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LOW-DOSE CANCER RISK MODELING MUST RECOGNIZE UP-REGULATION OF PROTECTION

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□ Ionizing radiation primarily perturbs the basic molecular level proportional to dose, with potential damage propagation to higher levels: cells, tissues, organs, and whole body. There are three types of defenses against damage propagation. These operate deterministically and below a certain impact threshold there is no propagation. Physical-static defenses precede metabolic-dynamic defenses acting immediately: scavenging of toxins; - molecular repair, especially of DNA; - removal of damaged cells either by apoptosis, necrosis, phagocytosis, cell differentiation-senescence, or by immune responses, - followed by replacement of lost elements. Another metabolic-dynamic defense arises delayed by up-regulating immediately operating defense mechanisms. Some of these adaptive protections may last beyond a year and all create temporary protection against renewed potentially toxic impacts also from non-radiogenic endogenous sources. Adaptive protections have a maximum after single tissue absorbed doses around 100 to 200 mSv and disappear with higher doses. Low dose rates initiate maximum protection likely at lower cell doses delivered repetitively at certain time intervals. Adaptive protection preventing only about 2 – 3 % of endogenous life-time cancer risk would fully balance a calculated induced cancer risk at about 100 mSv, in agreement with epidemiological data and concordant with an hormetic effect. Low-dose-risk modeling must recognize up-regulation of protection.

Keywords: Low-dose cancer risk, adaptive protections, hormesis

INTRODUCTION

Epidemiology so far fails to substantiate the claim of an increase in cancer incidence in humans following low-level exposure to ionizing radiation, below about 150 mGy or mSv. Rather a decrease in cancer risk has

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shown up repeatedly (Pollycove and Feinendegen 2001; Tubiana *et al.* 2005; Nair *et al.* 2009; Tubiana *et al.* 2009). Nevertheless, observed data are fitted using the linear-no-threshold (LNT) hypothesis (ICRP 1977) This hypothesis expresses proportionality between dose and risk, and is the basis for radiation protection regulation and most widely used. Despite contradicting epidemiological and experimental findings the LNT hypothesis is also applied to predict cancer risks of low-dose irradiation (Brenner and Hall 2007). What was a good intention years ago to protect workers from overexposure to ionizing radiation has been turned to producing a wide spread radiation phobia now.

The initial plausibility of the LNT-hypothesis derived from two assumptions: 1) immediate damages to the genetic material (DNA) from radiation absorption increase in proportion to the absorbed dose; 2) certain immediate DNA damage is amplified and propagates in organisms to cause the cancer incidence in an exposed population to rise in proportion to dose.

The second assumption is debatable for both epidemiological and experimental reasons. Regarding epidemiology, data show statistical constraints and require very large numbers of irradiated individuals to assess the carcinogenic risks of low doses (< 150 mSv), such large numbers are not available at present. Thus, modeling of data with the LNT hypothesis arrives at relative risks of cancer that are actually not observed (Heidenreich *et al.* 1997; Pollycove and Feinendegen 2001; Tanooka 2001; Preston *et al.* 2004, 2007; Cardis *et al.* 2007; Nair *et al.* 2009; Tubiana *et al.* 2009).

The LNT hypothesis assumes its scientific justification because of the immediate linear dose-effect relationships at the molecular level of the DNA; it does not consider the complex non-linear dynamics of oncogenesis in the body. Indeed, more recent discoveries on low-dose effects in experiments with various biological systems from cells to animals increasingly show specific responses of physiological damage control systems limited to low doses at various levels of biological organization (Feinendegen *et al.* 2004; Tubiana *et al.* 2005, 2009; Mullenders *et al.* 2009), and also discovered a low-dose induced reduction of the incidences of neoplastic transformation in culture cells and overt malignancies in animals (Azzam *et al.* 1996; Mitchel *et al.* 2003, 2008; Elmore *et al.* 2009). Such responses have not been observed at, and also were not expected from, high dose radiation exposures. In fact, new findings challenge the validity of the LNT-hypothesis, and now suggest that this hypothesis cannot be maintained (Tubiana *et al.* 2005, 2009; Feinendegen *et al.* 2007a,b).

Currently, the discussion of the low-dose risk of cancer has become polarized on how to best incorporate new findings into practical application. A case in point is the serious disagreement between recent statements by the French Academy of Sciences (Tubiana *et al.* 2005) and the

US National Academy of Sciences by way of its BEIR VII report (National Research Council 2006).

The present paper attempts to focus on the new radiobiological findings on low-dose related cancer risk. It hypothesizes that after low dose exposures clinical cancer develops as a consequence of the balance between cancer induction and cancer prevention by the cascade of the body's physiological defenses.

This paper emphasizes both the proportional relationship between absorbed dose and DNA damage, and the non-linearly operating body's defense systems that block damage propagation from the molecular level to the whole organism. There are at least three types of "defending" barriers: a physical-static one, and two metabolic-dynamic defenses. One of the latter two defenses responds soon after perturbation, while the other involves delayed up-regulations of defenses in terms of adaptive responses that appear with a delay of hours and last for various times up to more than a year after low-dose exposure. Adaptive protections can operate against both radiogenic and non-radiogenic DNA damage and its consequences. Applied to the observed experimental and epidemiological data, with their wide ranges of uncertainties, the modeling indicates not only the inconsistency of the LNT hypothesis but also the high probability of beneficial, i.e., hormetic effects following low-dose irradiation (Calabrese and Baldwin 2003).

THE MEANING OF ABSORBED DOSE IN THE LOW DOSE REGION

The term absorbed dose describes concentration and not the amount of the energy absorbed in the exposed mass such as an organ or the whole body (ICRU 1998;). The unit of absorbed dose (D) is the gray: 1 Gy (100 rad) = 1 J/kg. This is equivalent to 6.24×10^{15} eV per g mass, or 6.24×10^{6} eV per ng mass. The unit of the equivalently effective dose from different radiation qualitites is the sievert, Sv (ICRU 1998) At a sufficiently high value of absorbed dose from an external radiation field, absorbed dose in a large mass is identical to the absorbed dose in any small mass of the same exposed tissue; but the total energies absorbed in these masses are not the same (ICRU 1983)..

The above definition of absorbed dose poses problems when it comes to analyzing and understanding the effects both of low-dose, external sources, exposure (ICRU 1983, 2005) as well as heterogenous exposure to incorporated radionuclides, for instance in nulear medicine tests (ICRU 2002). In both instances ionizing radiation causes the deposition of energy from charged particle tracks that arise either through interaction of uncharged particles with charged particles, such as photons (x- or gamma rays) that can dislodge electrons from atomic orbitals, or through charged particles as they may be produced by accelerators or result directly from the decay of radionuclides (alpha-, beta-emssion). The ener-

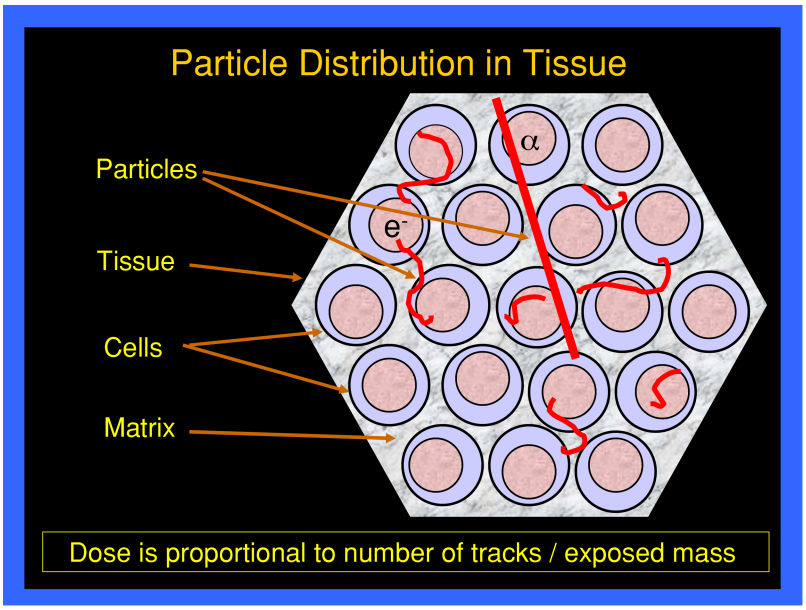

FIGURE 1: Scheme of particle distribution in tissues. Shown are several electrons and an alpha-particle. Clearly, total energy absorbed per unit mass correlates with the number of particles in that mass.

gy deposited by a single particle track in traversing a tissue micromass of 1 ng will be denoted in this paper by the term "microdose", and the event delivering this microdose is referred to as a "microdose event" (ICRU 1983).

Large absorbed doses D in the tissue create large numbers of microdose events per exposed micromass. The sum of energies delivered by multiple microdoses per given micromass is here denoted "cell-dose." As D in the body decreases, the number of microdose events per exposed micromass is reduced eventually below an average value of 1 per micromass. Then, the dose to each micromass becomes either 0 or it will be the microdose from a single track traversing the micromass, and only some fractional number of micromasses experience a microdose event (see Figure 1) (ICRU 1983).

