

HEALTH EFFECTS OF LOW-LEVEL IONIZING RADIATION

BEIR V—the National Research Council's fifth committee on the biological effects of ionizing radiation—found the population's risk of injury to be somewhat larger than estimated previously.

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The effects of ionizing radiation have received greater study than those of any other environmental agent. Within months after Wilhelm Roentgen's discovery of the x ray in 1895, early radiation workers experienced injurious effects of overexposure to radiation. In the century since, the study of such effects has received continuing impetus from the expanding use of radiation in medicine, science and industry and from the peaceful and military applications of nuclear energy.¹

The study of radiation injury has spurred the evolution of principles and procedures for protection that have been valuable in addressing the health hazards of environmental agents of all types, including pesticides, heavy metals and various cancer-causing chemicals. The whole notion of quantitative risk assessment based on non-threshold models has its roots in efforts to estimate the genetic and carcinogenic risks of low-level radiation.

Although the effects of large doses of radiation are well documented, the choice of the appropriate dose-response model for use in estimating the health hazards of small doses remains controversial. The notion that there might be no threshold for certain biological effects of radiation dates from the 1940s, when experiments in genetics suggested that the frequency of mutations varied in proportion to the dose of x rays, without any threshold.² The resulting concern about the possibility of heritable damage to future generations from global nuclear weapons fallout prompted detailed reviews of the risks by various national and international groups of experts, beginning in the 1950s. Among these groups were the National Academy of Sciences–National Research Council

(1956), the Medical Research Council⁴ (1956) and the United Nations Scientific Committee on the Effects of Atomic Radiation⁵ (1958).

Since those reviews, evidence implying that there might be no threshold for the carcinogenic effects or teratogenic effects (that is, those causing abnormal growth or structure) of radiation has further heightened public concern, prompting recurrent reevaluations of the pertinent data. The conclusions and implications of the most recent such reevaluation, the so-called BEIR V report of the NAS–NRC Committee on the Biological Effects of Ionizing Radiations,⁶ are the subject of this article.

