Supplementary Information

S1. Theoretical Framework Supporting the Mechanistic Aspects of the Proposed Hypothesis.

Ionising Radiation, Types of Radiation and Radiation Doses

Ionising radiation refers to energy carried by subatomic particles or high frequency electromagnetic waves with sufficient energy per quantum to remove electrons from atomic or molecular orbitals, thereby generating ion pairs in matter (Hall & Giaccia, 2019). Ionisation occurs when the energy transferred during an interaction exceeds the ionisation potential of the target substance (Hall & Giaccia, 2019).

Chemical and radiobiological sensitivity to ionising radiation is not directly determined by general measures of chemical reactivity. However, the electronic structure of a substance, including its redox properties and ionisation potential, may influence its susceptibility to radiation-induced electron displacement. Substances with lower ionisation potentials may require lower energy deposition to initiate electronic excitation and ionisation processes, potentially contributing to increased radiosensitivity. Nevertheless, redox behaviour and oxidative reactivity are governed by multiple thermodynamic and kinetic parameters and do not necessarily correlate directly with radiosensitivity in a deterministic manner (Joiner and van der Kogel, 2018; Hall & Giaccia, 2019).

Electronic ionisation and nuclear interactions involve changes within the atomic nucleus. Nuclear reactions such as neutron capture and subsequent decay processes may result in the transformation of one element into another, referred to as nuclear transmutation. These processes require nuclear scale interactions and are typically associated with high neutron flux environments (Hall & Giaccia, 2019; Joiner and van der Kogel, 2018).

Neutron activation can generate secondary radioactive isotopes in materials exposed to sufficiently high neutron fluxes, resulting in additional ionising emissions (UNSCEAR, 2008; Hall & Giaccia, 2019). Such processes are primarily associated with nuclear reactors and severe nuclear accidents and are generally negligible under environmental radiation conditions relevant to free-living vertebrates. Consequently, direct ionisation and reactive oxygen species (ROS)-mediated damage remain the principal mechanisms underlying radiation-induced biological effects in wildlife populations (Azzam et al., 2012; Hall & Giaccia, 2019).

Most of the biological damage in radiation accidents is caused by exposure to ionising radiation through direct ionisation of biomolecules and indirect effects mediated by the formation of reactive oxygen species (ROS) (Azzam et al., 2012). In rare high-neutron radiation environments, limited activation of materials may occur; however, this is generally considered a negligibly small contribution to overall biological effects compared with primary ionisation processes. Different types of ionising radiation vary in their biological effectiveness due to differences in linear energy transfer and interaction mechanisms (UNSCEAR, 2008).

Supplementary Table 1. Selected characteristics and health effects of ionising radiation types (compiled from UNSCEAR, 2008). This framework integrates established radiobiological

mechanisms with hypothesis-driven extrapolations and should be interpreted as a qualitative mechanistic synthesis requiring future empirical evaluation [15, 51, 93, 98, 100].

Particle type	Particles/Nature	Penetrating Power	Hazards to Organisms	Role in Development
Alpha (α)	Helium nuclei (heavy)	Low (Stopped by epidermis)	Critical if ingested/inhaled (internal exposure)	Severe localized tissue and DNA destruction
Beta (β)	Electrons / Positrons	Medium (penetrates 1-2 cm of tissue)	High for skin, eyes, and mucous membranes	Radiation burns; damage to epithelium and thyroid
Gamma (γ)	High-energy photons	High (passes through the entire body)	Total body irradiation of all internal organs	Systematic mutations; global disruption of cell division
Neutron	Free neutrons	High (variable by energy)	May cause induced radioactivity in tissues	Potential secondary activation effects in high-neutron environments

Dosimetry is the measurement of energy deposited in matter by ionising radiation. It quantifies the absorbed dose, defined as the energy imparted per unit mass of tissue, expressed in gray (Gy), where 1 Gy equals 1 joule per kilogram (UNSCEAR, 2008).

Although absorbed dose provides a fundamental physical measure of energy deposition, it does not fully describe biological effects, as it does not account for differences in radiation type or tissue sensitivity. To address this limitation, the concept of equivalent dose is used to estimate biological risk by incorporating radiation type through weighting factors (UNSCEAR, 2008; Hall & Giaccia, 2019).

Equivalent dose reflects the observation that different types of ionising radiation produce different levels of biological damage even when delivering the same absorbed dose. This is primarily due to differences in linear energy transfer and ionisation density, with high LET radiation generally producing more complex and severe cellular damage than low LET radiation. A mathematical expression is shown below, which can be used to calculate the biological dose of radiation from radioactive particles (UNSCEAR, 2008):

$$\mathbf{H = D \times W_r}$$

Where:

- H is the equivalent dose
- D is the absorbed dose (Gy)
- W_r is a dimensionless weighting factor

The use of the sievert (Sv) enables the comparison of biological effects across different types of ionising radiation by incorporating radiation weighting factors into a unified dosimetric

framework. This approach provides a standardised estimate of potential biological risk in vertebrates by accounting for differences in radiation quality and relative biological effectiveness. Radiation weighting factors reflect the greater biological impact of high linear energy transfer radiation, such as alpha particles, compared with low linear energy transfer radiation, such as X-rays and gamma radiation (UNSCEAR, 2008; Hall & Giaccia, 2019).

Supplementary Table 2. Generalised classification of dose rates and related biological effects on vertebrates, based on data from publicly available peer-reviewed literature (UNSCEAR, 2008). This classification is illustrative and not intended as a quantitative predictive dose-response model [15, 51, 93, 98, 100], [67, 76, 89, 94, 95, 96, 97, 106, 107].

Exposure category	Effective dose (mSv)	Exposure type	Biological effects (generalised, population level)
Natural background radiation	~2–10 mSv/year	Chronic environmental exposure	No detectable adverse effects; normal biological variability
Public exposure limit (ICRP recommendation)	1 mSv/year (above background)	Chronic regulated exposure	No expected deterministic effects
Occupational exposure limit	20 mSv/year (averaged over 5 years)	Chronic occupational exposure	No deterministic effects expected under controlled conditions
Diagnostic medical imaging (range per procedure)	~0.1–10 mSv	Acute single-event exposure	Very low risk; slight increase in stochastic cancer risk at population level
Higher-dose diagnostic procedures (e.g. CT range)	~5–20 mSv	Acute single-event exposure	Low risk; measurable but small stochastic risk increase
Threshold for transient tissue reactions (deterministic effects)	~500–1000 mSv (acute)	High-dose partial or whole-body exposure	Early biological responses (e.g. transient blood cell reduction) possible
Acute Radiation Syndrome (ARS) threshold	≥1000 mSv (≥1 Sv acute)	Acute whole-body exposure	Clinical symptoms: possible (nausea, lymphocyte depletion, fatigue)
Severe deterministic injury range	~2–6 Sv acute	Acute high-dose exposure	Hematopoietic syndrome; significant mortality risk without treatment
Approximate LD50/60 (no medical treatment)	~3–5 Sv acute	Acute whole-body exposure	~50% mortality within ~60 days
Very high exposure range	>6–8 Sv acute	Acute severe exposure	High mortality risk even with medical intervention
Extreme exposure range	>8–10 Sv acute	Acute catastrophic exposure	Near-certain mortality without intensive medical care

There is no direct universal conversion between absorbed dose (gray, Gy) and equivalent dose (sievert, Sv), as the relationship depends on radiation type through radiation weighting factors. Equivalent dose is calculated by applying these weighting factors to account for differences in biological effectiveness among radiation types. High LET radiation, such as alpha particles, is assigned a higher weighting factor due to its greater ionization density and increased biological damage per unit absorbed dose. Neutron radiation also exhibits energy dependent weighting

factors that vary with neutron energy spectrum, reflecting differences in interaction mechanisms and biological effectiveness (UNSCEAR, 2008; Hall & Giaccia, 2019).

Although ionization occurs almost instantaneously following radiation exposure, the resulting biological consequences develop over substantially longer timescales through the accumulation of molecular damage, reactive oxygen species (ROS) production, oxidative stress, and downstream cellular responses (Azzam et al., 2012; Hall & Giaccia, 2019). The magnitude of these effects depends on the capacity of exposed tissues to repair damage and maintain cellular homeostasis, factors that are expected to vary among proliferating developmental tissues and contribute to interspecific differences in developmental radiosensitivity.

These mechanisms suggest that variation in energy deposition patterns, radiation quality, and internal radionuclide distribution can lead to differences in effective dose delivered to proliferating radiosensitive tissues, particularly during postembryonic development. Such differences are expected to interact with proliferation (P) rates specific to tissues and repair capacity, thereby directly contributing to interspecific variation in developmental impairment under chronic radiation exposure, as proposed in the hypothesis.

Ionization processes provide the initial physical basis for radiation-induced biological effects. The resulting molecular damage triggers downstream cellular responses that determine the development of radiation-induced pathologies. These effects are most clearly understood at the cellular level, where structural and functional alterations reflect the integrated response to radiation exposure (Hall & Giaccia, 2019). Collectively, literature on radiobiological principles, dose-response relationships, radiation physics, and cellular radiation responses supports the mechanistic assumptions outlined in this section [13,17,30,41,55,73,92,95,103,105,109,110].

