RC I.
Radiation detriment calculation methodology

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Radiation detriment is a concept developed by the ICRP to quantify the burden of stochastic effects from low-dose and/or low-dose-rate exposures to the human population. It is determined from the lifetime risks of cancer for a set of organs and the risk of heritable effects, taking into account the severity of the consequences. The future ICRP Publication 152 (planned in 2022) will be presented: historical review, details of the procedure developed in Publication 103, sensitivity analysis on major sources of variation and uncertainty, and potential ways to improve the detriment calculation in the future.

Radiation detriment calculation methodology

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Refresher course n°1
May 31, 2022 - Budapest, Hungary

Enora Cléro

ICRP INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

Plan

- History of detriment
- Cancer risk estimation
- Calculation of detriment
- Potential evolution
- Conclusion and perspectives

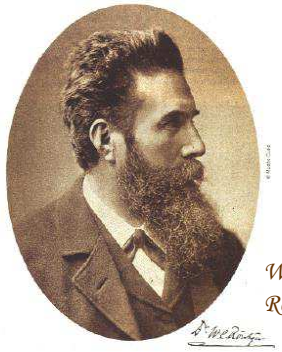
History of the effects of ionizing radiation

- **Discovery and first health effects**

  1895 Discovery of X-rays by W. Röntgen
  1st reported radiation-induced dermatitis in the following months

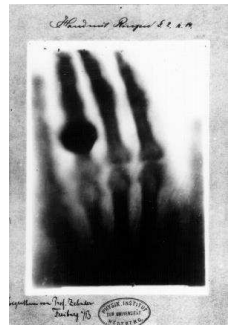
  1897 1st use of X-rays by military hospitals

  1906 1st reported radiation-induced skin cancer



Wilhelm Röntgen

First radiography
(*hand of Bertha Röntgen*)



- **Radiation protection**

  1928 Creation of the International X-ray and Radium Protection Committee (IXRPC), renamed International Commission on Radiological Protection (ICRP) in **1950**

  1959 ICRP Publication 1 : introduction of the linear no-threshold relationship (LNT)

  1966 ICRP Publication 9 : appearance of stochastic effects and “optimization principle”

Harmful effects of exposure to ionizing radiation

2 categories of effects

Tissue reactions

- Short-term effects (a few days to weeks) : skin burns, hair loss, sterility, hematopoiesis depression, intestinal syndrome... and long-term effects (several years) : circulatory diseases, cataract
- Occurring only above a dose threshold (a few hundred mGy to several Gy)
- Above this threshold, the severity increases with the dose
- Objective of Radiological Protection : avoid the occurrence of these effects

Stochastic effects

- Long-term effects (several years/decades) : cancers and heritable effects (occurring in the descendants of irradiated persons)
- Occurring at any level of dose without threshold
- Probability of occurrence increases with the dose
- Objective of Radiological Protection : limit the occurrence of these effects

Radiation detriment

History of the effects of ionizing radiation

- **Radiation detriment and its evolution**

1977 ICRP Publication 26 : definition of the detriment concept

> *" The Commission has introduced the concept of detriment to identify, and where possible to quantify, all the deleterious effects. In general, the **detriment** in a population is defined as the **mathematical "expectation"** of the harm incurred from an exposure to radiation, taking into account not only the **probability** of each type of deleterious effect, but also the **severity** of the effect. "*

1991 ICRP Publication 60 : re-evaluation of detriment (mortality data)

2007 ICRP Publication 103 : current methodology of detriment calculation

Major evolution in the calculation of the radiological detriment :

- Calculation of **nominal risks** based on **cancer incidence** risk models (instead of mortality)
- Revision of the estimation of the potential impact of **heritable effects**

2016 ICRP Task Group 102 on radiation detriment calculation methodology

→ Explain the current methodology in a detailed and reproducible manner (ICRP Publication 103, Appendix A)

→ For a future revised methodology, due to evolving evidence and understanding

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History of epidemiological studies of ionizing radiation

1950 **Radiologists** (1900-1930)

Radium dial **painters** (1910-1930)

Medical exposures for non malignant illnesses, radio-diagnosis (1920-1940)

Hiroshima-Nagasaki atomic bombs survivors : Life Span Study (1945)

1960 Uranium **miners** (1940-1990)

1970 Population exposed to fallout from **atmospheric nuclear weapons** (1950-1980)

Nuclear workers (1950-)

1980 Population exposed to **natural background radiation**

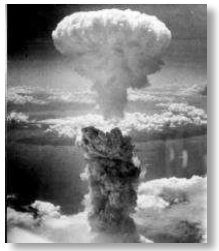
1990 Population exposed to releases from the **Tchernobyl** accident (1986)

2010 Children exposed to **CT-scan** examination, radio-diagnosis (1985-)

Population exposed to releases from the **Fukushima** accident (2011)

Study of Hiroshima and Nagasaki A-bomb survivors

Hiroshima (August 6, 1945)
300,000 habitants
≈ 16 kt TNT (^{235}U)
90 - 120,000 deaths



Nagasaki (August 9, 1945)
330,000 habitants
≈ 21 kt TNT (^{239}Pu)
60 - 80,000 deaths

Males and females, all ages (+ *in utero*)

Life Span Study (LSS cohort)

Mortality follow-up from 1950
Incidence follow-up from 1958
} → 60 to 70 years of follow-up

86,611 survivors with reconstructed individual doses
50,620 deaths (58%) in 2003 *(Ozasa et al. Rad Res 2012)*

➡ Radiation-induced cancers
Estimation of dose-response relationship
Latency period between exposure and risk occurence
Age effect …

放影研 Radiation Effects Research Foundation
RERF A Cooperative Japan-US Research Organization

Life Span Study : summary of results for cancers

- Demonstrated radiation induced risk for **many specific cancer sites** :
  leukaemia, breast cancer, lung cancer, thyroid cancer…
- The risk of solid cancer et leukaemia **increases with the dose**
- Excess relative risk per unit dose **decreases with age at exposure**
- **Latency** of a few years (leukaemia) to several decades (solid cancers)
- Dose-risk relationship still significant after exclusion of highly exposed individuals
- **No element to support the existence of a dose threshold**

Plan

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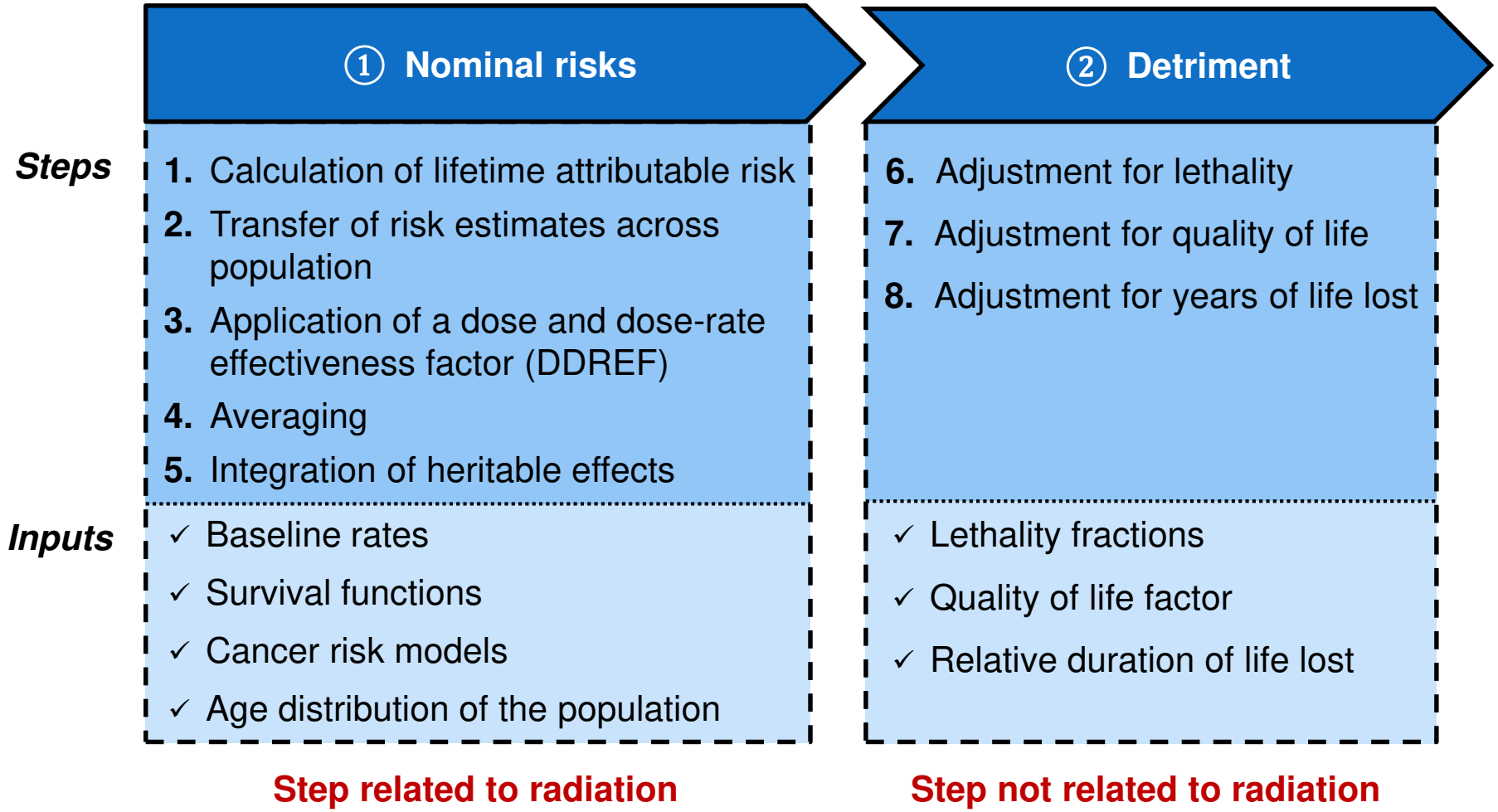
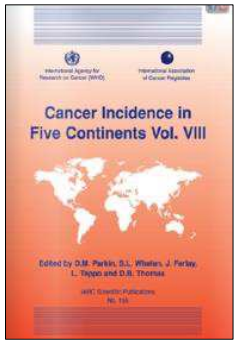
Detriment calculation in ICRP Publication 103

