ACTA ZOOLOGICA BULGARICA

Acta Zool. Bulg., in press

Terrestrial Ecology and Behaviour
Research Article

Published online 02 July 2026
DOI: https://doi.org/10.71424/azb78.3.003119

Small Mammals as Model Organisms for Studying DNA Damage Induced by Ionising Radiation and Radiomimetic Compounds

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Academic Editor: *Roumiana Metcheva*

Abstract: Ionising radiation (IR) and radiomimetic compounds (RMCs) induce a wide range of DNA lesions, including single- and double-strand breaks and oxidative DNA base damage. This can lead to genomic instability, mutagenesis and carcinogenesis. Small mammals are key *in vivo* models for studying these processes due to their physiological relevance, well-characterised responses to genotoxic stress, and the availability of a wide range of transgenic strains. This review analyses the latest developments in selecting animal models and the usefulness of small mammals in radiation research. It offers an in-depth overview of radiomimetic compounds, including bleomycin, cyclophosphamide, etoposide, and mitomycin C, and their mechanisms of action in mammalian models. The evidence reviewed demonstrates the value of several established model animal lineages (mouse, rat, vole, hamster, guinea pig) in validating biomarkers of exposure and effect, evaluating radioprotective and radiosensitising agents, and understanding tissue-specific and adverse reactions. A comprehensive analysis of the biological, genetic, and physiological traits that determine each species' suitability for radiation research was presented, covering aspects such as genome conservation, homology of DNA repair pathways to humans, lifespan, and reproductive characteristics. This highlights the role of small mammals as crucial in vivo models for radiation research, aiding in concept validation, elucidation of mechanisms, and biomarker discovery.

Key words: DNA damage, ionising radiation, mammal model organisms, radiation effects, radiobiology, radiomimetics

Introduction

Ionising radiation (IR) has been intensively studied since the 1890s in medical contexts and since 1945 as an environmental hazard. IR is the scientific "umbrella term" for a range of photonic spectra and charged particles that cause ionisation. Photonic types of IR, including gamma (γ) rays and X-rays, are part of the electromagnetic spectrum. Particle-type radiation notably includes alpha (α) rays (helium nuclei), beta (β^-) rays (electrons), β^+ rays (positrons), protons, neutrons, and some cosmic rays, consisting often of heavy nuclei. There is a vast amount of data on the biological effects and environmental behaviour of IR and radioactive materials, and IR is probably the best-studied environmental genotoxin (Hall & Giaccia 2006; Ostoich 2024). Classical radiation biology identifies genomic DNA as the principal

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target of ionising radiation (Ballarini, 2010). Early micro-irradiation experiments in the 1970s demonstrated that the cellular nucleus is the most sensitive cellular compartment, with cytoplasmic irradiation requiring colossal doses (>250 Gy) to affect cell proliferation and viability (Munro, 1970). IR induces DNA damage through direct ionisation of DNA and indirect effects via radiolysis of water, generating reactive oxygen species (ROS) such as hydroxyl radicals (-OH), superoxide anions (O_2^-), and hydrogen peroxide (H_2O_2). These mechanisms produce diverse DNA lesions, including base damage, single-strand breaks (SSBs), double-strand breaks (DSBs), DNA-protein crosslinks, and clustered lesions. DSBs are considered the most critical lesions because they can cause chromosomal aberrations, genomic instability, and cell death if unrepaired or misrepaired (Goodhead 1994, Ward 1988). Nevertheless, many questions remain in both radiobiology and radioecology, particularly issues relating to 1) low-dose effects, 2) the individual differences in radiation sensitivity and cancer susceptibility, and 3) the potential for transgenerational effects of radiation damage, such as genomic instability.

Small mammal models have become the cornerstone of radiation biology research, bridging cellular studies and human applications. They have long been used to conduct studies in the biomedical sciences; mice of different colours were bred in early medieval China and Japan, and Gregor Mendel himself attempted to study mouse genetics (Nishioka 1995, Rader 1999, Wilson & Reeeder 2005). Wild rodent populations exposed to environmental radiation, particularly in the Chernobyl and Fukushima exclusion zones, offer unique opportunities to study the effects of chronic low-dose radiation in ecologically relevant contexts. Wild small mammals provide insights into mitochondrial responses, transgenerational effects, and evolutionary adaptations to sustained radiation exposure (Kesäniemi et al. 2020). Small mammals, particularly rodents (Rodentia), have been popular laboratory animals for several reasons: (1) their short life cycle, enabling the breeding and rearing of large numbers of animals (Nishioka 1995); (2) their biological similarity to humans, including the omnivorous dietary preferences of murine rodents and similar biological responses to environmental stressors (Ryabokon & Goncharova 2006, Post 2012); (3) their small size and the relatively low cost of maintaining large rodent colonies, which have historically enabled large-scale experimental studies involving very high numbers of animals (Russell & Russell 1992); (4) their well-characterised status, with many readily available genetic backgrounds, including many transgenic varieties (Nishioka 1995, Rader 1999); and (5) practical considerations, including short generation times, manageable husbandry, and ethical acceptability compared to larger animals.

Mammalian models are also essential for understanding the complex, multi-tissue, systemic responses to radiation and radiomimetic compounds. Small mammals offer several critical advantages: (1) physiological relevance, with undamaged organ systems, tissue structure and immune responses; (2) genetic adaptability, particularly in mice; (3) well-documented radiation responses and extensive historical databases; and (4) evolutionary similarity of DNA repair pathways and cellular stress responses with humans. Selecting the right model organisms is crucial for applying findings to human health. Different species exhibit varying degrees of radiation sensitivity, DNA repair capacity, metabolic characteristics and genomic similarity to humans. Furthermore, radiomimetic compounds, chemical agents that induce DNA damage similar to that caused by ionising radiation, provide additional experimental tools for investigating the mechanisms of DNA damage and repair. Understanding the comparative biology of small mammal models and the mechanisms of action of radiomimetic compounds is essential for designing informative experiments and interpreting results in the context of human radiation biology.

This review provides a comprehensive analysis of small mammal models for studying DNA damage induced by ionising radiation and radiomimetic compounds. We begin with a brief overview of radiation mechanisms and a section on radiomimetic compounds and their applications in mammalian models, followed by a detailed comparative biology of model organisms. We then conclude with a critical discussion of model selection criteria and future directions.

