Chapter 4

# Understanding Low-Dose Exposure and Field Effects to Resolve the Field-Laboratory Paradox: Multifaceted Biological Effects from the Fukushima Nuclear Accident

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Additional information is available at the end of the chapter

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*"Everything should be made as simple as possible, but not simpler."*

*--- Albert Einstein*

**Abstract**

Many reports about the biological effects of the Fukushima nuclear accident on various wild organisms have accumulated in recent years. Results from field-based laboratory experiments using the pale grass blue butterfly have clearly demonstrated that this butterfly is highly sensitive to "low-dose" internal exposure from field-contaminated host-plant leaves. These experimental results are fully consistent with the filed-collection results reporting high abnormality rates. In contrast, this butterfly is highly resistant against the internal exposure to chemically pure radioactive cesium chloride under laboratory conditions. To resolve this field-laboratory paradox, I propose that the field effects, which are a collection of indirect effects that work through different modes of action than do the conventional direct effects, play an important role in the "low-dose" exposure results in the field. In other words, exclusively focusing on the effects of direct radiation, as predicted by dosimetric analysis, may be too simplistic. In this chapter, I provide a working definition and discuss the possible variation in the field effects. I include an example on the misunderstanding of the field effects In the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2017 Report. Lastly, I discuss a theoretical application of the butterfly model to humans.

**Keywords:** biological effect, ecological effect, field effect, Fukushima nuclear accident, low-dose exposure, indirect effect, UNSCEAR

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## 1. Introduction

In terms of economic loss, the Fukushima nuclear accident that occurred in 2011 and the Chernobyl nuclear accident that occurred in 1986 are the worst nuclear accidents in the history of mankind [1]. Although considerable research results have accumulated for the Chernobyl disaster, there are still considerable debates concerning its biological effects [2–4]. The reasons for these disagreements among researchers are likely multifaceted, but one reason stems from the fact that the Chernobyl nuclear accident occurred in the former Soviet Union, which made it difficult for international researchers to easily access the contaminated areas and the critical data. In addition, some important tools and methods for biological analyses, such as those for genomic analysis and computational applications, were not yet available at that time. Considering these points, the Fukushima nuclear accident is the first historical case in which researchers have been politically and technically allowed to perform field work and laboratory experiments after such a major nuclear accident. In other words, scientists working in the second decade of the twenty-first century are responsible for correctly evaluating the biological effects of the Fukushima nuclear accident.

Because of the large-scale nature of the accident, many research questions have been developed for studies on the biological consequences of the accident at the ecological, organismal, and molecular levels [5]. However, the most important question is to determine *how severe the biological impacts from the accident are*. This is different from questions that investigate how severe the biological impacts from radiation exposure (or, more precisely, effective radiation doses) are. That is, the direct impacts from the exposure to radiation are possibly only one type of the impacts from the accident. However, many researchers have tried to understand the biological impacts of the Fukushima nuclear accident by exclusively studying the effective doses based on radiation dosimetry. And dosimetric data are often exclusively used for risk assessment and management. The idea behind this approach is that radioactivity (and its direct exposure) is the sole "pollutant" that causes any biological impacts. There is no question that radiation doses are important; however, this cannot justify the exclusion of other factors that may cause more powerful effects on biological systems.

Another important presumption of using the dosimetric approach to determine biological impacts is that researchers completely understand the system in question (at least at first), enabling a precise level of prediction of the biological impacts that often reference the recommendations and mathematical simulations of the International Commission of Radiological Protection (ICRP) (e.g., [6–8]). That is, it is presumed that reference levels of the effects of radiation exposure on certain organisms such as humans are completely known and these references are credible and applicable to the case of the Fukushima nuclear accident. It is to be understood that the reference levels are just for protection purposes only as experience-based values to balance risk and benefit for residents, patients, workers, and researchers. Nonetheless, it can be said that dosimetric predictions mostly take a *we-know-all approach* regardless of researchers' awareness. Although there are many studies that support these reference levels, some dosimetric studies for the Fukushima nuclear accident often lack efforts to perform or incorporate field and laboratory studies that look for possible phenotypic and genetic effects; in other words, these studies often appear to conclude that such field and laboratory experiments are not necessary because the system has already been known well.

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In contrast, the biological and ecological approach may be called a *we-know-little approach*; in other words, the biological impacts of the accident reflect the things that we do not know well, and these are the topics that should be evaluated in field work and laboratory experiments in the real world. For example, studies using the biological approach may admit that organisms face many different stress conditions in the wild, and they are found in unique positions in the ecological network; as a result, sometimes unexpected consequences in terms of an organism's response to pollutants may be observed.

As discussed in the next section, we have been using *the pale grass blue butterfly* for Fukushima research since 2011; research began immediately after the Fukushima nuclear accident [9]. One of the most important types of experiments in the research on the pale grass blue butterfly in Fukushima is the so-called the internal exposure experiment. In this experiment, the field-collected host-plant leaves, which are contaminated at various levels (judged by the radiation levels of $^{137}Cs$ and $^{134}Cs$), were given to butterfly larvae collected from the least-contaminated area, i.e., Okinawa (approximately 1700 km southwest of the Fukushima Daiichi Nuclear Power Plant); these experiments resulted in high mortality and abnormality rates [9–12]. These results support the field reports of high rates of abnormality [9, 13–15]. A mutagenesis study of this butterfly produced similar phenotypes [16], and the effects on body size detected in the first paper [9] were also supported by the field and experimental results [17]. Although these field and experimental results may be surprising in light of the conventional view of radiation biology and physics, the experimental procedures were rigorous enough to support these conclusions [18].

