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Enora Clero, Michèle Bisson, Nathalie Velly, Eric Blanchardon, Eric Thybaud,
Yann Billarand

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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**

3
4 Enora Cléro¹, Michèle Bisson², Velly Nathalie², Eric Blanchardon¹, Eric Thybaud², Yann Billarand¹.

5
6
7 **Concise and informative title**

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

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10
11 ¹ Health and Environment Division, Institute for Radiological Protection and Nuclear Safety (IRSN), Fontenay-
12 aux-Roses, France.

13 ² Chronic Risks Division, French National Institute for Industrial Environment and Risks (INERIS), Verneuil-en-
14 Halatte, France.

15
16
17 **Corresponding author:** Yann Billarand

18 Institute for Radiological Protection and Nuclear Safety

19 PSE-Env/SEDDER

20 BP 17

21 F-92262 Fontenay-aux-Roses Cedex

22 France

23 Tel: +33 1 58 35 89 84 / Fax: +33 1 46 57 03 86

24 Mail: yann.billarand@irsn.fr

25 **Abstract**

26 This article aims at comparing reference methods for the assessment of cancer risk from exposure to genotoxic
27 carcinogen chemical substances and to ionizing radiation. For chemicals, cancer potency is expressed as a
28 toxicological reference value (TRV) based on the most sensitive type of cancer generally observed in animal
29 experiments of oral or inhalation exposure. A dose-response curve is established by modelling experimental data
30 adjusted to apply to human exposure. This leads to a point of departure from which the TRV is derived as the slope
31 of a linear extrapolation to zero dose. Human lifetime cancer risk can then be assessed as the product of dose by
32 TRV and it is generally considered to be tolerable in a 10^{-6} – 10^{-4} range for public in normal situation. Radiation
33 exposure is assessed as effective dose corresponding to a weighted average of energy deposition in body organs.
34 Cancer risk models were derived from the epidemiological follow-up of atomic bombing survivors. Considering
35 a linear-no-threshold dose-risk relationship and average baseline risks, lifetime nominal risk coefficients were
36 established for 13 types of cancers. Those are adjusted according to the severity of each cancer type and combined
37 into an overall indicator denominated radiation detriment. Exposure to radiation is subject to dose limits
38 proscribing unacceptable health detriment. The differences between chemical and radiological cancer risk
39 assessments are discussed and concern data sources, extrapolation to low doses, definition of dose, considered
40 health effects and level of conservatism. These differences should not be an insuperable impediment to the
41 comparison of TRVs with radiation risk, thus opportunities exist to bring closer the two types of risk assessment.
42

43 **Keywords**

44 Health risk assessment; Chemicals; Toxicological reference value; Radiation; Nominal risk; Detriment.
45

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53 **Code availability:** Not applicable.
54

55 **Abbreviations**

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

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

58 BMD: benchmark dose

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

60 CERCLA: Comprehensive Environmental Response, Compensation, and Liability Act

61 DDREF: dose and dose-rate effectiveness factor

62 EAR: excess absolute risk

63 ECHA: European Chemicals Agency

64 EFSA: European Food Safety Authority

65 ERR: excess relative risk

66 Gy: Gray

67 HCPH: French High Council for Public Health

68 ICRP: International Commission on Radiological Protection

69 LOAEL: lower observed adverse effect level

70 LNT: linear-no-threshold

71 LSS: Life Span Study

72 OEHHA: Office of Environmental Health Hazard Assessment (USA)

73 PBPK: physiologically based pharmacokinetic

74 POD: point of departure

75 REIC: risk of exposure-induced cancer

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

77 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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86 **Introduction**

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

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

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

134

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

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

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

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

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

162

163 **Input data**

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

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

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

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

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

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

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

205

206 **Methods**

207 *Steps of calculation for cancer potency*

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

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

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

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

247 The cancer potency, or cancer slope factor or lifetime excess cancer risk, according to organizations, is an estimate
248 of the risk of cancer incidence per unit dose for a lifetime exposure to a substance, which is generally expressed
249 per mg kg⁻¹ body weight per day or per µg m⁻³ in ambient air for the oral and inhalation route of exposure,
250 respectively (WHO 2009). Thus, for example, if the excess risk of a given cancer from inhalation exposure to a
251 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
252 exposed during his lifetime to 1 µg m⁻³ of the substance, in addition to the baseline risk of the cancer in an

253 unexposed population. For a population of 1 million individuals continuously exposed to 1 µg m⁻³ of the substance
 254 throughout life, 8 additional cancer cases related to this exposure are expected.