1. Types of DNA damage induced by IR and radiomimetics and their biological repair

1.1 Ionising radiation: types, mechanisms and the profile of IR-induced DNA damage

As already mentioned, IR encompasses electromagnetic radiation (X-rays, gamma rays) and particulate radiation (alpha particles, beta particles, protons, neutrons, heavy ions). These radiation types differ in linear energy transfer (LET), which describes the energy deposited per unit path length. Low-LET radiations (X-rays, gamma rays, beta particles) produce sparse ionisation tracks, while high-LET radiations (alpha particles, heavy ions) produce dense ionisation tracks with clustered damage (Goodhead, 1994). IR is remarkable for its low energy-to-effect ratio. A human

LD_{50} dose, delivered to an average 70 kg person, is just 4 Gy (1 Gy = 1 J/kg), or, in terms of calories, around 67 cal of thermal energy constitutes a lethal dose for the average person (Hall & Giaccia 2006, Ostoich 2024). Thermodynamically negligible (and undetectable by our senses) amounts of energy in the form of IR induce DNA damage, which alters cellular proliferation and can kill, at high doses, predictably and in a dose-dependent way (or "deterministically"), by inducing acute radiation syndrome (ARS), and, at lower doses, "stochastically" by causing malignancies, including solid cancers and leukemias (Dörr et al. 2017). In mammalian cells, 1 Gy of standard photonic radiation (for instance, γ-rays above 250 keV) induces, dependent on the animal species and cell type, approximately: ~30 DSBs, ~600 SSBs, and >600 events of DNA base damage (Nikjoo et al. 2002, Hall & Giaccia 2006).

Ionising radiation produces diverse DNA lesions: (1) base damage; (2) SSBs, typically 1000 SSBs per cell per Gy; (3) DSBs, approximately 40 DSBs per cell per Gy, considered the most critical lesion; (4) DNA-protein crosslinks, covalent bonds between DNA and proteins; and (5) clustered lesions, multiple lesions within 1-2 helical turns, particularly characteristic of high-LET radiation and difficult to repair. While DNA DSBs seem the least numerous of these lesions, they are the most cytotoxic lesion and correlate best with cell killing and mutagenesis leading to cancer and hereditary disease; a single unrepaired DSB can lead to cell death (Nikjoo et al. 2002, Rothkamm & Löbrich 2003). Radiation-induced DNA damage correlates well with cell killing and mutagenesis; nevertheless there are several open venues for research, namely: (1) cell signalling as the target (radiation-induced bystander effects (RIBE) and abscopal effects) (Kadhim et al. 2013, Mothersill et al. 2019), (2) low-dose effects and the genetic basis of individual radiosensitivity (Foray et al. 2016, Lohynská et al. 2022), (3) genomic instability and other instances of trans-generational effects (Dubrova et al. 1996), and (4) relationships between cell aging and radiation damage (Gosselin et al. 2009).

1.2 Radiomimetic-induced DNA damage

Radiomimetics are chemical compounds that cause in vitro and in vivo genetic damage similar to that caused by ionising radiation. Among a wide range of genotoxic substances capable of inducing DNA damage, only a very small subset can be considered radiomimetics; for instance, most organic DNA-alkylating agents (e.g. ethyl methanesulfonate (EMS), N-ethyl-N-nitrosourea (ENU), diethylnitrosamine (DEN), etc.) are very powerful mutagens, but have relatively low capacity for inducing cytotoxic DNA lesions like DSBs (Mientjes et al. 1998). Other alkylators, such as N-methyl-N-nitrosourea (MNU), mimic radiation-induced endpoints by inducing chromatid-type aberrations and micronuclei in vivo (Jovtchev et al. 2002), making them useful for mechanistic studies. Crucially, ROS such as H_2O_2 induce large numbers of SSBs but very few direct DSBs and therefore do not mimic the direct damage caused by IR (Valverde et al. 2018). The relatively few compounds capable of being classified as radiomimetics include: (1) a small range of alkylating agents, including several nitrogen mustards (e. g. cyclophosphamide, uramustin, melphalan) and some nitrosoureas (carmustin, lomustin, etc.) (Deli 2022); (2) some antimetabolitic DNA synthesis inhibitors (e.g. 5-fluorouracil (5-FU), cytarabine, decitabine, 6-mercaptopurine, methotrexate) - although it should be noted that these are not direct radiomimetics and affect only actively replicating cells (Parker 2009); (3) bacteria-derived radiomimetic glycopeptides, typically from *Streptomyces* species (bleomycin, zeocin, zorbamycin, etc.) (Deli 2023), which are well-established chemotherapeutics due to their unique ability to induce DSBs in dividing cells; and (4) several chromoprotein antitumor antibiotics, typically enediynes (e.g. kedarcidin, C-1027 (lidamycin), neocarzinostatin, etc.), are in development as chemotherapeutics and act as powerful inducers of catalytic DNA cleavage, and perhaps most closely emulate the effects of IR (Deli 2023). Radiomimetics provide several experimental advantages: (1) precise dose control and uniform exposure without radiation safety requirements; (2) ability to study specific damage types and repair pathways; (3) investigation of combined modality treatments (radiation plus chemotherapy); (4) mechanistic dissection of damage recognition, signalling, and repair; and (5) development and testing of radioprotectors and DNA repair modulators (Deli 2023). Nevertheless, despite occasional similarities between DNA damage induced by chemical genotoxins and IR-induced DNA damage, the term "radiomimetic" should be used with caution. Both alkylators and antimetabolites are strong replication inhibitors but weak DSB inducers; additionally, alkylating agents induce proportionally more DNA cross-links than IR does. Strictly speaking, chemical compounds don't exactly imitate the damage induced by IR; still, due to similarities in molecular effects, "radiomimetic" can be a useful "umbrella term" for this group of chemotherapeutic agents and general inducers of DNA damage.