The microdose values compose a spectrum according to charged particle energies from a given radiation quality. This spectrum may vary by a factor of up to 10 or more, around the mean value. According to the radiation quality, the mean microdoses have defined values, as shown in Table 1 middle column. In case of exposure from incorporated radionulcides, the overlaying and more or less severe topographical heterogeneity of decays occurring localized in the tissue of interest makes dosimetry more difficult and has been delt with extensively (ICRU 2002).

In the context of comparing man-made low-level exposures, for instance in diagnostic medicine, with exposure from natural sources of

$\bar{z}_{F1}$ ($\bar{x}$ Microdose) in mGy (1 mGy = 6.24 keV / ng)

Cell doses are multiples of microdoses.

	mGy	*ROS / hit / ng*
^{60}Co γ-rays	~ 0.3	~ *45*
^{137}Cs γ-rays	~ 0.4	~ *60*
250 kVp x-rays	~ 0.9	~ *135*
100 kVp x-rays	~ 1.0	~ *150*
10 MeV protons	~ 6.0	~ *900*
4 MeV α-particles	~ 350.0	~ *52.5 x 10^3*

TABLE 1: The energy absorbed per micromass, here of 1 ng, per particle traversal is formally called specific energy with the symbol z, and $\bar{z}_{F1}$ is the fluency-derived mean value of z (33). The table gives the value of $\bar{z}_{F1}$ and the approximate number of reactive oxygen species (ROS) produced by this value in the hit micromass.

background radiation the following considerations may be helpful in risk assessment. As an example, the exposure of tissue to 100 kVp x-rays causes on average 1 electron track delivering about 6 keV per 1 ng mass - corresponding to the average cell mass—and the mean microdose is about 1 mGy (ICRU 1983). A body dose of 1 mGy from 100 kVp x-rays then means an average of about 1 microdose event in each ng mass of the exposed tissue. One mGy per year accordingly means that about 1 event per ng occurs per year, or each ng experiences on average 1 microdose of 1 mGy once about every 365 days.

Normal background radiation causes whole body absorbed doses in the range of several mSv per year from different radiation sources and qualities, largely cosmic gamma rays with a relatively small contribution from alpha irradiation coming mainly from inhaled radon. Background radiation may vary considerably with altitude and geographic region, and may be more than ten-fold higher than the average value at sea level in the northern hemisphere. The above considerations imply that every ng or cell in the body experiences a microdose event several times a year. More specifically, taking an adult body to have 7 x 10^{13} ng, and a year to have about 3.2 x 10^7 seconds, then, for the sake of easy calculation, an annual whole body dose of 1 mGy from chronic exposure to x-rays causes around 2.2 x 10^6 1 mGy-microdose events per second on average in the

whole body, and each of those events would have the potential of triggering secondary consequences.

Such calculations are easy also for other radiation qualities than 100 kVp x-rays. The mean microdose values are displayed for a few different types of radiation in Table 1. Thus, if the background radiation field would be equivalent to gamma rays from ^{137}Cs delivering about 0.4 mGy per microdose event, chronic exposure to an annual whole body dose of 2 mGy would cause on average 1 microdose event 5 times a year in each ng in the body, or each ng would experience on average 1 event every 2.4 months.

PRIMARY BIOLOGICAL INTERACTIONS

Each microdose event causes numerous atomic ionizations and excitations stochastically along the particle track depending on the type of radiation. Biological tissues consist by weight of ~ 75 % water. Hence, a correspondingly large fraction of ionizations induce hydrolysis resulting in different kinds of reactive oxygen species (ROS); on average about 25 ROS are produced by hydrolysis for each keV absorbed in tissue. The number of ROS per each mean microdose event from different radiation qualities is also listed also in Table 1, right column. In general, ROS are both signaling molecules and can be toxic (Sen *et al.* 2000) depending on concentration. When produced by irradiation ROS attack largely at random all kinds of biochemical substrates in the immediate and in some distant molecular "neighborhood" of the site of their creation, and add to biochemical damage by direct ionizations.

The ROS induced by radiation are biochemically similar to those that are constantly and abundantly produced in different cellular compartments, mainly mitochondria, during normal oxidative metabolism. Mitochondria alone let leak out some 10^9 ROS into the cytosol per cell per day (Pollycove and Feinendegen 2003). One needs to consider the effects of both endogenous and radiogenic ROS in conjunction with direct effects especially on DNA. The combined latter effects generally are more toxic but much less frequent than the first. Most relevant are damages to DNA, be they from ROS, direct ionizations or from both, as discussed further below.

DAMAGE TO DNA AND ITS REPAIR

Biological responses to ionizing radiation, wherever they become observable either acute or delayed, appear to always originate because of changes in cellular molecules, especially the DNA. The immediate DNA damage and cellular responses to it are quite well understood, and includes inter-molecular cross links of various kinds, base changes, single strand breaks (SSB), and the more serious double strand breaks (DSB) (Hall and Giaccia 2005).

It needs be stressed that the radiation-induced immediate damages to DNA increase linearly with dose. The reason for this linearity is the dose dependent number of microdose events produced, and each of them causes a given degree of damage according to their energy spectrum characteristic for a given type of radiation. Thus, as dose increases, the number of microdose events according to the given spectrum increases, and with them the number of individual damage sites caused by each one of the events. A dose effect curve for immediate DNA damage in tissue actually conforms to a linear "Impact-Number-Effectiveness Function" without threshold (Bond *et al.* 1995). This linear function though is not identical in various cell types, and it is lost as complex biological systems respond to low doses in various ways to the initial damages, as discussed below.

Within minutes after irradiation there is a plethora of DNA and chromatin modifications involved in DNA repair (Hall and Giaccia 2005). Immuno-histochemical methods now allow, for instance, the microscopic observation of DNA double strand breaks in individual cells (Rothkamm and Löbrich 2003; Sedelnikova *et al.* 2004). Well within 24 hours, the fluorescent foci, supposedly indicative of double strand breaks, decrease to a lower number, closer to that of the background "spontaneous", i.e. pre-irradiation, number (Rothkamm and Löbrich 2003). By way of this technique one has learned that experimentally non-irradiated cells, depending on type and age, contain on average from about 0.1 to numerous DNA double strand breaks at steady state, a finding strongly disputed for years (Sedelnikova *et al.* 2004). In contrast, at background radiation level, the probability of a radiation induced DNA DSB to occur per day per average cell in the human body is about 1 in 10 000 (Pollycove and Feinendegen 2003).

The capacity of normal cells to repair damage to DNA and other cellular components is genetically determined and may vary individually. Today, more than 150 genes have been described to be involved in DNA repair at high and low doses (Franco et al 2005; Feinendegen *et al.* 2007a; 2008). Some genes are active only in low-dose stress responses; others again are modulated only after high doses (Franco *et al.* 2005; Mullenders *et al.* 2009; Tubiana *et al.* 2009). This reproducible data alone already contradicts the justification of the LNT hypothesis for assessing health detriment as function of low dose. Moreover, low dose irradiated confluent cells in culture appear to stall DNA repair until cell proliferation begins again (Rothkamm and Löbrich 2003). Indeed, an immediate induction of DNA repair is reported in proliferating culture cells to be elevated at low doses of about 1 mGy of x- and gamma radiation (Day *et al.* 2006; Mullenders *et al.* 2009; Tubiana *et al.* 2009).

In general, then, immediate damages of DNA provoke ready attempts at structural and functional reconstitution at the cell level. Radiation induced effects in tissues are determined eventually by the degree of remaining DNA- and cell damage.

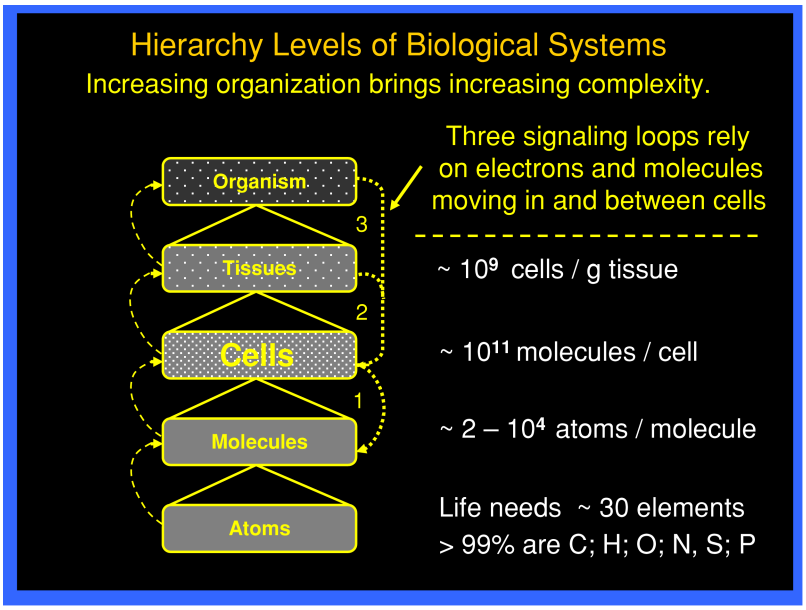

FIGURE 2: The body may be viewed being organized in hierarchical levels with increasing complexity from bottom up. Intricate signaling within and between the various levels always involves cells. The three principal signaling loops assure functional integrity of the body in the face of abundant threats by toxic impacts from external and internal sources.

