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NOTE

Reflections on effects of low doses and risk inference based on the UNSCEAR 2021 report on 'biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation'

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Abstract

The 2021 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report summarises the knowledge on biological mechanisms of radiation action at low doses where, due to low statistical power of epidemiological investigations, the level of cancer risk must be inferred. It is the fourth UNSCEAR report since 1994 that looks into biological effects following low dose exposure with the aim of examining whether they support the assumption of the linear non-threshold (LNT) dose response for radiation-induced cancers. The conclusions of all four reports are affirmative. The new aspect of the 2021 report is that it focuses on the process of cancer risk inference. The aim of this article is to discuss the consequences of the conclusions regarding LNT and the possibilities of inferring risks from biological studies.

1. Introduction

The latest 2021 scientific report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) describes biological mechanisms of low dose radiation exposure [1]. It is the fourth UNSCEAR report since 1994 that touches this topic and it is interesting to summarise its conclusions in light of the other reports. Moreover, the report discusses inference of cancer risks from low-dose and low-dose-rate radiation studies and it is worth to look into the epistemology of this procedure.

2. How UNSCEAR prepares its reports

UNSCEAR was founded by the United Nations General Assembly in 1955 with the aim to report on the levels and effects of ionising radiation from nuclear bomb tests. Later, it broadened its scope to include levels and effects from environmental, occupational, medical and accidental exposures. Being a United Nations organisation, UNSCEAR is composed of representatives from member states, currently 27 (www.unscear.org). The specific topic of each UNSCEAR report is suggested by a member state and then decided by voting. An elected team of experts prepares a draft report that is first reviewed by critical reviewers and then opened to comments by representatives from member states. Following an often lively debate during an annual meeting, the final version of the report is approved. The debates reflect the convictions of the representatives, many of who are scientists, but also the interests of the states that they represent. So the process of shaping the final version of a report has been compared to multi-dimension tightrope balancing or rope pulling. Nevertheless, the crossing of swords between representatives and search for consensus ensures that the reports are, in general, balanced and of a high quality. Moreover, UNSCEAR stresses that it communicates not only the results of its findings regarding sources, effects and risks of radiation, but also confidence in and limitations of the evaluations in a balanced and considered manner, so that the findings

not be misinterpreted or misused [2]. This aim also shines through the latest 2021 report on biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation [1].

3. Biological effects of low doses and conclusions regarding the shape of doses response for radiation induced cancer

Although UNSCEAR reports deal with health effects from low dose exposure scenarios, they initially did not focus on the problem of uncertainty in risk assessment of low dose exposure (defined initially as below 0.2 Sv and later as below 0.1 Sv). UNSCEAR appreciated the lack of statistical power to precisely assess the level of risk at low doses but clearly stated that it is unlikely that the risk per unit dose at very low doses is any greater than that at high doses [3]. Moreover, the working hypothesis was that, based on mechanistic considerations, 'it has to be accepted that there is finite risk of cancer induction, however small, even at the lowest doses' [3]. The same approach was adopted in 1966 by the International Committee on Radiological Protection [4] and became known as the linear non-threshold (LNT) hypothesis.

In the 1980s data began to accumulate suggesting the existence of radio-adaptive responses, whereby cells exposed to a low dose became refractory to a subsequent high dose [5–7]. Although the mechanism could not be pinned down, it was assumed that low radiation doses trigger DNA repair processes that remove radiation lesions and perhaps even reduce spontaneous damage [8]. These results fuelled, also among UNSCEAR members [9], the belief in hormetic or beneficial effects of radiation that dominated during the early years of the 20th century [10]. Urged by some representatives, UNSCEAR decided to publish a report with the aim to check whether the conventional estimates of risks of stochastic effects at low doses have been overstated because no allowance was made for adaptation processes. In the 1994 report [11], available literature on adaptive response in cells, experimental animals and humans was reviewed. The report concludes that evidence does not exist to support the assumption that adaptive responses convey beneficial effects to the organism that would outweigh the detrimental effects of exposure to radiation.

A new report on biological effects at low radiation doses was published in 2000 [12]. It did not specifically focus on adaptive responses but aimed at providing an overview of data available on the relationship between radiation exposure and the induction of cancer and hereditary disease, with emphasis on the extent to which radiation effects can be observed at low doses. It concludes that, although mechanistic uncertainty remains, studies on DNA repair and cellular/molecular processes of radiation tumorigenesis provide no good reason to assume that there will be a low-dose threshold for the induction of tumours in general. However, a strictly linear dose response should not be expected in all circumstances. Regarding adaptive responses UNSCEAR, similarly as in 1994, concludes that there are no indications that it would modify the shape of the dose response, although it could alter the magnitude of an effect [12].

