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Current evidence for a role of epigenetic mechanisms in response to ionizing radiation in an ecotoxicological context★

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ABSTRACT

The issue of potential long-term or hereditary effects for both humans and wildlife exposed to low doses (or dose rates) of ionising radiation is a major concern. Chronic exposure to ionising radiation, defined as an exposure over a large fraction of the organism's lifespan or even over several generations, can possibly have consequences in the progeny. Recent work has begun to show that epigenetics plays an important role in adaptation of organisms challenged to environmental stimulae. Changes to so-called epigenetic marks such as histone modifications, DNA methylation and non-coding RNAs result in altered transcriptomes and proteomes, without directly changing the DNA sequence. Moreover, some of these environmentally-induced epigenetic changes tend to persist over generations, and thus, epigenetic modifications are regarded as the conduits for environmental influence on the genome.

Here, we review the current knowledge of possible involvement of epigenetics in the cascade of responses resulting from environmental exposure to ionising radiation. In addition, from a comparison of lab and field obtained data, we investigate evidence on radiation-induced changes in the epigenome and in particular the total or locus specific levels of DNA methylation. The challenges for future research and possible use of changes as an early warning (biomarker) of radiosensitivity and individual exposure is discussed. Such a biomarker could be used to detect and better understand the mechanisms of toxic action and inter/intra-species susceptibility to radiation within an environmental risk assessment and management context.

1. Introduction

Activities like ore mining and milling, nuclear accidents and production and testing of nuclear weapons have resulted in enhanced concentrations of radionuclide pollutants in the environment. This can lead to long-term or chronic exposures of organisms defined as an exposure over a considerable fraction of the lifespan of the organism (IAEA, 1992). The issue of biological effects induced by chronic sub-lethal doses of ionising radiation along with the question on the potential hereditary effects for both humans and wildlife is a topic of considerable debate and concern. This has been reinforced after the Chernobyl and Fukushima accidents, especially with respect to the quantification (and reduction if possible) of the magnitude of risk to ecosystems when exposed chronically for multiple generations. This concerns both short-term and chronic exposure over several generations and heritable effects

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on unexposed progeny. To improve the scientific basis for risk assessment for both human and environment in chronic exposure scenarios as observed e.g. in Chernobyl and Fukushima exclusion zones (CEZ and FEZ), an enhanced understanding of the mechanisms that underpin these responses is needed. This will lead to a better understanding of the complex interplay between exposure, organism physiology and phenotypic response over extended timescales (e.g., Marczylo et al., 2016). Comprehensive reviews of the observed phenotypic effects observed in wildlife in CEZ and FEZ have been published e.g. by Hinton et al. (2007), Geras'kin et al. (2008), Lourenco et al. (2016) Steinhauser et al. (2014), Strand et al. (2014), Batlle (2016) and Beresford et al. (2016). The amounts of radionuclides released into the environment after the Chernobyl accident (5300 PBq, excluding noble gases) were about tenfold of those of the accident in Japan (520 PBq) (Steinhauser et al., 2014). Despite this difference both exclusion zones have common features such as (i) for both areas the exposure can be divided in 3 time-periods depending on the exposure rates as described in paragraph 6, (ii) the degree to which spatial and temporal heterogeneity is present in the distribution of the radionuclides (including the presence of hot particles); (iii) the presence of other additional pollutants (e.g. from historical land use); (iv) the challenge of finding comparable control conditions and (v) the difficulty to estimate the exact exposure dose rates. Additionally and of importance for interpreting observations made in these contaminated regions, both exclusion zones have undergone changes induced by the removal of human presence and occupancy leading to specific ecological changes that are hard to distinguish from the possible radiological impact (Beresford and Copplestone, 2011). The unique nature of these study areas means that the interpretation of field data from these sites needs careful contextual consideration and have led to contrasting and sometimes conflicting reports on effects observed in the CEZ and FEZ (Beresford and Copplestone, 2011; Garnier-Laplace et al., 2013).

Long-term exposures to environmental stressors have been linked to lasting responses in organisms within, but also over multiple exposed generations (Mirbahai and Chipman, 2014; Schultz et al., 2016; Jimenez-Chillaron et al., 2015; Marczylo et al., 2016; Hanson and Skinner, 2016). Yet, the outcome of a long term-exposure to pollutants is not always predictable. For example, chronic exposure to pollutants or adverse conditions has been shown to lead to changed phenotypes (Singer et al., 2016; Gonzalez et al., 2016; Potters et al., 2007) resulting in adaptation within a population (Costa et al., 2012; Coors et al., 2009; Bible and Sanford, 2016). In contrast, there is also evidence suggesting that long term exposures to environmental stressors can lead to an increased population sensitivity (Parisot et al., 2015) that may result in population declines (Vasseur and Cossu-Leguille, 2006). This makes predicting the long-term and/or transgenerational consequences of exposure to a stressor a particular challenge for estimating risks to populations (Groh et al., 2015).

Selection has been recognised as a major mechanism through which adverse environmental conditions can impact the phenotypes of successive generations. Selection of alleles associated with tolerance can lead to changes in the phenotypic characteristics within a population and, hence, is known to be a key driver of changes in population level sensitivity to pollutant effects (Van Straalen and Roelofs, 2007). Detailed studies of populations inhabiting polluted sites have identified numerous cases of modified phenotypes and also of specific genetic selection at loci that lead to biochemical changes that underpin adaptation. Examples cover exposure to radionuclides, trace metals and persistent organic pollutants and taxa such as cladocerans (Hochmuth et al., 2015; Jansen et al., 2015), collembola (Costa et al., 2012; Nota et al., 2013), chironomids (Groenendijk et al., 1999; Loayza-Muro et al., 2014), terrestrial and freshwater annelids (Kille et al., 2013; Langdon et al., 2003; Levinton et al., 2003), fish (Wirgin et al., 2011; Shaw et al., 2014; Reid et al., 2016; Theodorakis and Shugart, 1997), plants, birds (Ellegren et al., 1997) and small mammals (Theodorakis et al., 2001). Although selection for enhanced tolerance is a commonly observed phenomenon, some data have shown that rapid adaptation towards heavy-metals or radionuclides in organisms cannot be explained only by increased mutation rates, but could also be due to non-genetic changes in the activity of functional genes and these might be heritable over generations (Geras'kin et al., 2013; Kovalchuk et al., 2003; Mirbahai and Chipman, 2014; Kille et al., 2013; Wang et al., 2017). This has revealed further levels of complexity probably provided by relevant epigenetic mechanisms relating to structure and regulation of gene expression and splicing that have the potential to transfer information over generations.

In this paper an overview is given of epigenetic changes induced after long-term (within and over generations) exposure to ionising radiation. Although different epigenetic mechanisms will be discussed the main focus of the current review will be on comparing the evidence from both lab and field studies on changes in DNA methylation.

2. Overview of epigenetic mechanisms

The first definition of epigenetics, as 'the causal interactions between genes and their products, which brings the phenotype into being', was provided by Waddington (1939) long before any mechanistic understanding of the relevant processes had developed. This definition has since been refined. For example, Wu and Morris (2001) defined epigenetics as 'Nuclear inheritance which is not based on changes in DNA sequence' or Bird (2007) as 'the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states'. This reflects that epigenetics is now widely seen as 'the study of the landscape of mitotically and/or meiotically heritable changes in gene activity and transcript architecture, including splicing variation, that cannot be explained solely by changes in DNA sequence (Vandegehuchte and Janssen, 2011; Allis et al., 2007; Berger et al., 2009).

