

**DEVELOPMENTS IN RADIATION HEALTH SCIENCE
AND THEIR IMPACT ON RADIATION PROTECTION**

**OECD Nuclear Energy Agency
COMMITTEE ON RADIATION PROTECTION
AND PUBLIC HEALTH**

**Report of the
Working Group on Science and Technology Affecting Radiation Protection
Sub-Group on Radiation Health Sciences (WGST-RHS)**

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1. Introduction

At its March 1996 meeting, the Committee on Radiation Protection and Public Health (CRPPH) decided to initiate the implementation of the main recommendations for future work that resulted in follow-up to its Collective Opinion “Radiation Protection Today and Tomorrow” published in 1994.

The Collective Opinion had pointed out that scientific and technological developments in the near future may be expected which might have a profound influence on the concepts and the practice of radiation protection (RP). In particular, the Collective Opinion had identified a number of lines of research in radiation health sciences, particularly in molecular biology and epidemiology, which might result in modifications to the scientific basis of the System of Radiation Protection and to its practical application.

The CRPPH therefore decided to set up a working group to prepare a reflection paper on the relationship between scientific knowledge on radiation health effects, including its uncertainties, and the application of the “precautionary principle” in regulatory radiation protection.

The current report is the outcome of that work and includes a synthesis of the current scientific debate about the use of the linear, no-threshold (LNT) dose-effect hypothesis as a practical model for the regulation of radiation protection. It identifies key elements of science on which there is common agreement, areas of uncertainty or debate, and the potential practical implications of various possible developments in scientific knowledge. It reviews the present status of knowledge in the following fields of radiation health sciences which may have an implication for radiation protection:

- dose-effect relationships;
- causality;
- genetic susceptibility;
- combined effects.

Certain aspects of these issues are treated herein, as well as their potential policy and application implications, which are currently being discussed

in the applied radiation protection and scientific communities (UNSCEAR 93, UNSCEAR 94). The objective of this report is to provide decision makers and non-specialists with some insight into the critical points in these discussions. The report also seeks to provide an understanding of the scientific issues, and an appraisal of the possible developments in the practice and regulation of radiation protection in view of the scientific debate; it does not, however, engage in the debate itself.

2. Current status of knowledge

The current status of knowledge in radiation protection research can be summarised as follows:

- The chief somatic effect of ionizing radiation at low doses is the induction of cancer. At high doses, greater than 500 mGy, deterministic effects (such as erythema, cataracts, infertility) are known to occur.
- Ionizing radiation at dose levels of interest for radiation protection is considered to be a weak carcinogen.
- There is firm evidence of radiation-induced cancer risk in humans at acute doses in excess of 200 mGy.
- No positive biological effects have been observed in humans exposed to acute doses of ionizing radiation.
- Various tissues and organs exhibit a wide range of sensitivity to radiation-induced cancers.
- Radiation-induced, solid cancers have a long latency period, generally greater than ten years. Leukaemia and thyroid cancer in children can appear as soon as a few years after exposure.
- Various host factors (such as age at exposure, time after exposure, gender, genetic predisposition, etc.) and environmental factors (such as cigarette smoking, infectious agents, etc.) influence cancer risk at exposure levels where radiation effects have been observed.
- Cellular repair mechanisms are known to exist. However, misrepair and residual DNA damage occur.

- The yield of primary molecular and cellular events sometimes depends linearly on absorbed energy. However, many multi-step biological processes are known to be non-linear.
- Epidemiological studies alone will not provide definitive evidence of the existence or non-existence of carcinogenic effects due to low dose or low dose-rate radiation; the lack of epidemiological evidence for the existence of low dose and low dose-rate radiation-induced effects is not proof that such effects do not exist.
- The developing embryo/foetus is more sensitive to exposure to ionizing radiation than are children and adults.
- Epidemiological studies have not detected hereditary effects of radiation in humans with a statistically significant degree of confidence.