Furthermore, in recent years, many field reports have accumulated on the possible effects on various organisms [5], and these are consistent with our results. Such studies include the bird and arthropod populations [19–21], gall-forming aphids [22], Japanese monkey [23, 24], barn swallow [25], goshawk [26], rice plant [27, 28], fir tree [29], red pine tree [30], and intertidal species populations including the rock shell [31]. Furthermore, the possible changes induced by the nuclear accident have been reported at the biochemical level. For example, stress responses in cattle may have been induced in contaminated areas [32]. Changes in gene expression have been reported in the small intestine of pigs [33]. Other reported cases include DNA damage in bovine lymphocytes [34], enhanced spermatogenesis [35], and chromosomal aberrations [36, 37] in large Japanese field mice; however, there are reports in which mammalian testes collected from bull, bore, Inobuta, and large Japanese field mice in the contaminated area did not show any noticeable abnormalities [38–40].

In contrast, one of the most recent results of ours came from a series of similar internal exposure experiments in which radioactive $^{137}Cs$ was supplied to larvae as a form of chemically pure cesium chloride solution in an artificial diet; however, the results have not yet been published. It is likely that the pale grass blue butterfly is highly resistant to internal irradiation alone, as expected from the conventional understanding of insects' high resistance to irradiation. This discrepancy between the two systems may be called *the field-laboratory paradox*. The difference between the two systems is clear. The former system used contaminated leaves from the real world, while the latter system used an "ideal" pure source of cesium chloride in an artificial diet. I conclude that the latter system is not entirely relevant to the case of the Fukushima nuclear accident, and the former system may be heavily influenced by several different modes of the indirect field effects that are not well known to researchers. A similar situation has already appeared in mammals and aphids. An experiment on internal $^{137}Cs$ irradiation in mice did not indicate any detectable change in the litter size and sex ratio [41]; in contrast, at least some of the field data have suggested adverse effects in mammals, as discussed above. Striking morphological abnormalities of aphids reported from the polluted areas [22] were not reproduced in the process of embryogenesis and egg hatching by irradiation experiments, although a change in developmental time was detected [42].

Precise dosimetric analysis of larvae may provide additional information that satisfies dosimetrists; however, dosimetric analysis does not play a major role in reaching the conclusions stated above if the radioactivity concentration of the diet is known to us. What is important is the fact that the same experimental system was employed in studies of the pale grass blue butterfly; the two experiments simply used different types of food, i.e., either the field-harvested contaminated leaves or the artificial diet containing $^{137}Cs$. Moreover, the results from the former experiment are fully supported by the field work. Based on the butterfly case and the mammalian case discussed above, this kind of field-laboratory paradox is likely widespread among organisms of various taxa. Indeed, a literature survey showed that the controlled laboratory effects and field effects were very different in terms of their sensitivity levels; the field cases from Chernobyl were eight times more sensitive than the laboratory-controlled external irradiation cases [43].

Undoubtedly, dosimetric analysis provides a different level of insight. For example, the inferred genetic mutations that are heritable over generations in this butterfly [9] are likely caused by the high-level acute exposure immediately incurred after the accident rather than by the low-level chronic exposure [12, 44, 45]. To evaluate these effects, it is important to dosimetrically understand the absorbed doses of the butterfly at the initial time of the event.

In this chapter, I will discuss several important issues associated with "low-dose" radiation exposure and field effects; additionally, I propose the importance of non-dosimetric studies in conjunction with conventional dosimetric studies. Borrowing the famous phrase from Shakespeare's *Hamlet*, researchers who engage in the biological consequences of the Fukushima nuclear accident may consider the following: "*To be or not to be* (i.e., dosimetry), *that is the question*." However, the answer is clear: both approaches are necessary to advance this scientific field to a higher level. In other words, the final answer to this question is "*to be and not to be*." I believe that this is the only way to reveal a holistic picture of the biological impacts of the Fukushima nuclear accident, which would serve as a basis for risk assessment and management of nuclear pollution.

## 2. The pale grass blue butterfly: a versatile indicator

Multiple biological approaches should be used to understand the real-world phenomena resulting from the Fukushima nuclear accident. Furthermore, to understand biological phenomena in general, it is customary for biologists to concentrate on a few *surrogate species* or

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*model species*. For example, in developmental genetics, the fruit fly *Drosophila melanogaster* is an important model species [46]. In conservation biology, many types of surrogate species are often proposed, including indicator, umbrella, keystone, and flagship species, to evaluate the quality of the natural environment [47]. The simultaneous use of multiple indicator species from different taxonomic groups is generally favorable [47] but may be difficult in practice. To understand biological impacts of the Fukushima nuclear accident, studies that use *indicator species* are likely required.

If only a single (or a few) species is used in biological studies of the Fukushima nuclear accident, the pale grass blue butterfly is one of the ideal systems of choice in that it is associated with (and almost dependent on) the living environment of humans; as a result, the butterfly reflects the health of the human environment [12, 44, 45, 48]. Using this butterfly, efficient field work can be performed, and relatively fast and precise experiments can be performed in the laboratory [49, 50]. Other advantages of using this butterfly have been discussed elsewhere [12, 44, 45, 48].

It should be noted that using nonhuman model organisms to obtain information relevant to humans is not a novel approach in biomedical sciences. In fact, it is a common practice to use the fruit fly and even yeast to infer the molecular mechanisms of human diseases. The fruit fly is used not because it is the invertebrate most similar to humans but because it is practically useful for experimental manipulation. This model organism approach to human-related research is valid because, at the molecular level, there are many commonalities among organisms. Furthermore, as discussed in Taira et al. [12] and Otaki [48], radiation effects are molecular events. DNA may be damaged "directly" by radiation or "indirectly" by other ionized molecules, such as water (note that the usage of "direct" and "indirect" here is different from the terminology discussed in most parts of this chapter). The molecular-level ionizing mechanisms are universal in all organisms, including humans and this butterfly species. In this sense, the butterfly data are applicable to humans. Likely, the unconventional field effects that are discussed below may also occur in universal molecular events. Thus, the field effects that were detected in the butterfly are also likely applicable to humans, at least to some extent; however, the precise mechanistic understanding of the field effects on the molecular events is still unclear.

