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Radiation Effects after Low Dose Chronic Long-Term Exposure

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Preliminary remarks

Medical doctors who have to treat patients after a possibly chronic- or protracted long term radiation exposure should be able to decide quickly if there is the suspicion of unusual exposure and what will be the optimal diagnostic and therapeutic regime for a special patient

Chronic long term radiation exposure from the epidemiological point of view is not going to be the subject of the presented article - even if the statistical determination of late effects is very important. In addition, the evaluation of exposure quantity and quality as the main objective of radiation protection is also important. However, this topic should also not be the basis of this overview.

Medical doctors should keep in mind that a pathophysiological model is important from which the principle mechanisms of chronic long term exposure at different biological levels can be derived and elucidated (Fig.1). In limits these physiological based mechanisms enables the organism to adapt to unusual radiation fields without direct clinical health impairment The details of such a model have been discussed elsewhere [1].

The key problem for the medical personnel in charge is, which diagnostic methods and therapeutic techniques are available and meaningful to recognize a chronic radiation exposure, to treat the patient in an optimal way and prevent secondary effects?

Examples for low dose chronic exposure

In the scientific literature at least three accidents have been described concerning people accidentally exposed to chronic irradiation and becoming ill after a long symptom free period

The oldest accident to be to referred to occurred in Mexico on Feb. 21, 1962 [2]. A 10 year old boy found a stainless steel capsule of about 1 5 cm and put it in his pocket without knowing that it contained ^{60}Co After 7 days his mother found the capsule and put it on the kitchen shelf. In the resultant radiation field all family members were exposed. 24 days after the beginning of the radiation exposure the little boy (E.E.P) was hospitalized and diagnosed as suffering from the signs and symptoms of a severe aplastic anemia of unknown etiology. He died due to panmyelopathy 12 days later His 2 $^1/_2$ year old sister, mother and grandmother also died after being in and out of the accidental radiation field for 120, 115 and 90 days, respectively (Table 1) Only after the grandmothers death the authorities took notice, discover and seize

the radiation source. By that time the father, who was exposed only intermittently, was also examined and found to have a severe hematopoietic failure He was treated only with antibiotics. His bone marrow recovered spontaneously within 8 weeks

The evaluation of the radiation dose was performed by retrospective accident reconstruction Accordingly, the involved persons accumulated at maximum between 17 - 52 Sv or 9 - 29 Sv at minimum. The daily doses of the lethally injured persons were between 156 and 321 mSv. The father, who recovered from bone marrow impairment was estimated to have received about 82 - 143 mSv/d.

A very similar accident occurred in Algier on May 5, 1978 [3]. On its way from Algier to Setif a truck lost a chrome-steel stick which contained a ^{192}Ir source Two boys, three and seven years old, found this "valuable toy" without knowing about its dangerous content. Comparable to the Mexico accident, the grandmother who found the children's toy put it on the kitchen shelf. In this radiation field, 7 persons were exposed: the two boys, the grandmother and 4 young women. After 38 days authorities found the source. All the exposed family members were examined The little boys only showed radiation induced skin damage primarily to both hands. No data were given in the literature for the outcome of the grandmother The four women were sent to the Curie-Foundation in Paris for further treatment of their health impairments due to a severe hematopoietic failure. They were treated on the intensive care unit with transfusion therapy and anitibiotics showing a slow spontaneous regeneration of the hemopoiesis. The estimated radiation exposure doses for the women were between 316 - 368 mSv/d at maximum or 263 - 329 mSv/d at minimum (Table 2).