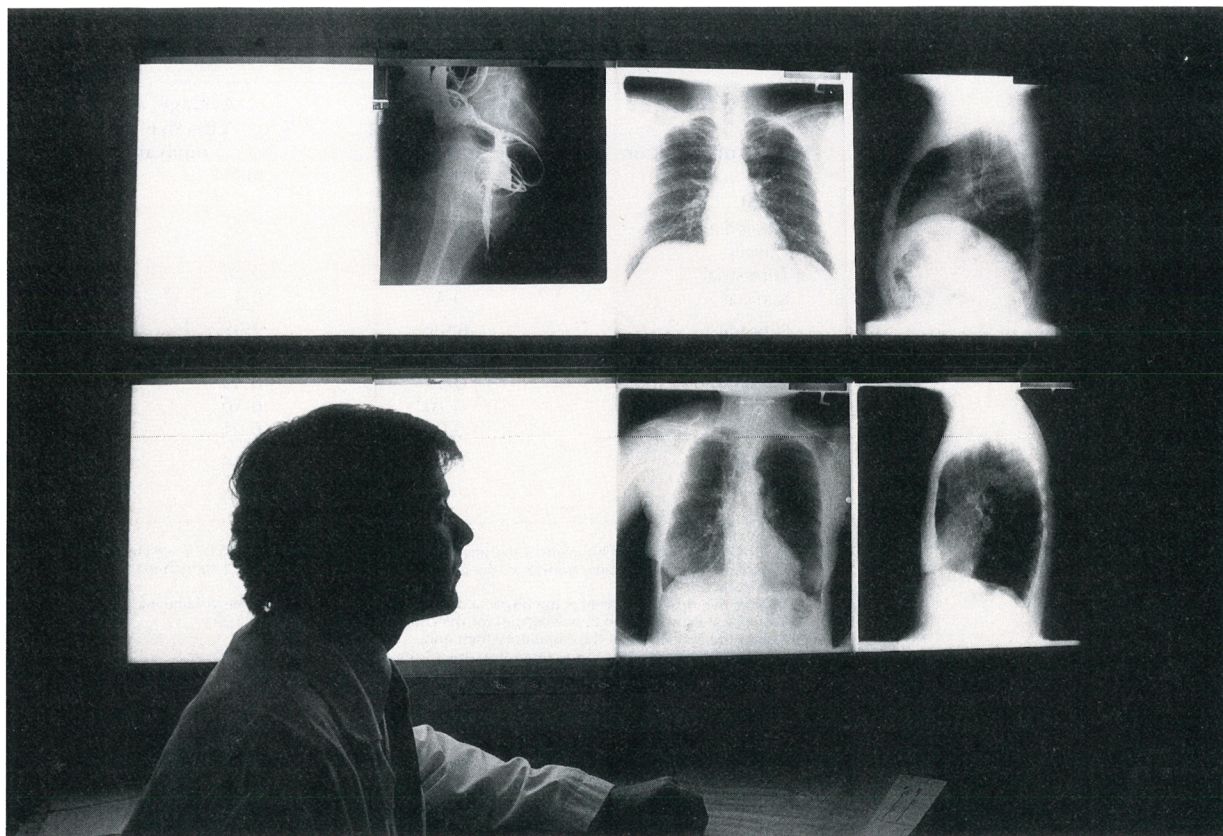
Major types of radiation injury

In contrast to the other forms of radiation, ionizing radiation has the capacity to break chemical bonds; it imparts its energy to living cells through random interactions with atoms, giving rise to ions and reactive radicals. These, in turn, cause molecular changes that may lead ultimately to biological injury.⁶

The spatial distribution of ionization events along the path of an impinging particle depends on its energy, mass and charge, as well as on the density of the absorbing tissue. X rays and gamma rays are, in general, sparsely ionizing—that is, they are characterized by a low rate of linear energy transfer—whereas charged particles are typically densely ionizing. Because the probability of biological injury increases with the extent of damage to critical molecules within the cell, the relative biological effectiveness of high-LET radiations such as protons and alpha particles generally exceeds that of low-LET radiations such as x rays and gamma rays.

A sufficiently large dose of radiation will kill any living organism. A dose to the human body of 0.5–1.5 grays will cause radiation sickness.⁷ (The gray is the SI

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X-ray images under review by a radiologist. Medical diagnostics expose the average American to 0.53 millisievert of ionizing radiation annually.

unit of absorbed dose; $1 \text{ Gy} = 1 \text{ J/kg} = 100 \text{ rads}$.) Exposure to a smaller dose can cause any of a wide variety of injuries, depending on the conditions of irradiation.

For those types of injury that result from the killing of substantial numbers of cells in the affected organs—injuries such as depression of the blood count, impairment of immunity or reduction of fertility—threshold doses exist below which such injuries are not detectable.⁸ In contrast, for those types of injury that are known or presumed to result from damage to individual cells—injuries such as gene mutations, chromosome aberrations or malignant transformations—the frequency of injury is assumed to increase with increasing dose without any threshold.^{6,7} Injuries of the latter type are therefore viewed as “stochastic” phenomena, the frequency of which may depend in small part on low-level natural background radiation (see table 1).

Genes. Although any molecule in the cell can be altered by irradiation, DNA is the most critical molecular target because damage to a single gene may kill or profoundly alter the cell. A dose of x radiation large enough to have a high probability of killing a cell—1–2 Gy, for example—produces dozens of lesions in the cell’s DNA molecules; however, most of the lesions are in principle repairable. Hence the fate of a given DNA lesion depends heavily on the success with which it is repaired.

