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HORMESIS:

IMPLICATIONS FOR TOXICOLOGY, MEDICINE AND RISK ASSESSMENT

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ABSTRACT BOOK

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Phytochemical Hormesis

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Diets rich in vegetables and fruits are associated with reduced risk of several major diseases including cancers, cardiovascular disease, diabetes and neurodegenerative disorders. Many dietary supplements are phytochemicals for which biological mechanisms of action are unknown. Most research in this field has focused on the antioxidant properties of phytochemicals as being their principle mechanism of action. However, evolutionary considerations and emerging research findings suggest that many of the beneficial chemicals in vegetables and fruits are toxins that active specific or generalized adaptive cellular stress response pathways. Examples of such hormetic phytochemicals include resveratrol, sulforaphanes and curcumin. Intracellular hormesis responses involve proteins such as antioxidant enzymes, heat-shock proteins, sirtuins, phase 2 enzymes, anti-apoptotic proteins and growth factors. In this view, phytochemicals exert their beneficial effects by acting as low-dose toxins that increase the resistance of cells to more severe stress.

Biphasic Dose-efficacy in Antiangiogenic Therapy

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Many biological processes can be modeled by linear functions. Examples include blood pH, oxygen tension, and hematocrit. However, it has recently been recognized that the activity of certain biological processes, especially those in vascular biology, can be optimally described by a biphasic function. The antiangiogenic and anti-tumor activities of interferon-alpha are optimal at low doses, but not higher doses, i.e., a U-shaped dose-efficacy curve.[1] The dose-efficacy curve of endostatin for anti-tumor activity is similar, whether the therapy is administered as a protein, [2, 3] or as gene therapy.[4] In fact, when endothelial cells are incubated *in vitro* with endostatin at increasing concentrations, gene expressions also reveal a U-shape dose response.[5] Another angiogenesis inhibitor, rosiglitazone, displays a U-shaped dose-efficacy curve.[6] Anti-cancer cytotoxic chemotherapy, administered at frequent low doses is more effective in tumor-bearing mice than high doses of chemotherapy administered less frequently.[7, 8, 9].

The mechanism of the biphasic response of vascular endothelium to different angiogenesis inhibitors is unclear. However, the function of the biphasic response may be to protect endothelium from surges in plasma concentrations of endothelial regulatory molecules. The principles of hormesis in the physical sciences and in toxicology may provide insights for vascular biology.

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How Does the Concept of Adaptive Response In Radiation Relate to the Concept of Radiation Hormesis?

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The adaptive response to radiation was originally defined as the protective effect of a prior low dose against the harmful effects of a subsequent high dose. Hormesis is a term used to describe an opposite effect, usually stimulatory, induced by a low dose of an agent, compared to the usually harmful effect of a high dose.

The adaptive response to radiation has been tightly conserved throughout evolution. Enhanced capacity for error free repair of DNA double strand breaks is at its core in lower organisms, and this response has been conserved up to and including mammalian cells. In lower organisms the response to radiation is part of a more general response that can be induced by a variety of stressors. In those organisms, radiation resistance can be induced by many other stressors and visa versa. Important aspects of this cross adaption remain in mammalian cells. Examples in a variety of cells and organisms, including mammals, will examine the influence of the adaptive response on radiation hormesis, and its implications for radiation risk assessment.

Hormesis in Carcinogenesis: Evidence for a Threshold in Carcinogenicity of Non-genotoxic Environmental Carcinogens

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Recently hormesis has attracted interest in the field of carcinogenesis. With non-genotoxic agents there is now considerable experimental evidence in support of this concept. In particular, several *in vivo* studies have provided support for the idea that non-genotoxic carcinogens may inhibit hepatocarcinogenesis at low doses. Here, we report examples and discuss possible mechanisms of carcinogenic hormesis using phenobarbital (PB) as a typical compound. Firstly, the dose-dependence of hepatocarcinogenic effects of PB was investigated in a rat liver medium-term bioassay (Ito test). Male 6-week-old F344 rats were initiated with diethylnitrosamine (DEN) and then given PB in the diet along with partial hepatectomy at week 3. Quantitative values for preneoplastic lesions, glutathione *S*-transferase placental form (GST-P) positive foci in the liver were increased dose-dependently in rats given PB at 60-500 ppm. However, those for doses in the range of 1-7.5 ppm demonstrated a decrease as compared to 0 ppm, with significant differences at 1 and 2 ppm (hormetic effect). For clarification, rats were treated with PB at doses of 0, 2, 15 and 500 ppm in diet for 10 or 33 weeks after DEN initiation. Formation of GST-P positive foci and liver tumors (adenomas and carcinomas) was similarly inhibited at 2 ppm. Interestingly, generation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), cellular proliferation within the areas of GST-P positive foci and apoptosis in background liver parenchyma were also suppressed by the 2 ppm dose of PB. Suppression of 8-OHdG formation might be related to enhanced mRNA expression of the 8-OHdG repair enzyme, Ogg1. In addition, in a medium-term bioassay, inhibition effects were also noted at low dose for induction of GST-P positive foci by other non-genotoxic carcinogens, α-benzene hexachloride and 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane. These results clearly indicate that non-genotoxic environmental carcinogens can exhibit a threshold for their carcinogenic potential.

RADIATION SESSION

Protective Bystander Effects Following Low Dose Ionizing Radiation Exposure
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Adaptive Response in pKZ1 Mouse Prostate after Whole Body Exposure to Very Low X-Radiation Doses
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Radiation-Induced Neoplastic Transformation *In Vitro*, Hormesis and Risk Assessment
Leslie Redpath, University of California Irvine, Irvine, CA

Low Dose Radiation Exposure and Modulation of High Dose Effects on Embryogenesis and Heritable Mutations
Douglas R. Boreham, McMaster University, Hamilton, Ontario, Canada

Prolongation of Life Span of Disease Model Mice by Low Dose Rate Irradiation
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Biological System Response to Ionizing Radiation Invalidates the Linear-no-Threshold-Hypothesis
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Smoking and Hormesis as Confounding Factors in Radiation Pulmonary Carcinogenesis
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Protective Bystander Effects Following Low Dose Ionizing Radiation Exposure

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Recent efforts to characterize the dose response for bystander effects in the low dose region, have resulted in a surprising number of "positive" bystander effects, where survival of cells receiving signals from low dose (1-5mGy) exposed cells, show enhanced survival. The dose response curve for mammalian cells over the range 27μGy-5Gy appears to divide into three distinct regions; 1: from 100mGy-5Gy where there is a progressive increase in the toxicity of the bystander signal with dose, 2: from 3mGy-100mGy where the bystander signal toxicity is constant with increasing dose and 3: 27μGy-3mGy where a hormetic effect is seen. The shift in response at 3mGy from a hormetic to a toxic bystander effect can be conformed using a calcium signal biomarker. Hormetic or beneficial bystander effects were also seen at higher doses in rainbow trout cell lines. Here doses in the 10-50 cGy range produced survival rather than toxic signals. This is consistent with survival data suggesting that trout cells are an order of magnitude less sensitive to ionizing radiation than mammalian cells. Protective bystander effects may be related to induction of signals stimulating repair mechanisms or anti-apoptotic mechanisms in recipient cells, which are then better able to withstand or repair randomly or spontaneously occurring damage unrelated to radiation exposure. Protective bystander effects were also found to be related to genetic background, gender and lifestyle factors, with females showing less toxic effects than males and anti-oxidants suppressing the toxicity. Clearly, the consequences of radiation exposure in the low dose region are complex but it is concluded from these studies, that the mechanisms determining radiation responses at low doses are very different from those operating at high doses and that protective responses are common. This makes it hard to justify adherence to the LNT hypothesis as an operating tool when dealing with low dose exposures.