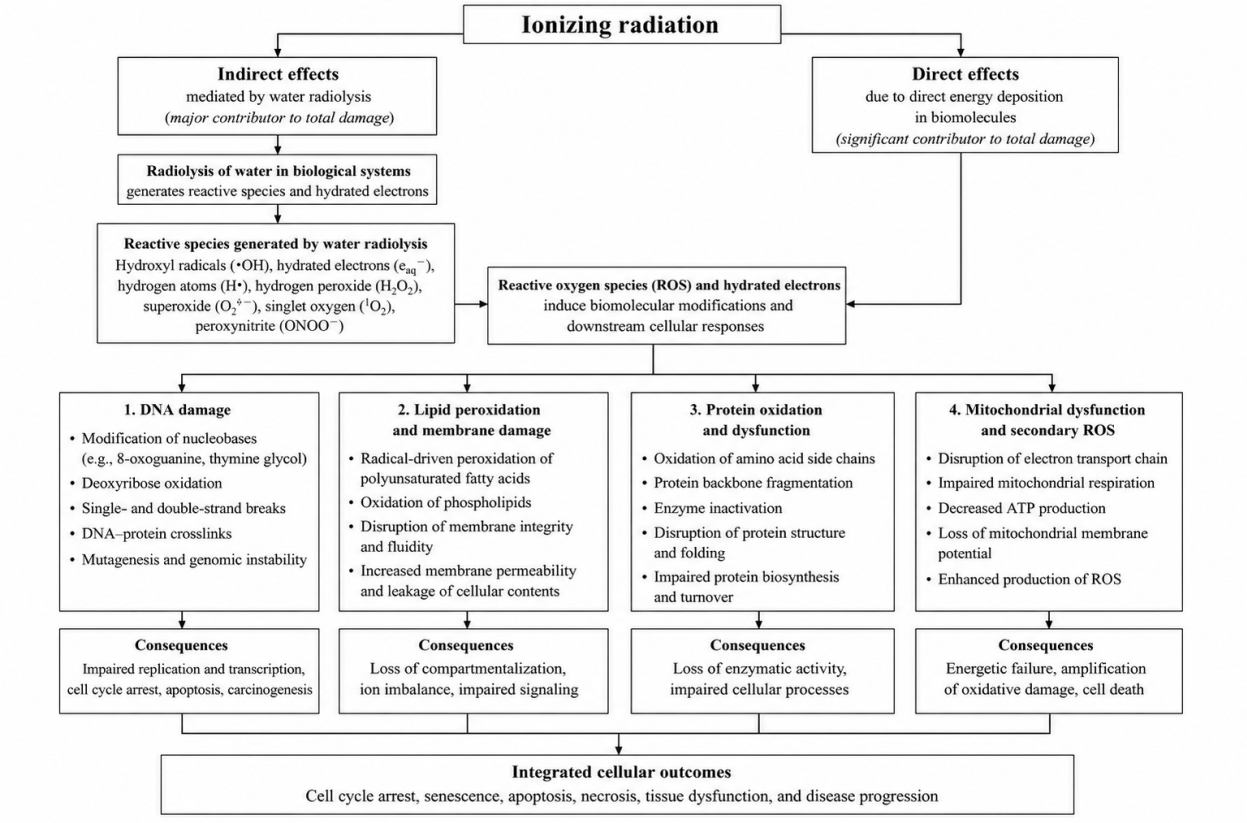
The effect of ionizing radiation on the functioning of eukaryotic cells

Ionizing radiation exerts significant biological effects on eukaryotic cells primarily through the generation of molecular damage to cellular macromolecules (Supplementary Figure 1). Ionizing radiation possesses sufficient energy to remove tightly bound electrons from atoms, producing charged particles (ions) that initiate a cascade of chemical reactions within biological tissues. In eukaryotic cells, the primary target of ionizing radiation damage is deoxyribonucleic acid (DNA), whose structural integrity is essential for optimal cellular functioning, replication, and gene expression. Damage to DNA may occur either directly through energy deposition onto the DNA molecule or indirectly through the radiolysis of water molecules, leading to the production of reactive oxygen species (ROS) (such as: hydroxyl radicals, hydrogen radicals, hydrogen peroxide, superoxide ions) that subsequently attack nucleic acids, sugar-phosphate backbones, proteins, and membrane phospholipid bilayer (Supplementary Figure 1) (Hall & Giaccia, 2019; Reisz et al., 2014). Most radiation-induced biological damage is mediated indirectly through ROS generated by water radiolysis, while a smaller fraction results from direct ionization of biomolecules (Hall & Giaccia, 2019; Azzam et al., 2012), (Supplementary Figure 1). Effects vary depending on cell cycle phase, oxygenation status, and tissue-specific proliferation rate.

Among the most critical forms of radiation-induced DNA damage are single-strand breaks (SSBs), double-strand breaks (DSBs), base modifications, and DNA crosslinking. DSBs are particularly deleterious, as they can compromise chromatin integrity and lead to mutations, chromosomal rearrangements, or cell death if not accurately repaired (Jackson and Bartek, 2009). Eukaryotic cells respond to such lesions through coordinated DNA repair pathways, including homologous recombination and non-homologous end joining. Key regulatory proteins such as ATM kinase and p53 orchestrate cell-cycle checkpoints and DNA damage responses following irradiation (Jackson and Bartek, 2009; Santivasi and Xia, 2014). Beyond genomic damage, ionizing radiation induces oxidative stress through elevated levels of reactive oxygen species (ROS), which disrupt cellular redox balance and interfere with multiple metabolic processes (Supplementary figure 1). Mitochondria are particularly sensitive to oxidative stress due to their central role in oxidative phosphorylation and ATP production, as well as their proximity to endogenous ROS generation sites. Mitochondrial DNA is especially vulnerable to radiation-induced damage due to limited protective and repair capacity compared with nuclear DNA.

Consequently, radiation exposure can impair mitochondrial function, leading to altered energy metabolism, reduced ATP production, and downstream effects on cellular homeostasis (Azzam, Jay-Gerin and Pain, 2012; Spitz et al., 2004).

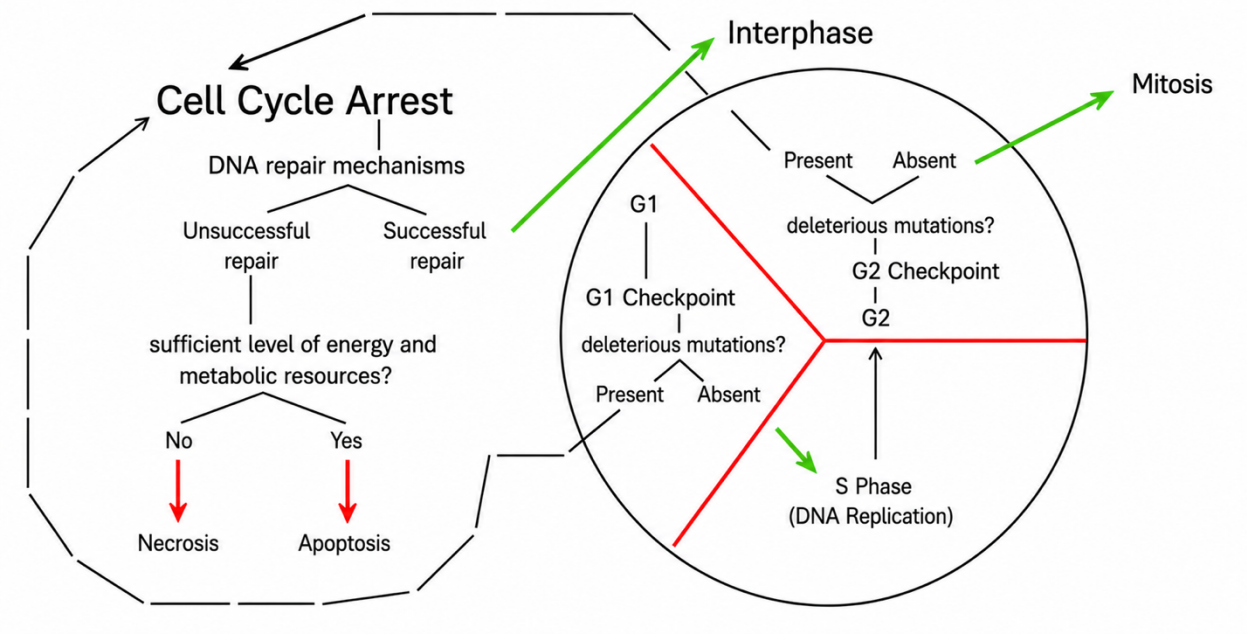
Supplementary Figure 1 Summarizes the effects of ionizing radiation to the intercellular macromolecules, organelles and metabolic processes. (Jackson, Stephen P. and Bartek, Jiri. 2009; Eriksson and Stigbrand, 2010) [14, 37, 45, 80, 81], [31, 40, 63, 74, 91, 92], [5, 9, 10, 30, 53, 54, 62, 75, 82, 83, 110].



Ionizing radiation can also modulate cell cycle progression by activating DNA damage checkpoints (Supplementary Figure 2). In response to DNA lesions, cells transiently arrest the cell cycle to permit repair processes to restore genomic integrity. This regulation is mediated by checkpoint signaling pathways acting primarily at the G1/S and G2/M transitions, which integrate DNA damage signals to control cell-cycle progression. The checkpoint activation is a key protective mechanism that maintains genomic stability in multicellular organisms following exposure to ionizing radiation (Jackson and Bartek, 2009). Because postembryonic growth depends on sustained proliferation (P) of progenitor and differentiating cell populations, radiation-induced checkpoint activation may disproportionately affect developing tissues relative to mature tissues, potentially contributing to growth retardation and developmental abnormalities.

If the severe DNA damage cannot be repaired successfully, the cell usually undergoes the programmed cell death (apoptosis) to prevent the propagation of mutations. However, apoptosis is an active process and may only occur if the cell has the sufficient amount of energy and metabolic resources, necessary for the programmed death of the cell (Jackson, Stephen P. & Bartek, Jiri. 2009). Severe damage may lead to necrotic cell death under conditions of energy depletion. The balance between apoptosis and necrosis is dependent on the context and influenced by metabolic state (Supplementary Figure 2). Necrosis (unlike Apoptosis) causes the cell to burst and release most of the toxins, aggressive enzymes and mineral ions from the lysosomes and peroxisomes into the extracellular space. The blood vessels become hyperpermeable and cause severe local inflammation near the necrotic tissue leading to profound swelling and abnormal rise of pressure in damaged tissue. (Eriksson and Stigbrand, 2010). [32,42,50,59,94]

Supplementary Figure 2 A Schematic illustration of the cell cycle dynamics under conditions of ionizing radiation. (Jackson, Stephen P. and Bartek, Jiri. 2009; Eriksson and Stigbrand, 2010) [7, 22, 34, 41, 49, 50, 78, 80, 81].



Under conditions of severe cellular damage, necrotic cell death may occur, leading to the uncontrolled release of intracellular contents and subsequent inflammatory responses in surrounding tissues. Unlike apoptosis, which limits damage by removing compromised cells in a regulated manner, necrosis can amplify local tissue injury and exacerbate secondary cellular dysfunction (Eriksson and Stigbrand, 2010). In developing organisms, such processes may compromise cellular integrity within proliferating tissues, thereby increasing the likelihood of growth disruption and developmental abnormalities following chronic radiation exposure.

Because postembryonic growth relies on sustained proliferation (P) of progenitor and differentiating cell populations, radiation-induced activation of cell-cycle checkpoints may disproportionately affect developing tissues compared with fully differentiated tissues, thereby potentially contributing to growth retardation and developmental impairment.

Ionizing radiation also disrupts cellular redox homeostasis through the generation of reactive oxygen species (ROS), increasing oxidative stress and placing elevated demand on NADPH-dependent antioxidant systems. These systems, including glutathione peroxidase (GPx) and thioredoxin reductase (TrxR), are essential for maintaining protein integrity, lipid stability, and DNA repair capacity. Both pathways rely indirectly on NADPH, which is primarily generated via the pentose phosphate pathway. When ROS production exceeds antioxidant capacity, depletion of NADPH impairs redox recycling of glutathione and thioredoxin, thereby amplifying oxidative damage to DNA, proteins, and lipids (Lu and Holmgren, 2014; Azzam et al., 2012). [1,57,81,108,110].