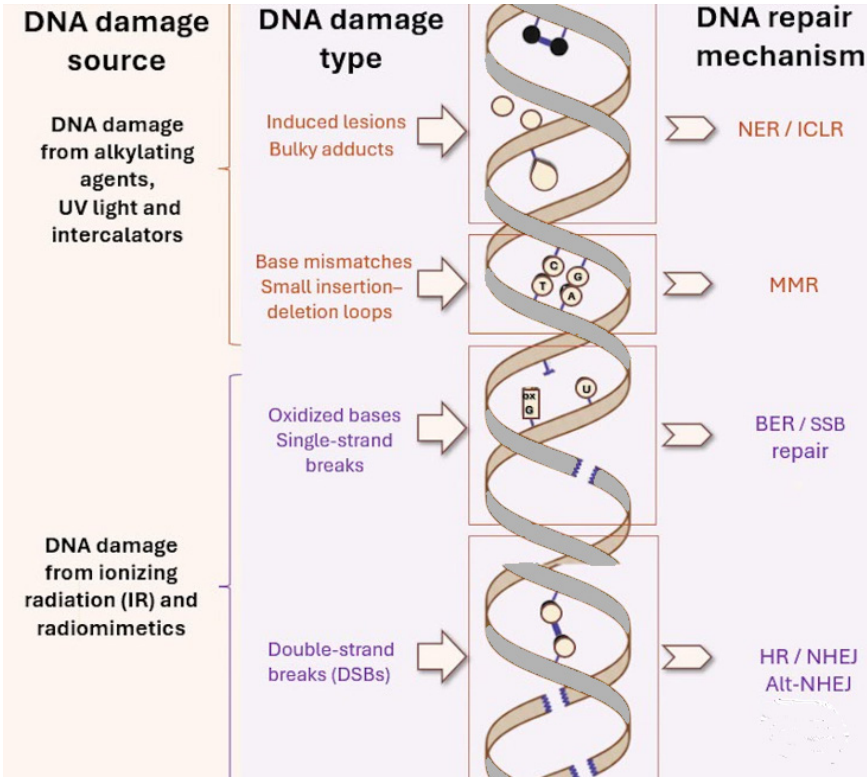

Fig. 1. Types of DNA damage characteristic of ionising radiation and molecular genotoxins, with the mammalian DNA repair systems responsible for their repair (based on Boland et al., 2005, Dexheimer, 2012, and Ostoich, 2024). Legend: NER (Nucleotide Excision Repair), ICLR (Interstrand Cross-Link Repair), MMR (Mismatch repair), BER (Base Excision Repair), SSB repair (Single Strand Base repair), HR (Homologous Recombination), NHEJ (Non-homologous End Joining), Alt-NHEJ (Alternative Non-Homologous End Joining)

1.3 Mammalian DNA repair systems

In the early 1980s, it was observed that, at the cellular level, most sublethal IR-induced DNA damage within mammalian chromatin is repaired quite quickly and often quite effectively (Elkind, 1984). Although mammals are characterised by relative radiosensitivity compared to invertebrates, they are equipped with sophisticated DNA repair machinery consisting of seven distinct DNA repair systems, of which three complementary systems have evolved to repair DSBs (Lindahl & Barnes 2000, Valverde et al. 2018, Ostoich 2024). Mammalian cells utilise various DNA repair pathways: Base excision repair (BER) fixes oxidative base damage and SSBs; Nucleotide excision repair (NER) removes bulky DNA adducts; Mismatch repair (MMR) corrects base mismatches; Homologous recombination (HR) repairs DSBs using the sister chromatid as a template, primarily during S/G2 phases; Non-homologous end joining (NHEJ) joins DSBs directly, functioning throughout the cell cycle but being error-prone; Alternative non-homologous end joining (Alt-NHEJ) repairs DNA double-strand breaks quickly but is error-prone, often causing deletions or chromosomal translocations, unlike the more accurate standard NHEJ; Interstrand cross-link repair (ICLR) removes covalent bonds formed between two opposite strands of the double helix, which otherwise block essential processes like replication and transcription. By “unhooking” the cross-link and utilising homologous recombination, the cell can restore the integrity of the genetic code and prevent chromosomal instability. Unrepaired or misrepaired DSBs can lead to chromosomal aberrations (dicentrics, translocations, deletions), genomic instability, mutations, cell death, or malignant transformation (Hoeijmakers, 2001; Jackson & Bartek, 2009). Fig. 1 summarises the major types of DNA damage induced by ionising radiation and radiomimetic compounds, together with the corresponding repair pathways in mammalian cells.

As evident from Fig. 1, ionising radiation, as well as bleomycin/enedyine-type chemical radiomimetic compounds, is characterised by a comparatively high direct induction of DSBs (Hall & Giaccia 2006, Ballarini 2010, Deli 2022, 2023). The principal

difference between IR, on one hand, and bleomycins and enedyines, on the other, is in the kinetics of DNA damage. Radiation-induced DNA damage (both direct and ROS-induced) occurs within 1 second of exposure (Wardman 1991, Mikkelsen & Wardman 2003, Hall & Giaccia 2006). Chemical radiomimetics, on the other hand, act on cells continuously and induce DNA damage in a concentration-dependent manner, with a propensity to produce more DNA lesions in actively replicating cells (Deli 2022, 2023). Unlike radiation and bleomycin/enedyine-type radiomimetics, ROS inducers, including direct oxidizers (e.g. hydrogen peroxide (H_2O_2), molecular oxygen (O_2), ozone (O_3), permanganate ions (MnO_4^-), etc. and indirect catalytic producers of ROS (e.g. molecular iron (Fe^{2+}), and doxorubicin ($C_{27}H_{29}NO_{11}$, PubChem 31703) produce vast amounts of SSBs and base oxidation, but very few DSBs; oxidative damage is rapidly repaired by BER and DNA ligases (Wardman 1991, Mikkelsen & Wardman 2003, Valverde et al. 2018). In contrast, DNA-alkylating agents, intercalators (e.g. 4′,6-diamidino-2-phenylindole (DAPI), propidium iodide (PI), ethidium bromide (EtBr), etc.) and crosslinkers (nitrogen mustards (e. g. cyclophosphamide and uramustin), cisplatin, Mitomycin C) produce mostly nucleotide damage (resolved fast by the NER and MMR systems) and replication errors resulting in point and frameshift mutations; they are effective cytostatics and mutagens, but have comparatively low cytotoxicity (Fergusson & Denny 2007, Deli 2022, 2023).

2. IR and radiomimetic effects at tissue, organ, system, and organism levels.

Early X-ray pioneers noted that different organs and cell types responded differently to ionising radiation (IR). In 1906, Bergonié and Tribondeau observed "higher effects of Röntgen-ray exposure on fast-dividing cells," and Claudius Regaud achieved X-ray sterilisation of rams (*Ovis orientalis aries*) in an experiment which paved the way for cancer radiotherapy (Bergonié 1906, Regaud & Nogier 1911). Today we know that the most radiosensitive mammalian tissue is the bone marrow stem cell pool, followed by white blood cells, intestinal epithelia, mucosal and endothelial tissues, and the lens of the eye (Hall & Giaccia 2006, Bolch et al. 2016). Mammalian acute lethality after IR exposure, usually at whole-body doses exceeding 4 Gy come from the Acute Radiation Syndrome (ARS), characterized by: 1) hematopoietic disruption leukopenia, immune and hematological impairment (bone marrow phase), lethal in 4-8 weeks, 2) at doses exceeding 8 Gy, a universally lethal gastrointestinal syndrome coming from stem cell depletion in the intestinal mucosa (lethal in 2-4 weeks), and 3) a promptly lethal (within 1-2 days) neurovascular syndrome at very high doses exceeding 35 Gy (Handford et al. 1960, Bond & Robertson 1963, Donnelly et al. 2010, Dörr et al. 2017).

