



Cancer risk from chronic exposures to chemicals and radiation: a comparison of the toxicological reference value with the radiation detriment

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1 **Cancer risk from chronic exposures to chemicals and radiation:**
2 **a comparison of the toxicological reference value with the radiation detriment**

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7 **Concise and informative title**

8 Comparison of calculations of cancer risk due to chemicals and radiation.
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Abstract

This article aims at comparing reference methods for the assessment of cancer risk from exposure to genotoxic carcinogen chemical substances and to ionizing radiation. For chemicals, cancer potency is expressed as a toxicological reference value (TRV) based on the most sensitive type of cancer generally observed in animal experiments of oral or inhalation exposure. A dose-response curve is established by modelling experimental data adjusted to apply to human exposure. This leads to a point of departure from which the TRV is derived as the slope of a linear extrapolation to zero dose. Human lifetime cancer risk can then be assessed as the product of dose by TRV and it is generally considered to be tolerable in a 10^{-6} – 10^{-4} range for public in normal situation. Radiation exposure is assessed as effective dose corresponding to a weighted average of energy deposition in body organs. Cancer risk models were derived from the epidemiological follow-up of atomic bombing survivors. Considering a linear-no-threshold dose-risk relationship and average baseline risks, lifetime nominal risk coefficients were established for 13 types of cancers. Those are adjusted according to the severity of each cancer type and combined into an overall indicator denominated radiation detriment. Exposure to radiation is subject to dose limits proscribing unacceptable health detriment. The differences between chemical and radiological cancer risk assessments are discussed and concern data sources, extrapolation to low doses, definition of dose, considered health effects and level of conservatism. These differences should not be an insuperable impediment to the comparison of TRVs with radiation risk, thus opportunities exist to bring closer the two types of risk assessment.

Keywords

Health risk assessment; Chemicals; Toxicological reference value; Radiation; Nominal risk; Detriment.

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Abbreviations

ANSES: French Agency for Food, Environmental and Occupational Health & Safety

ATSDR: Agency for toxic substances and disease registry (USA)

BMD: benchmark dose

BMDL: lower limit of the confidence interval of the benchmark dose

CERCLA: Comprehensive Environmental Response, Compensation, and Liability Act

DDREF: dose and dose-rate effectiveness factor

EAR: excess absolute risk

ECHA: European Chemicals Agency

EFSA: European Food Safety Authority

ERR: excess relative risk

Gy: Gray

HCPH: French High Council for Public Health

ICRP: International Commission on Radiological Protection

LOAEL: lower observed adverse effect level

LNT: linear-no-threshold

LSS: Life Span Study

OEHHA: Office of Environmental Health Hazard Assessment (USA)

PBPK: physiologically based pharmacokinetic

POD: point of departure

REIC: risk of exposure-induced cancer

RIVM: National Institute for Public Health and the Environment (Netherlands)

Sv: Sievert

78 TRV: toxicological reference values
79 UNSCEAR: United Nations Scientific Committee on the Effects of Atomic Radiation
80 US-EPA: United States Environmental Protection Agency
81 WHO: World Health Organization
82

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Introduction

To comply with the regulatory obligations, operators of facilities liable to release radioactive and chemical substances perform impact assessments with a view to getting the authorization to operate their facilities or to propose remediation strategies for polluted sites with abnormal levels of remaining radioactive or chemical substances. To appraise the impact of chemical and/or radioactive substance releases, analyses of the environmental dispersion and exposure pathways are performed and then used to figure out potential doses incurred by a reference group or a representative person. These results are compared with reference or regulatory values to make sure that provisions implemented to control releases are appropriate. For the main French nuclear facilities, the national Institute for radiological protection and nuclear safety (IRSN) is often requested to evaluate the impact studies of chemical and radioactive releases on human health and environment. To address chemical issues, IRSN resorts to methodologies of the national Institute for industrial environment and risks (Ineris), which is a leading organization in France with a mission to contribute to the prevention of risks caused by economic activities to health, environment and the safety of people and goods. It is often involved in the assessment of the impact of chemical substance releases to support either the authorities or the operators. The methodological framework is generally applied to assess risks linked to: 1) future emissions of industries or 2) media that have already been polluted, helping authorities to manage risks (Ineris 2016; NRC 1983). As radioactive substances are known to lead to potential carcinogenic effects like some chemical substances, an increasing need to compare the impact of ionizing radiation and chemical substances on human health is arising from Non-Governmental Organizations which are questioning the management of the radiological risk with respect to other risks and from decision makers to help allocation of resources. Conclusions of a report recently published by the Nuclear energy agency push also comprehensive approaches to better address the optimization principle: *“overall optimization implies the need to consider chemical and other hazards alongside the radiological hazards, adopting proportionate health, safety and risk management strategies and applying corresponding regulatory requirements based on a common protection objectives”* (NEA 2020). On the one hand, the impact of radioactive release results have so far been overwhelmingly provided in terms of radiation doses (energy deposited in living tissues). On the other hand, the impact of carcinogenic chemical substances is expressed in terms of excess cancer risk. An increasing trend is to use the same concept of excess risk for radioactive releases (Frischknecht et al. 2000; Walsh et al. 2019). The most common way to do so may consist in the use of the nominal risk coefficient adjusted to the detriment of the International Commission on Radiological Protection (ICRP 2007) to convert the dose to the whole body (effective dose) into health detriment attributable to radiation exposure.

Commonalities and differences between chemical substances and radiation risk management have been already listed by Tran et al. in 2000, who also discussed the way reference values are established and both risk management systems. While the approach of Tran et al. was mainly interested in the comparison of risk management systems, here we focus on the comparison of the construction of the reference values in order to identify the elements of a possible common approach taking into account the overall risk from both chemical and radiological exposure. Comparisons of environmental impact assessment of radioactive and chemical substances were also recently investigated by the Norwegian radiation protection authority, who concluded in particular these three points: 1) non-radiological hazards associated with radioactive wastes have been of regulatory interest for a number of years and yet the effects of non-radioactive materials within such wastes have historically been under-researched; 2) superimposition of a non-radiological performance assessment onto a radiological assessment and vice versa, taking account of different compliance points and assessment criteria, different regulatory end points and potentially the effect of additive and/or synergistic effects is difficult to fit into current regulatory frameworks that were designed separately; 3) the hazard associated with the non-radioactive component of radioactive waste may be greater than that of the radioactive component (NRPA 2018).

This article aims at recounting the way the toxicological reference values (TRV) expressing cancer potency for chemical substances on the one side, and the nominal risk coefficients adjusted to the detriment for radioactive substances on the other side, are built. The feasibility to convert an effective dose from exposure to radioactive substances into an excess risk in a way similar to that for no-threshold effect chemical substances is investigated.

1. Health risk assessment for chemical substances: assessment of toxicological reference values

In chemical toxicology, the dose is the incorporated amount of a substance per unit body weight. It may also be expressed as a time-integrated concentration of the substance in the environment. An adverse effect is defined as a *“change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences”* (WHO 1994). Toxicological reference value is a generic term for values determined for hazard limits used in risk calculation. These TRVs are usually developed

for two routes of exposure (oral exposure or inhalation, essentially). Values of different natures are established for threshold and no-threshold effects. For the first type of effects, a threshold, that is a level of exposure below which a significant adverse effect is not expected, can be defined (US EPA 1994). On the other hand, effects such as mutagenicity or carcinogenicity are thought to be no-threshold endpoints; thus, no exposure to genotoxic carcinogenic substances can be presumed to be without any risk of adverse effect. The same substance can have both threshold and no-threshold effects, involving different mechanisms of action on different organs or even on the same organ. Both types of effects are considered and taken into account by impact studies. TRVs are developed by national and international organizations such as ANSES, WHO, EFSA, US EPA, ATSDR, OEHHA, Health Canada or RIVM. Each organization has its own methodology; however, they are close enough so that the values defined are considered as equivalent (Ineris 2016).

The effects induced by most substances are threshold effects, that is to say that no adverse effect is observed below a certain level of dose. This category mainly covers systemic effects, including reproductive effects and non-genotoxic carcinogenic effects. In this case, the threshold TRV is the quantity of a product, or its concentration in the air, to which an individual may be exposed without causing any deleterious effect over a given period such as acute (under 14 days), sub-chronic (from 14 days to 1 year) or chronic (from 1 year to entire life) exposures.