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

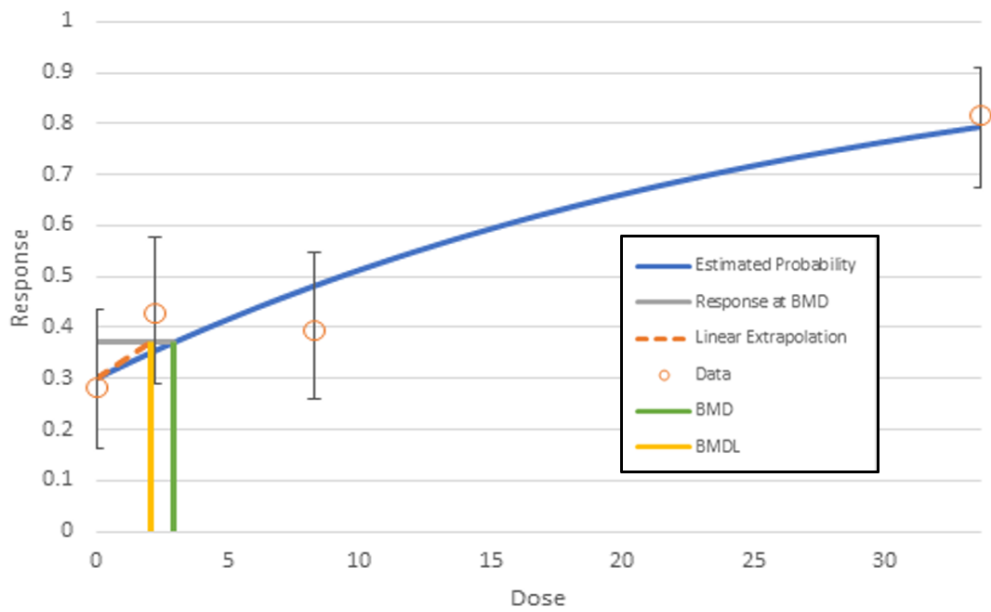
263 ***Example of construction of the TRV for carcinogenic effects for inhalation exposures to tetrachlorethylene***
 264 ***(from US EPA 2012b)***

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

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

Tetrachloroethylene concentration administrated to animals (ppm)		Liver total oxidative metabolism (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)