Besides ARS, other mammalian tissues are affected by IR dose-dependently and deterministically in ways that can result in chronic impairment and delayed mortality; these include: 1) damage to salivary glands resulting in xerostomia; 2) sterility and/or premature menopause; 3) vascular damage resulting in telangiectasias and poor tissue perfusion; 4) lung fibrosis and delayed toxicity to the smooth cardiac muscle; 5) temporary or permanent alopecia, skin erythema, desquamation, and skin scarring; 6) lymphatic vessel damage resulting in lymphedemas; and 7) damage to stem cells in the ocular lens that can lead to cataracts (Hall & Giaccia 2006, Donnelly et al. 2010, Bolch et al. 2016, Dörr et al. 2017). At lower doses, including very low-doses, IR induces morbidity and mortality in a probability-based way, or "stochastically", by causing solid cancers and haematological malignancies (Natarajan et al., 1998; Dörr et al., 2017; Lohynská et al., 2022). This has been described at length elsewhere (Hall & Giaccia 2006, Donnelly et al. 2010, Lohynská et al. 2022). Similar to normal-tissue sensitivities to acute IR damage, different tissues have diverging levels of cancer susceptibility; radiation-induced skin cancers, thyroid cancers, and leukaemia are common, while, for instance, IR-induced hemangiomas or neuroblastomas are exceedingly rare (Hall & Giaccia 2006, Donnelly et al. 2010, Bolch et al. 2016, Lohynská et al. 2022).

Radiomimetics possess supracellular effects similar to ionising radiation, including the ability to disrupt chromosomal DNA, cell cycles, and tissue kinetics, and to target fast-proliferating tissues (malignant neoplasms as well as fast-turnover normal tissues like the oral mucosa and the bone marrow) (Deli 2022, 2023). Similar to IR, these chemicals pose the risk of immunosuppression at high doses and a stochastic risk of secondary carcinogenesis even at lower doses; nevertheless, they remain valuable tools in research and medicine.

3. Small mammal models: Strategic rationale in IR and radiomimetic research

Selecting an appropriate mammalian model is a critical decision that influences experimental design, data interpretation and the relevance of the results when applied to humans. A detailed comparison of the biology of the primary small mammal models used in radiation research highlights key traits rel-

evant to DNA damage studies, including genome similarity to humans, conserved DNA repair pathways, radiation sensitivity, lifespan, reproductive traits, and the accessibility of genetic tools. Several key factors must be considered when choosing mammalian models for radiation research. The fidelity of the model varies because different species exhibit distinct radiation tolerances and biological responses to IR, which affects how well the data can be extrapolated to humans and other mammals. Approximations are necessary when modelling human biology, since mice, despite being over 95% genetically similar to humans, show differences in radiation responses, DNA damage response (DDR), and the effects of cell cycle checkpoints and tumour suppressor genes. Unlike humans, who are prone to carcinomas, mice mainly develop sarcomas (Post, 2012). Laboratory rats typically provide better biological approximations. Larger mammalian models are preferred to align with human physiology and clinical conditions more closely. The model's development level also matters; for example, mice and rats have well-studied genomes and many transgenic models are used in radiation research. Ethical considerations and efforts to reduce animal testing, guided by Directive 2010/63/EU, as amended by Regulation (EU) 2019/1010 and Directive (EU) 2024/1262, aim to increase transparency and, eventually, replace animal testing, which must be justified and conducted humanely when necessary. Organism size influences dosimetric considerations; smaller animals tend to have less uniform dose distributions and different energy deposition patterns during local and whole-body irradiation, often necessitating the use of porcine models in radiation oncology. Various radiation modalities, such as high-energy photons (radiotherapy-grade γ-rays and megavoltage X-rays) and accelerator-grade protons or heavy nuclei, each with unique Bragg peaks, render models smaller than mini pigs inadequate for radiotherapy and diagnostics. Immunological differences, especially relevant in studies of IR-induced inflammation, vascular damage, acute radiation syndrome, and fibrosis, must also be considered. Lifespan and cell proliferation rates significantly impact biological responses to low-dose and chronic irradiation by influencing DNA repair kinetics.

The selection of animal models based on their interspecific differences in radiosensitivity is also very important. There are invertebrate animal species with spectacular radioresistance. Tardigrades can withstand 5000 Gray with 50% loss in viability (LD_{50} = 5000 Gy) (Horikawa et al. 2006). Much more modestly, the LD_{50} for humans without medical intervention is 4-4.5 Gy; for mice, ~5.5-7.5 Gy; and for rats, ~7.1 Gy (DiCarlo et al. 2011). Extensive animal testing in the early 1960s has shown that, among other mammals, goats (*Capra hircus*) are highly radiosensitive (LD50 = 2.4 Gy). At the same time, Mongolian gerbils (*Meriones unguiculatus*) are significantly more radioresistant and withstand a dose four times that (LD_{50}=10 Gy) (Bond & Robertson 1963). The discrepancy and significant variation in effect that radiation exposure has on individual species, the potential for combined injuries after accidental radiation exposure, and interspecies variability make it extremely difficult for a single animal model to capture the effects of IR; therefore, a variety of species have been used in different contexts (DiCarlo et al. 2011).

4. Primary small mammal models: Comparative biology and applications in IR research

4.1 The House Mouse (*Mus musculus* Linnaeus, 1758)

4.1.1 Genomic and genetic characteristics

The laboratory mouse is the most extensively used mammalian model in biomedical research. The establishment of laboratory animal strains dates back to 1909–1910, when Loeb and Lathrop developed strains of inbred house mice (Nishioka 1995, Rader 1999). Laboratory mouse strains are inbred to the point of being genetically identical to each other. Different strains of mice had different propensities to develop cancer (typically mammary cancer), and cancer risk seemed to run in mouse families (Suckow et al. 2023). Today, radiation biologists and radioecologists use a variety of mouse strains, including BALB/c, Swiss Albino, and C3H (derived from the original Loeb and Lathrop experiments).

The mouse genome (approximately 2.5 Gb) shares ~85% sequence homology with the human genome at the nucleotide level, and ~99% of mouse genes have human orthologs (Mouse Genome Sequencing Consortium, 2002). Crucially, the DNA repair pathways of mice and humans are highly similar, including BER, NER, MMR, HR, and NHEJ) (Hoeijmakers 2001). The mouse's genetic makeup is highly adaptable. Thousands of inbred strains are available, each with defined genetic backgrounds and phenotypic characteristics. Genetically engineered mouse models (GEMMs) enable precise manipulation of DNA repair genes, tumour suppressors, and radiation response pathways. Castle et al. (2017) emphasise that GEMMs accurately replicate primary cancers at the anatomical, histopathological, and genetic levels, thereby preserving the tumour microenvironment for study.