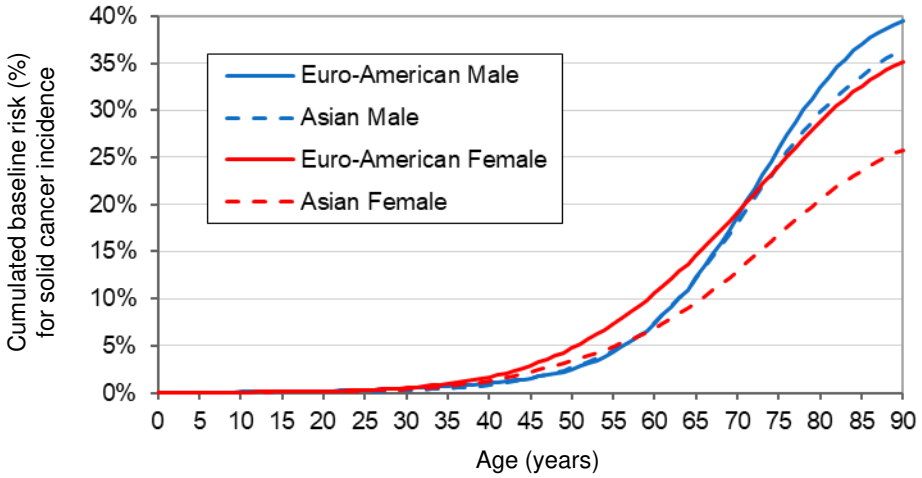


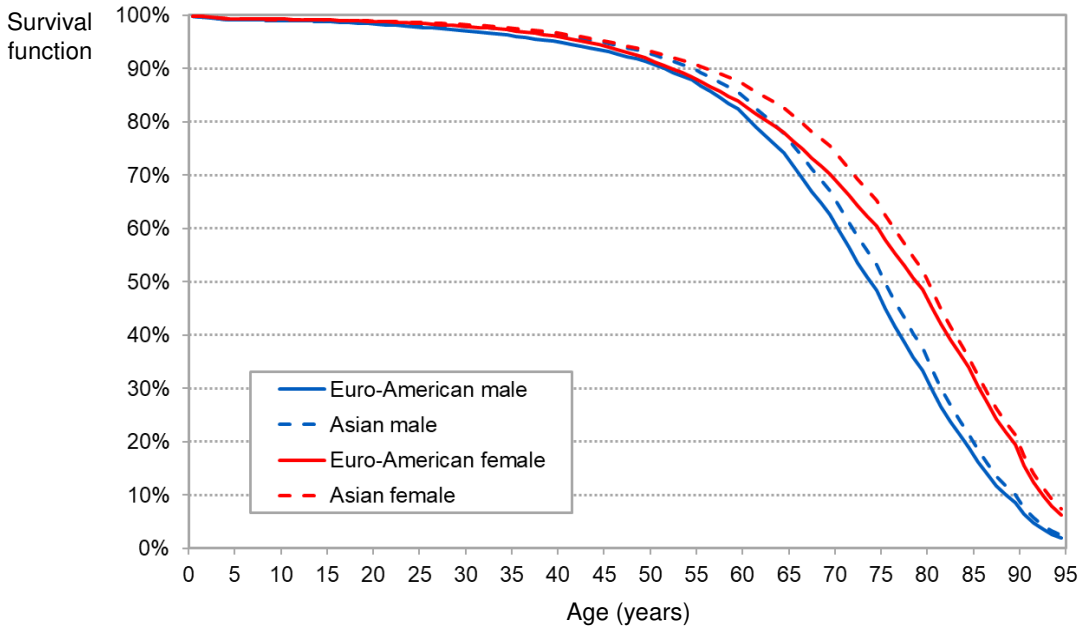
Calculation of nominal risks : data



4 reference populations

- Asian and Euro-American, males and females composite populations
- Baseline cancer rates and survival functions (IARC-WHO, period 1993-1997)





Models of dose-risk relationship

- For 13 specific cancer types
- Models derived from the Japanese cohort of A-bomb survivors (LSS, 1958-1998)
- Incidence risk models expressed by sex, attained age, age at exposure, dose

Assessment of radiation-induced risks: necessary assumptions

① Nominal risk ② Detriment

Transposition : application of the relationship to a population different from the one on which it was estimated

→ Variability in baseline cancer rates

→ Multiplicative / additive model : ERR / EAR

Extrapolation : application of the relationship below the dose range over which it has been estimated

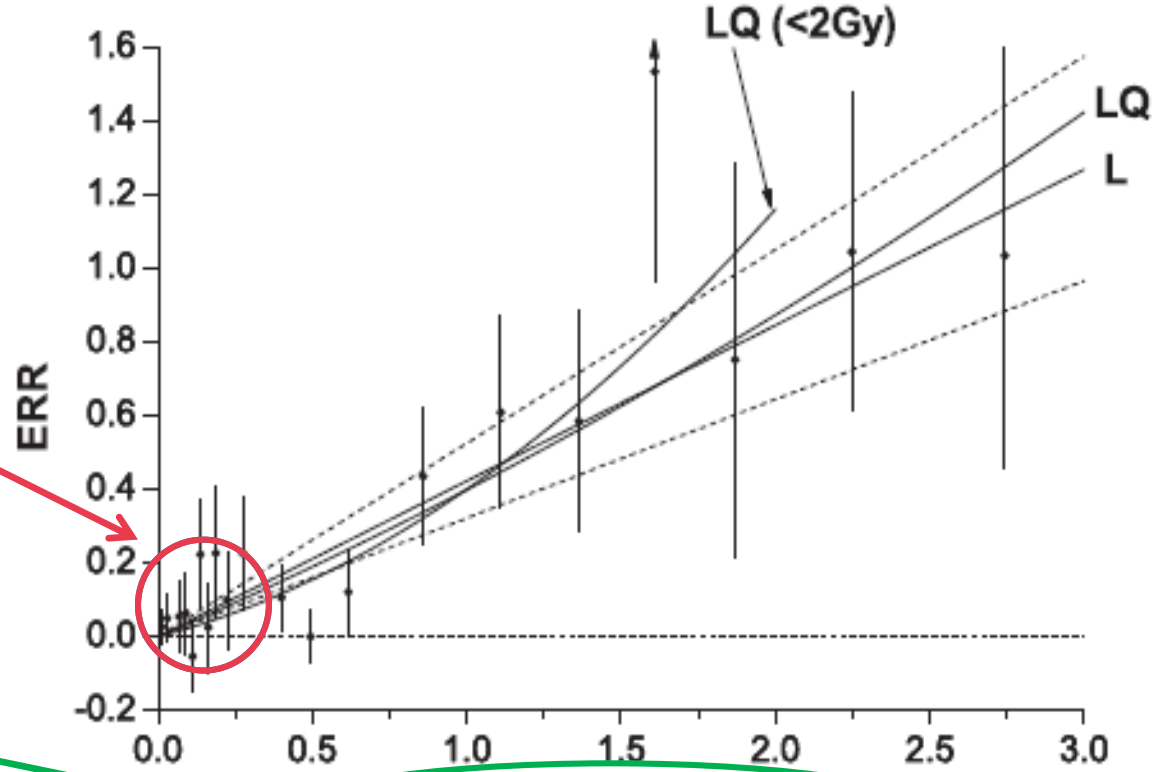
→ Type of risk models (linear, quadratic…) to extrapolate results to low doses

Analogy : application of the relationship to exposure situations different from that of the population on which it was estimated

→ DDREF (Dose and Dose Rate Effectiveness Factor)

Reduction factor for estimating the effect of IR delivered at low doses and low dose rates