A third accident occurred in Estonia on Oct. 21, 1994 [4]. Two apparently valuable looking steel cylinders (1 -2 cm in diameter, 4 and 15 cm in length) were found by three young men in a waste disposal site The cylinders contained ^{137}Cs. Not being aware of its content one of the men placed one cylinder in his jacket and later stored the jacket in the entrance hall of his home A few days later, he died in a hospital due to kidney failure The doctors did not recognize the etiology and pathogenesis of the sickness. In the meantime, a 13 year old boy took the cylinder and put it in his tool box were it was confiscated by the police on November 18, 1994. The boy was treated in a hospital for radiation induced skin damage (ulcer of one hand) and bone marrow impairment. Except for the one victim who died at the hospital, 3 days after finding the cylinder, all others recovered spontaneously from more or less severe hemopoietic symptoms, such as granulocytopenia and thrombocytopenia Dose estimations for all involved persons are shown in Table 3. Patient Hi.Ri. accumulated during exposure more than 4 Sv with a daily total body dose of more than 1000 mSv. Comparatively the 13 year old (Ra.Tu.) received a cumulative dose of about 2.5 Sv over a time period of 28 days that correspond to a daily dose of about 89 mSv. He showed spontaneous regeneration of the hemopoiesis. Since this had been predicted on the basis of other accidents, treatment with cytokines was placed on a "stand-by" position but not used.

Possibilities and limitations of tolerance after continuous low-dose radiation exposure

Based on these examples of the accidental radiation exposure, it can be recognized that there are certain radiation exposure levels which can be tolerated by the organism over a particular period of time without direct clinical health impairment.

As it is shown in Fig 2 the normal background exposure rate for Europe is about 2,4 mSv/y [5] In other regions of the world, for example Kerala (India), the background level can be as much as 10 times higher [6]. The radiation exposure of "Category A" radiation workers in Germany is not allowed to exceed 50 mSv/y [7]. The radiation level of the uranium miners (WISMUT Workers) was about 100 mSv/y during the so called "wild years" (1945 - 1955) [8] The radiation exposure of the people in the Techa River Region in the South Ural due to the release of radioactive waste into the river was reported to amount in many persons at least 40 - 250 mSv/y during the first 5 years (1949 - 1954) and about 25 mSv/yr in the following years [9] (Fig.3).

Converting these dose levels into daily doses, the dose rates are between 0.007 mSv and 0.274 mSv Obviously, no clinical consequences have been observed at the reported dose rates. However, in over 900 "Techa River Persons", a "chronic radiation syndrome" was diagnosed. Hence, it must be assumed that at least in this group of patients the exposure rates were significantly higher than the lower limits cited above

The description of the accidents with protracted or chronic radiation exposure resulting in clinical signs and symptoms showed daily dose rates more than 10.000 times higher compared to normal background exposures. The daily doses which obviously could be tolerated up to a period of three months were found in the accident victims to be about 80 - 300 mSv. Depending on such radiation levels, dose rates can be tolerated from days up to weeks without severe clinical symptoms In the Algerian accident doses about 300 mSv/d were tolerated for nearly 40 days After that time, the victims showed a bone marrow failure which regenerated spontaneously after leaving the radiation field.

Pathophysiologic mechanisms for cell system tolerance in elevated radiation fields

Which pathophysiology mechanisms permit the organism to live in a radiation field for days, weeks or years without direct health impairment?

Two previous animal investigations should be considered when addressing this question First, in the 1950th the working group of Lamerton in London investigated the clinical consequences from chronic total body irradiation [10]. Rats were exposed to ionizing radiation from a ^{137}Cs source for 23,5 h/d. At dose rate levels of 1760 mSv/d for around 15 days all animals developed a pancytopenia and died. In contrast, it requires around 50 days for the hematopoiesis to collapse at radiation doses of 840 mSv/d With 500 mSv/d the animals survived more than 200 days. Variations in the blood cell counts were observed, but the animals developed a balance between cell production and cell loss Around 160 mSv/d no collapse of hematopoiesis was seen during the first year of exposure

Detailed preclinical studies using a canine model were performed by the working group of Tom Fritz and Tom Seed between 1978 and 1990 at the Argonne National Laboratory [11]. Dogs were exposed during their entire life span to total body irradiation from a ^{60}Co source between 37.5 and 540 mSv/d. Two patterns of effects have been found. With daily radiation doses of more than 75 mSv/d impairment or failure of hematopoiesis was seen in a radiation-dose dependent time period. The animals died from conditions such as hematopoietic aplasia, septicemia or MPD (myeloproliferative disease) This pattern could be described as the hematological form of chronic radiation exposure syndrome. The second pattern mainly concerned the early appearance of malignancies These were the consequences of radiation exposures of less than 75 mSv/d. This pattern can be referred to as the "oncogene form" of the chronic radiation exposure syndrome. Moreover, it is not certain as whether there can be a third pattern postulated involving "radiation induced early aging". Early aging was seen in the Argonne dogs and it cannot be explained by the appearance of tumors.