4.1.2 Radiation response characteristics and experimental applications

Mouse radiation sensitivity varies significantly among strains. The $LD_{50/30}$ (lethal dose for 50% of animals at 30 days post-irradiation) for whole-body gamma irradiation ranges from approximately 6.5 to 9.5 Gy depending on strain, sex, and age (Grahn 1958). C57BL/6 mice, one of the most commonly used strains, have an $LD_{50/30}$ of approximately 7-8 Gy (Suman et al. 2012). Recent work by Down et al. (2024) demonstrates strain-specific differences in radiation-induced tissue injury: C57BL/6J mice show high sensitivity to enteritis and develop extreme pleural effusions at 14 Gy in partial-body irradiation models, while C57L/J mice exhibit severe latent pulmonary injury and pneumonitis lethal at 12 Gy, comparable to human disease patterns. Mice develop acute radiation syndrome (ARS) following high-dose exposure, with hematopoietic, gastrointestinal, and neurovascular sub-syndromes depending on dose. At lower doses, mice are susceptible to radiation-induced cancers, particularly lymphomas and solid tumours, with latency periods of months to years (Ullrich 1984). Murine models (BALB/c) have been used extensively for mechanistic and genetic studies on a large scale, including foundational work in radiation genetics, such as the work of Russell & Russell (Megamouse project conducted at Oak Ridge National Laboratory, TN, USA), which used millions of mice to determine spontaneous and IR-induced mutation frequencies (Russell et al. 1958, Russell & Russell 1992).

4.1.3 Physiological and Practical Considerations

Mice have short lifespans (2-3 years), rapid reproductive cycles (gestation ~19-21 days, sexual maturity ~6-8 weeks), and large litters (6-12 pups), facilitating multi-generational studies. Their small size (20-40 g adult body weight) enables economical housing and reduces the requirements for the radiation source (Fox et al. 2007). However, their small blood volume (~2 mL total) can limit serial sampling for biomarker studies (Fox et al. 2007). Metabolic differences from humans include a higher metabolic rate, different drug metabolism kinetics, and distinct immune system characteristics (although humanised mouse models address some immunological differences). Mice are obligate nose breathers, which affects inhalation toxicology studies (Suckow et al. 2023). Despite these differences, the mouse remains the gold standard for radiation research due to its genetic tools, extensive databases, and practical advantages.

4.2 The Common Rat (*Rattus norvegicus* Berkenhout, 1769)

4.2.1 Genomic and physiological characteristics

The rat genome (approximately 2.75 Gb) exhibits overall homology to the human genome, similar to that of the mouse genome, with ~90% of rat genes having human orthologs (Genome sequence of the Brown Norway rat, 2004). DNA repair pathways are highly similar to those of humans, making rats suitable models for DNA damage studies (Suckow et al. 2019). The rat's primary advantage over the mouse is its larger size (adult body weight 250-500 g), which facilitates surgical procedures, serial blood sampling, pharmacokinetic studies, and behavioural assessments. Rat physiology and pharmacokinetics are often considered closer to those of humans than those of mice, particularly for the cardiovascular, renal, and neurological systems (Ellenbroek & Youn 2016). The larger blood volume (~15-20 mL total) enables repeated sampling for biomarker kinetics without compromising animal welfare (Suckow et al. 2019).

4.2.2 Radiation response and experimental applications

Rats exhibit radiation sensitivity comparable to that of mice, with $LD_{50/30}$ values for whole-body gamma irradiation ranging from approximately 6.5 to 9 Gy, depending on strain (Casarett 1968). Commonly used strains include Sprague-Dawley, Wistar, Fischer 344, and Long-Evans, each with distinct characteristics. Rats have been extensively used in ARS studies, particularly for hematopoietic and gastrointestinal subsyndromes, due to their size advantage for physiological monitoring and supportive care interventions (Suckow et al. 2019). Rats are particularly valuable for studying radiation-induced cardiovascular and neurocognitive effects, as well as late tissue injury. Their larger brain size facilitates neurobehavioral testing and neuroimaging. Rats have been used extensively in testing of radioprotectors and radiomitigators (Singh & Seed 2017). Rats have been employed for a long time in studies of the uptake and tissue distribution of different α-emitting transuranic actinides (e.g. ^{214}Pu, ^{239}Pu, $^{241/242}$Pu, ^{241}Am, etc.) by autoradiography, metabolic analysis, as well as in testing new bioimaging tracers (Ericsson & Ullberg 1958, Haines & Priest 1984, Bergström et al. 2003). Strains such as Wistar are often used to study the neurological and developmental damage induced by IR, as well as organ-level damage (GI tract damage during ARS, lung fibrosis, cardiovascular damage) (Liu et al. 2010, Fujimoto et al. 2021).

4.2.3 Genetic tools and limitations

Historically, rats lagged behind mice in the availability of genetic tools. However, recent advances, including CRISPR/Cas9 gene editing (Shrock & Güell 2017), zinc finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs), have enabled the generation of genetically engineered rat models (GERMs) with targeted gene disruptions and knock-ins (Ellenbroek & Youn 2016). Transgenic rat models of DNA repair deficiencies and cancer predisposition are now available, though the catalogue remains smaller than for mice. Practical considerations include higher housing costs, longer generation times (gestation ~21-23 days; sexual maturity ~6-8 weeks), and smaller litters (6-12 pups) than in mice. Lifespan is 2.5-3.5 years (Sharp & Villano 2012). Despite these limitations, rats remain valuable for studies requiring larger body size, more complex behavioural assessments, or closer pharmacokinetic similarity to humans.

4.3 Voles (Microtus species)

4.3.1 Ecological and evolutionary context

Voles (genus *Microtus*) represent a unique category of small mammal models, distinguished by their use in radioecological studies rather than controlled laboratory experiments. Several *Microtus* species inhabit regions affected by radioactive contamination, most notably the Chernobyl Exclusion Zone and areas affected by nuclear weapons testing. The bank vole (*Myodes glareolus*, formerly *Clethrionomys glareolus*) and common vole (*Microtus arvalis*) have been extensively studied in these contexts (Goncharova & Ryabokon 1995; Ryabokon & Goncharova 2006).

4.3.2 Genomic characteristics and conservation

The vole genome has been sequenced for several species, revealing approximately 2.4-2.6 Gb genome size with conserved mammalian DNA repair pathways (Carpenter et al. 2021). However, genomic resources for voles are less developed than for mice and rats. Voles exhibit high genetic diversity in natural populations, which complicates standardisation but also provides opportunities to study natural variation in radiation response.