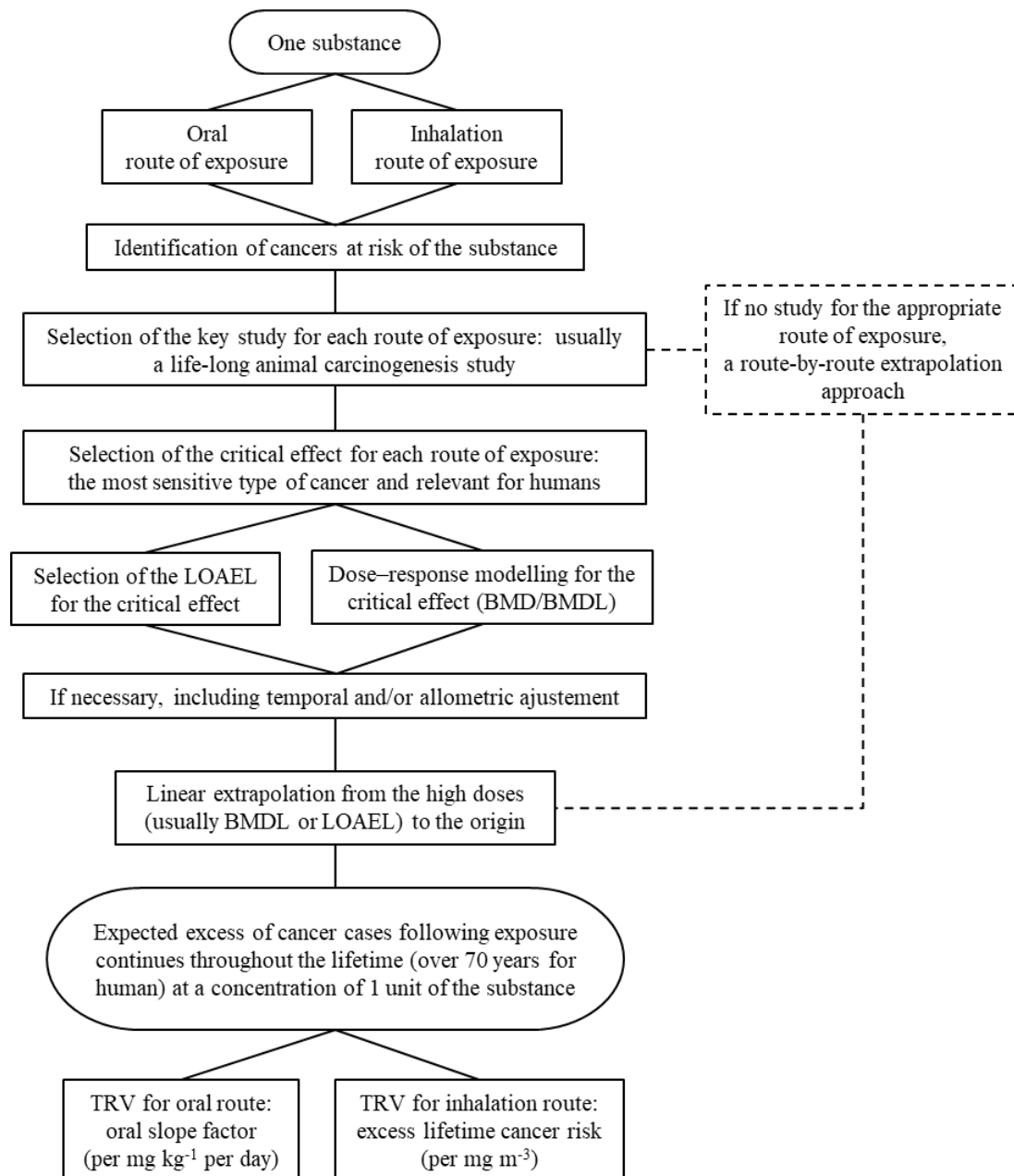
284 * This corresponds to “response” in Figure 1.



285

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

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



291
292 **Figure 2.** Flowchart on calculation methodology of excess cancer risk due to chemical substances.
293

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

296 In the field of ionizing radiation, the exposure is quantified in terms of radiation dose. The absorbed dose (in grays,
297 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
298 organ or tissue. The effective dose (in sieverts, Sv) is an average of the absorbed doses to the whole body with
299 weighting factors accounting for the relative radio-sensitivity of the different organs and tissues, and the damaging
300 effectiveness of the different types of radiation. Absorbed dose is used in research, while effective dose is used for
301 regulatory purposes. Two types of health effects are considered: tissue reactions and stochastic effects. Tissue
302 reactions occur only above a dose threshold, from a few hundred mGy to several Gy, such as skin burn, hair loss,
303 depression of haematopoiesis, acute radiation syndrome, infertility or cataract. The severity of tissue reactions
304 increases with dose. Stochastic effects, i.e. cancers and heritable effects, occur randomly among people exposed
305 to radiation and are considered to be no-threshold effects by ICRP and NCRP (ICRP 2007, NCRP 2018). Unlike
306 tissue reactions, the frequency of occurrence, not the severity, of stochastic effects increases with radiation dose.
307 The carcinogenic effects of ionizing radiation have been demonstrated in Japanese survivors of atomic bombings

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

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

317

318 **Input data**

319 *Nominal risk coefficient*

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

322 *Carcinogenic effects*

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

331 Based on epidemiological studies concerning groups of population specifically exposed to radiation with estimated
332 individual doses (mostly the Life Span Study (LSS) of Hiroshima and Nagasaki atomic bomb survivors, Preston
333 et al. 1994, Preston et al. 2007), radiation-associated cancer incidence risk models were developed for 11 organs
334 or tissues: oesophagus, stomach, colon, liver, lung, female breast, ovary, bladder, thyroid, other solid cancers (see
335 footnote in Table 2) and leukaemia. For each cancer site, modelling of the radiation-associated risk has been made
336 using either a multiplicative (excess relative risk, ERR) or additive (excess absolute risk, EAR) model (see Figures
337 3 and 4) depending on age, sex and dose, with a linear dose-response for solid cancers and a linear-quadratic dose-
338 response for leukaemia. The minimum latency period used in ICRP Publication 103 is five years for each type of
339 cancer, corresponding to the shortest time in which a specified radiation-induced tumour is known or believed to
340 occur after exposure (Cléro et al. 2019).