These mechanisms indicate that radiation-induced developmental impairment is strongly influenced by proliferative activity and metabolic demand within exposed tissues. During

embryonic and postembryonic development, rapidly dividing cell populations are particularly vulnerable to DNA damage and oxidative stress due to replication-associated genomic instability and limited temporal windows for repair. Consequently, interspecific differences in developmental timing, tissue proliferation dynamics, and metabolic rate may contribute substantially to variation in radiosensitivity and developmental outcomes under chronic radiation exposure.

Ionizing radiation disrupts cellular homeostasis through combined DNA damage, oxidative stress, mitochondrial dysfunction, and impairment of antioxidant defences (Azzam et al., 2012; Hall & Giaccia, 2019).

These effects are predicted to be especially consequential in germline tissues, where continuous proliferation (P) and meiotic processes increase susceptibility to mutation accumulation and cell loss, thereby linking somatic developmental effects to reproductive fitness consequences.

The cellular consequences of radiation exposure are strongly influenced by the capacity of cells to detect, signal, and repair DNA damage. These processes involve integrated DNA damage response networks, checkpoint signaling pathways, and multiple repair mechanisms that determine whether damaged cells recover, undergo apoptosis, or accumulate persistent genomic alterations. Consequently, variation in DNA repair efficiency may represent an important contributor to interspecific differences in developmental radiosensitivity [7,22,35,52,53,62,82], [43,57,84,85], [5,9,10,27,31,51,65,79,86,87,110].

The effect of ionizing radiation on gametogenesis

Ionizing radiation impacts gametogenesis through its interaction with germline-specific developmental features, including prolonged proliferative activity, meiotic recombination, and stage-dependent changes in DNA repair capacity (Hall & Giaccia, 2019; UNSCEAR, 2008). These characteristics create multiple temporally distinct sensitivity windows in which radiation-induced lesions may be differentially repaired, eliminated, or fixed within germline lineages.

Spermatogenic radiosensitivity is stage-dependent and reflects shifts in proliferative dynamics, chromatin organization, and repair capacity across differentiation. In mitotically active spermatogonia, repeated cell division increases vulnerability to replication-associated genomic lesions, with damaged cells either eliminated through checkpoint-controlled apoptosis or, in sublethal cases, retained within clonal lineages. During meiosis I, programmed double-strand break formation and homologous recombination create a structurally constrained window in which exogenous DNA lesions may interfere with synapsis and crossover fidelity, increasing the probability of chromosomal mis-segregation or elimination of affected cells. In post-meiotic spermatids, reduced DNA repair capacity and highly condensed chromatin increase the likelihood that lesions persist and become fixed as mutations.

In addition, oxidative stress may impair mitochondrial function and membrane integrity, contributing to reduced sperm viability and functional competence. Overall, spermatogenic sensitivity reflects the interaction between proliferative amplification, meiotic recombination

architecture, and progressive reduction in DNA repair redundancy across differentiation stages (Azzam et al., 2012; Hall & Giaccia, 2019).

Supplementary Table 3. Summarises the relative radiosensitivity levels at different stages of spermatogenesis across vertebrates. (Meistrich, 2013; Hall & Giaccia, 2019; Xie et al., 2022). [20, 32, 38, 64, 71, 74, 77, 90, 109].

Stage / Phase	Radiosensitivity level	Causes for such level of radiosensitivity
1. Proliferation (spermatogonia, mitosis)	High	Active cell division - high vulnerability to DNA damage, G1/S and G2/M checkpoints trigger apoptosis, but some mutations escape and are transmitted further
2. Growth (interphase before meiosis 1, 2n4c)	Moderate	DNA replication is the S phase - mutations can be fixed; high ROS affects biosynthetic processes (e.g., acrosome formation), but no major chromosomal rearrangements
3. Prophase 1 (leptotene - diakinesis)	Very high (critical)	Synapsis and crossing-over is associated with programmed DNA breaks and recombination, radiation induces mis repair, chromosomal aberrations, and faulty recombination
4. Metaphase 1	High	Chromosomes are condensed and aligned causing damage to spindle apparatus or chromosomes is linked to segregation errors
5. Anaphase 1 - Telophase 1	High	Chromosome segregation is linked to the risk of nondisjunction and aneuploidy under radiation-induced damage
6. Meiosis 2	Moderate - High	Mitosis-like division in haploid cells may cause reduced repair capacity and increases mutation fixation
7. Spermatids (1n1c)	Very high	Lack of homologous chromosome is associated with no repair via homologous recombination, so DNA damage is directly fixed as mutations occur
8. Spermiogenesis	Moderate	No cell division is associated with fewer new DNA lesions, but high sensitivity to ROS and radicals may cause structural and functional defects

Oogenic radiosensitivity is shaped by extended temporal arrest, asymmetric repair capacity across developmental phases, and metabolic reactivation during maturation. The prolonged dictyate arrest represents a long-lived vulnerability window during which cumulative oxidative stress and gradual decline in DNA repair efficiency may increase susceptibility to lesion persistence. Upon post-pubertal activation, increased metabolic demand and mitochondrial activity elevate endogenous reactive oxygen species production, potentially exceeding antioxidant buffering capacity and increasing fixation probability of oxidative lesions. During meiotic maturation, chromatin condensation and spindle formation introduce additional structural

sensitivity, while reduced repair redundancy further increases the likelihood of permanent genomic alteration following damage. Overall, oogenic sensitivity reflects the interaction between prolonged exposure time, metabolic reactivation, and progressive reduction in repair capacity across developmental stages.

Gametogenesis exhibits stage-dependent radiosensitivity driven by interactions between proliferative activity, meiotic recombination, chromatin state, and repair capacity. These effects determine whether radiation-induced damage is repaired, eliminated, or fixed within germline lineages.

Variation in germline developmental duration and proliferative architecture may therefore contribute to differences in cumulative exposure to radiation-sensitive cellular states, potentially influencing interspecific variability in developmental and reproductive sensitivity under chronic exposure. This framework is a mechanistic synthesis based on established radiobiological principles (S1) and should be interpreted as a qualitative model generating testable hypotheses rather than a quantitative dose-response framework. [4,14,38,47,107]

Supplementary Table 4. Summarizes the relative radiosensitivity levels at the different stages of oogenesis, and their causes. (Hall & Giaccia, 2019;Azzam et al., 2012) [20, 32, 38, 64, 71, 74, 77, 90, 109].

Oogenesis stage	Dominant biological process	Primary radiosensitivity determinants	Relative sensitivity
Primordial germ cell proliferation	Mitotic expansion of the germ cell population	Rapid proliferation, DNA replication associated damage	High
Oogonial proliferation	Mitotic divisions of oogonia	High cell cycle activity, replication stress	High
Meiotic entry	Initiation of meiosis and homologous recombination	Programmed DNA double strand breaks, recombination machinery activity	High
Primary oocyte arrest (dictyate stage)	Long term meiotic arrest	DNA repair capacity, follicular support, cumulative damage susceptibility	Moderate
Folliculogenesis and oocyte growth	Oocyte maturation and cytoplasmic accumulation	Oxidative stress, mitochondrial integrity, follicular microenvironment	Moderate
Mature oocyte (preovulatory)	Completion of maturation processes	Chromosome segregation fidelity, spindle integrity	Moderate to high

Ranking reflects the proposed framework and available evidence rather than direct quantitative comparison across all vertebrate taxa. This framework integrates established radiobiological mechanisms with hypothesis-driven extrapolations and should be interpreted as a qualitative model requiring empirical validation. [2,6,20,21,29,33,39,40,67,57,74,78,88,94,46,].

Effects of ionizing radiation on vertebrate embryogenesis and embryonic development

Vertebrate embryogenesis represents a temporally constrained system of rapidly changing cellular states in which radiosensitivity is governed by the interaction between DNA damage induction, cell-cycle regulation, chromatin accessibility, and the stage-dependent capacity of DNA repair and checkpoint systems (Hall & Giaccia, 2019; Jackson & Bartek, 2009). Ionizing radiation generates spatially clustered DNA lesions, including double-strand breaks (DSBs), oxidized bases, and complex damage sites, whose biological consequences depend not only on dose but on whether lesions occur in phases of active replication, chromatin remodeling, or differentiation.

A central mechanistic determinant of embryonic radiosensitivity is the developmental regulation of DNA damage response (DDR) competence. Early embryonic cell cycles are characterized by abbreviated G1 and G2 phases and reduced checkpoint enforcement, limiting the temporal window for damage recognition prior to DNA synthesis. As a result, radiation-induced lesions are frequently carried into S-phase, where replication fork progression across damaged templates is associated with fork stalling, collapse, and activation of ATR-dependent replication stress responses. When damage burden exceeds repair capacity, this can culminate in replication catastrophe or apoptotic elimination of affected blastomeres, while sublethal lesions may be propagated clonally through subsequent divisions, generating mosaic genomic instability (Bartek & Lukas, 2007; Jackson & Bartek, 2009).

During fertilization and early zygotic activation, radiosensitivity is increased by chromatin decondensation and epigenetic reprogramming events. Protamine-to-histone exchange in paternal chromatin contributes to transient relaxation of DNA packaging, increasing physical accessibility to ROS-mediated and direct ionization-induced damage. This stage coincides with genome-wide epigenetic reconfiguration, during which DNA methylation patterns and chromatin states are actively reset. Radiation exposure during this window can therefore simultaneously induce structural DNA damage and disrupt epigenetic re-establishment, increasing the likelihood of persistent transcriptional dysregulation in downstream lineages (Hall & Giaccia, 2019; Azzam et al., 2012).

During cleavage, embryonic blastomeres operate under conditions of maximal proliferative velocity with minimal genomic buffering capacity. Although core repair pathways remain active, their effectiveness is constrained by rapid cycling and limited checkpoint duration. Radiation-induced DNA lesions in this context are either resolved through apoptosis or transmitted through mitotic divisions when below lethality thresholds.

This creates a binary developmental outcome structure: early elimination of severely damaged lineages versus survival with embedded mutational load, contributing to developmental mosaicism and instability across embryonic tissues.

At implantation, radiosensitivity shifts toward cell-environment and signaling interface dependency, particularly involving trophoblast differentiation and embryo–maternal communication. Successful implantation requires coordinated expression of adhesion molecules, cytokine signaling, and proteolytic remodeling of the endometrium.