HIERARCHY LEVEL RESPONSES IN BIOLOGICAL SYSTEMS

To fully appreciate the sequence of events to be reckoned with after irradiation, the body may be viewed as a composite of hierarchy levels of "protection" organization, as shown in Figure 2.

Responses to the primary molecular perturbations and damages first involve the cells that have experienced one or more microdose events within a given period of time. The initially responding cells may transfer their perturbation or damage to neighboring non-irradiated cells causing so-called bystander effects, which may be damaging and/or induce defenses (Mothersill and Seymour 2006). Similarly, energy deposition events in the intercellular matrix may affect non-irradiated cells (Barcellos-Hoff and Brooks 2001). These two damage categories are commonly referred to as non-targeted effects in contrast to targeted effects referring to the immediate damage in irradiated cells. If damage becomes lethal in many cells in a tissue, acute radiation effects may result in acute illness, the symptoms of which depend on the organ where cell death occurs; this again depends on the absorbed dose because stem cells and differentiated cells in different organs have different radio-sensitivities (Hall and Giaccia 2005; Fliedner *et al.* 2005). On the other hand, individual cells having escaped lethal radiation effects, may still suffer malignant transformation and eventually cause cancer with metastases. The

mechanisms of malignant transformation may include genomic instability induced in exposed cells and "handed down" to the cell's progeny over several cell generations (Kadhim *et al.* 2006; Dziegielewski *et al.* 2008).

Whereas the incidence of immediate DNA damage rises linearly with dose, damages to DNA and cells from both by-stander and matrix effects, and from genomic instability appear to have different dose thresholds, probably below 150 mGy, and reach plateaus with increasing dose at about 300 to 500 mGy. Immediate plus secondary damages to DNA and cells, i.e. targeted and non-targeted radiation damages, all induce the body's defenses against such damaging events and damage propagation to subsequent higher levels at tissues and the whole organism.

THREE EXAMPLES OF PHYSIOLOGICAL DEFENSES OF COMPLEX BIOLOGICAL SYSTEMS

The extent of the targeted and non-targeted damage and its propagation in cells, tissues and finally perhaps the whole body depend on the type and degree of initial homeostatic perturbations and on the tolerance of homeostatic controls and defenses that operate at sequentially higher levels. Signaling loops coordinate controls within and between cells, between cells of different tissues and/or organs, and within the whole body, all are subject to gene modulations (Guyton and Hall 2005). Therefore, certain defects in the involved genes may change individual susceptibility to radiation drastically.

One may, in general, discern three prototypes of defense: physical-static ones, and two metabolic-dynamic ones, usually involving enzymes according to the individual's genome.

The physical-static barriers prevent impacts from changing matter, from disrupting a material structure and consequently its function in a system. For instance, a certain impact size, i.e., force is required to move a body such as a stone on a surface in a given direction—well known and described by physical laws. Similarly, a certain target-specific impact is needed to injure the skin, or to kill a cell, or to break an inter-atomic bond in a molecule. Moreover, tissue damage only occurs if a minimum number of cells that are essential to structure and function have been removed from their structural and functional places in tissue. Obviously, there are thresholds for a force to overcome a physical-static barrier before an effect can be registered at the impacted object. With increasing magnitude of the impact the effect becomes larger or more severe and eventually reaches a maximum. The corresponding impact-size-effectiveness function that describes the relationship between impact-size and severity of effect gives graphically a sigmoid shaped curve.

Metabolic defenses can operate practically instantly at all levels of organization in normal organisms against potentially life-threatening

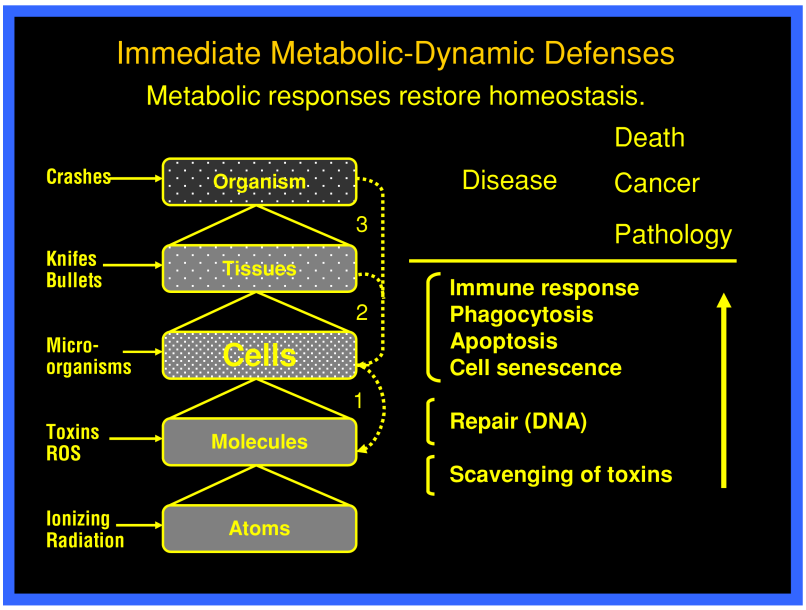

FIGURE 3: Threats at the various organizational levels of the body are met by physical-static and metabolic-dynamic defenses against damaging impact, damage creation and damage propagation. These defenses are successful if they restore homeostasis, from the molecular to the tissue-organ level. Only when the defense barriers are overcome, pathology develops with acute and late health effects, such as cancer. The individual defenses respond with individual probabilities

events, which are shown schematically in Figure 3. An example of defense at the tissue level presents the protection by the skin against manifold different types of impacts. If injured, the normal skin promptly initiates protective responses leading, for instance, to wound healing through signal-induced cell death, cell necrosis, phagocytosis, cell proliferation and differentiation. At the molecular level, DNA damages of various kinds, be they base alterations, strand breaks or intermolecular linkages, induce a large number of specific repair responses (Hall and Giaccia 2005)

With a holistic view of systemic function at various levels one may distinguish the following prompt metabolic-dynamic defenses, as shown in Figure 3. These may be grouped into three categories (Feinendegen *et al.* 1995; 1999; 2004;; 2007a,b; Feinendegen and Neumann 2005):

a) defenses by scavenging mechanisms at the atomic-molecular level;
b) molecular repair, especially of DNA, with reconstitution of essential cell constituents and functions;
c) removal of damaged cells by induced cell death, i.e., apoptosis, cell necrosis, and an immediate immune response in an immunized body, with phagocytosis of killed cells, or by cell proliferation towards senescence.

In this context it is important to adhere to careful definitions. Thus, repair of a skin wound involves removal of damaged cells and cell debris as well as cell proliferation and differentiation. Therefore, terms like defense, repair and damage removal must be linked to the levels where the damage occurs. Repair, damage removal, and replacement of damaged and/or lost molecules and cells in the course of tissue reconstruction for maintenance of tissue function can be concordant events

Like the physical-static barriers metabolic-dynamic barriers do not operate at a level always proportional to the degree of perturbation. In fact, these mechanisms of protection appear to allow perturbation to a certain degree before they begin to act to restore homeostasis, and, thus, prevent propagation of damage to successively higher levels of organization. This means, an impact must be large enough to overcome a threshold before structure and/or function are perturbed sufficiently to threaten the next higher level. There are many common daily examples with this principle response pattern.

In general then, only when homeostatic perturbations overwhelm structural and functional barriers at successive levels, from chemicals to molecules, to cells, to tissue, etc., disease can develop..

The above described cascade of defenses also operates against local damage and damage propagation from ionizing radiation. Since increasing doses of ionizing radiation with large numbers of microdose events in the exposed tissues eventually overwhelm barriers at all hierarchical levels, high doses in large target volumes may allow damage at basic levels to propagate with minimal or no inhibition, and thus to evolve into clinically evident disease. As a consequence, many, but definitely not all, dose-response functions expectedly tend to be linear at higher doses, but not so at low doses.

There is a second metabolic-dynamic type of barrier which becomes activated by low-degree perturbations at a given level of biological organization. This barrier type is commonly referred to as stress response. It expresses an adaptation of the exposed system to better withstand renewed exposure to a potentially damaging impact by an agent that may be identical to the initial agent or mimics this agent. A common experience of this type of adaptation is the development of callus in a chronically burdened skin, or immunization for protecting the body against exposure to an infecting agent. Another example is properly conducted physical training to strengthen muscles and the cardiovascular system to improve physical endurance and/or athletic performance. A fourth example is properly dosed exposure to sunlight to induce tanning which will protect against a higher-degree exposure to sunlight by reducing the probability of sun burn. Adaptive protections result from up-regulation of existing cascades of metabolic-dynamic barriers described above. In contrast to the promptly acting barriers, however, adaptive protections appear after a

delay and increase to a maximum after one or repetitive stimulating impacts followed by a decline after the stimulus has disappeared. This decline is comparatively slow and may be observed for months to more than a year; some immunizations even protect for a life time.

Thus, low-dose irradiations, in contrast to high doses, can cause adaptive protections to function in cells, tissues, animals and humans. There is a wide-spread misunderstanding of these low-dose induced adaptive protections only to act against renewed radiation and not to radiomimetic perturbations. Yet, adaptive protections defend also against other agents that cause DNA damage (Wolff *et al.* 1988), as referred to below.