Model fitted on the LSS data



Acute external exposure

Calculation of nominal risks : steps

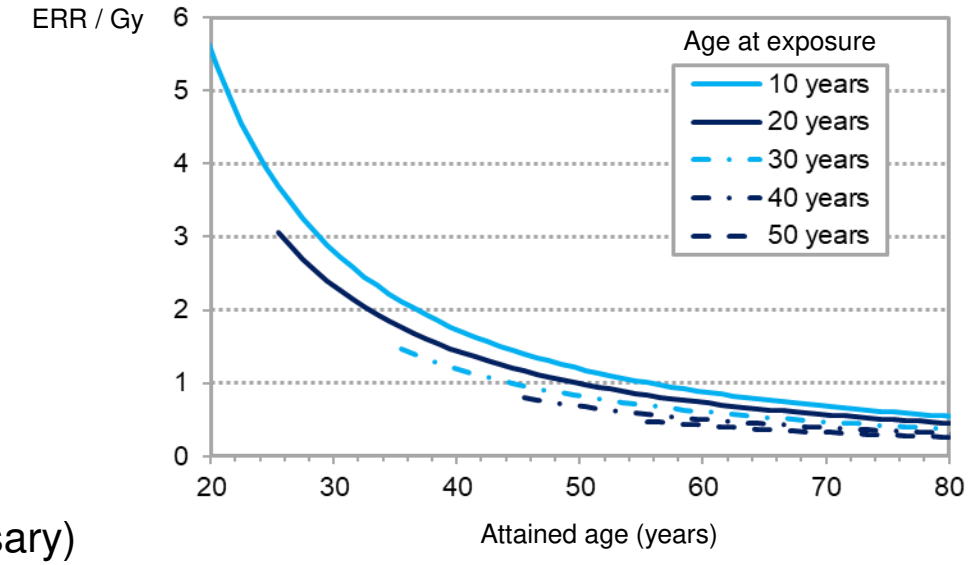
1. Lifetime risk

- Incidence risk models, minimum 5 years of latency
  - Solid cancers (10 organs) : linear model
  - Leukaemia : linear-quadratic model

- Calculation of **Risk of Exposure Induced Cancer** (REIC)
  - Cumulated risk up to attained age 95 years (95th anniversary)
  - **Exposure scenario** : acute exposure to 0.1 Gy for each year of age
    - Whole population : 0-90 years at exposure
    - Adult workers : 18-65 years at exposure

(Cléro et al. JRP 2019)

Modification of the ERR for all solid cancer (sex average) by age at exposure and attained age

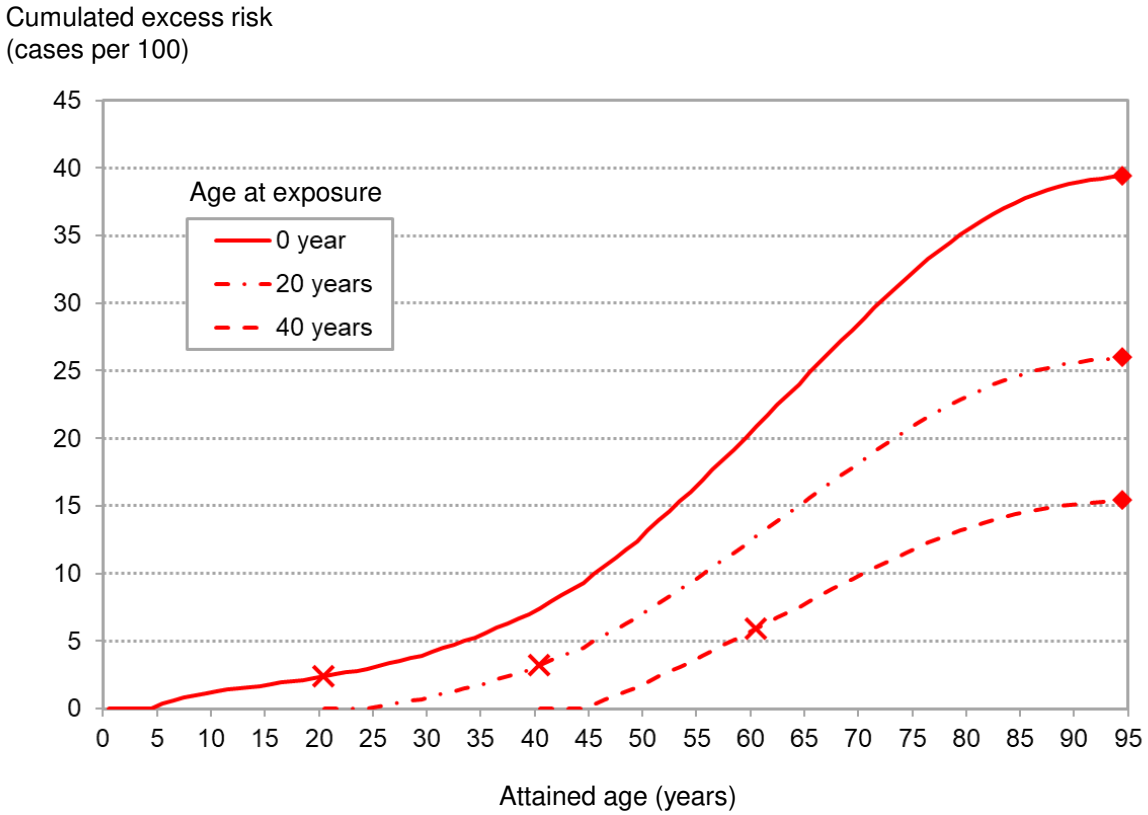


$$REIC_c(e,d) = \int_{a=e+L}^{\infty} [\mu_c(a|e,d) - \mu_c(a)] S(a|e,d) da$$

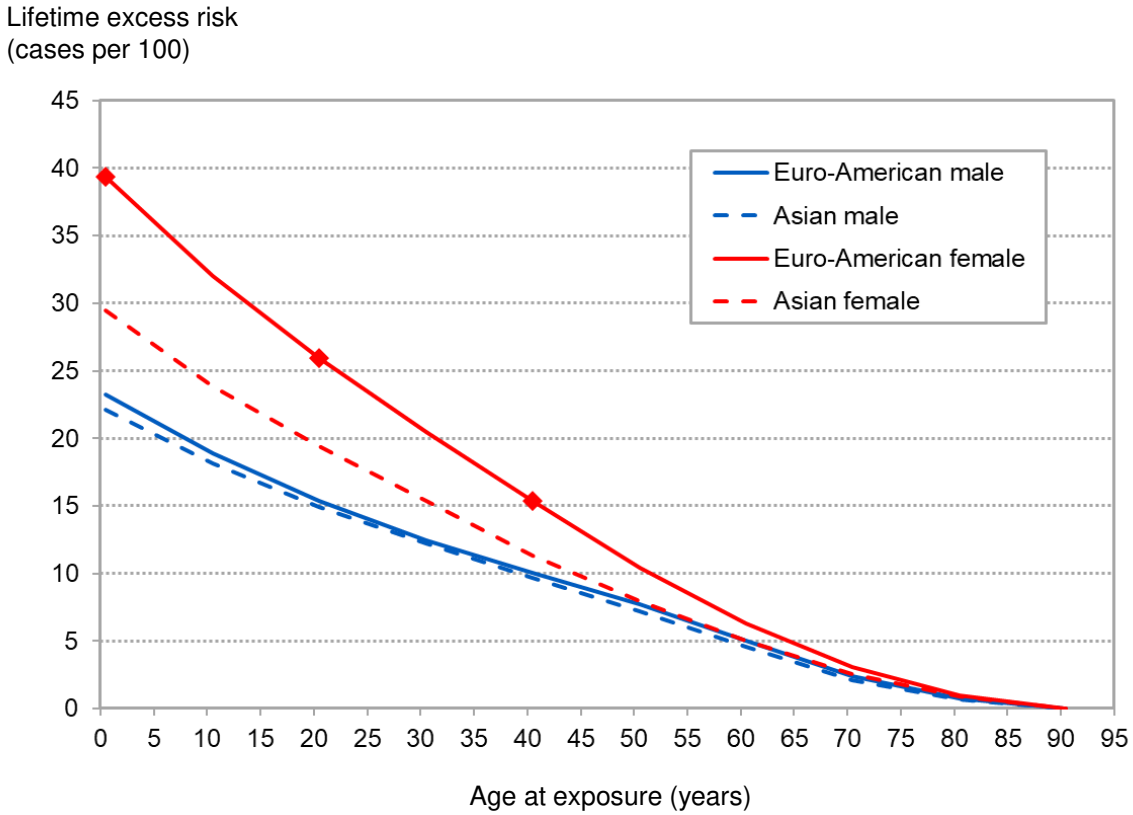
where : $\mu_c(a)$ = annual risk of incidence from cancer c at age a
$\mu_c(a|e,d)$ = annual risk of incidence from cancer c at age a given exposure d at age e
$S(a|e,d)$ = probability of the individual surviving to age a given exposure d at age e
L = latency period