Radiation-induced oxidative stress and DNA damage can disrupt these integrated processes by altering gene expression programs governing trophoblast invasion and vascular interface formation, leading to implantation failure even in the absence of widespread embryonic cell death (Staun Ram & Shalev, 2005).

During gastrulation and organogenesis, radiosensitivity is driven by morphogen-controlled patterning systems operating near nonlinear stability thresholds**.** Developmental signaling networks such as Wnt, BMP, Nodal, and FGF function as tightly regulated spatial gradients that define axis formation, germ layer specification, and organ primordia initiation. Radiation-induced perturbations in these pathways—either through direct transcriptional disruption or ROS-mediated modification of signaling intermediates—can produce disproportionate phenotypic effects due to amplification through developmental feedback loops. At this stage, progressive lineage commitment reduces developmental plasticity, meaning that even localized damage can propagate into large-scale structural defects.

In the fetal period, radiosensitivity becomes **tissue-specific and proliferation-state dependent**, with highest vulnerability in systems undergoing sustained cell turnover, particularly the central nervous system, hematopoietic system, and gonads. Neural tissues are especially sensitive due to prolonged neurogenesis, migration, and synaptic organization, which require tightly regulated coordination of cell-cycle exit and differentiation. Radiation-induced DNA damage in these populations can trigger apoptosis or aberrant differentiation programs, while oxidative stress may further impair mitochondrial function and energy-dependent developmental processes. As a result, fetal radiation exposure produces heterogeneous outcomes ranging from growth retardation to neurodevelopmental impairment and long-term functional deficits.

Across all stages, embryonic radiosensitivity is not governed by a single linear dose–response relationship but emerges from the interaction between DNA lesion induction, checkpoint architecture, repair pathway availability, and developmental plasticity constraints. These parameters vary dynamically throughout ontogenesis, producing a shifting landscape of vulnerability in which identical radiation exposures generate qualitatively different outcomes depending on developmental timing and cellular context. [23,61,83,106].

Collectively, embryogenesis can therefore be conceptualized as a temporally structured system of differential genomic vulnerability, in which ionizing radiation acts not only as a source of molecular damage but as a perturbation of developmental information processing. Increasing developmental duration expands the temporal window in which cells occupy highly sensitive regulatory states, thereby increasing the probability that radiation-induced lesions become fixed

within critical developmental lineages. This provides a mechanistic basis for the hypothesis that species with prolonged developmental trajectories may exhibit increased cumulative developmental disruption under chronic exposure conditions. [18,28,60,68,73,75,90]

Supplementary Table 5. Summarises the radiosensitivity levels of different stages of embryogenesis and embryonic development of vertebrates, with the focus on radiation-induced effects and their associated risks. (Azzam et al., 2012; Clevers, 2006; Staun-Ram & Shalev, 2005; Heyer et al., 2000). The relative radiosensitivity and risk categories presented in Table 5 represent a qualitative synthesis of the cited literature and are intended to illustrate general developmental trends rather than universal rankings applicable to all vertebrate taxa. These rankings are conceptual and may vary significantly across vertebrate taxa [4, 23, 28, 58, 79, 102], [18, 27, 57, 60, 65, 69, 72, 86, 88].

Stage	Fertilization	Proliferation and Fragmentation	Implantation	Gastrulation and organogenesis	Fetal period
Features of the stage	Decondensation of the sperm nucleus, substitution of sperm DNA proteins for histones	Ultrafast mitotic cell division, absence of G1 and G2 control points	Activated and coordinated by the transmission of intercellular signals	Coordinated by signaling pathways (Wnt, BMP, Nodal and FGF), very weak activity of control points G1, G2	The Wnt, BMP, Nodal, and FGF systems move from the formation of the axes of the embryo body to intensive growth, mineralization, and functional structure of organs.
The effect of ionizing radiation on the development at the stage	Radiation-induced modifications of sperm DNA, demethylation, change of genetic markers	Nucleotide modifications, DNA strand breaks, accumulation of radiation-induced mutations	Destabilization of trophoblast proteolytic activity and the molecular profile of the uterine endometrium, cytokine deficiency	Accumulation of radiation-induced genomic and developmental abnormalities resulting from disrupted developmental signaling and DNA repair	Direct DNA destruction by ionizing radiation, radicals, and ROS, as well as damage to the regulatory pathways of Wnt, FGF, and BMP
Potential outcomes associated with radiation exposure	Aberrant gene expression, impaired structural integrity of functional genes, impaired homeostasis and metabolism leading to zygote mortality	Massive cell apoptosis, aneuploidy, exceeding of the regenerative threshold	Failure of implantation resulting in preclinical embryonic loss	Accumulation of radiation-induced malignant DNA mutations leading to massive cell apoptosis and death of the embryo	Defects such as growth retardation, cataracts, and kidney dysfunction, as well as risks that significantly increase the likelihood of developing cancer in the postembryonic development of the vertebrate

All radiosensitivity classifications presented are qualitative and intended for comparative synthesis across developmental stages rather than quantitative dose-response estimation. Sensitivity categories are relative within this synthesis and not derived from quantitative dose–response scaling.

While embryogenesis constitutes a critical period of radiosensitivity, developmental vulnerability does not end at hatching or birth. Continued growth, tissue differentiation, and physiological maturation during postembryonic development involve ongoing proliferative activity that may remain susceptible to radiation-induced damage. Therefore, understanding species-specific responses to chronic ionizing radiation exposure requires consideration of both embryonic and postembryonic developmental processes, as cumulative radiosensitivity is expected to depend on

the duration and intensity of proliferative activity throughout ontogenesis, as well as the metabolic demands and architectural features of the proliferating tissues. This framework integrates established radiobiological mechanisms with hypothesis-driven extrapolations and should be interpreted as a qualitative model requiring empirical validation.

Postembryonic development of vertebrates under conditions of chronic exposure to ionizing radiation

Postembryonic development in vertebrates is governed by coordinated regulation of stem cell proliferation, endocrine signalling, tissue differentiation, and metabolic homeostasis. Chronic ionizing radiation perturbs these processes through persistent DNA damage, replication stress, and reactive oxygen species mediated metabolic imbalance (UNSCEAR, 2008; Hall & Giaccia, 2019). These insults activate DNA damage response pathways including p53 dependent checkpoint signalling, leading to sustained cell cycle arrest, apoptosis of proliferating cells, and progressive depletion of progenitor pools. Unlike acute exposure, chronic irradiation produces a cumulative damage regime in which the balance between repair, misrepair, and mutation fixation determines long term genomic instability. Because tissues differ in proliferative rate, stem cell architecture, and metabolic demand, radiation effects are heterogeneous across organs and species, generating interspecific variability in developmental outcomes. Chronic exposure therefore produces systemic impairment involving growth suppression, tissue degeneration, reproductive decline, and altered neuroendocrine regulation (UNSCEAR, 2008).

1. General mechanisms of the effect of ionizing radiation on the postembryonic development of vertebrates.

Ionizing radiation induces four coupled biological processes: genotoxic stress, oxidative stress, epigenetic remodeling, and proliferative suppression. Water radiolysis generates reactive oxygen species within femtoseconds, while direct ionization produces DNA lesions including base modifications such as 8 oxoguanine, single strand breaks, and double strand breaks (Hall & Giaccia, 2019). Under chronic exposure, biological outcome is governed by the equilibrium between DNA repair fidelity, misrepair, and mutation fixation rather than initial lesion frequency alone. Oxidative stress extends beyond nuclear DNA damage to include lipid peroxidation, protein oxidation, and mitochondrial dysfunction. Damage to mitochondrial DNA and respiratory chain complexes reduces adenosine triphosphate production while increasing electron leakage, reinforcing reactive oxygen species generation in a self amplifying feedback loop (Azzam et al., 2012). This effect is especially pronounced in metabolically active tissues with high energetic demand. Epigenetic alterations involve persistent changes in DNA methylation, histone structure, and transcriptional regulation, producing long term reprogramming of gene expression that can persist across cell generations even after exposure cessation (Jackson and Bartek, 2009). Proliferative suppression occurs through activation of DNA damage checkpoints at G1 to S and G2 to M transitions. This leads either to apoptosis or permanent arrest of stem and progenitor cells, with strongest effects in bone marrow, intestinal epithelium, gonads, and nervous tissue due to high turnover and limited tolerance for genomic instability (Hall & Giaccia, 2019).

Collectively these mechanisms converge on a common outcome characterized by reduced proliferative capacity in renewing tissues due to persistent activation of DNA damage signalling and metabolic stress. This usually leads to systemic prioritization of repair and maintenance over growth, producing developmental slowdown and functional impairment across multiple organ systems (Ward, 1994; Hall & Giaccia, 2019; Azzam et al., 2012). [41,55,92,98,99,100,101]

2. System level integration

Postembryonic development integrates growth, organ maturation, endocrine regulation, neurobehavioural development, and reproduction. Chronic ionizing radiation disrupts these processes through cumulative genomic damage and persistent oxidative metabolic stress (UNSCEAR, 2008; Hall & Giaccia, 2019). At the system level, sustained activation of p53 dependent checkpoint signalling produces a shift in cellular resource allocation from proliferation (P) toward DNA repair, antioxidant defence, and damage containment. Because organ systems differ in proliferative dynamics and stem cell organization, radiation effects are non uniform, producing differential vulnerability across tissues. This generates a systemic trade off state in which organismal growth and differentiation are suppressed in favor of maintenance and survival pathways. The magnitude of this shift is determined by proliferative duration, turnover rate, endocrine sensitivity, and metabolic demand, providing a mechanistic basis for interspecific variability in postembryonic radiation sensitivity.

3. The effect of ionizing radiation on the processes of growth and ontogenesis of the main organ systems in the postembryonic development of vertebrates.

3.1 Growth and somatic development

Somatic growth relies on balanced stem cell proliferation, differentiation, and endocrine signalling. Chronic radiation disrupts this balance through persistent DNA damage and oxidative lesions, inducing checkpoint activation, proliferative arrest, and apoptosis of progenitor populations (Jackson and Bartek, 2009; Ciccia and Elledge, 2010). This reduces regenerative capacity and diverts metabolic resources toward repair processes.

At the organismal level, radiation impairs growth hormone and IGF-1 signalling, reducing mitogenic efficiency and peripheral responsiveness. The outcome is reduced growth plate activity, stunted linear growth, reduced body mass, delayed sexual maturation, and altered skeletal mineralisation. Severity depends on tissue turnover rate and endocrine sensitivity.

3.2 Nervous system and behavioural development

Neurodevelopmental tissues are highly radiosensitive due to prolonged progenitor activity and high energetic demand. Radiation induced DNA damage reduces neurogenesis through checkpoint activation and apoptosis, while mitochondrial dysfunction limits adenosine triphosphate availability required for synaptogenesis and circuit maturation (Azzam et al., 2012; Hall & Giaccia, 2019). This may produce impaired neuronal connectivity and disrupted network refinement, with long term consequences for behaviour and cognitive function.