LOW-DOSE INDUCED ADAPTIVE PROTECTIONS

Over the past three decades, experimental data in cultured cells and in animals have established that low doses of low-LET type radiation can, with a delay of several hours after a single irradiation, up-regulate physiological defenses discussed above (Feinendegen *et al.* 1999; 2004; 2007a,b; Mullenders *et al.* 2009, Tubiana *et al.* 2009). Up-regulation was quantified, for instance, regarding: scavenging of ROS that lasted for more than 10 hours (Zamboglou *et al.* 1981; Feinendegen *et al.*1984;1995; Hohn-el-Karim *et al.* 1990); DNA repair lasting for several days (Olivieri *et al.* 1984; Wolff *et al.*1988); apoptosis to reach a maximum about 4 hours after single exposure and to continue being elevated for more than 2 weeks following cessation of repetitive low-dose exposures (Kondo 1988; Fujita *et al.* 1998) and an increased immune response lasted for months and even more than a year with concomitant reduction, for instance, of metastases (James and Makinodan 1990; Tubiana *et al.* 2005; 2009). An integrated effect of adaptive protections shows in the degree of reduction of neoplastic transformations in cultured cells as well as primary cancer and metastases in animals following a single low-dose irradiation (Azzam *et al.* 1996; Feinendegen *et al.* 2004; Mitchel et. al. 2003; 2008; Elmore *et al.* 2009). In cultured cells a single low-dose, low-LET irradiation reduced neoplastic transformation to about 30 % of the transformation incidence in non-irradiated controls; and a threshold for neoplastic transformation existed in such cells even after high cell doses from accelerated particles (Azzam *et al.* 1996; Elmore *et al.* 2009).

Like in the case of immediately protecting responses, adaptive protections do not necessarily develop proportionally to the degree of the perturbing event. Adaptive protections are related to dose in that they appear after single exposure at a low threshold of cell dose, increase to a dose around 100 mGy, then disappear as doses increase beyond 200 mGy of low-LET radiation and are hardly, or not at all, seen above about 500 mGy (Feinendegen *et al.* 1996; 1999; 2007a). An exception is apoptosis, in that its incidence apparently increases linearly over a certain dose

region beyond single doses of 500 mGy, whereas at doses below about 100 mGy, there is evidence of apoptosis incidence to fall below the control level (Liu *et al.* 1996). In addition, unrepairable DNA damage obviously predisposes cells to induction of apoptosis more frequently than normal cells (Chandra *et al.* 2000). High-dose irradiation of mammals with alpha-particles *in vivo* suggests induction of the body's immune responses via the activation of immune cells in the neighborhood of high-LET damaged single cells (Harder 2008).

Adaptive responses are well known, for instance, following so-called oxygen stress (Chandra *et al.* 2000; Finkel and Holbrook 2000: Sen *et al.* 2000), which also may in part be associated with radiation induced adaptive protection (Feinendegen *et al.* 1995, 2000; Feinendegen 2002: Hohnel-Karim *et al.* 1990). As referred to above, a normal average cell experiences a mitochondrial leak of about 10^9 ROS molecules per day, i.e. about 100 ROS molecules per millisecond, in the cytoplasm outside mitochondria, mainly from metabolic reactions; and additional small ROS bursts come from various responses to external cell signaling (Pollycove and Feinendegen 2003; Sen *et al.* 2000). An average microdose event, for instance produced by 100 kVp x-rays, creates about 150 ROS in the hit cell within a fraction of a millisecond. Both metabolic and radiation induced ROS can trigger oxidative stress responses in terms of adaptive protections depending on concentrations, species, tissues and cells (Finkel and Holbrook 2000; Feinendegen and Neumann 2000; Feinendegen 2002). In this context, normal background irradiation with its causing single microdose events per cell several times a year, as explained above, should be seen also as inducers of maintaining homeostasis (Feinendegen 2002), for instance by inducing apoptosis of pre-damaged cells (Chandra *et al.* 2000).

To repeat, adaptive protections were assumed initially to be confined to DNA repair following renewed irradiation (Olivieri *et al.* 1984; Wolff *et al.* 1988). Yet, it has become clear that the delayed stimulated protections may not only involve all physiological defenses but also operate against non-radiogenic damage, such as damage from endogenous toxins, like ROS (Chandra *et al.* 2000; Feinendegen *et al.* 1995) and from chemical mutagens (Wolff *et al.* 1988). Cells rarely can afford the energy "costs" associated with creating a special response to a rare or unique perturbation. The broad effectiveness of adaptive protections at all levels of biological organization, against both radiogenic and non-radiogenic damage, expresses a hormetic response, and is crucial in estimating probabilities of late radiation effects such as cancer, as will be discussed in more detail below.

The effect of cascades of homeostatic responses against propagation of primary damage at the DNA level to successive higher levels of the cell's organization may be expressed by a set of equations shown schematically in Figure 4.

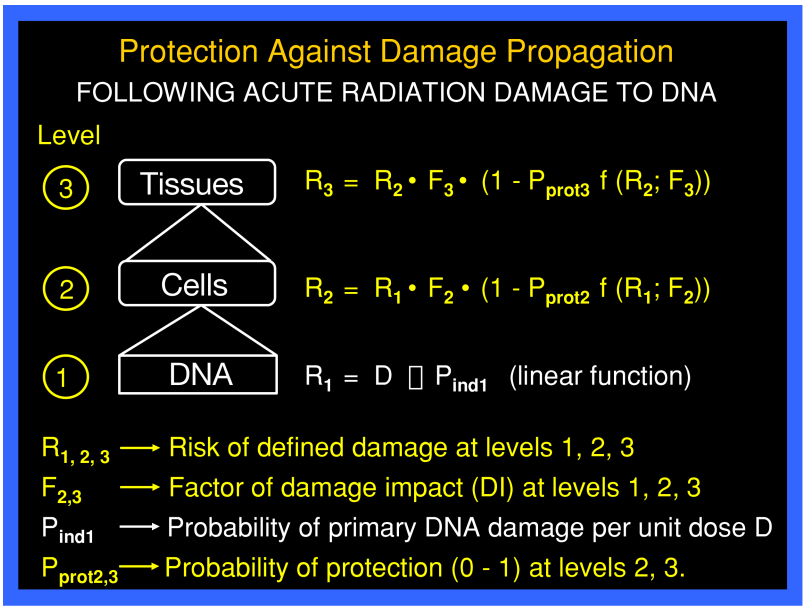

FIGURE 4: Damage propagation to successive higher level of organization, from DNA, to cells, to tissue, and the effect of protection at the cell and tissue levels may be expressed schematically by a simple set of equations.

PHYSIOLOGICAL DEFENSES AGAINST CANCER

The various physiological barriers against damage and damage propagation sketched out above also operate in the course of oncogenesis, as illustrated in Figure 5. Even if the protective mechanisms against cancer still are not fully understood, their effects are obvious. An illustrative example is the very low probability of a radiation induced average DNA double strand break in a potentially oncogenic blood-forming human tissue stem cell to bring about a lethal leukemia. This probability has been estimated to be close to 10^{-12} (Feinendegen *et al.* 1995). The claim that even a single DNA double strand break, however grave, in a human stem cell may lead to cancer is scientifically unjustified.

Low-dose induced cancer is, nevertheless, assumed by many to increase proportionally with dose. This opinion hypothesizes that irrespective of dose a certain, however small, fraction of radiogenically transformed cells escapes all barriers and expands into clinical cancer. The probability of such an escape of a transformed cell may be estimated from experimental and epidemiological observations. Thus, the probability of neoplastic transformation in a cell *in vitro* is about 10^{-5} per low-LET microdose event (Hall and Giaccia 2005) and the probability of lethal leukemia per low-LET microdose event in a human hemopoietic stem cell *in vivo* is a about 10^{-14} (Feinendegen *et al.* 1995). Assuming that the *in vitro* probability also applies *in vivo*, the quotient 10^{-14} / 10^{-5} is about

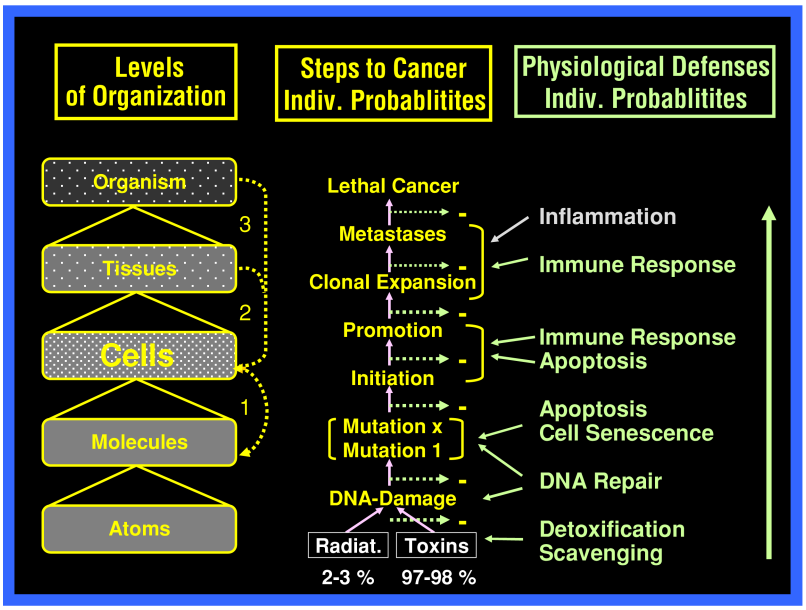

FIGURE 5: The metabolic defenses also operate against the development of cancer. The various steps to clinical cancer have individual probabilities. About 1 in 10^9 cancer cells may escape defense barriers and cause clinical tumors and disseminated metastases. In industrialized countries, about 2-3 % of cancer incidence is being attributed to background radiation, as is calculated on the basis of the LNT hypothesis (adapted from Feinendegen *et al.* 2007a,b).