3. What remains unknown

The following points remain unresolved at the low doses and dose rates of interest in radiation protection:

- The shape of the dose-effect relationship at low doses and dose rates for radiation carcinogenesis in humans, is in question.
- The roles of host factors (such as age at exposure, time after exposure, gender, genetic predisposition, etc.) and environmental factors (such as cigarette smoking, infectious agents, etc.) as determinants of radiation risk are uncertain.
- For the same absorbed dose, different types of radiation (alpha, beta, gamma, neutron) show different efficiencies at inducing biological effects; the basis of biological effectiveness' of different radiations at inducing late effects in humans at low doses and low dose rates are not yet sufficiently understood.
- The mechanism of carcinogenesis, whether induced by radiation or by other agents, is believed to be a multi-step process which is not fully understood. The origin of cancer is hypothesised to be the result of mutational events to critical genetic loci, and of other factors such as hormone status, age, immune function, etc. The effects of radiation on specific steps of carcinogenesis are not fully understood.
- Although damage to DNA is assumed to be a key step in radiation carcinogenesis, it is not known what critical lesions in DNA are responsible for gene or point mutations and chromosomal aberrations leading to cancer. The cause of an individual cancer cannot be specifically tied to a given insult, such as radiation exposure.
- It is not known how many tumorigenic cells are necessary to produce a cancer *in vivo*.

- It is unclear why organs and tissues vary in radiosensitivity. At present we do not know whether the sensitivity to radiation can be predicted from the spontaneous incidence of most cancers.
- We do not have methods to measure an individual's radiation sensitivity.
- The influence of repair processes on human radiogenic risk at low dose and low dose rate is not fully understood; however, biological and chemical repair processes of radiation damage are known to occur in cells. This contributes to the uncertainty in dose and dose-rate correction factors used to estimate radiogenic risk.
- It is unknown whether adaptive response, observed in single cells under certain conditions, influences radiogenic risks in humans.
- It is unclear whether positive biological health effects of low doses of radiation exist in humans.

Certain aspects of these open questions are addressed in more detail in the following section, as are possible consequences and implications for radiation protection.

4. Dose-effect relationship: Science and policy implications

The debate on the dose-effect relationship began many decades ago, and we can observe today that the debate is still not closed. A transcription of paragraph (7) of ICRP Publication 9 (1965) is reported here:

The mechanism of the induction by radiation of leukaemia and other types of malignancy is not known. Such induction has so far been clearly established after doses of more than 100 rads, but it is unknown whether a threshold dose exists below which no malignancy is produced. If such a threshold dose did exist, there would be no risk of the induction of malignancy, as long as the threshold was not exceeded. As the existence of a threshold dose is unknown, it has been assumed that even the smallest doses involve a proportionately small risk of induction of malignancies. Also, because of the lack of knowledge of the nature of the dose-effect relationship in the induction of malignancies in man – particularly at those dose levels which are relevant in radiological protection – the Commission sees no practical alternative, for the purposes of radiological protection, to assuming a linear relationship between dose and effect, and that doses act cumulatively. The Commission is aware that the assumptions of no threshold and of complete additivity of all doses may be incorrect, but is satisfied that they are unlikely to lead to the underestimation of risks. Information is not available at the present time which would lead to any alternative hypothesis.

Although much has been learned about radiogenic cancer since the publication of ICRP 9, questions remain open about the shape of the dose-response curve at low doses and low dose rates including the existence of a threshold dose (UNSCEAR 93, UNSCEAR 94). In other words, radiation protection has been operating for more than three decades on the basis of these cautious and reasonable but unproved assumptions.

The aims and objectives of radiation protection have been extended, expanded and clarified from ICRP 9 (1965) through ICRP 26 (1977) to ICRP 60 (1990). Recommended dose limits have, however, decreased because of an increase in the LNT-derived (linear no-threshold hypothesis) risk coefficients.

The LNT hypothesis is not supported by all radiobiologists and radiation protection experts, and a number of attempts have been carried out to prove or to disprove it. However, results to date are not conclusive in either direction. This is one of the main reasons for the continuation of the debate of these last few years. At present, the LNT hypothesis remains the underlying philosophical foundation of radiation protection.

Scientific questions are not the only driving factors in the debate over the use of the LNT hypothesis. There are also significant questions being posed from social, political and economic standpoints, for example public fear of radiation because there is risk associated with any dose no matter how small, the cost of implementing radiation protection policies, etc.