Since Hermann J. Muller’s pioneer observations on the genetic effects of x rays in the fruit fly, the mutagenic effects of radiation have been documented in many types of organisms. At a particular genetic locus, the frequency of mutations has generally been observed to increase in proportion to the dose of radiation, at least

over the low-to-intermediate dose range. This relationship implies that a mutation can result from traversal of the gene by a single ionizing particle. In a variety of mammalian cells, including human lymphocytes, human red blood cell precursors, mouse spermatogonia and mouse oocytes, the frequency of mutations⁷ induced at a given locus by acute irradiation is about 10^{-5} – 10^{-4} per cell per sievert. (The sievert is the SI unit of dose equivalent, which is the product of the absorbed dose and the biological effectiveness of the type of radiation; $1 \text{ Sv} = 1 \text{ J/kg} = 100 \text{ rem}$.) However, radiosensitivity varies markedly among germ cell maturation stages, complicating extrapolation from one age, sex or species to another.⁹ Moreover, the reduced frequency of mutations per unit dose seen at low doses and low dose rates of gamma radiation in some types of cells (mouse spermatogonia, for example) implies that the premutational damage resulting from traversal by a single photon track is partially repairable in such cells.

No increase in the frequency of inherited abnormalities has been detectable thus far in the children of the A-bomb survivors, but owing to the limited numbers of children and the relatively small average dose of A-bomb radiation received by their parents, the absence of a detectable increase is not inconsistent with the mutation rate observed in animal experiments.^{6,9} On the basis of the animal data, it is estimated that a dose of more than 1 Sv would be required to double the frequency of heritable mutations in human germ cells, from which it may be inferred that less than 2% of all genetically related diseases in the human population are attributable to natural background radiation (see table 2).

Table 1. Ionizing radiation received by US population^a

Source of radiation	Average annual dose equivalent to soft tissue ^b	Average annual effective dose equivalent ^c	
	(mSv)	(mSv)	(% of total)
Natural			
Inhaled (radon)	24 ^d	2.0	55
Cosmic	0.27	0.27	8
Terrestrial	0.28	0.28	8
Internal	0.4	0.4	11
Subtotal	0.95 ^e	2.95	82
Artificial			
Medical	0.53	0.53	15
Consumer products	0.10	0.10	3
Other	0.01	0.01	0.3
Subtotal	0.64	0.64	18
Total		3.59	100

^a Per capita. From ref. 6.^b The dose equivalent in millisieverts is the physical dose in milligrays multiplied by a weighting factor that depends on the linear energy transfer of the particle. The factor varies from 1 for gamma rays to 20 for alpha particles.^c The effective dose equivalent is the physical dose equivalent weighted for the volume and radiosensitivity of the tissue exposed, and thus weighted for the consequent probability of injury.^d Dose to the epithelium of the respiratory tract only.^e Excluding dose equivalent to the respiratory tract from radon and its daughters.

Chromosomes. Radiation can cause the breakage and rearrangement of chromosomes, and it can interfere with the normal segregation of chromosomes to daughter cells at the time of mitosis, or cell division, thus altering the number and structure of chromosomes in the cell. Within the low-to-intermediate dose range, the frequency of radiation-induced chromosome aberrations increases in proportion to the dose. In human blood lymphocytes irradiated in culture, the rate of increase is approximately 0.1 aberration per cell per sievert. The frequency of aberrations as a function of dose in such cells has been characterized well enough for the cytogenetic analysis of circulating blood lymphocytes to serve as a crude biological dosimeter in radiation accident victims.¹⁰

Cells, tissues and organs. The effects of radiation on cells, tissues and organs include a wide diversity of reactions, varying markedly in their manifestations and time courses.⁸ Inhibition of cell division, for example, may be detectable microscopically almost immediately after

intensive irradiation, while tissue breakdown, scarring and other degenerative changes are not characteristically observed until weeks, months or years later. In general, cells are more sensitive to radiation while they are dividing than between divisions.

