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COMMENTARY

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The Southern Urals radiation studies

A reappraisal of the current status

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Abstract In the late 1940s and early 1950s the nuclear workers of the Mayak Production Association in the Southern Urals were exposed to high doses from γ-rays and from incorporated plutonium. In addition, the population of the Techa riverside downstream of the plutonium-production sites received continued exposures from external γ-rays due to fission products released into the river and from the internal radiation due to incorporation of the fission products. Based on two international coordination meetings in 1998 and 2000, a synopsis has been given recently in this journal of the radioepidemiological studies on these exposed populations. This commentary describes the current status of these singular investigations with regard to the dosimetry, the assessment of late health effects, and the risk estimation both for the Mayak nuclear workers and the Techa riverside population. A central issue are newly published reduced estimates of the external dose to the Techa riverside population which imply substantially increased risk coefficients for solid cancer. Unless the new dosimetry system, TRDS-2000, has missed a major dose contribution, there is now conspicuous disagreement with current risk estimates. Unaccounted doses from atmospheric releases of fission products and from radiological screening of the Techa riverside population need to be explored, but underestimation of the short lived fission products released into the river appears to be a more critical factor. It is furthermore argued that even if TRDS-2000 were confirmed it would remain questionable whether risk estimates can be based on organ-specific doses when they are obtained in a population with a much higher bone-marrow exposure that may possibly have caused an 'abscopal' radiation effect.

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Introduction

A recent special issue of *Radiation and Environmental Biophysics* [1] has brought together various reports which summarise – based on two international coordination meetings at Schloss Elmau in 1998 and 2000 – the status of radioepidemiological studies that are related to past radiation exposures in the former Soviet Union. The major focus of these studies is on high, prolonged radiation exposures of nuclear workers and population groups in the Southern Urals. The exposures took place predominantly in the early years of the Cold War. They were caused by the Plutonium Production Association *Mayak*, which employed – at the time without adequate radiation protection – tens of thousands of workers in its nuclear reactors and in its radiochemical and plutonium production plants and, likewise, exposed the inhabitants of the Techa riverside villages through controlled and uncontrolled releases into the river of large amounts of fission products.

Even before these events became known outside the borders of the Soviet Union, it was recognised by Russian scientists and Government authorities that major dosimetric and epidemiological investigations were required to identify late health effects due to the radiation exposures and, thus, to derive out of these fateful events improved knowledge on radiation risks. Important parts of the work had already been achieved by the Russian scientists, and it was clear that the investigations could substantially add to the conclusions from other radiation studies, especially to those from the follow-up of the A-bomb survivors. In fact, the results could supersede the current risk estimates, because it had become possible for the first time, to observe the effects of substantial low dose rate exposures of large groups of people. If reliable data can be obtained, they will be more representative and relevant to occupational radiation protection and to

radiation protection of the population than the inferences from the acute high dose rate exposures of the Japanese A-bomb survivors.

The subsequent considerations outline first the current status of the research and discuss then new complexities that arise from recently published data.

Current status

The two major lines of research are the investigation of health effects among the Mayak nuclear workers [2, 3, 4] and the follow-up of the Techa river populations [5, 6, 7, 8]. Other on-going inquiries, such as the mortality study of the population of Ozyorsk [9, 10] or potential studies, such as the follow-up of the population in the East Ural Radioactive Trace (EURT), the consequence of the Kyshtym accident in 1957 [2], are also of considerable interest. But the considerations will here relate to the primary lines of work and, in particular, to newly emerging issues that may demand a reassessment of the aims and potential targets of the investigations.

Mayak nuclear workers

The health studies among roughly 26,000 Mayak nuclear workers offer the singular possibility to observe and quantify the effects of plutonium on man. They have also considerable potential to provide solid cancer and leukaemia risk estimates for prolonged γ-ray exposures.

There are three separate sub-cohorts, the reactor workers, the workers from the radiochemical plants, and those from the plutonium production plants (see later Table 1). The reactor workers were exposed to γ-rays and, to a minor degree, to neutrons. The workers at the Mayak radiochemical plants and the plutonium fabrication sites were predominantly exposed to inhaled plutonium nitrate and plutonium oxide and dioxide, respectively. This caused high doses, primarily to the lungs, liver and bone. In all three groups – and especially in the radiochemical plant workers – the γ-ray exposures, too, were large.