Calculation of nominal risks : steps

Cumulated excess risk
for all solid cancers (Euro-American females)
by age at exposure, using an ERR-based model



Lifetime excess risk at 95 years
for all solid cancers, using an ERR-based model



Calculation of nominal risks : steps

2. Transfer of risk estimates across populations

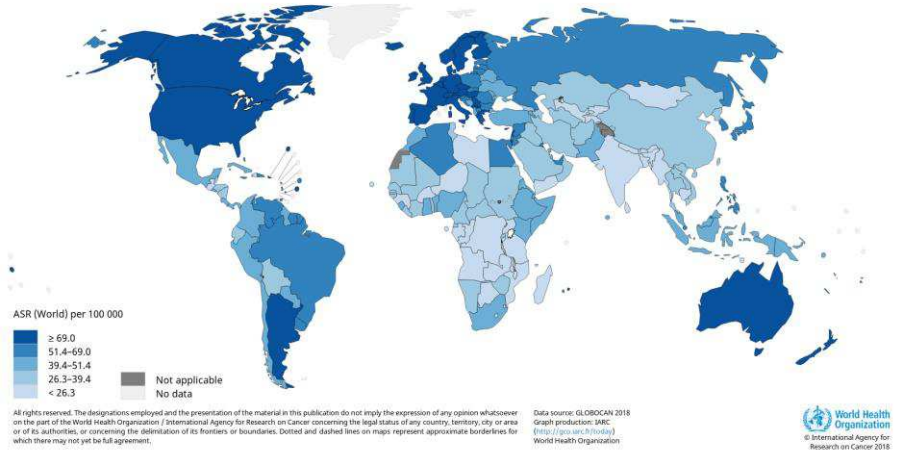
- It is problematic to transfer site-specific risk estimates of radiation-associated cancers from one population to the other if the corresponding baseline rates differ

- Illustration of the variability in baseline rates between countries

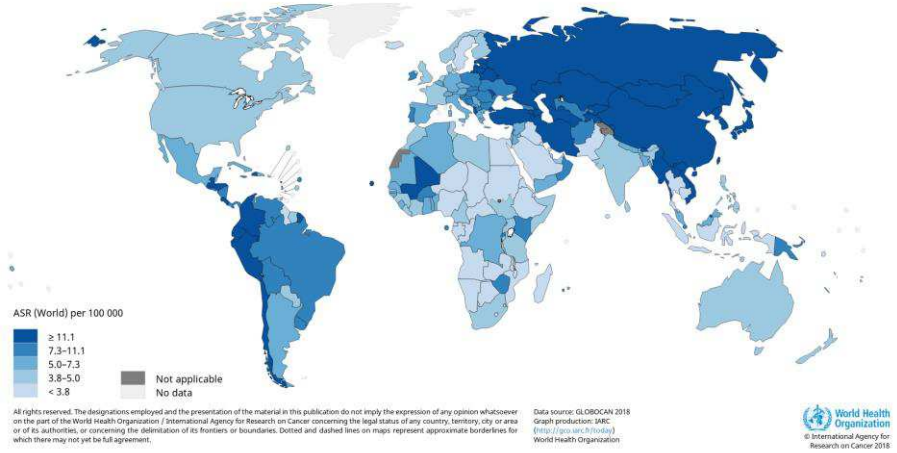
Standardized annual mortality cancer rates per 100.000 people (WHO 1988)

Country	Lung (M+F)	Breast (F)	Stomach (M+F)
USA	53	32	6
Japan	25	8	41
United-Kingdom	57	42	16
France	32	27	10

Estimated age-standardized incidence rates (World) in 2018, breast, all ages



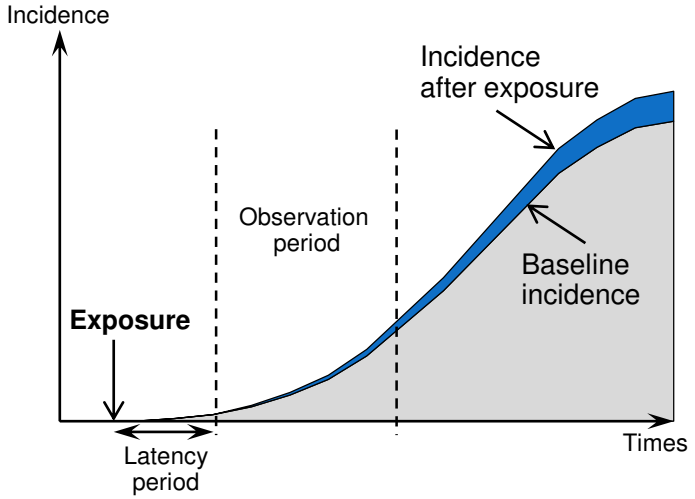
Estimated age-standardized incidence rates (World) in 2018, stomach, both sexes, all ages



Calculation of nominal risks : steps

2. Transfer of risk estimates across populations

- Weighted transfer of Excess Relative Risk (ERR) and Excess Absolute Risk (EAR) based models
- ERR:EAR weights
  - 0:100% for breast cancer
  - 100:0% for thyroid cancer
  - 30:70% for lung cancer
  - 50:50% for all others (including leukaemia)

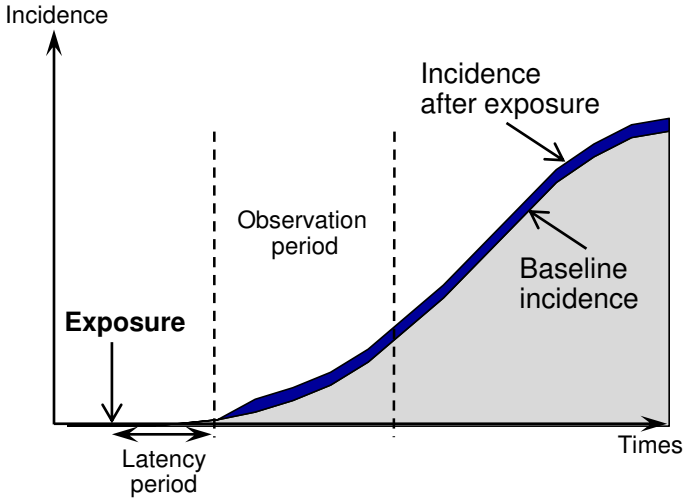


Excess risk depends on the dose + baseline risk

Multiplicative model

Effects of exposure proportionnal to baseline risk

Excess Relative Risk (ERR)



Excess risk depends on the dose only

Additive model

Effects of exposure in addition to baseline risk

Excess Absolute Risk (EAR)

Calculation of nominal risks : steps

3. Application of a Dose and Dose-Rate Effectiveness Factor (DDREF)

- **Experimental studies** show that biological effectiveness of radiation exposure at low doses and low dose rates is usually lower compared with exposures at high doses and high dose rates, suggesting that dose-specific estimates based on high-dose, acute exposure data should be divided by a DDREF for applications to low-dose, continuous or fractionated exposures.

- ICRP recommended that a DDREF of 2 be used for radiological protection purposes
  Applies to doses below 0.2 Gy or dose rates less than 0.1 Gy per hour at doses ≥ 0.2 Gy

- Lifetime risk estimates adjusted downward by **a factor of 2** to account for a DDREF **for all solid cancers**