The percentage of cells that retain the ability to divide tends to decrease exponentially with increasing radiation dose, with a dose of 1–2 Sv generally sufficing to halve the number. When radiation is absorbed in small increments over an extended period rather than in a single brief exposure, a larger dose is usually tolerated, owing to compensatory repair of radiation injury between exposures.⁸

In tissues whose cells must be continually replaced through the proliferation of other cells, irradiation can interfere with normal renewal by killing dividing cells, thus giving rise to tissue breakdown and impairment of tissue function. In general, relatively large doses are required for significant loss of function, and so the low

Table 2. Heritable diseases due to background radiation^a

Type of genetic disease or detriment	Natural prevalence	Contribution from natural background radiation ^b	
		First generation	Equilibrium generations
Dominant and X-linked diseases	10 000	20–105	300
Recessive diseases	2 500	3	45
Chromosomal abnormalities	4 000	6	3
Congenital abnormalities	20 000–30 000	30	30–300
Diseases of complex inheritance			
Heart disease	600 000	Not estimated	
Cancer	300 000	Not estimated	
Selected others	300 000	Not estimated	

^a Estimates of the contribution of background ionizing radiation to the burden of heritable diseases in the general population. Numbers are cases per million live-born; values are rounded. From refs. 6 and 7.^b Average dose equivalent to gonads of 0.95 mSv per year (see table 1), or about 28 mSv per generation (30 years).

levels of radiation that meet contemporary exposure limits for radiation workers do not produce gross tissue injury.⁵

Embryo. Prenatal irradiation at critical stages of organ formation in the embryo can disturb normal growth and development. Such effects have been observed after doses of less than 0.25 Sv in experimental animals and after only slightly larger doses in children.⁹ Dose-dependent disturbances in brain development, including, for example, severe mental retardation, and in IQ scores and school performance have been observed in those children of atomic-bomb survivors who were between the 8th and 15th weeks of prenatal development (and, to a lesser extent, between the 16th and 26th weeks) at the time of irradiation.^{6,9} Although the data do not suffice to define precisely the threat that small doses of radiation pose to the developing brain, they imply that the risks of injury to the developing embryo are larger than have been estimated heretofore, and they underscore the need to minimize the radiation exposure of the embryo and fetus.⁶

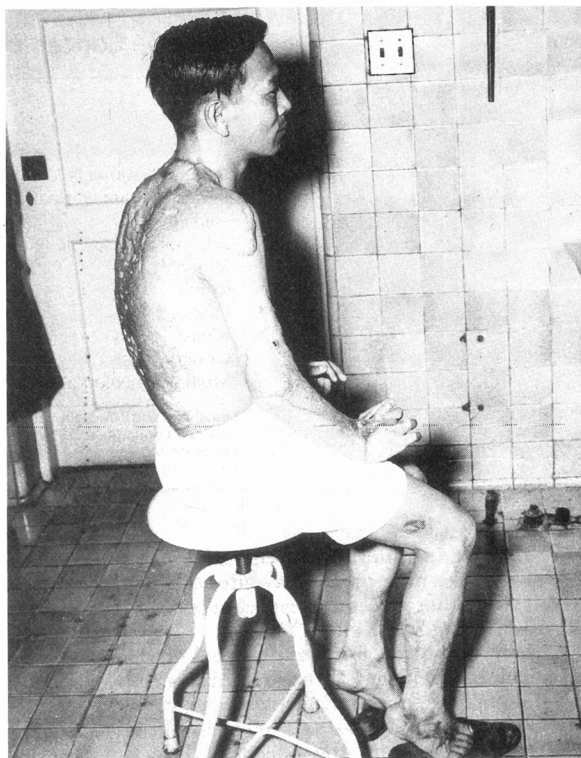
Effects on cancer incidence

Epidemiological studies of the atomic-bomb survivors, patients exposed to radiation for medical purposes and other irradiated populations indicate that radiation can increase the frequency of many types of human cancer, depending on the conditions of exposure. (Table 3 gives some examples taken from the A-bomb survivor studies.) The cancers induced by radiation do not appear until years or decades later, however, and they are indistinguishable from those induced by other causes. Moreover, with few exceptions the increased rates of cancer have been evident only after relatively large doses—on the order of 0.5–2.0 Sv. For most types of cancer, we have only fragmentary information about the relationship between dose and incidence.^{6,7}