The study of lung-cancer mortality in the "core cohort" of early Mayak workers has provided the first quantitative risk estimates for plutonium that are directly based on human experience [11, 12, 13]. The substantial excess of lung-cancer has been seen in the analyses to be predominantly associated with the plutonium inhalation, and it was concluded that a lung dose from plutonium of 1 Sv increases the lung cancer mortality by about 60%. This was a still uncertain value which has been obtained without the use of smoking information for the cohort. However, the general agreement with the order of magnitude of earlier assumptions is of considerable importance. The dose-dependence in this cohort study appears to be quite linear, with no indication of a threshold. This is in striking contrast to the conclusion of an earlier lung cancer case-control study of Tokarskaya et al. [14] where a high threshold dose was inferred for lung cancer due to plutonium inhalation; new findings on this critical issue are mentioned in a subsequent section. For the γ-ray contribution to the lung dose, the cohort study has suggested fairly low risk [13], but still with high statistical uncertainty.

The other two organs that received substantial doses from plutonium are bone and liver. In line with expectations, Koshurnikova et al. [15] and Gilbert et al. [16] have reported high excess relative risks for bone and liver cancer in the highest plutonium-exposure category of the workers. While the results are still preliminary, they are the first firm evidence based on human data of bone and liver cancers due to plutonium.

The exceptional potential of the study implies that the dosimetric as well as the epidemiological parts of the study need to be continued and extended with maximum possible support.

Techa river study

While the Mayak workers study is singular with regard to the health effects of plutonium, the Techa river study is seen as the one extraordinary basis to obtain more reliable risk estimates for a general population exposed over an extended period to low dose rate γ-rays. More than 25,000 inhabitants of the Techa riverside villages were exposed, predominantly during the early 1950s, to external γ-radiation from fission products in the river and on its floodplains. In addition, they incorporated from drinking water and through the food chain large activities first of

Table 1 Essential characteristics of the "core cohort" of male Mayak workers with plutonium measurements where applicable (initial employment 48–58); status end of 1999 [27]. Hired at Mayak 1948–1958: 8,927 male and 3,592 female workers. Reconstruction of individual exposure history (external and, where applicable, internal) and collection of smoking information for 4,212 male workers (219 lung cancer cases) and 1,732 female workers (19 cases)

	Reactors	Radiochemical plant	Pu production
Number of workers	2,197	1,339	676
Number of lung cancer deaths	92	77	50
Fraction of deaths due to lung cancer	8.3%	13.5%	18.6%
Number of workers alive in 1999	1,114 (50.7%)	770 (57.5%)	407 (60.2%)
Person years at risk	78,813[a]	19,474[b]	11,003[b]
Mean follow-up time	35.9 years	41.9 years	41.3 years
Mean cumulated α-dose	–	0.140 Gy	0.450 Gy
Mean cumulated γ-dose	0.904 Gy	1.973 Gy	0.510 Gy
Mean duration of work	15.8 years	29.1 years	17.9 years

[a] Person years calculated since year of first employment
[b] Person years calculated since year of first urine sampling

short-lived fission products, such as ^{89}Sr, and subsequently long-lived activity, especially from ^{90}Sr [17]. The study is, therefore, of particular interest also as a unique source of knowledge on the late effects of bone and bone-marrow exposures from ^{90}Sr. In Western countries the potential effects of ^{90}Sr began to be of great concern in the period of the atmospheric tests of nuclear weapons; subsequently attention was directed at ^{90}Sr releases due to potential accidents in nuclear installations. Since that time there have been numerous radiobiological investigations of the dosimetry and the effects of radiostrontium. But in 1991 it could still be stated [18] that there were no cases of human exposure to ^{90}Sr on record which would provide direct guidance concerning the kinds of effects to be expected or their frequency. At about the same time the situation changed fundamentally, as the events in the Southern Urals became known. The work of the Urals Research Center for Radiation Medicine (URCRM) [5, 6, 7, 8] has since attracted great interest and has been integrated into broad international co-operations.

The central question in the Techa river study is, as stated, the dose-rate effect. This question is crucial to radiation protection. Can the epidemiological investigation confirm the current assumption that low dose rate exposures to sparsely ionising radiation carry less risk per unit dose – and certainly no greater risk – than acute exposures? If it can provide an answer, the study will be as important as the follow-up of the A-bomb survivors.

The International Commission for Radiation Protection (ICRP) has, on the basis of radiobiological findings, introduced the *dose and dose rate effectiveness factor* (*DDREF*=2) [19]. This factor scales down the observed risk among the A-bomb survivors with their acute exposure to the presumably lower risk from low dose rate irradiation.