Adaptive Response in pKZ1 Mouse Prostate after Whole Body Exposure to Very Low X-Radiation Doses

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Humans are exposed to natural environmental radiation at an extremely low dose and dose rate compared to man-made medical and occupational exposures. An adaptive response is a decreased biological effect induced by a priming radiation dose given prior to a challenge dose. Adaptive responses contradict the linear-no-threshold model of risk estimation. The pKZ1 mouse recombination assay enables detection of chromosomal inversions as a mutation end-point. The pKZ1 assay is the only mutation assay which has detected modulation of a mutagenic endpoint after X-irradiation with doses lower than 1 mGy, and a non-linear dose response was observed between 1 μGy and 10 mGy (Hooker *et al*, 2004. Radiat. Res. 162:447-52.).
pKZ1 mice were exposed to priming radiation and then to challenge radiation 4 hours later, and inversion frequency was quantified in prostate three days later. We demonstrated that very low (10 mGy, 1 mGy and 10 μGy) X-radiation doses induced a chromosomal inversion adaptive response for a 1000 mGy high challenge dose. These are the lowest X-radiation doses reported to induce an adaptive response for any endpoint. The same doses did not result in the induction of an adaptive response for non-specific staining in pKZ1 prostate, which is thought to be a measure of apoptosis or senescence. Reverse adaptive response experiments will also be discussed.

The mutant spectrum was indirectly measured by the distribution of inversions in 50 prostatic glands screened. Distinct patterns of the distribution of inversions in the prostatic glands screened were observed between sham-treated, single dose and priming + challenge groups. This was suggestive of preferential induction and/or repair of different types of damage as a result of different irradiation protocols. The results presented here suggest that at very low doses, an adaptive response can be induced independently of the relative magnitude of the priming and challenge doses.

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Radiation-Induced Neoplastic Transformation *In Vitro*, Hormesis and Risk Assessment

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Dose-response curves for various low-LET radiation sources have consistently been demonstrated to be J-shaped for the cancer-relevant endpoint of neoplastic transformation *in vitro*. Most of these studies have been performed where the radiation has been delivered at intermediate to high dose-rates (30-3000 mGy/min), where the threshold dose for induction of neoplastic transformation is around 100-200 mGy. Below these doses, the transformation frequency is less than that seen spontaneously, indicative of a hormetic effect. More recently, data has been obtained for low dose rates (<2 mGy/min) of low-LET radiation, and again hormetic effects are apparent but with threshold doses now being >1000mGy. Similar trends have been reported in animal experiments as well as in human epidemiologic studies. Indeed, the relative risks for induction of neoplastic transformation *in vitro* in the dose range 1 to 1000 mGy agree well with those for incidence of radiation-induced breast cancer and leukemia in humans. These findings support the notion that the endpoint of neoplastic transformation *in vitro* is a plausible endpoint to not only study mechanisms involved in response to low doses of radiation, but also to provide information of potential importance to risk assessment.

Low Dose Radiation Exposure and Modulation of High Dose Effects on Embryogenesis and Heritable Mutations

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It is well known that high dose exposures can induce mutations in rodent germline cells and cause malformation in developing fetuses. We have examined the effects of low dose priming exposures (adapting doses) at modifying the consequences of high dose exposures for both heritable germline mutations and malformations in developing fetuses. We compared germline mutation rates at expanded simple tandem repeat (ESTR) DNA loci in offspring from irradiated male mice. To study the effects of adapting exposures on teratogenesis in developing fetuses, we measured changes in tail length and number of limb digits of fetal mice that were irradiated *in utero*. Mutation rates in the offspring derived from high dose irradiated male mice were significantly elevated. However, high dose mutation rates in offspring from adapted males were not significantly elevated. Prior low dose exposure also modified the teratogenic effects of high dose exposures in fetal development that was dependent upon gestational time. We have shown that heritable mutations can be reduced in offspring if male mice are adapted prior to being exposed to high doses of radiation. We have also shown that malformations after high dose in utero exposures can be significantly alter by prior adapting exposures to the pregnant female and fetuses.

Prolongation of Life Span of Disease Model Mice by Low Dose Rate Irradiation

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We examined the effects of low dose rate gamma irradiation on physical status and life span in disease model mice. In Type II diabetic C57BL/KsJ-*db/db* mice, the urine glucose level was improved in some of the mice irradiated at 0.70 mGy/hr but not in the non-irradiated control mice. Mortality was delayed and a healthy appearance was prolonged in the irradiated mice by about 20-30 weeks compared with the control mice; The last mouse in the non-irradiated control group died at the 121st week, and the one in the irradiated group, at the 147th week. In severe autoimmune MRL-*lpr/lpr* mice, the immunological status was kept better and the incidence of a number of symptoms, including lymphadenopathy, splenomegaly and proteinuria, was suppressed in the mice irradiated at 0.35 or 1.2 mGy/hr. The life span was prolonged in the irradiated mice. Four-week-old female klotho mice (*kl/kl*), a premature-aging syndrome model, were irradiated with gamma rays at 0.35, 0.70 or 1.2 mGy/hr. All of the 20 non-irradiated mice died by 65th day of age; while the last mouse in the group irradiated at 0.7 mGy/hr died on 120th day of age. The irradiation at 0.35 mGy/hr was less effective, and no life span prolongation was observed in the mice irradiated at 1.2 mGy/hr.

Biological System Response to Ionizing Radiation Invalidates the Linear-no-Threshold-Hypothesis

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Biological systems function by complex signaling within and between hierarchical levels of organization: the basic physical/chemical level, the cellular level, the tissue-organ level, and the whole organism. Individual genetically controlled protections operate at each level, to defend against toxic substances, to repair, and remove damage. Ionizing radiation can cause primary DNA damage proportional to dose over a wide dose range and secondary damage from bystander effects and genomic instability. DNA repair may result in residual damage. New data support a model in which propagation of residual cell damage to higher levels meets above named mechanisms, which act as successive barriers under genetic control against damage becoming clinical detriment. Moreover, doses below about 0.2 Gy initiate adaptive responses, which amplify the above named mechanisms against damage induction and propagation partially or *in toto* with a delay of hours after the insult and may last for more than several months. At higher doses damage prevails. Adaptive responses also operate against endogenous damage. Damage induced homeostatic perturbation at a level and its type and degree determine the extent of immediate protection at this level, the probability of damage propagation to higher levels, and of the adaptive responses, all in a non-linear fashion under genetic control. Propagation of maximal perturbation eventually causes system collapse. Low-dose irradiation, then, leads to DNA damage and to an ascending repetition of non-linear responses that protect at successive levels under genetic control. In fact, theory and observation support even a reduction as well as constraint of spontaneously occurring cancer at low doses, a hormetic response. The degree of individual protection at low doses may become predictable by modern genetic screening methods. Thus, low doses also appear of interest to clinical therapy.