10^{-9} and expresses the probability of the affected cell to escape all *in vivo* defense mechanisms. The claim of constancy of the effectiveness of defense barriers *in vivo* irrespective of dose is contradicted by the induced adaptive protections following low doses but not high doses.

DAMAGE AND PROTECTION IN THE "DUAL-PROBABILITY-MODEL" OF CANCER RISK

In the attempt to assess cancer risk from low dose exposure realistically, both probabilities, of damage and of protection after low-dose irradiation, need to be taken into consideration. To do so coherently and effectively, one should try to choose a model into which all the phenomena that affect low-dose responses can be accommodated. Instead of examining the various types of protections individually (Heidenreich and Hoogenweem 2001; Schöllnberger *et al.* 2005), an average degree of protection may be preferable for modeling (Feinendegen *et al.* 1995; Scott 2004; Leonard 2007), in which all mechanisms are incorporated and yield together a probability value between 0 and 1, i.e. between no and full protection against a risk of induction of a clinical cancer.

The model of choice here derives from an approach proposed in 1995 (Feinendegen *et al.* 1995). It rests on the dual effect of low doses in both causing damage and protection (Feinendegen *et al.* 1999, 2000,

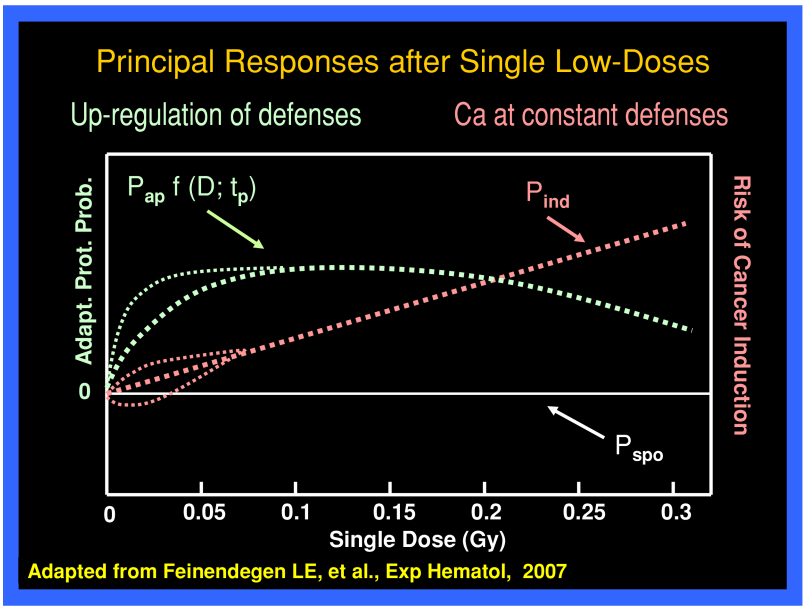

FIGURE 6: Schematic representation of the dual responses to single low doses feeding into the "Dual-Probability-Model" in Figure 7: a) Low doses of ionizing radiation can up-regulate physiological defenses with delay and some last beyond a year. The up-regulated defenses are also called adaptive protections and depend on dose D and on he time t_p of their action: the probability of protection ranges from 0 – 1 and is P_{ap} f (D; t_p). b) The risk of radiation induced cancer assumes constant defenses in the body at every dose D according to the LNT hypothesis and is expressed here by the value of P_{ind} per unit dose. - There are uncertainties at low dose levels shown by light dotted lines: stemming from detrimental by-stander effects. genomic instability, as well as induction of repair; and adaptive protections (adapted from Feinendegen *et al.* 2007a,b). Note that the scales of the two probabilities P_{ind} and P_{ap} f (D; t_p) are independent of each other.

2004, 2007a,b). Figure 6 shows as a function of dose the model inputs of the two opposing effects: a) the risk of cancer per unit dose, denoted by P_{ind}, mainly according to the LNT hypothesis; b) the probability of protection against cancer as a function of D and time of effectiveness t_p, denoted by P_{ap} f (D; t_p); with the base line showing the probability of life time "spontaneous" cancer incidence that is observed in industrialized countries, denoted by P_{spo}. Whereas the probability of protection according to experimental observations rises with increasing doses to a maximum at about 100 to 200 mGy and then falls towards 0 as doses increase beyond 300 mGy, the cancer risk rises linearly with dose if existing defenses against cancer are constant irrespective of dose. The figure includes for cancer risk (red line) in the low dose range detrimental secondary effects and repair induction. It also acknowledges adaptive protections (green line) to appear at various low dose levels. Note that the scales for the two probabilities, P_{ind} and P_{ap} f (D; t_p) are independent of each other.

In order to grasp the full consequence of low-dose induced adaptive protections one must recall that the probability of endogenous, non-radi-

ogenic, i.e. spontaneous, cancer (P_{spo}) at any time outweighs the probability of cancer from average background radiation, probably by a factor of 30 to 50, if the LNT hypothesis is applied. It is to be noted that this probability quotient is much lower than the quotient of about 1000 for DNA double strand breaks (DSB) at any time from endogenous sources to those from background radiation per average cell in an adult human (Pollycove and Feinendegen 2003). This quotient of about 1000 only expresses quantities. Yet, with respect to qualities a large percentage of radiogenic DNA DSB are more complex, of the multi-damage type (Nikjoo *et al.* 1999), and thus probably cause more cellular damage than simple DSB from endogenous sources, perhaps by a factor of 20 to 30 (Pollycove and Feinendegen 2003).

Following a single low dose irradiation one may, thus, rightly assume that the delayed and especially the long lasting adaptive protections operate mainly against endogenous cancer rather than cancer induced by irradiation (Feinendegen *et al.* 1995), as it is implied also by experimental evidence (Mitchel *et al.* 2003, 2008). The risk of cancer following a single low-dose exposure, therefore, would at every dose level be the difference between the calculated radiogenic cancer risk at constant defenses, and the prevented cancer risk being the sum of the probabilities of protection against radiogenic as well as spontaneous cancer risks. This approach gives the "Dual-Probability-Model" illustrated in Figure 7.

Thus, in accordance with previous reports (Feinendegen *et al.* 2007a,b, 2008) and considering here a balance of effectiveness of the potential consequences from by-stander damage on the one hand, and low-dose induced prompt repair on the other,

R	=	clinically observed risk of cancer induced by a single dose D
P_{ind} D	=	radiation induced lethal cancer risk calculated with constant defenses in the system, based on the LNT hypothesis, from a single dose D,
P_{ap} f (D; t_p)	=	probability of adaptive protection (0 -1) as function of D and time of effectiveness t_p, with target to be defined,
P_{spo}	=	"spontaneous" life time cancer risk of the exposed individual, in industrialized countries,

then taking the targets of protection to be both P_{spo} and P_{ind} D,

$$R = P_{ind}\, D - P_{ap}\, f\,(D;\, t_p)\ (P_{spo} + P_{ind}\, D) \qquad [1]$$

This "Dual-Probability-Model" allows to estimate the probability of adaptive protection, P_{ap} f (D; t_p), by assigning a value of R from epidemiological data, and for P_{ind} and P_{spo}, as follows:

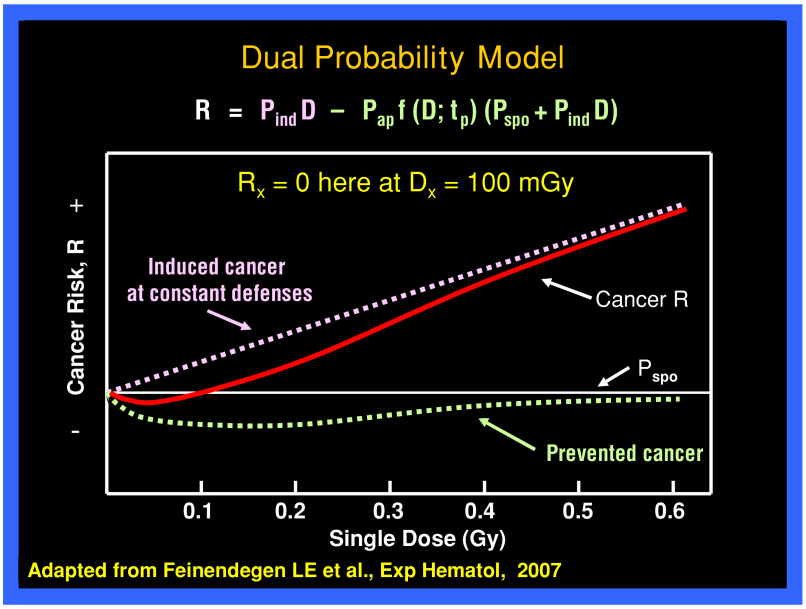

FIGURE 7: This Figure illustrates the applicability of the "Dual-Probability-Model" for assessing low-dose cancer risk. - Adaptive protections, as shown in Figure 5 and 6, may also operate against non-radiogenic damage and thus reduce "spontaneous cancer. The product of the probability of protection against spontaneous cancer, from 0 to 1, and the probability of spontaneous cancer gives the probability of cancer prevention The clinically observed cancer risk R, then, is the difference between the probabilities of radiation induced cancer and of prevented cancer, given by the solid line. Assuming here a maximum value of P_{ap} f(D, t_p) at 100 to 200 mGy, the reduction of cancer risk to and below the spontaneous risk appears as an obvious hormetic effect, despite the low values of P_{ap} f(D, t_p), see table 2 and 3 (adapted from Feinendegen *et al.* 2007a,b).