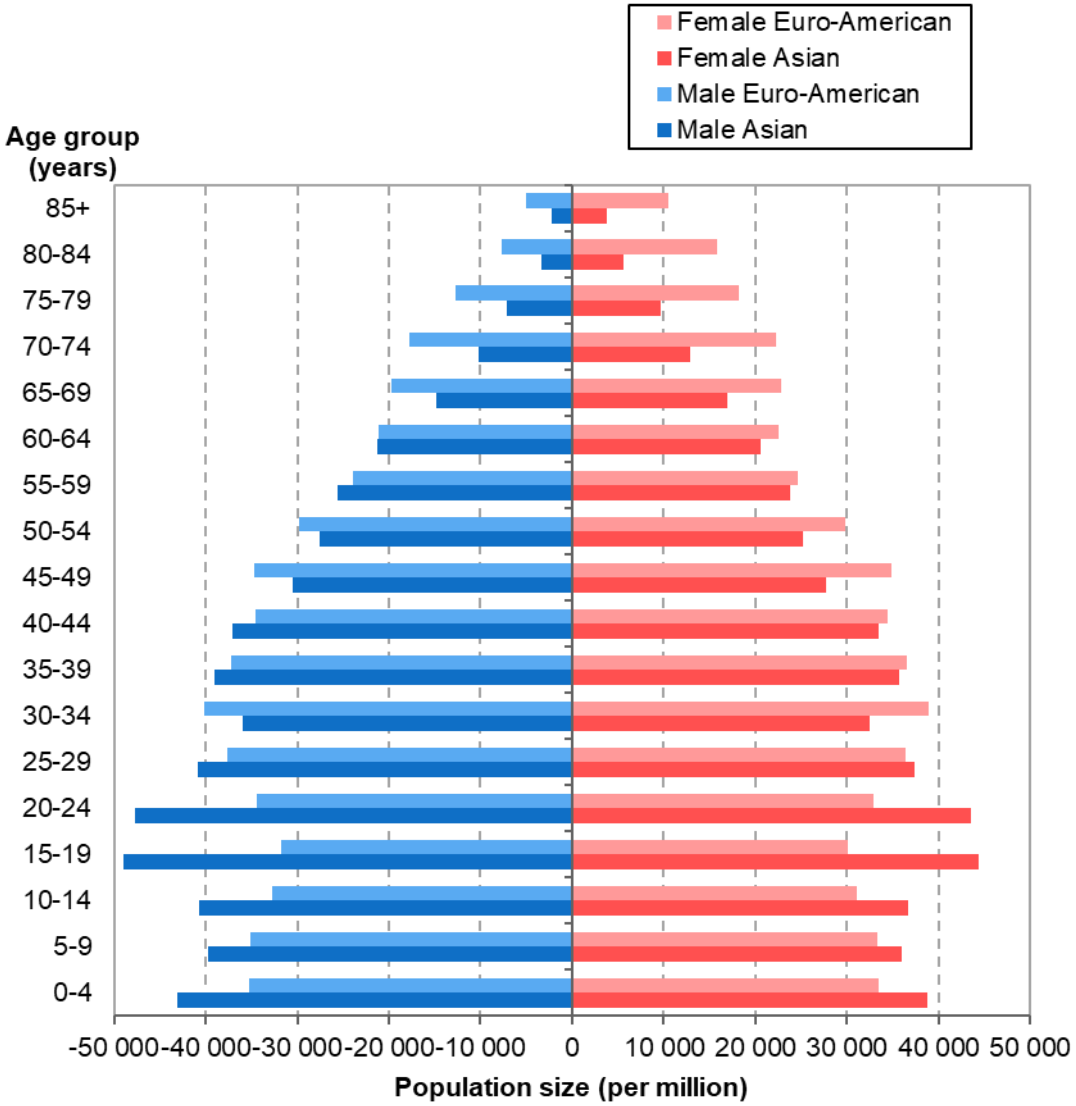
- **No application of a DDREF for leukaemia**,
  where the linear-quadratic model accounts for a change of slope at low doses in the dose-risk relationship

- Same DDREF applied to males and females, the general population and adult workers

Calculation of nominal risks : steps

4. Averaging

- For each cancer site, nominal risk is an **age-sex-population weighted average** of lifetime risks (estimated REIC)
- Weight assigned in **proportion to the population** of each age group in the reference population (average individual representative of the population)



Calculation of nominal risks : steps

5. Integration of heritable effects

- **Heritable effects** : health effects occurring in the descendants of exposed individuals to ionizing radiation (Mendelian diseases, chronic diseases and congenital abnormalities)
- Never observed in human populations, but observed in animals (drosophila, rodents)
- Frequency of transmissible mutations estimated by the UNSCEAR in 2001 : risks are expressed as the predicted number of additional cases (i.e. over the baseline) of different classes of genetic disease per million live births per Gy for a population exposed to low-LET, low-dose or chronic irradiation, generation after generation
- On the basis of UNSCEAR (2001), the **risk of heritable effects** in the whole population associated with gonadal dose for the first two generations was estimated by ICRP to be around **20 cases per 10,000 people per Gy**
- Same values applied to both males and females

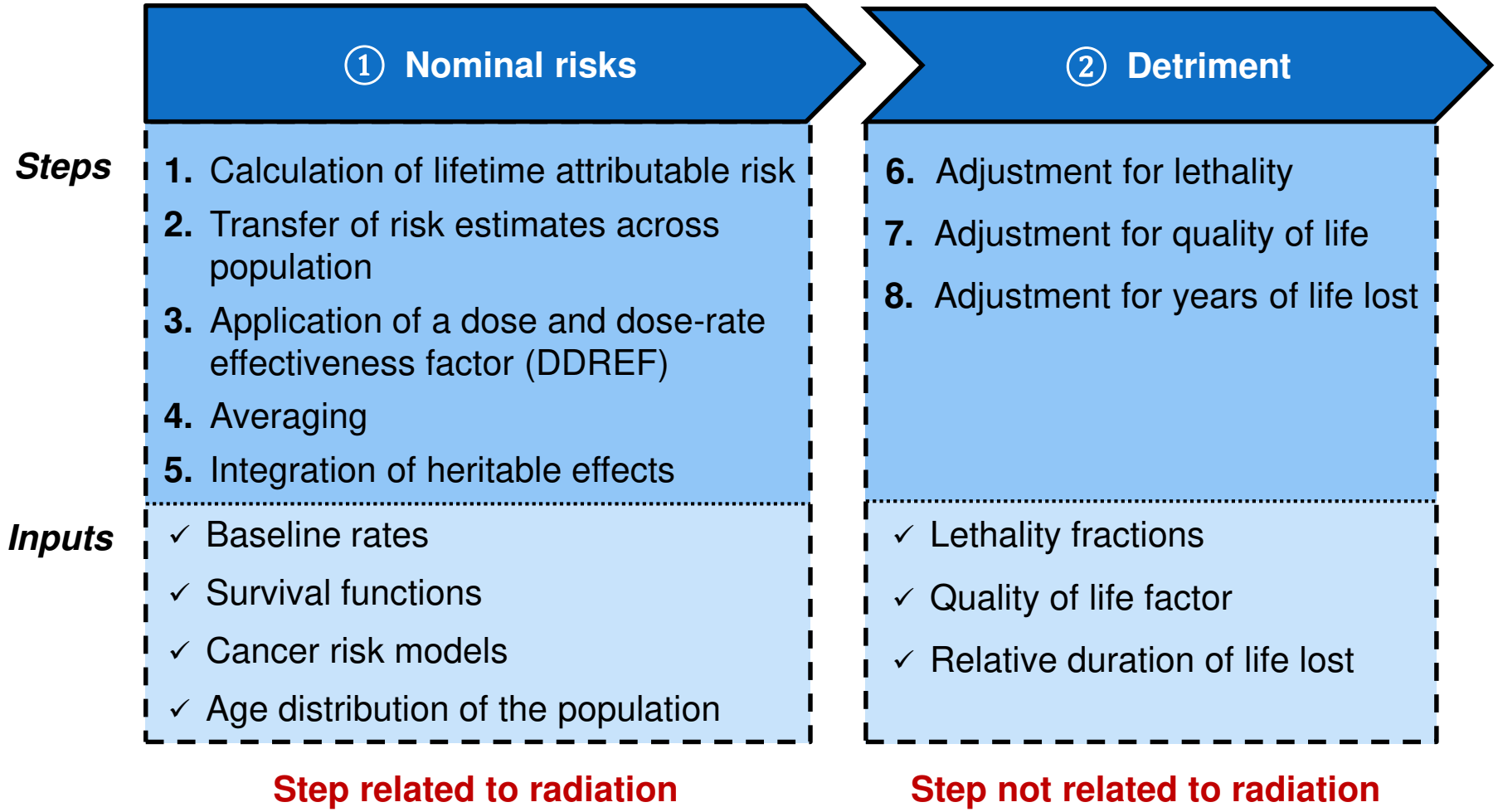
Results : whole population

	Tissue/organs	Nominal risk
		R
ICRP 1991-1992	Œsophagus	15
	Stomach	79
	Colon	65
	Liver	30
	Lung	114
	Bone	7
	Skin	1,000
	Breast	112
	Ovary	11
	Bladder	43
	Thyroid	33
	Bone marrow	42
	Other solid cancers	144
UNSCEAR 2001	Gonads (heritable)	20
	Total	1,715

Nominal risks for the whole population

- Correspond to numbers of cases per 10,000 people per Gy
- Derived from weighted lifetime risk estimates based on incidence risk models from the A-bomb survivors cohort (except bone and skin cancer + heritable effects)

Detriment calculation in ICRP Publication 103



Calculation of radiation detriment

6. Adjustment for lethality

- Nominal risks converted to fatal risks by multiplying by lethality fractions
- Lethality fractions derived from survival rates by cancer site from the US SEER programme (Surveillance Epidemiology and End Results, 1980-1985) published in 1989
- Factor close to 1 for highly lethal cancers → for example : liver (k = 0.95), lung (k = 0.89)
  and close to 0 for those that seldom cause death → for example : skin (k = 0.002), thyroid (k = 0.07)

7. Adjustment for quality of life

- Thought to reflect pain, suffering, and any adverse effects of cancer treatment (expert judgement)
- Factor applied to the non-lethal fraction of cancers → for example : 0 for skin, 0.2 for thyroid

Calculation of radiation detriment

8. Adjustment for years of life lost

- Thought to reflect differences in the age distribution of cancer types (ICRP Publication 60, 1991)
- Factor greater than 1 for cancers occurring early in life → for example : leukaemia (l = 1.63), thyroid/breast (l = 1.29) and less than 1 for cancers occurring late in life → for example : bladder (l = 0.71), lung (l = 0.80)

Same set of values (lethality / quality of life / years of life lost) applied to males and females, the whole population and adult workers.