The dose-incidence data for leukemia are more extensive than those for most other types of cancer. They imply that during the first 25 years after irradiation the incidence of this disease varies as a linear-quadratic function of the radiation dose to the bone marrow, resulting in approximately 2–3 additional cases of leukemia per year per 10 000 persons at risk per sievert. However, different types of leukemia increase differently for the same dose, age at irradiation and time after exposure, and no increase in the incidence of chronic lymphatic leukemia has been detected.⁶

Substantial dose-incidence information is also available for breast cancer. The incidence appears to increase in proportion to the dose, and the rate of increase appears to be roughly the same whether the dose is absorbed instantaneously, as in the atomic-bomb survivors, or over many months, as in women subjected to multiple fluoroscopic examinations of the chest during treatment for pulmonary tuberculosis.⁶ The additivity of widely spaced small exposures implies that there may be relatively little repair of precarcinogenic damage in the breast, and thus little if any threshold for carcinogenic effects on this organ.⁶

The incidence of thyroid cancer is increased in A-bomb survivors, persons who were treated with x rays for ringworm of the scalp in childhood, persons who were treated with x rays to the neck in infancy for enlargement of the thymus gland or other benign conditions, Marshall Islanders exposed to nuclear fallout and various other acutely irradiated populations. However, no such increase in incidence has been detected^{6,7} in persons exposed to diagnostic doses of iodine-131. The data have been interpreted⁶ to indicate that the risk of thyroid cancer increases as a linear, nonthreshold function of the



Survivor of the Hiroshima atomic bomb. Kiyoshi Kikkawa was photographed at a hospital in Kyoto 27 months after the explosion. Studies of the A-bomb survivors have played a big role in estimates of the risks of exposure to ionizing radiation.

dose, but that the rate of increase varies depending on age, sex and type of radiation, with females being roughly twice as susceptible as males, children twice as susceptible as adults, and rapidly delivered x rays three or more times as effective as radiation from iodine-126 or iodine-131. In the population as a whole, the average lifetime risk is estimated⁶ at 7.5 fatal thyroid cancers per 10⁴ persons per gray.

During prenatal life, susceptibility to radiation-induced carcinogenesis appears to be relatively high, judging from the elevated risk of leukemia, and possibly other childhood cancers, observed in children who were exposed to x rays prenatally in the course of radiographic examinations of their mothers.^{6,7} The risk of childhood cancer is also elevated in association with increased irradiation from environmental sources, both natural and man-made, but the evidence for a causal relationship is inconclusive.⁶ The hypothesis that irradiation of a child's parents also increases his or her risk of cancer, through effects transmitted via the germ cells, has been suggested to account for the "cluster" of childhood leukemia cases in the neighborhood of the Sellafield nuclear plant in the UK.¹¹ However, the incidence of cancer is not detectably increased in the children of the atomic-bomb survivors,¹² and the rate of transmission via the germ cells implied by this hypothesis is not consistent with the observed dose-response relationships for mutations or other hypothetical mechanisms of germ-cell-mediated carcinogenesis.¹³ Also implicating some cause other than radiation for the excess of childhood leukemia noted around Sellafield and certain

Table 3. Cancer deaths in A-bomb survivors^a

	Total	Control subjects	Subjects exposed to ≥ 0.01 Gy ^b	Estimated no. attributable to exposure ^c
Number of subjects	75 991	34 272	41 719	—
Number of cancer deaths				
Leukemia	202	58	144	80
All cancers except leukemia	5 734	2 443	3 291	260
Stomach	2 007	854	1 153	73
Colon	232	103	129	19
Lung	638	253	385	44
Breast	155	57	98	22
Urinary tract	133	49	84	19
Multiple myeloma	36	13	23	7

^a Hiroshima and Nagasaki bombs; data from 1950–85. From ref. 19.

^b Shielded kerma dose, 1986 dosimetry system. The kerma ("kinetic energy released in material") is a unit of exposure and is expressed in grays. The average dose in this group was 0.30 Gy.