3.3 The immune system

The immune system is highly sensitive due to continuous lymphocyte turnover and clonal expansion. Chronic radiation induces apoptosis in bone marrow and thymic populations via DNA damage checkpoints, leading to reduced immune cell abundance, impaired effector responses, and weakened immune surveillance (UNSCEAR, 2008; Hall & Giaccia, 2019).

3.4 The endocrine system

Endocrine disruption arises from damage to hormone producing tissues and regulatory feedback circuits. Radiation induces apoptosis in thyroid and gonadal tissues, reducing hormone output and suppressing systemic metabolic regulation (Hall & Giaccia, 2019). Secondary activation of the hypothalamic pituitary adrenal axis elevates glucocorticoids, further suppressing proliferation (P) and amplifying lymphoid atrophy. Gonadal dysfunction impairs steroidogenesis and delays reproductive maturation.

3.5 The reproductive system and reproductive development

Reproductive impairment results from combined germ cell loss, somatic gonadal damage, and endocrine disruption. Germ cells undergo checkpoint mediated apoptosis following DNA damage, while surviving cells may accumulate mutations and epigenetic instability (Jackson and Bartek, 2009; Hall and Giaccia, 2019). This is associated with reduced fertility, delayed reproductive maturation, and increased risk of heritable genomic instability.

3.6 Respiratory system

Respiratory effects arise from epithelial DNA damage and oxidative stress, particularly following inhalation of radionuclides. Chronic injury usually leads to impaired epithelial regeneration, inflammatory signalling, and fibrotic remodeling, reducing gas exchange efficiency (UNSCEAR, 2008).

3.7 Skin and integumentary system

The integument is directly exposed to external radiation, leading to epidermal stem cell depletion, lipid peroxidation, and dermal fibrosis (Hall and Giaccia, 2019; UNSCEAR, 2008). Reduced keratinocyte proliferation (P) impairs barrier repair, while hair follicle stem cell loss reduces regenerative capacity.

Across organ systems, chronic ionizing radiation induces a convergent biological state characterized by persistent DNA damage signalling, oxidative stress, and suppression of proliferative activity. Developmental outcome is therefore determined not solely by absorbed dose, but by the interaction between proliferative duration, metabolic demand, and tissue specific regenerative capacity.

This framework is consistent with a mechanistic interpretation in which interspecific variability in postembryonic developmental sensitivity under equivalent exposure conditions and supports the hypothesis that species with extended proliferative developmental windows experience greater cumulative impairment. The effects are interpreted in the Supplementary Table 6.

Supplementary Table 6. Conceptual framework integrating biological modifiers of developmental radiosensitivity during chronic ionizing radiation exposure in vertebrates. The

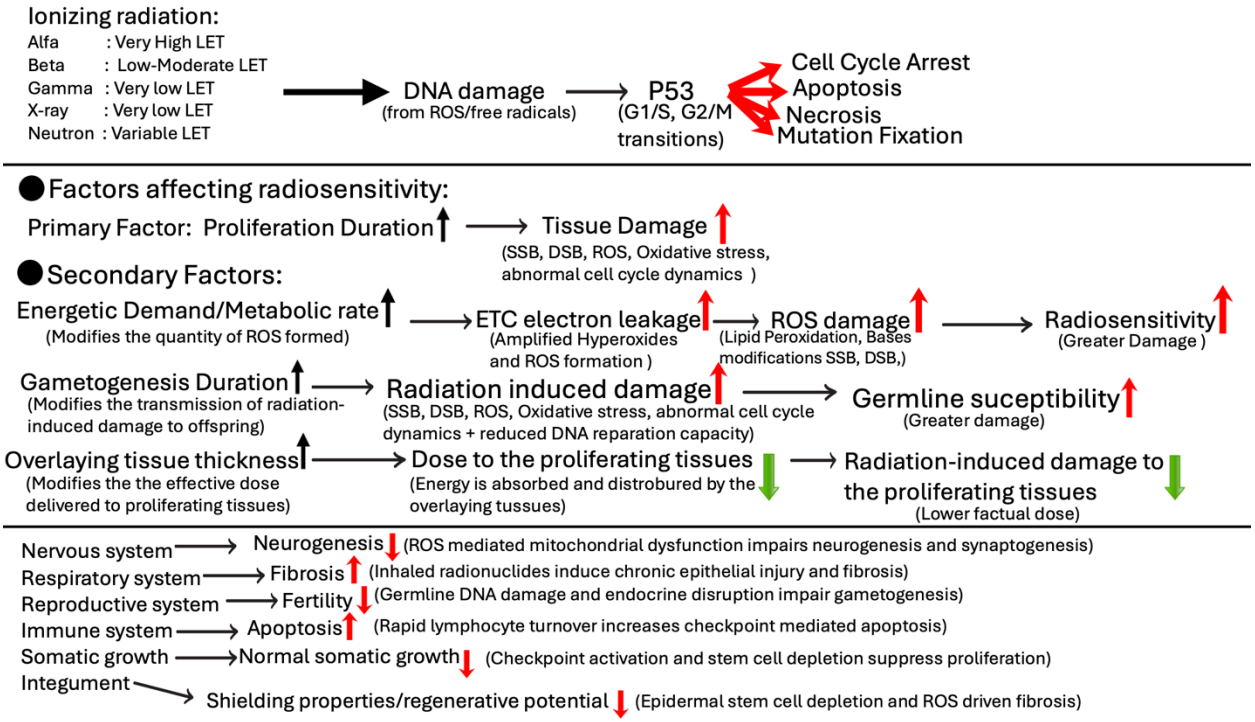
framework presented here should be interpreted as a mechanistic synthesis integrating current evidence and generating mechanistically derived directional expectations rather than as a quantitatively calibrated model, the magnitude of these effects is context-dependent and may vary with dose rate, life stage, and species-specific physiology. Interactions between variables are non-linear and may be synergistic or compensatory [67, 76, 89, 94, 95, 96, 97, 106, 107], [18, 27, 57, 60, 65, 69, 72, 86, 88], [4, 23, 28, 58, 79, 102].

Organ, organ system or process	**Mechanism**	**Outcome**	**Interspecific susceptibility variable**	**Link to the hypothesis**
Somatic growth	Checkpoint activation and stem cell depletion suppress proliferation	Growth retardation and delayed maturation	Duration of postembryonic proliferation dependent on GH, IGF and metabolic rate	Species with prolonged developmental growth phases accumulate greater proliferative suppression under chronic exposure
Nervous system	ROS mediated mitochondrial dysfunction impairs neurogenesis and synaptogenesis	Cognitive and behavioral deficits	Length of neurodevelopmental window and energetic demand	Species with extended neural maturation remain susceptible to lesion fixation for longer periods
Immune system	Rapid lymphocyte turnover increases checkpoint mediated apoptosis	Immunosuppression	Immune turnover rate, metabolic activity	High turnover immune systems accumulate greater cumulative proliferative damage
Reproductive system	Germline DNA damage and endocrine disruption impair gametogenesis	Reduced fertility and reproductive success	Duration of reproductive maturation and radionuclide accumulation	Extended reproductive development increases cumulative germline exposure
Respiratory system	Inhaled radionuclides induce chronic epithelial injury and fibrosis	Reduced respiratory efficiency	Ventilation rate; habitat exposure	Species with high metabolic demand or higher airborne exposure accumulate higher internal dose
Integumentary system	Epidermal stem cell depletion and ROS driven fibrosis	Barrier dysfunction and impaired regeneration	Surface exposure, epithelial turnover	Greater environmental contact increases local tissue burden

Integrative effect to the organism	Persistent proliferative suppression and oxidative stress reprogram development	Developmental instability and reduced fitness	Proliferative duration, radionuclide retention and metabolic rate	Developmental radiosensitivity is determined more strongly by biological integration of dose than by ambient external dose alone

This conceptual model generates several potentially testable expectations. First, vertebrate species with longer postembryonic developmental periods are expected to exhibit greater cumulative developmental impairment under comparable chronic radiation exposure. Second, tissues characterized by prolonged stem cell activity and high proliferative turnover are predicted to show stronger radiation-associated dysfunction than tissues with lower proliferative demand. Third, species with prolonged gametogenesis or higher mass-specific metabolic rates are expected to experience amplified developmental defects due to increased internal dose and oxidative stress burden. Finally, Developmental impairment is expected to correlate more strongly with cumulative biologically effective dose integrated across development than with ambient external dose rate alone Supplemental Figure 3 (UNSCEAR, 2008; Hall & Giaccia, 2019; Azzam et al., 2012). Collectively, the mechanisms summarized throughout this section provide the mechanistic basis for the proposed hypothesis that variation in developmental duration, proliferative activity and metabolic demand contribute to interspecific differences in developmental radiosensitivity under equal external doses of chronic ionizing radiation. However, the relative contribution of developmental duration, metabolic rate, radionuclide accumulation, and tissue architecture remains difficult to quantify across vertebrate taxa because standardized comparative datasets are limited.

Supplementary Figure 3. A schematic, summarizing the mechanistic aspects of the proposed hypothesis, with a focus on the interspecific modifiers of tissue radiosensitivity within proliferating cells. This framework integrates established radiobiological mechanisms with hypothesis-driven extrapolations and should be interpreted as a qualitative model requiring empirical validation. [8,11,12,34,44,45,58,71,89,91], [15,54,97,102,104], [16,37,70,96].



S2. Data extraction and thematic synthesis approach

Thematic analysis

Selection Criteria

A deductive thematic synthesis approach was applied to a previously compiled systematic review dataset (n = 20) and additional peer-reviewed studies selected to address predefined mechanistic domains, including radionuclide transfer, internal dose formation, oxidative stress, DNA damage response, and proliferative tissue sensitivity. Studies were coded against these domains using a structured extraction matrix. Additional studies were included using theoretical sampling to improve mechanistic coverage within the predefined framework. The results of this thematic analysis are shown in Supplementary Table 7.

The thematic synthesis dataset (n = 9) was assembled through purposive theoretical sampling to ensure coverage of predefined mechanistic domains. Although partially overlapping with the systematic review dataset (n = 20), the thematic synthesis was constructed separately to address specific mechanistic questions.

This study formalises a multi-scale mechanistic framework linking environmental radiation exposure to interspecific variation in developmental outcomes through a structured input–process-output architecture. The model defines environmental and biological exposure variables as inputs**,** biophysical and cellular mechanisms as transformation processes, and developmental sensitivity as emergent outputs modulated by organismal traits. This framework is intended as a conceptual, hypothesis-generating synthesis rather than a quantitative predictive model.