Smoking and Hormesis as Confounding Factors in Radiation Pulmonary Carcinogenesis

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Among potential confounding factors in risk estimation for radiation pulmonary carcinogenesis are passive and active cigarette smoke exposures, and radiation hormesis. Significantly increased lung cancer risk from ionizing radiation at lung doses <1 Gy is not observed in never smokers. Relative risk values from lung cancer of >20 in heavy smokers, RR < 3 for never smokers subjected to passive smoke, and the uncertainty of the interaction of radiation and smoking, makes an accurate estimate of lung cancer risk from low doses of radiation problematic. This is especially true for epidemiological study cohorts where the majority of participants are smokers. The way to stop all radiation related cancers in the lung at doses of less than a Gray is to stop smoking. Radiation hormesis involves low-dose-induced protection and high-dose-induced harm. The Linear No-Threshold (LNT) hypothesis advocated by NCRP, EPA, ICRP and BEIRVII for cancer risk estimations ignores radiation hormesis and the presence of a threshold. The risk of lung cancer found in epidemiological studies was less than the expected risk for spontaneous cancer (hormetic effect) for worldwide nuclear weapons and power plant workers, shipyard workers, fluoroscopy patients, inhabitants of high dose background radiation, and those exposed to indoor radon. The protective effect was noted for low- and mixed high- and low-LET radiations in both genders. Many studies showed a protection factor (PROFAC) > 0.30 (30% avoided) against the occurrence of lung cancer. The rather ubiquitous nature of the radiation hormesis responses in cellular, animal and epidemiological studies negates the Healthy Worker Effect as an explanation for radiation hormesis. The LNT hypothesis is wrong and does not represent the true nature of the dose-response relationship, since low doses or dose-rates commonly result in thresholds and reduce cancer incidences below the spontaneous rate. Low dose radiation can stimulate DNA repair/apoptosis to suppress and eliminate cigarette-smoke induced transformed cells in the lung, reducing lung cancer occurrence in smokers.

TOXICOLOGY SESSION

Oxidative Stress: Dose Responses and Application to Hormesis
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Arsenic Induced Hormesis: Underlying Mechanisms and Timing
Elizabeth T Snow, Deakin University, Burwood, Australia
Troy R Durham, Deakin University, Burwood, Australia
Robert M Kozlovski, Deakin University, Burwood, Australia
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Unravelling the Mechanisms Behind Hormesis in Plants
Nina Cedergreen, Royal Veterinary and Agricultural University, Tåstrup, Denmark
Jens C. Streibig, Royal Veterinary and Agricultural Universit, Tåstrup, Denmark
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Hormesis Model Dominates Threshold Model in Large Scale NCI Anti-tumor Drug Screening Data
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Nonlinear Dose-Response Mechanisms – Simulation with Bio-Mathematical Models
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Oxidative Stress: Dose Responses and Application to Hormesis

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Oxidative stress occurs when the cellular level of reactive oxygen species override the antioxidant capacity of the cell and results in oxidative damage to critical cellular macromolecules. Oxidative stress in humans has been implicated as a cause or contributing factor in a number of age-related and chronic diseases. To counteract the effects of oxygen radicals and oxidative damage, mammalian species possess a number of enzymatic and non-enzymatic antioxidants as well as oxidative repair enzymes. Research examining the induction of oxidative stress and damage following exposure to a variety of xenobiotic agents has demonstrated that the biological responses elicited by reactive oxygen species are dose-related and biphasic. Exposure to high levels of oxidants or long exposure periods to reactive oxygen species can induce oxidative damage and may be lethal. Conversely, low levels of cellular oxidants have been shown to stimulate antioxidant defense pathways (including catalase, glutathione peroxidase, superoxide dismutase), which result in the detoxification of reactive oxygen species. In addition, low levels of reactive oxygen species induce the synthesis of enzymes that repair oxidative damage to DNA including enzymes involved in base excision repair pathways as well as oxidative DNA repair enzymes. Further through activation of signaling cascades, oxidants are capable of stimulating expression of survival genes. As such the biological effects to low levels of reactive oxygen species are protective against oxidative damage and lethality. These data highlight the importance of understanding the biological relevance of dose-response relationships in toxicology.

Arsenic Induced Hormesis: Underlying Mechanisms and Timing

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Arsenic is an environmental contaminant that is generally considered to be toxic with no beneficial purpose other than as a means to kill unwanted pests, plants, animals or people. It is also a well-recognized human carcinogen that preferentially interacts with proteins. By so doing it can induce changes in gene expression, oxidative stress, and an increase in reactive oxygen species, which ultimately produce oxidative DNA damage and, with time and continued exposure, cancer. Arsenic has also been used as an anticancer drug that preferentially produces apoptosis and differentiation in specific target cells. However recent results show that low doses of arsenic, in the range to which many people are exposed during the normal course of their lives, can up regulate protective mechanisms within human cells that can both promote the repair of DNA damage and prolong cellular lifespan. Cellular processes showing a hormetic response to arsenic include proliferation, base excision DNA repair, and telomerase activity. Other cellular pathways, such as the expression of redox genes show a dose-dependent response to higher, more toxic, doses of As, but no subsequent down-regulation or hormesis. Arsenic-induced hormesis is transient in nature and involves the direct regulation of RNA polymerase II. There also appears to be an involvement of the EGF receptor and Rac-dependent signalling. In contrast, Map-kinase-dependent responses involve higher doses of As and do not exhibit hormesis. The possible mechanisms involved in As-dependent responses showing hormesis will be discussed and compared to non-hormetic responses.