Results : whole population (cases per 10,000 people per Sv)

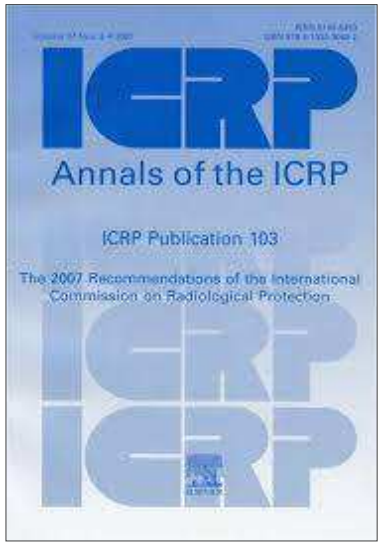
Tables A.4.1 and A.4.5 - Publication 103, ICPR 2007

Tissue/organs	**Nominal risk**	Letality fraction	Non-fatal case weight	Relative cancer free life lost	**Detriment**	Relative detriment
	R	k	q	l	D	
Œsophagus	**15**	0.93	0.935	0.87	**13.1**	0.023
Stomach	**79**	0.83	0.846	0.88	**67.7**	0.118
Colon	**65**	0.48	0.530	0.97	**47.9**	0.083
Liver	**30**	0.95	0.959	0.88	**26.6**	0.046
Lung	**114**	0.89	0.901	0.80	**90.3**	0.157
Bone	**7**	0.45	0.505	1.00	**5.1**	0.009
Skin	**1,000**	0.002	0.002	1.00	**4.0**	0.007
Breast	**112**	0.29	0.365	1.29	**79.8**	0.139
Ovary	**11**	0.57	0.609	1.12	**9.9**	0.017
Bladder	**43**	0.29	0.357	0.71	**16.7**	0.029
Thyroid	**33**	0.07	0.253	1.29	**12.7**	0.022
Bone marrow	**42**	0.67	0.702	1.63	**61.5**	0.107
Other solid cancers	**144**	0.49	0.541	1.03	**113.5**	0.198
Gonads (heritable)	**20**	0.80	0.820	1.32	**25.4**	0.044
Total	**1,715**				**574.2**	1

$$D = [\,(R \times k) + R \times (1-k) \times q\,] \times l$$

W_T : *effective dose*

Radiation detriment (cases per 10,000 people per Sv)



(ICRP Publication 103, 2007)

Tissue/organs	Whole population		Adult workers	
	Detriment	Relative detriment	**Detriment**	Relative detriment
	D		***D***	
Œsophagus	**13.1**	0.023	**14.2**	0.034
Stomach	**67.7**	0.118	**51.8**	0.123
Colon	**47.9**	0.083	**43.0**	0.102
Liver	**26.6**	0.046	**19.7**	0.047
Lung	**90.3**	0.157	**120.7**	0.286
Bone	**5.1**	0.009	**3.4**	0.008
Skin	**4.0**	0.007	**2.7**	0.006
Breast	**79.8**	0.139	**32.6**	0.077
Ovary	**9.9**	0.017	**6.6**	0.017
Bladder	**16.7**	0.029	**19.3**	0.016
Thyroid	**12.7**	0.022	**3.4**	0.046
Bone marrow	**61.5**	0.107	**23.9**	0.057
Other solid cancers	**113.5**	0.198	**65.4**	0.155
Gonads (heritable)	**25.4**	0.044	**15.3**	0.036
Total	**574.2**	1	**422.0**	1

Radiation detriment

Detriment-adjusted nominal risk coefficients (per 100 people per Sv)

for stochastic effects after exposure to radiation at low dose rate

Exposed population	Cancers	Heritable effects	Total
Whole population	5.5	0.2	**5.7**
Adult workers	4.1	0.1	**4.2**

(ICRP Publication 103, 2007)

Field of application

- Average individual (averaged on sex, age at exposure, region)
- Doses below 0.2 Gy or dose rates less than 0.1 Gy per hour at doses ≥ 0.2 Gy
- Detriment has to be used only for the purposes of radiological protection (not for individual risk assessment)

Tissue weighting factors (W_T)

Tissue/organs	Relative detriment Whole population	W_T
Œsophagus	0.023	0.04
Stomach	0.118	0.12
Colon	0.083	0.12
Liver	0.046	0.04
Lung	0.157	0.12
Bone	0.009	0.01
Skin	0.007	0.01
Breast	0.139	0.12
Ovary	0.017	
Bladder	0.029	0.04
Thyroid	0.022	0.04
Bone marrow	0.107	0.12
Other solid cancers *	0.198	0.12
Gonads (heritable)	0.044	0.08
Brain	-	0.01
Salivary glands	-	0.01
Total	**1.000**	**1.00**

(ICRP Publication 103, 2007)

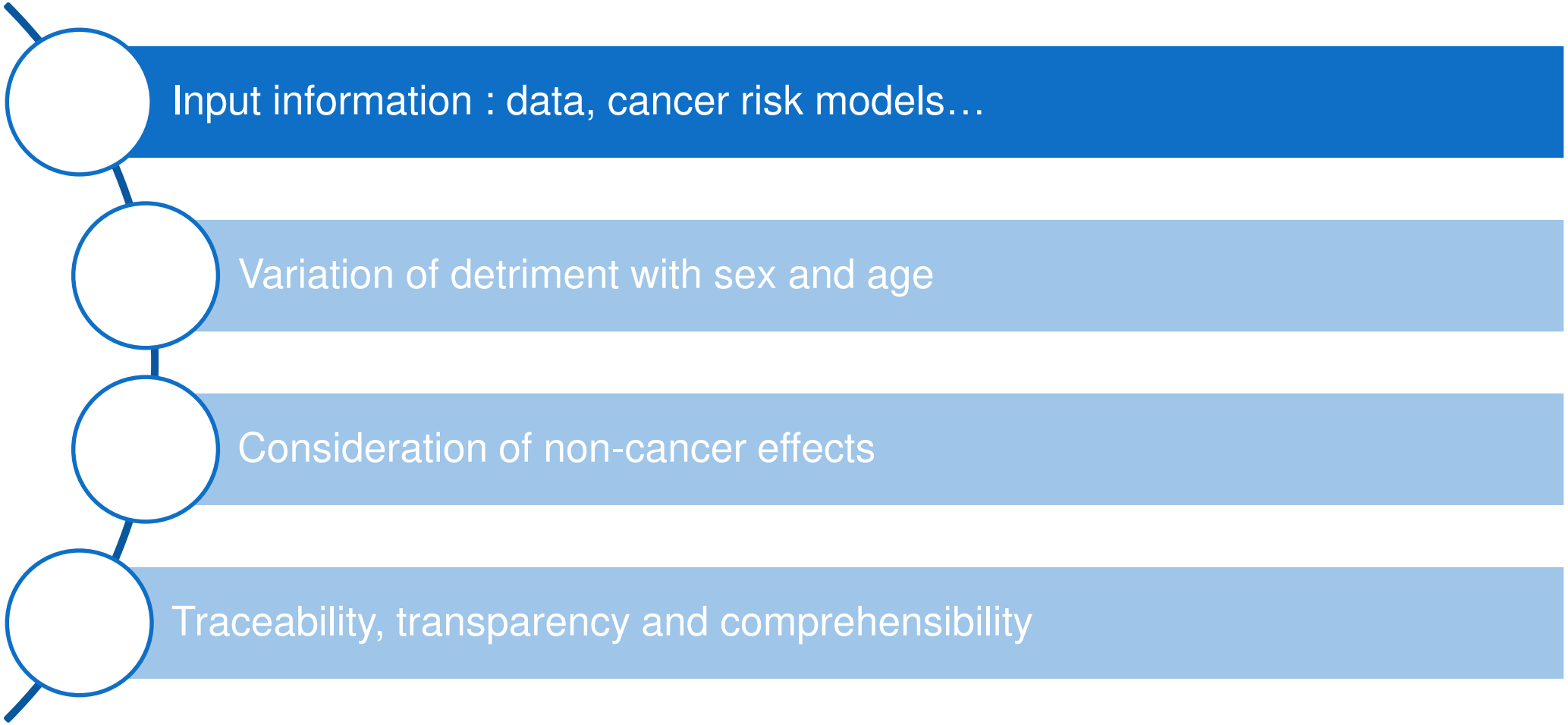
W_T values used in the calculation of the **effective dose** are derived from the detriment values **for the whole population**

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

Plan

- History of detriment
- Cancer risk estimation
- Calculation of detriment
- Potential evolution
- Conclusion and perspectives

Potential evolution of detriment



Potential evolution : update/improvement of input information (1/2)

Reference population data

- Asian : composite rates from Shanghai (China), Osaka, Hiroshima and Nagasaki (Japan)
- Euro-American : composite rates from Sweden, United-Kingdom and the US Surveillance Epidemiology and End Results (SEER) program