The epigenetic landscape is shapen by three epigenetic marks; DNA methylation, histones and it's post translation modifications and small RNA interactions. Together they shape the structure of the DNA called chromatin (Allis and Jenuwein, 2016). These major epigenetic players are engaged in a network of interconnected 'cross-talk' (Irato et al., 2003; Iorio et al., 2010) and orchestrate gene expression that "… underpins the differences between species, ecotypes and individuals" (Mattick et al., 2009; Brautigam et al., 2013). Well established as a key mechanism involved in the aetiology of human disease (Huang et al., 2003), it is only relatively recently that the significance of epigenetic mechanisms in toxicology (Szyf, 2007), ecology (Bossdorf et al., 2008) and evolutionary biology (Rapp and Wendel, 2005), has begun to emerge. Within ecology, it has been suggested that epigenetics could define "… where the environment interfaces with genomics … (and could provide a) rapid mechanism by which an organism can respond to its environment without having to change its hardware" (Pray, 2004). Studies on plants have indicated that epigenetic systems provide functional links between the detection of environmental change and regulation of gene expression (Bossdorf et al., 2008; Grativol et al., 2012; Whittle et al., 2009; Rasmann et al., 2012; Verhoeven et al., 2016; Sahu et al., 2013; He and Li, 2018). Similarly in animals, the role of specific components or changes of the epigenome in species responses to environmental stress has been demonstrated (Vandegehuchte and Janssen, 2014; Schott et al., 2014; Marsh and Pasqualone, 2014; Mirbahai and Chipman, 2014;

Wang et al., 2017; Marczylo et al., 2016). Thus epigenetic mechanisms appear to play an important role in determining the physiological responses of species to long-term multigenerational exposure, including to persistent stressors such as radionuclides.

To integrate emerging understanding of epigenetic mechanisms with existing mechanistic knowledge in radioecology, a clear understanding of long-term effects induced by ionizing radiation exposure of non-human species and their potential (epigenetic) mechanistic basis is needed. To provide this, we here give a brief overview of the evidence of trans- and multigenerational effects in organisms exposed to ionising radiation. The potential role and value of epigenetic analyses in site-specific studies in radioecology will be discussed, including their relevance for future radiological risk assessment. As the most widely studied mechanism and its potential to be transferred to the next generation, special attention will be given to changes in DNA methylation (locus-specific or total) as a possible marker for exposure to ionising radiation, including under field conditions.

3. The biology of epigenetic mechanisms

DNA methylation, histone modifications, and small non-protein coding RNA molecules are the major known epigenetic mechanisms. DNA methylation is the addition of a methyl group to the one of the DNA bases (cytosine or adenine). Most prevalent DNA methylation is on the fifth position of the cytosine ring (5-methyldeoxycytidine, mC). In vertebrates this usually but not exclusively located at in CpG sites. For example, in *Drosophila* methylation is mostly found in the context of CpT dinucleotides (Feil and Fraga, 2012), in honey bees there appears to be a clear distinction of CpG sites in exons and non-CpG sites in introns (Cingolani et al., 2013) and in plants and embryonic stem cells also at CHG and CHH sites (H = A,T or C) in addition to CpG (Feil and Fraga, 2012; Cingolani et al., 2013).

In vertebrates, around 60% of genes are associated with CpG islands that occur at or near the transcription start site of, particularly, housekeeping genes (Gardiner-Garden and Frommer, 1987). The hypermethylation in CpG rich promoters can be associated with the repression of gene expression (Bock, 2012). In invertebrates, methylation is targeted more towards gene body, potentially playing a role in alternative splicing and gene function diversification (Flores et al., 2012; Asselman et al., 2016). Cytosines can be methylated via maintenance and de novo methyltransferase enzymes (Law and Jacobsen, 2010). In vertebrates, maintenance methylation by DNMT1 occurs during the S-phase of mitosis, where the newly synthesized DNA strand is methylated using the original strand as template. De novo DNA methylation is undertaken DNMT3 family members, although recent insights have shown redundancy between to two DNMT family members (Lyko, 2018). *De novo* DNA methylation is undertaken DNMT3 family members. In plants the homologues of DNMT3, DOMAINS REARRANGED METHYLTRANSFERASE 1/2 (DRM1/DRM2) are responsible for the de novo methylation whereas maintenance of CG methylation is conducted by DNA METHYLTRANSFERASE 1 (MET1) which is a homolog for DNMT1 (Law and Jacobsen, 2010; Chan et al., 2005). In addition the plant specific CHROMOMETHYLASE 3 (CMT3) is responsible for maintaining methylation in a context of CHG and together with DRM1/DRM2 for methylation in a CHH context (Chan et al., 2005). Although the methyltransferase enzymes are the core proteins involved in methylation, they are recruited and guided to their specific interaction targets by proteins, such as UBIQUITIN-LIKE, CONTAINING PHD AND RING FINGER DOMAINS 1 (URHF1) and PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA) (Baubec et al., 2015). A further insight that has recently emerged is that DNA methylation represents only one part of the DNA methylation cycle. Recently, Tet methylcytosine dioxygenases (previously named ten-eleven translocation (TET) proteins) have been identified as crucial proteins in putative demethylation pathways (Coulter et al., 2013; Scourzic et al., 2015). Indeed, the dynamics between methylation and hydroxymethylation exemplifies the balance of DNA methylation at specific regions as well as globally during early developmental reprogramming (Wu and Zhang, 2014).

Histone modifications occur as post-translational modifications predominantly to the N and C terminal tails of histone proteins. Histone proteins are organised in octamer structures forming nucleosomes as the fundamental units of chromatin (Berr et al., 2011). Initially histones were thought of as primarily structural proteins. However, it is now recognised that they play a pivotal role in regulating gene expression via structural changes of chromatin (Jung and Kim, 2012; Margueron et al., 2005). Major histone modifications include acetylation, methylation, phosphorylation and ubiquitination (Bannister and Kouzarides, 2011). A key role played by histone isoforms and post-translational modifications that is highly relevant to ionising radiation exposure, is their involvement in DNA damage repair (Hunt et al., 2013; Mondal et al., 2016). DNA repair requires multiple steps, including the initial signalling of the break, the opening of the compact chromatin to facilitate access for repair factors, and afterwards the restoration of the chromatin state (Hunt et al., 2013; for details see Huertas et al., 2009). An authoritative overview of the post-translational modifications in histones triggered in response to DNA damage is given by Mendez-Acuna et al. (2010). Changes of histone modifications have also been linked to exposure to different pollutants in both mammalian and non-mammalian species (Kim et al., 2012b; Mendez-Acuna et al., 2010; Santos et al., 2011; Wang et al., 2017). Observations of heterochromatin state maintenance over multiple successive generations following exposure to heat or osmotic stress in *D. melanogaster* suggests a mechanism by which the effects of stress are inherited epigenetically via the regulation of chromatin structure (Seong et al., 2011).