Unravelling the Mechanisms Behind Hormesis in Plants

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Hormesis in plants have been known for decades. In fact, one of the first herbicides, MCPA, was developed with the purpose of enhancing yield in crops, and atrazine was considered for use as a growth enhancer, due to its positive effects on yield at low doses. Dosing, however, proved to be difficult, and both chemicals have since then mainly been recognized for their deleterious effect on plants at higher doses. As most research on plants and chemicals has been done with the purpose of herbicide development, focus has been on adverse effects, and hormesis is normally only commented on as outliers relative to the sigmoid dose-response curve. In plants, hormesis has been observed for several endpoints such as leaf area and length, plant height, dry weight increase, nutrient uptake, root growth, *etc.* But hormesis measured on one endpoint is not necessarily correlated to hormesis measured on other endpoints. There are theories which predict that hormesis observed in one trait must occur at the expense of development in another trait, or with a cost over time. When it comes to the molecular and physiological processes behind the hormesis response almost nothing is known. In our project, we have developed dose-response models that include hormesis, to statistically quantify the size and dose range of the maximal hormesis response in plants. Using the model we have tested the size and frequency of hormesis for different chemicals on datasets on algae (*ca.* 150 datasets), *Lemna minor* (*ca.* 350 chemicals), aquatic macrophytes (*ca.* 35 datasets) and crops (*ca.* 50 datasets). The outcome of analysing these data was used to select eight chemicals and ten endpoints for tests on barley. We analysed the response of the different endpoints with the hormesis models. The information about the morphological response of the plants in the dose ranges giving hormesis will form the basis for hypotheses concerning the physiological mechanisms initiating hormesis responses. The next step will be to test these hypotheses by measuring biochemical changes and gene expression, which we hope will lead us to a better understanding of the mechanisms behind hormesis in plants.

Hormesis Model Dominates Threshold Model in Large Scale NCI Anti-tumor Drug Screening Data

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Which dose response model best explains low dose responses is a critical issue in toxicology, pharmacology, and risk assessment. The present paper utilized the US NCI yeast screening database which contains the replicated effects of approximately 2,200 chemically diverse possible anti-tumor drugs on cell proliferation of 13 different yeast strains (i.e., ~57,000 dose responses). Using multiple evaluation methods (i.e., bench mark dose (BMD)-based method, traditional no observed effect level (NOEL) method and dose-response pattern method) to assess whether the threshold or the hormetic (biphasic) dose response model best fits for the observed data, the findings indicate that the observed data were generally and strikingly inconsistent with the predictions of the threshold model while being consistent with hormetic model predictions. The data indicate that the hormetic pattern is approximately 2.5 times more common than the threshold model. These findings markedly extend previous reports indicating that the hormetic dose response model outperforms the threshold model in predicting the distribution of responses below the toxicological threshold. These results have broad implications for those areas of the biological sciences dependent on the design and assessment of dose response relationships, since they not only challenge the continued use of the threshold model as the default model in toxicology and risk assessment but indicate its fundamental inability to provide useful prediction in the critical low dose domain. While the data led to a rejection of the threshold model for low dose prediction, they strongly support the hormetic as the low dose default model in toxicology and risk assessment.

Nonlinear Dose-Response Mechanisms – Simulation with Bio-Mathematical Models

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Important low-dose mechanisms such as detrimental bystander effects, low-dose hyper-radiosensitivity (HRS) and apoptosis-mediated protective effects were implemented into a deterministic multistage model for neoplastic transformation: the State-Vector Model (SVM). The new models are tested on various data sets that show supra-linear or U-shaped dose-responses. It is also investigated whether the model without the new low-dose features can explain LNT-shaped dose-responses. Data on detrimental bystander effects (1) were fitted with additional terms in the initiation model that add to the damage accumulation at low doses. One data set (2) shows features of a low-dose HRS and it can be explained by reduced repair rates, an effect that has been associated with HRS. The protective effects of low-dose low dose rate gamma-radiation (3) can be explained with the SVM when apoptosis is included. The model can describe the various data sets at low and high doses after incorporation of biological features that had been associated with the data sets. The model without specific low-dose mechanisms can be used to simulate LNT-shaped dose-responses.
The SVM approach will be contrasted and compared with a compartment model that links the protective effects of low doses of low LET radiation to the induction and repair of DNA damage.

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PRACTICAL ISSUES WHEN USING HORMESIS IN RISK ASSESSMENT SESSION

Risk Assessment and Recognizing Hormesis During Hazard Identification
Elizabeth A. Doyle, US Environmental Protection Agency, Washington D.C.

Incorporating Mode of Action Understanding of Hormesis into Dose Response Assessment
Lynne T. Haber, Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH
Andrew Maier, Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH
Michael L. Dourson, Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH

Fluoridation as a Case Study in Hormesis
Dennis E. Jones, Agency for Toxic Substances and Disease Registry, Atlanta, GA
Christopher T. De Rosa, Agency for Toxic Substances and Disease Registry, Atlanta, GA
Carolyn Tylenda, Agency for Toxic Substances and Disease Registry, Atlanta, GA

Meta-Hormesis for Uncertain Risks: Arsenic as a Case Study
Louis Anthony (Tony) Cox, Jr., Cox Associates, Denver, CO

Detailed Case Study of Hormesis for Radiation
Colin Seymour and Carmel Mothersill, McMaster University, Hamilton, ON, Canada

Risk Assessment and Recognizing Hormesis During Hazard Identification

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In a regulatory setting, limitations of data are often compensated for by developing science policy. Science policy ensures consistency in use of data, but may also reduce the flexibility of the risk assessor in applying data. Data quality and quantity are key concerns in the hazard identification and dose response phases of risk assessment. Recognizing hormesis during the hazard identification process may be difficult due to the nature of the available data, or because of the impact of science policy on data application and interpretation. Examples of the conflict between science policy and available data in EPA risk assessments will be presented using micronutrients as an example.

Incorporating Mode of Action Understanding of Hormesis into Dose Response Assessment

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A mechanistic perspective is essential to understanding the risk-assessment implications of biphasic dose response curves. A key issue is the implications for extrapolation from the exposure levels used in experimental animal studies to environmentally-relevant exposure levels. This presentation reviews some key modes of action that can lead to biphasic dose response curves, focusing primarily on noncancer endpoints. These include (1) essential elements and nutrients (e.g., chromium and copper), (2) different targets for toxicity and benefit (e.g., ethanol benefits to heart at low doses vs. central nervous system and liver effects at high doses), (3) stimulatory and inhibitory receptors within same organ, and (4) protein induction (e.g., metabolic or repair enzymes). Examples from the published literature are used to highlight the mechanistic basis for biphasic dose-response curves and implications for risk assessment. A framework for using mode of action data to improve extrapolation to low doses is considered.