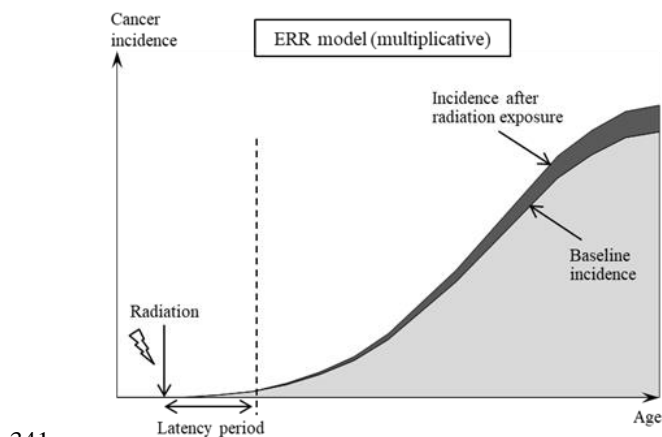


Figure 3. Illustration of a constant excess relative risk (ERR) model: multiplicative model.

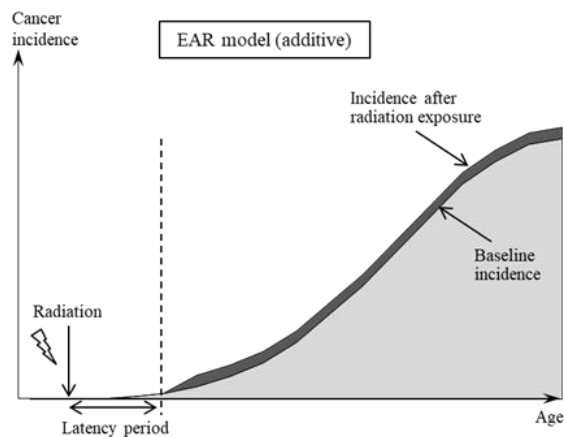


Figure 4. Illustration of a constant excess absolute risk (EAR) model: additive model.

342 *Heritable effects*

343 For the risk of heritable effects, which corresponds to serious hereditary abnormalities in descendants (in 2
344 generations) due to mutations induced in germ cells after radiation exposure, estimates are based on experimental
345 studies. The nominal risk for heritable effects is relatively minor compared to those for cancers, representing about
346 1% of the global nominal risk.

347

348 ***Radiation detriment***

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

353

354 **Methods**

355 ***Calculation steps for nominal risk coefficient***

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

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

366 For each of the eleven cancer sites, the considered exposure scenario was an acute exposure to 0.1 Gy (whatever
367 the exposure route – ingestion, inhalation, external irradiation) for each year of age at exposure, with an age range
368 0-89 years for the general population and 18-64 years for workers. Lifetime risks were estimated at the attained
369 age of 95, i.e., an age range 0-94 years for the general population and 18-94 years for workers, weighted over age
370 categories within each reference population, and multiplied by 10 to obtain lifetime risks per 1 Gy.

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

379

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

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

389

390 ***Additional calculation steps for radiation detriment***

391 To calculate radiation detriment (D) associated with each cancer type, nominal risk coefficients (R) were adjusted
392 with factors of lethality (k), quality of life (q) and years of life lost (l , representing an average shortening of life
393 expectancy in years among people developing a cancer). The following formula was used: $D = [(R \times k) + (R \times (l$
394 $- k) \times q)] \times l$.

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

400 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
 401 gender and age at exposure from 18 to 64 years). Conversely, the excess cancer risk from a given chemical
 402 substance is expressed for individuals continuously exposed to 1 unit of the considered substance during their
 403 lifetime. By comparison, for a continuous exposure of 1 mSv per year during the first 90 years of life, radiation
 404 detriment in the general population would be around $5 \cdot 10^{-3}$ (i.e., approximately 50 detrimental cases expected at
 405 the attained age of 95 in a population of 10,000 individuals continuously exposed to 1 mSv per year from birth to
 406 age 90).