In contrast to the uniform molecular markings found in many organisms, the manifestation of these effects (i.e., phenotypic effects) may be very different among species. In butterflies, morphological abnormalities such as leg and wing deformation are relatively frequent; however, no suitable counterpart of this phenotypic effect can be identified in humans. Such organismal-level phenotypic effects (i.e., disease manifestations) in humans are not readily inferable from butterfly data.

## 3. Targeted and nontargeted effects

The dosimetric approach often states that ionizing radiation targets DNA directly or indirectly through the ionization of water molecules (hence, they are called targeted effects) and that the degree of DNA damage is linearly reflected in the biological consequences. These statements mean that biological effects can be predicted by the effective dose. Although this approach is widely accepted and utilized for assessing the biological impacts of nuclear disasters, the approach entirely ignores other potential molecular pathways and dismisses the complexity of the biological and ecological responses to the various known and unknown materials that are released from nuclear reactors.

In contrast to the conventional targeted effects, the last two decades have experienced a surge of *nontargeted effects* of ionizing radiation [51–56]. The nontargeted effects include bystander effects, genomic instability, adaptive responses, and other modes, and these nontargeted effects are likely caused by the reactive oxygen species produced by irradiation [51–56]. In this sense, the nontarget effects may be referred to as the indirect effects (note that in this chapter, nontargeted effects are classified into the same category as the direct effects as a matter of convenience to some extent). In terms of the nontargeted effects, it is important to remember that they are not readily predictable by doses, and many of them are latent. Therefore, the nontarget effects may not be detected in acute irradiation experiments, but they may manifest in the field. Furthermore, the field-laboratory paradox discussed above may have originated, at least partly, from the influence of the nontargeted effects in the field. In fact, the nontargeted effects, such as genomic instability, may have played significant roles in the observed increase in butterfly morphological abnormalities in the fall of 2012 [9, 13].

However, even the nontarget effects may not adequately explain the all effects that manifest in the field. For example, there could be possible nonradioactive by-products released from a reactor and naturally occurring nonradioactive materials that are "activated" by the radioactive materials released from a reactor. There may also be ecological interactions that could amplify small irradiation effects to larger levels throughout a food web. These possibilities may be potential sources of the *field effects* (or more precisely, *field-specific effects*), which would not be observed in controlled laboratory experiments that use an artificial source of radiation, such as $^{60}$Co and chemically pure $^{137}$Cs. However, these field-specific effects should not be confused with (or dismissed as) confounding factors because these field effects are elicited by the nuclear accident. Similarly, nontargeted effects do not have to be field-specific effects; nontargeted effects may be observed in controlled laboratory experiments that use an artificial radiation source and a simple biological system, such as a cell culture system. In other words, the nontargeted effects may be uncovered with conventional radiation biology, which investigates universal mechanisms of radiation effects, but the field-specific effects may be uncovered with *pollution biology*, which investigates the real-world phenomena; however, these two fields cannot be separated in a meaningful way in the case of nuclear accidents.

In this chapter, I refer to both the conventional targeted effects and the nontargeted effects as the "direct" effects (or "primary" effects) (**Figure 1**); however, in some literature, the nontargeted effects or one mode of the nontargeted effect are referred to as the indirect effects. It is understood that laboratory-based controlled irradiation experiments, irrespective of high or low doses, primarily examine the direct effects of ionizing radiation. In contrast, as mentioned above, other potential unconventional indirect effects of nuclear pollution are collectively called the field effects (**Figure 1**) [48, 57]. The field effects are often dependent on a biological (including ecological) context.