Inputs (I) comprise: (i) environmental radionuclide availability and spatial distribution, (ii) ecological transfer parameters governing trophic uptake and biomagnification, and (iii) species-specific ecological and physiological traits influencing exposure acquisition (e.g., feeding ecology, habitat use, and life-history strategy). These inputs determine the magnitude and pathway of internal radionuclide incorporation across organisms.

Process layer (P) consists of sequential mechanistic transformations operating across scales: (i) radionuclide ingestion and internal dose formation (M1), (ii) ionising radiation-induced water radiolysis and reactive oxygen species (ROS) generation (M2), (iii) induction of DNA damage, checkpoint activation, and repair pathway engagement (M3), and (iv) modulation of damage fixation probability by tissue proliferative activity, developmental stage, and stem-cell turnover dynamics (P/M4). These processes collectively define the translation of absorbed radiation energy into biological injury and repair outcomes.

Outputs (O) are defined as measurable or inferable biological consequences, including: (i) cellular-level outcomes (e.g., survival, apoptosis, mutational fixation, and proliferative arrest), (ii) tissue-level effects (e.g., impaired neurogenesis, hematopoietic disruption, and developmental patterning defects), and (iii) organismal-level variation in developmental sensitivity and fitness-related traits across species under equivalent external exposure conditions.

Within this framework, interspecific differences in developmental radiosensitivity emerge as a function of variation in both exposure acquisition (input heterogeneity) and damage propagation/repair dynamics (process heterogeneity), rather than differences in absorbed dose alone. The model is mechanistically structured but not parameterised as a quantitative dose-response system; instead, it generates directional expectations regarding relative sensitivity and exposure-outcome coupling across vertebrate taxa. Each mechanistic level (I, P, O) is explicitly mapped to corresponding literature-derived domains (Table S7–S9). Study inclusion for thematic synthesis was not intended to be exhaustive, but purposefully structured to achieve mechanistic domain saturation.

Supplementary Table 7. Thematic analysis of 9 manually selected studies with their relevance to the mechanistic directional expectations in the hypothesis.

Study	**Empirical Focus**	**Mechanistic domain targeted**	**Contribution to the hypothesis components**	**Interpretive support derived**
1. Belyaev et al. (2023)	Radionuclide exposure and ecological effects in fish within contaminated aquatic systems	Environmental exposure is associated with organismal bioaccumulation	Supports internal radionuclide incorporation in aquatic vertebrates and links habitat contamination to	Provides ecosystem level evidence that environmental contamination translates into biologically relevant internal exposure, indirect support for

			biological dose variability	interspecific exposure variability
2. Metian et al. (2019)	Radiocesium transfer and bioaccumulation in aquatic food webs	Trophic transfer and bioaccumulation dynamics	Consistent with the hypothesis that dietary exposure and trophic position determine internal radionuclide burden	Provides robust mechanistic evidence that internal dose is governed primarily by ecological transfer pathways rather than ambient exposure
3. Smith et al. (2003)	Potassium chloride intervention in Chernobyl contaminated lake system	Modulation of radionuclide uptake	Demonstrates that environmental chemistry can significantly alter organismal radionuclide uptake and internal dose	Experimental evidence supporting causality between environmental availability and internal dose acquisition
4. Dighton et al. (2008)	Radionuclide accumulation in fungi and ecological implications	Invertebrate bioaccumulation and environmental retention	Extends internal dose framework to additional biological reservoirs, indicating long term ecosystem redistribution of radionuclides	Supports ecological persistence and secondary exposure pathways contributing to cumulative dose
5. Pimblott & LaVerne (2017)	Radiolysis of water and ROS production under ionizing radiation	Ionizing radiation chemistry and oxidative stress initiation	Establishes primary physicochemical mechanism generating ROS following ionizing radiation exposure	Provides foundational mechanistic basis for indirect radiation-induced biological damage through ROS formation
6. Karabuluto glu et al. (2021)	X-ray induced oxidative stress and metabolic effects in murine hematopoietic stem and progenitor cells	Cellular oxidative stress and proliferative vulnerability	Supports increased sensitivity of proliferative cell populations to radiation-induced oxidative damage	Demonstrates dose dependent cellular dysfunction in radiosensitive proliferative systems
7. Friedberg (2003)	DNA damage and repair mechanisms in response to ionizing radiation	Genomic instability and repair pathways	Consistent with the hypothesis that proliferative tissues are disproportionately vulnerable due to replication-associated DNA damage	Provides mechanistic basis for developmental susceptibility in proliferating and rapidly dividing tissues

8. Azzam et al. (2012)	Radiation-induced adaptive and oxidative stress responses	ROS signalling and cellular adaptation to oxidative stress	Supports the role of ROS as both damaging and signalling mediator in radiation response pathways	Demonstrates complexity of oxidative stress responses, including adaptive and regulatory mechanisms
9. Fisher & Fowler (2005)	Radionuclide transfer across marine food webs	Ecological transfer and biomagnification	Provides conceptual and empirical framework for trophic level dependent radionuclide exposure	Establishes ecological basis for variability in internal dose driven by feeding ecology and trophic structure

Across ecological systems, radionuclide transfer through trophic networks is consistently identified as a primary determinant of organismal exposure. Research demonstrates that radiocesium is efficiently incorporated into aquatic food webs, resulting in measurable bioaccumulation in organisms and making internal exposure strongly dependent on dietary and trophic pathways (Metian et al., 2018; Fisher & Fowler, 2005). Empirical evidence from contaminated fish populations further suggests that internal radionuclide burdens are directly associated with environmental contamination conditions (Belyaev et al., 2023). Experimental manipulation of contaminated ecosystems shows that reducing environmental availability of radionuclides significantly decreases organismal uptake, reinforcing the role of internal dose as a key exposure determinant (Smith et al., 2003). In addition, fungal accumulation studies demonstrate that radionuclides are retained across multiple biological compartments, contributing to long term environmental redistribution and secondary exposure pathways (Dighton et al., 2020).

At the molecular level, ionizing radiation interacts with biological systems primarily through water radiolysis, resulting in the generation of reactive oxygen species (ROS), as widely reported in radiochemical literature (Pimblott & LaVerne, 2017). These ROS (M2), can induce oxidative stress, which has been widely implicated as a central mediator of radiation-induced biomolecular damage. Oxidative stress contributes to DNA lesions, including strand breaks and base modifications, which are particularly significant in proliferative tissues due to replication associated vulnerability (Friedberg, 2003). Cellular studies further demonstrate that radiation exposure induces dose dependent oxidative stress responses and metabolic disruption in hematopoietic progenitor cells (Karabulutoglu et al., 2021). Radiation exposure also activates complex stress response pathways in which ROS (M2) function both as damaging agents and signalling molecules involved in adaptive and regulatory cellular responses (Azzam et al., 2012).

Although ecological and cellular studies operate at different biological scales, their findings converge on a mechanistic pathway directly relevant to the proposed hypothesis. Radionuclide transfer through food webs determines the magnitude of internal exposure (Metian et al., 2018; Fisher & Fowler, 2005), while cellular studies demonstrate that internalised radiation generates

reactive oxygen species, DNA damage, and activation of checkpoint-mediated repair pathways (Pimblott & LaVerne, 2017; Azzam et al., 2012; Jackson & Bartek, 2009). Because these processes disproportionately affect proliferating cell populations, their developmental consequences are expected to accumulate over time through replication-associated lesion fixation and progressive stem cell depletion.

Species with longer periods of postembryonic growth and tissue maturation experience a greater number of cell divisions and prolonged dependence on stem-cell-driven tissue maintenance, thereby increasing the probability of radiation-induced damage propagation and proliferative disruption. Consequently, equivalent environmental exposure may plausibly contribute to divergent developmental outcomes among species depending on differences in life history traits, tissue turnover rates, and internal radionuclide accumulation dynamics. (UNSCEAR, 2008; Hall & Giaccia, 2019).

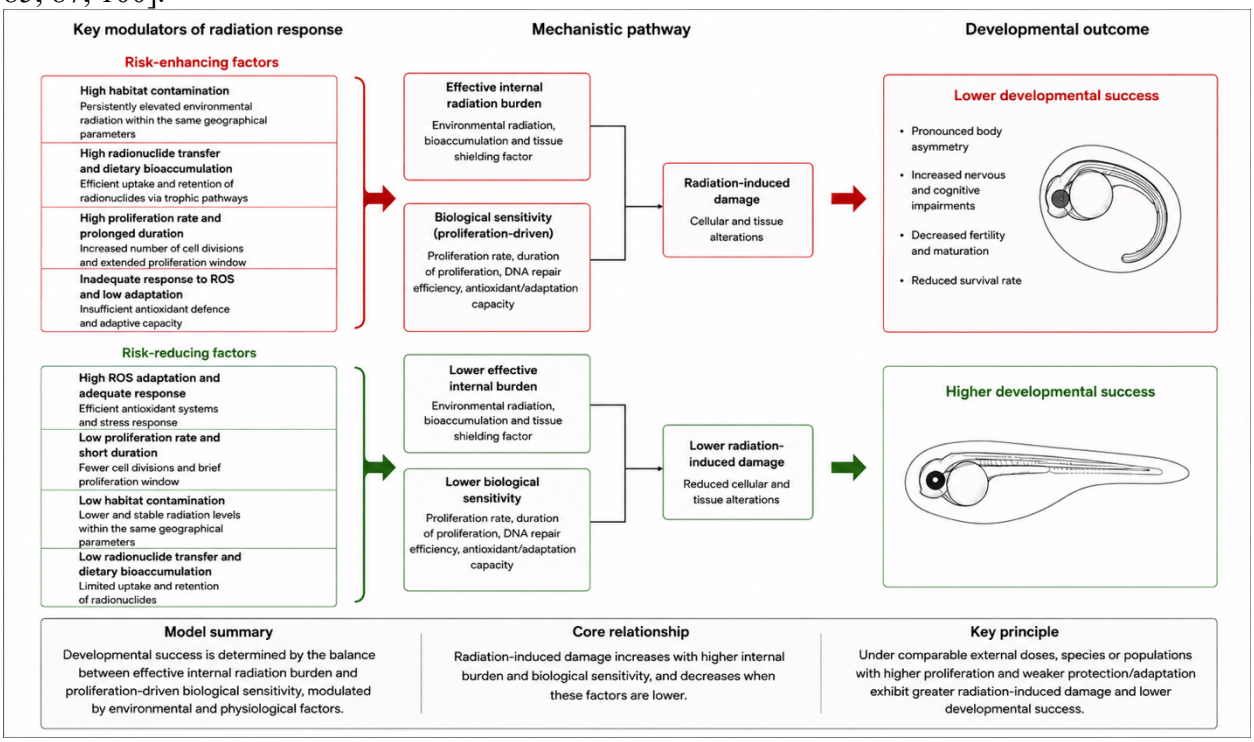
This integrated framework links environmental contamination to internal dose formation and downstream cellular injury, consistent with mechanistic explanations for interspecific variation in developmental sensitivity under chronic ionising radiation exposure.