The principle hematological findings characterizing the response of hematopoiesis in dogs to continuous low dose total body irradiation [12] can be seen in figure 4. For more than 4 years dogs were exposed to a daily radiation dose level of 25 mSv At this exposure level, granulocyte counts declined to a constant level of about 5 x 10^9/l. The colony stimulating activity (CSA) – a granulocyte regulation factor in the blood – showed increased levels Finally, an increased level of stab forms of granulocytes were found in the blood indicating the strain on the granulocyte system. Similar to the granulocyte count the erythrocytes and thrombocytes adjusted to the new situation resulting in lower but stable blood levels. These patterns can be explained by additional radiation induced cell loss in the hematopoietic progenitor cell compartments which are compensated by an increase in cell production under the influence of appropriate stimulators and shorter granulocyte maturing time.

A biomathematical model of granulocytopoiesis for estimation of stem cell numbers was developed in cooperation with the Department of Measurement, Control and Microtechnology at the University of Ulm [13] This model consists of 26 differential equations which describe the time evolution of the system It describes 6 cell and two hormone compartments The application of the model shows that it is possible to simulate the blood cell changes. For example, changes in granulocyte counts after continuous total body irradiation with 4mSv/d, 10 mSv/d, 25 mSv/d and 170 mSv/d could be simulated if the relative kill rate in the stem cell compartment increased from 2 to 10 per 1000 stem cells A higher kill rate would cause system collapse [14].

Thus, the most important question to be answered if a patient is suspected to have been exposed to chronic or protracted whole body radiation exposure is, whether his cell renewal systems are capable of compensating the radiation induced cell loss by additional cell production in the stem cell and the

hematopoietic progenitor compartments.

The animal experiments show that the risk of a system failure, for example during the first 3 - 4 months after the beginning of the exposure, increase, if the radiation levels exceed certain thresholds. For rats this radiation level is around 500 mSv/d, for dogs around 75 mSv/d and for humans around 90 mSv/d. These "threshold-limit-values" are extremely important and reflect the cell system radiation sensitivity characteristics of a mammalian species. It can be shown by these limits, that the biological and clinical effective radiation level per day is about 600 fold higher than the allowed occupational radiation exposure (50 mSv/a or 0,137 mSv/d).

Diagnostic and therapeutic possibilities

Which diagnostic methods and therapeutic approaches are available for medical doctors to recognize and treat a victim after chronic or protracted long term radiation exposure?

The starting point for answering this question is the observation that at radiation levels of less than 100 mSv/d the critical organ 'hematopoiesis' (consisting of several feedback regulated cell renewal systems) is able to stabilize the blood cell concentration for erythrocytes, granulocytes and thrombocytes. This guarantees an adequate system function so that no secondary infections, bleedings or significant anemia will develop. If the radiation level is higher than 200 - 300 mSv/d, the collapse of the hematopoietic system can be predicted to occur within 2 or 3 months. Patients will show signs and symptoms of a progressively severe bone marrow failure with resulting infections from granulocytopenia, bleedings due to thrombocytopenia and eventually develop anemia This threatening system failure can go undiscovered for days or weeks because people initially do not suffer from clinical symptoms (see the accidents in Mexico, Algeria and Estonia)

What should a medical doctor do if there is the suspicion of chronic or intermittent radiation exposure? The first thing is to obtain a detailed case history, especially accident information and personal exposure conditions like the beginning and the end of the exposure period (if known) and the quality of external or internal irradiation or contamination After that, one has to evaluate primary organ reactions, for example, radiation induced lesions of the skin, appendices and underlying tissues [15]. The next step is to ascertain laboratory data concerning the peripheral blood and lesions of the bone marrow.