From the initial assessments, primarily on the basis of preliminary leukaemia data, the impression had been generated that the Techa river risk estimates might be lower by a factor 2 or 3 than the values deduced from the A-bomb data [19]. This seemed to support the dose and dose rate effectiveness factor *DDREF*=2. Subsequently, when the Techa river dosimetry system 1996 (TRDS-1996) and improved data on cancer mortality became available, it was concluded that the risk estimates, both for solid cancers and leukaemia, were largely in line with, but apparently not smaller than, the results from the A-bomb study. The excess relative risk for solid cancer among the A-bomb survivors is about *ERR*/Gy=0.5, the excess risk for leukaemia is about 2.6 per 10,000 person year Sv. Kossenko [6] has reported on the basis of the Techa river data the value *ERR*/Gy=0.65 for solid cancer mortality, and an excess risk for leukaemia of 0.85 per 10,000 person year Sv for the follow-up through 1982. Roughly speaking, this meant that the solid cancer risk estimate was close to the estimate from the A-bomb data without *DDREF*, while the leukaemia estimate appeared to be lower.

A considerable effort was then invested into the creation of a further improved Techa river dosimetry system (TRDS-2000) [21, 22, 23, 24]. The resulting estimates of external exposure turned out to be substantially lower. Accordingly, the risk estimates for solid cancers must, with the new dosimetry, exceed the currently assumed values considerably. If confirmed, this will have very severe impact on radiation-protection regulations. The issue is, therefore, central to current discussions.

New results and emerging issues

Mayak nuclear workers

A number of new developments in the plutonium dosimetry for the Mayak workers and some improved risk analyses were recently reported [25].

The continued work on the reconstruction of individual external doses to the Mayak workers now indicates that the monitoring data from the early years, i.e. the years with the highest exposures, have been overestimated by up to 50%. Current γ-ray risk estimates for the Mayak nuclear workers are, therefore, underestimates, and there is a need for a continued effort towards the dose reconstruction.

The new reports include also an assessment of neutron doses within a group of nearly 5,000 Mayak reactor workers. On average the neutron absorbed dose in this group of workers is substantially below 1% of the total absorbed dose, which is less than the average among the A-bomb survivors in Hiroshima [26]. It is thus unlikely that the follow-up of the Mayak workers can provide risk estimates for fast neutron exposures. However, a relatively small subgroup of workers had, during the early phase of the reactor operations, neutron absorbed dose contributions of several percent. Apart from the A-bomb survivors, the relatively few victims of critical accidents, and the limited number of neutron-therapy patients, there has been no cohort with substantial neutron exposures. It is, therefore, desirable to assess, in spite of the limited group size, the dosimetry and the health data for these Mayak reactor workers.

There has been, likewise, considerable effort to improve, on the basis of the excretion measurements and autopsy data of the Mayak workers, the metabolic models for plutonium. There remains, nevertheless, considerable uncertainty on the retention times of plutonium dioxide and plutonium nitrate and on the distribution of the activity in different compartments of the lung. The overall changes in the estimates of lung dose are somewhat less than the changes of model parameters. This is so, because the effect of increased retention times is partly compensated by the fact that a large part of the retained activity is, by now, buried in scar tissue of the lung parenchyma.

Table 1 gives the main characteristics for the “core cohort”, i.e. those workers who had been hired at Mayak up to 1958 and had been measured for incorporated plutonium. The extended cohort of those who were

employed before 1972 comprises nearly 19,000 workers (12,500 hired up to 1958). The new analysis of lung cancer in this cohort of male workers accounts for smoking as the main confounder and obtains an excess relative risk for lung cancer from plutonium of *ERR*/Gy=4.5 (95% CI 3.2–6.1) [27]. Translated into dose equivalent, this corresponds to a 23% increase of lung cancer due to a lung dose of 1 Sv from plutonium. This is substantially less than the earlier estimates. Part of the change is due to the fact that the heavy smoking habits of the workers are now taken into account, but part of the decrease is also due to the introduction of the new dosimetry *Doses-2000*.

For lung cancer from external γ-rays the new analysis provides the low value *ERR*/Gy=0.06 (–0.07 to 0.2). Since this has been based on the uncorrected monitoring doses which are, as now reported, overestimates, the result need not be in conflict with the current estimate, *ERR*/Gy=0.34, from the follow-up of the A-bomb survivors.