Fluoridation as a Case Study in Hormesis

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ATSDR has recently updated its Minimal Risk Level (MRL) for fluorides. Several chemicals, including chromium, zinc, and manganese, have previously been shown to exhibit hormetic effects that have impacted derivation of their respective MRLs. Fluoride has also been shown to have a hormetic effect on dental health, causing a dose-dependant decrease in dental caries and a dose-dependant increase in dental fluorosis. The optimal fluoride dose in drinking water for minimizing both dental caries and dental fluorosis has been determined to be 1 ppm, a concentration equivalent to the 0.7-1.2 ppm recommended by the US Department of Health and Human Service (DHHS) for fluoridation of municipal water supplies. Fluoride has also been shown to have adverse effects on bone, but the literature has been inconsistent, with conflicting reports of both increased and decreased effects on bone strength and fracture rates. However, a recent human ecological study in China that examined more than 8,000 subjects exposed to six different fluoride drinking water concentrations reported a biphasic or hormetic effect on bone fracture rates, with an optimum fluoride concentration of 1.00-1.06 ppm (Li et al., 2001). Overall bone fracture rates were significantly lower ($p<0.05$) in the 1.00-1.06 ppm group than in the most highly exposed group ($\geq$4.32 ppm fluoride) as well as in the least exposed group ($\leq$0.34 ppm fluoride). Accordingly, we used the 1.00-1.06 ppm group, equivalent to a daily fluoride intake of 0.055mg/kg/d, as the comparison group, and determined a NOAEL of 0.15 mg/kg/d for the group with the highest level of exposure that did not show a significant increase in bone fractures. An uncertainty factor of 3 for human variability was applied to the NOAEL to derive a chronic oral MRL of 0.05 mg/kg/d. Interestingly, the optimal fluoride dose in drinking water for reduction of bone fractures is essentially the same as the optimal dose for reduction of dental caries and prevention of dental fluorosis. This may be the only instance of two different beneficial hormetic effects reported for a single chemical produced by different purported mechanisms of action.

Meta-Hormesis for Uncertain Risks: Arsenic as a Case Study

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It is sometimes asked whether hormesis should be adopted as a default model for risk management decision-making. This paper addresses a related question, using arsenic and cancer risk as a case study: When low-dose modes of action are unknown or very uncertain, but there is at least some evidence favoring a U-shaped dose-response relation and some evidence favoring a strictly increasing (e.g., low-dose linear) dose-response relation, *how should a risk manager set permissible exposure limits to best protect human health?* Such situations of mixed evidence, with partial support for mutually inconsistent hypotheses or models and/or for different mechanisms of hormetic and adverse effects, are important in many applications of low-dose risk assessment.

Advances in statistical decision methodology, such as Bayesian model averaging, enable objectively better (more likely to truly reduce human health risks) risk management decisions in such situations than can *any* single default model. We first prove that that multi-model decision-making (in which decisions hedge against model uncertainty, using predictions from different models) dominates single-model decision-making whenever there is sufficient uncertainty about the correct model. Next, we show that *whenever there is sufficient uncertainty about the existence and magnitude of hormesis at low doses, optimal decision-making (i.e., minimizing expected human health risk given available information) requires acting as if hormesis were known to be present.* That is, the best decision is not to eliminate exposure, but to set a positive threshold for permissible exposures. We call the phenomenon of a U-shaped effective dose-response model arising from multiple uncertain models, *meta-hormesis.* We provide a mathematical framework for developing such dose response assessments despite model uncertainties, even if the presence of statistically and biologically significant hormesis is uncertain; show how optimal permissible exposure thresholds vary with uncertainty about the true dose-response function at low doses and illustrate (for arsenic) how meta-analysis of studies can be used to set practical thresholds to protect human health. Finally, we discuss how meta-hormesis changes in the presence of co-carcinogeneis, e.g., potentiation of B(a)P genotoxicity by low levels of co-exposure to arsenic.

Key Words: Arsenic dose-response model, Bayesian model-averaging, optimal statistical decisions, hormesis, meta-hormesis

Detailed Case Study of Hormesis for Radiation

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Skepticism is an old scientific and philosophical tradition, but it does not sit well in the modern scientific world. In grant applications scientists have to sell themselves and their ideas, thus losing ant semblance of objectivity. Grants are often awarded on salesmanship, not scientific ability. Perhaps more important though is that science is a buyer's market – the scientist can only sell what the buyer (the grant awarding agencies) want. The direction of science is often shaped without any informed debate or detailed analysis.

The scientist becomes a seller of information, and in this role becomes a propagandist. As his/her product is the true one, so all others are necessarily false. The scientist is no longer selling knowledge, because knowledge is empirical, rational and can be tested. The scientist is selling belief, in a way that is analogous to T.V, advertisements, In advertisements, the product comes wrapped up in a lifestyle – buy the product and the lifestyle will also be acquired.
The scientific belief sold is that there is an answer to the problem, that a certain true and sure answer, exists. There is little room for uncertainty, and little room for the skeptical tradition. Ideas become fixed, and knowledge becomes belief. This is the point at which scientific discourse and argument fail, because knowledge is ambivalent but belief is certain.

Belief limits debate and argument as certainty precludes the alteration of position. It is this that has polarized the nuclear debate. Nuclear proponents and opponents believe in their respective positions, partly because of "advertisements" of nuclear and anti nuclear lifestyles. There is, and always will be, a link in the human psyche between nuclear weapons and nuclear power. Power stations can always blow up and become weapons. So, to a certain extent, the division becomes one of belief in people – are they inherently good and capable or bad and incapable.

As long as belief predominates, no discourse is possible. Belief may be rational or irrational, but debate only becomes possible when "I believe" becomes" I think based on the evidence I have seen".

The question then becomes one of how to dismantle a fixed belief based system and assemble a flexible knowledge based system. Generally attacking a belief based system leads to entrenchment with possible paranoid overtones. Attempting to establish and disseminate a consistent body of scientific knowledge, which is the Calabrese approach is more useful, although such knowledge will always be viewed by some through the lens of belief. Acceptance of the concept of uncertainty as a normal feature of life would also allow both dialogue and more precise statements to be made. Instead of "nuclear power is good" – a belief and a moral judgment, a statement would be that "based on this evidence I accept this plant is operated safely".

"Nuclear power is bad" would become" based on this evidence I think that nuclear power is not the correct option". Although it is impossible to eliminate moral values from argument, the link between belief and moral judgment (nuclear power good/bad) must be broken to allow discourse.

This will be difficult, as both belief and moral judgments tend to allow mainly for absolute values. Skepticism and an acknowledgement of uncertainty enter the realm of competing interests and relative values. It is only in this realm that any consensus on the future of nuclear power can be reached, It is also in this realm that hormesis or adaptive effects must be debated; otherwise they are simply accepted as part of the "good" effects of radiation or not believed at all. Relative risk follows the dictate of Paracelsus, and states that all substances are poisons if the dose is large enough. Radiation is not unique, and must be judged in the same degree as other chemicals. As with other chemicals there will be doses at which there is no detectable effect, and doses which tend to show a beneficial effect. As with other chemicals there will be abnormally sensitive organisms and abnormally resistant organisms. Debate can only occur in this area of uncertainty and competing risks when there is no overlying belief.