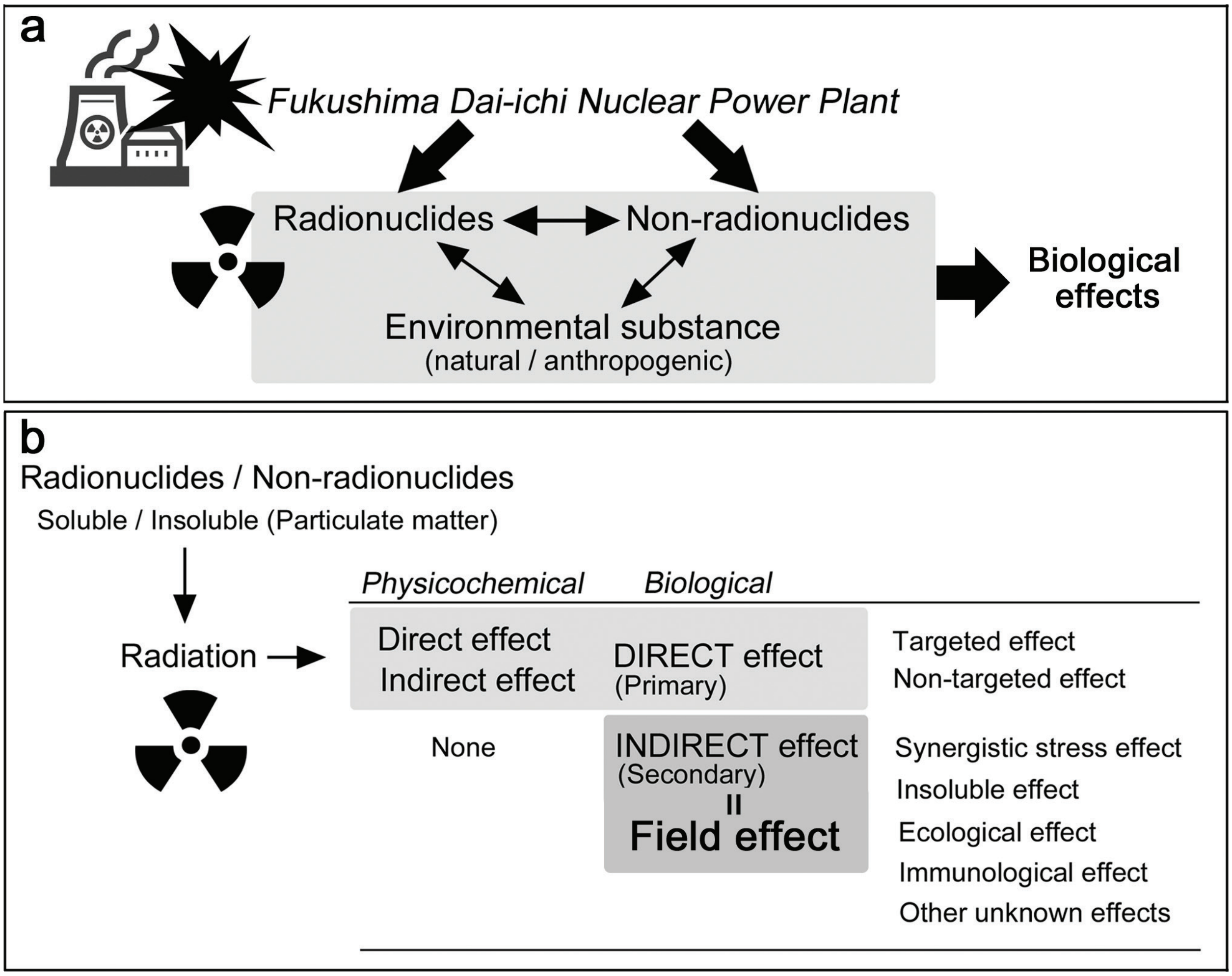


**Figure 1.** Possible effects of the explosion of the Fukushima Dai-ichi Nuclear Power Plant. (a) Overall pathways. The Fukushima Dai-ichi Nuclear Power Plant released radionuclides as well as non-radionuclides that may not be fully identified. They interact with each other, and they also interact with environmental substances. Environmental substances could be natural (biotic or abiotic) or anthropogenic. The collective outputs of these interactions manifest as biological effects. The illustration of a nuclear power plant was obtained from a free illustration site called Icon-rainbow (http://icon-rainbow.com/). (b) Multifaceted radiation effects. Released substances may be radionuclides or non-radionuclides, and they may be soluble or insoluble as particulate matter. Physicochemically, ionizing radiation has direct or indirect effects on the major biological target, i.e., DNA. However, both types of effects may be considered as biological direct (or primary) effects. In contrast, there are multiple biological indirect (i.e., secondary) effects, depending on the context from which the organism in question faces. The latter is often field-specific, and thus called the field-specific effects (or simply the field effects).

## 4. Field effects (1): synergistic effects

The biological indirect effects are a collective expression of all biological effects of the nuclear accident excluding the effects of the direct radiation exposure. Because any wild biological system has diverse and complex relationships with biological and chemical species, there are numerous indirect pathways that can affect organisms. Below, the field effects are roughly categorized into three groups: synergistic effects, effects from particulate matters, and ecological effects (**Figure 2**).

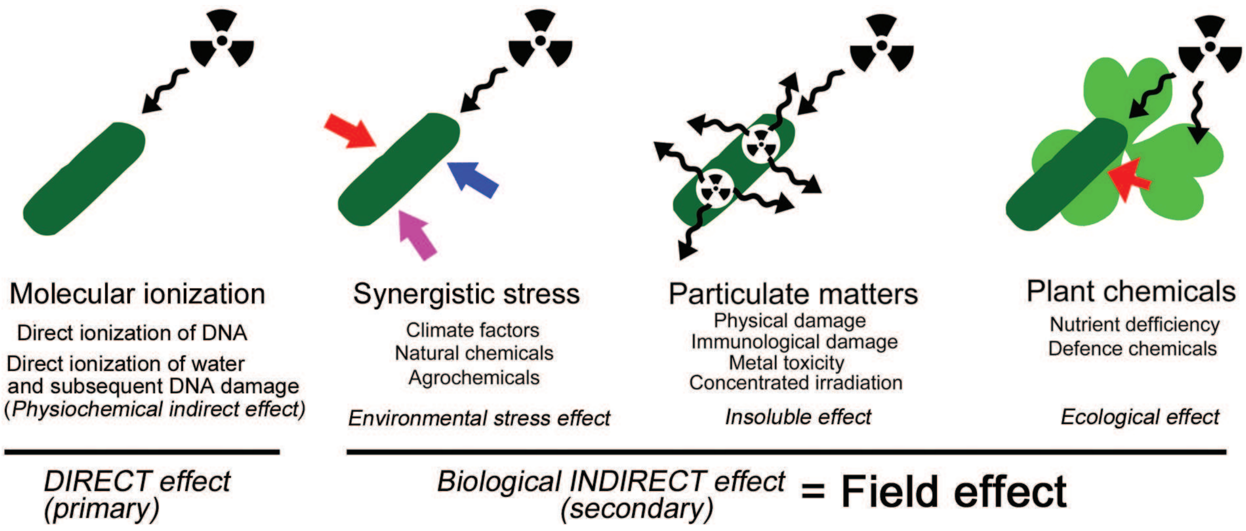


**Figure 2.** Four possible types of effects on the larvae of the pale grass blue butterfly (green bars). Molecular ionization is the direct (i.e., primary) effect, while the other three modes (synergistic stress, particulate matter, and plant chemicals) are biological indirect (i.e., secondary) field effects.

