PROCORE - FRANCE/HONG KONG JOINT RESEARCH SCHEME
COMPLETION REPORT

Project Reference Number

F-HK004/12T

Project Title

Multiple Stressor Effect of Uranium and Gamma Ray on Zebrafish
鈾和伽瑪射線對斑馬魚的複合應激源效應

Particulars

	Hong Kong team	French team
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Funding Period

	1st year	2nd year (if applicable)
Start Date	1 Jan 2013	1 Jan 2014
Completion Date	31 Dec 2013	31 Dec 2014

Objective(s) as per original application

1. To explore and develop protocols and biological endpoints using the zebrafish, *Danio rerio*, as a model (including adult fish, embryos and the cell line ZF4) to study the multiple stressor effect of uranium exposure and gamma irradiation on aquatic organisms;
2. To study the multiple stressor effects of various environmentally realistic (i) levels of uranium and (ii) external gamma dose rates on the zebrafish.
3. To explore the mechanism behind the multiple stressor effects of uranium and gamma ray on the zebrafish.

[Please attach relevant document(s)]

i) Outline of proposed research and results obtained

Living organisms are exposed to a mixture of environmental stressors, and the resultant effects due to such exposures are referred to as multiple stressor effects (MSEs). Evidence showed that toxicity could be modified by simultaneous or sequential exposures to multiple environmental agents (*1,2*), and the appraisal of the probability and seriousness of the effects due to these exposures was referred to as a cumulative risk assessment (*3*). Sexton and Hattis (*3*) gave a comprehensive review on multiple stressor effects, and in particular discussed in depth fundamental issues regarding cumulative risk assessment. MSEs might not be simply the sum of effects from individual stressors, and the effect of interactions can be generally divided into four broad categories: independence, dose additivity, synergism and antagonism (*2,4*).

The mixture of ionizing radiation and heavy metal appears to be a priority for studies. Both stressors can affect a large number of organisms for a prolonged duration. Routine or accidental fallout from nuclear reactors will expose living organisms to ionizing radiations. Nuclear accidents at Chernobyl in Ukraine, Three Mile Island in USA, and most recently at Fukushima in Japan remind us that safety issue of nuclear power, including the associated contingency planning and risk assessment, is still a major concern. Nevertheless, the MSEs of heavy metals and ionizing radiation, and the underlying mechanisms have not been extensively studied. At the moment, the groups of radionuclides and heavy metals are separately regulated, which has effectively assumed no interactive effects between radiation and chemicals. This assumption is used because of insufficient information on the multiple stressor effects. However it is unknown whether this assumption leads to under- or to over-estimate the associated ecological risk.

The purpose of the original proposal was to carry out a study on the MSEs of uranium and gamma ray on the zebrafish, *Danio rerio*. However, after commencement of the project and discussion between the two research groups, we decided to first carry out a pilot study on the MSE of depleted uranium (DU) and alpha particles on the zebrafish (*Danio rerio*) embryos. The zebrafish, *Danio rerio*, has become a preferred vertebrate model in recent years for studying human disease. Interestingly, the zebrafish and human genomes share considerable homology, including conservation of most DNA repair-related genes (*5*). Furthermore, the embryonic development is rapid so the major organ systems become evident within 48 h post fertilization (hpf). There have been a growing number of research works using the zebrafish or the embryos as a vertebrate model to study the in vivo response to ionizing radiation (*6-11*).

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ii) Significance of research results

Most previous studies on MSEs were based on stressors in the toxic zone (TZ). However, hormetic response, which is characterized as a biphasic dose-response relationship exhibiting a low-dose stimulation and a high-dose inhibition, has now been widely accepted as a universal phenomenon. As such, it is pertinent to study the MSEs based on stressors in both the hormetic zone (HZ) and TZ. Our results provided information on the MSEs from four schemes, namely, (1) HZ alpha-radiation dose + HZ DU exposure, (2) TZ alpha-radiation dose + TZ DU exposure, (3) TZ alpha-radiation dose + HZ DU exposure, and (4) HZ alpha-radiation dose + TZ DU exposure. All the findings regarding the four different exposure schemes showed that the MSE critically depended on the dose-response zones with which each individual stressor was associated. As such, we believe we have developed a new and important research field in radiation ecotoxicology, i.e., MSEs of stressors in hormetic and toxic zones.

iii) Research output

(1) CYP Ng, S Pereira, SH Cheng, C Adam-Guillermin, J Garnier-Laplace, KN Yu. Combined effects of depleted uranium and ionising radiation on zebrafish embryos. Radiation Protection Dosimetry 2015, ncv269. doi: 10.1093/rpd/ncv269 (in press)
(2) CYP Ng, S Pereira, SH Cheng, C Adam-Guillermin, J Garnier-Laplace, KN Yu. Combined effects of alpha particles and depleted uranium on zebrafish (*Danio rerio*) embryos. In preparation for publication.

iv) Potential for or impact on further research collaboration

As descripted in iii) above, we have developed a new and important research field in MSEs of stressors in hormetic and toxic zones. There are many important stressors needed to be examined. For example, gamma radiation is the next ionizing radiation to be studied. In fact, the IRSN has extensive previous experience in the investigation of the radiobiological effects of gamma radiation in the environment. There are huge potentials on further research collaboration.