For no-threshold effects, i.e. mainly for carcinogenic and genotoxic effects, the TRV is a cancer potency expressed as a lifetime excess cancer risk per dose unit that is the slope of linear-no-threshold (LNT) relationship between the dose, or concentration, of the substance and the probability of occurrence of the effect. The elements presented below concern the approach for no-thresholds effects.

Input data

The information available on health effects of chemicals varies widely from one substance to another both in terms of the number of publications available and the nature of the studies. Two types of data can be used for the development of a TRV for no-threshold effects: epidemiological and experimental data.

Most epidemiological studies are conducted among workers, although studies in the general population sometimes exist. If relevant epidemiological data are available, they will be used as a priority. However, different factors are often limiting their applicability, such as the size of the studied population, the characterization of the exposure (duration, frequency, level), co-exposure to several substances, etc. The reference population depends on the type of epidemiological studies (non-exposed workers, paired population, mortality register, etc.).

For new substances or for those without epidemiological data, experimental studies are needed. Life-long animal carcinogenesis studies are generally used even though they are often few in number because of the constraints of this type of study (number of animals, conditions and duration of exposure, etc.). In the absence of studies for the appropriate route of exposure, a route-to-route extrapolation (ingestion to inhalation for example) is often used provided its relevance can be demonstrated. In the absence of valid and relevant studies, it is not possible to build a TRV even if the carcinogenic potential of the substance has been shown.

For each substance, it is necessary to carry out a literature review, and an analysis of all effects on organs and mechanisms of action, to propose a selection of the available data and a synthesis. Then, it is possible to identify the relevant data, the critical effects and to determine the mechanism of action to be retained (with threshold and/or without threshold). *“The critical effect is the first adverse effect, or its known precursor, that occurs as the dose rate increases; its designation is based on the evaluation of the overall data base”* (US EPA 1994). The critical effect is the first to appear at the lowest tested dose level resulting in an observable effect, and avoiding an unacceptable level of this critical effect is likely to protect against all the carcinogenic effects of the tested substance. This effect is quantified in a single study with a dose effect relationship at the lowest possible exposure levels. The choice of the critical effect is the fundamental stage of the construction of the TRV and the most difficult because it has to take into account the relevance and concordance of the effect in regard of all available data on the substance from the various available epidemiological and experimental studies. Generally, few epidemiological data are available on the carcinogenic effects of chemicals and it is often necessary to use animal data that have been obtained from exposure by a different route of exposure than the one of interest. It is therefore essential to ensure the relevance of the observed effects in humans and / or for the considered route of exposure.

In general, dose-response estimates are based on data from the entire dose-response curve for the critical effect. The dose-response model reflects the characteristics of the dose-response curve, particularly in providing estimates of the slope. From epidemiological data, the cancer potency can be calculated using epidemiological indicators (relative risk, odds ratio, etc.). From animal data, the experimental data which are the lower observed adverse effect level (LOAEL) can be used but as far as possible, it is preferred to use the benchmark dose (BMD) which is *“a critical dose value based on modelling of experimental data, which takes into account the entire dose-*

response relationship” (US EPA 2012a). These different indicators can be used as point of departure (POD) for calculating the TRV.

Depending on the location in the body, the studies can highlight several types of (benign and/or malignant) tumours. When the carcinogenic mode of action shows or leads to suspect the possible evolution of a benign tumour (precursor lesion) into a malignant tumour within the same organ and at identical tissue location, it is possible to accumulate the incidences of these tumours (benign and malignant). However, it is generally not recommended to appraise the incidences of tumours in different organs or tissues.

Methods

Steps of calculation for cancer potency

Cancer potency, so-called TRV, is calculated from a dose response curve fitting experimental data. Whatever the method applied to determine a TRV, the two underpinning hypotheses for genotoxic carcinogenic substances are: 1) there is no threshold and 2) the shape of the dose-response curve is a straight line at low doses. We know that these standpoints are questionable because different types of adaptive responses exist, varying with the level of exposure or dose. Nevertheless, these protective hypotheses still prevail for the determination of TRVs for regulatory purposes. Obviously, this has a strong impact on the methods which have been applied to the build-up process so far.

The linearity of the dose response was especially supported by Hermann Joseph Muller’s work during the 1920s. He was awarded the Nobel prize in medicine twenty years later, in 1946, for the “discovery of the production of mutations by mean of X-ray irradiation”. Muller demonstrated that the DNA damage was in proportion with the radiation dose and this result was very rapidly applied to carcinogenic chemical substances (Calabrese 2009). With the objective to cure cancer, funds allocated to research on carcinogenesis have been sharply increased since the beginning of the 70s as illustrated by US President Nixon’s crusade against cancer launched in 1971. Over the following decades, these efforts lead to a better understanding of carcinogenesis and allowed to characterize different steps for cancer development as set out by Hanahan and Weinberg (Hanahan 2000). These breakthroughs were in favour of moving from a statistical modelling approach to a mechanistic modelling approach to determine TRVs, with the latter embedding the knowledge of carcinogenesis in the structure of models (Hartwig et al. 2020).

Even if the data set formed by an experimental or an epidemiological study is not the same, the TRV construction method is essentially similar, with two steps: modelling data from the critical study and linear extrapolation from high doses to origin (US EPA 2005). The first step is to establish a dose-response curve from experimental data, including effects generally observed at the higher doses in the critical study, which allows to determine the BMD, generally corresponding to an estimated low effect level (e.g. 1-10% incidence of an effect). The derivation of the BMD is directly linked to the selected critical study and involves a dose-response modelling which depends on a number of factors such as, the route of administration, relevance of animal species tested, gender and strain-specific effects, duration of exposure, choice of critical effect and availability of mechanistic understanding of the effect and of relevance to humans. The models should include the variability of the data, using for example multi-step models that allow the calculation of the BMD and the lower limit of the confidence interval of the BMD (BMDL). It is the BMD/BMDL pair that allows one to appraise the relevance of the modelling. Some existing TRVs have been determined with statistical models (e.g. Weibull Probit). The choice of the best model depends on the data of the study. Different models are usually tested and the one that best fits the data of the study is selected, or alternatively the average value of the different modeling can be retained (Scholze et al. 2001). Setting the response at x%, the best fit model allows to get the BMDx. In addition, all the other tested models allow to get a range of doses for a same response. The use of this distribution allows to determine a BMDL (lower limit of the confidence interval, e.g. at 95%) for the response at x%, this BMDL corresponding to the POD.

The second step is a simple linear extrapolation from the BMDL to the origin (Calabrese 2009). The slope of the straight line connecting the BMDL to the origin represents the cancer potency. In the case where the models do not allow to determine the BMD and the BMDL, another point of the dose-response curve may be used as the POD for calculating the cancer potency, depending on the available data; the approach will be substantially identical to that described previously.

The cancer potency, or cancer slope factor or lifetime excess cancer risk, according to organizations, is an estimate of the risk of cancer incidence per unit dose for a lifetime exposure to a substance, which is generally expressed per mg kg⁻¹ body weight per day or per µg m⁻³ in ambient air for the oral and inhalation route of exposure, respectively (WHO 2009). Thus, for example, if the excess risk of a given cancer from inhalation exposure to a given substance is 8 10⁻⁶ per µg m⁻³, the added risk of developing this cancer is 8 10⁻⁶ for a person continuously exposed during his lifetime to 1 µg m⁻³ of the substance, in addition to the baseline risk of the cancer in an

unexposed population. For a population of 1 million individuals continuously exposed to $1 \mu\text{g m}^{-3}$ of the substance throughout life, 8 additional cancer cases related to this exposure are expected.

In order to reduce the uncertainties, adjustments of the dose or concentration could be envisaged but this approach is not very usual for calculating reference values for no-threshold effects. However, since the critical study is most often an experimental study, adjustments (such as allometric factor, physiologically based pharmacokinetic (PBPK) modelling, etc.) are considered in order to account for biological and physicochemical differences between the experimental model and the individual of interest in the calculation of the cancer potency. This type of adjustment is applied, for instance, to take into account the differences in size, and thus doses, between the animal species of the critical study (most often rodent - rat or mouse) and humans in case of inhalation exposure, or differences in general metabolism when the exposure is oral.