First, *synergistic effects* with other environmental factors, including climate conditions and chemical stressors, may exist in the wild. When an organism experiences stress from a single source, the stress may be managed relatively well; however, when stress is imposed by two different sources, the harmful effects may be synergistically enhanced beyond their individual actions. In laboratory conditions, the "climate" conditions are usually constant, and additional stressors are not usually provided; thus, synergy is often difficult to predict using conventional irradiation experiments alone. Logically, the synergistic effects of radiation exposure and other stressors have been an important topic in radiation biology [52, 53, 58–61]. However, in my opinion, such synergistic stress effects have not been fully appreciated in radiation biology. Importantly, synergistic stress effects are not limited to exposure to radiation. Here, I briefly discuss two examples that may be insightful for this line of discussion.

A discrepancy has been recognized between the laboratory and field results in phenotypic plasticity studies. In an authoritative textbook, Gilbert and Epel [62] stated the following: "Phenotypic plasticity means that animals in the wild may develop differently than those in the laboratory" and "This has important consequences when we apply knowledge gained in the laboratory to a field science such as conservation biology." One specific example provided in the textbook states that some frog tadpoles are up to 46 times more sensitive to pesticides in the presence of predators that release chemicals in the wild than they are in the laboratory [63, 64]. The conclusion stated that "ignoring the relevant ecology can cause incorrect estimates of a pesticide's lethality in nature" [63]. I believe that the same principle applies to radioactive materials from nuclear reactors.

Another insightful case was reported in the epidemic caused by the bacterium *Clostridium difficile* [65, 66]. For this bacterial epidemic outbreak to occur in North America and Europe, the widespread use of a food additive, trehalose, played a crucial role. Infected mice had higher mortality rates when fed food that contained trehalose [66]. Without the trehalose-rich environment that newly emerged in this century, the deadly endemic would not have occurred.

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Although trehalose alone may not be a significant stressor, this case illustrates an example of an unexpected synergistic interaction between toxic substances that were otherwise benign environmental chemicals.

## 5. Field effects (2): particulate matter

Second, what was released from the Fukushima nuclear reactors was a plume of materials that caused *particulate air pollution*; regardless of whether these particulates were radioactive, the released materials were dispersed as atmospheric aerosols [67, 68]. There is no question that atmospheric aerosols cause respiratory and cardiovascular diseases in humans [69–72]. Indeed, natural radon attaches to air dust, and when this dust is inhaled, it is believed to cause lung cancer [73]. There is no reason to believe that the particulate air pollution from the nuclear reactors was safe for butterflies or other wild organisms. However, to my knowledge, any discussion from this viewpoint is scarce.

It should be noted that the plume from the nuclear reactors contained two types of radioactive materials: soluble and insoluble forms. Soluble materials, such as a form of inorganic salt, are solubilized quickly in environmental water. Additionally, insoluble materials have been detected as spherical particles [74, 75], and they are attached on the surface of any material. At least some of these particles (i.e., particulate matter) may bind to nonradioactive common air dust [68, 69]. Based on the results of the internal exposure experiments in which field-collected polluted leaves were fed to butterfly larvae, the ingestion of particulate matter present on the surface of leaves may have caused digestive and immunological effects [9–12].

## 6. Field effects (3): ecological effects

Third, when one examines the interactions of multiple species based on a food web or an ecological system as a whole, one may be able to discover radiation effects that would not be discovered by a single-species approach; consequently, observations like this may indicate important field effects. This may be called *the ecological effects*. A similar concept has recently been addressed in radioecology [76]; however, this topic is often discussed from the viewpoint of the bioaccumulation of radioactive materials or organic materials in high-order consumers. Although bioaccumulation is important, it is based on a dosimetric viewpoint.

The ecological system that the pale grass blue butterfly inhabits is relatively simple due to its monophagous nature [48]. Thus, this butterfly and its associated ecosystem may serve as a “model ecosystem” to investigate both the population dynamics and the environmental influences through the ecological food web after the Fukushima nuclear accident. It appears that in the case of the pale grass blue butterfly “model ecosystem,” the quality of its host plant, *Oxalis corniculata*, is probably important and is determined by the quality of the soil and air. When soil is contaminated with radioactive materials and other pollutants, such as agrochemicals, the quality of the host-plant leaves decreases. Similarly, air pollutants (i.e., particulate matter) that cover the surface of leaves, whether radioactive or not, may change the physiological functions of the leaves. Thus, the quality of the soil and air will affect the health of the larval butterflies that eat the affected leaves.

The decrease in plant quality for larvae may originate from two different causes: a decrease in certain favorable chemicals (e.g., essential nutrients) in leaves and an increase in unfavorable chemicals (e.g., reactive oxygen species and defense chemicals) in leaves. In the former scenario, the lack of an essential vitamin in the leaves may be fatal for butterfly larvae because larvae are dependent on vitamins that are supplied through the ingestion of leaves. A similar case of thiamine (vitamin $B_1$) deficiency has been recognized as one of the major consequences of environmental pollution and destruction in Europe and North America; however, the precise causes of this deficiency are difficult to identify [77–80].

The latter possibility of the decrease in plant quality for butterfly larvae may occur if plants are stressed by even low levels of exposure to radioactive materials; this exposure can produce reactive oxygen species, defense chemicals, or another substance that is harmful to larvae. Reactive oxygen species are known to be produced by various abiotic stressors, and the production of defense chemicals are induced by insect bites in many plants [81–83]; however, whether radiation stress can trigger such responses in *O. corniculata* and in plants in general is unknown. The upregulation of unfavorable chemicals and the downregulation of favorable chemicals for larvae may occur simultaneously.

Consequently, biochemical changes in producers (i.e., plants) affect primary consumers (i.e., herbivorous animals) and then secondary consumers (i.e., carnivorous animals). These food-mediated effects of pollutants can radiate through an ecological food web, and it is indirect field effects that are different from the bioaccumulation paradigm. It is reasonable to imagine that damage to keystone species that have connections with many other species may cause relatively large effects on the ecosystem; however, recent research posits that anthropogenic disturbances on a small number of any species may cause instability in an ecosystem [84, 85].