Short interfering RNAs and microRNAs are functional non-coding RNA molecules. They are not translated into proteins and are involved in gene repression via RNA deactivation and degradation (Castel and Martienssen, 2013). Single microRNAs may on average interact with ~400 different protein coding genes. Hence, changes in microRNA expression are proposed to be a key component of organism response to stressor exposure (see e.g. for plant responses Huang et al., 2016). Reduced expression of microRNA has been found in response to insecticide and fungicide exposure (Qi et al., 2014; An et al., 2013). MicroRNAs have been shown to be intimately involved in cellular response to metals such as cadmium and arsenic (Liu et al., 2016; Meng et al., 2011; Gielen et al., 2012). Important roles of non-coding RNAs in the epigenetic inheritance of DNA methylation through cell division and guiding de novo methylation after meiosis indicate key interactions between epigenetic pathways (Calarco et al., 2012; Larriba and del Mazo, 2016). In plants e.g. DNA and histone methylation by DRM2 activity and subsequent gene silencing can also be mediated by siRNAs ARGONAUTE (AGO4) and polymerase V (POLV) (Holoch and Moazed, 2015; Neeb and Nowacki, 2018). Hence dynamic interactions of different epigenetic mechanisms would be expected in response to environmental challenge.

The relative role of the different epigenetic mechanisms can vary between species. The majority of eukaryotic phyla possess cytosine methylation ranging from ≪1% in some taxa (e.g. many arthropods) to >10% for annelids, molluscs and vertebrates, with species such as *C. elegans* even proposed to lack cytosine methylation completely (Regev et al., 1998) or to be very low (~0.0033%) (Hu et al., 2015). Because of those variations in DNA methylation levels, it was initially uncertain how important cytosine

methylation may be among those phyla. However, evidence of the importance of DNA methylation in heritable responses in invertebrates following stressor exposure has begun to emerge, as well as for other epigenetic mechanisms (Seong et al., 2011; Schultz et al., 2016; Stern et al., 2014; Klosin et al., 2017). For some species, and particularly in *C. elegans*, a second DNA modification based on methylation of the N-6 position on adenine may also act as an alternative form of DNA methylation (Greer et al., 2015). In addition, the balance between DNA methylation, post-translational modifications and types of microRNA molecules (both of which are species specific and highly dynamic), presents a challenge to tease apart the roles that different epigenetic mechanism play in gene expression dynamics and ultimately phenotypic responses to stress including those in species exposed to radionuclides and other pollutants over extended timescales (Lim and Brunet, 2013).

4. Main methods used to detect DNA methylation changes

This review will mainly focus on the evidence for DNA methylation changes induced by radiation in different animals and plants and this in both lab and field conditions. The measurement of total DNA methylation levels is now routine using molecular genetic and biochemical protocols. These analyses provide a useful picture of overall methylation states. The methods have the advantages of reasonable cost per sample, established protocols, sensitivity to overall methylation pattern change and rapid sample processing (Table 1). Two global methylation methods that are commonly used are methylation sensitive amplified fragment length polymorphisms (meAFLP) and measuring the % of methylated cytosine by HPLC-MS/MS. The meAFLP technique is based on the use of two restriction enzymes, HpaII and MspI. Both HpaII and MspI recognize a CCGG sequence. MspI is able to cut both methylated recognition sites as well as unmethylated ones. In contrast, HapII is unable to cut at such locations when methylated (i.e. only unmethylated recognition sites are cut). Methylation of these restriction sites can be assessed by electrophoretic recording bands cut by MspI but not HapII on a fragment analyser (e.g. capillary sequencer). The method has been shown to demonstrate limited variability and has the benefit of an internal control (EcoRI) to account for variability in the amount of DNA input. The detection of methyl groups by HPLC-MS/MS allows highly sensitive quantification of methylated and hydroxymethyl cytosines (5 mC and 5-hmC) present in a hydrolysed DNA sample. The specific ability to detect and measure 5hmC is a specific advantage of this technique, given its recently demonstrated roles in development (Pastor et al., 2011; Song et al., 2011; Xu et al., 2011).

Although useful, application of global methylation analysis methods do not allow analysis of the specific methylation states needed to assess functional links between changes in site specific methylation, gene expression changes and phenotypic changes to be made. The use of methylation mapping techniques can provide improved resolution to identify and assess specific genes/regulatory regions of interest that are differentially methylated under specific treatment or exposure conditions. The number of options to study DNA methylation have become more diverse and methods such as reduced representation or whole genome bisulfite sequencing, are now considered close to routine. The value of these genome wide methylation mapping techniques is that they go beyond the level of an overall change to identify the gene associated sites of differential methylation. These methods are of course limited when an organism reference genome is either not available or is poorly assembled or annotated. Hence, significant effort needs to be given to genome resource development before these methods can be used to study autochthonous species.

5. Laboratory evidence for multigenerational and transgenerational effects including those induced by ionising radiation

The interest in understanding the effects of persistent pollutants, including radionuclides, on population exposed for more than a single generation is ongoing. Therefore studies of multigenerational and transgenerational stressor effects on apical phenotypes have become more common. For multigenerational studies,

Table 1
Pros and cons of DNA methylation methods. 5-mC (methylcytosine), 5-hmC (hydroxymethylcytosine), AFLP-MS (methylation specific amplification fragment length polymorphism), HPLC-MS/MS (high performance liquid chromatography coupled with tandem mass spectrometry), ELISA assay (enzyme-linked immunosorbent assay), MeDIP seq (methylated DNA immunoprecipitation coupled with next-generation sequencing), WGBS (whole genome bisulfite sequencing), RRBS (reduced representation bisulfite sequencing).

Method	Principle	Methylated base detected	Pros	Cons
AFLP-MS	Cut DNA with restriction enzymes and analyse on a fragment analyser	5-mC	Low cost per sample No need for sequenced genome Low DNA amount (250–500 ng) Low processing time	Detection of global methylation Specific equipment needed
HPLC-MS/MS	Detection of methyl groups on hydrolysed DNA sample	5-mC & 5-hmC	Medium cost per sample No need for sequenced genome Low processing time	Detection of global methylation High DNA amount (50–1000 ng) Specific equipment needed
5 mC ELISA assay	Use of monoclonal antibodies sensitive and specific for 5-mC	5-mC	Low cost per sample No need for sequenced genome No specific equipment needed Low processing time	Detection of global methylation High DNA amount (100–2000 ng)
MeDIP seq	Immunoprecipitation sequencing	5-mC	Detection of site specific methylation Low DNA amount (300 ng)	High cost per sample Need for sequenced genome Specific equipment needed High processing time
WGBS	Bisulfite conversion and DNA sequencing	5-mC & 5-hmC (oxBS-seq)	Detection of site specific methylation Low DNA amount (30 ng)	High cost per sample Need for sequenced genome Specific equipment needed High processing time
RRBS	Bisulfite conversrion and DNA sequencing	5-mC & 5-hmC (oxBS-seq)	Detection of site specific methylation	High cost per sample Need for sequenced genome High DNA amount (1000 ng) Specific equipment needed High processing time

exposure to the stressor in question is maintained in a continuously cultured and exposed population for successive generations (e.g., continuously exposed F0, F1, F2 etc.) to allow the consequences of multigenerational exposure to be assessed. Phenotypes are observed in those generations directly exposed. For these multigenerational cases, the simplest expectation is that the observed toxicity in the offspring is not greater than that in parents exposed over their full life-span (i.e. embryo until death), at least over initial generations, with possible development of tolerance over longer time-scales. Transgenerational experiments, on the other hand, consider not just effects on the exposed generation, but also effects on subsequent unexposed generation(s) reared after hatching in stressor free conditions (Skinner and Guerrero-Bosagna, 2009; Skinner, 2016; Groot et al., 2016). In such studies, stressor effects may be expected as a result of exposure of the F0 mothers in F1 embryo and F2 germline, but not in later offspring. The simplest expectation from transgenerational experiments is thus of physiological effects no greater than those observed in F0s, only in F1s (and possibly F2s), with no further such effects on the later (F3 etc.) generations.