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

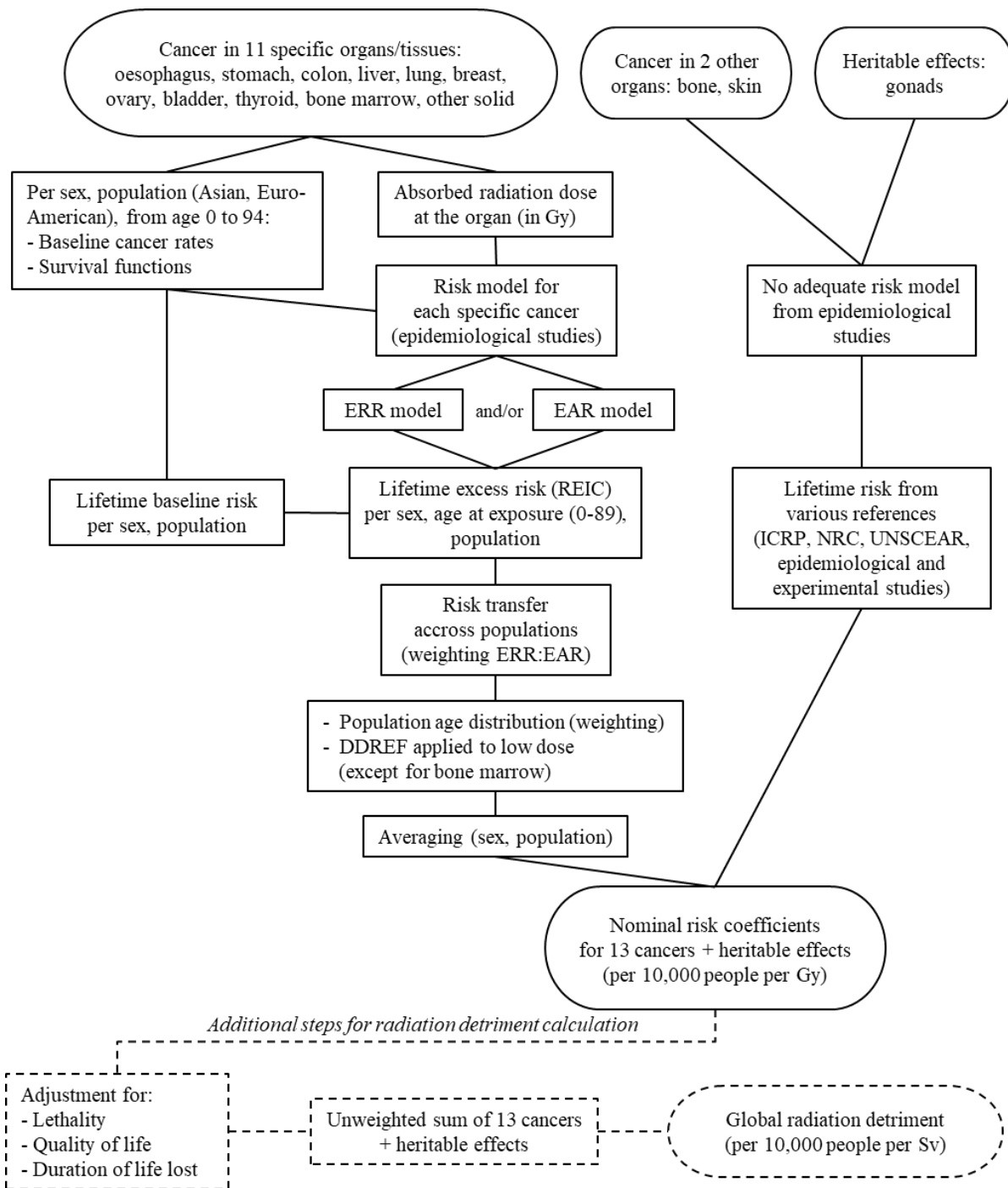
411
 412 **Table 2.** Steps and parameters for calculating radiation detriment, from nominal risk coefficients to detriment for
 413 the general population, age 0-89 years at exposure (ICRP 2007).

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

414 * Expressed in cases per 10,000 people per Gy.
 415 ** Expressed in cases per 10,000 people per Sv.
 416 *** 14 remainder tissues: adrenals, extra-thoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral
 417 mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

418
 419 The key steps of the calculation methodology of excess health risk for radiation exposure are summarized in a
 420 flowchart presented in Figure 5.