It is important to emphasize that this thematic analysis does not provide direct empirical measurement of interspecific developmental impairment in vertebrates under chronic environmental radiation exposure. Instead, it synthesises mechanistic evidence across ecological and cellular domains to construct a plausible explanatory model. Accordingly, this mechanistic framework is consistent with the hypothesis and provides a plausible explanation for interspecific variation, but direct empirical testing is required rather than direct observational validation across all biological levels. The absence of direct developmental datasets linking internal radionuclide dose variation to vertebrate life history outcomes represents a limitation of the current evidence base. This framework is mechanistically derived and not intended as a quantitative dose-response model.

In conclusion, the integrated evidence supports a mechanistically consistent model in which internal radionuclide accumulation is a key determinant of effective biological dose. Together, ecological and cellular evidence are consistent with a mechanistically coherent framework linking environmental radionuclide transfer to internal exposure and downstream biological effects. Radionuclide movement through food webs contributes to variability in internal dose, while internalised ionizing radiation induces oxidative stress, DNA damage, and activation of checkpoint-mediated repair pathways. These processes preferentially affect proliferating cell populations and may accumulate over developmental time, depending on tissue turnover and metabolic demand. Variation in developmental outcomes among species is consistent with differences in exposure duration, physiological rate, and internal radionuclide accumulation. This framework is mechanistically derived, does not constitute a quantitative dose-response model, and instead generates hypotheses for future empirical testing of interspecific differences in developmental sensitivity under chronic radiation exposure.

Supplementary Figure 4 Summarizes the interspecific physiological aspects of vertebrates, that modulate radiosensitivity, factual dose and developmental outcome, with the same external dose, based on the results of the thematic analysis. [8,11,12,34,44,45,58,71,89,91], [8, 11, 12, 33, 36,

85, 87, 100].



S3. Organization of the Evidence Base

The the evidence base comprises three evidence tiers: (i) studies included in the systematic review (n = 20), (ii) studies used in the thematic synthesis (n = 9), and (iii) foundational literature used for mechanistic evaluation, structural consistency, and contextual comparison.

Systematic review studies were selected using predefined inclusion and exclusion criteria applied to a structured literature search. In contrast, studies included in the thematic synthesis were selected purposively to ensure coverage of predefined mechanistic domains and to address conceptual gaps identified during systematic screening. Foundational literature was selected based on established relevance to radiobiological mechanisms, oxidative stress pathways, and ecological dosimetry frameworks, including widely accepted theoretical and regulatory sources. Literature included in Table 10 was selected a priori based on its foundational role in defining mechanistic components (P, M1–M4) or establishing canonical dose-response and radiobiological principles. The evidence base was structured into three hierarchical layers corresponding to their role in model construction, evaluation and structural consistency assessment:
(i) primary empirical studies used for systematic parameter extraction,
(ii) mechanistic enrichment studies used for domain completion,
(iii) foundational theoretical and regulatory sources used for structural consistency assessment and explanatory ability of the framework.

Each dataset is fully documented in Supplementary Tables 8–10.

Supplementary Table 8. A full list of scientific literature included in the systematic analysis, with key conclusions and a stable reference to the relevant source.

ID	Main Authors and Shortened title	Year	Scientific Journal or Source	Key Findings	Permanent link
1	Zhu Y, Lv Q, Yang T, et al. Ionizing radiation (IR) induces sex-specific reproductive and developmental toxicity in zebrafish.	2025	ScienceDirect	Chronic ionizing radiation exposure reduces reproductive success, altered gonadal development, and increased offspring developmental abnormalities in a sex dependent manner	https://www.sciencedirect.com/science/article/abs/pii/S0141113625007202
2	Hurem S, Martín LM, Brede DA, et al. Dose-dependent effects of gamma radiation on early zebrafish development and gene expression.	2017	PLOS ONE	Increasing gamma dose produced delayed embryogenesis, increased malformations, impaired hatching success, and altered developmental gene-expression pathways	https://doi.org/10.1371/journal.pone.0179259
3	E. Pasqual, et al. Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence	2020	Environment International	Low-dose developmental radiation exposure was linked to cognitive deficits, impaired neurodevelopment, and behavioral abnormalities	https://www.sciencedirect.com/science/article/pii/S0160412019317076
4	Verreet T, Verslegers M, Quintens R, et al. Prenatal ionizing radiation exposure and cortical migration defects	2016	PMC	Radiation disrupted cortical layering, neuronal migration, and fetal brain organization	https://pmc.ncbi.nlm.nih.gov/articles/PMC4921147/
5	Antonelli F, Casciati A, et al. Long-Term Effects of Ionizing Radiation on the Hippocampus: Linking Effects of the Sonic Hedgehog Pathway Activation with Radiation Response	2022	PubMed	Radiation reduced hippocampal neurogenesis and altered regenerative signaling pathways associated with neural stem-cell maintenance	https://pubmed.ncbi.nlm.nih.gov/34830484/
6	Isabell Prager, et al. Dose-dependent short- and long-term effects of ionizing	2016	PMC	Radiation-Induced White Matter and Hippocampal Disruption Driving Long-Term Pediatric Cognitive Decline	https://pmc.ncbi.nlm.nih.gov/articles/PMC5064349/

	irradiation on neural stem cells in murine hippocampal tissue cultures: neuroprotective potential of resveratrol				
7	Matsuya Y, et al. Dose-rate effects in radiation-induced cellular biological damage, focused on the cell cycle dynamics	2018	Scientific Reports	Biological damage varied substantially depending on radiation dose rate despite comparable cumulative doses	https://doi.org/10.1038/s41598-018-26556-5
8	D. Einor, et al. Ionizing radiation, antioxidant response and oxidative damage: A meta-analysis	2016	PubMed	Ionizing radiation increased ROS production, oxidative macromolecular damage, and compensatory antioxidant responses	https://pubmed.ncbi.nlm.nih.gov/26851726/
9	Upadhyayula Sai Srinivas, et al. ROS and the DNA damage response in cancer	2018	PubMed	Ionizing radiation persistently disrupted cellular redox signaling and oxidative homeostasis	https://pubmed.ncbi.nlm.nih.gov/30612957/
10	Jasminka Talapko, et al. Health Effects of Ionizing Radiation on the Human Body	2024	PMC	Exposure to ionizing radiation altered developmental gene-expression pathways involved in cell cycle regulation, apoptosis, and tissue differentiation	https://pmc.ncbi.nlm.nih.gov/articles/PMC11052428/
11	Wang Z, Zhang J. Genetic and epigenetic effects of developmental radiation exposure	2024	PubMed	Reveals long-term toxicities in childhood cancer survivors are driven by a complex interplay of treatment-induced genotoxicity, inherited genetic variations, and persistent epigenetic remodeling.	https://pubmed.ncbi.nlm.nih.gov/39511414/
12	Saurabh Saini, et al. Radiation-induced DNA damage sensing and immune response pathways	2025	PubMed	Ionizing Radiation activated DNA repair pathways, apoptosis signaling, and inflammatory immune responses	https://pubmed.ncbi.nlm.nih.gov/39425547/
13	Mohsen Mohammadgholi, et al. Crosstalk between oxidative stress and inflammation induced by ionizing radiation	2024	PubMed	Radiation-induced oxidative stress increased the inflammatory signaling and secondary tissue injury	https://pubmed.ncbi.nlm.nih.gov/37026495/

14	Salma Akter, et al. Assessing the Risks of Prenatal Radiation: Effects on Pregnancy and Neonatal Development	2025	PubMed	Prenatal and perinatal radiation exposure disrupted organogenesis, growth, and physiological development across multiple organ systems	https://pmc.ncbi.nlm.nih.gov/articles/PMC12563580/
15	UNSCEAR. Sources, Effects and Risks of Ionizing Radiation	2021	United Nations (UNSCEAR)	Postembryonic irradiation may cause organ-specific damage, notably affecting the thyroid, marrow, and brain, leading to growth suppression through chondrocyte injury. Long lifespans elevate the long-term risk of solid tumors and accelerated tissue aging.	https://www.unscear.org/unscear/en/publications/2020_2021_1.html
16	Bossew P, et al. Estimating terrestrial gamma dose rate by decomposition of ambient dose equivalent rate	2017	Journal of Enviormental Radioactivity	Environmental gamma exposure varied spatially according to radionuclide distribution and terrestrial conditions	https://www.sciencedirect.com/science/article/abs/pii/S0265931X16300364
17	Jelin BA, et al. Quantifying annual internal effective 137Cs dose using body-burden measurement	2015	PubMed	Internal cesium bioaccumulation contributed substantially to total effective dose and varied among individuals	https://pubmed.ncbi.nlm.nih.gov/25757885/
18	Steinhauser G, Saey PRJ. 137Cs in wild boar meat: Chernobyl vs Fukushima	2016	Journal of Radioanalytical and Nuclear Chemistry	Wild boars exhibited prolonged radiocesium retention due to ecological and dietary characteristics	https://doi.org/10.1007/s10967-015-4417-6
19	Tagami K, Howard BJ, Uchida S. Time-dependent transfer factor of radiocesium in Japan	2016	Environmental Science & Technology	Radiocesium transfer from soil to animals differed substantially among habitats and species over time	https://pubs.acs.org/doi/10.1021/acs.est.6b03011
20	Beresford NA, et al. Radionuclide transfer to wildlife in the Chernobyl Exclusion Zone	2018	Journal of Environmental Radioactivity	Wildlife species occupying different ecological niches accumulated markedly different radionuclide burdens and effective doses	https://www.sciencedirect.com/science/article/pii/S0265931X17309384

Supplementary Table 9. A full list of scientific literature included in the thematic analysis, with key conclusions and a stable reference to the relevant source.