The results – both for plutonium and γ-rays – may change as the dosimetry will be further improved and as the study cohort is extended, but they document even at this point the high potential of the follow-up of the Mayak nuclear workers.

A related item of considerable interest is a new lung cancer case-control study on the Mayak workers [28]. This study suggests no threshold in plutonium dose and actually excludes a threshold above 0.3 Gy, which is in direct contrast to the threshold of 0.8 Gy reported for the earlier case-control study by Tokarskaya et al. [14].

The collective γ-ray dose to the Mayak workers is, according to the present dose estimates, substantially larger than the combined collective dose to all western cohorts of nuclear workers. Even more importantly, it covers a much broader dose range. It has, thus, the potential to provide γ-ray risk estimates for solid cancer in the organs not exposed to plutonium. Up to now, there have been only preliminary studies, but a very low value *ERR*/Gy=0.08 has been reported for solid cancer in the organs with no appreciable dose contribution from plutonium. This is in remarkable contrast to the emerging high risk estimates for solid cancer from the study on the Techa riverside population. However, the low estimate appears to be largely determined by the comparatively few cases at the highest doses. For the subcohort with external doses up to 2 Gy the estimate would be closer to *ERR*/Gy=0.25, and if the monitored γ-ray doses are corrected in line with the newest assessment, there need then be no disagreement with the results from the follow-up of the A-bomb survivors.

Techa river study

The new dosimetry: implications and uncertainties

The Extended Techa River Cohort (ETRC) comprises currently about 30,000 persons [5, 6, 7, 8] who were exposed at low dose rates over an extended period of several years. As stated, there were two contributors to the exposure. One contribution was from penetrating external γ-rays due to fission products in the Techa river itself and on its banks and floodplains. For brevity this whole body exposure component is termed *external exposure*. The second contribution was from radionuclides in the river which were incorporated through drinking water and the food chain. A major component of the resultant *internal dose* is the exposure of the skeleton and the bone marrow by the β-rays of the long-lived incorporated ^{90}Sr and its decay product ^{90}Y. The internal dosimetry is supported by more than 30,000 refined measurements of the strontium body burden in more than 10,000 members of the Techa river population [17, 23, 24]. The contribution of short-lived fission products, such as ^{89}Sr, may also be important, but it is still insufficiently quantified.

In the former dosimetry system (TRDS-96) the external doses were smaller than the internal doses, but they were still of comparable magnitude. On the basis of these doses, excess solid cancer and leukaemia rates were estimated that appeared – as already stated in the section "Current status" – to be consistent with the risk estimates obtained from the follow-up of the A-bomb survivors, but did not reflect the dose and dose rate effectiveness factor *DDREF*=2 currently postulated by ICRP [19].

The doses from external exposure are subject to considerable uncertainty, because they depend in each Techa riverside village on the distance between houses and the river and also on the assumed time that was spent at or near the river. The new dosimetry system (TRDS-2000) [23, 24] has been established in order to reduce these uncertainties. While the earlier system is now considered to have overestimated external exposures, the new system aims at realistic estimates. The TRDS-2000 external doses are based on the actual distributions of distances of the houses from the river, while in the earlier dosimetry it was, in general, assumed that people lived in the first row of houses next to the river. Also the times spent at or near the river are now assumed to be less than in the earlier assessment. The overall result is a very substantial reduction of doses from external radiation. Figure 1 gives average doses for the Techa riverside villages as obtained in the two dosimetry systems [24]. Table 2 lists the mean and median bone-marrow and soft-tissue doses[1] [8].

The bone-marrow dose estimates have slightly decreased. The risk estimate for leukaemia is now somewhat in excess of the result from the A-bomb data, but the difference is not statistically significant and it is due mostly to the data at higher doses. However, there is a great impact of the changed dosimetry on the risk estimate for solid cancer mortality. The former estimate was *ERR*/Gy=0.65 [5, 8]. As the soft tissue dose estimates have been lowered by almost a factor of 3, the value is now larger than *ERR*/Gy=1.5.