P_{ind} = 6×10^{-5} induced lethal cancer risk / person / mGy, from atom bomb data according to the LNT-hypothesis (Preston *et al.* 2004. 2007)

P_{spo} = 2.5×10^{-1} "spontaneous" cancer risk / individual life time, in industrialized countries,

By taking into consideration that P_{ind} is comparatively negligibly small vs. P_{spo}, the risk estimate, R_x, at a given dose D_x from epidemiological studies conforms to

$$R_x = P_{ind}\, D_x - P_{ap}\, f\,(D_x;\, t_{p1})\, P_{spo} \qquad [2]$$

Rearranging equation [2] to

$$P_{ap}\, f\,(D_x;\, t_{p1}) = (P_{ind}\, D_x - R_x)\ /\ P_{spo} \qquad [3]$$

gives the probability of protection for a value of R_x at a given dose D_x. with the protection target being the life time risk of cancer P_{spo}. For instance,

Dose-Risk Function - Acute Exposure - Adult Person

assuming max. adaptive protection at D_x 100 - 200 mGy

measured R_x at 100 mGy = 0

D (mGy)	P_{ind} D ($\cdot 10^{-3}$)	P_{ap} f (D; t_p) ($\cdot 10^{-2}$)	P_{ap} f (D; t_p)P_{spo} ($\cdot 10^{-3}$)	R ($\cdot 10^{-3}$)
1	0.06	0.4	1.0	- 0.9
10	0.6	1.0	2.5	- 1.9
50	3	2.0	5	- 2
100	**6**	**2.4**	**6**	**0**
200	12	2.4	6	6
400	24	1.0	2.5	21.5
600	36	0.2	0.5	35.5

TABLE 2: Numerical values of the graph in Figure 7 for a given set of assumptions made on the basis of experimental evidence, as explained in the text.

letting the cancer risk R_x be 0 at 100 mGy, as compatible with most epidemiological data, and inserting the above defined values of P_{spo}, and of P_{ind} for 100 mGy being approximately 6 x 10^{-3}, the value of P_{ap} f (D_x; t_{p1}) becomes

$$P_{ap}\ f\ (D_x;\ t_{p1}) = (6 \times 10^{-3} - 0)\ /\ 2.5 \times 10^{-1} \qquad [4]$$

or

$$P_{ap}\ f\ (D_x;\ t_{p1}) = 2.4 \times 10^{-2} \qquad [5\}$$

In other words, a very small degree of adaptive protection covering about 2.4 % of a person life time cancer risk in industrialized countries would be sufficient to balance the assumed cancer risk at 100 mGy, based on the LNT hypothesis.

In fact, the application of the dose effect curve for overall protection as seen in Figure 6, together with the degree of protection in equation 5 to an epidemiologically estimated R value of 0 at 100 mGy, and assuming that the maximum adaptive protection here occurs at 100 to 200 mGy, yields a hormetic effect up to 100 mGy, as illustrated by the solid line in Figure 7 The numerical values of the data in Figure 7 are in Table 2, where at the given doses, however, effects of potential by-stander damage and of prompt repair induction are omitted.

Values of P_{ap} f (D; t_p) at 100 mGy

With various R_x at D_x = 100 mGy

P_{ind} = 6 • 10^{-5} / mGy; and P_{spo} = 2.5 • 10^{-1}

R_x (• 10^{-3})	P_{ap} f (D_x; t_p) (• 10^{-2})
6	0
4	0.8
2	1.6
0	2.4
-2	3.2
-4	4.0

TABLE 3: Numerical values of protections covering life time risk of spontaneous cancer in industrialized countries, as they are expected at 100 mGy with different values of risk estimated from epidemiological observations in irradiated populations.

If the degree of protection at 100 mGy would cover more than 2.4 % of the life time cancer risk, the cancer risk after 100 mGy would fall below the control value, and show up as a hormetic effect at 100 mGy. Increasing P_{ind} by a factor of 2 to a value of 12 x 10^{-3}, for instance by a dominant by-stander damage, the protection probability would attain 4.8 % with R_x being 0 at 100 mGy. Assuming, for instance, dominating by-stander damage at 50 mGy to increase P_{ind} by a factor of 2 to 6 x 10^{-3}, with R_x measured at 50 mGy being 0, the protection probability would become again 2.4 % (see equation 4).

The above listed low-dose induced reductions in the R values, even if small, could add to the failure to observe any statistically significant increase in radiation induced cancer risk at doses below about 100 mGy in epidemiological analyses of exposed cohorts of humans. In fact, the registered data in these analyses without data modeling at low doses indicate reduced cancer risks more frequently than increases of risk, with borderline statistical significance (Pollycove and Feinendegen 2001; Preston *et al.* 2004).

According to above equation 4, the values of P_{ap} f (D_x; t_{p1}) that would operate at different, epidemiologically estimated values of risk at 100 mGy are shown in Table 3. It is obvious that only less than 5 % of a person's life time risk of cancer need be covered by low-dose induced adaptive protection in order to produce a hormetic effect in terms of a reduction of the risk of spontaneous cancer at 100 mGy. These predictions of

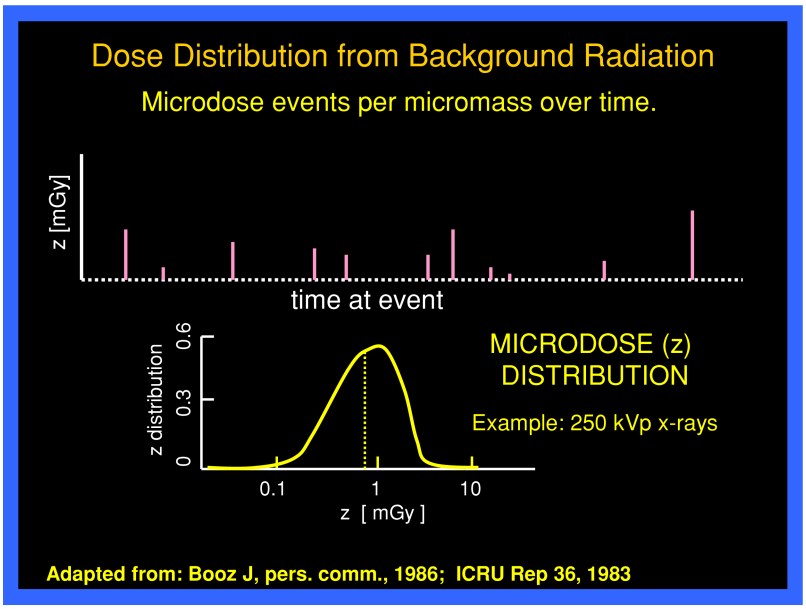

FIGURE 8: Chronic irradiation conforms to repetitive irradiations of micromasses. Microdoses z occur per micromass over time stochastically with various values, upper part, according to their spectrum depending on radiation quality, lower part for 250 kVp x-rays.

adaptive protection probabilities are well in line with experimental data on protection effectiveness following single low-dose exposure.

CHRONIC IRRADIATION

The above model is applicable also to chronic or repetitive low dose irradiation. During chronic irradiation individual microdoses from a given quality of radiation occur in an exposed micromass at time intervals the mean length of which is determined by the dose rate. For a given dose rate of a defined radiation quality, there is a proportional relationship between the mean microdose value, as shown in Table 1, and the mean time interval between two consecutive microdose events. The higher the mean microdose the longer is the mean time interval between two consecutive microdose events at given dose rate. An example of stochastic distribution of events per micromass and appropriate time intervals between two consecutive events for 250 kVp x-rays is shown schematically in Figure 8.

Radiation quality determines the range of the microdose values and their time intervals and thus the probabilities of cellular reactions to the individual microdoses, in terms of damage and protection. The time interval between two consecutive microdose events in a given cell or cell group then allows for the cellular responses to develop fully or not. Here all types of responses need attention regarding the degree of damage and its propagation.