Numerical correction factors (such as dose-rate effectiveness factors, radiation weighting factors), are based on inferences from biological and epidemiological studies. These are used in definitions of quantities and units of dose, to account for differences in radiosensitivity due to dose and dose-rate effects, and for the effects of different types of radiation. There is an ongoing debate in this area as to the usefulness of absorbed dose, and of such correction factors, as the basis for predicting the biological effects of various radiations and intensities. In the important example of lung cancer risks from exposures to radon and its daughter products, inferences from the Hiroshima/Nagasaki (HN) survivors data using the concept of equivalent dose were found to disagree with epidemiology findings from uranium miners and for the general population. This discrepancy has been addressed in ICRP 65 by using a “dose conversion” factor; however, additional work is necessary to resolve this important conceptual problem.

In spite of affirmations from different sides of the debate and in spite of the absence of a clear and definitive explanation of cancer induction mechanisms, we have to note that some data reinforce the use of a LNT model and some clearly demonstrate the existence of a threshold. In case of internal contamination a threshold-like effect is observed in, for example, the radium painter cases for bone sarcoma (Rowland, 1994, Thomas, 1994), the bone cancers in dogs after internal contamination (Griffith, 1995), and the inhaled plutonium dioxide experiments with rats and beagle dogs for lung cancers (Sanders, 1993, Park, 1991). For external irradiation, non-linear and threshold-like effects have been observed in animal studies and human epidemiological studies for specific endpoints, for example, the non-linear response of different solid-tumour cancers in HN survivors (Kellerer and Nekolla, 1997). Moreover, it seems clear that the design of experiments could influence the shape of the relationship. The smaller the target the more the linear relationship is sometimes obvious, perhaps because primary molecular events are often linear (and may serve as a dosimeter), whilst on higher levels of biological organisation (tissues, organs, organisms) highly non-linear processes are likely and

sometimes observed (Thomas, 1995). As further examples, the *in vitro* transformation dose-effect relationship for hematopoietic cells shows a non-threshold behaviour. However, for the leukaemia response in HN survivors, there are strong indications that curvilinearity, linear-quadratic-threshold or linear-quadratic models provide better descriptions of the data than linear non-threshold (Muirhead, Little, 1997). The important and rapidly expanding fields of molecular biology, molecular epidemiology and complex system modelling are expected to contribute significantly to our knowledge and understanding of the carcinogenesis process.

This statement is of real importance for the future evolution of science in the field of radiation protection. One should be aware that molecular biology, which is now considered as a powerful and useful tool in the biological field, should not be perceived by decision makers as the only methodology necessary in research aimed at understanding the dose-effect relationships, but other approaches (such as animal studies, cytogenetics, immunology, etc.) which address effects particularly at the level of tissues, organs and organisms, remain indispensable.

The publication in 1996 of the latest data from the analysis of HN survivors (Pierce D. *et al.*, Radiat. Res. 1996, 146, 1-27) is an important event for radiation protection. One of the most important points is that this document does not contradict the risk coefficient estimates used in ICRP 60 and does not suggest changes in the validity of the “precautionary principle” which is the basis for the latest ICRP recommendations. It should also be remembered that such data arises under the conditions of exposure experienced by the atomic bomb survivors followed by the Life Span Study (LSS).

The Pierce paper suggests a statistically significant solid cancer mortality risk at doses as low as 50 mSv (Pierce *et al.*, 1996). Even if true, this would not confirm the validity of the linear model for assessing the risk of cancer from radiation exposure at low doses, but would only indicate a new and lower limit for the value of a possible threshold. However, using the same data, Heidenreich *et al.* (Heidenreich, 1997) do not find any evidence for increased tumour rates below 200 mSv in the atomic bomb survivors data. In addition, Kellerer and Nekolla (Kellerer, 1997) conclude that even a purely quadratic dose-effect relation for gamma rays up to 2 Gy, and a linear relationship for neutrons are statistically consistent with the Hiroshima data. Pierce and Preston confirm that, “in view of the complicating issues of possible biases at very low doses, perhaps one cannot say with absolute certainty that there is statistically significant evidence of true effect below 200 mSv” (Heidenreich, 1997).