4.3.3 Radiation response in natural populations

Voles from chronically contaminated areas such as Chernobyl have been studied for the multi-generational effects of radiation exposure. Ryabokon and Goncharova (2006) documented transgenerational accumulation of radiation damage in small mammals chronically exposed to Chernobyl fallout, with elevated mutation rates, chromosomal aberrations, and developmental abnormalities persisting across generations. These studies provide unique insights into population-level effects, evolutionary adaptation to radiation stress, and ecological consequences of environmental contamination. Voles exhibit radiation sensitivity comparable to that of laboratory mice and rats. However, precise LD_{50} values vary across species and are less well characterised, as research has been focused more on field studies rather than controlled laboratory irradiation. Voles have short lifespans (1-2 years in the wild, up to 3 years in captivity), rapid reproduction (gestation ~21 days, sexual maturity ~4-6 weeks), and large litters (4-8 pups), making them suitable for multi-generational studies (Kirsch 2024).

4.3.4 Advantages and limitations

The primary advantage of voles is their ecological relevance for studying real-world radiation exposure scenarios, including chronic low-dose exposure, environmental contamination pathways, and population-level effects (Geras'kin 2016). They serve as sentinel species for environmental monitoring. However, limitations include underdeveloped genomic resources, limited availability of transgenic tools, challenges in laboratory husbandry (some species are difficult to breed in captivity), and high genetic variability in wild populations, which complicates standardisation.

4.4 The Hamster

4.4.1 Species and genomic characteristics

Several hamster species are used in research, most commonly the Syrian or golden hamster (*Mesocricetus auratus*) and the Chinese hamster (*Cricetulus griseus*). The Chinese hamster ovary (CHO) cell line, derived from *C. griseus*, is one of the most widely used mammalian cell lines in biotechnology and radiation biology research (Wu et al. 1985). The hamster genome (approximately 2.4-2.5 Gb) exhibits similar DNA repair pathways to those of humans. Notably, hamsters have unique characteristics in DNA repair, particularly in the repair of radiation-induced DNA double-strand breaks. Some hamster cell lines exhibit deficiencies or alterations in specific DNA repair pathways, making them valuable for dissecting repair mechanisms (Thompson & Suit 1969).

4.4.2 Radiation response and unique characteristics

Hamsters exhibit radiation sensitivity generally comparable to that of mice and rats, with $LD_{50/30}$

values for whole-body irradiation ranging from approximately 7 to 10 Gy, depending on species and strain. Syrian hamsters have been used extensively in radiation carcinogenesis studies, particularly for pancreatic cancer and melanoma induction. A unique feature of Syrian hamsters is the cheek pouch, an immunologically privileged site that accepts xenografts without rejection. This has been exploited in radiation biology studies of tumour response to radiation and combined-modality treatments (Begg et al. 1979; Sakamoto et al. 1974). The cheek pouch model allows direct visualisation and measurement of tumour response *in vivo*. Hamsters have been valuable for studying radiation-induced DNA repair kinetics and chromosomal aberrations. Chinese hamster cells, particularly CHO cells, have been instrumental in identifying DNA repair genes and pathways through complementation studies and mutant analysis (Thompson & Suit 1969).

4.4.3 Limitations

Hamsters have significant limitations as model organisms. Genomic resources are less developed than for mice and rats. Transgenic and gene-editing tools are limited, though CRISPR/Cas9 has been successfully applied in recent years (Liu et al. 2021). Hamsters have relatively long generation times (gestation ~15-18 days, sexual maturity ~6-10 weeks) and smaller litters (5-9 pups) than mice. Syrian hamsters are solitary and aggressive, requiring individual housing, which increases costs. Lifespan is approximately 2-3 years (Tambare & Murkunde 2021). Despite these limitations, hamsters remain valuable for specific applications, particularly in studies that exploit the cheek pouch model or the unique DNA repair characteristics of hamster cell lines.

4.5 The Guinea Pig (*Cavia porcellus* Linnaeus, 1758)

4.5.1 Genomic and metabolic characteristics

The guinea pig genome (approximately 2.7 Gb) exhibits conserved DNA repair pathways with humans (Dawson 2011). Guinea pigs are phylogenetically distinct from mice and rats (belonging to the suborder *Hystricomorpha* rather than *Myomorpha*), resulting in unique physiological characteristics. A notable feature of guinea pigs is their inability to synthesise vitamin C (ascorbic acid) due to a non-functional L-gulono-γ-lactone oxidase gene, a characteristic shared with humans and other primates (Drouin et al., 2011). This makes guinea pigs valuable models for studying oxidative stress and antioxidant mechanisms relevant to radiation biology, as vitamin C is an important antioxidant that can modulate radiation-induced oxidative damage. Guinea pigs also exhibit immune system characteristics more similar to those of humans than those of mice in some respects, including complement system components and certain cytokine profiles (Padilla-Carlin et al. 2008). Their larger size (adult body weight 700-1200 g) facilitates surgical procedures, serial sampling, and physiological monitoring (Pignon & Mayer 2020).

4.5.2 Radiation response

Guinea pigs exhibit radiation sensitivity generally comparable to that of other rodents, with $LD_{50/30}$ values for whole-body irradiation ranging from approximately 4 to 7 Gy, depending on strain and experimental conditions (Casarett 1968). They have been used in radiation studies of skin effects, hematopoietic syndrome, and immune system responses. Guinea pigs have been particularly valuable for studying radiation-induced skin injury and wound healing due to their relatively large skin surface area and skin structure similar to that of humans. They have also been used in studies of radiation effects on the auditory system and for testing radiation countermeasures (Rodgers et al. 2016).

4.5.3 Limitations

Guinea pigs have significant practical limitations. They have long generation times (gestation ~59-72 days, sexual maturity ~8-10 weeks), small litters (2-4 pups), and relatively long lifespans (4-8 years), making multi-generational studies impractical (Pignon & Mayer 2020). They are expensive to house due to their large size and specific dietary requirements (vitamin C supplementation). Genomic resources are less developed than for mice and rats, and transgenic tools are very limited. Behavioural characteristics include skittishness and stress sensitivity, which can complicate experimental procedures. Despite these limitations, guinea pigs remain valuable for specific applications where their unique metabolic characteristics (vitamin C metabolism) or physiological features (skin structure, immune characteristics) provide advantages over other rodent models.