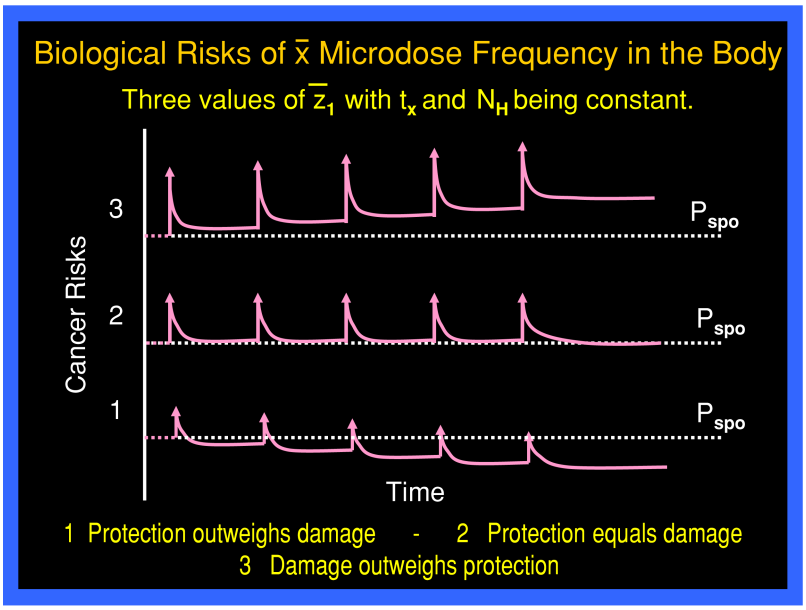

FIGURE 9: The biological risk of chronic irradiation depends of the values of microdoses and the time interval between consecutive microdose events. Mean values for both may be used for assessing risk. The term "cancer risks" here expresses the probability of cancer induction by the hit cell at the time during exposure, with the added time intervals allowing for repair and protection. Shown schematically are three scenarios: 1. where protection outweighs damage; 2. where protection equals damage; 3. where damage outweighs protection.

To appreciate biological effects of dose rates or repetitive irradiations properly it appears paramount to consider the following questions: What are the individual microdose values that may cause damage and induce prompt metabolic defenses and adaptive protections at a given time interval between consecutive events; and what are the values of the time intervals that allow for defined damage manifestation and prompt and late responses to individual microdose events. The answers to these questions are very fragmentary, yet appear crucial in understanding results both of low dose-rate experiments (Vilenchik and Knudson 2000; Ishizaki *et al.* 2004) and of epidemiological investigations from cohorts of chronically exposed mammals and people with reduced rather than increased cancer incidences (Tanooka 2001; Mitchel *et al.* 2003, 2008; Cardis *et al.* 2007; Nair *et al.* 2009). A schematic display of possible consequences of different low dose-rate scenarios is in Figure 9.

CONCLUSION

Current radiogenic cancer epidemiology reports cannot overcome their statistical constraints and these papers do not assure the validity of the LNT-hypothesis at low doses. In fact, the LNT hypothesis is inconsis-

tent with many experiments, both in the laboratory and in the human exposure realms.

Low doses may cause at the molecular level, especially in the DNA, targeted and non-targeted effects. These may propagate in succession to increasingly complex levels of biological organizations, from molecules to cells, to tissues, and the whole body. In this fashion it seems opportune to distinguish between trigger and responses with the latter encompassing both increased perturbations, as well as defenses to restore homeostasis. There appear to be three principle types of defense barriers against damage and its propagation: physical-static ones, and two metabolic-dynamic defenses. One of the latter type operates promptly and the other by way of delayed up-regulation of protection at successive levels of organization, i.e., by adaptive protections. These operate also against a multitude of constantly arising endogenous mutagenic toxins and their consequences. The actual observed cancer risk of low-dose irradiation, thus, appears to express the balance between cancer induction and cancer prevention by metabolic-dynamic defenses through prompt and adaptive protections. The consequences of these experimental findings are not contradicted by epidemiological data on radiation induced cancer from low doses.

The type and extent of cell defenses are under genetic control. Thus, effects of low-dose irradiation are expected to vary among individuals, and may even become predictable by individual gene-expression profiles. This information promises to have clinical applications, for instance, in treating cancer with low-dose irradiation.

Radiation biology has advanced to provide sufficient data that justify the rejection of the validity of the LNT-hypothesis in concepts of collective dose or collective effective dose for predicting cancer risks of single, chronic or repetitive low-level exposures.

It is suggested that an appropriate consensus conference provides new guidance based on scientific evidence in order to arrive at optimal radiation risk estimates with their impact on radiation protection.

Frequently voiced arguments that the new low-dose experimental data are either irrelevant, or questionable, or irreproducible are not in line with scientific methodology. In fact, these arguments apply more to the claimed constructs that support the LNT hypothesis, a hypothesis which must constantly be examined as such—a hypothesis always to be tested by new data—not in law.

REFERENCES

Azzam EI, de Toledo SM, Raaphorst GP, and Mitchel REJ. 1996. Low-dose ionizing radiation decreases the frequency of neoplastic transformation to a level below the spontaneous rate in C3H 10T1/2 cells. Radiat Res 146: 369 – 373

Barcellos-Hoff MH and Brooks AL. 2001. Extracellular signaling through the microenvironment: a hypothesis relating carcinogenesis; bystander effects, and genomic instability. Radiat Res 156: 618 – 627

Bond VP, Benary V, Sondhaus CA, and Feinendegen LE. 1995. The meaning of linear dose-response relations, made evident by use of absorbed dose to the cell. Health Phys 68: 786 – 792

Brenner DJ and Hall EJ. 2007. Computed tomography—an increasing source of radiation exposure. N Engl J Med 357: 2277 - 2284

Calabrese EJ and Baldwin LA. 2003. Toxicology rethinks its central belief. Nature 421: 691 - 692

Cardis E *et al.* 2007. The 15-country collaborative study of cancer risk among radiation workers in the nuclear workers in the nuclear industry: Estimates of radiation-related cancer risks Radiat Res 167: 396 - 416

Chandra J, Samali A, and Orrenius S. 2000. Triggering and modulation of apoptosis by oxidative stress. Free Radic Biol Med 29: 323 - 33

Day TK, Zeng G, Hooker AM, Bhat M, Scott BR, Turner DR, and Sykes PJ. 2006. Extremely low priming doses of X radiation induce an adaptive response for chromosomal inversions in pKZ1 mouse prostate. Radiat Res 166: 757-766

Dziegielewski J, Baulch JE, Goetz W, Coleman MC, Spitz DR, Murley JS, Grdina DJ, and Morgan WF. 2008. WR-1065, the active metabolite of amifostine, mitigates radiation-induced delayed genomic instability. Free Radic Biol Med. 45: 1674 - 1681

Elmore E, Lao X-Y, Kapadia R, and Redpath JL. 2009. Threshold-type dose response for induction of neoplastic transformation by 1 GeV/nucleon iron ions. Radiat Res 171: 764 - 770

Feinendegen LE, Muehlensiepen H, Lindberg C, Marx J, Porschen W, and Booz J. 1984. Acute and temporary inhibition of thymidine kinase in mouse bone marrow cells after low-dose exposure. Intern J Radiat Biol 45: 205 - 215

Feinendegen LE, Loken MK, Booz J, Muehlensiepen H, Sondhaus CA, and Bond VP. 1995. Cellular mechanisms of protection and repair induced by radiation exposure and their consequences for cell system responses. Stem Cells 13 (suppl 1): 7 - 20

Feinendegen LE, Bond VP, Sondhaus CA and Muehlensiepen H. 1996. Radiation effects induced by low doses in complex tissue and their relation to cellular adaptive responses. Mutat Res 358: 199 - 205

Feinendegen LE., Bond VP, Sondhaus CA, and Altman KI. 1999. Cellular signal adaptation with damage control at low doses versus the predominance of DNA damage at high doses. C.R Acad Sci Paris, Life Sciences 322: 245 - 251

Feinendegen LE, Neumann RD, eds. 2000. Cellular Responses to Low Doses of Ionizing Radiation. Workshop of the US Department of Energy (DOE), Washington, DC, and the National Institutes of Health (NIH), Bethesda, MD, held on April 27 – 30, 1999 at the Mary Woodward Lasker Center, Cloister, NIH DOE Report Publication SC-047,

Feinendegen LE, Bond VP, and Sondhaus CA. 2000. The dual response to low-dose irradiation: Induction vs. prevention of DNA damage. In: Biological Effects of Low Dose Radiation, ed. T. Yamada, C. Mothersill, B.D. Michael, C.S. Potten. Excerpta Medica. International Congress Serie 1211. Elsevier, Amsterdam, London, New York, Oxford, Paris, Shannon, Tokyo, p. 3 - 17

Feinendegen LE. 2002. Reactive oxygen species in cell responses to toxic agents. Human & Experimental Toxicology 21: 85 - 90

Feinendegen LE., Pollycove M., and Sondhaus CA. 2004. Responses to low doses of ionizing radiation in biological systems. Nonlinearity in Biol Toxicol Med 2: 143 - 171

Feinendegen LE and Neumann RD. 2005. Physics must join with biology in better assessing risk from low-dose irradiation. Rad Prot Dosim 117: 346 - 356