The main conclusions that can be drawn from the above-mentioned papers are:

- A substantial fraction (25%) of all observed solid cancers has been detected by studies of the HN survivors during the last five years of follow-up (1985-1990). A consequence of this is that the presently accepted time-projection model could undergo a careful re-examination. Data from the last five years of follow-up further supports the application of a relative-risk model, with risk coefficients which are independent of time since exposure. However, of the solid-tumour cancers predicted to occur in the HN survivors, a substantial fraction is not expected to be detected until after 1990. Hence, further confirmation of the appropriateness of the relative-risk model must wait for additional follow-up data.
- In the period 1985-1990, the excess of leukaemia appears to be negligible, confirming that risk for this endpoint diminishes with time since exposure. For leukaemia, a linear-quadratic relationship appears to fit the data adequately for HN survivors (Little, 1996, Muirhead, 1997).
- The new data, from the period 1985 to 1990, do not suggest any substantial change in the risk coefficient per unit dose using the LNT hypothesis.

In the Life Span Study, 200 mSv is the smallest dose for which a statistically significant radiogenic risk has been observed.

- The paper by Pierce *et al.* provides a useful analysis of an additional five years of follow-up data in the LSS. However, it provides no improvement of our knowledge on the extrapolation of the shape of the dose-effect relationship at low (continuous/chronic) dose rates, which are of paramount interest in radiation protection.

Other studies

In addition to the above-mentioned work, studies of populations of exposed children have shown statistically significant radiogenic risk at dose levels lower than the 200 mSv observed in HN survivors.

- Studies of thyroid cancer incidence in children following radiation exposure therapy have been reviewed by Shore *et al.*, (Shore,1993), and a combined analysis of these studies has recently been performed by Ron *et al.*, (Ron, 1995). These authors concluded that the available studies are unanimous in suggesting that there is a thyroid cancer risk

associated with low doses and that there is convincing evidence for a raised risk at about 0.1 Gy.

- The association between childhood cancer and X-ray exposure of the abdomen of the pregnant mother for diagnostic purposes, presented in the Oxford Survey of Childhood Cancers (OSCC), showed a raised risk of childhood cancer, with a statistically significant incidence from doses of about 10-20 mGy (Bithell, 1989).

Impact on radiation protection

In view of the current status of knowledge and of the “precautionary principle”, the use of the LNT assumption and of the current System of Protection is still justified where a unified approach must be applied to all sources and practices, including the use of the concept of dose and equivalent dose.

However, this approach to limiting radiation risk need not be automatically applied by experts to estimate risk in specific circumstances where a specified population or particular affected individual can be identified, and where the nature of radiation exposure and the associated cancer risks are known and can be specifically assessed. In all cases, experts should use the best scientific information available concerning a given exposure situation. They may choose not to use the LNT assumption or other dosimetric concepts in their assessment, but rather to derive this assessment from a realistic use of the specific information available for that particular situation.

Examples of the use of such an approach are 1) the application of a dose convention for occupational and non-occupational exposures to radon; 2) the development of practices (criteria) for the release from regulatory control of contaminated sites for unrestricted use; and 3) the case of the long-term disposal of radioactive waste:

- 1) The risk from exposure to radon can be estimated based on two different approaches: evidence from epidemiological studies (from uranium miners for example); or a model of the lungs and processes therein used to estimate dose (ICRP Publication 65) to be used in conjunction with risk estimates from ICRP Publication 60. The latter risk estimates are a factor of three higher than those from the epidemiological approach. The specific knowledge from epidemiological studies may be a more reasonable approach to risk estimates in such cases, rather than using the generic risk estimates from ICRP Publication 60 which are based on the concept of dose,

risks observed after acute external irradiation, and on the linear non-threshold hypothesis.

- 2) When releasing a site from regulatory control for unrestricted use, the type and mixture of radionuclides involved should be considered. If the specific effects of ingestion and inhalation of these radionuclides are known in detail, then this information, rather than the generic “average” values, should be used.
- 3) Where only specific long-lived radionuclides are involved and the exposure route is mainly the ingestion pathway, specific dose conversion and risk functions should be used if they are known.

Therefore, a discussion could be launched on the role and the alternative use of the “unified concepts approach”, and on the alternative use of a “specific expertise approach” in assessments and decisions concerning specific exposure situations.