421



422
423 **Figure 5.** Flowchart on calculation methodology of excess health risk due to radiation exposure.
424

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

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

435 average level among workers exposed to radiation, the upper limit for occupational exposure was set ten times
436 higher, at 50 mSv per year. Considering that the level of acceptability for risks to the general public was an order
437 of magnitude lower than for occupational risks, an annual dose limit of 5 mSv was set for public exposure (ICRP
438 1977a). With the advancement of knowledge on risk, these limits were lowered in subsequent recommendations
439 to 20 mSv per year and 1 mSv per year, respectively for workers and members of the public (ICRP 1991, ICRP
440 2007). A similar rationale was followed, for example, by the US EPA to make the decision to remediate polluted
441 sites with radioactive contamination (US EPA 1997) which set the life span tolerable risk for the public for
442 pollution remaining in place at 10^{-4} for individual cancer excess risk for both radioactive and chemical substances.
443 For a relevant comparison of risk induced by exposure to chemical substances and to radiation, we have to make
444 sure that the slope factors (or reference values for risk per unit exposure) used to express the level of excess risk
445 have the same meaning in terms of health effects.

446

447 **How are the reference values used in health risk assessment?**

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

453 *Cancer risk assessment for chemical substances*

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

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

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

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

486 *Cancer risk assessment for radiation exposures*

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

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

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

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

517

518 **Main differences and points of comparison of these values**

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

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

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

539 *1/ Animal vs human data modelling*

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

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

550 *2/ Exposure to low levels: extrapolation vs interpolation of source data*

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

558 For radioactive substances, risk models are estimated from epidemiological data for each cancer site and applied
559 in the calculation of a nominal risk coefficient, allowing interpolation of risk under the assumption of linearity,
560 without an extrapolation from a point of departure to lower doses such as performed for chemical substances. The
561 ICRP's methodology assumes a LNT dose-risk relationship for stochastic effects (cancer and heritable diseases),
562 i.e., an increment in dose induces a proportional increment in risk at low doses. In the calculation of nominal risk
563 coefficients, risk models for specific cancer sites mainly come from the LSS following Japanese survivors having
564 received an acute dose estimated from 0 to 4 Gy (for colon absorbed dose), depending on the location of individuals
565 at the moment of the explosion. In this epidemiological study, about two-thirds of participants (around 68,000
566 people) received low doses, i.e. estimated colon dose less than 100 mGy. Many other epidemiological studies
567 analysed the relationship between radiation exposure and health effects, in different situations of (occupational,
568 medical, environmental) exposure of different populations (adults, children, various countries) and with various
569 quality criteria (study protocol, dosimetry, statistics). According to the epidemiological studies with high-quality
570 data, the observed results are reasonably consistent with the LNT assumption. To date, although uncertainties
571 persist for low doses, there are no elements in favour of the existence of a threshold (NCRP 2018, Shore et al.
572 2018, Hauptmann et al. 2020). Furthermore, experimental studies have shown that different types of radiation may
573 demonstrate different effectiveness in inducing biological damages. For a same absorbed dose, alpha radiation and
574 neutrons cause a higher frequency of adverse health effects than photons and electrons (ICRP 2007). To account
575 for this relative biological effectiveness, the absorbed dose (in Gy) from each type of radiation is multiplied by a
576 radiological weighting factor (in addition to tissue weighting factors based on relative radiation detriments) when
577 calculating effective dose (in Sv).

578 *3/ Exposure doses vs absorbed dose*

579 Usually, the TRVs are developed on the basis of separate studies and dose-response curves for each route of
580 exposure (oral and inhalation). The unit actually used to quantify the dose depends on the route. For inhalation,
581 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.
582 The construction of an inhalation TRV embarks choices on respiratory flowrates and its unit is inverse of an
583 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
584 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
585 of exposure needs to input data about diet. For both exposure routes, the exposure is supposed to occur over the
586 life span.

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

595 *4/ Health effects: critical organ vs whole body effect*

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

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

603 *5/ Probability of cancer occurrence vs detriment*

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

609 *6/ Confidence interval on dose vs mean value of risk estimate*

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

616

617 **Opportunity to close the gaps between the two approaches to calculating cancer risk due to radiation or** 618 **chemicals**

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

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

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

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

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

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

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

687

688 **Conclusion**

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

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

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

729

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