There are cases where the simplest expectations of multigenerational and transgenerational exposure are met, including examples for plants (Iglesias and Cerdan, 2016; Groot et al., 2016; Molinier et al., 2006), earthworms (Hertel-Aas et al., 2011), zebrafish (Baker et al. (2014) (Schwindt et al. (2014) and mice (Ziv-Gal et al. (2015). However, critical analysis of reported multigenerational exposures covering a range of stressor types including radionuclides, metals, nanomaterials, organic chemical and antibiotics, suggests that, at least over the durations used in the laboratory (usually < 10 generations) the simplest expectation of similar sensitivity to F0 in later generations are not always be met. In a number of published cases, an increasing sensitivity in later generations has been observed (see Table 2 and examples below). While this prevalence may partly result from publication bias and from the clonal organisms used, the high frequency of such responses does suggest that increased sensitivity, at least over the initial generations of a multigenerational exposure, may be a common phenomenon (see Table 2).

For exposure to radiation and radionuclides there are a number of multigenerational lab-studies that have reported patterns of increased generational sensitivity for continuously exposed populations (see Table 2 for exposure details). For daphnids it has been reported that the progeny of organisms continuously exposed to gamma radiation, Am^{421} (and depleted uranium) show higher sensitivity in the F1 and F2 generations than that for parents depending on the endpoint measured (Pane et al., 2004; Biron et al., 2012; Alonzo et al., 2008b; Parisot et al., 2015). Similarly, Zaka et al. (2004) exposed 5-day old *Pisum sativum* plants over three generations to different acute doses of gamma radiation. Results indicated that doses apparently harmless for the parental plants adversely affected the F2 generation. *Arabidopsis thaliana* plants exposed to different dose rates of gamma radiation during the vegetative growth stage for one or two generations also showed greater response in the later generation. In this case, increased responses of antioxidative enzyme activity were measured in multigenerationally exposed plants (van de Walle et al., 2016). This response was accompanied by phenotypic changes, such as accelerated flowering after multigenerational exposure (Horemans et al. pers. comm).

Transgenerational studies with radionuclides or after radiation-exposure have shown responses not just in continuously exposed generations, but also in later unexposed generations. A study of reproductive effects of gamma radiation in the nematode *C. elegans* exposed from F0 to F2, either continuously or only at F0 generation also found transgenerational effects in F2 organisms greater than in the initially exposed nematodes (Buisset-Goussen et al., 2014). Daughter cells of chronically gamma-radiation-exposed *Lemna minor* plants died off notwithstanding only a limited growth reduction in the exposed mother colonies (10–30%) indicating that the effects were, thus, greater in the recovering non-exposed plants than in the exposed F0s (Van Hoeck et al., 2017). These examples of transgenerational effects leading to increased sensitivity of progeny

Table 2
Overview of lab-based studies in which ecotoxicological relevant model organisms were exposed to radiation, radioisotopes or other toxins for multiple generations; F0=Parental organism, F … = offspring with the number indicating the generation.

Species	Chemical	Generations	Observed phenotype	Ref
C. elegans	Gamma radiation 7–42 mGy/h	F0–F2	Greater reproduction effects in multigenerationally and transgenerationally exposed F2s than F0 generation	Buisset-Goussen et al. (2014)
D. magna	Gamma radiation 0.007–35 mGy/h	F0–F2	Toxicity on multiple traits increased from F0to F2	Parisot et al. (2015)
D. Rerio	Gamma radiation 9–53 mGy/h	F0–F1	Effect on DNA damage, transcription, lipid peroxidation and demographic endpoints in F1	Hurem et al. (2017), Hurem et al. (2018b), (2018a)
D. Rerio	Uranium 20–250 μg/L	F0–F1	Effect on DNA damage, transcription, DNA methylation and demographic endpoints in F1	Bourrachot et al. (2014), Gombeau et al. (2017)
D. magna	Americium 0.3–15 mGy/h	F0–F2	Threshold for effects on reproduction reduced from 1.5 $mGyh^{-1}$ in F0 generation to 0.3 $mGyh^{-1}$ in F2 and F3	Alonzo et al. (2008a,b)
D. magna	Uranium 2–50 μg/L	F0–F1	Greater reduction in fecundity in F1 than F0at 50 μg/L	Plaire et al. (2013)
D. magna	Nickel 42–85 μg/L	F0–F1	Greater reduction of ATP levels in F1 compared to F0	Pane et al. (2004)
C. elegans	Ag nanoparticles EC30-value	F0–F10	Greater (10 fold) sensitivity in F2, F5, F8 and F10 generations compared to P generation	Schultz et al. (2016)
D. magna	Ag nanoparticles EC10-EC50	F0–F10	Population growth rate at 10 μg/L reduced by 80% in F2s compared to 21% in F0 generation	Volker et al. (2013)
D. magna	Penta-chlorophenol 0.0002–2 μmol/L	F0–F3	Population growth rate reduction increases from 28.2% to 34.9% −46.3% in F0, F1, F2 generations	Chen et al. (2014)
D. magna	Tetracycline 0.1–5 mg/L	F0–F1	NOEC decreased from 5 mg/L to 0.1 mg/L from F0 to F3	Kim et al. (2012a,b)
D. magna	Enrofloxacin 13 mg/L	F0–F1	Reproduction NOEC decreased from 30 mg/L to 3.1 mg/L from F0 to F1 generation	Bona et al. (2015)
C. elegans	Uranium 4–50 μg/L	F0–F16	Greater maximal length but increased sensitivity to uranium across the generations	Goussen et al. (2015)
C. elegans	Uranium 4.6 μg/L	F0–F22	Increase of sensitivity from F0 to F6 and subsequent adaptation until F22	Dutilleul et al. (2014)

match similar results found for other stressors, suggesting a possible common mechanism (Schultz et al., 2016; Moon et al., 2017; Annacondia et al., 2018; Groot et al., 2016).

The current multigenerational and transgenerational toxicity literature is dominated by lab-studies with relatively high exposure dose rates (7–420 mGy/h, see Table 2) and for ecotoxicological relevant species like *C. elegans*, *D. magna* and zebrafish (Table 2). For *C. elegans* and *D. magna*, the experimental populations that have been used in most laboratories, multigenerational and transgenerational exposure studies are clonal. Hence, the potential for selection of alleles that may lead to evolution of tolerance in later generations in a multigenerational exposure experiment is limited. This is true especially because the majority of such experiments are conducted over only a relative limited number of generations (<10 and usually ≤ 3). Indeed, when nematodes were continuously exposed for 22 generations to U, adaptation was shown to occur (Dutilleul et al., 2014). Although many studies have shown generationally increased sensitivity and its transfer, the clonal nature of species may be accentuated, because the limited genetic variation of the inbred strains. In the study of Dutilleul et al. (2014) for nematodes discussed above, the population used that showed adaptation composed of wild isolates with increased genetic diversity above the clonal *C. elegans* strains used for previous multigenerational studies. Hurem et al. (2018b) showed effects on the transcriptome in offspring from irradiated zebrafish that were even accentuated in offspring produced from the same parents does, however, indicated the potential to identify epigenetic responses in a genetically diverse population.

Multigenerational exposure experiments by their nature involve continuous incubation of populations with a toxicant or stressor, with generational phenotyping to allow detection of changes in sensitivity. In such studies, increased sensitivity in the progeny could theoretically arise if any toxicant induces “damage” that can be transferred to subsequent exposed generations. Indeed Parisot et al. (2015) highlighted a possible role of DNA damage in multigenerational effects by finding a correlation between increased sensitivity and the transmission of DNA damage in daphnids exposed to gamma radiation. This possible role of DNA damage and genome instability in multigenerational and transgenerational effects may lead to hypotheses about the type of stressors that may cause such phenomena.