Conclusions and recommendations

In conclusion, the latest data from HN survivors supports the use of the present risk estimates for acute irradiation. Thus, they reinforce the basis for the dose limits recommended in ICRP Publication 60. However, these new data do not solve the debate on the LNT hypothesis. From a radiation protection point of view, it should be considered unlikely that future data from the HN Life Span Study will significantly change the current basis of the System of Radiation Protection or the numerical values of dose limits.

This conclusion should in no way be interpreted as a denial of the essential importance of fundamental research into the mechanisms of cancer induction, and should not affect the scientific basis of the System of Radiation Protection.

Information on the existence of thresholds or threshold-like effects in specific cases, essentially in the area of internal irradiation from radionuclides could be considered in the analysis and radiation protection management of those situations where this is relevant. The CRPPH should initiate a deeper reflection of the use of an “expertise approach” in specific cases, noting that this is not inconsistent with the

current System of Radiation Protection. This reflection should include the feasibility, and, in particular, the significance of the practical application and the potential misuse of such an expertise approach, perhaps illustrating this view with a series of case studies for which the expertise approach is appropriate.

5. Causality: Science and policy implications

For some time, radiation protection experts have sought to establish whether the origin of an individual case of solid tumour or leukaemia might eventually be identifiable as radiogenic. Research is currently ongoing in many areas affecting this issue. The current state of knowledge is as follows:

- Biomarkers which would identify particular solid tumours or leukaemias as being initiated by radiation-induced cellular changes are not currently recognisable.
- The risk of individuals developing cancer depends upon their age and sex, on the amount of time which has elapsed since an exposure, as well as on endogenous and exogenous factors; these dependencies must be taken into account during studies of causation.
- In general, it is assumed that most tumour types which occur spontaneously, excepting for example chronic lymphatic leukaemia (CLL), can be induced by radiation.
- Currently, no biological dosimeters have been identified which are capable of reliably recording exposures at the low doses and dose rates usually of interest for radiation protection purposes.
- The presence of biomarkers of radiogenic effects, chromosomal aberrations for example, may have no consequence and may reflect exposure, but may not reflect radiogenic health risk.

If one assumes that biomarkers for radiogenic effects will eventually be identified, at this point it would make sense to preserve biological samples from well-characterised exposure cohorts (such as Hiroshima/Nagasaki, Cheliabinsk, Chernobyl, etc.) for retrospective epidemiological studies.

At present, in the absence of instruments to establish causality in individual cases of cancer, the resolution of questions of insurance, worker employability, and worker compensation will have to be based on assessments of

attributable risks (such as estimates of the probability of causation inferred from epidemiological data).

Impact on radiation protection

Assuming that biomarkers for radiation exposure at low levels may eventually be identified, the impact on the criteria for worker compensation would be significant. This would, however, most likely not initially affect the regulation and application of radiation protection. However, the identification of biomarkers would probably stimulate molecular epidemiological studies of the dose-time-effects relationships, particularly with regard to the effects of low dose and low dose rates. In the longer term, the results of such studies could potentially have a great affect on the System of Radiation Protection, including public perception of radiation risks.

Even if a “perfect” biomarker could be identified, there would remain the uncertainty as to whether a given radiation-induced effect was due to radiation exposure from natural, occupational or medical sources.

Other types of biomarkers might serve as early indicators of the later development of a tumour. This would be a great advantage to the early treatment of such health effects. Such early identification might also present ethical considerations: these must be addressed (see also Chapter 6 on genetic susceptibility).

Presently, it is not known whether tumour cells carry the signature of their causative agents. Biomarkers and biological dosimeters are not yet available at the dose levels relevant to radiation protection. However, developments in this area have a great potential to stimulate molecular epidemiological studies whose results, in turn, might significantly affect radiation protection. The CRPPH should continue to monitor progress in the area of biomarker research, and through this monitoring CRPPH members may attempt to foster international co-operation and collaboration among such national research programmes. Such developments will have implications in the area of the assessment of cancer causality in individuals. This will also have implications to national programmes in the areas of employment/employability, health insurance, and worker compensation.

There are many ways in which national governments assess cancer causality and attribute worker benefits. The CRPPH should consider preparing a document comparing the various national programmes in the area.

