Attributing health effects to ionizing radiation and inferring risks

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## Definition of very low, low, moderate and high doses

<table>
<thead>
<tr>
<th>Dose category</th>
<th>Range of absorbed dose (for low-LET radiation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>&gt; 1000 mGy</td>
</tr>
<tr>
<td>Moderate dose</td>
<td>100 mGy – 1000 mGy</td>
</tr>
<tr>
<td>Low dose</td>
<td>10 mGy – 100 mGy</td>
</tr>
<tr>
<td>Very low dose</td>
<td>&lt; 10 mGy</td>
</tr>
</tbody>
</table>

(Source: UNSCEAR 2012)
Basic remarks (1)

First of all, one has to be very careful to distinguish „health effect“ (something that is actually observed) and „health risk“ (something that is expected).

In general, health effects are related to the past and health risks to the future.
Basic remarks (2)

- It makes a difference to attribute in the individual case or in the case of a population.
- The possibility to attribute is different for deterministic and for stochastic effects.
For practical reasons, deterministic (tissue) and stochastic effects are distinguished

- **Deterministic („inevitable“) effects:**
  - Radiation syndromes
  - Skin damage
  - Infertility
  - Epilation

- **Stochastic („random“) effects:**
  - Malignancies (solid cancer and leukaemia)
  - Heritable effects
Deterministic and stochastic effects

Dose-effect-relations

Severity
Frequency

Radiation dose

Deterministic effect
(requires many damaged (=killed) cells)

Stochastic effect
(requires just one damaged (=modified) cell)
Deterministic (tissue) effects
Deterministic (tissue) effects

Skin burn after interventional cardiology procedure

69 year old patient with a long-standing heart-disease; diagnostics showed severe ischaemia in the distribution of the left anterior descending coronary artery; he underwent a cardiac catheterization that included dilatation and stenting.
Why attributing this health effect to ionizing radiation?

- The lesion appeared shortly after the intervention;
- the temporal sequence is characteristic of many radiation burns following high doses;
- the site of the lesion is consistent with the diagnosis;
- a review of the actual images from the procedure showed an exact correlation with anatomical structures underlying this lesion;
- the size of the lesion was consistent with the diameter of the radiation beam used for this procedure.
Stochastic (cancer) effects
The well-known problem

Number of persons affected

100 mSv

United Nations Scientific Committee on the Effects of Atomic Radiation
Conclusions regarding LNT

A lot of biological mechanisms are affecting the response of organisms in the low dose range.

Most, if not all, of these mechanisms show a non-linear dose response.

In addition, individual differences are to be expected.

Thus, an exactly linear, non-threshold response is highly unlikely.

But!:

For practical reasons, the convention to use the LNT approach in radiation protection is justified.
Problems with the terms deterministic and stochastic

It is not clear whether the LNT approach for stochastic effects is correct.

For two radiation-induced types of health effects that came into focus recently, it is not at all clear whether they are deterministic or stochastic:
- Cataracts
- Cardiovascular diseases (CVDs)
Common problem of stochastic effects: lack of a biomarker

20% spontaneous cancer deaths
10% additional cancer deaths due to 1 Gy
But: Can we expect to find a biomarker indicating causation by ionizing radiation?

- There is strong evidence that carcinogenesis is a multistep process;
- Most likely, ionizing radiation can induce all necessary steps;
- But in many (all?) cases other agents may do part of the job;
- Thus, we cannot expect to find a pure radiation-specific biomarker, but, at best, a biomarker indicating some contribution by ionizing radiation;
- Is it realistic to find such a marker?
Is attribution possible in population studies?

- Yes, it is possible to attribute stochastic health effects in populations to ionizing radiation.
- But:
  - A serious problem in population studies is to overcome the statistical fluctuations;
  - With decreasing dose uncertainty increases (not linearly, but to the square!);
  - Thus, it is not surprising that for a mixed population a statistically significant increase in radiation-induced cancer deaths is seen only from about 100 mSv upwards.
Is attribution possible when individuals are affected?

No, it is not possible to attribute a stochastic health effect in an individual to ionizing radiation.

The major reason: up to now, no biomarker has been found that clearly tells us, which agent caused a specific cancer.
What can be done in the individual stochastic case?

One can try to calculate probabilities.

„Assigned share“ (frequently called „Probability of causation“) can be estimated based upon individual characteristics (type of cancer, gender, age at exposure, age at diagnosis, dose ...).

Using this concept, you never can be sure that the specific individual cancer was indeed caused by radiation, meaning that you cannot attribute with certainty.
An important aspect to be kept in mind:

- We do know that low and very low doses can induce biological effects.
- We do not know to which extent these biological effects develop to health effects.
Example for a (serious) biological effect in the very low dose range

Histone phosphorylation

Histones

induced by 1.2 mSv!

spontaneous

Source: Rothkamm, Löbrich | PNAS | vol. 100 | 5057
Conclusions (1)

An observed health effect in an individual could be unequivocally attributed to radiation exposure if the individual were to experience tissue reactions (often referred to as “deterministic” effects), and differential pathological diagnosis were achievable that eliminated possible alternative causes.

Other health effects in an individual that are known to be associated with radiation exposure — such as radiation-inducible malignancies (so-called “stochastic” effects) — cannot be unequivocally attributed to radiation exposure, because:

- radiation exposure is not the only possible cause and
- there are at present no generally available biomarkers that are specific to radiation exposure.
Conclusions (2)

- An increased incidence of stochastic effects in a population could be attributed to radiation exposure through epidemiological analysis — provided that, inter alia, the increased incidence of cases of the stochastic effect were sufficient to overcome the inherent statistical uncertainties.

- Although demonstrated in animal studies, an increase in the incidence of hereditary effects in human populations cannot presently be attributed to radiation exposure; this may be due to the large fluctuation in the spontaneous incidence of these effects.
Conclusions (3)

In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation.

The reasons are:

- the uncertainties associated with the assessment of risks at low doses,
- the current absence of radiation-specific biomarkers for health effects and
- the insufficient statistical power of epidemiological studies.

Therefore, it is not reasonable to multiply very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels.
Conclusions (4)

One has to keep in mind, however, that public health bodies need to allocate resources appropriately, and that this may involve making projections of numbers of health effects for comparative purposes.

This method, though based upon reasonable but untestable assumptions, could be useful for such purposes provided that

- it were applied consistently,
- the uncertainties in the assessments were taken fully into account, and
- it were not inferred that the projected health effects were other than notional.
## Shortest possible summary

<table>
<thead>
<tr>
<th>Effect</th>
<th>Attribution unequivocally possible?</th>
</tr>
</thead>
<tbody>
<tr>
<td>deterministic</td>
<td>yes (in almost all cases)</td>
</tr>
<tr>
<td>stochastic</td>
<td>population</td>
</tr>
<tr>
<td></td>
<td>yes (if the radiation effect overcomes the inherent uncertainties of the study)</td>
</tr>
<tr>
<td>individual</td>
<td>no</td>
</tr>
</tbody>
</table>
In depth information can be obtained from the UNSCEAR 2012 Report, Annex A (http://www.unscear.org/unscear/en/publications/2012.html)