[1] The term *soft tissue* is here and in the following used, somewhat loosely, for all organs and tissues not directly exposed by the bone-seeking radionuclides ^{90}Sr and ^{239}Pu

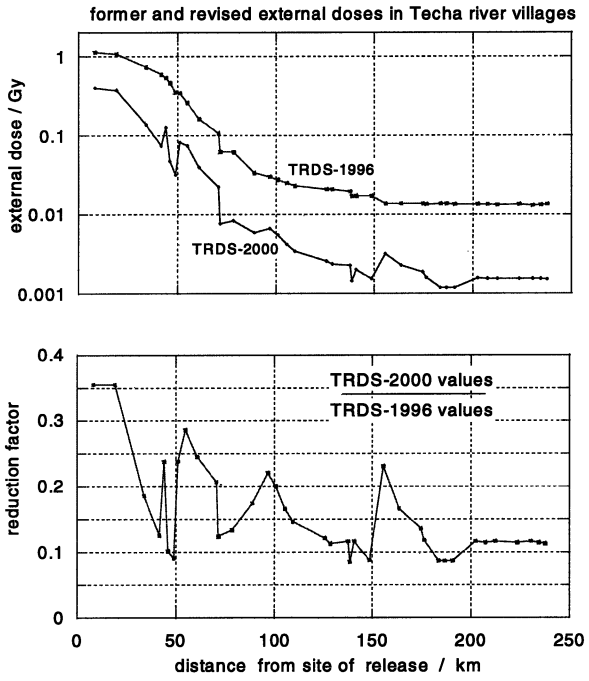

Fig. 1 *Upper panel:* The doses from external exposure in Techa riverside villages according to the former dosimetry system (TRDS-1996) and the revised system (TRDS-2000) [24, p. 43]. *Lower panel:* The reduction factor for the external doses from TRDS-1996 to TRDS-2000

Table 2 Mean and median doses to soft tissue and to the bone marrow according to the earlier Techa river dosimetry and the revised dosimetry system [8]

	Soft tissue dose	Bone marrow dose
TRDS-1996		
Mean	99 mGy	405 mGy
Median	17 mGy	267 mGy
TRDS-2000		
Mean	35 mGy	353 mGy
Median	7 mGy	253 mGy

The new estimate for solid cancer exceeds the value from the follow-up of the A-bomb survivors by at least a factor of 3. Since the low dose rate condition admits no reduction factor, *DDREF*=2, the difference to the current risk coefficient amounts actually to a factor of 6. If this result were confirmed, it would be a very major departure from current assumptions, with severe consequences for the practice of radiation protection. To illustrate the magnitude of the estimate, it suffices to note that the value *ERR*/Gy=1.5 corresponds (with the ICRP conversion to life-time attributable risk, but without *DDREF*) to a life-time attributable solid cancer mortality of 0.3/Gy, rather than the current ICRP estimate of about 0.05/Gy [19]. This risk coefficient would attribute a striking 12%–15% of the total cancer mortality to the life-time dose (about 100 mGy) from natural radiation exposure. It is clear that this would change judgments in radiation protection fundamentally.

Before a result with such implications is accepted, there is a need to explore possible confounders or sources of error. The first question is whether TRDS-2000 may have failed to account for a major external dose contribution. Two potential factors have been considered: either much higher than previously assumed atmospheric releases by Mayak or a high level of x-ray screening, with large doses from fluoroscopy, among the Techa river population. While these two confounders deserve consideration, it appears unlikely, in the absence of specific information, that they could have contributed sufficient collective dose to reduce the risk estimates by anything like a factor of 2.

There is, on the other hand, the likelihood that a major dose contribution from short lived fission products may have been missed in the Techa river dosimetry system; as N.A. Koshurnikova has argued, it would be difficult to explain any cases of the chronic radiation syndrome (CRS) solely on the basis of the highly protracted ^{90}Sr exposures. Vorobiova et al. [21] conclude from their review of historical monitoring data: "The results of measurements based on experimental techniques available in the early 1950's do not permit the satisfactory determination of radionuclide composition and gamma activity of the early releases from the Mayak complex". In consequence they based their assumptions on values in the 1956 doctoral thesis of D. I. Ilyin [30] who, as chief of the Mayak central laboratory, was familiar with the technological processes. While this was a natural procedure, it is apparent that it can not exclude a presently unaccounted for external and internal dose contribution in the critical period 1950 to 1952, when more than 98% of the liquid waste releases into the Techa took place. Such a contribution could resolve the incongruity, and the problem deserves therefore careful scrutiny. In this issue of *Radiation and Environmental Biophysics* a new approach to the Techa river dosimetry is presented by Y. Mokrov [31] which suggests that the dose contribution of the short-lived fission products has, indeed, been substantially larger in the early years than is assumed in the TRDS-2000. There is clearly a need for further investigations.