6. Genetic predisposition: Science and policy implications

Certain genetic diseases, including ataxia telangectasia (AT), xeroderma pigmentosum (XP), and severe combined immunodeficiency (SCID) are known to predispose individuals to cancer. The primary disorders in these diseases affect either the maintenance and stability of the genetic material or the function of the immune system. The characteristic increase in cancer risk associated with these hereditary conditions may not necessarily be confined to individuals who fully manifest the disease. For example, AT heterozygotes (1% of the population) have been reported to be at increased risk for various malignancies, particularly breast cancer (Swift, 1991).

AT is of particular interest in radiation protection. Individuals with AT also have an acute sensitivity to ionizing radiation. The implications for radiation protection of a genetic test for AT are significant. Genetic screening tests may identify radiosensitive individuals who are otherwise normal. In June 1995 Savitsky *et al.* discovered the single gene responsible for AT. A genetic test for AT has now been developed (Telatar *et al.*, 1996). However, the reliability of the test as a screening tool for increased cancer risk remains questionable.

Importance of radiosensitivity as a contributing factor in human carcinogenesis

Radiosensitivity would appear to be a minor host factor in carcinogenesis if considered in relation to diet and cigarette smoking. Cigarette smoking and diet account for approximately two-thirds of cancers (Doll and Peto, 1981). Also, age is a major determinant of risk for almost all cancers. This varies considerably with cancer type. Age is particularly important for lung, prostate and colon cancer; older individuals being more at risk than younger persons.

Genetic predisposition could be an important component of risk for major human cancers. A significant proportion of lung, colon and breast cancer have a genetic component. Approximately 14% of colon cancer cases annually observed may have a genetic predisposition. Mutations associated with familial adenomatous polyposis and non-polyposis colorectal cancer enhance colorectal

cancer risk in the population (reported in UNSCEAR 1993). A similar percentage (15%) of lung cancer may also have a genetic predisposition. Cigarette smoking seems to increase the risk of lung cancers in individuals with genetic predisposition. Lastly, breast cancer appears to be genetically influenced in 5 to 10% of cases. Moreover 9 to 18% of breast cancer patients may carry the AT gene (Swift *et al.*, 1991). Although ionizing radiation at high doses (greater than 1 Gy) is a known risk factor for breast cancer, there is little evidence that mammography increases risks, even in women heterozygous for AT.

Impact on radiation protection

Exposure limits for the general population and for workers are based on the “average” radiosensitivity of individuals in the exposed population. An exception to this is the use of supplementary equivalent-dose limits for pregnant workers because of the greater radiosensitivity of the developing embryo and foetus.

The possible reduction of exposure limits and modifications of existing radiation protection practices to account for radiosensitive sub-populations is an important issue that requires careful consideration. The alternative between reducing exposure limits for radiosensitive individuals or reducing exposure limits for the entire population to account for the most radiosensitive sub-groups is a critical aspect of this issue. However, doubts may be raised about the net public health benefit of such changes. Current radiogenic cancer risk estimates may already reflect the responses of the most sensitive component of the population if we are correct in the assumption that the prevalence of genetic susceptibility in the major radio-epidemiological studies is similar to that in the general population (Mossman, 1997).

The first stage of this reflection should address the clear identification of the individuals at higher risk. If with today’s approach, for a general population, we could use a precautionary attitude taking into account uncertainties in scientific results, selection of individuals at risk for purposes of specific dose limitation could not tolerate large uncertainty.

For workers, it could be attractive to develop genetic sensitivity tests before employment. Therefore, it is time to discuss the potential results of science in this field.

Based on these types of considerations it should be discussed whether tests capable of detecting any high radiosensitivity should be based on voluntary acceptance or on employer sorting. It seems reasonable that information concerning

individual worker radiosensitivity should be personal and confidential. Employees who have declared high radiosensitivities should be provided with additional information regarding job-specific strategies to reduce dose. Where possible, employers should provide optional job responsibilities entailing smaller radiation exposure possibilities.

Such recommendations appear, however, difficult to implement, particularly in companies where alternative job opportunities may not be available.

Except for individuals with a pronounced familial history of cancer, genetic screening may not be advisable in some instances. Genetic tests are currently uncertain, and there is a lack of clear association of mutations detected in a screening test with an increased risk of cancer. Test results may thus create a false sense of security if tests are either positive or negative. The questions of the risks and benefits of genetic tests, particularly for individuals with positive results, should be further explored. Particularly, the psychological impact in case of positive result of a genetic test, should be carefully considered.