The role of both paternal and maternal effects has received much research attention in ecology and toxicology (Frost et al., 2010; Wigle et al., 2007). Within these studies there is strong evidence that indicate how the direct exposure of the developing embryo and germline can be adversely affected as a result of exposures to environmental pollutants. However, in addition to these more direct effects, there is evidence of a potential role of the epigenome in the transfer of aberrant phenotypes to F1 offspring and indeed to generations beyond (Bowman and Choudhury, 2016; Chen and Baram, 2016; Wang et al., 2017). For example, exposing *C. elegans* to nanoparticles resulted in aberrant phenotypes, that were persistent in future unexposed populations for 3 or more generations (Greer et al., 2011; Katz et al., 2009; Rechavi et al., 2014; Schultz et al., 2016). When transgenerational effects occur over these generation scales, germline exposures alone cannot be solely responsible, with the potential that epigenetic mechanisms may be intimately involved.

6. Evidence for long-term effects induced by radiation on the environment coming from field studies

The nuclear accidents of Chernobyl and Fukushima have made it possible to investigate possible effects of radiation on a whole range of organisms exposed to radionuclides under field conditions over extended timescales. The temporal changes that occurred in radiation exposure in the CEZ and the FEZ, have resulted in a specific time course of responses among non-human biota in the regions (IAEA, 2006; Beresford et al., 2016; Beresford and Copplestone, 2011; IAEA, 2015). The most pronounced biological effects were seen in the first and second phases after the accident. In these early stages, the high doses experienced shortly after the accident by the forest located to the west of the Chernobyl reactor, later designated as the Red-forest. In this Red-forest massive death of pine trees was observed, while deciduous species survived despite an early loss of leaves and damage to woody tissues (Arkhipov et al., 1994; Kryshev et al., 2005). Similar morphological differences such as loss of apical dominance were recently also reported in Japanese red pine in the FEZ (Yoschenko et al., 2016). In the first phase after the nuclear accidents, direct effects such as a decrease in numbers of small mammals as well as reduced development or survival of embryos was also seen (Geras'kin et al., 2008) and the loss of specific groups of soil biota were also recorded in the most contaminated areas (Krivolutsky, 1996; IAEA, 2006). These effect could also be linked to the high levels of initial exposure that were experienced following both nuclear accidents. Initial dose rates in the most contaminated areas of CEZ were as high as 5 mGy/h (IAEA, 2006).

The second phase characterised by a decrease in dose rates due to disapearence of short-lived radioisotopes and wash-out and run-off (IAEA, 2006). This phase started from two months after the accidents, was associated with reductions (up to a factor of 30) in the density of invertebrates living in the forest litter experiencing greatest contamination. These decreases were linked to radionuclide exposure effects on reproduction and recruitment (Krivolutsky, 1996).

In the third exposure phase resulting from the Chernobyl accident, most strongly affected populations of species of pine trees and soil invertebrates were shown to slowly start to recover (Arkhipov et al., 1994; Zelena et al., 2005). Recovery from the initial negative effects was also found in birch pollen, embryonic cells of herbaceous plants like evening primrose embryonic cells (Boubriak et al., 2008) and *Arabidopsis thaliana* (Kovalchuk et al., 2004) and in exposed birds (Galvan et al., 2014). In this phase Cs-137 and Sr-90 are the main contributors to the dose with some additional Am-241 and Pu-isotopes for CEZ and Cs-137/134 for FEZ (Horemans et al., 2018; Saenen et al., 2017). Ambient dose rates now measured are maximally 0.5 mGy/h and these can be found in the forest western from the nuclear power plant designated as the Red Forest (Beresford, personal communication).

In addition to changes observed at individual or population levels, the radiological impacts within both the CEZ and the FEZ, have also been reported at the sub-organismal level. Aberrant cell frequencies were found in the root meristem of plant seedlings (Geras'kin et al., 2011). Increased mutation rate (Kuchma et al., 2011) and gene deregulation (Zelena et al., 2005), have been seen in pine trees. Increased mitochondrial DNA haplotype and nucleotide diversity have been reported in bank voles (Matson et al., 2000; Baker et al., 2001), chromosomal aberrations in mice (Kubota et al., 2015) and in soil invertebrates, increased DNA damage in earthworms (Fujita et al., 2014). Most of these studies so far have, however, failed to find a link between these observed sub-organismal effects and impacts at higher level of biological complexity such as radiation-induced phenotypical changes and long-term effects on population dynamics (Meeks et al., 2009; Meeks et al., 2007).

The adaptive responses that have been indicated during the extended third phase of exposure following the two accidents at Chernobyl and Fukushima are at least in part due to the reduction over time in dose rates and, hence, exposure. Although a memory-effect of the early high exposures cannot be excluded, the

decreased exposure in the third phase might allow both increased *in-situ* recruitment and survival leading to positive population growth, as well as the survival of inwardly migrating individuals (Jackson et al., 2004; Boubriak et al., 2008; Boubriak et al., 2016). Additionally it is also possible that increased tolerance, through selection and as a result of favourable mutations may make a contribution (Kovalchuk et al., 2003). However, in *Arabidopsis* no additional mutations compared to plants collected in control sites were found in the CEZ (Abramov et al., 1992). Ostensibly the probability of favourable mutations may be seen as unlikely. Assuming a germline mutation rate in plants of about 10^{-5} to 10^{-6} per gamete, one would expect only one mutation in 500,000 plants (Kovalchuk et al., 2003). Consequently it has been proposed that rapid adaptation may be more strongly linked to epigenetic processes in the development of locally adapted phenotypes at polluted sites (Kovalchuk et al., 2003).

7. Evidence for a role of epigenetics in long-term or transgenerational responses to radiation-induced stress

Studies on the effects of stressors on the epigenome of organisms under environmentally relevant exposure conditions have covered examples for ionising radiation exposure and for a range of chemical and non-chemical stressors in different species. Within these studies, a range of epigenetic mechanisms and endpoints have been considered (for review see e.g. Aluru, 2017; Bruce et al., 2007; Kim et al., 2012b; Mirbahai and Chipman, 2014). Initial adaptive changes resulting from exposure to these different stressors have been found for key components of the epigenome, such as DNA methylation (Vandegehuchte and Janssen, 2011; Marczylo et al., 2016), non-coding RNAs (Kure et al., 2013; Wang et al., 2013; Song et al., 2012) and histone modifications (Raut and Sainis, 2012; Mondal et al., 2016). Changes in microRNA expression have further been shown to be involved in metabolism following starvation and the transfer of longevity (Greer et al., 2011; Katz et al., 2009; Rechavi et al., 2014). In plants, small RNAs play an important role in chromatin remodelling and DNA methylation through RNA-directed DNA methylation also in different abiotic stresses in plants (Hirayama and Shinozaki, 2010).