Example of construction of the TRV for carcinogenic effects for inhalation exposures to tetrachlorethylene (from US EPA 2012b)

A carcinogenicity study of inhalation (6 hours per day, 5 days per week; lifetime) by mice was selected for the construction of a TRV for carcinogenic effects (JISA, 1993). A BMD modelling was performed based on the incidence of adenomas and hepatocellular carcinomas in male mice. For the construction of the TRV, a temporal adjustment was made from a discontinuous exposure in the experimental study to an application of continuous exposure. The incidence of total hepatic oxidative metabolism was considered the best indicator of hepatic carcinogenesis in surviving males. Then, an extrapolation of animal data to humans was performed based on the internal dose calculated on the total hepatic oxidative metabolism by using a PBPK model (Table 1). Metabolized tetrachloroethylene was scaled with body weight to the 0.75 power according to a wide body of empirical evidence on metabolic rates variations between animals and humans associated with enzymatic processes (US EPA 2005) so that the dose metric was expressed as $\text{mg kg}^{-0.75}$ per day. The slope of the curve representing the lifetime excess cancer risk is presented in Figure 1 as a function of internal dose (total hepatic oxidative metabolism). A multi-stage linear extrapolation model was used taking a BMDL for the response at 10% (BMDL10) as a POD. This is the lower limit of the 95% confidence interval on the dose for a response level of 10 converted into a risk unit, equivalent for humans, for inhalation exposure. The slope represented with the dashed line in Figure 1 is the TRV of the tetrachloroethylene.

Table 1. Example of the data used to calculate the BMD for inhalation exposure to tetrachloroethylene (or perchloroethylene, from US EPA 2012b): incidence of hepatocellular adenomas and carcinomas in male mice in the study of JISA (1993) and internal dose calculated on the total hepatic oxidative metabolism by using a PBPK model.

| Tetrachloroethylene concentration administrated to animals (ppm) | | Liver total oxidative metabolism ($\text{mg kg}^{-0.75}$ per day) Calculated for a human continuous exposure | Incidence of hepatocellular adenomas and carcinomas (%)* |
|--|-----------------------|--|--|
| Administered concentration | Continuous equivalent | | |
| 0 | 0 | 0 | 13/46 (27) |
| 10 | 8.9 | 2.25 | 21/49 (43) |
| 50 | 36 | 8.25 | 19/48 (40) |
| 250 | 110 | 33.6 | 40/49 (82) |

* This corresponds to “response” in Figure 1.

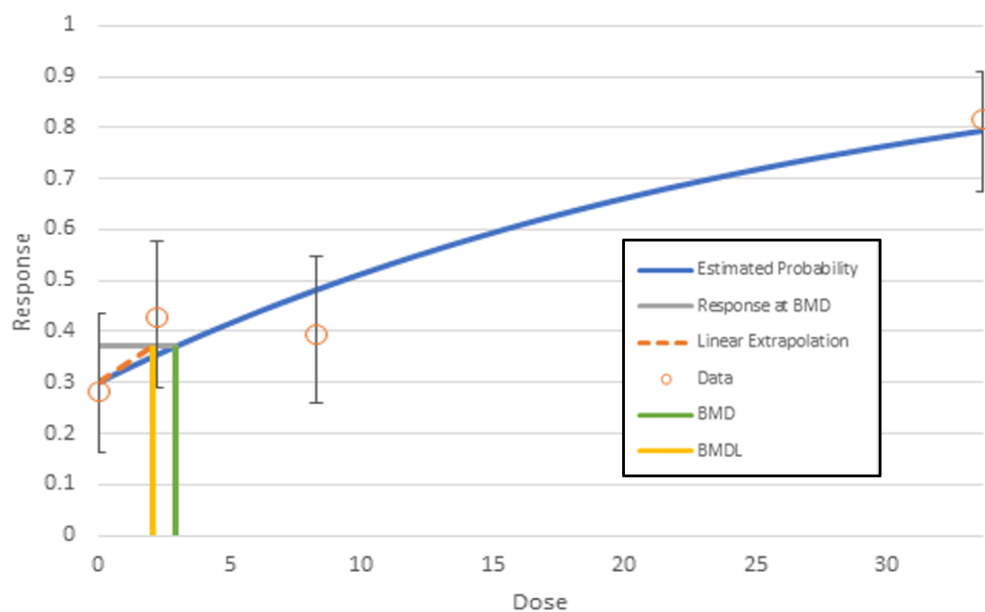


Figure 1. Example of tetrachloroethylene (from US EPA 2012b). Dose-response modelling of male mouse hepatocellular tumours associated with inhalation exposure to tetrachloroethylene, in terms of liver total oxidative metabolites, response data from JISA (1993).

The key steps of the calculation methodology of excess health risk for a given chemical substance are summarized in a flowchart presented in Figure 2.

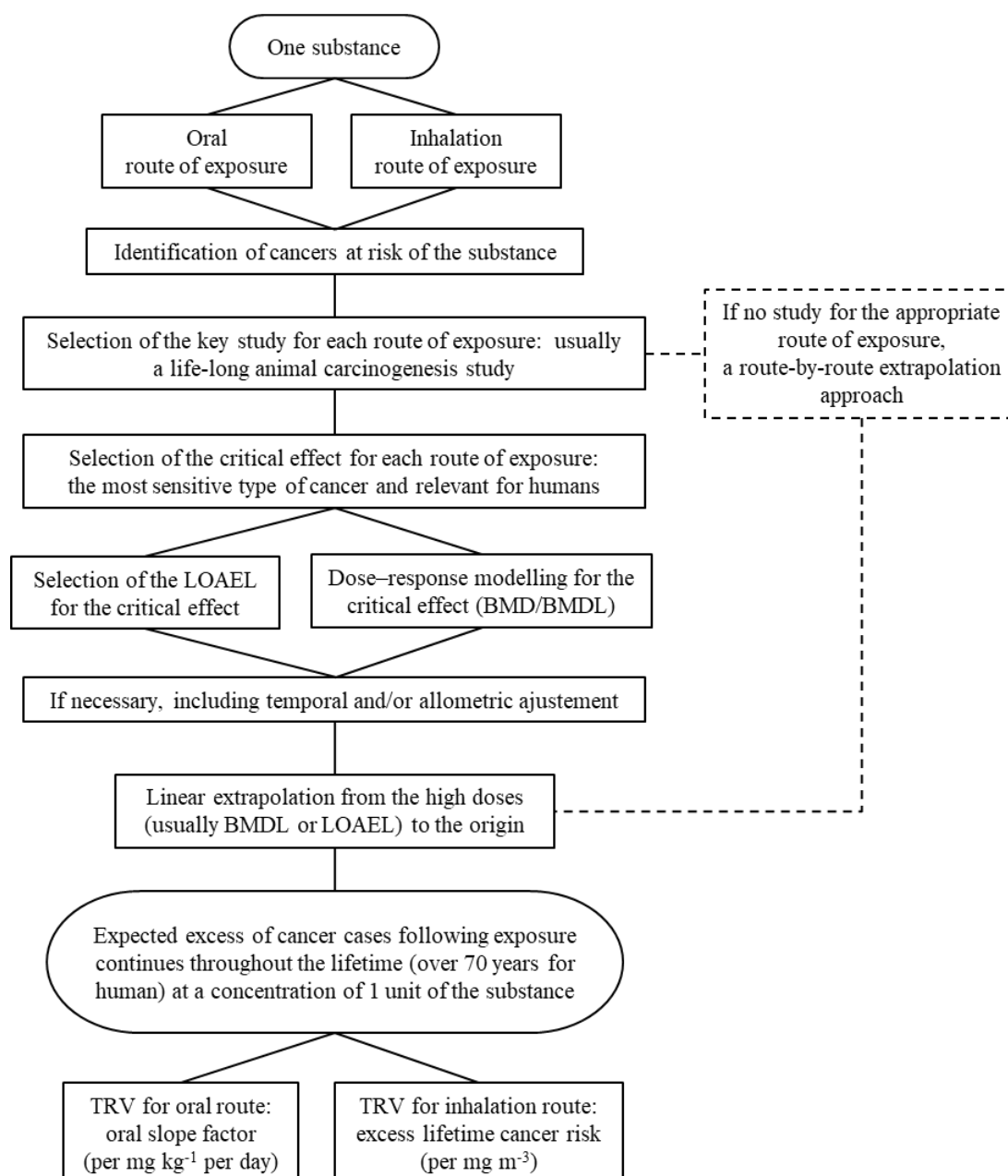


Figure 2. Flowchart on calculation methodology of excess cancer risk due to chemical substances.