These questions would raise significant ethical and social problems and, therefore, they should be treated out of the field of radiation protection by philosophers, sociologists, employers, trade unions and politicians, who will have the final responsibility to decide and to control. Radiation protection scientists should contribute, as experts, to the dialogue in this area.

For the public, the significance of enhanced radiosensitivity within the general population is not clear. One possible area of concern is the use of mammograms in women who have a genetic predisposition for breast cancer. Swift *et al.* (1987, 1991) have argued that women heterozygous for AT should avoid mammography because of their enhanced radiogenic risk. However, the low dose delivered in this diagnostic X-ray has not been linked, so far, to increased breast cancer risk among predisposed women (Mossman, 1997).

In conclusion, genetic predisposition is likely to become an important issue in radiation protection, particularly in the case of workers as it might impact national policy in the areas of employability, insurability and compensation. However, if science is able to give useful information in the future, the discussion of the use of such data should not be made only within the radiation protection field, but should be a broader responsibility of other segments of society. Even though the problems of employability, insurance and compensation for individuals at greater risk are, strictly speaking, outside the radiation protection field, the radiation

protection community should be involved in their discussion in this context. Therefore, the CRPPH seems to not be the right forum for such a discussion. The Committee should, however, study the radiological aspects of these issues in order to be prepared to inform the decision makers of the possibility of such an evolution and of its consequences in the field of radiation protection and probably in many other areas of industrial activities.

7. Quantifying combined health effects from different agents: Science and policy implications

Combined exposures are a basic consequence of living. A multitude of natural and man-made agents have the potential to interact with biological materials in ways leading to irreversible changes or reversible deviations from homeostasis. In addition, it is well known from epidemiological and toxicological studies that interactions exist between different toxic agents at moderate to high dose levels (Burkart *et al.*, 1997). Some of these interactions lead to effects which are greater or lesser than what simple addition of the effects from exposure to single agents would predict.

There are many examples of interactions between ionizing radiation and other toxic agents. They are reviewed in UNSCEAR documents. Responses observed in humans range from antagonism to synergism. The available data are not comprehensive and are generally more observational/descriptive than mechanistic. In most cases, findings from existing studies have involved high exposure levels which may occur only in certain situations, e.g. combined tumour therapies. Inferences, therefore, for today's occupational and environmental exposures are difficult to draw.

As discussed in Chapter 3, the radiation dose-effect relationship is at this point uncertain at low doses and low dose rates. The assessment of health effects from single chemical agents at low levels found in environment and occupational settings is also prone to large uncertainties. For the combined effects, there is scarcity of experimental and epidemiological data and, even more, of appropriate models to explain and predict combined effects of different noxious agents (radiation, chemicals, etc.). However, it should be kept in mind that these large uncertainties are mainly due to the fact that neither exposure alone nor combinations of radiation with other agents results in significant health effects at those low doses and dose rates normally occurring in the environment or at workplaces. Equally, it should be remembered that the effects of ionizing radiation on man are observed in populations (for example, the HN survivors) who live in today's environment, including its ubiquitous environmental pollutants. In consequence, such human studies cannot be carried out for single, isolated noxious agents.

With the exception of exposure to ultra-violet radiation, asbestos and maybe radon daughters, the projected excess relative risk from environmental exposures for a specific endpoint, and even for the lifetime risk are generally too low to be directly accessible by epidemiological studies. However, examples of more than additive interactions have been established with cigarette smoking. Occupational exposures to both asbestos (Selikoff, 1979) and radon daughters (Lubin, 1994), in smokers were shown to increase lung cancer mortality well beyond the level expected from the sum of the independent actions of the two agents.

In another area, concerns have been raised that persons with human immunodeficiency virus infection may have an enhanced susceptibility to ionizing radiations: this is related to the HIV-induced decrease of the pool of CD4+ lymphocytes and the hyperactivation of the immune system related to the disease that may render the immune system more susceptible to ionizing radiation-induced damages. Furthermore, repopulation of lymphocyte compartment after immunosuppression following exposure to irradiation may increase HIV replication, as it is well known that lymphocyte proliferation enhances provirus expression and thereafter results in an increasing number of infected cells (Dormont, 1998). However, little scientific data are available to quantify this and, perhaps, radiation sensitivity of such individuals should be carefully evaluated and considered within the context of immune suppression in response to radiation exposure.