## 7. Possible field effects on humans

Among the three modes of action of the field effects discussed above, the second mode (i.e., particulate matter) is associated with immunological responses that may be prominently problematic for humans because humans have very effective (and, thus, very sensitive) immunological systems, some of which insects do not have. A small amount of radioactive or nonradioactive aerosol from a nuclear reactor can potentially cause large and fatal physiological effects in some human individuals via immunological sensitization. However, immunological responses vary among individuals, and it is known that immunological sensitivity to chemicals (i.e., allergens) greatly varies among human individuals. However, once sensitized, humans can detect a remarkably small number of molecules and manifest allergic symptoms. It is possible that radioactivity denatures proteins, which makes naturally occurring proteins immunogenic. The protein-denaturing effect of ionizing radiation as well as its association with immunogenicity may be one of the important topics that should be experimentally tested. As a whole, these effects can collectively be called *the immunological effects*.

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The consequences of allergic reactions are complex, but one example of a type of reaction is kidney failure, which can include *nephrotic syndrome*; I have reported a case in which nephrotic syndrome was likely induced by the immunological field effects of the Fukushima nuclear accident [86]. Indeed, a general relationship between immunological sensitization and nephrotic syndrome has been demonstrated [87–92]. This relationship has not been rigorously tested; however, this is not surprising because nephrotic syndrome is a collection of diseases that have various etiologies.

Regarding the first mode of the field effect discussed above, the synergistic effects are potentially numerous in human society and in human living environments. One of the potential stressors is cedar pollen, which causes Japan-wide allergic reactions in the spring of each year, including 2011 immediately before and after the Fukushima nuclear accident. It is possible that the aerosol from the Fukushima reactors attached to cedar pollen to worsen *pollen allergy* (i.e., *hay fever*). Other potential stressors for humans may include other air pollutants, food additives, agrochemicals, and work stress. Stress resistance varies among individual humans, and some people that were not very stress resistant may have become sick after the Fukushima nuclear accident.

Regarding the third mode of the field effects discussed above, changes in plant chemicals may affect human health. Additionally, the nutritional quality of fruits and vegetables may have declined. However, different from the pale grass blue butterfly, humans are not monophagous. Moreover, vitamin supplementation is now popular in many countries including Japan. As such, this type of field effect may not manifest in humans; however, this mode may cause serious adverse impacts in the pale grass blue butterfly.

## 8. UNSCEAR 2017 Report

Because the field effects of "nuclear" pollution may be a new concept, at least to some extent, misunderstanding or confusion about this issue may prevail. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2017 Report [93] provides an example. This report mentioned our studies in paragraph 125, in which H8 refers to Hiyama et al. [9], and M9 and M10 refer to Møller et al. [19] and Møller et al. [20], respectively.

> *125. The Committee had made reference to studies in which effects in various terrestrial biota had been observed in areas with enhanced levels of radioactive material as a result of the FDNPS accident [H8, M9, M10]. It had noted that the substantial impacts reported for populations of wild organisms from these studies were inconsistent with the main findings of the Committee's theoretical assessment. The Committee had expressed reservations about these observations, noting that uncertainties with regard to dosimetry and possible confounding factors made it difficult to substantiate firm conclusions from the cited field studies.*

It is understandable that our study is "inconsistent with the main findings of the Committee's theoretical assessment" (i.e., the dosimetric simulations). I agree that "uncertainties with regard to dosimetry" should be overcome in the near future; however, without precise dosimetric data, the findings that conclude the biological effects were correlated with the ground radiation dose and/or the distance from the nuclear reactors and that state the biological effects in the field were reproduced dose-dependently in laboratory experiments are entirely valid. The main reason for this discrepancy is the exclusion of the field effects in the UNSCEAR assessment. In contrast, our experiments were constructed to reflect real-world phenomena, including the direct effects and indirect field effects. Furthermore, contrary to the UNSCEAR statement above, there were no major confounding factors in our study [9] because it consisted of controlled laboratory experiments.

Moreover, the UNSCEAR statement completely ignores the process of logical judgment in terms of the cause of the Fukushima nuclear accident. The causality of the effects of the accident should be evaluated systematically according to logical postulates such as "the Postulates of Pollutant-Induced Biological Impacts" [45]. This includes six clauses that must be met to prove the causality of the pollutant(s) from a given source, i.e., spatial relationship, temporal relationship, direct exposure, phenotypic variability or spectrum, experimental reproduction of external exposure, and experimental reproduction of internal exposure [45]. The causality should not be judged solely from a dosimetric standpoint.

The UNSCEAR 2017 Report [91] further commented on our paper in paragraph 134, in which H9 and O12 refer to Hiyama et al. [14] and Otaki [48], respectively.

> *134. Hiyama et al. [H9] provided further evidence to suggest that the high abnormality rates observed in the pale grass blue butterfly were induced by "anthropogenic radioactive mutagens." However, Otaki [O12] synthesized the results from several studies of the effects on the same species of butterfly following the FDNPS accident, and reported that ionizing radiation was unlikely to be the exclusive source of the environmental disturbances observed.*

The above comments on our research are misleading; specifically, the last sentence wrongly implies that "the environmental disturbances observed" were caused by unknown confounding factors that were not related to the Fukushima nuclear accident. Rather, in Otaki [48], I mentioned the importance of the field effects from both radioactive and nonradioactive materials from the Fukushima Dai-ichi Nuclear Power Plant. In other words, "ionizing radiation" (i.e., the direct effects in the context of Otaki [48]) was not the exclusive source. It is entirely valid to say that the high abnormality and mortality rates observed in the butterfly were caused by the pollutants from the Fukushima nuclear accident. This UNSCEAR case indicates the low level of understanding regarding the field effects and the lack of fundamental logic among the researchers who contributed to the formulation of these paragraphs in the UNSCEAR 2017 Report [93]. On the other hand, these misleading comments may be understandable, considering that we presented the topic of indirect field effects only briefly in our previous papers. There is an urgent need for more precise explanations and experimental validation of this issue.