2. Health risk assessment for radiological substances: calculation of nominal risk coefficient and radiation detriment

In the field of ionizing radiation, the exposure is quantified in terms of radiation dose. The absorbed dose (in grays, Gy, with $1 \text{ Gy} = 1 \text{ J kg}^{-1}$) is the energy deposited by radiation in an organ or tissue divided by the mass of this organ or tissue. The effective dose (in sieverts, Sv) is an average of the absorbed doses to the whole body with weighting factors accounting for the relative radio-sensitivity of the different organs and tissues, and the damaging effectiveness of the different types of radiation. Absorbed dose is used in research, while effective dose is used for regulatory purposes. Two types of health effects are considered: tissue reactions and stochastic effects. Tissue reactions occur only above a dose threshold, from a few hundred mGy to several Gy, such as skin burn, hair loss, depression of haematopoiesis, acute radiation syndrome, infertility or cataract. The severity of tissue reactions increases with dose. Stochastic effects, i.e. cancers and heritable effects, occur randomly among people exposed to radiation and are considered to be no-threshold effects by ICRP and NCRP (ICRP 2007, NCRP 2018). Unlike tissue reactions, the frequency of occurrence, not the severity, of stochastic effects increases with radiation dose. The carcinogenic effects of ionizing radiation have been demonstrated in Japanese survivors of atomic bombings

in Hiroshima and Nagasaki, as well as in other populations exposed to medical, occupational or environmental radiation sources (UNSCEAR 2008, UNSCEAR 2020). In the framework of environmental impact studies for nuclear facilities or polluted sites, the levels of exposures due to the releases from the facility or to radioactive substances already spread in the environment are usually not sufficient to cause tissue reactions, that is why only stochastic effects, in particular cancers, are taken into account.

Over the past decades, the ICRP has used the concept of radiation detriment to quantify the overall harm to health from stochastic effects of low-level radiation exposure of different parts of the body. ICRP Publication 103 describes the calculation of the radiation detriment from nominal risk coefficients, based on the probability of cancers and heritable effects (ICRP 2007, Cléro et al. 2019).

Input data

Nominal risk coefficient

The calculation of nominal risk coefficients includes the risks of radiation-induced cancers and of heritable effects in human.

Carcinogenic effects

For the risks of radiation-induced cancers, health data relate to four reference human populations: Euro-American men, Euro-American women, Asian men and Asian women. The Asian and the Euro-American data were averaged to form a composite population. Baseline incidence rates were obtained for these four populations using cancer incidence data from selected populations with long-running cancer registries (China and Japan for Asia; Sweden, United Kingdom and United States for Euro-America). Population-based cancer incidence rates and survival functions (probability to be alive at a given age), derived from the mortality rates, came from the 8th edition of Cancer Incidence in Five Continents (cancer rates measured by registries during the period 1993-1997, Parkin et al. 2002). Each of the four reference populations was distributed among 5-year age categories.

Based on epidemiological studies concerning groups of population specifically exposed to radiation with estimated individual doses (mostly the Life Span Study (LSS) of Hiroshima and Nagasaki atomic bomb survivors, Preston et al. 1994, Preston et al. 2007), radiation-associated cancer incidence risk models were developed for 11 organs or tissues: oesophagus, stomach, colon, liver, lung, female breast, ovary, bladder, thyroid, other solid cancers (see footnote in Table 2) and leukaemia. For each cancer site, modelling of the radiation-associated risk has been made using either a multiplicative (excess relative risk, ERR) or additive (excess absolute risk, EAR) model (see Figures 3 and 4) depending on age, sex and dose, with a linear dose-response for solid cancers and a linear-quadratic dose-response for leukaemia. The minimum latency period used in ICRP Publication 103 is five years for each type of cancer, corresponding to the shortest time in which a specified radiation-induced tumour is known or believed to occur after exposure (Cléro et al. 2019).

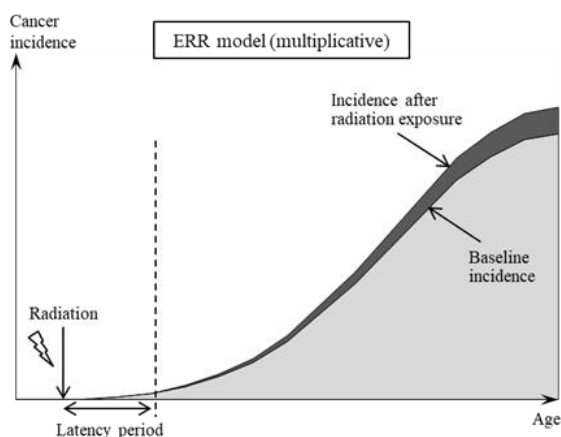


Figure 3. Illustration of a constant excess relative risk (ERR) model: multiplicative model.

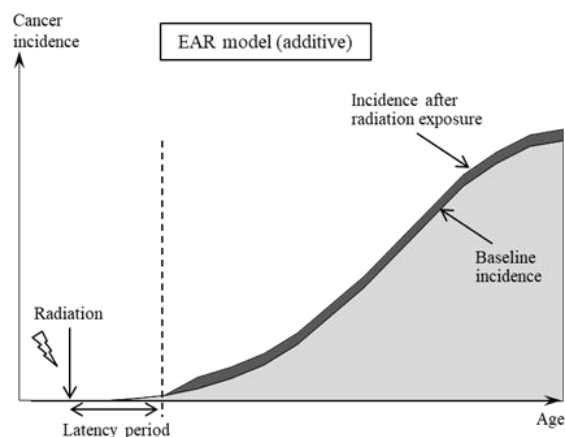


Figure 4. Illustration of a constant excess absolute risk (EAR) model: additive model.

Heritable effects

For the risk of heritable effects, which corresponds to serious hereditary abnormalities in descendants (in 2 generations) due to mutations induced in germ cells after radiation exposure, estimates are based on experimental studies. The nominal risk for heritable effects is relatively minor compared to those for cancers, representing about 1% of the global nominal risk.

Radiation detriment

Then, for the calculation of radiation detriment, the lethality fractions were used to convert nominal risk coefficients (based on excess incident cancers) to fatal cancer risks, taking into account the impact of medical treatment for some cancer types. The quality of life, reflecting pain, suffering and any adverse effects of cancer treatment, was also considered, as well as the years of life lost, as explained below.

Methods

Calculation steps for nominal risk coefficient

The nominal risk corresponds to an estimate of the radiation-associated lifetime risk, averaged over age, gender, ethnicity, different cancer sites and combined with risk of heritable effects. It is expressed in cases per 10,000 persons per Gy for 13 types of cancer and for heritable effects (see Table 2).

The lifetime baseline risks (i.e., the cumulated cancer risks without radiation exposure – regardless of natural background) and the lifetime excess risks (i.e., the cumulated risks of developing cancer due to radiation exposure) were estimated in the four reference populations for 11 organs or tissues (oesophagus, stomach, colon, liver, lung, female breast, ovary, bladder, thyroid, other solid cancers and leukaemia). In ICRP Publication 103, the risk of exposure-induced cancer (REIC) approach was used to calculate the excess lifetime risk estimates taking into account age at exposure (years), radiation exposure (organ dose in Gy), annual baseline risk of cancer incidence, attained age (years), latency period (years) and survival function.

For each of the eleven cancer sites, the considered exposure scenario was an acute exposure to 0.1 Gy (whatever the exposure route – ingestion, inhalation, external irradiation) for each year of age at exposure, with an age range 0-89 years for the general population and 18-64 years for workers. Lifetime risks were estimated at the attained age of 95, i.e., an age range 0-94 years for the general population and 18-94 years for workers, weighted over age categories within each reference population, and multiplied by 10 to obtain lifetime risks per 1 Gy.