Assessment of interactions

A simple starting point is the interaction of two agents producing both typical stochastic effects such as cell killing or cancer induction. What may be straightforward for the simple case where two agents each display a linear dose-effect relationship becomes much more ambiguous with non-linear dose-effect relationships and/or threshold phenomena.

If one looks at a quadratic dose-effect relationship, additional increments of a single agent can be considered interacting with earlier increments, because their effect per unit dose is higher and depends on the earlier exposures. The term synergism has sometimes been used for such situations. Although mathematically correct, this notion would imply that even different agents with the same mode of action produce synergism in any combination of concentrations as soon as their dose-effect relationship is non-linear and bent upwards. From a mechanistic point of view, synergism should be defined in a more restricted manner. Synergism implies that the combined effect of different agents results from action on different

rate-limiting steps of a multi-step process, at different sites of a molecule or by different molecular mechanisms.

In the case of non-linear dose-effect relationships, heteroadditivity is present when two agents act on different pathways, i.e. truly independent, and the single effects can be added independently of the respective form of the dose- effect curves. Isoadditivity, in contrast, is present when agents A and B act by the same or a similar mechanism. In this case, doses from agent B have to be treated like additional dose increments of agent A. Only identification and quantitative elucidation of all the mutational or other events which drive cells to malignancy will provide the information needed to make specific predictions on the risk from combined effects.

Clearly, direct damaging effects to the genome (i.e. genotoxicity) are of primary importance when examining radiation-induced carcinogenesis and when considering how radiation can act in concert with other agents. In addition, over the last few years it has become increasingly apparent that a wide variety of agents can work through non-genotoxic mechanisms. Conceptually, then, one has to envision a wide range of ways in which radiation can interact with genotoxic or non-genotoxic agents.

A mixture of agents could contain factors affecting different steps (DNA damage and growth factor secretion) or alternate pathways contributing to the same steps (different growth factors). For protection purposes, the class of combined effects to be considered in detail results from interactive effects arising from agents with different action spectra. Predisposition by one agent, e.g., changes in sensitivity, might lead to deviations from additivity towards synergism or antagonism. Theoretically, the most critical interactions are multi-step mechanisms for which two different agents would promote different steps which normally have low probability of occurrence. In such a situation, highly synergistic effects from combined exposures could result. However, other than for radon (initiation) and smoking (promotion), little experimental or human evidence exists of such dangerous combinations at the workplace or in the environment.

Impacts on radiation protection

In combined exposures to non-specific genotoxic agents, with potentially non-linear dose-effect relationships, supra-additivity must be considered. This was correspondingly found in important combinations such as tobacco smoke and high-LET ionizing radiation. The collective influence of multiple factors and, more especially, tobacco smoke further increases the uncertainties in estimates of risk for populations to low doses of ionizing radiation. Epidemiology indicates that indoor

radon exposure and cigarette smoking warrant special consideration due to the large proportion of the world population exposed to high levels of both toxic agents. Sound results in this field could have significant implications in regulation and risk mitigation strategies.

Radiogenic risks should not be considered in isolation, particularly at exposures of interest to radiation protection. Risk profiles can be complicated, and individuals are exposed to many different types of insults. Inferences of population-based risk estimates from epidemiological studies may not always be validly transferred across ethnic and cultural boundaries, and such transfers should be carefully considered.

In summary, it can be said that interactions between radiation and other physical, chemical and biological agents are an important modifier in many biological processes and outcomes. Their implications for the limitation of individual and collective health risks in a unified concept including exposures from all important agents need careful consideration. To achieve this, fundamental research, as well as the development of conceptual models, are necessary. Based on these achievements, existing epidemiological data should be re-evaluated in view of these interactions and new studies should be developed to investigate specifically the effects of combined agents. However, in one particular case – radon exposure and cigarette smoking – new clear results could have public health policy, mitigation strategy and regulatory implications in the next few years. The CRPPH should continue to monitor progress in the area of combined effects research, and through this monitoring CRPPH members may attempt to foster international co-operation and collaboration among national research programmes.

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ANNEX

Membership of the WGST-RHS at the time of preparation of the report

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