## 9. Extrapolating butterfly toxicology to humans

The evaluation of the field effects may not be straightforward because of its indirect nature; however, our system for the internal exposure experiments likely reflects both the direct effects and some of the indirect field effects based on the use of the field-collected host-plant leaves for butterfly larvae. Because the larvae are highly resistant against the internal exposure to pure radioactive cesium (unpublished data), the high mortality and abnormality rates from the contaminated leaves can be largely attributed to the indirect field effects. It should be noted that what was measured in our experiments was the radioactivity concentration of radiocesium; however, other radioactive and nonradioactive materials were released from the Fukushima nuclear reactors, and these materials may have also contaminated the leaves. In this sense, *the radioactivity concentrations of radiocesium can be considered as an indicator of the degree of the pollution*. This is an important difference from the conventional dosimetric approach. To our knowledge, quantitative toxicological data that reflected some of the field effects were available only for butterflies. Thus, it is interesting to apply these data to humans to roughly grasp the collective effects of the Fukushima nuclear accident. Although there is no rigorous reason to believe that the butterfly data are applicable to humans, this attempt can be justified because of the lack of human-specific data and data from other organisms that reflect both the direct effects and indirect field effects.

The basic experimental strategy was to collect the polluted food (i.e., plants) from Fukushima and feed the plant samples to butterfly larvae from Okinawa, which was the least polluted locality in Japan. When non-contaminated leaves were fed to larvae, normal individuals emerged. However, when polluted leaves were fed to larvae, morphologically abnormal adults emerged, and the mortality of larvae and pupae was high. The abnormality rate and the mortality rate were then obtained for each polluted diet. Because the radioactivity concentration of radiocesium species ($^{134}$Cs plus $^{137}$Cs) in foods (Bq kg$^{-1}$ diet) and the amount of food that each larva ate (g) was available, a dose-response curve was obtained [12].

*The half abnormality dose* (equivalent to median toxic dose, $TD_{50}$; called $TD_{50}$ hereafter) of radiocesium for the butterfly was first obtained in Nohara et al. [10] based on the power function fit for data points from relatively high-dose diets. Later, the data points from the relatively low-dose diets were added to the previous data [11]. The mathematical model fits for these combined data were performed using the power function and Weibull function models [12]; the sigmoidal data fit with the Weibull function model yielded a $TD_{50}$ value of 0.45 Bq body$^{-1}$ (meaning that a cumulative dose of 0.45 Bq per larva results in abnormality or death in 50% of the population). A loose threshold was detected at approximately 10 mBq body$^{-1}$.

The mean body weight of larvae was 0.0346 g. Therefore, the $TD_{50}$ can be read as 13 kBq kg$^{-1}$ body weight. Here, I assume an average Japanese male person (30–49 years old) has a body weight of 68.5 kg, according to a survey by the Ministry of Health, Labour and Welfare [94]. For this average person, 13 kBq kg$^{-1}$ body weight is multiplied by 68.5 kg body weight, resulting in a $TD_{50}$ of 890.5 kBq body$^{-1}$ for an average Japanese male human. This average person eats 1.555 kg diet day$^{-1}$ when nutritional balance is maintained [95].

Based on these data, the radioactivity concentration of diets required to reach the $TD_{50}$ value in a given time span in a Japanese male human can be calculated (**Figure 3a**). To consume 890.5 kBq in 1 day, 890.5 kBq must be contained in a 1.555 kg diet; thus, the radioactivity concentration of 573 kBq kg$^{-1}$ diet must be consumed to reach the $TD_{50}$ value in 1 day. To consume 890.5 kBq within 1 year (365 days), a 1.57 kBq kg$^{-1}$ diet is required. Similarly, a 157 Bq kg$^{-1}$ diet and a 15.7 Bq kg$^{-1}$ diet are required to reach the $TD_{50}$ value in 10 years and 100 years, respectively. Clearly, a 15.7 Bq kg$^{-1}$ diet is mostly negligible for this average person between the age of 30 and 49 because he will naturally die before he reaches a 50% chance of becoming sick. However, *a 157 Bq kg$^{-1}$ diet is not negligible for this average person because there is still a 50% chance of becoming sick in the next 10 years*.

Additionally, the number of days (or years) required to reach the $TD_{50}$ value when 100 Bq kg$^{-1}$ diet or 10 Bq kg$^{-1}$ diet is consumed can be calculated (**Figure 3b**). *When an average Japanese male human consumes a 100 Bq kg$^{-1}$ diet, it takes 16.7 years to reach the $TD_{50}$ value*. This is a non-negligible time span. However, a 10 Bq kg$^{-1}$ diet may be negligible because it takes 167 years to reach the $TD_{50}$ value, which is beyond the human lifespan.

Considering that the amount (becquerel) of radioactivity concentration of $^{134}Cs$ and $^{137}Cs$ discussed above is as low as the amount of naturally occurring $^{40}K$, a counter argument to this discussion would be that no harmful effect is expected from the conventional dosimetric view. However, it should be remembered that the amount of radiocesium is simply an indication of pollution levels in terms of the field effects. Moreover, we have experimental evidence that artificial radiocesium is clearly harmful at radioactivity levels as low as those observed for radiopotassium (unpublished data). I will discuss this important issue if there is an opportunity to do so in the future.

It should also be remembered that the discussion above completely ignored the dose-rate effects and the physiological differences between butterflies and humans, which include different biological half-lives and organ accumulation of cesium species. This study also ignored the different types of indirect field effects that may be species-specific, depending on the ecological status of a species. It should also be noted that *the $TD_{50}$ state is toxicologically convenient to evaluate potential effects, but it means a devastating massive outbreak of diseases in terms of public health*. Another viewpoint to consider is that toxicological evaluations are often misleading and give the impression that anything that does not reach the $TD_{50}$ value within a reasonable time or does not exceed the limit is completely safe for everybody. Scientists and politicians should pay special attention to minorities who may still be affected at this level [48, 96].