To provide a reasonable basis for generalising across populations with different baseline risks, a weighting of the ERR and EAR lifetime risk estimates was applied. ERR:EAR weights of 50:50% were assigned for all cancer sites, except female breast (0:100%), thyroid (100:0%), and lung (30:70%). Experimental studies have shown that the effectiveness of radiation in producing biological damages per unit exposure is usually lower at low dose and low dose rate than at high dose and high dose rate. Therefore, a dose and dose-rate effectiveness factor (DDREF) of 2 was applied to low-dose risks, except for leukaemia for which the linear-quadratic risk model already accounted for a DDREF. The DDREF applies specifically to doses below 0.2 Gy or to higher doses when the dose rate is less than 0.1 Gy per hour (ICRP 1991) and was implemented in low dose risk management.

For bone cancer, the nominal risk coefficient was taken from ICRP Publication 60 (ICRP 1991), based on the fourth Committee on Biological Effects of Ionizing Radiations (BEIR IV) report of the United States National Research Council (NRC 1990), because no specific risk model was relevant. For skin cancer, no specific risk model was adequate either, due to differences between countries in risk related to skin pigmentation, thus the nominal risk coefficient was taken from ICRP Publication 59 (ICRP 1992) based on epidemiological and experimental results published before 1990.

Lastly, mainly based on experimental studies (UNSCEAR 2001), the risk of heritable effects associated with gonadal dose was estimated to be around 20 cases per 10,000 people per Gy in the general population and 12 cases per 10,000 per Gy in the working population (60% of that for the general population).

Additional calculation steps for radiation detriment

To calculate radiation detriment (D) associated with each cancer type, nominal risk coefficients (R) were adjusted with factors of lethality (k), quality of life (q) and years of life lost (l , representing an average shortening of life expectancy in years among people developing a cancer). The following formula was used: $D = [(R \times k) + (R \times (1 - k) \times q)] \times l$.

A single global radiation detriment was calculated as the unweighted sum of the 14 site-specific detriments for a reference human (child/adult exposure for general population, man/woman, Asian/Euro-American). The radiation detriment is expressed in terms of numbers of detrimental cases per 10,000 persons per Sv of low dose radiation, for the general population and for workers. As indicated in Table 2, the global detriment is 574 per 10,000 persons per Sv in the general population (i.e., per 10,000 persons exposed to 1 Sv whatever gender and age at exposure

from 0 to 89 years) and 422 per 10,000 persons per Sv in workers (i.e., per 10,000 persons exposed to 1 Sv whatever gender and age at exposure from 18 to 64 years). Conversely, the excess cancer risk from a given chemical substance is expressed for individuals continuously exposed to 1 unit of the considered substance during their lifetime. By comparison, for a continuous exposure of 1 mSv per year during the first 90 years of life, radiation detriment in the general population would be around $5 \cdot 10^{-3}$ (i.e., approximatively 50 detrimental cases expected at the attained age of 95 in a population of 10,000 individuals continuously exposed to 1 mSv per year from birth to age 90).

The relative radiation detriments, corresponding to the proportion (in percentage terms) of site-specific detriments in the global radiation detriment, are used (through the tissue weighting factors w_T) in the calculation for the effective dose which is an indicator commonly used to assess radiation-induced health risk in the general population (whatever age and gender).

Table 2. Steps and parameters for calculating radiation detriment, from nominal risk coefficients to detriment for the general population, age 0-89 years at exposure (ICRP 2007).

| Organ/tissue | Nominal risk coefficient | Lethality fraction | Non-fatal case weight | Relative cancer free life lost | Detriment |
|--------------------|--------------------------|--------------------|-----------------------|--------------------------------|------------|
| | R^* | K | q | l | D^{**} |
| Oesophagus | 15 | 0.93 | 0.935 | 0.87 | 13.1 |
| Stomach | 79 | 0.83 | 0.846 | 0.88 | 67.7 |
| Colon | 65 | 0.48 | 0.530 | 0.97 | 47.9 |
| Liver | 30 | 0.95 | 0.959 | 0.88 | 26.6 |
| Lung | 114 | 0.89 | 0.901 | 0.80 | 90.3 |
| Bone | 7 | 0.45 | 0.505 | 1.00 | 5.1 |
| Skin | 1000 | 0.002 | 0.002 | 1.00 | 4.0 |
| Breast | 112 | 0.29 | 0.365 | 1.29 | 79.8 |
| Ovary | 11 | 0.57 | 0.609 | 1.12 | 9.9 |
| Bladder | 43 | 0.29 | 0.357 | 0.71 | 16.7 |
| Thyroid | 33 | 0.07 | 0.253 | 1.29 | 12.7 |
| Bone marrow | 42 | 0.67 | 0.702 | 1.63 | 61.5 |
| Other solid *** | 144 | 0.49 | 0.541 | 1.03 | 113.5 |
| Gonads (heritable) | 20 | 0.80 | 0.820 | 1.32 | 25.4 |
| Total | 1715 | | | | 574 |

* Expressed in cases per 10,000 people per Gy.

** Expressed in cases per 10,000 people per Sv.

*** 14 remainder tissues: adrenals, extra-thoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

The key steps of the calculation methodology of excess health risk for radiation exposure are summarized in a flowchart presented in Figure 5.

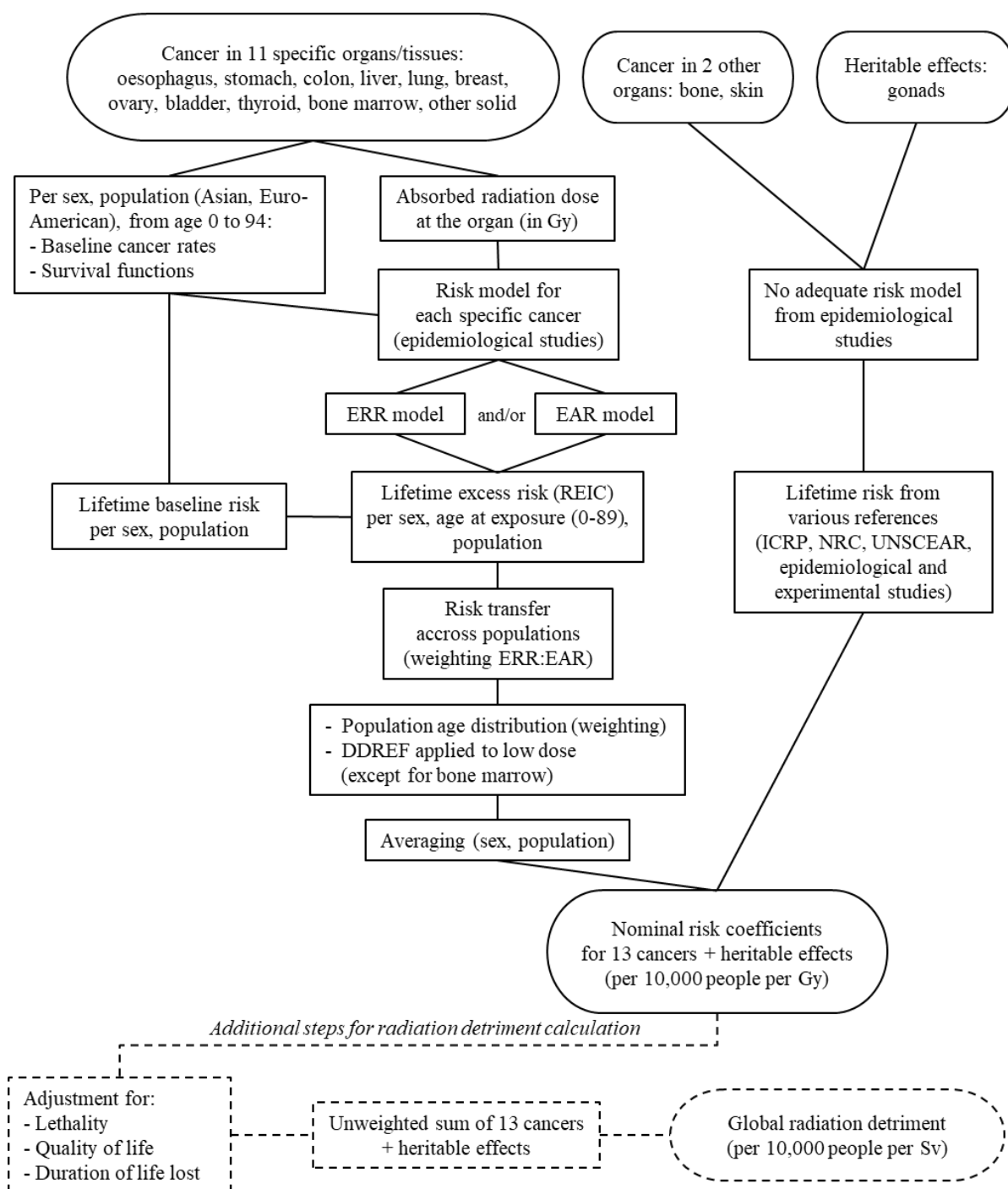


Figure 5. Flowchart on calculation methodology of excess health risk due to radiation exposure.