Baseline rates

- Data correspond to the period 1993-1997

Cancer severity parameters

- Lethality fractions, quality of life, years of life lost per cancer site : mainly based on approximate judgment-based values
- Same parameter values used for males and females, the general population and adult workers
- More universal metrics, such as Disability-Adjusted Life Years (DALYs), are now available to estimate and characterize the quality of life for many cancer types

Potential evolution : update/improvement of input information (2/2)

Cancer risk models

- Risk models for 11 organs were derived from the LSS (Preston et al. 2007 / leukaemia not published) without incorporating findings from other epidemiological studies
- Nominal risks for bone cancer and non-melanoma skin cancer were taken from Publications 60 and 59 (ICRP, 1991 and 1992)
- No specific risk models for the brain and salivary glands

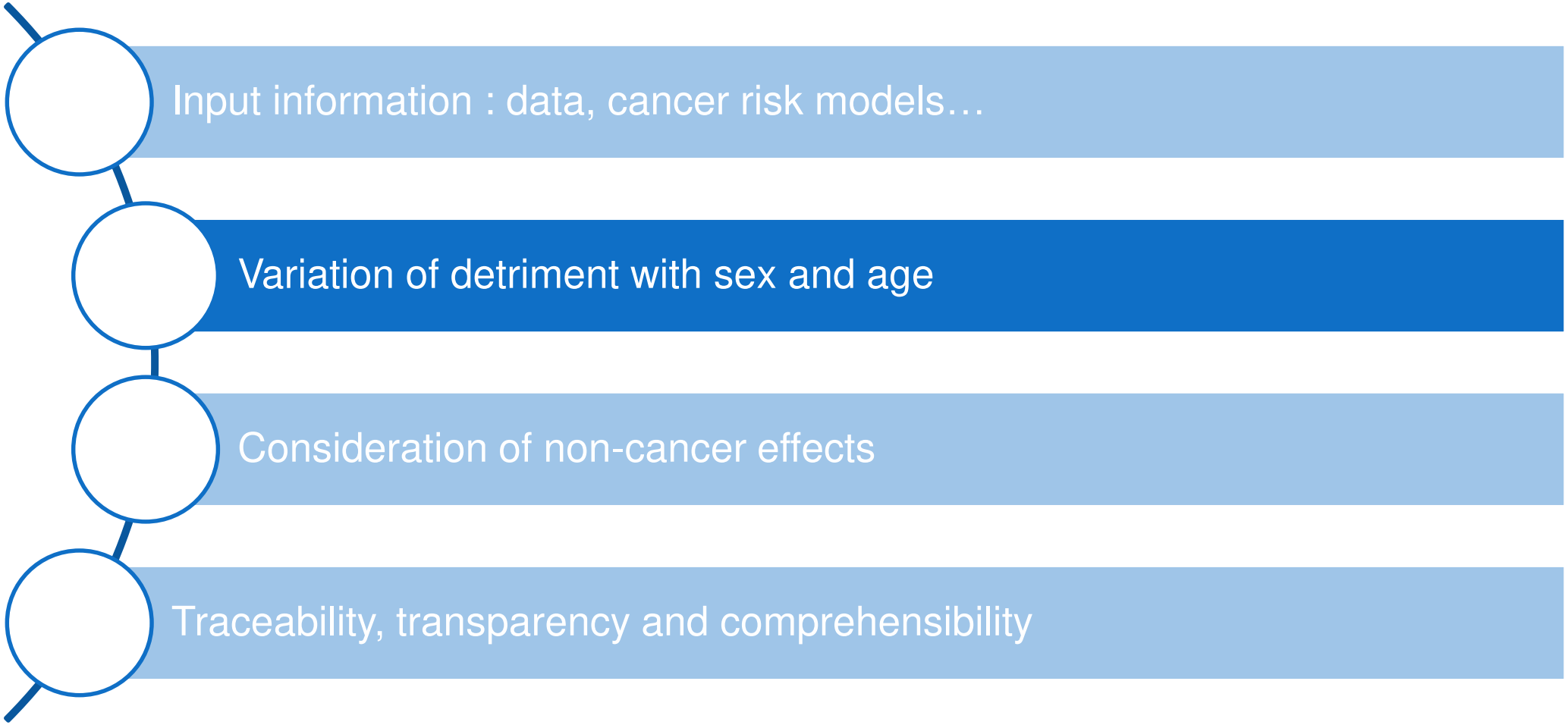
Transfer of risk estimates across population and DDREF

- Application of a DDREF of 2 and weighting scheme ERR:EAR for transfer between populations have to be reviewed in the light of recent results

Knowledge about heritable effects

- Integration of heritable effects based on risk assessment published by the UNSCEAR in 2001
- In recent years, new findings have been obtained, including epigenetic inheritance
  An update of the scientific literature on radiation and heritable effects is recommended

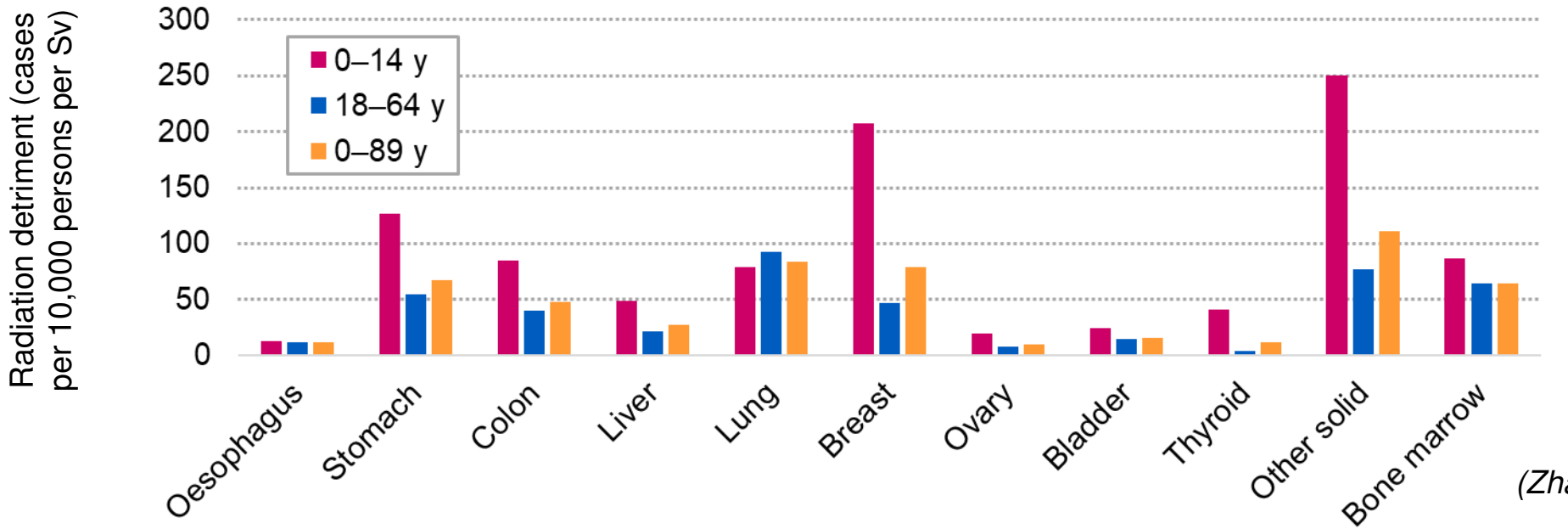
Potential evolution of detriment



Potential evolution : consider variation with age and sex

Variation of detriment with age

- Age at exposure has a large impact on radiation detriment : in particular, an exposure during childhood leads to higher lifetime risks for most cancer sites compared with the same exposure during adulthood
- *In utero* exposure not taken into account in the detriment calculation

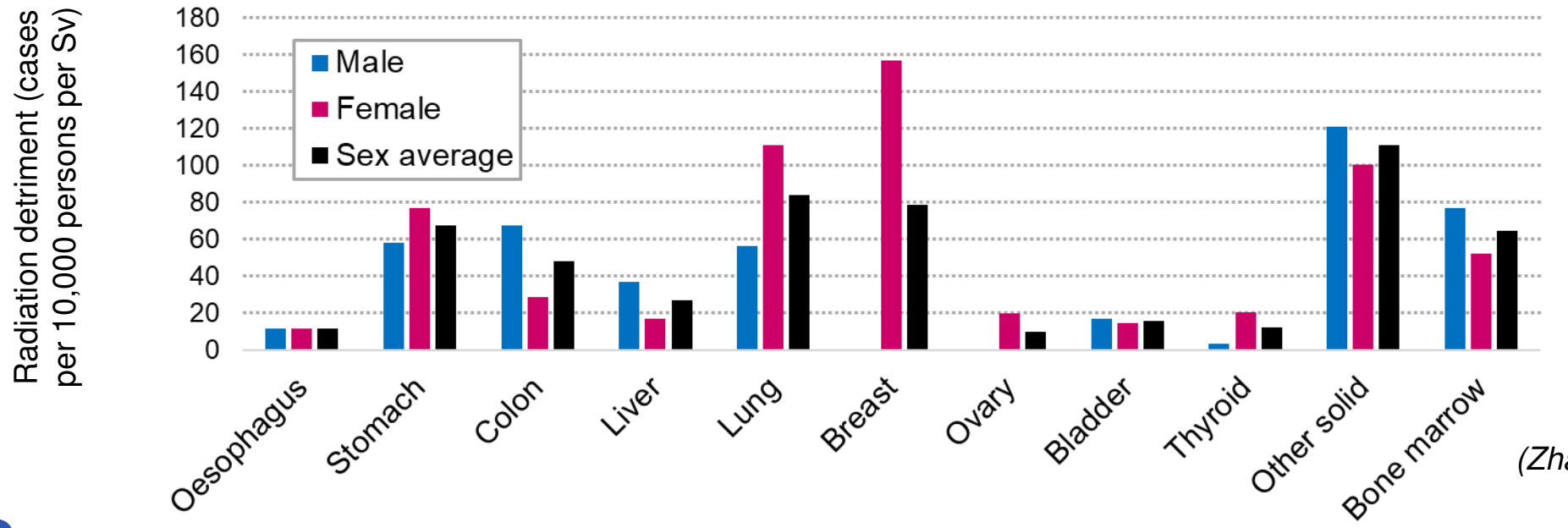


(Zhang et al. IJRB 2020)