But what would the implication be if it turned out that there is no major flaw in the new dosimetry? Could there be other confounders? In the following it will be argued that high solid cancer risk estimates for the Techa riverside population need not necessarily invalidate current risk estimates, even if the present TRDS-2000 dose estimates were to be confirmed.

Possible limitation of the site-specific approach to risk estimation

Studies on radiation-induced cancer are focused on the interrelation between increased cancer rates and the dose to the tissue or organ where the tumour arises. This makes

sense, since it is plausible that cancer tends to arise from transformed cells in the relevant organs. If a specific organ is irradiated, tumour excess rates in this organ are related to the dose in the organ. If, as was the case in the A-bomb survivors, the dose is more or less uniformly distributed in the body, it is likewise natural to use the organ-specific dose as reference in the consideration of dose-effect relations. Except for tumours that depend on endocrine factors, such as breast or thyroid cancer [32, 33], the site-specific consideration is a natural point of view under most exposure circumstances. It has, thus, become an almost unreflected proposition, that specific tumour excess rates are accounted for in terms of organ-specific radiation doses. The definition by ICRP of the effective dose and the tissue weighting factors corresponds to this point of view [19].

The Techa river exposure situation was, of course, always recognised to be special, since the dose to the red bone marrow was largely due to internal exposure, while the soft tissue doses were primarily due to the external exposure. However, the two dose contributions appeared to be of roughly comparable magnitude and, knowing that on the cellular level there was no principal difference in radiation quality, one had little reason to depart from the accustomed organ-specific approach.

When the Techa river dosimetry was revised, this brought about a qualitative change, namely a much larger imbalance of bone-marrow and soft-tissue doses. With the new dosimetry the mean bone marrow doses are now 10 times larger than the mean soft-tissue doses (see Table 2). As pointed out in the preceding section, there may be a need to account for presently disregarded dose contributions from short-lived fission products. But even if this correction will be required, the ratio of bone-marrow to soft-tissue doses need not greatly decrease, because the short-lived ^{89}Sr could significantly increase the bone-marrow doses.

Under the condition of highly non-uniform radiation exposure there is a need to question the validity of the organ-dose specific approach to the derivation of risk estimates. Can observations at low soft-tissue doses be taken as representative, if obtained in a cohort with a much more serious insult to the red bone marrow? Can the possibility be excluded that the cancer rates in other organs are appreciably co-determined by the exposure of the bone marrow? A possible interdependence between bone-marrow damage and solid cancer rates could be too weak to be noted under normal exposure conditions, but it might still outweigh the direct effect, if the bone- marrow dose exceeds the organ dose by an order of magnitude.

Animal experiments with ^{90}Sr would be expected to provide some evidence, whether an indirect or *abscopal*[2] radiation effect exists with regard to tumour induction. A large number of such experiments have been performed in the past in different species including mice, beagles, minipigs, and monkeys (for a compilation and assessment of the literature see [18, 35]). Although these studies were designed to determine increases of bone cancer and leukaemia, even such increases have been difficult to observe within the limited numbers of animals, except at very high doses. Especially for bone cancer no excess was seen – in contrast to the experiments with ^{226}Ra – at doses up to about 20 Gy. While excess rates of malignancies were noted in several experiments in tissue near bone, the studies were not directed at the assessment of cancer rates in organs or tissues not directly exposed to the radiation. Experiments with minipigs exposed to dietary ^{90}Sr [36] were an exception, because they demonstrated an increase in general soft tissue cancer incidence. At the time this was attributed in part to blood-borne ^{90}Sr [18], i.e., the possibility of an abscopal effect was not considered.

In the absence of more informative experimental evidence, an indirect effect due to the internal exposure of the bone marrow by ^{89}Sr and ^{90}Sr cannot be postulated, but neither can it be excluded.

Changes of the immune status due to the bone-marrow exposure may be the most obvious possibility of an abscopal effect, since effects on the immune system are a prominent aspect in the health studies on the Techa river cohort [7]. Substantially increased rates of malignancies have recently been demonstrated in immune-suppressed renal transplant patients [37]. These observations contradict the earlier assumption that the immune system provides surveillance only against cancers caused by viruses. In the meantime, studies on knock-out mice have provided increasing evidence for a more general immunosurveillance against spontaneous and carcinogen-induced tumours [38, 39].

