

Individual Sensitivity

Why do we care about Individual Sensitivity?

- This IS an issue at high doses (for deterministic effects in radiation therapy)
- It is not known whether Individual Sensitivity is an issue at low doses
 - But, we know that cell sensitivity is related to a deficiency in DNA repair, to abnormal signaling pathways, abnormal genes, etc. Which may be related to development of cancer, thus these things this may be an issue
- There may be two different types of sensitivity
 - For deterministic effects (at high doses) and for stochastic effects (at low or high doses)
 - There may be different sensitivities among organs and tissues
- If we knew that there were hyper-sensitive individuals, this would be an issue, but it is not reasonable to act unless you know more about WHO is hyper-sensitive (how large a group), and how hyper-sensitive they are (twice the average population? Ten times the average population? Etc.)
- It is known that there are age and gender-specific differences in risk
 - On average, women are twice as sensitive as men
 - On average, young children are 5 times more sensitive than older individuals
 - Note that ICRP currently uses DOSE as the primary RP quantity, not RISK, so these differences are not inherently taken into account
 - There are some people who KNOW they are genetically susceptible (e.g. from family health history)
- These issues may pose ethical and regulatory challenges to the current approach to RP

What do we KNOW now about Individual Sensitivity?

What we know (or mean)

- 'low dose' means levels experienced by workers and public
- 'high dose' refers here to patients undergoing radiation therapy
- On the order of 5% of patients are hypersensitive to radiation (This is based on cancer patients who have received high-doses)
 - We will probably have a predictive test to identify such people in the not-to-distant future
 - A small sub-set of this population (5%) is very hypersensitive
- It is suspected that there are patients who are hypo-sensitive to radiation, but the size of this group is not known
- There are differences in cell sensitivity (e.g. epithelial cells are more sensitive than bone cells)

What do we KNOW now about Individual Sensitivity?

Low dose (diagnostic, occupational, public exposure levels) considerations

- We know that cellular response is quantitatively and qualitatively different at high and low doses
- There is limited epidemiological evidence of effects below 100 mSv in adults, and 50 mSv in children, but these are the exception
- We know that there are non-targeted effects at extremely low doses, but we do not know what the consequences of this may be
- Classical epidemiology has not and can not provide any evidence of individual sensitivity

What do we KNOW now about Individual Sensitivity?

At low dose-rate considerations

- Dose fractionation results in less effect for low LET radiation (need to consider DDREF)
- From animal studies, there is contradictory evidence concerning the benefit or detriment of low doses
- There is evidence for a genetic component to the effect of low dose-rate in animal studies
- Studies of high background areas have been carried out showing chromosome aberrations (but no increase in cancer), but there is a need to better understand the effects of confounding factors (e.g. stress, smoking, lifestyle, etc.) in these studies
- There is evidence that there are environmental, lifestyle etc. co-factors that affect radiation effects

What do we NOT KNOW now about Individual Sensitivity that we WANT to know?

High dose considerations

- Need to know more about mechanisms and consequences/applicability of effects caused by hypersensitivity
- We need models and predictive tests (fitting acceptable standards) to better understand the risk of secondary tumors from therapy: e.g.
 - at what range of exposures these may occur?
 - what is the age-at-exposure effect?

What do we NOT KNOW now about Individual Sensitivity that we WANT to know?

- What is the scale of the contribution of individual sensitivity to radiation effects (behavioral, environmental, genetic, social-economic status, age, gender, health status, etc.)
- What are credible strategies to answer these questions?
 - Are single-cell models relevant to organism effects of sensitivity
 - Are animal models relevant to human individual variation
 - Do different levels of natural background have different effects on cells, tissues or organisms?
 - If LNT is applied generally, can it also be applied to understand the response of a genetically hypersensitive population?
 - Need more info on age and gender dependence of risk (particularly at low doses)
 - What fraction of the population is genetically sensitive (at what exposure levels)? What are their distributions (geographic, shape of distribution curve, etc.)
 - How much more sensitive are they?
 - To high exposures
 - To low exposures
 - To High or Low LET
 - Dose rate
 - Does high-dose sensitivity imply low-dose sensitivity?
 - What is the specificity of radiation to risk as compared to other carcinogens
 - How do 'lifestyle choices' affect individual sensitivity?
 - What about potential individual sensitivity to effects other than cancer and heritable effects, i.e. circulatory diseases?

Science Issues: where we need more information

- Need more info on age and gender dependence (particularly at low doses)
- What fraction of the population is genetically highly sensitive? What are their distributions (geographic, shape of distribution curve, etc.)
- How much more sensitive are they?
- Does high-dose sensitivity imply low-dose sensitivity? Can this be experimentally explored?

Regulatory Issues:

where we need more information

- Does our current approach to RP (limits, etc.) ALREADY protect hypersensitive people?
- Should we need to change the RP regulatory approach, would it be best to:
 - Lower dose limits for all ?
 - OR –
 - Re-evaluate protection approaches for sensitive individuals from high-exposure work?
 - The choice will in part depend on the size of the sensitive population, the level of its sensitivity, and the ease and validity of identifying sensitive individuals
- If hyper sensitivity is an issue (At 2x? At 10x?), there would be a need to explore implications in the area of emergency response workers, and, depending on the relevant level of exposure perhaps also of protection of the public (sensitive groups) in emergency situations (implications for current approach to planning emergency response optimisation for women, pregnant women and children)

How to Address the questions raised by science?