In the bone marrow not only quantitative changes but also qualitative changes are important After a chronic long term exposure mitotically connected cell abnormalities and immature blood cell precursors (expression of extramedullary hematopoiesis) can be expected in blood leukocyte concentrate smears as well as in bone marow smears [16] In the bone marrow dose dependent regeneration islands will be seen in histological sections. In combination with the important analysis of cytokines, measurement of the quantity and quality of circulating progenitor cells for additional cell loss rate should be determined. The proof of stable or unstable chromosomal aberrations in lymphocytes or progenitor cell cultures could

also be used as a typical sign for chronic radiation exposure.

In summary, if there is a suspicion for a long term radiation exposure a detailed hematological assessment is necessary, keeping in mind that if the radiation level was not higher than 100 - 200 mSv/d a spontaneous regeneration of the hematopoiesis is most likely to occur.

From this information certain therapeutic approaches can be inferred. Even if there is - like in the Algerian or Mexico accident - a severe impairment of hematopoiesis, it is feasible to assume that a spontaneous regeneration of the system is possible. In this case, the treatment regime should include all steps of a 'gnotobiotic' therapy (antibiotics, sterile isolation) and the preparedness for thrombocyte transfusions in case of severe thrombocytopenic purpura. If there is evidence for a threatening or existing bone marrow failure cytokine therapy should be initiated for the stimulation of granulopoiesis and thrombopoiesis.

If all signs indicate that the damage of the bone marrow is irreversible - meaning a total aplastic marrow in at least two bone marrow sections without regeneration islands - a stem cell therapy following current severe aplastic anemia clinical treatment protocols is indicated for such patients [17].

Summary

Depending on the place of resident human beings receive during one year on average 2,4 - 20 mSv (0,0066 - 0,055 mSv/d) in the form of normal background radiation (Fig 2). Obviously, the organism is able to quantitatively compensate the resulting cell loss by additional cell production The accepted dose levle for occupational radiation exposure is 50 mSv/y (0,14 mSv/d) Unusual long term radiation exposure was found in the Uranium miners and the radiation accident in the South Urals with daily radiation doses of about 100 mSv

In accidents resulting from the loss of radiation sources in Mexico (1962), Algeria (1978) and Estonia (1994), the daily absorbed radiation exposure doses were much higher (Fig 3) Exposure doses between 80 mSv/d and 400 mSv/d resulted in a severe strain of hematopoiesis and skin.

The overall strain limits of the hematopoiesis are determined by the remaining function of the stem cell compartment and, of course, the overall levels of progenitor and proliferative cell production [18]

To determine the extent of cell system impairment by chronic, repeated or protracted radiation exposure, a professional medical examination is necessary which considers the pathophysiological mechanisms of critical system failure. The available diagnostic methods have developed and considerable improved during the last years. It should be state of the arts to obtain daily data on the peripheral blood count and blood smear until the system is completely recovered. Cell system alterations should, for example, be analyzed by quantitative progenitor cell assays The determination of lymphocyte subpopulations, lymphocyte proliferation tests and phagocytosis tests are necessary to review the patients immunology status. All common functional tests helpful in the examination of the organ systems can be helpful to detect primary or secondary reactions of the cardio-vascular-system, the impairment of the

central and peripheral nervous system, the gastro-intestinal-tract, digestion, hormone-system and the clinical immune status Cytogenetic studies to assess the frequency of the unstable and stable chromosomal aberrations are helpful to confirm the exposure of the organism to ionizing radiation.

To determine the optimal therapy, it is extremely important to know the extent of system impairment and to decide early in the course whether the critical cell systems have the capacity to regenerate spontaneously or not. If the outlook is a irreversible bone marrow failure, stem cell transplantation should be considered as if one is treating a "severe aplastic anemia" Skin lesions should treated adequately and quickly to prevent patients from secondary wound infections and late effects.