However there is another potential pathway. As Fliedner [40] relates, Alexander Alexandrovich Maximov, the founder of today's unified theory of haematology and then a young professor at the St. Petersburg Military Medical Academy, had the notion as early as 1909 of a "blood stem cell" with the potential to replicate, proliferate and differentiate into different cell lineages depending on local tissue conditions: "The easily transportable form, the small lymphocyte, circulates with the blood and lymph stream throughout the organism and is able to regain after a sufficient time lag of inactivity its full developmental potential" [41]. Maximov's prescient notion of what he had earlier termed the "wandering cells at rest" and "polyblasts" [42] has been strikingly confirmed in recent years. A large number of studies (see [43, 44, 45, 46, 47, 48, 49, 50, 51]) have made it clear that bone marrow stem cells are remarkably pluripotent, that a substantial fraction – of the order of 1% – circulates in the peripheral blood, and that they can migrate to various tissues to proliferate and differentiate there.

The idea of pluripotent blood stem cells – rejected for a long time by classical haematology – was initially brought back by experimental radiobiological research [52, 53, 54, 55]. Bond et al. [53] explained their observations: "The findings that histiocytes, or specific cells of the reticuloendothelial system, may be multipo-

[2] The term *abscopal* or "off-target" has been introduced by Mole [34] for a radiation effect in an organ that has not by itself been irradiated.

tential in character, and may be transported to needed sites normally via the blood stream, are pertinent in connection with protection against x-radiation by parabiosis and by regionally fractionated exposures". Since bone-marrow stem cells are involved in restitution processes in different tissues and organs, it appears equally likely that irradiated bone-marrow stem cells might initiate, through the same pathway, malignant growth.

As a matter of fact, the above mechanism has recently been invoked by Gössner et al. [56] for the induction of fibrosarcomas and malignant fibrous histiocytoma (MFH) of bone by internal emitters. They state that HLA-DR blood monocyte-like cells appear to turn into precursors of fibroblasts and chondrocyte-like cells through transdifferentiation. According to Labat et al. [57] these circulating monocytes are a subset of bone-marrow cells with similarities to pericytes which are primitive mesenchymal cells that are also potential precursors of fibrohistiocytic tumours. As Gössner points out in a new look at the pathogenesis of late radiation effects [58] there has for a long time been a reductionist focus upon a single target cell for a single tissue or organ, a focus that is likely to be broadened now to a more holistic view on synergistic morpho-functional tissue units. There is clearly a need for further exploration of the relevant cell and tissue interactions and of the challenges they present to dosimetry.

The possibility of an abscopal effect is, at this point, a merely speculative explanation of the high solid cancer-risk estimates among the Techa riverside population which correspond to the low external dose estimates in TRDS-2000. But – as has been stated – even if a correction for a higher contribution of short-lived fission products should be required in TRDS-2000, a large ratio between bone-marrow and soft-tissue doses might be retained, and the possibility of abscopal effects will then be of no less interest. There is thus reason to explore new radiobiological models, and risk-modelling computations will need to be performed that involve both the external and the internal doses. The Techa river study retains its exceptional status, but it poses profound questions with regard to radiation-risk assessment.

Conclusion

The Mayak nuclear workers are the one cohort that has provided information on late health effects in man due to the incorporation of plutonium. With regard to plutonium dosimetry the enormous data set [3, 25] from excretion measurements and from autopsies is an invaluable resource which offers, for the first time, the possibility to construct a reliable plutonium-dosimetry model. The task is evidently crucial to the evaluation of the Mayak health data. In addition, there is the important possibility to improve decisively the current ICRP model.

The excess lung-cancer rate from plutonium has been quantified in terms of the "core cohort" of workers with plutonium-excretion measurements and, in the most recent analysis, with accounting for smoking information. However, a majority of the Mayak workers of the plutonium facilities – many of them deceased – have not undergone plutonium-excretion measurements. Extending the analysis to include the much larger cohort of workers without plutonium measurements, will be a major challenge. This will require optimal algorithms to apply the work-place specific information from the measured group of workers to the dose estimation of the workers whose work-place history is known, but who have not undergone plutonium measurements.

The correlation of excess cancer risk with the γ-ray exposures has provided initial results that point to very low risk coefficients. However, the dose dependencies are still insufficiently quantified and, in addition, the results of the new external dose reconstruction need to be utilised, which will increase the risk estimates. In contrast to the Techa river cohort, there is little reason to consider a potential bias due to the bone-marrow exposure, because the doses to the bone marrow are not greatly in excess of the doses to the other organs. In addition, the comparative analysis of the different subcohorts makes it possible to recognise and quantify any bias, if it should exist. There is no doubt that the large number of reactor workers will be a highly important basis for obtaining low dose rate γ-ray cancer-risk estimates for the organs not exposed to the plutonium α-rays.