Although long a controversial issue and still not fully elucidated, recent evidence has suggested that in plants, vertebrates and invertebrates, epigenetic marks induced by adverse conditions encountered by the parents can be partly stable across generations (Uller et al., 2015; Klosin et al., 2017; Whittle et al., 2009; Saze, 2012; Pecinka and Mittelsten Scheid, 2012; Sudan et al., 2018; Stassen et al., 2018; Norouzitallab et al., 2019). Such retention can potentially lead to transgenerational heritable changes in offspring (Verhoeven et al., 2010; McCarrey, 2012; Guerrero-Bosagna and Jensen, 2015; Guerrero-Bosagna et al., 2012). Evidence has been accumulated for the transfer of DNA methylation patterns in the germline (Verhoeven et al., 2010; Verhoeven et al., 2016). As an example of the link between epigenetic mechanisms and transgenerationally altered phenotypes a study of transgenerational response to temperature in *C. elegans* has identified altered trimethylation of histone H3 lysine 9 as a mechanism for transgenerational inheritance (Klosin et al., 2017). On the other hand, in *Arabidopsis*, nickel chloride caused a change in DNA methylation patterns and some of this was inherited by the following generation (Li et al., 2015). In the offspring of mechanically wounded *Mimulus guttatus* plants changes in methylation could be associated with transgenerational plasticity (Colicchio et al., 2018). Depending on the methylation context, CG or non-CG methylation, these changes were found to be in gene coding regions or transposable elements, respectively (Colicchio et al., 2018). Dandelions (*Taraxacum officinale*) also showed altered DNA methylation that was largely inherited by the next generation of the asexually reproducing plants when exposed to a number of different stressors (Verhoeven and van Gurp, 2012; Verhoeven et al., 2016).

A growing number of papers also indicate that exposure to ionising radiation will lead to changes in epigenetic markers (Table 3). For example, scots pine trees present in the most contaminated areas around the Chernobyl nuclear reactor have been found to have hypermethylated DNA, with this hypermethylation directly (Kovalchuk et al., 2003) or transiently associated with the radiation dose received (Volkova et al., 2018). Further work established that the genomes of young trees planted on contaminated soil showed higher levels of cytosine methylation than trees in uncontaminated soil. However, levels of cytosine methylations in plants grown in clean soil from seeds taken from previously exposed plants were not found to differ significantly from controls Kovalchuk et al. (2003). Hence these results are suggestive of a within generation genome methylation effect, rather than of any multigenerational or transgenerational mechanism, as a result of exposure during the somatic development. However, since only overall levels of DNA methylation inheritance was addressed, the potential for loci specific cannot be discounted.

In a study of the progeny of *Arabidopsis* sp. sampled in three consecutive years from areas with different levels of contamination within the CEZ, higher resistance to mutagens in progeny of plants from the most contaminated sites compared to unexposed plants was identified (Kovalchuk et al., 2004). This difference in sensitivity could be attributed to higher expression of free radical scavenging enzymes and DNA-repair enzymes and was associated with global genome hypermethylation in the contaminated site plants. It was hypothesised from these data that epigenetic regulation of gene expression and genome stabilization may play a key role in the underlying processes that stabilise *Arabidopsis* genome architecture under exposure to ionizing radiation exposure (Kovalchuk et al., 2004). A number of papers have proposed a link between epigenetic effects and non-targeted effects (NTE) such genomic instability and bystander effects (Schofield and Kondratowicz, 2018). However, while the existence of non-targeted effects is well established (Morgan, 2002; Kadhim et al., 2004; Pouget et al., 2018; Burdak-Rothkamm and Rothkamm, 2018), and studies have shown an association between the two effects (e.g., Kaup et al., 2006; Xu et al., 2015), evidence of a causal relationship is more elusive, since NTE could be either a mechanism or a consequence of epigenetic changes (Schofield and Kondratowicz, 2018). Changes in the level of DNA methylation may be intimately linked with transcription remodelling in response to radiation exposures, including changes to the pathways involved in antioxidant defence and DNA repair. Confirmation of such effects would require the use of combined genome wide DNA methylation mapping and transcriptomic approaches to allow loci specific methylation to be associated with gene expression phenotypes in exposed plants.

A study of the pale blue grass butterfly *Zizeeria maha* within the FEZ has provided a further indication of the potential for heritable epigenetic changes in a population exposed to ionising radiation (Hiyama et al., 2012; Hiyama et al., 2013). Mild morphological abnormalities were observed on some individuals of adult butterflies collected one month after the accident, but an increase of the severity of these abnormalities occurred in the F1 generation that were further inherited by F2 progeny. These abnormalities and their transgenerational transfer were proposed to be attributable either to random mutation on important genes or through epigenetic mechanisms. As the underlying mechanisms of these effects were not studied by the authors, leaving the mechanistic basis of the observed effects and their inheritance remain an open question.

Recently a number of European research groups have combined research efforts to study possible epigenetic changes in organisms

Table 3
Overview of studies in which changes in epigenetic mechanisms (DNA methylation, histone modifications or miRNA's) are measured in organisms exposed to radiation in a long-term set-up (within or over generations) either in laboratory or field conditions. F0=Parental organism, F … = offspring with the number indicating the generation, CEZ: Chernobyl Exclusion Zone, FEZ: Fukushima Exclusion Zone.

		Organism	Experimental conditions	Epigenetic changes	Additional endpoints	Reference
Laboratory exposed	Plants	*A. thaliana*	F1, F2, multigenerational (F0 from CEZ, 1.8 −4.4 μGy/h) methyl methane sulfonate (140 μM) or Rose Bengal (10 μM)	DNA methylation: hypermethylation in both F1 and F2	Higher resistance to mutagens, increased expression of ROS scavenging enzymes and DNA repair enzymes	Kovalchuk et al. (2004)
		P. sylvestris	F0, trans- and multigenerational set up, on contaminated soil both acute (~10Gy) and chronic (~80Gy) (F0 from CEZ, (absorbed dose 1986: >60Gy, 10–60Gy, 1–10, 0.1–10Gy),	DNA methylation: hypermethylation in exposed	–	Kovalchuk et al. (2003)
		A. thaliana	F1, F2 transgenerational, Progeny of plants collected at CEZ 1.8–4.4 μGy/h	DNA methylation: hypermethylation	–	Kovalchuk et al. (2004)
		A. thaliana	F0, F1, F2, mutligenerational, 14 day exposure during vegetative state, 22, 38, 86, 457 mGy/h	DNA methylation: dose-dependent hypermethylation, strongest in F2	Changes in ROS-scavenging enzymes, DNA repair and developmental traits, mutants in methyltransferases showed increased sensitivity to radiation	van de Walle et al. (2016), Saenen et al. (2017)
	Invertebrates	*D. magna*	F0, F1, F2 and F3 transgenerational, F0 exposed for 25 days, 6,5 μGy/h or 41.3 mGy/h	DNA methylation: hypomethylation but dose-rate independent	Reduction in fecundity in F0, no adverse effects in F1, F2, F3	Trijau et al. (2018)
	Vertebrates	*D. rerio*	F0, F1, F2, F3, transgenerational, exposure during gametogenesis, 8.7 mGy/h, 28 days	DNA methylation: Genome-wide in F1, locus-specific regions up to F3	Linked to gene pathways changes and adverse effects in progeny	Hurem et al. (2018b), Kamstra et al. (2018), Hurem et al. (2017)
		D. rerio	F0, F1, multigenerational, exposure during gametogenesis, 8.7 mGy/h, 28 days	miRNA expression in F1 embryos	–	Martin et al. in prep
		D. rerio	F0, F1, F2 transgenerational, gametogenesis, 8.7 mGy/h, 28 days	Histone modifications (hypermethylation) at specific loci in F0 and F1 but no longer in F2	–	Lindeman et al. (2019)
		S. salar	F0-embryo's, exposure from one-cell fertilized eggs till early gastrula stage, 1, 10, 20 or 30 mGy/h	Histone modification (hypermethylation) at specific loci at highest dose rate	–	Lindeman et al. (2019)
Field collected	Plants	*P. sylvestris*	F0, (Belarus, Chernobyl affected area), annual absorbed dose: 10–158 mGy or 1–14 μGy/h	DNA methylation: transient with dose, hypermethylation	–	Volkova et al. (2018)
		C. bursa pastoris	F0, FEZ: total dose rates: 0.13–38 μGy/h	DNA methylation: no change	–	Horemans et al. (2018)
		A. thaliana	F0, CEZ: total dose rates: 0.1–160 μGy/h	DNA methylation: Hypomethylation at highest dose rates	–	Horemans et al. (2018)
		G. max	F0, after 7 generations CEZ, total accumulated dose: 1–132 mGy	DNA methylation: slight increase (10%) in radio-contaminated samples	Increased levels of single and double DNA strand breaks	Georgieva et al. (2017)
	Invertebrates	Earthworms (*A. calinginosa, O. lacteum*)	F0, CEZ, total dose rates 0.12–41 μGy/h	DNA methylation: site-specific differences *A. calinginosa.* for no or limited changes found for *O. lacteum*	–	Saenen et al. (2017)
	Vertebrates	*H. arborea*	F0, FEZ, total dose rate 0.38–41,7 μGy/h	DNA-methylation: hypermethylation, dose-dependent	Concomitant with increased DNA damage	Saenen et al. (2017)