Apart from adaptive responses, two phenomena were discovered in the 1980/1990s that that could modify the shape of the dose response relationship: genomic instability and bystander effect. Today, all three are summed under the term non-targeted effects [13]. In 2006 UNSCEAR published a report with the goal 'to evaluate how non-targeted effects may affect risks associated with radiation exposure, the understanding of radiation-induced carcinogenesis, and the mechanistic basis for interpreting epidemiological data on radiation effects' [14]. The report concludes that data currently available do not require changes in radiation risk coefficients for cancer and hereditary effects of radiation in humans. This view is consistent with that published in the scientific literature [15].

The 2021 report [1] is the most recent one on biological effects of low dose radiation. UNSCEAR stresses that its focus is not on describing effects but rather on biological mechanisms of radiation actions at doses mostly in the low to moderate range relevant for cancer risk inference. The report summarises recent knowledge on DNA damage and repair, chromatin remodelling and epigenetics, gene and protein expression, non-targeted effects, the immune system and modelling of cancer mechanisms. It concludes that accumulated knowledge on mechanisms of effects directly related to cancer induction such as DNA damage, repair and mutations, imply a dose-risk relationship without a threshold at least down to 10 mGy. At the lowest dose levels effects mediated by reactive oxygen species dominate and may drive the promotional action of radiation.

All UNSCEAR reports published since 1994 on effects and mechanisms of low doses very consistently state that, overall, no data exist that question the validity of LNT. On the contrary, analysis of DNA damage and response suggest that its activation by radiation follows a linear dose response. New studies should and will be carried out to close still existing gaps but in view of the knowledge gained so far, it appears unlikely that results of any single one will overthrow the consensus conclusion. One could assume that after nearly 30 years of scrutinising research results, the scientific and radiation protection community would accept this as the reality. However, this is not the case [16–18]. The argument often brought forward by the LNT antagonists is that the thinking of traditional radiation researchers is trapped in the paradigm according to

which radiation increases the risk of cancer, however small, even at the lowest doses [17, 19]. Notwithstanding the fact that Kuhn´s paradigm shift hypothesis is a gross oversimplification of the nature of science [20, 21], LNT antagonists seem to forget that a belief in hormetic effects of radiation prevailed during the early years of the 20th century [10]. It was not based on evidence, but rather on the gut feeling that it must be so. Such reasoning is not different from that used today such as that 'evolution has provided all extant plants and animals with defences that repair […] damage or remove the damaged cells, conferring on the organism even greater ability to defend against subsequent damage' [17]. In fact, results from observations and experiments accumulating during the 20th century lead to the gradual realisation (a paradigm shift) that the risk of radiation induced cancer is directly proportional to the dose without a dose threshold. Using the vocabulary of clinical medicine, it can be claimed that the early assessment of low dose risk resembles the era of 'clinical judgment' or 'art of medicine' that dominated until the middle of the 20th century, while that adopted later by, *inter alia* UNSCEAR, resembles that of 'evidence-based medicine' or 'science of medicine' that we live in today.

Another, rather naïve but populistic argument brought forward by the LNT antagonists is that the general population will stop fearing radiation if scientists and radiation protection bodies agree that low doses of radiation are safe [17, 22]. The unspecific term 'fear' is interchangeably used with the clinical term 'phobia' which demonstrates that the authors of such statements do not understand what they write about. Apart from this, it is difficult to imagine how the introduction of a threshold dose demarcating the border between safe and non-safe radiation could calm citizens who breathe the air of contemporary risk society [23, 24]. And then the fact remains that such step would run against available evidence so meticulously collected and analysed by UNSCEAR [1, 11, 12, 14].

4. In what way are studies on biological mechanisms relevant for the inference of cancer risk?

As already stated, the aim of the UNSCEAR 2021 report [2] was not to summarise data describing radiation effects at low doses but to synthesise the knowledge on biological mechanisms of radiation actions at doses relevant for cancer risk inference. Before discussing how the report attempts to fulfil this aim let us look into the terms risk and inference.

Risk is a polysemous term, impossible to define in a general sense [25, 26]. In the fields of medicine and health protection it is defined as the probability (in the sense of statistical theory) that a particular adverse event occurs during a defined period of time [26]. This definition is adopted by UNSCEAR [2] and the ICRP (http://icrpaedia.org/Risk). Risk can be expressed in absolute or relative terms but its value is estimated from observational studies on exposed individuals. Estimation becomes difficult in the low dose region because studies lack statistical power. In such situations risk must be inferred. UNSCEAR defines the term inference as the process of drawing conclusions from scientific observations, evidence and reasoning in the presence of uncertainty [2]. Inference of cancer risks from low-dose and low-dose-rate radiation means estimating the probability of cancer incidence or mortality from relevant observational studies.