A dedicated effort over many years has made it possible to develop and secure essential dosimetric and epidemiological information for the Techa river study. While the complexity of the dose reconstruction and of the health follow-up was fully realised, it was felt – up to the recent past – that a successful solution of these problems might then provide rather straightforward risk estimates for low *LET* radiation and, thus, reliable conclusions on the dose and dose rate effectiveness factor (*DDREF*).

The high solid cancer risk estimate which is implied by the reduced external doses in TRDS-2000 directs attention to possible confounders. The need to assess possibly unaccounted for dose contributions and to exclude an effect modification due to the bone-marrow exposure makes the risk estimation by now less straightforward than earlier envisaged. This has made the work more difficult, but has not made it less important and it poses questions that may lead to basic new insights on radiation late effects.

It is apparent that the solid cancer risk estimates must, in terms of the TRDS-2000, exceed substantially the estimates that are derived from the A-bomb data. Both the dosimetric data and the health data will continue to evolve, but they are well beyond the stage of tentative exploration. Accordingly it needs to be acknowledged that current risk estimates and current assumptions on the dose-rate effect are at issue.

As is now demonstrated by Mokrov [31], the current dosimetry system appears to have missed a substantial external dose component from short-lived fission prod-

ucts in the first years of the reactor operation. In this context experimental dose reconstruction requires added attention. At present the limited number of luminescence measurements on quartz particles from bricks for external dose reconstruction does not show a major discrepancy to TRDS-2000 [24]. But many more of the measurements are required to make full use of their potential and to minimise the uncertainties in external dose estimation. Attention will also need to be given to the further use of bio-indicators, such as chromosome aberrations and EPR measurements in teeth. At the same time it will be crucial to make full use of the recent analyses at Mayak to assess the source term, i.e., the spectra of fission products in the liquid waste releases to the Techa river in the early years of operation of the Mayak facilities [21, 31, 59].

As has been pointed out, the familiar organ-dose specific approach to solid cancer risk estimation needs to be questioned with regard to the Techa river population. Abscopal effects – the analogue on the organ level of "bystander effects"– have, apart from endocrine effects on certain tumour entities, not been considered in epidemiological studies. But the issue requires attention. In particular the observed changes of immune status among the Techa riverside population [7] need to be reviewed in relation to the solid cancer incidence after radiation exposure. The issue of the *CRS* is of particular interest in this connection. The other potential pathway, the proliferation and transport via the blood stream of pluripotent bone marrow stem cells and their proliferation and differentiation in various organs and tissues, has become a topic of great interest in recent investigations. These processes need to be examined to explore whether or not irradiated bone marrow stem cells can contribute to malignant growth in the various organs.

The development of a definitive Techa river dosimetry system must retain high priority, but it may require several additional years. Since the published interim results suggest, together with the new dosimetry, much higher risk estimates than currently assumed, there can be no moratorium on the discussion of risk estimates from the Techa river follow-up. Thus, there is even at this point a need to explore in terms of cross-tabulated soft tissue and bone-marrow doses the association with the cancer incidence and mortality data. If the soft-tissue and the bone-marrow doses are not too narrowly correlated, direct evidence might so be obtained for or against bone-marrow exposure as a modifier of the solid cancer rates. But the uncertainties in the Techa river dosimetry must be kept in mind when the results are assessed.

The Mayak nuclear workers study and the follow-up of the Techa riverside residents are the two central parts of the Southern Urals studies, but there are additional current and potential investigations of importance. There is particular interest in the health follow-up of the Techa river off-spring cohort, and likewise in the extension of the Techa river study to the population in the East Ural Radioactive Trace [2]. It is also essential to continue the health follow-up of the Ozyorsk population and to reconstruct the dosimetry for this population [9].

M. F. Kisselev has outlined [25, 60] the potential of related research projects that can be initiated at other nuclear weapon centres of the former Soviet Union, such as Seversk (the former Tomsk-7) and Zhelesnogorsk (the former Krasnoyarsk-26). Such extensions will add considerable strength to the current investigations and can go a long way towards meeting in a joint international effort the responsibilities inherited from the conflicts and tragedies of the past.

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