exposed to ionizing radiation, in the laboratory or *in situ* (Chernobyl or Fukushima), in a range of species (plants, earthworms, fish, frogs) (Table 3). The focus of the combined efforts was to better understand the possible role of these mechanisms in the induction of long-term/transgenerational effects and their relevance as possible biomarkers of ionising radiation (Adam-Guillermin et al., 2013). The organisms chosen were all reproductive non-clonal organisms. Hence the work addresses multigenerational and transgenerational effects in genetically diverse populations. For example, in offspring of zebrafish that were exposed to ionising radiation during gametogenesis, a large number of differentially methylated regions were observed, with five specific loci showing a persistent effect up to the third generation (Kamstra et al., 2018). These methylation changes could be linked to changes in gene pathways and adverse effects found in progeny (Hurem et al., 2017; Hurem et al., 2018b). In the same exposure study, miRNA expression was measured in first filial offspring and histone marks H3K4me3, H3K9me4 and H3K27me3 at 3 specific loci (Lindeman et al., 2019). There were 23 differentially expressed miRNAs indicating a multifaceted response to ionising radiation exposure (Kamstra et al., personal communication). Differentially enriched histone marks were observed as well at the three measures loci in F1 offspring, but interestingly these effects were diminished in F2 offspring (Lindeman et al., 2019). Although only exposed embryo's were analysed similar changes in histone markes were found for Atlantic salmon (*Salmo salar*) at higher dose rates (Lindeman et al., 2019).

A dose-rate dependent induction of total methylation levels was observed in *A. thaliana* plants exposed in the lab to different levels of gamma radiation for up to three generations (Saenen et al., 2017)). Moreover triple methyltransferase mutants (*drm1drm2cmt3*) of *A. thaliana* showed increased sensitivity to irradiation including an increased induction of oxidative stress (Saenen et al., 2017).

In the clonal cladoceran *Daphnia magna*, transgenerational inheritance of DNA methylation changes were studied using bisulphite sequencing, after irradiation of generation F0 to 6.5 μGy/h or 41.3 mGy/h (Trijau et al., 2018). Significant methylation changes at specific CpG positions in every generation were found, independent of dose rate and with a majority of hypomethylation. The total number of common differentially methylated regions was greatest between generations F2 and F3, with three specific persistent loci associated to genes known to play a role during exposure to ionising radiation. The results above suggest a role of enhanced methylation induced by chronic exposure to radiation in lab-conditions and indicate the multi- and transgenerational natures of these responses.

For earthworms, studies of DNA methylation in the laboratory and CEZ have shown effects of ionising radiation exposure on DNA methylation pattern as measured by methylated AFLP analysis (Saenen et al., 2017). There are, however, specific challenges in the interpretation of the role of radionuclide exposure in these responses. Large differences in genetic diversity that may occur between morphological similar earthworm “species” may, for example, make it difficult to identify DNA methylation changes unless clades are assessed separately. Indeed clades of the earthworm *Lumbricus rubellus* were found to differ in the nature of their genetic and DNA methylation responses to soil contamination by copper and arsenic (Kille et al., 2013). A similar response was found within an analysed laboratory experiment, where both between and within species allelic differences precluded the identification of a clear DNA methylation profile response to exposure. In CEZ collected earthworm from two species *Aporrectodea caliginosa* and *Octolasion lacteum*, a clear site specific change in DNA methylation status was found (Saenen et al., 2017) in *Aporrectodea caliginosa*, while only limited separation was found for *Octolasion lacteum*. While these site specific changes in DNA methylation patterning may indicate a response to radionuclide exposure, a caveat is that the earthworms were collected from sites that differ in the prevailing ecosystem characteristics (wetland and garden sites).

An *in situ* study of DNA methylation in frogs collected from a range of differently polluted sites within the Fukushima impacted area indicated that DNA methylation measured as methylated cytosines increased with total absorbed dose rate, up to 7 μGy/h. This increase was concomitant with increased levels of DNA damages (Saenen et al., 2017). As in the study for *A. thaliana* in the CEZ (Kovalchuk et al., 2004), this finding of higher DNA methylation associated with increased DNA damage and repair activity supports a functional role of the epigenome in maintaining DNA integrity. These results are in agreement with previous work done on zebrafish exposed to depleted uranium, where changes in DNA methylation patterns both at specific restriction sites and across the whole genome, were observed in F_0 adults and F_1 at the same time as DNA damages (Gombeau et al., 2016; Gombeau et al., 2017). A transient increased methylation with the dose rate was also observed in needles of *Pinus sylvestris* plants collected in radioactively contaminated areas of Belarus (Volkova et al., 2018). In contrast no dose dependent changes in total methylation levels were observed for *C. bursa pastoris* plants sampled in spring 2016 in contaminated areas of FEZ. For *A. thaliana* plants collected in CEZ a decrease in global DNA methylation was found in the highest contaminated fields (Horemans et al., 2018).

Overall the range of studies of the epigenetic response of species to radionuclide exposure in the laboratory point to a role of the epigenome in adaptive responses. The field studies with plants (pine trees and *Arabidopsis*) showed the potential for ionising radiation to induce changes in DNA methylation levels under field conditions (Georgieva et al., 2017; Kovalchuk et al., 2003; Kovalchuk et al., 2004). For invertebrates, the laboratory and studies in the CEZ and FEZ have partially supported a role of increased methylation in response to radiation among the majority of species studied to date. The challenge from these field studies remains to unequivocally link the observed effects on the epigenome to radiation exposure, rather than to other aspects of environmental variation across the CEZ and FEZ. Studies that specifically investigate changes in mutant lines with reduced DNA methyltransferase activity, as outlined above for *Arabidopsis*, provide initial causal evidence on the validity of such as link.

8. Knowledge gaps on epigenetic changes induced by ionising radiation

Although all three different epigenetic layers have been implicated as key mechanisms involved in determining the long-term and transgenerational responses of species to pollutant, including ionising radiation exposure, a majority of studies have to date focussed on the role of DNA methylation (Norouzitallab et al., 2019; Sun et al., 2018; Meehan et al., 2018; Burgio et al., 2018). In cases where difference in DNA methylation response following exposure to ionising radiation are observed, a number of aspects that need further consideration in future work can be drawn.