How can knowledge on biological mechanisms of radiation actions be relevant for cancer risk inference? Can risk be directly inferred from results of biological studies? The obvious answer is no, because risk is a numerical value that can only be derived from epidemiological studies. So how can mechanistic studies help in refining risk assessment? The answer is given in the 2012 [2] and 2021 [1] reports which list two ways in which biological information can be linked to epidemiological results:

(a) By improved understanding of the mechanisms of radiation action relevant for stochastic effects such as cancer. This will help in deciding the shape of the dose response relationship for the risk of adverse radiation effects, notably cancer, in the low dose range. Due to low statistical power of epidemiological studies, the level of risk at low doses is inferred from high doses by back extrapolating the significant dose response relationship. Here several models are possible such as LNT, supralinear, linear-quadratic, threshold and hormetic. Improved mechanistic understanding of the effects will help in deciding which model should be used.
(b) By identifying biomarkers of radiation exposure or of radiation-related disease that will help in epidemiological assessment of risk. How? A biomarker of radiation exposure will help in determining the dose received by an individual, allowing an accurate dose response relationship. A biomarker of disease will help in reducing the impact of confounding by competing, non-radiation related causes of the studied effect.

The UNSCEAR 2021 report [1] analyses the results from several areas of biological research that can be helpful in inferring risk from epidemiological results such as DNA damage and signalling, epigenetics, gene

expression, non-targeted effects, effects on the immune system and at the whole organism level. What are the conclusions? With respect to the shape of the dose response, the results for DNA damage and signalling clearly speak for a linear dose response relationship down to some 10 mGy. The results from other research areas are not conclusive. It is obvious that the described effects can potentiate or attenuate the risk of stochastic effects, but there is insufficient data to decide the net direction. Possibly, the heterogeneity and complexity of stochastic effects such as cancer make it impossible to draw an overarching conclusion.

The report also discusses progresses in application of biologically-based mechanistic models of carcinogenesis to predict the shape of the dose response. Somewhat surprisingly, the vast majority of studies published until now rely on the relatively simple two-stage clonal expansion model, without considering the biological mechanisms outlined above. Notwithstanding some differences between exposure to low and high linear energy transfer (LET) radiation, the majority of modelling results are consistent with the assumption that radiation acts both on initiation and on clonal expansion of cancer. Importantly, most models predict a linear dependence on dose and dose rate, at least for low LET radiation.

A reader searching for results demonstrating how biomarkers help in inferring risk from low dose epidemiological results will be disappointed. Appropriate biomarkers do not yet exist. Of course, the dicentric chromosome is a validated, radiation-specific biomarker of exposure but it is not sensitive enough to detect low doses [27]. The UNSCEAR 2021 report [1] discusses DNA damage response foci and gene expression as potential biomarkers. Low radiation doses induce foci, but the response is transient and not radiation specific. For gene expression, there is evidence of specific responses to low and high doses, and low and high dose rate, but there is no consensus on a gene expression profile to distinguish low- from high-dose exposure nor low-dose-rate from high-dose-rate exposure. Also, the response is not radiation-specific and its duration has not been studied beyond that of a few days. Further investigations are needed to identify radiation biomarkers.

5. Some words of warning at the end

As described above, the UNSCEAR 2021 report [1] lists ways in which studies on biological mechanisms are relevant for inference of cancer risk. However, it never explicitly states that risk cannot be directly inferred from such studies. The studies are important, but the results serve to support the process of risk inference from observational studies. One could argue that such statement is not needed because the fact is obvious. However, it is not, and the report can actually awake the wrong hope of the contrary. Already the title is suggestive. And in paragraph 14 the report states that mechanistic data should be 'included into a risk-assessment framework'. Moreover, it advocates the use of the adverse outcome pathway (AOP) approach for 'improving the assessment of risks of radiation health effects'. The AOP approach is a way of organising and presenting biological mechanisms related to an adverse effect such as cancer. It is currently promoted as a promising tool to improve radiation risk assessment [28]. There is no doubt that AOP is an excellent method of systematising molecular events involved in stochastic effects induced by radiation. But it does not serve as basis for assessing risks. Even vaguely promising that it can do so is as dangerous as promising that the introduction of a 'safe dose threshold' will remove peoples´ fears of radiation. It is of utmost importance to precisely describe the aims and possible outcomes of investigations.

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