BIOMEDICAL SESSION

Memory Molecules and Hormones
John E. Morley, Saint Louis University Health Sciences Center, St. Louis, MO
Susan A. Farr, Saint Louis University Health Sciences Center, St. Louis, MO

Biphasic Dose Response of Steroid Hormone Action
Roberta Diaz Brinton, University of Southern California, Los Angeles, CA

Role of Hormesis in Life Extension by Caloric Restriction
Edward J. Masoro, University of Texas Health Science Center, San Antonio, TX

Hormesis, Control Theory, and Substance Use Disorders
David B. Newlin, RTI International, Baltimore, MD

Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer
Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM
Jennifer Di Palma, Lovelace Respiratory Research Institute, Albuquerque, NM

Streptolysin O Enhances Keratinocyte Migration and Proliferation and Promotes Skin Organ Culture Wound Healing
Marjana Tomic-Canic, Hospital for Special Surgery, New York, NY
Stephen W. Mamber, Beech Tree Labs, Delanson, NY
Olivera Stojadinovi, Hospital for Special Surgery, New York, NY
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Memory Molecules and Hormones

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The regulation of memory involves a large number of neurotransmitters which modulate learning and recall. These neurotransmitters produce their activity in the hippocampus and throughout the limbic system. All of these neurotransmitters have a bell shaped curve of action. Low doses enhance memory and high doses cause amnesia. Also when animals are over trained low doses can become amnestic. This was first demonstrated with the acetylcholine esterase inhibitor, tacrine. Subsequently, this has been shown to be the case for all classes of neurotransmitters.

Classically amyloid-beta protein has been considered to be an amnestic agent involved in the pathogenesis of Alzheimer's disease. This gave rise to the question of what is the physiological role of amyloid-beta peptide? Our recent studies have shown that blocking amyloid-beta peptide activity in young mice with DFFVG and antibiodies or antisense to amyloid-beta protein produces amnesia. Very low dose amyloid-beta protein enhances memory. Preliminary data with Dr. Kel Yamada at Washington University suggests similar effects of amyloid-beta protein inhibitors.

Hormesis appears to be a universal property of memory enhancing transmitters.

Biphasis Dose Response of Steroid Hormone Action

Roberta Diaz Brinton, Ph.D., University of Southern California

Our scientific endeavors over the past two decades have focused on determining estrogen mechanisms of action that underlie estrogen-dependent neuron survival and memory function. Results of these endeavors have yielded critical insights into the proactive defense and memory mechanisms of estrogen action which now allow us to translate our basic science understanding into therapeutic development to ***prevent*** age-associated neurodegenerative disease and loss of cognitive function. The ultimate goal of our translational NeuroSERM development efforts is to generate small molecule therapeutics that easily penetrate the blood brain barrier and which activate estrogenic mechanisms that ***prevent*** age-associated neurodegenerative disease and loss of cognitive function women and potentially in men. Our therapeutic target is the brain which is not the organ(s) (bone, breast, uterus) used to determine hormone efficacy for pharmaceutical development although the major indicator for estrogen (ET) or hormone therapy (HT) is for the cessation of hot flushes, a brain mediated response directly attributable to the loss of estrogen. Optimal ET or HT dosing for therapeutic outcomes in brain requires an understanding of ET and HT mechanisms of action, dose response profiles and temporal constraints for inducing advantageous outcomes of ET or HT while avoiding or reducing potential adverse outcomes. Responses of neural systems to estrogens occur over a billion-fold range with in vitro models that exceeds the physiological range at both extremes. Our *in vitro* and *in vivo* models for hormone therapy indicate multiple interactive pathways with mechanisms. While it is commonly accepted now that a one size dose does not fit all women, efficient predictive biomarkers on which to base dose and hormone therapy optimization do not yet exist for the 20+ million women in the US who are or are approaching menopause. *Research Supported By*: National Institutes of Aging and National Institutes of Mental Health to RDB

Role of Hormesis in Life Extension by Caloric Restriction

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Caloric restriction (CR) markedly extends the life of rats and mice as well as that of several other species. CR also retards age-associated physiological deterioration and the occurrence and/or the progression of age-associated diseases. It has been shown that the levels of CR that retard aging are low intensity stressors. Moreover, CR enhances the ability of rats and mice of all ages to cope with intense stressors, which indicates that it has a hormetic action in these species. It is hypothesized that hormesis plays a role in the life-extending and anti-aging actions of CR. The evidence supporting this hypothesis will be presented and the findings opposing it will be critically considered. Also, the evidence indicating that hormesis is not the only process contributing to CR-induced life extension will be assessed. The conclusion is that two general processes are involved in the CR-induced life extension. One is the reduced endogenous generation of damaging agents, such as reactive oxygen species. The second is hormesis, which enhances the processes that protect against the action of damaging agents and promotes processes that repair the damage once it occurs.

Hormesis, Control Theory, and Substance Use Disorders

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Drugs of abuse demonstrate clearly nonlinear, non-monotonic dose-effect curves and biphasic time-action curves (Calabrese & Baldwin, 2003). The initial psychostimulant and later sedative and impairing effects of acute alcohol (over minutes and hours) mirror the sensitization of stimulant properties in early alcohol abuse and the subsequent debilitating and subjective "need" for the drug in alcohol dependence (over years). The rising blood alcohol curve is experienced as euphoric and the falling curve as dysphoric; this biphasic effect is exaggerated among individuals most vulnerable to developing alcoholism (sons of alcoholic fathers) (Newlin & Thomson, 1990). Virtually all drugs of abuse have locomotor activating effects at low doses and early in the acute response to the drugs (Wise & Bozarth, 1987); again, this is parallel to the primarily activating effects of these drugs in early abuse and de-activating effects in addiction. Moreover, locomotor activation in rodents to novelty or to the drug itself, and ADHD and conduct disorder in human children, are predictive of subsequent self-administration and addiction. Drug conditioning research has shown that the conditioned response in anticipation of drug administration in rodents is always activating, even though abused drug responses have both activating and de-activating aspects depending on what is measured and when. In addition, the drug response "oscillates" over days in rodents, as revealed by variation in the magnitude and direction of the drug response when administered again one, two, or more days after a large dose. We interpret these patterns of effects (above) in terms of control theory. The broad generality of hormesis implies it is a characteristic of organisms rather than the agents—such as abused drugs—that perturb them. We use control theory, which developed in engineering research, to model the psychobiological systems that may control drug responses in rats and humans.

Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer

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The term "radiation hormesis" as used here involves low-dose, low linear-energy-transfer (LET) radiation activation of **coo**perative **p**rotective **p**rocesses (COOPP) in the body [immune system, high-fidelity DNA repair/apoptosis (presumed *p53*-dependent), and a novel apoptosis mechanism (presumed *p53*-independent)]. The presumed p53-independent novel apoptosis mechanisms has been called the protective apoptosis mediated (PAM) process and involves reactive oxygen and nitrogen species and specific cytokines (e.g., transforming growth factor β). Stochastic low-LET radiation thresholds that vary for each person activate the PAM process, the immune system, and the presumed *p53*-dependent high-fidelity DNA repair/apoptosis. Higher stochastic thresholds inactivate the PAM process and suppress the immune system (implicating a complex hormetic process). The indicated thresholds depend on low-LET radiation dose rate and photon radiation energy. Two forms of radiation hormesis are described that have application to preventing and curing cancer in human populations. Medical radiation hormesis (which is associated with applications of small doses of diagnostic X-rays) activate COOPP which leads to removal of precancerous neoplastically transformed and other aberrant cells (e.g., mutants) from the body, thereby reducing the risk of cancer for persons bearing such cells (e.g., some long-time heavy smokers). Therapeutic radiation hormesis involves use of small fractionated doses of low-LET radiation (alone or in combination with apoptosis sensitizing agents targeted at the neoplastic cells of interest) or small protracted doses (e.g., via radioimmunotherapy or radon therapy) to repeatedly activate COOPP over an extended period to eliminate existing cancer cells from the body. A mathematical model applicable to dose-response relationships for medical radiation hormesis will be discussed and applied to data for suppression of lung and breast cancer in humans by application of fractionated doses of diagnostic X-rays. [This research was supported by the Office of Science (BER), U.S. Department of Energy (DOE) Grants DE-FG02-03ER63671 and DE-FG02-03ER63657.]