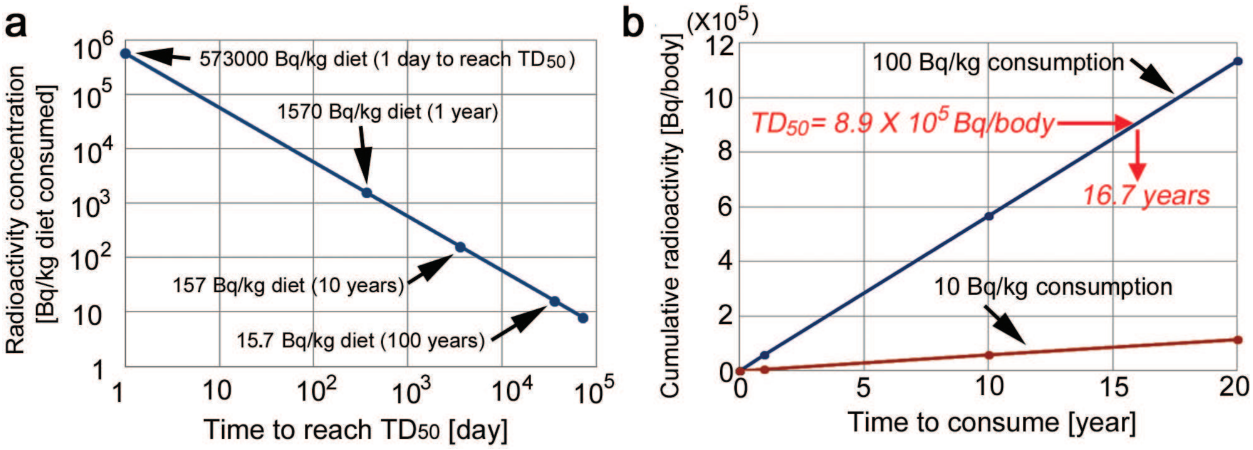


**Figure 3.** Extrapolation of toxicological data from the pale grass blue butterfly to an average Japanese male human. (a) Linearly extrapolating the butterfly data to understand the relationship between radioactivity concentration in consumed diet and time to reach $TD_{50}$. For example, to reach the $TD_{50}$ value in 10 years, an average daily consumption of a diet containing 157 Bq kg$^{-1}$ diet is required. (b) Linear relationship between cumulative radioactivity in a body and time to reach $TD_{50}$. Lines with daily 100 Bq kg$^{-1}$ consumption and 10 Bq kg$^{-1}$ consumption are shown. When an average of 100 Bq diet is consumed daily, it takes 16.7 years for a Japanese male human to reach the $TD_{50}$ value ($8.9 \times 10^5$ Bq body$^{-1}$).

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Having mentioned these points, a discussion based on the $TD_{50}$ value is probably as insightful as a discussion on the current political dose limits, which are based on the effective dose limits recommended by the ICRP [97]. In these conventional cases, no field effects were considered. Fortunately, based on the discussion above, the current regulation limit in Japan, i.e., 100 Bq $kg^{-1}$ for general foods, may not be a completely wrong value. In fact, this value can be considered as a starting point for this type of discussion. I believe that the theoretical results above are an important first step from which we can at least present the potential values for risk assessment and management.

## 10. Conclusions and future perspectives

It can be concluded that the "low-dose" exposure from the Fukushima nuclear accident imposed potentially non-negligible toxic effects on organisms including butterflies and humans through field effects. At the high-dose exposure, the same field effects would exist, but they would likely be masked by the acute damage. The direct effects may be assessed reasonably by dosimetric analysis even in the field cases, especially for high-dose cases. The field-laboratory paradox is not really a paradox; rather, it indicates our fragmentary knowledge on the real-world pollution caused by this nuclear accident.

Although this chapter sheds light on one important low-dose issue, there are many other issues associated with the field effects that should be studied both in the field and in the laboratory. One of these issues is the *adaptive and evolutionary responses* of organisms to environmental radiation in contaminated areas. The pale grass blue butterfly appears to have evolutionarily adapted to the environmental pollutants [98]. This adaptive evolution may be largely in response to the field effects because the butterfly is essentially very resistant to direct irradiation without any possible adaptive response (unpublished data). However, the direct ionizing damage on DNA would also play an important role in adaptive response if such damage exists.

Simply because there are multiple effective pathways of the field effects, *sensitivity variations* to different modes may vary considerably among species and even among individuals in a given species. The net effects may be determined through synergistic amplification. To further understand the effects of the Fukushima pollution, multifaceted scientific approaches that are firmly based on field work and field-based laboratory experiments (such as the internal exposure experiments using the field-harvested leaves) are expected in the future. A mechanistic understanding of the indirect field effects is also necessary to advance this field of pollution biology.

Simultaneously, studies on the mechanisms of the direct ionizing effects in the field (although the final effects may also be affected by the indirect field effects) should be advanced. As pointed out by Steen [99], multifaceted analyses at the DNA and genomic levels are expected to reveal evidence for direct DNA damage in the field after the Fukushima nuclear accident. I believe that the immediate early exposures to short-lived radionuclides impacted DNA directly, which then might have been inherited to subsequent generations. Such evidence would firmly establish the adverse biological effects caused by the Fukushima nuclear accident at the molecular level. Furthermore, spatiotemporal changes of such DNA damage would reveal population-level dynamics of adaptive evolution in the field, serving as an important case of the real-world evolution in evolutionary biology as well as in radiation pollution biology. Borrowing the famous phrase from *Hamlet* again, I would state, "*To be and not to be* (i.e., the direct and indirect field effects), *that is the answer*".

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