In summary, rodent models are relatively inexpensive, readily available across a wide range of genetic backgrounds, well characterised, and offer a wide range of transgenic varieties. On the other hand, when closer approximations to human biology are required, such as in radiation oncology, experimental radiotherapy, medical imaging, and the study of vascular radiation injury, the model of choice is mini pigs (van der Velden et al. 2022, Wil-

Table 1. Radiomimetic compounds in mammalian models

Radiomimetic	Mechanism of action	Applications in small mammal models
Bleomycin (BLM) glycopeptide antibiotic	Induces SSBs and DSBs; preferentially cleaves DNA at 5'-GC-3' and 5'-GT-3' sequences	Mouse models for radiation biology research and as a tool for studying DNA damage and repair mechanisms (Phillips et al. 1979, Luca et al. 1988, Kranjc et al. 2005, Wirsdörfer et al. 2017, Zong et al. 2015) Rat models for BLM-induced pulmonary fibrosis models, which share mechanistic features with radiation-induced lung injury (Wirsdörfer et al. 2017, Li et al. 2022) Hamster models for the interaction between BLM and radiation on cell survival and DNA damage (Wu et al. 1985)
Cyclophosphamide (CP) alkylating agent and nitrogen mustard	CP needs hepatic cytochrome P450 to activate it into phosphoramide mustard, which alkylates DNA at guanine's N7, creating cross-links that block replication and transcription, causing fork collapse and DNA double-strand breaks.	Mouse models for studying DNA damage, immune suppression, combined treatments with radiation, immunosuppressed models for xenografts, and hematopoietic recovery after myeloablation, paralleling radiation-induced hematopoietic syndrome (Luca et al. 1988, Jagetia, 2018) Rat models for investigation of bladder toxicity (hemorrhagic cystitis from acrolein), neurotoxicity, and cardiotoxicity (Saeed et al 2026, Sherif et al. 2020)
Etoposide (VP-16) topoisomerase II inhibitor	Induces DSBs, which closely resemble radiation -induced DSBs in terms of activating DNA damage response pathways (ATM/ ATR signalling, γH2AX foci formation, checkpoint activation)	Mouse models for studying radiobiologically oxic and hypoxic cells in a C3H mouse mammary carcinoma in situ; in models of DNA repair deficiency for synthetic lethality (Grau et al. (1992) Rat models for investigating the neurotoxicity and cardiotoxicity of topoisomerase II inhibitors
Mitomycin C (MMC) natural antibiotic and a DNA crosslinker	Alkylates DNA at the N2 position of guanine, forming monoadducts, inter- and intrastrand crosslinks.	Mouse and rat models for studying DNA crosslink repair, Fanconi anaemia, and combined modality cancer treatments
Hydrogen peroxide (H_2O_2) ROS	Induces oxidative DNA damage by directly oxidising DNA bases, SSBs, and at higher concentrations, DSBs	Mouse models for studying oxidative stress in ageing, neurodegenerative diseases, and radiation biology; mice deficient in antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase) show enhanced sensitivity to H_2O_2, paralleling their increased radiation sensitivity (Valverde et al. 2018)
Doxorubicin (Adriamycin) is an anthracycline antibiotic widely used in cancer chemotherapy	Induces DNA damage through intercalation into DNA, disrupting replication and transcription, inhibiting topoisomerase II, stabilising the enzyme-DNA cleavage complex and producing DSBs and generation of ROS, producing oxidative DNA damage	Mouse models for studying cancer, cardiotoxicity, and DNA repair Rat models for studying cardiotoxicity due to their larger heart size, facilitating cardiac function monitoring and their similarity to human cardiac physiology. Doxorubicin-induced cardiomyopathy in rats is a well-established model for studying mechanisms and interventions (Luca et al. (1988)

son et al. 2011). These inbred porcine models are necessary due to their larger size, which is required for testing external imaging diagnostics such as CT and PET, as well as penetrating external-beam radiotherapy, including isotopic sources, linear accelerators, and proton and ion beams (Wilson et al. 2011).

5. Small mammal models in radiomimetic research

In experimental radiobiology, radiomimetic compounds are widely applied in mammalian models to simulate radiation-induced DNA damage under controlled conditions. They are particularly useful for studying dose–response relationships, DNA re-

Fig. 2. Genetically modified mouse strains in radiation research: A) C3H mice with a high incidence of spontaneous tumours, particularly mammary tumours, B) ATM-deficient mice, sensitive to ionising radiation and with defective HR repair systems, and C) Nude mice with impaired DSB repair, athymia and immune deficiency, and no xenograft rejection. Image sources: Charles River Labs, Belgium, and AnLab, s.r.o., Czech Republic.

pair kinetics, and tissue-specific sensitivity in vivo, especially when controlled radiation exposure is not feasible. Rodent models are extensively used to evaluate the genotoxic and cytotoxic effects of compounds such as bleomycin and cyclophosphamide, providing important insights into mechanisms of DNA damage and repair (Table 1).

6. Selected transgenic animal models and radioecological monitor species

In addition to standard laboratory animal strains, various transgenic models have been developed to meet the needs of radiation research and radiation oncology. These include:

Radiosensitive mice. ATM-deficient mice are knockouts of the protein Ataxia telangiectasia mutated (ATM), a DDR signalling protein. ATM responds to DNA DSBs by eliciting cell cycle arrest, upregulating DNA repair, or inducing p53-dependent apoptosis. ATM-deficient Mice were developed in the 1990s based on the C57BL/6J strain. These animals are extremely sensitive to ionising radiation (LD_{50} is 3-3.5 Gy as opposed to 6-7 Gy for wild-type). They have a smaller thymus, spleen, lymph nodes, and bone marrow than wild-type mice, and are slightly immunodeficient (Wang et al., 1997; Pietzner et al., 2013).

Cancer-susceptible mice: C3H. C3H mice were first developed in the United States in 1920 by Haldane and were extensively inbred in the 1930s. They are susceptible to a wide range of pathogens and produce a high incidence of spontaneous tumours, particularly mammary tumours. C3H are aggressive, hyperactive, display symptoms of anxiety and neurodegeneration, and are the most sensitive strain to radiation-induced oncogenesis (Heston & Vlahakis, 1968, Větvička 1990).

Immunodeficient mice: nude mice. Nude mice have impaired immunity, no thymus, and exhibit T-cell deficiency. Researchers can transplant any human or mouse tumour into nude mice (they do not reject transplanted cells and organs). Nude mice have impaired DSB repair. They are very susceptible to infection and should be handled in sterile facilities. They are indispensable models in radiation oncology and xenograft biology (Fogh 2014).

Some key transgenic mouse models for radiation research are presented in Fig. 2:

As a note, several wild rodent species are good monitors of environmental radioactivity, particularly anthropogenic radioisotope contamination. Wood mouse species (*Apodemus flavicollis, A. sylvaticus*) are well-established as monitor species for IR-induced and chemically initiated genomic instability (Ryabokon & Goncharova 2006, Mitkovska et al. 2020). Bank voles (*Myodes glareolus*) and, to a lesser degree, snow voles (*Chionomys nivalis*) are very prone to ^{137}Cs bioaccumulation due to their strongly herbivorous diet (Metcheva et al. 2008, Ostoich et al. 2022, Beltcheva et al. 2024). This corroborates well earlier data from the Chernobyl Exclusion Zone confirming that cricetids, in particular *M. glareolus* and the tundra vole *Microtus oeconomus*, are species with particularly high radiocesium (^{134}Cs, ^{137}Cs) bioaccumulation (Chesser et al. 2000, Beresford et al. 2020).