Streptolysin O Enhances Keratinocyte Migration and Proliferation and Promotes Skin Organ Culture Wound Healing

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ML-05, a modified form of streptolysin O, a hemolytic and cytotoxic bacterial toxin, is currently being investigated as a treatment for collagen-related disorders such as scleroderma and fibrosis. ML-05 was shown to modulate or reduce collagen levels in two *in vivo* murine models of scleroderma and fibrosis. Furthermore, ML-05 may be effective in promoting wound healing and alleviating the formation of hypertrophic scars and keloids. To investigate the effects of ML-05 on wound healing processes, *in vitro* wound healing scratch assays (using human primary epidermal keratinocytes and dermal fibroblasts) and an *ex vivo* human skin organ culture wound model were utilized. In wound scratch assays, ML-05 markedly enhanced keratinocyte migration and proliferation. At 48 hours post-treatment, keratinocyte migration (using cells pretreated with mitomycin C to inhibit proliferation) was optimal at 0.2-2 units/ml. Keratinocyte proliferation (no pretreatment of cells) also was markedly enhanced by ML-05 (0.02-0.2 units/ml). ML-05 did not affect either migration or proliferation of dermal fibroblasts, indicating that the effects of ML-05 on cell migration/proliferation may be keratinocyte-specific. However, the spatial orientation of fibroblasts within the scratch zones appeared to be more orderly if ML-05 was present. ML-05 also was tested in a dose-dependent manner (0.02-20 units/ml) in a human skin organ culture wound model. Skin explant samples were "wounded" by punch biopsy. Two different application methods were used: Addition to the culture media (dermal exposure) or direct topical application to the wound surface. ML-05 was found to accelerate wound healing over 4-6 days as measured by wound reepithelialization in comparison with that in untreated control cultures, particularly after topical application. Therefore, ML-05 may have potential as a wound healing agent capable of promoting reepithelialization through stimulation of keratinocyte migration and proliferation.

POSTERS

LDR Does not Induce Adaptive Response in Tumor Cells
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Wei Li, Jilin University, Changchun, China
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Empirical models for hormesis
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Christian Ritz, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark
Jens Carl Streibig, The Royal Veterinary and Agricultural University, Taastrup, Denmark

Identifying Non-linear Radiation Dose Responses In Vivo: Exploring Bystander Effects
Benjamin J. Blyth, Flinders University and Medical Centre, Bedford Park, South Australia
Tanya K. Day, Flinders University and Medical Centre, Bedford Park, South Australia
Pamela J. Sykes, Flinders University and Medical Centre, Bedford Park, South Australia

Expected Lives Saved due to Medical, Therapeutic, Environmental and other Forms of Radiation Hormesis
Jennifer Di Palma, Lovelace Respiratory Research Institute, Albuquerque, NM
Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM

Effects of Low Doses of Dietary Lead on Red Blood Cell Production in Three Successive Generations of Swiss Mice
Ivo Iavicoli, Catholic University of Sacred Heart, Rome, Italy
Giovanni Carelli, Catholic University of Sacred Heart, Rome, Italy

Hormesis as a Confounding Factor in Epidemiological Studies of Radiation Carcinogenesis
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LDR Does not Induce Adaptive Response in Tumor Cells

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Biological effect of low-dose radiation (LDR) is distinguishable from those induced by high dose radiation. Hormetic and adaptive response are the two examples of such distinguishable effects of LDR. However, whether the adaptive response induced by LDR occurs in tumor cells, especially under in vivo condition, remains elusive. In the present study, we firstly used four tumor cell lines: human small cell lung carcinoma cell line (NCI-H446), human glioma cell line (U251), human erthroleukemia cell line (K562), and human acute promyelocytic leukemia cell line (HL60), and irradiated these cells with LDR at 25 to 200 mGy or 75 mGy + 1 Gy. No hormesis and adaptive response was noted in these cells. To further validate the in vitro finding into an in vivo condition, we implanted U251 and NCI-H446 cells into nude mice to form tumors in vivo. The tumor-bearing mice were then irradiated with 75 mGy plus 4 Gy or 4 Gy alone. Pre-exposure of tumor-bearing mice to 75 mGy X-rays did not provide any protection from 4-Gy-X-rays-induced tumor growth inhibition. In contrast, exposure of tumor-bearing mice to 75 mGy/4 Gy even provide a better inhibition of tumor growth than exposure of these mice to 4 Gy X-rays alone. These studies indicated that LDR does not induce adaptive response in certain tumor cells under in vitro and in vivo conditions, which is an important phenomenon with a potential to be applied in clinics (Supported in part by National, Natural Scientific Foundation of China).

Empirical models for hormesis

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During the past two decades, the phenomenon of hormesis has gained increased recognition. To promote research in hormesis, a sound statistical quantification of important parameters, such as the level and significance of the increase in response and the range of concentration where it occurs, is strongly needed.

We present a brief illustration of the capabilities of statistical models describing hormetic dose response data. Such models have been derived by Brain and Cousens (1989) and Cedergreen *et al* (2005) by slight extensions the commonly used 4-parameter log-logistic model.

Recently open source software, in the form of an extension package to the statistical software **R** (www.bioassay.dk), has been made available. Using this software we are able to assess the statistical significance of the hormetic effect. Furthermore we can obtain estimates of relevant parameters: EC10, EC50, EC90 etc. with standard errors as well as estimates of the maximal response and dose at which the maximal response is obtained.

The readily available software makes modelling and quantification of hormesis just as easy as fitting an ordinary dose response model.