- These issues are too large for a single national approach to successfully address them all
 - Need an infrastructure
 - Need a ‘broad common strategy’ to ‘focus efforts’
- These questions are sub-categories of the broader question of whether or not low dose exposures (e.g. 10 mSv) do or do not cause any health effects
- These questions can not be answered quickly, thus we will be forced to live with uncertainty for some time yet
- Four approaches:
 - In-vitro models
 - Limited capabilities
 - Mechanistic studies possible
 - Animal models
 - Controlled, low-dose experiments
 - Question of applicability to humans
 - Molecular epidemiological models:
 - Need fingerprints of tumor causality
 - Link studies to other, ongoing cancer studies (e.g. Icelandic genetic study)
 - In Humans:
 - Need signature or pre-determined endpoint for such studies to be useful
- We will need to discuss how to judge the likelihood of these studies to deliver answers?
- Age, diet, lifestyle, other risk-modifying factors influence sensitivity or not?? Need to re-test to keep results ‘up-to-date’, as parameters may change during life
- Training and competence in RP must be maintained

What would we do differently IF we knew now what we would like to know?

IF we:

- Have a tool to predict individual sensitivity
- Know how many people are more sensitive, and what is their sensitivity distribution
- Know how much more sensitive they are
- Know the relationship between sensitivity to acute effects and stochastic effects
- Know whether low-dose effects are negative, positive or both
- Know the effect of dose rate

What would we do differently IF we knew now what we would like to know?

At high dose in therapy:

- Would need to develop clinical guidelines
- Individual patient treatment
- Treatments would be improved (doses increased or decreased)

At high doses in emergency situations

- Triage of victims in terrorist events or large-accidents would improve
- Emergency workers could be pre-selected for their resistance to radiation health effects:
 - Ethical Questions, Labor Questions
 - Separate dose restrictions could be developed for this group

What would we do differently IF we knew now what we would like to know?

At low dose in the workplace:

- If the increase (or decrease) in sensitivity is low (e.g. on the order of the factor of 2 but within the current range of RP uncertainty) there would be a need to assess the costs and benefits of change to the current RP or labor management approach – stakeholder involvement would be needed in the discussions
- If the increase (or decrease) in sensitivity is large (e.g. on the order of one or two orders of magnitude) the employer may have a duty to inform about the existence of the test, to test workers, and inform them of the results.
 - EX: the risk to the fetus is much higher than to an adult, but in this situation the protection of the fetus is specifically addressed during pregnancy
 - EX: people with asthma are not allowed to work in habitually dusty environments
 - Issues may include:
 - Insurance coverage based on increased sensitivity would be a key question
 - Allowing the individual to work in an increased risk environment would be an employer, employee, regulator (and social?) issue
 - If there are individuals with NO RISK from radiation exposure, would they be treated differently at work?
- There is international text on genetic discrimination – start here

What would we do differently IF we knew now what we would like to know?

At low dose to the public:

- The types of issues that would need to be addressed (through appropriate stakeholder processes) would include:
 - Education and information of the public
 - Availability of genetic susceptibility test results - interpretation
 - Implications for insurance, employment
 - Is it possible that genetic susceptibility would be linked to greater or lesser risks of contracting other diseases?
 - Implications for people living in high-background areas
 - Medical diagnostic or screening campaigns
 - Medical – legal screening
 - Need to re-evaluate dose limits
 - Implications for the optimisation of protection for
 - Operational releases
 - Accident situations
 - Waste disposal
 - Exclusion and exemption
 - Consider consequences of other possible sensitivities (e.g. to UV)

What could or should we do now while we wait for the answers to these questions

- No specific actions are proposed for the following exposures:
 - In the workplace
 - For the general public
 - From screening of the general public (medical, medico-legal, etc.)
- In emergency management situations
 - Consider specifically targeting optimisation of protection to 'known' sensitive groups (e.g. children and pregnant women)
- In Diagnosis
 - The group suggested that all radio-diagnostic imaging machines should include dose assessment capabilities as implemented in DICOM headers of digital images
- In therapy situations
 - Raise awareness about individual sensitivity and the risks of secondary cancers
 - Promote good practice, and validate therapy standards
 - Use genetic testing to investigate the risks of secondary cancers
 - Discuss ethical and practical aspects of 'tailor-made' therapy approaches to be ready should tools become available in the coming years
- In general, there is a need to raise awareness of the importance of organ doses
- If specific issues related to individual sensitivity arise, it was suggested that their discussion, particularly of ethical aspects, should involve stakeholders – no agreement was reached in the Breakout session on the value of doing this
- Maintain training and competence in RP
- Reflect on how to 'live with uncertainty'
- Discuss how to judge the likelihood that studies will answer questions
- Criteria and methods for the selection of emergency workers