Conclusion

The review confirms the important role of small mammals as model organisms for studying DNA damage induced by ionising radiation and radiomimetic compounds. At the same time, it is increasingly clear that no single model can fully capture the complexity of biological responses observed in both natural populations and humans. Different groups of small mammals provide complementary information. Laboratory species, especially mice and rats, are indispensable for controlled experiments and for investigating the mechanisms of DNA damage and

repair. Their main advantages include well-characterised genomes, the availability of transgenic models, and the ability to replicate experimental designs. However, their responses are not always directly comparable to those in humans, particularly regarding long-term effects, species-specific physiological differences, and patterns of carcinogenesis.

Small wild rodents are especially valuable for radioecological research because they offer insights into long-term, low-dose radiation exposure in natural environments. This includes effects across generations, adaptive responses, and impacts on populations. Such factors are increasingly important as they mirror more realistic radiation conditions than those simulated in laboratories. Other species, such as hamsters and guinea pigs, occupy more specialised niches and can help define experimental parameters based on their physiological and metabolic traits. However, practical issues and the availability of genetic tools often restrict their use. These differences highlight the necessity of carefully choosing the right model organism. Selecting an appropriate model depends on the study's goals, whether the study focuses on mechanisms, organism responses, or ecological significance. Often, using multiple models together yields a more comprehensive understanding of radiation effects across various levels of biological organisation. An additional important aspect is examining low-dose effects and adaptive responses. While these are well understood at the cellular level, their expression in organisms and populations is less well studied and understood. Small mammal models, especially those that combine laboratory and field studies, could help fill this knowledge gap. Recent advances in noninvasive and alternative methods, such as sophisticated cell and tissue cultures and computational techniques, offer promising ways to minimize animal use in experiments. Nevertheless, these approaches are not yet capable of replacing in vivo models for predicting complex tissue, organ, and whole-organism interactions. In summary, small mammal models remain vital in radiation biology and radioecology, primarily because they connect molecular mechanisms to organismal and ecological responses, provided these limitations are recognised and addressed.

A major advantage of small mammalian models lies in their ability to integrate molecular, cellular, and systemic responses to radiation exposure. Recent years have seen a rise in two tendencies that compete yet partially complement each other: (1) improvements in transgenic mammalian laboratory models, and (2) the development of new in vitro systems and other New Approach Methodologies (NAMs) that reduce the need for animal testing (Kaplan et al. 2024). While significant progress has been made in efforts to reduce animal testing by eliminating false-positive results through in vitro assays using advanced cell culture and model systems, there is no indication that animal testing will be replaced in the near future. On the contrary, advances in genetically altered animal models provide deeper insights into multifactorial diseases (e.g., various cancers, diabetes, metabolic diseases) and diseases that affect multiple organ systems simultaneously. There is a distinct possibility that increasing computational power and advanced AI simulations based on machine learning and Hidden Markov Models will limit the need to employ transgenic models. Still, in all conceivable scenarios, laboratory animals will not be retired in the next two to three decades and beyond. Mammalian models, in particular murine and porcine models, remain indispensable as models in radiation biology and as monitor species in radioecology.

The inherent weakness of every model is that it is an approximation, an "ersatz" by definition. This applies to small mammals as model organisms in radiation biology and oncology, particularly when extrapolating to human biology. In the words of Butterworth and Williams (paraphrasing the British statistician George E. P. Box), "all (animal) models are wrong, but some are useful" (Butterworth & Williams 2021). While in the EU we strive to limit animal testing under Directive 2010/63/EU, Regulation (EU) 2019/1010, and Directive (EU) 2024/1262, partially by developing new cell cultures, cell-based assays, predictive simulation techniques, and artificial tissues, animal testing remains necessary for the basic needs of radiation research. Despite current advances in cell culture, organoid systems, and pre-clinical testing, and the bioethical need to limit the use of experimental animals, small mammals will remain indispensable models in radiation biology and monitor species in radioecology for the foreseeable future. In this context, small mammal models remain uniquely suited to bridge molecular DNA damage and repair mechanisms with tissue- and organism-level radiation effects, thereby continuing to play a central role in radiation biology and radioecology. There is a growing abundance of animal models for radiation research, e.g. the emergence of genetically distinct murine models for different human radiosensitivity syndromes (Chan et al. 2021) and mice with accelerated radiation-induced senescence phenotypes (Matos-Rodrigues et al. 2020, Cabral et al. 2021, Kim et al. 2021).

The future of small mammal models in radiation research should be considered within the framework of the 3Rs: replacement, reduction, and refinement (Russell & Burch, 1959). Replacement entails substituting animal models with non-animal alternatives whenever feasible. For radiation studies, this includes advanced in vitro systems like 3D organoids, tissue-on-a-chip configurations, and co-culture models that mimic tissue structure and cell interactions; human cell-based models such as primary cells, induced pluripotent stem cells, and humanized cell lines that better reflect human radiation responses; and in silico models, including computational simulations of radiation transport, DNA damage, and repair processes. Nonetheless, replacing animal models entirely is currently impractical for radiation research because systemic responses, tissue interactions, immune reactions, and long-term effects cannot yet be fully simulated in vitro or in silico. Van der Velden et al. (2022) highlight that, while innovations aiming for animal-free research are progressing, animal models remain vital for cardiovascular and other complex physiological studies, including radiation research. Reduction aims to minimize animal use while preserving scientific integrity. Strategies encompass enhanced experimental design, such as power analysis, optimized sample sizing, and appropriate statistical techniques; choosing strains with well-characterized radiation responses to reduce variability; sharing data through radiation response databases for meta-analyses and to prevent redundant experiments; and conducting studies with multiple endpoints, measuring various outcomes from the same animals to maximize data collection. Refinement focuses on elevating animal welfare and reducing suffering via non-invasive monitoring methods, like imaging techniques (MRI, CT, PET), and using accessible biomarkers (blood, urine) to decrease reliance on invasive procedures.

Acknowledgements: This work was supported by a grant from the Bulgarian National Science Fund, Ministry of Education and Science, Project No. KP-06-N71/13 “Contribution and Interrelation Between the DNA Repair (DDR), Chaperone, and Antioxidant Systems in the Formation of Adaptive Response”.

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Received: 29.01.2026
Accepted: 24.05.2026