(i) Global methylation alone may be too coarse a measure of epigenetic change to be able to see all biologically relevant differences induced by exposure to low dose rates. As such, differences in methylation might be located in specific sequences of the genome but cannot be detected by global measurements. Therefore, it is important to also include other techniques (e.g. whole genome or reduced representation sequencing) in order to identify specific epigenetic

changes and to link these observations to effects on gene expression and physiological change (Paun et al., 2019).

(ii) Different DNA methylation response in function of cell type, tissues (as seen in the depleted uranium exposure in zebrafish by Gombeau et al., 2016), or age (as seen in frogs exposed at Fukushima (Saenen et al., 2017), could induce a mosaic of DNA methylation response at the whole organism level, limiting the capability to identify a clear change in methylation pattern. This argues for the analysis of more homogenous tissues or cell types.

(iii) Initial changes of DNA methylation resulting from an initial radiation exposure may be lost in individuals exposed over generations of chronic exposure as found for pine trees by Kovalchuk et al. (2003) and in the second generation of lab-exposed *A. thaliana* in a laboratory exposure to gamma radiation. Such results suggest that DNA methylation may be a transient acting potential as an intermediate state preceding later genetic selection and adaptation.

(iv) Genetic diversity of species between isolated local populations within the CEZ and FEZ may mean that populations exposed to different levels of radiation may show markedly different epigenetic responses, precluding the identification of a clear exposure response relationship. The presence of natural and man-made barriers to dispersal, which may result in population isolation, across these two zones, may accentuate such differences (Meeks et al., 2007).

(v) Although less commonly studied than DNA methylation, the work done to date on the responses of other epigenetic mechanisms like microRNAs or histone modifications to ionising radiation exposure, suggest that these complimentary epigenetic mechanisms may play roles in the response to radiation that may even dominate over DNA methylation changes (Putiri and Robertson, 2011; Brautigam et al., 2013);

(vii) Long time exposure to radiation might result in selection of alleles linked to tolerance, potentiated potentially by increased mutation (as is seen for frogs in FEZ) that may lead to genetic adaptation that might negate differences in DNA methylation. An interplay between epigenetic changes, notably DNA methylation, and the targeting of mutation has been proposed mechanisms (Putiri and Robertson, 2011; Brautigam et al., 2013).

(vii) Confounding factors (habitat, soil type, water chemistry; climate etc.) may increase the variability between the samples that may result in changes in DNA methylation that overlie and obscure effects due to ionising radiation making it difficult to link epigenetic change to exposure (see discussion, Garnier-Laplace et al., 2013).

9. Differential DNA methylated regions as possible biomarkers for exposure or effect of a pollutant and its use in risk assessment

There is a strong interest in finding possible biomarkers for exposure and effects of radiation and additionally those that can be markers for long-term effects. Loci specific changes of DNA methylation have been proposed as possible biomarkers for different environmental cues (Meehan et al., 2018) and could possibly be used as molecular fingerprints for e.g. genotoxicity induced when exposed to ionising radiation. However, it is also recognised that significant challenges related to the effects of genetic background and the influence of confounding factors also exist (Pernot et al., 2012). Further studies at environmental realistic doses are needed to assess the prevalence of such responses, including under field conditions. In particular, the use of more targeted methods are needed that identify loci specific changes in DNA methylation, histone modification and the expression of relevant miRNAs.

A clear conclusion that emerges from past and ongoing studies concerning the role of the epigenome in response to chronic radiation exposure, lies in the interpretation of changes in methylation patterns from field collected samples in respect to attribution of the principal driver of effects. Specific challenges relate to working with some autochtonous species for which genome resources may be lacking and, the influence of confounding factors which may mask the causal response between ionising radiation exposure and epigenetic changes. In efforts to attribute changes to specific stressor effects, epigenetic approaches may be more powerful indicators of effects when linked to known biomarkers using, for example, transcriptional analysis. When used in conjunction with other mechanistic measurements, epigenetic analysis has the potential to enhance the ecological relevance of molecular biomarkers, as described in the Adverse Outcome Pathway concept (Groh et al., 2015). Given the critical need to establish the nature of effect of prolonged low level exposures, this integrated approach seems a promising way forward, building as it does on existing mechanistic knowledge.

The risk assessment process for radiation and radionuclides is largely based on using results from short-term bioassays to predict the effects of exposures in the field. The validity of this laboratory to field extrapolation is one of the key uncertainties in risk assessment (Lourenco et al., 2016). A comparison of field vs laboratory studies has indeed shown that species sampled in the field were 8 times more sensitive than those studied under laboratory controlled conditions (Garnier-Laplace et al., 2013) indicating the need for further torough lab to field studies. One of the largest differences between laboratory bioassays and field exposures is exposure duration. This is true within a single generation (intergenerational exposure), but even more so when subsequent generations are exposed to the same stressful environment (multigenerational exposure) or when exposure of the parent generation has a subsequent effect on the non-exposed offspring (transgenerational exposure). When multigenerational exposures occur, these may result in effects in later generations that match, and can even exceed those found in exposed F0s (see Table 2). The biological response of species mediated through the genome and epigenome appear to play a role in the development of such effects. Such findings may require a more refined understanding to support and reduce the uncertainty in risk assessment for chronic low dose exposures. Hence, the mechanisms that underlie differential responses within and over generations to previous (sub-lethal) radiation-exposure require further studies to provide a baseline for the development of new approaches such as Adverse Outcome Pathways on low dose radiation exposure, to the risk assessment for both wildlife and human.

10. Conclusions and recommendations for further development and application

Work reported to date in both lab and field have indicated changes in DNA methylation resulting from chronic exposure to low dose of ionising radiation. A common conclusion from this work is that both laboratory and field studies have demonstrated changes in overall methylation in organisms exposed chronically to ionising radiation. Generally a chronic enhanced ionising radiation level induced hypermethylation or methylation pattern change which could be taken as a response to induce DNA stability. The main advantage of laboratory studies is the ability to set up controlled multi/transgenerational studies, and avoid confounding factors like local difference in soil characteristics, microclimate.

Together with the use of homogeneous populations, this allows for greater insight into the underling mechanisms and processes. Field studies can provide the increased environmental realism of the responses studied. Although data suggest that methylation changes can be observed in different organisms a lower dose rates than those seen in laboratory experiments. The challenge remains to unequivocally link such observations to a specific cause. Furthermore, processes linked to the potential for population adaptation and interactions with other environmental stressors can add a further level of complexity as compared to laboratory studies. Improvements could be made by increasing site coverage and further targeted work on molecular mechanisms, as well as data on the background levels and variations in methylation changes.

From the studies presented here, it can be concluded that DNA methylation might be the key to transferring the response to ionising radiation from one generation to the next. Whereas measuring total DNA methylation can be performed without any prior information on genetic background of the species, the rapid technical evolution and the decreasing cost of sequencing analyses will offer a wider comparison of radiologically induced DNA methylation in different biological models and provide greater insight into the underlying mechanisms. An important step will be to compare the sensitivity, reliance and above all specificity of DNA methylation as a possible biomarker of ionising radiation exposure at environmentally relevant levels, with other epigenetic mechanisms such as histone modifications and microRNAs linked to responses at higher level biological complexity e.g. changes in growth and reproduction.

Declaration of interest

None.

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