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Identifying Non-linear Radiation Dose Responses In Vivo: Exploring Bystander Effects

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The general population is daily exposed to chronic, low doses of ionizing radiation (IR) from both natural and artificial sources. The shape of the radiation dose-response curve at these low doses is currently linearly extrapolated from high dose data due to difficulties assessing radiation effects after near-background exposures. At odds with this Linear Non-Threshold model, are the phenomena collectively referred to as the Radiation-induced Bystander Effect (RIBE). The RIBE describes a collection of *in vitro* observations that suggest the presence of a soluble, transmissible factor(s) released from irradiated cells that can induce a biological response in un-irradiated cells. The induction, nature and magnitude of the RIBE varies between cell culture systems, radiation sources and end-points measured. Validation of the RIBE *in vivo* has been mired by the difficulty in selectively irradiating cells within an animal model. Using the pKZ1 *in vivo* mouse mutagenesis assay, this research is aimed at studying the RIBE with an adoptive transfer of syngeneic splenic T cells receiving chronic low radiation doses from the internal β-particle emitter tritiated thymidine. The donor cells, a proportion of which will lodge in the recipient animal's spleen, can be tracked with a fluorescent tracer dye allowing localized effects to be examined. By examining the induction of chromosomal inversions, apoptosis and proliferation as well as candidate signaling and effector molecules, the presence of a RIBE *in vivo* can be evaluated. If a RIBE is indeed induced after chronic exposure to low dose radiation, this would challenge the assumed linearity of low radiation dose effects and suggest a possible mechanism for previously observed hormetic and hypersensitive low dose responses.

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Expected Lives Saved due to Medical, Therapeutic, Environmental and other Forms of Radiation Hormesis

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We describe three forms of radiation hormesis (medical, therapeutic, and environmental) and their implications for saving lives. Medical radiation hormesis is postulated to be responsible for the removal of precancerous cells from the body after application of diagnostic low linear-energy-transfer (LET) X-rays (e.g., chest X-rays, mammograms, and CT scans). Data is presented showing that fractionated, low doses of diagnostic X-rays have suppressed spontaneous lung and breast cancer occurrence in human subjects. Therapeutic radiation hormesis is postulated to cure existing cancer via applications of easily tolerated fractionated (e.g., X-rays or gamma rays) or continuous low rate exposure (e.g., radioimmunotherapy using beta radiation) to low doses of low-LET radiation. Therapeutic radiation hormesis has been used to successfully treat ovarian, colon, and hematologic cancers without any symptomatic side effects. Low-dose, low-dose-rate radioimmunotherapy (using beta radiation) has also been used successfully to treat follicular lymphoma. Environmental radiation hormesis is associated with reduced cases of cancer as a result of exposure to elevated levels of natural background radiation (e.g., radon in the home and cosmic rays) and has been demonstrated in previous studies by others. Radiation hormesis related to cancer suppression has also been demonstrated for some nuclear worker populations exposed at low rates to low- or low- plus high LET radiations. A low-dose form of a novel hormetic relative risk (RR) model is used to calculate expected lives saved due to each indicated form of radiation hormesis for specific populations. The cancer *RR* is calculated as $1 - PROFAC$ for doses > 0, where the protection factor (*PROFAC*) is the proportion of cancers (or cancer deaths) prevented that otherwise would have been expected to occur. Implications for cancer prevention and cancer therapy will be discussed. [This research was supported by the Office of Science (BER), U.S. Department of Energy (DOE) Grants DE-FG02-03ER63671 and DE-FG02-03ER63657.]

Effects of Low Doses of Dietary Lead on Red Blood Cell Production in Three Successive Generations of Swiss Mice

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Lead (Pb) is a xenobiotic that, after absorption, can determine in humans toxic effects on a number of tissues or organs, such as the haematological system. In the last twenty years, the implementation of protection and prevention devices in industrialised countries has resulted in a remarkable decline in occupational exposure to lead and its compounds. Moreover, the elimination of Pb from gasoline, soldering in canned foods and other sources has led to a generalized and considerable decrease in Pb exposure among the general population. Nevertheless, studies on possible neurobehavioural and cognitive changes in children even at very low Pb exposure suggest that there are no threshold effects. Furthermore, since little research has aimed at assessing the effects of low level Pb exposure, *ad hoc* experimental studies are needed.

Our recent experiments on Swiss mice were performed by administering eight Pb acetate doses in a solid purified phytoestrogen-free rodent diet, 0.02, 0.06, 0.11, 0.2, 2, 4, 20 and 40 ppm (as Pb). Mothers were fed lead acetate during gestation and suckling of the offspring. After weaning, the latter were administered the same diet as the mother. We studied the effects on some haematological parameters (erythrocyte count, hematocrit, haemoglobin level) of the first generation. Diet Pb levels were designed to provide exposure below and above the normal background level (0.2 ppm). 0.02 ppm was the lowest level used as further reduction in dietary Pb would have altered the diet composition, thereby changing its nutritional validity.
Modest increases in dietary Pb acetate resulted in a decreased erythrocyte count and a reduction in hematocrit and haemoglobin levels in both males and females. Surprisingly Pb concentrations below the normal background value led to a significant increase in the erythrocyte count and in hematocrit and haemoglobin levels.

Here we report the study that followed up the exciting results obtained for the first generation. For each of the eight Pb exposure groups, we selected eight males and eight females for both the second and third generation in order to assess possible changes in the haematological parameters observed for the first generation.

The results obtained closely resemble those of the first generation.

Our findings clearly suggest the occurrence of haematological and reproductive effects at very low Pb doses, even ten-fold below the normal background level.

In our animal model, and for the wide range of Pb doses investigated (1:2000), no dose threshold was observed for the biological effects investigated in the second and third generations.

The observation of effects in Swiss mice at PbB levels < 1 μg/dl, i.e. well below those of the general population, raises concern for both Pb risk evaluation and the risk management of Pb exposure in relation to public health.

Hormesis as a Confounding Factor in Epidemiological Studies of Radiation Carcinogenesis

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Biological mechanisms for ionizing radiation effects are different at low doses than at high doses. Radiation hormesis involves low-dose-induced protection and high-dose-induced harm. The protective component is associated with a reduction in the incidence of cancer below the spontaneous frequency, brought about by activation of defensive and repair processes. The Linear No-Threshold (LNT) hypothesis advocated by the International Commission on Radiological Protection (ICRP) and the Biological Effects of Ionizing Radiation (BEIR) Report VII for cancer risk estimations ignores hormesis and the presence of a threshold. Cancer incidences significantly less than expected have been found in a large number of epidemiological studies including, airline flight personnel, inhabitants of high radiation backgrounds, shipyard workers, nuclear site workers in scores of locations throughout the world, nuclear power utility workers, plutonium workers, military nuclear test site participants, Japanese A-bomb survivors, residents contaminated by major nuclear accidents, residents of Taiwan living in ^{60}Co contaminated buildings, fluoroscopy and mammography patients, radium dial painters, and those exposed to indoor radon. Significantly increased cancer was not found at doses <200 mSv*. Evidence for radiation hormesis was seen in both sexes for acute or chronic exposures, low or high LET radiations, external whole- or partial body exposures, and for internal radionuclides. The ubiquitous nature of the Healthy Worker Effect (HWE)-like responses in cellular, animal and epidemiological studies negates the HWE as an explanation for radiation hormesis. The LNT hypothesis is wrong and does not represent the true nature of the dose-response relationship, since low doses or dose-rates commonly result in thresholds and reduce cancer incidences below the spontaneous rate. Radiation protection organizations should seriously consider the cost and health implications of radiation hormesis.