

Contents

1. Executive Summary
2. Introduction
3. Biophysical Aspects
 - 3.1 Microdosimetry and its relevance
 - 3.1.1 Ionizing track structure
 - 3.1.2 Quantitative characterization of energy deposition
 - 3.1.3 Definition of "low dose"
 - 3.2 Independent cellular effects at low doses
 - 3.2.1 Dose-response per traversal
 - 3.2.2 Clonality of tumors
 - 3.2.3 Abscopal effects
 - 3.4 Dose response in susceptible subpopulations
 - 3.5 Summary
4. DNA repair and processing after low dose of radiation
 - 4.1 Radiation-induced lesions, their repair, and their misrepair
 - 4.1.1 Single-strand breaks
 - 4.1.2 Base damage and loss
 - 4.1.3 DNA-protein cross-links
 - 4.1.4 Double-strand breaks
 - 4.1.5 Locally-multiply-damaged sites
 - 4.1.6 Spontaneous DNA damage
 - 4.1.7 Effects of LET
 - 4.1.8 Mismatch repair
 - 4.2 Cell cycle checkpoints
 - 4.3 Programmed cell death (apoptosis)
 - 4.4 Impact of cell cycle checkpoints and apoptosis on the dose response
 - 4.5 The adaptive response
 - 4.6 Summary
5. Mutagenic effects
 - 5.1 Introduction
 - 5.2 Potential mechanisms of mutagenesis
 - 5.2.1 Replication errors
 - 5.2.2 Mutations arising during repair
 - 5.2.3 Inducible DNA repair
 - 5.3 Dose-response studies with low-LET radiation
 - 5.3.1 Human cells in vivo
 - 5.3.2 Animal cells in vivo
 - 5.3.3 Mammalian cells in vitro
 - 5.3.3.1. Assays at the hprt locus
 - 5.3.3.2 Assays at other genetic loci
 - 5.3.3.3. Dose rate effects
 - 5.3.3.4. Effect of genetic background
 - 5.3.3.5. Inducible systems
 - 5.3.3.5.1. Genomic instability
 - 5.3.3.5.1. Adaptive response
 - 5.4 Dose-response studies with high-LET radiation
 - 5.5 Summary
6. Chromosome aberrations

A/50

- 6.1 Misrepair, misreplication, and chromosome aberration formation
 - 6.1.1 Chromosome-type aberrations
 - 6.1.2 Chromatid-type aberrations
 - 6.1.3 Mechanisms of formation of chromosome aberrations
 - 6.1.3.1 Low-LET radiations
 - 6.1.3.2 High-LET radiations
 - 6.1.4 Dose-response curves: acute and chronic exposures
 - 6.1.4.1 Low-LET radiations
 - 6.1.4.2 High-LET radiations
- 6.2 Distribution of aberrations within and among cells
 - 6.2.1. Intercellular distribution
 - 6.2.2. Inter- and intrachromosomal distribution
- 6.3 Uncertainties in shapes of dose-response curves at low doses
 - 6.3.1 Nonlinear and threshold responses
 - 6.3.2 Effect of adaptive response
 - 6.3.3 Efficiency of DNA repair
 - 6.3.4 Inducibility of DNA repair and cell cycle checkpoints
 - 6.3.5 Genetic susceptibility
- 6.4 Association between chromosome aberrations and cancer
- 6.5 Biological dosimetry
 - 6.5.1 Acute exposures
 - 6.5.2 Chronic exposures
 - 6.5.3 Evidence for thresholds
 - 6.5.4 Implications
- 6.6 Summary
 - 6.6.1 Interpretation
 - 6.6.2 Research needs
- 7. Oncogenic transformation in vitro
 - 7.1 Dose-response relationships
 - 7.2 Shape of the dose-response relationship
 - 7.3 The dose rate effect
 - 7.4 Modulation
 - 7.5 Genomic instability
 - 7.6 Summary
- 8. Carcinogenic effects in laboratory animals
 - 8.1 Introduction
 - 8.2 Characteristics and multistage nature of carcinogenesis
 - 8.3 Dose-response relationships
 - 8.3.1 Background
 - 8.3.2 Leukemia
 - 8.3.2.1 Thymic lymphoma
 - 8.3.2.2 Myeloid leukemia
 - 8.3.2.3 Other hematologic neoplasms
 - 8.3.3 Sarcomas: osteosarcoma
 - 8.3.4 Rodent mammary tumors
 - 8.3.4.1 Mouse mammary adenocarcinomas
 - 8.3.4.2 Rat mammary tumors
 - 8.3.4.3 Hormonal effects
 - 8.3.4.4 Oncogenes and experimental mammary cancer
 - 8.3.4.5 Summary

- 8.3.5 Thyroid neoplasia
- 8.3.6 Mouse Lung tumors
- 8.3.7 Rat renal neoplasms
- 8.3.8 Skin tumors
- 8.4 Life shortening
- 8.5 Summary
- 9. Carcinogenic effects in human populations
 - 9.1 Considerations in using epidemiological data for low-dose risk assessment
 - 9.1.1 Introduction
 - 9.1.2 Weaknesses of certain types of studies
 - 9.1.3 Ecological studies (Studies of aggregated epidemiologic data)
 - 9.1.4 Case-control studies
 - 9.1.5 Cohort studies
 - 9.2 Examination of the dose response at low doses
 - 9.2.1 Total solid cancers
 - 9.2.2 Leukemia
 - 9.2.3 Thyroid cancer
 - 9.2.4 Breast cancer
 - 9.2.5 Lung cancer
 - 9.2.5.1 Low-LET irradiation
 - 9.2.5.2 High-LET irradiation
 - 9.2.6 In utero irradiation
 - 9.2.7 Impact of modifying factors on the dose response
 - 9.2.7.1 Host susceptibility and sensitivity to cancer
 - 9.2.7.1.1 Theory
 - 9.2.7.1.2 Current information
 - 9.2.7.2 Interactions between radiation and other risk factors
 - 9.3 Summary
- 10. Genomic Instability
 - 10.1 Occurrence in neoplastic cells
 - 10.2 Mechanisms of genomic instability
 - 10.3 Unusual features of genomic instability
 - 10.4 Conclusion
- 11. Adaptive responses
 - 11.1 Types and dose-response relationships of adaptive responses
 - 11.2 Implications for the linear-nonthreshold model
- 12. Research Needs
- 13. Discussion and conclusions
- Appendix A. Acknowledgement of data submitted to Committee
- References