Number	Reference Shortened title and Main authors	Year of Publishment	Journal/Source	Key finding	Permanent link

1	Belyaev VV, Volkova OM, Gudkov DI, Prishlyak SP, Skyba VV. Radionuclide exposure and ecological impacts on fish in contaminated aquatic systems.	2023	ScienceDirect	Internal radionuclide incorporation in aquatic vertebrates and links habitat contamination to biological dose variability	https://www.sciencedirect.com/science/article/abs/pii/S0265931X23000620
2	Metian M, Pouil S, Fowler SW. Radiocesium transfer and bioaccumulation in aquatic food webs.	2018	ScienceDirect	Dietary exposure and trophic position determine internal radionuclide burden	https://www.sciencedirect.com/science/article/abs/pii/S0265931X1830568X
3	Smith J, & Bulgakov A. Application of potassium chloride to a Chernobyl-contaminated lake ecosystem.	2003	University of Portsmouth Research Portal (PubMed)	Environmental chemistry can significantly alter organismal radionuclide uptake and internal dose	https://pubmed.ncbi.nlm.nih.gov/12670770/
4	Dighton, J, et, al. Fungi and ionizing radiation from radionuclides.	2008	Oxford Academic FEMS Microbiology Letters	Extends internal dose framework to additional biological reservoirs, indicating long term ecosystem redistribution of radionuclides	https://doi.org/10.1111/j.1574-6968.2008.01076.x
5	Pimblott SM, LaVerne JA. Et, al. Inhibition of Radiolytic Molecular Hydrogen Formation by Quenching of Excited State Water.	2017	The Journal of Physical Chemistry	Primary physicochemical mechanism generating ROS following ionizing radiation exposure	https://arxiv.org/abs/1702.06161
6	Karabulutoglu M, Finnon R, Cruz-Garcia L, Hill MA, Badie C. Oxidative stress and X-ray exposure–dependent survival and metabolic changes in murine HSPCs.	2021	PubMed	Increased sensitivity of proliferative cell populations to radiation-induced oxidative damage	https://pubmed.ncbi.nlm.nih.gov/35052515/
7	Friedberg EC. DNA damage and repair.	2003	Nature	Proliferative tissues are disproportionately vulnerable due to replication-associated DNA damage	https://www.nature.com/articles/nature01408
8	Azzam EI, Jay-Gerin J-P, Pain D. Ionizing radiation-induced adaptive responses.	2012	Free Radical Biology and Medicine	ROS acting as both damaging and signalling mediator in radiation response pathways	https://pubmed.ncbi.nlm.nih.gov/22182453/
9	Fisher NS, Fowler SW. Transfer of metals and radionuclides in marine food webs.	2005	Inter-Research Marine Ecology Progress Series Journal	Ecological basis for variability in internal dose driven by feeding ecology and trophic structure	https://www.int-res.com/journa

					ls/meps/articles/meps290027

Supplementary Table 10. A full list of scientific literature included in the structural consistency and expectation assessment procedure, with key findings and links to the relevant sources. Literature included in this section was selected to evaluate structural consistency and directional expectations of the mechanistic framework across classical radiobiology, oxidative stress biology, and ecological dosimetry domains. Selection was based on their established role in defining radiosensitivity, dose-response relationships, oxidative stress mechanisms, or ecological transfer models.

Authors	Year	Shortened Title	Source	Key Finding	Permanent link
Bergonié J, Tribondeau L	1906 (reprinted 2003)	Interpretation of some results from radiotherapy and an attempt to determine a rational treatment technique	Yale Journal of Biology and Medicine	Established foundational relationship between tissue proliferation and radiosensitivity. Rapidly dividing cells are most sensitive	https://pmc.ncbi.nlm.nih.gov/articles/PMC2582716/
Vogin G, Foray N	2013	The law of Bergonié and Tribondeau: A nice formula for a first approximation	International Journal of Radiation Biology	Formalized proliferation–differentiation law as predictive framework for radiosensitivity	https://doi.org/10.3109/09553002.2012.717732
Tucker SL, Turesson I, Thames HD	1992	Evidence for individual differences in the radiosensitivity of human skin	European Journal of Cancer	Demonstrated variability in tissue radiosensitivity within individuals	https://www.sciencedirect.com/science/article/abs/pii/095980499290004L
Withers HR	1992	Biological basis of radiation therapy for cancer	The Lancet	Showed proliferative fraction as key determinant of tumor radiosensitivity	https://doi.org/10.1016/0140-6736(92)90218-R

Mauch P et al.	1995	Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy	International Journal of Radiation Oncology Biology Physics	Identified extreme radiosensitivity of stem/progenitor compartments	https://doi.org/10.1016/0360-3016(94)00430-S
Spitz DR et al.	2004	Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation	Cancer Metastasis Reviews	Linked oxidative metabolism to radiation response and stress amplification	https://doi.org/10.1023/B:CANC.0000031769.14728.bc
Yamamori T et al.	2012	Ionizing radiation induces mitochondrial reactive oxygen species production, in context under controll of the cell cycle checkpoint	Free Radical Biology and Medicine	Demonstrated mitochondrial ROS amplification after irradiation	https://doi.org/10.1016/j.freeradbiomed.2012.04.033
Bedard K et al.	2012	NOX5: from basic biology to signaling and disease	Free Radical Biology and Medicine	Showed enzymatic ROS generation as mediator of oxidative stress	https://doi.org/10.1016/j.freeradbiomed.2011.11.023
Durante M, Cucinotta F	2008	Heavy ion carcinogenesis and human space exploration	Nature Reviews Cancer	Described environmental radiation field effects and high LET sensitivity	https://doi.org/10.1038/nrc2391
Pan K, Wang WX	2016	Radiocesium uptake, trophic transfer, and exposure in three estuarine fish	Chemosphere	Showed trophic transfer as determinant of internal radionuclide exposure	https://www.sciencedirect.com/science/article/abs/pii/S0045653516310840?via%3Dihub
Howard BJ et al.	1991	Transfer of radiocesium to ruminants	Health Physics	Demonstrated dietary transfer and internal dose accumulation	https://doi.org/10.1097/00004032-199112000-00002

Howard BJ et al.	2001	Countermeasures for animal products: a review of effectiveness and potential usefulness after an accident	Journal of Environmental Radioactivity	Showed ecological countermeasures and transfer modulation	https://doi.org/10.1016/S0265-931X(01)00050-9
Bazala MA et al.	2008	Transport of radiocesium in mycelium	Journal of Environmental Radioactivity	Demonstrated strong bioaccumulation in fungal systems	https://doi.org/10.1016/j.jenvrad.2008.01.004
Garnier-Laplace J et al.	2013	Radiosensitivity under field conditions in Chernobyl wildlife	Journal of Environmental Radioactivity	Showed ecological variability in chronic radiation exposure responses	https://doi.org/10.1016/j.jenvrad.2012.01.013
Vives i Batlle J et al.	2007	Inter-comparison of absorbed dose rates for non-human biota	Radiation and Environmental Biophysics	Demonstrated variability in dose distribution across species	https://doi.org/10.1007/s00411-007-0124-1
Copplestone D et al.	2008	The FREDERICA radiation effects database development	Journal of Environmental Radioactivity	Provided integrated ecological radiation effects database	https://doi.org/10.1016/j.jenvrad.2008.01.006
Bréchignac F et al.	2016	Ecological effects of radiation on populations and ecosystems to improve protection of the environment against radiation	Journal of Environmental Radioactivity	Established ecosystemic level radiation protection framework	https://doi.org/10.1016/j.jenvrad.2016.03.021
Ulanovsky A, Pröhl G	2012	Dosimetry for reference animals and plants	Annals of the ICRP	Standardized ecological dosimetry models	https://doi.org/10.1016/j.icrp.2012.06.034

Valentin J.	2002	ICRP reference anatomical and physiological values	Annals of the ICRP	Provided standardized physiological reference parameters	https://doi.org/10.1016/S0146-6453(03)00002-2
UNSCEAR	1993	Sources and effects of ionizing radiation: UNSCEAR 1993 report	UNSCEAR	Radiation effects cannot be predicted from absorbed dose alone; biological response depends on the interaction of dose, dose rate, exposure conditions, and characteristics of the exposed biological system	https://www.unscear.org/unscear/en/publications/1993.html

Supplementary Table 11. Results of the qualitative structural consistency assessment of the mechanistic radiosensitivity framework. Studies were classified according to directional agreement between framework-derived expectations and reported empirical findings (consistent, partially consistent, or inconsistent). Consistency classifications indicate compatibility with the proposed framework but do not constitute independent validation.

Study	Model component	Predicted directional relationship	Observed directional relationship	Qualitative classification
Bergonié & Tribondeau (1906/2003)	P	Higher proliferative activity increases radiosensitivity	Rapidly dividing cells are more radiosensitive	Consistent
Vogin & Foray (2012)	P	Proliferation state determines radiosensitivity ranking	Radiosensitivity follows proliferation-based rule	Consistent
Tucker et al. (1992)	M3	Tissue intrinsic properties modify sensitivity variability	Human skin shows inter-individual radiosensitivity variation	Partially consistent
Withers (1992)	P	High proliferative fraction increases radiation response	Tumors with high proliferation are more sensitive	Consistent
Mauch et al. (1995)	P	Stem/progenitor compartments show highest sensitivity	Hematopoietic stem cells highly radiosensitive	Consistent
Spitz et al. (2004)	M2	Oxidative metabolism amplifies radiation response	Redox-linked metabolic reactions enhance stress response	Consistent
Yamamori et al. (2012)	M2	Mitochondrial activity increases	Radiation induces mitochondrial ROS production	Consistent

		ROS-mediated damage		
Bedard et al. (2012)	M2	Enzymatic ROS generation amplifies cellular injury	NOX family increases oxidative stress signaling	Consistent
Durante & Cucinotta (2008)	M4	Environmental radiation field intensity increases damage risk	High LET radiation increases biological damage	Consistent
Pan & Wang (2016)	M1	Dietary transfer increases internal radionuclide dose	Radiocesium accumulates via trophic transfer	Consistent
Howard et al. (1991)	M1	Dietary intake increases internal contamination burden	Ruminants accumulate radiocesium via feed	Consistent
Howard et al. (2001)	M1	Countermeasures reduce internal radionuclide load	Ecological interventions reduce transfer efficiency	Consistent
Bazala et al. (2008)	M1	Organisms concentrate radionuclides in tissues	Fungal systems strongly accumulate radiocesium	Consistent
Garnier-Laplace et al. (2013)	M4	Chronic field exposure modifies ecological radiosensitivity	Chernobyl wildlife shows exposure-dependent responses	Consistent
Vives i Batlle et al. (2007)	M3	Anatomical structure alters dose distribution	Species-specific absorbed dose rates vary	Consistent
Copplestone et al. (2008)	M4	Integrated ecological exposure frameworks predict effects	FREDERICA links exposure to ecological outcomes	Consistent
Bréchignac et al. (2016)	M4	Ecosystem-level exposure modifies population response	Radiation effects vary at ecological scale	Consistent
UNSCEAR (1993)	P and M1–M4	Biological response depends on system interactions rather than absorbed dose alone.	Dose-response is system-dependent and non-linear	Consistent