Feinendegen LE, Pollycove M and Neumann RD. 2007a. Whole body responses to low-level radiation exposure. New concepts in mammalian radiobiology. Experim Hematol 35: 37 - 46

Feinendegen LE, Paretzke HG, and Neumann RD. 2007b. Damage propagation in complex biological systems following exposure to low doses of ionizing radiation. Atoms for Peace, an International Journal, 1: 336 - 354

Feinendegen LE, Paretzke HG, and Neumann RD. 2008. Response to Comments by Dr. de Saint Georges: Damage propagation in complex biological systems following exposure to low doses of ionizing radiation Atoms for Peace, an International Journal 2: 206 - 210

Finkel T and Holbrook NJ. 2000. Oxidants, oxidative stress and the biology of aging. Nature (London) 408: 239 - 247

Fliedner TN, Dörr H, and Meineke V. 2005. Multi-organ involvement as a pathogenic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoetic indicators of effect. Brit J Radiol Suppl 27: 1 - 8

Franco N, Lamartine J, Frouin V, Le Minter P, Petat C, Leplat JJ, Libert F, Gidrol X, and Martin MT. 2005. Low-dose exposure to gamma rays induces specific gene regulations in normal human keratinocytes. Radiat Res 163: 623 - 635

Fujita K, Ohtomi M, Ohyama H, and Yamada T. 1998. Biphasic induction of apoptosis in the spleen after fractionated exposure of mice to very low doses of ionizing g radiation, *in* Apoptosis, its role and mechanism. Ed. Takeshi Yamada and Yoshiyuki Hashimoto, Business Center for Academic Societies Japan, Tokyo; p. 201 – 218

Guyton AC and Hall JE. 2005. Textbook of Medical Physiology; 11th Edition.. W.B. Saunders Company, USA

Hall EJ and Giaccia AJ. 2005. Radiobiology for the Radiologist. Sixth Edition, Lippincott Williams & Wilkins; New York, USA

Harder, D. 2008. Ionisierende Strahlung and die Dosiabhängigkeit ihrer Wirkung. Nova Acta Leopoldina NF 96 355: 21 – 44

Heidenreich WF, Paretzke HG, and Jacob P. 1997. No evidence for increased tumour rates below 200 mSv in atomic bomb survivors. Radiat Environ Biophys 36(3): 205–207

Heidenreich WF and Hoogenweem R. 2001. Limits of applicability for the deterministic approximation of the two-step cloncal expansion model. Risk Anal. 21: 103 - 105

Hohn-el-Karim, K., Muehlensiepen H, Altman KI, and Feinendegen LE. 1990. Modification of effects of radiation on thymidine kinase. Intern J Radiat Biol 58: 97-110

ICRP (International Commission on Radiation Protection) 1977. Recommendations of the International Commission on Radiological Protection, ICRP Publication 26, Annals of the ICRP 1 No. 3

ICRU (International Commission on Radiation Units and Measurements) 1983. Microdosimetry. Report 36, ICRU, Bethesda, MD, USA.

ICRU (Internationalõ Comnission on Radiaiton Units and Measurements) 1998. Fundamental Quanititis and Units for Ionizting Radiaiton, Report 60, ICRU, Bethesda, USA

ICRU: (International Commission on Radiation Units and Measurements) 2002. Acsorbed Dose Specification in Nuclerar Medicine, Report 67, Journal of thw ICRU; Oxford Journals, Oxford University Press, Oxford, UK

ICRU: (International Commission on Radiation Units and Measurements) 2005. Patient Dosimetry of X-rays Used in Medical Imaging, Report 74, Journal of the ICRU; Oxford Journals, Oxford University Press, Oxford, UK

Ishizaki K, Hayashi Y, Nakamura H, Yasui Y, Komatsu K, and Tachibana A. 2004. No induction of p53 phosphorylation and few focus formation of phosphorylated H2AX suggest efficient repair of DNA damage during chronic low-dose-rate irradiation in human cells. J Radiat Res (Tokyo).45: 521 - 525

James SJ and Makinodan T. 1990. T-cell potentiation by low dose ionizing radiation: possible mechanisms. Health Physics 59: 29 - 34

Kadhim MA, Hill MA, and Moore SR. 2006. Genomic instability and the role of radiation quality. Radiat Prot Dosimetry 122: 221 - 227

Kondo S. 1988, Altruistic cell suicide in relation to radiation hormesis. Intern J Radiat Biol 53: 95 - 102

Leonard BE. 2007. Adaptive response and human benefit: Part I – a microdosimetric dose dependent model. Intern J Radiat Biol 83: 115 - 131

Liu SZ, Zhang YC, Mu Y, Su X, and Liu JX. 1996. Thymocyte apoptosis in response to low-dose radiation. Mutat Res. 358: 185 - 191

Mitchel REJ., Jackson JS., Morrison DP. and Carlisle, SM. 2003. Low doses of radiation increase the latency of spontaneous lymphomas and spinal osteosarcomas in cancer prone, radiation sensitive Trp53 heterozygous mice. Radiat Res 159: 320-327

Mitchel RE, Burchart P, and Wyatt H. 2008. A lower dose threshold for the in vivo protective adaptive response to radiation. Tumorigenesis in chronically exposed normal and Trp53 heterozygous C57BL/6 mice. Radiat Res 170: 765 - 775

Mothersill C and Seymour CB. 2006. Radiation-induced bystander effects and the DNA paradigm: an "out of field" perspective: Mutat Res 59: 5 - 10

Mullenders L, Atkinson M, Paretzke H, Sabatier L, and Bouffler S. 2009. Assessing cancer risk of low-dose radiation. Nature Reviews / Cancer 9: 596 - 604

Nair RR, Rajan B, Akiba S, Jayalekshmi P, Nair MK, Gangadharan P, Koga T, Morishima H, Nakamura S, and Sugahara T. 2009. Background radiation and cancer incidence in Kerala, India-Karanagappally cohort study. Health Phys 96: 55 - 66

National Research Council, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. 2006. Health risks from low levels of ionizing radiation: BEIR VII, Phase 2. Washington, DC: The National Academies Press

Nikjoo H, O'Neill P, Terrissol M, and Goodhead DT. 1999. Quantitative modelling of DNA damage using Monte-Carlo track structure method. Radiat Envrion Biophys 38: 31 – 38

Olivieri G, Bodycote J, and Wolff S. 1984. Adaptive response of human lymphocytes to low concentration of radioactive thymidine. Science 223: 594- 597

Pollycove M and Feinendegen LE. 2001. Biologic response to low doses of ionizing radiation: Detriment versus hormesis. Part 2: Dose responses of organisms. J. Nucl. Med. 42: 26N - 32N

Pollycove M and Feinendegen LE: 2003. Radiation-induced versus endogenous DNA damage: Possible effect of inducible protective responses in mitigating endogenous damage. Human & Exper Toxicol 22: 290 - 306

Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K. 2004. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res 162: 377 - 389

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, and Kodama K. 2007. Solid cancer incidence in atomic bomb survivors: 1958 – 1998. Radiat Res 168: 1 – 64

Rothkamm K and Löbrich M. 2003. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses', Proc Natl Acad Sci US 100: 5057 - 5062

Schöllnberger H, Stewart RD, and Mitchel REJ. 2005. Low-LET-induced radioprotective mechanisms within a stochastic two-stage cancer model. Dose-Response 3: 508 – 518

Scott BR. 2004. A biological-based model that .links genomic instability; bystander effects, and adaptive response Mutat Res 568: 129 - 143

Sedelnikova OA, Horikawa I, Zimonjic DB, Popescu NC, Bonner WM, and Barrett JC. 2004. Senescing human cells and ageing mice accumulate DNA lesions with unrepairable double-strand breaks. Nature Cell Biol 6: 168 - 170

Sen K, Sies H, and Baeurle P, eds. 2000. Redox Regulation of Gene Expression. Academic Press, San Diego, USA

Tanooka H. 2001. Threshold dose-response in radiation carcinogenesis: an approach from chronic beta-irradiation experiments and a review of non-tumour doses. Int J Radiat Biol 77: 541 - 551

Tubiana M, Aurengo A, Averbeck D, et al, 2005. Dose-effect relationships and the estimation of the carcinogenic effects of low doses of ionizing radiation. Academy of Medicine (Paris) and Academy of Science (Paris) Joint Report No. 2

Tubiana M, Feinendegen LE, Yang C J M. and Kaminski JM. 2009. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. Radiology 251: 13 - 22

Vilenchik MM and Knudson AG. 2000. Inverse radiation dose-rate effects on somatic and germ-line mutations and DNA damage rates. Proc Natl Acad Sci US 97: 5381-5386

Wolff S, Afzal V, Wienke JK, Olivieri G, and Michaeli A. 1988. Human lymphocytes exposed to low doses of ionizing radiations become refractory to high doses of radiation as well as to chemical mutagens that induce double-strand breaks in DNA. Intern J Radiat Biol 53: 39 - 49

Zamboglou N, Porschen W, Muehlensiepen H., Booz J, and Feinendegen LE. 1981. Low dose effect of ionizing radiation on incorporation of iodo-deoxyuridine into bone marrow cells. Intern J Radiat Biol 39: 83 - 93