3. Discussion on the comparison of excess cancer risk calculation methodologies used for chemical substances and for radiation exposures

Historically, the regulated levels of radiation exposure have often been expressed in units unique to radiation (Calabrese 2009). Nevertheless, for cancer risks due to environmental exposures, these levels are rooted in the assumption that the level of risk accepted by regulators for radiation shall be the same than for other carcinogenic substances or in comparison to other risks. It was done for occupational exposure limits when stochastic effects (cancer and heritable effects) were introduced in the radiation protection system: the limit for effective dose recommended by the ICRP (1977a) was set in reference to occupational risks incurred in other fields. A deadly accident occurrence of 10^{-4} per year was observed in industries recognized as having high standards of safety (ICRP 1977b) and this level of risk corresponded to a radiological exposure of 5 mSv per year. To aim at such

average level among workers exposed to radiation, the upper limit for occupational exposure was set ten times higher, at 50 mSv per year. Considering that the level of acceptability for risks to the general public was an order of magnitude lower than for occupational risks, an annual dose limit of 5 mSv was set for public exposure (ICRP 1977a). With the advancement of knowledge on risk, these limits were lowered in subsequent recommendations to 20 mSv per year and 1 mSv per year, respectively for workers and members of the public (ICRP 1991, ICRP 2007). A similar rationale was followed, for example, by the US EPA to make the decision to remediate polluted sites with radioactive contamination (US EPA 1997) which set the life span tolerable risk for the public for pollution remaining in place at 10^{-4} for individual cancer excess risk for both radioactive and chemical substances. For a relevant comparison of risk induced by exposure to chemical substances and to radiation, we have to make sure that the slope factors (or reference values for risk per unit exposure) used to express the level of excess risk have the same meaning in terms of health effects.

How are the reference values used in health risk assessment?

For exposure either to chemical substances or to radiation, the TRVs or the detriment through the effective dose concept are used to perform health impact studies in which very often several chemicals or several radionuclides are at stake. The steps of these studies are quite similar for chemicals and radiation and then the results, expressed in terms of dose or excess cancer risks are compared to regulatory limits or reference levels. Special features of the health impact assessment are briefly reviewed hereafter.

Cancer risk assessment for chemical substances

For carcinogenic chemical substances, human health risk assessment is a quantitative assessment composed of four successive steps: (1) hazard identification; (2) dose-response relationship evaluation; (3) exposure assessment; (4) risk characterization (NRC 1983). The first two steps are addressed above in section 1. The result of the four steps process is a cancer risk estimate that represents the incremental probability that an individual will develop cancer over a lifetime as a result of a specific chronic exposure to a carcinogenic chemical (US EPA 1989). A human receptor is defined as an individual that is vulnerable to the adverse effects of a hazardous substance or agent.

For the ingestion route, the cancer risk estimate can be expressed as the product of a lifetime average daily dose by a cancer slope factor (i.e. by a TRV). However, it is recommended to separately evaluate exposure at different ages, because the dose varies with age-related features such as body weight and food and water consumption rates. For the inhalation route, the risk estimate can be expressed as the product of an average inhalation concentration by a lifetime excess cancer risk per exposure unit. The chronic daily exposure is generally averaged over a 70-year lifetime.

Risk is assessed for each substance of concern and for each exposure route. The comparison of cancer risks for each substance and for each exposure route allows ranking substances, emission sources and routes that contribute significantly to the risk. For a given human receptor, it is recommended to sum the cancer risks caused by all chemicals through a given route of exposure. Risks are usually summed without taking into account potential antagonistic or synergistic effects of carcinogens. Individuals may also be exposed through several routes of exposure. Cancer risks from different routes of exposure are assumed to be additive for a given human receptor exposed over a given time period (US EPA 1989).

Risk characterization is completed by a discussion of uncertainties and limitations associated with risk assessment. Risk assessment is considered as a complex process for which uncertainty occurs at every step of the process. Lifetime cancer risks below a value set in a 10^{-4} - 10^{-6} range are generally considered to be tolerable. This level is commonly chosen by public health agencies all over the world as a reference value. For instance, the World Health Organization indicates that “*guideline values [for drinking-water quality] are conservatively presented as the concentrations in drinking-water associated with an estimated upper-bound lifetime excess cancer risk of 10^{-5}* ” (WHO 2017). Other examples are US EPA (US EPA 1997) who was recommending a 10^{-4} - 10^{-6} range for individual risk over the lifetime in the framework of CERCLA and the high council d for public health in France who set a domain of compliance for individual risk excess below 10^{-5} over the lifetime (HCPH 2010). Risks exceeding the tolerable level do not systematically lead to expect toxic effects (US EPA 2007). Such estimate however triggers further review of the underlying scientific basis of the calculation to reduce uncertainties that might lead to a potential overestimate of risk (if possible) or, if not, to modify conditions prevailing on site.

Cancer risk assessment for radiation exposures

For radioactive substances, the excess cancer risk has as yet been little used to assess the impact of a radioactive release on human health (such as WHO 2013, UNSCEAR 2020). The more common indicator is the effective dose concept that may be assessed from either environmental or bioassay measurement, using biokinetic models and

dose per intake coefficients. When evaluating specific situations of exposure, the effective dose of representative individuals is compared with the relevant regulatory dose limit, which is 20 mSv per year for occupationally exposed workers or 1 mSv per year for the general public (ICRP 1991, ICRP 2007). Doses above the dose limit are considered to be unacceptable. Below the limit, the exposure still has to be reduced as low as reasonably achievable, which is the implementation of a process more than a precise value to achieve. However, with a view of comparing different risk factors, the sum of effective doses for all individuals (collective dose) may be converted into risk for a population: it was done in a French study of cancers related to lifestyle and environmental factors (Soerjomataram et al. 2018), including radiation exposures (Marant-Micallef et al. 2019a, b) as well as chemical agents (Desbiolles et al. 2019). Such analyses remain complex and prone to contention. In contrast with conservative exposure evaluations conducted to assess compliance with dose limits, these calculations should use best estimates of parameters. To avoid aggregation of low individual doses over extended time periods and wide geographical regions the range in effective dose and the time period should be limited and specified (ICRP 2007). To avoid extremes of extrapolation, it can be useful to present the doses, and hence the assessed health effects, on a temporarily and spatially disaggregated manner, taking other factors, such as age and sex, into account. Examples of such disaggregation were considered by the United Kingdom Committee on Medical Aspects of Radiation in the Environment (COMARE 2016).

For the general population, the overall detriment (integrating all radiation induced cancer types + heritable effects) is 574 cases per 10,000 persons per Sv (see above). So, for example if the collective dose is 10 Man.mSv the population detriment is $5.74 \cdot 10^{-4}$. To be consistent with the way nominal risk coefficients and detriment coefficients were designed, this should apply only to a population whose features are close to the reference population used to calculate these coefficients. In other words, it is not appropriate to apply the whole population detriment to exposure incurred by children in a kindergarten or by inhabitants of a retirement home immersed in a radioactive plume.

This detriment coefficient may also be used to obtain a rough indication of the risk for one person to suffer from cancer because of the exposure to ionizing radiation (whatever age and sex). However, this indicative result does not replace cancer risk assessment based on epidemiological data for a given individual exposed to ionizing radiation because the genuine excess risk is strongly dependant on age and sex (ICRP 2021).

Main differences and points of comparison of these values

Since health impacts can be appraised in terms of excess cancer risk for both chemical and radiological exposure, there is an increasing interest in considering that the radiological excess risk estimated with the detriment is equivalent to a chemical excess risk estimated with a TRV (NEA 2020). But commonalties and differences between detriment and TRVs need to be clearly underlined to cautiously handle the comparison of risk from radiations and chemical substances.