Potential evolution : consider variation with age and sex

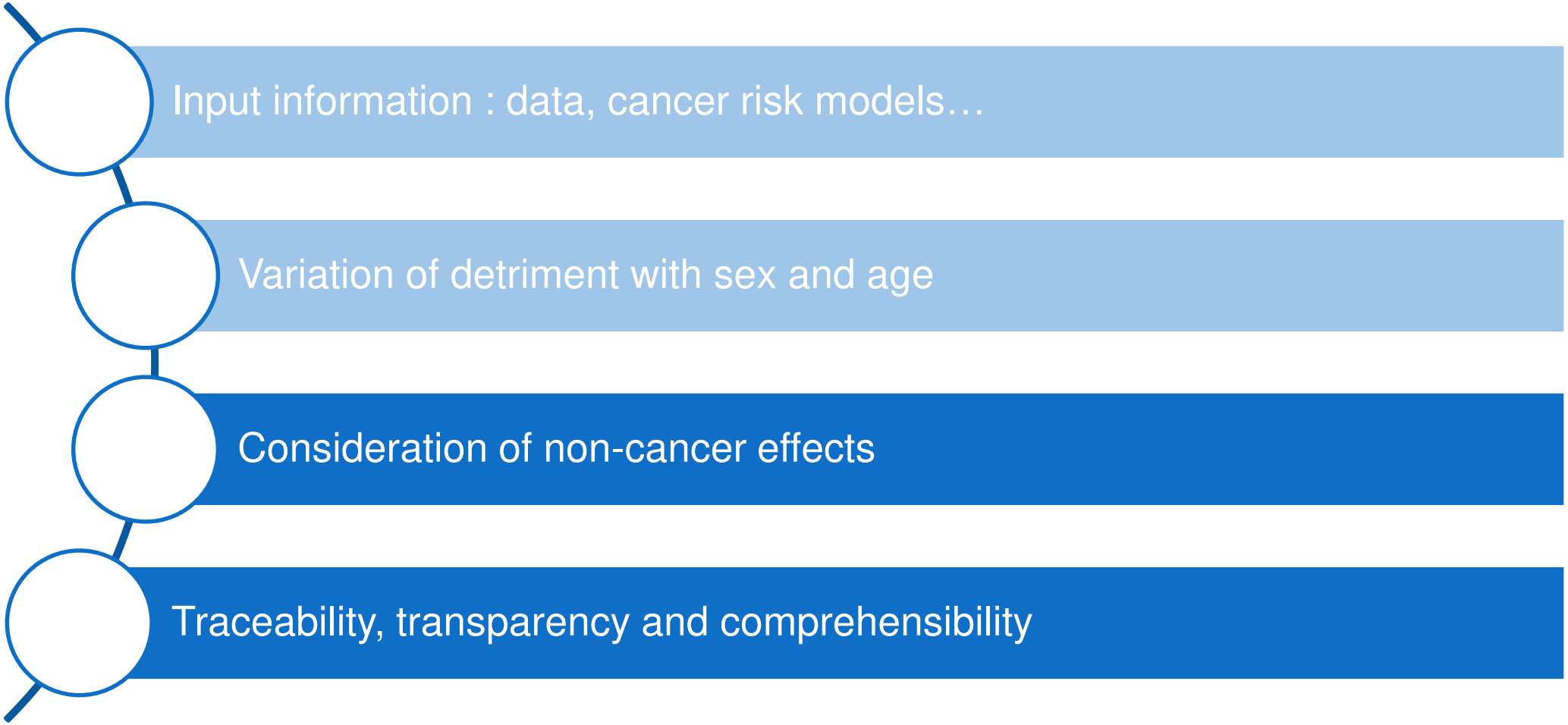
Variation of detriment with sex

- Differences due to sex are notable for some tissues : it is recommended to calculate detriments for both sexes and for certain ages, and to average them only in the last step to obtain a nominal value
- The relative contribution of each cancer site to the global detriment varies considerably with sex and age, but these variations are not considered in the W_T set



(Zhang et al. IJRB 2020)

Potential evolution of detriment



Potential evolution : consideration of non-cancer effects

- In recent years, evidence has accumulated that some non-cancer diseases, particularly **circulatory diseases** and **cataract**, may be induced at much lower doses than previously considered
- In Publication 118 (ICRP, 2012), the Commission proposed to classify these diseases as **“tissue reactions”**, with a threshold of 0.5 Gy independent of dose rate
- The Commission has not decided to include circulatory diseases and/or cataract in the calculation of detriment, but it remains an **open question**, which requires consideration in a broad context
- If these effects were to be included, a detailed calculation of lifetime risk appears highly challenging

Potential evolution : traceability, transparency and comprehensibility

- Calculation of radiation detriment consists of **many steps** in which a wide range of information is processed, including risk models, health statistics along with various other parameters
- The detriment calculation is oriented to the assessment of the global health impact of radiation : however, the resultant values are not easy to comprehend, and it is difficult to compare them with other commonly-used health risk indices
- It is desirable to improve the presentation so that the make-up of radiation detriment becomes **more comprehensible** to non-specialists
- It will be increasingly important to accurately document and publish the calculation procedure for ensuring **transparency** and **traceability**

Plan

- History of detriment
- Cancer risk estimation
- Calculation of detriment
- Potential evolution
- Conclusion and perspectives

Conclusion

- **Radiation detriment** is an integrated concept aiming to **reflect the global harm** due to **stochastic effects** of radiation exposure at **low doses**, considering both the **probability** and the **severity** of each type of effect
- The concept was first introduced in 1977 (Publication 26)
  The methodology and scope have evolved over more than 40 years to consider new scientific knowledge about the harmful health effects of radiation exposure at low doses
- The calculation process of radiation detriment consists of two main parts :
  1) The first part is the **calculation of nominal risks**, which is an estimate of the lifetime risk of stochastic effects averaged over sex, age and population
  2) The second part is the **calculation of detriment** in which the nominal risk is adjusted for severity
- Although the Annex A of **Publication 103** (ICRP, 2007) explains the data and models for the detriment calculation, the details were **not fully documented** and a part of the calculations was difficult to reconstruct
  → The calculation process has been clarified thank to the work of the **ICRP Task Group 102** :
  details of the procedure have been provided, which resolve ambiguity and correct misdescriptions in Publication 103

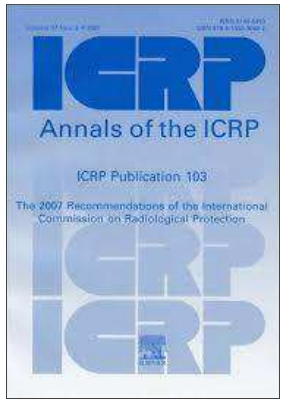
Conclusion

- There is a need to **update the detriment calculation** process, by considering **recent knowledge** in cancer incidence and treatment, and progresses in scientific understanding of radiation health effects (update baseline rates, cancer risk models, DDREF, weighting scheme for risk transfer, consideration of heritable effects, cancer severity parameters…)
- To improve the consideration of **risk variations between sexes and with ages**
- To consider and justify whether or not to include **non-cancer effects** in radiation detriment
- To ensure **transparency** and **traceability** of detriment calculation, and to **improve understanding** by non-specialists

Perspectives

- ICRP Task Group 102 report to be published in 2022 :
  ICRP Publication 152 "Radiation Detriment Calculation Methodology" (this summer?)
  - Concept, History, Calculation Methodology, Sensitivity to Parameters, Potential Evolutions

- **System review in the next decade**



- Recognise gaps
- Consider needed updates
- Identify building blocks : essential work required for the next general recommendations

In parallel, implementation of other WP/TGs on dose quantities, DDREF, circulatory diseases, heritable effects, detriment for cancer (cancer risk models), cancer severity assessment…

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Thanks

ICRP Task Group 102 members (2016-2021)

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