Figures and Tables

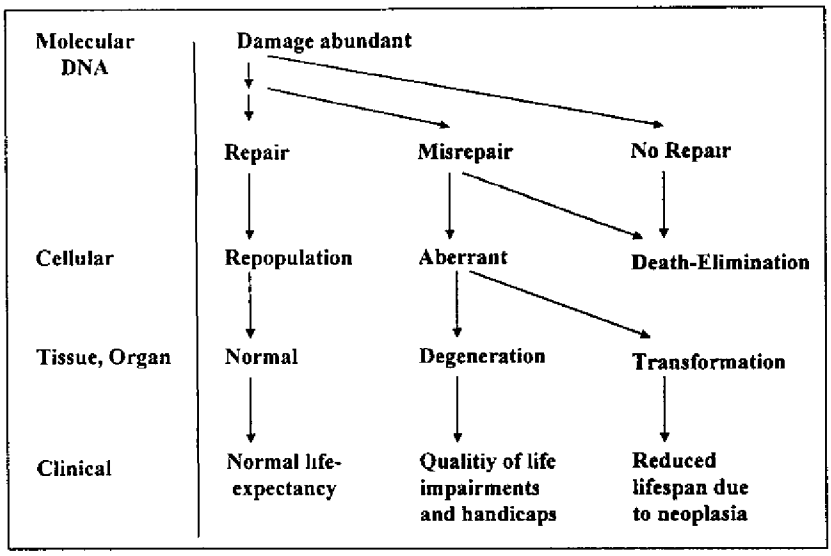

Figure 1: Pathophysiological concept of a radiation induced "effect – cascade"

Table 1: Radiation accident Mexico 1962; ^{60}Co source

Victim	Duration of Exposure [d]	Cumulative Total Body Dose[Sv]		Total Body Dose per Day [mSv]		Survival [d]
		Maximum	Minimum	Maximum	Minimum	
E.E.P.	24 (7 / 17)*	51.65	29 4	2152.08 for 7 d 760 for 17 d 250	1225	12
M.E.E.	120 (3 / 117)*	18 72	13.73	156 for 3 d 899 for 117 d 135	114 4	22
M.C.E.	115	29.3	19 95	254.78	173 48	2
A.I.G.	90	28 97	18.18	321.89	202	90
J.E.I.	120	17.16	9.94	143	82.83	> 100

* higher radiation dose for 7 and 3 days, respectively

Table 2: Radiation accident Algier 1978, ^{192}Ir source

Victim	Duration of Exposure[d]	Cumulative Total Body Dose[Sv]		Total Body Dose per Day [mSv]		Survival [d]
		Maximum	Minimum	Maximum	Minimum	
D.J.	38 (6-8 h/d)	14	12	368	316	> 100
N.G.	38 (6-8 h/d)	14	12.5	368	329	> 100
F.A.	38 (6-8 h/d)	13	11	342	289	> 100
N.D.	38 (6-8 h/d)	12	10	316	263	> 100

Table 3: Radiation accident Estonia 1994; ^{137}Cs source

Victim	Duration of Exposure[d]	Cumulative Total Body Dose [Sv]	Total Body Dose per Day [mSv]	Survival [d]
Hi.Ri.	55 min (PBI) 4 (TBI)	183 > 4	n. c. > 1000	7
Iv.Hi. 27 y	< 1 h	> 0 05	n. c.	> 100
Ra.Tu. 13 y	30 - 40 min (PBI) 28 (TBI)	20 - 30 right hand 8 - 10 left hand 2.5	n. c. n. c 89.3	> 100
Al.Sa. 78 y	7	2 - 2.5	286 - 357	> 100
Hi.Ra. 28 y	15 sec	0.02	n. c.	> 100
By. Ku. 35 y	3	0.35 - 0.55	117 - 183	> 100

TBI = total body irradiation, PBI = partial body irradiation, n. c = not calculated