Basically, both TRVs and the nominal risk coefficient are slope factors designed to reflect a risk of cancer in the general population at low level of exposure over a lifetime, which increases linearly with incurred doses. Despite many debates, mainly due to the use of a dose-risk relationship based on data obtained in a range of exposure higher than the situations the management system is applied to, the principle of linearity was retained for protection against cancers induced by radiation (ICRP 2007) and confirmed by recent epidemiological studies even in the low-dose range (below 100 mSv) (NCRP 2018, Hauptmann et al. 2020, UNSCEAR 2018, UNSCEAR 2020). This concept was also adopted for chemical substances (Calabrese 2009). In addition to its adequate consistency with epidemiological data, the linear dose-risk relationship is also a convenient management tool providing equivalence between health risk and dose, with the latter being much easier to monitor, and guaranteeing the additivity of risks from multiple doses resulting from several events or sources of exposure. Thus, the use of the LNT model for both chemical substances and radiation is a science-informed decision adopted to facilitate the management of risk but not a rule scientifically proved.

The discussion below aims at highlighting the differences that may cause issues in the direct comparison of the results of chemical and radiological risk assessments. The main points arising from the first two chapters and flowcharts above are listed below.

1/ Animal vs human data modelling

For the radiation detriment, excess cancer risks are based on epidemiological data (mainly from the Japanese survivors of atomic bombings) and cancer baseline rates in men and women aged 0-94 from Asian and Euro-American populations. Because of differences of baseline cancer rates across populations, both multiplicative and additive risk models are used and combined for each cancer site. In the calculation methodology for chemical substances, the excess risk of cancer is based on the difference between the cancer rate in the control animals and the cancer rate observed at a given exposure to chemical substances. Extrapolation to humans is mainly based on

the ratio of basic metabolic rates without any consideration for a baseline rate for humans. Thus, unlike epidemiological data, these data do not make it possible to take into account variations with age or gender. Furthermore, compared with the radiological methodology, one can say only additive risk models are considered to assess excess risk due to chemical exposure.

2/ Exposure to low levels: extrapolation vs interpolation of source data

For chemical substances, the studies used for the construction of TRVs for carcinogenic effects are carried out after exposures at relatively low doses, even if they are much higher than environmental exposures, over the entire life of the animal. For practical consideration, a linear extrapolation from the POD to low doses at encountered environmental level has usually been adopted. This approach is not suitable for all types of tumours and depends on the mode of carcinogenic action. It mainly corresponds to substances which react with DNA or exhibit direct mutagenic activity. When there is insufficient data to determine the mode of action, linear extrapolation is used by default because it is considered to be a health-protective approach (US EPA 2005).

For radioactive substances, risk models are estimated from epidemiological data for each cancer site and applied in the calculation of a nominal risk coefficient, allowing interpolation of risk under the assumption of linearity, without an extrapolation from a point of departure to lower doses such as performed for chemical substances. The ICRP's methodology assumes a LNT dose-risk relationship for stochastic effects (cancer and heritable diseases), i.e., an increment in dose induces a proportional increment in risk at low doses. In the calculation of nominal risk coefficients, risk models for specific cancer sites mainly come from the LSS following Japanese survivors having received an acute dose estimated from 0 to 4 Gy (for colon absorbed dose), depending on the location of individuals at the moment of the explosion. In this epidemiological study, about two-thirds of participants (around 68,000 people) received low doses, i.e. estimated colon dose less than 100 mGy. Many other epidemiological studies analysed the relationship between radiation exposure and health effects, in different situations of (occupational, medical, environmental) exposure of different populations (adults, children, various countries) and with various quality criteria (study protocol, dosimetry, statistics). According to the epidemiological studies with high-quality data, the observed results are reasonably consistent with the LNT assumption. To date, although uncertainties persist for low doses, there are no elements in favour of the existence of a threshold (NCRP 2018, Shore et al. 2018, Hauptmann et al. 2020). Furthermore, experimental studies have shown that different types of radiation may demonstrate different effectiveness in inducing biological damages. For a same absorbed dose, alpha radiation and neutrons cause a higher frequency of adverse health effects than photons and electrons (ICRP 2007). To account for this relative biological effectiveness, the absorbed dose (in Gy) from each type of radiation is multiplied by a radiological weighting factor (in addition to tissue weighting factors based on relative radiation detriments) when calculating effective dose (in Sv).

3/ Exposure doses vs absorbed dose

Usually, the TRVs are developed on the basis of separate studies and dose-response curves for each route of exposure (oral and inhalation). The unit actually used to quantify the dose depends on the route. For inhalation, the unit is an airborne concentration (usually expressed in $\mu\text{g m}^{-3}$ or mg m^{-3}) and thus relates clearly to an exposure. The construction of an inhalation TRV embarks choices on respiratory flowrates and its unit is inverse of an airborne concentration i.e. $(\mu\text{g m}^{-3})^{-1}$ or $(\text{mg m}^{-3})^{-1}$. For ingestion, the dose is the daily mass incorporated per body weight, with a TRV expressed in $(\text{mg}_{\text{pollutant}} \text{kg}_{\text{bodyweight}}^{-1} \text{per day})^{-1}$. So the assessment of the response to this route of exposure needs to input data about diet. For both exposure routes, the exposure is supposed to occur over the life span.

For radiation, the nominal risk coefficient is established in relation with absorbed dose estimated in studies of external irradiation. Biokinetic and dosimetric models were developed to evaluate the radiation dose absorbed by organs in situations of internal contamination with radionuclides (oral, ingestion, transcutaneous). The absorbed dose resulting from all routes of exposure may thus be summed. Therefore, to obtain the level of excess risk, the nominal risk coefficient is multiplied by an absorbed dose which may be the result of a combination of different routes of exposure, whereas each TRV is multiplied by an exposure for the corresponding route. In order to foster the mutual understanding between chemical risk assessment and radiation risk assessment, it would be very useful to adopt similar definitions of exposure and dose, along the line that doses are the results of exposures.

4/ Health effects: critical organ vs whole body effect

In both types of exposure, the effects considered are based on clinical observations of the frequency of cancers. TRVs are determined on the basis of the critical effect chosen among all of the known cancers. This critical effect corresponds to the cancer observed at the lowest dose whatever the organ. This option is supposed to be protective against all cancers likely to occur due to exposure to a chemical substance without a threshold effect. For the nominal risk coefficient, excess cancer risks are estimated separately for several cancer sites. Assuming a

homogeneous exposure of the whole body, their unweighted sum represents a total excess risk of cancer incidence per unit of absorbed dose.

5/ Probability of cancer occurrence vs detriment

The TRVs, like the nominal risk coefficients, are established on the basis of the likelihood to develop a cancer. But the calculation methodology for radiation detriment also includes additional steps using adjustment factors to take into account the severity of each type of cancer (lethality, quality of life affected by the disease, relative years lost due to the disease). This approach is needed in order to obtain a unique indicator representing the total disease burden caused by homogeneous exposure of the whole body to radiation.

6/ Confidence interval on dose vs mean value of risk estimate

As underlined in Tran et al. (2000), estimates of cancer risk from radiation exposures correspond to “central” or “best” risk estimates based on epidemiological data over the whole range of exposure, whereas estimates of cancer risk from chemical substances usually correspond to the slope of a linear extrapolation to zero dose from the lower bound of the 95% confidence interval on the lowest dose causing significant response in animals, according to the model(s) used. Attributing the observed effect to the lowest likely dose causing this effect is a hypothesis that maximises the risk estimated for low doses.

Opportunity to close the gaps between the two approaches to calculating cancer risk due to radiation or chemicals

As mechanistic methods to assess the TRV of new chemical substances are deemed robust enough neither by the French Agency for Food, Environmental and Occupational Health & Safety nor by the European Chemicals Agency (Anses 2017; ECHA 2012), animal experiments with standardized exposure protocols should still be used for a long time in the future. Thus, in the near future, there might be no mere opportunity to reduce differences 1 and 2. Nevertheless, results obtained from epidemiological cohorts and animal experiments both aim at modelling dose-response in the same way, as a LNT relation at low levels. So the differences of data sources should not be an insuperable impediment to the comparison of TRVs with nominal risk coefficients for radiation. In addition, biologically-based mechanistic models that combine understanding of human carcinogenesis with epidemiological studies are successfully used in the field of ionizing radiation and may help to improve the evaluation of cancer risk in the low dose range as biological data on radiation effects in humans build up (Rühm et al. 2017, Castelletti et al. 2019).

