to dose rate effects than are solid tumors'.

6 Quantitative uncertainty analysis

In this chapter the concept of a quantitative uncertainty analysis is clearly described and applied to an uncertain knowledge about the existence of a low-dose threshold for radiation risks. It is somewhat unclear, however, why the authors apply a DDREF and *additionally* allow for the uncertain possibility of a threshold. Thus the resulting uncertainty distribution includes the reduction of the slope at low doses due to both, the DDREF and the possibility of a threshold. Probably it is more consistent to allow either for a DDREF or for a threshold.

7 Conclusions

The SSK agrees with the following conclusions of the Task Group Report:

- Epidemiological studies of cancer risk following radiation exposure provide the primary basis for estimation of radiation-related risk in human populations. At low doses, however, risk estimates are highly uncertain because of statistical fluctuations and other variations in the baseline risk.
- There is some epidemiological evidence linking increased childhood cancer risk to in utero exposures at doses in the order of 10 mGy.
- Epidemiology and animal experiments have demonstrated that after low and moderate dose exposures of the small intestine, of bone and of skin radiation-related tumors occur, if at all, with a markedly lower probability than expected from high dose exposures. Therefore, the existence of a threshold for tumor induction is more probable in these organs than in others.
- Even a single track through a cell is likely to induce clustered damages, which are unique for ionizing radiation. There is emerging evidence that such closely spaced lesions can compromise the repair machinery. There is therefore no evidence for a radiation dose below which all radiation-induced damage can be repaired with fidelity.
- Not much is known about the relation of radiation-related adaptive response, genomic instability, bystander effects and low-dose hypersensitivity in vivo and carcinogenesis. At the current state it is too early to derive conclusions on cancer risks after low-dose exposure.
- Presently, a threshold in the order of 10 mGy can not be excluded for most cancer sites. However, there are some indications for a small cancer risk in this dose range. The LNT model remains the most adequate risk model for guidance of radiation protection.

As stated in the Task Group Report, the SSK acknowledges *'…the predominant importance of DNA DSB induction and post-irradiation error-prone NHEJ repair for the induction of aberrations, and the apparently critical role for radiation-induced aberrations in the pathogenesis of cancer in these experimental models…'*. According to the Task Group Report these effects '*…argue against the proposition of a low dose threshold in the dose response.'* The SSK recommends, however, to be cautious with general conclusions from these observations for the dose-response relationship in the low-dose range. The complex

intercellular interaction in the body and the role of the immune system in the process of carcinogenesis are far from an understanding of their implications for risk estimations.

Overall, the SSK agrees with the main statements in the Task Group Report, it is, however, suggested to add several aspects important for low-dose extrapolation of radiation related cancer risk. A main point is here the combination of epidemiological and radiobiological data. Carcinogenesis is a very complex process, and radiation effects may influence the process on various stages. Radiation may cause among others mutations, epigenetic events, genomic instability, apoptosis, or affect the control of initiated cells. A radiobiological effect on one type of these events does not necessarily imply that cancer risk has the same dose dependence as the effect itself. The SSK recommends analyses of epidemiological and animal experimental data with models of carcinogenesis, because these models allow in contrast to non-mechanistic models a consideration of radiobiological effects in a more appropriate way.

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