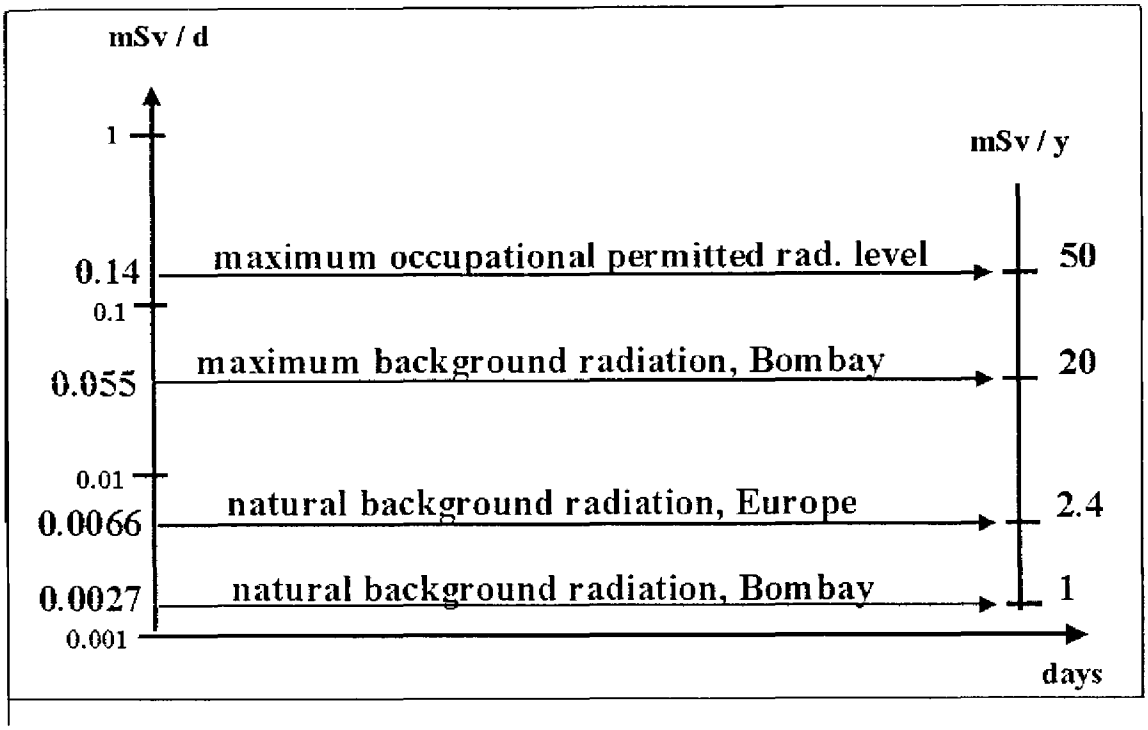

Figure 2. Background and occupational permitted exposure doses

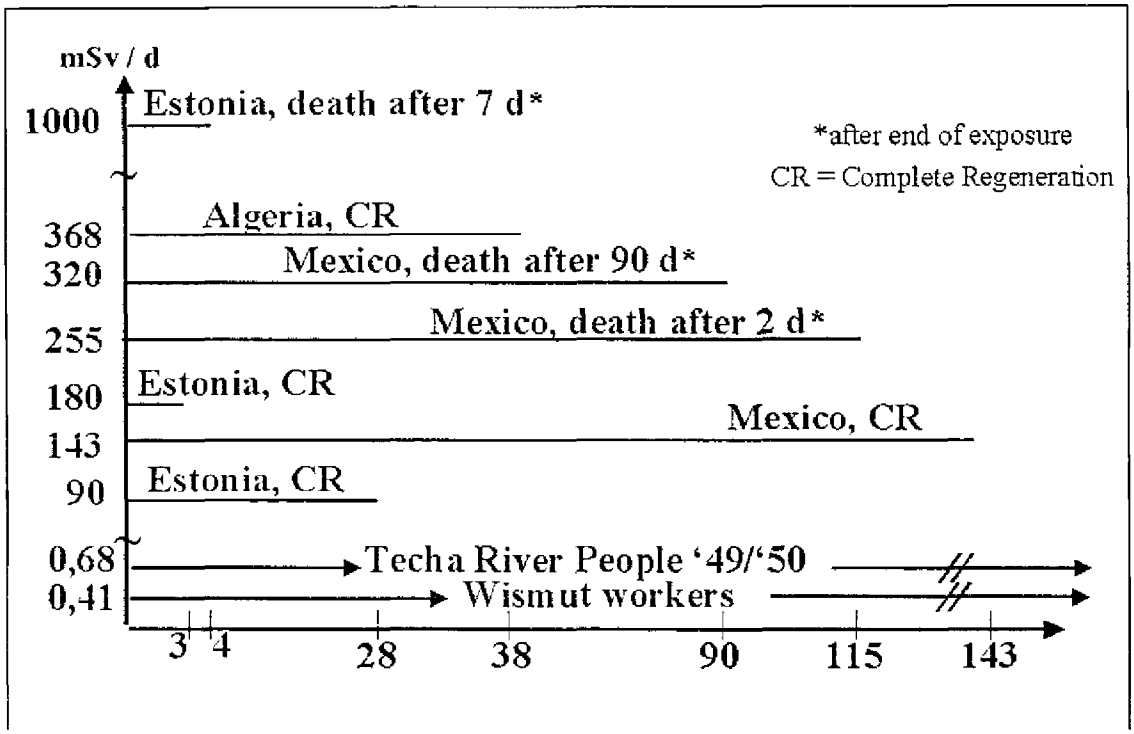

Figure 3: Examples for accidental ill-defined and/or intermittent radiation exposure