In view of the other differences listed above, the depiction of the construction process for TRV and radiation detriment provide opportunities to reduce the gap towards a more meaningful comparison of excess cancer risk associated with chemical and radiation exposure.

To address difference 3 about doses, from the chemical side, an ongoing development consists in considering dose instead of exposure. This may be done by modelling the behaviour of a chemical substance in the body and it could change the concept of exposure-response curve to a concept of dose-response curve, which would apply to all routes of exposure. However, this approach requires experimental data to relate internal dose to the measurement of a biomarker of exposure. While many aspects and applications of this approach are currently under study, particularly in the context of monitoring exposures at the workplace, it suffers from many limits and is currently only feasible for a very limited number of substances, even though these substances tend to be the ones most commonly of interest, such as lead. Nevertheless, beside the breakthrough in the use of the dose concept for chemicals, in the current default approach used in environmental impact studies, lifetime excess cancer risk (cancer potency) resulting from several substances and/or several routes of exposure is assumed to be additive, without considering toxic interactions. This assumption is similar to that applying to dose and thus allows to reduce the gap between dose and exposure, even though this additivity hypothesis is not supported by scientific evidence (US EPA 2007), and consequently to reduce the gap between the chemical approach (route by route) and the radiological approach (total dose due to all routes). Further complication can still be brought by interactions in the presence of multiple stressors: simultaneous exposure to several chemical substances or to ionising radiation and to chemicals may enhance detrimental effects, as confirmed in the case of radon and tobacco, or produce unexpected outcomes, while the knowledge of such combined effects is still relatively weak. In practice, however, a high level of accuracy is not always warranted in the comparison of chemical and radiological risks. To support decisions in the management of a situation involving both, even an analysis relying on largely uncertain information is preferable to ignoring the question of their relative dangerousness level.

To deal with differences 4 and 5 from the radiological side, the use of the nominal risk coefficients instead of detriment would bring results of lifetime excess cancer risk from ionizing radiation closer to that resulting from exposure to chemical substances. However, since exposure to radiation may be heterogeneous over body regions,

especially in case of internal contamination, a well-established scenario of exposure, including the knowledge of radionuclides involved, is necessary to be able to estimate the absorbed dose incurred by each organ and tissue and then to determine the frequency of each type of cancer using the corresponding nominal risk coefficient in Table 2. The sum of nominal risks for all organs and tissues is the overall risk of cancer due to radiation exposure. It depends upon the scenario of exposure and the nature of radionuclides involved because they drive differently the energy deposition in the different body regions. This consideration allows to cope with the difference between detriment and occurrence. To be closer to chemical risk assessment, the highest risk determined for a given radiological exposure scenario could correspond to the critical organ associated with this scenario (e.g., thyroid for radioiodine inhalation and/or ingestion). An alternative would be that cancer incidence in all organs due to exposure to a mixture of carcinogenic genotoxic substances be added, keeping in mind that TRVs do not allow to encompass the whole cancer potency of each genotoxic substance.

A specific issue is radio-induced skin cancer. Table 2 shows that skin cancer is the most frequent cancer in terms of incidence after radiation exposure. The induction of this cancer site by radiation is dramatically reduced in the detriment calculation because of its very low value of the lethal fraction ($k = 0.002$). ICRP publication 103 indicates that the value of the nominal risk coefficient did not come from the LSS because of a too high sensitivity of the baseline rate to the skin pigmentation. So, as detailed by ICRP publication 59 (ICRP 1992), skin cancer risk assessment came mainly from experimental data. Then radiation detriment was established on the basis of lethality data for humans affected by non-melanoma skin cancers since no association between ionizing radiation and melanoma was detected. More generally, a review of the state of knowledge on skin cancer and other cancer types, and a revision of the nominal risk coefficients and radiation detriment (including risk models, baseline rates, DDREF, etc.) are planned by ICRP for the next future.

About difference 6, the 95% confidence intervals of radiation-risk-model parameter estimates, used in the calculation of nominal risk coefficients, are provided for the different cancer sites in the LSS (Preston et al. 2007). To be more conservative as in risk assessment for chemical substances with the use of BMDL, it could be interesting to study the impact of shifting the starting point of nominal risk calculation from the mean value to the upper limit of the 95% confidence intervals, in the same way as Zhang et al. (2020) did for other parameters in a sensitivity analysis of parameters and methodological choices used in calculation of radiation detriment. Nevertheless, while the use of the lower boundary of the confidence interval has advantages, it also has disadvantages including: 1/ the boundary is less well-known than the best estimate; 2/ the less is known about the carcinogenicity of a substance, the wider is the confidence interval and thus the higher the protection level; 3/ realistic estimates are needed in decision making about different alternatives.

Conclusion

Basically, the TRV and the nominal risk coefficient describe an increase of cancer risk resulting from a low level of chemical and radiation exposure over the life span. These values are constructed mostly from data of different natures (data sources, health effects, exposures, risk estimates, etc.) but with the same objective of protecting individuals from exposure to a harmful agent within a management system based on a LNT dose-response relationship.

The ways the TRVs and the radiation detriment are established allow a comparison of excess cancer risk due to exposure to chemical substances and to ionizing radiation. For instance, a comparison of the basis of these different protection standards in terms of tolerable risks of cancer incidence was done recently for occupational exposure by the German Commission on Radiological Protection (Rühm et al. 2020), underlying inter alia that in Germany standards for carcinogenic substances are given for each substance individually whereas standards for radiation are set for all sources of exposures. Nevertheless, beyond commonalities, the TRV and the radiation detriment do not exactly reflect the same excess cancer risk. As a result, a comparison of dose limits or reference levels set in the field of radiation protection (typically 1 to 20 mSv per year) translated into risk excess by using the detriment with guidance values for other carcinogenic substances (typically 10^{-5} or 10^{-4} over the life span) must be considered cautiously. With a scenario of exposure to radionuclides, it is possible to evaluate radiation energy deposition (dose) in the different organs and tissues and then to assess the lifetime excess risk of each type of cancer by multiplication of dose estimated in each sensitive region with the corresponding nominal risk coefficient. The sum of the excess risks of each type of cancer can be considered as a global lifetime excess cancer risk from ionizing radiation. To go further in the comparison with chemicals, the highest risk among the thirteen types of cancer could be considered as the radiological cancer excess risk. An alternative would be that cancer incidence in all organs due to exposure due to a mixture of carcinogen genotoxic substances be added, keeping in mind that TRVs do not allow to encompass the whole cancer potency of each genotoxic substance. It must also be noted that the use of exposure for chemicals, rather than dose as used for radiation, leads to the definition of a different TRV for each route of exposure.

The health consequences of low dose radiation exposure are evaluated in an increasing variety of situations. For example, the World Health Organization estimated absorbed doses and lifetime cancer risks for different cancer sites following radiation exposure at different ages during the Fukushima nuclear accident (WHO 2013). Applying the same methodology, with risk models based on the LSS, Walsh et al. (2019) demonstrated how reference dose levels translated differently into specific cancer risk levels depending on age at exposure, gender, time since exposure, and type of cancer within the German population. ICRP is also planning new recommendations that may well include new parameters (Cléro et al. 2019, Zhang et al. 2020) which would need more transparency and comprehensibility for non-specialists in radiation protection (Breckow 2020). This growing trend on improving the understanding and the estimate of health consequences could help to get broader types of results than effective doses by the use of alternative quantities such as lifetime excess cancer risk for the most sensitive organ. Moreover, assuming that it may be relevant to complete the assessment of effective dose with that of lifetime excess cancer risk in specific situation of exposure opens the opportunity to set common limits to manage both radiological and chemical risks. This perspective requires an investigation with regard of the perception of risk by the public. Beyond the mere comparison of the meaning of a TRV and of the radiation detriment, more studies and research are necessary to better combine the results within a health impact study when both radiation and chemical exposures are involved.

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