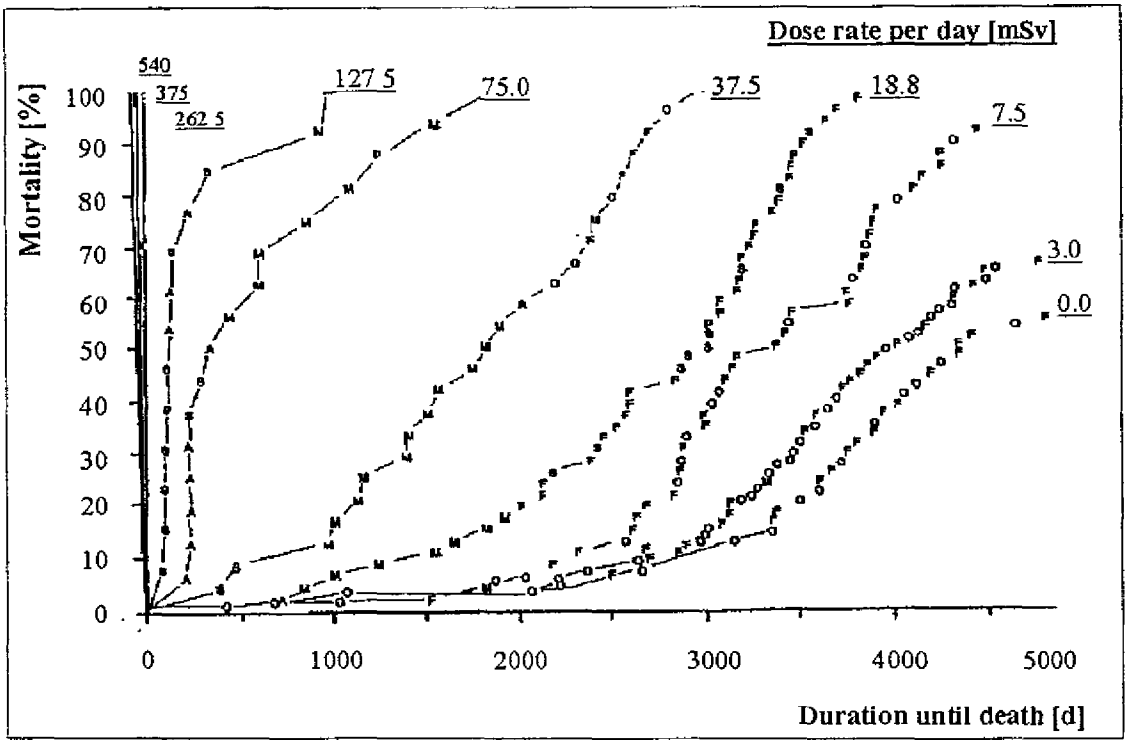

Figure 4 Findings after continuos low-dose total body irradiation in dogs
A = Aplasia; S = Septicemia; M = Myeloproliferative disorders, F = Tumor; O = Others

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