^c Based on comparison of observed numbers of deaths with number expected.

other nuclear installations in the UK is the finding of similar excesses near prospective sites of nuclear plants¹⁴ as well as in other places experiencing population influxes like those around such sites.¹⁵

In the absence of more precise knowledge of the biological mechanisms through which small doses of radiation may exert carcinogenic effects, we can estimate the risks of cancer attributable to low-level radiation only by extrapolation from the effects of larger doses. In analyzing the relationship between the mortality rates from various forms of cancer and such factors as age at irradiation, time after irradiation, sex and dose, the BEIR V committee depended heavily on data derived from study of the A-bomb survivors, since that population is large and includes persons of both sexes and all ages who were exposed to an unusually wide range of doses.⁶

For leukemia, the committee found that a linear-quadratic model fit the available dose-response data better than any other model. For all types of cancer other than leukemia, however, the committee preferred a linear dose-response model, because no significant departure from linearity was discernible in the relevant dose range. The committee recognized, however, that the risks at low doses and low dose rates might be smaller than projected by the linear model, and it acknowledged that "for low-LET radiation, accumulation of the same total dose over weeks or months . . . is expected to reduce the lifetime risk appreciably, possibly by a factor of 2 or more." The committee made no attempt to specify more precisely the

degree to which the risks might be reduced, because it was unable to find any basis for doing so that could be justified scientifically. However, from its review of data on populations exposed to low-level occupational or environmental radiation, the committee was unable to rule out the possibility "that there may be no risks from exposures comparable to natural background radiation."⁶

Caution justified

Taken at face value, the BEIR V estimates imply that no more than 3% of all cancers in the general population are attributable to natural background radiation. (See the second row in table 4.) However, the estimates also imply that inhalation of radon may cause up to 20% of lung cancers in *nonsmokers*, and that the lifetime cancer risks of those exposed to radiation occupationally may also be significantly increased. (See the third row in table 4.) Thus, the estimates provide justification for efforts to minimize unnecessary exposure to ionizing radiation. At the same time, they imply that the risks associated with small increases in background radiation—such as may exist in the vicinity of nuclear plants—are likely to be too small to be detectable epidemiologically, a conclusion in keeping with the negative findings of the latest study of cancer rates around nuclear installations in the US.¹⁶

Table 4. Risk of radiation-induced cancer^a

Radiation exposure	Excess fatal cancers	
	(per 100 000 persons exposed)	(% of normal expectation)
Single, brief exposure to 0.1 Sv (10 rem)	790	17
Continuous lifetime exposure to 1 mSv/yr (0.1 rem/yr)	560 ^b	3
Continuous exposure to 0.01 Sv/yr (1 rem/yr) from age 18 until age 65	3000 ^b	16

^a Projected lifetime risk of cancer from whole-body irradiation. From ref. 6.

^b Value likely to be an overestimate because it includes no allowance for reduced carcinogenicity of radiation at low dose rates.

Table 5. Historical evolution of risk estimates

Source of estimate	Deaths per 10 000 persons ^a	
	Additive risk projection model ^b	Multiplicative risk projection model ^c
BEIR I, 1972 (ref. 20)	120	620
UNSCEAR, 1977 (ref. 21)	100–260	—
BEIR III, 1980 (ref. 17)	80–250	230–500
NRC, 1985 (ref. 22)	290	520
UNSCEAR, 1988 (ref. 7)	400–500	700–1100
BEIR V, 1990 (ref. 6)	—	885

^a Lifetime excess cancer mortality attributable to 1 Gy of rapid, whole-body, low-linear-energy-transfer irradiation. Values rounded.

^b Assumes that excess mortality from cancer caused by a given dose of radiation is expressed as a constant number of extra cancer deaths per year, irrespective of the underlying spontaneous rate in the population.

^c Assumes that excess mortality is expressed as a constant percentage of the underlying rate, which generally increases exponentially with advancing age.



In a commercial airliner, passengers receive a radiation dose equivalent of about 2 microsieverts per hour during a subsonic flight at an altitude of 8 km. Flight crew members receive about 1 millisievert per year. (For comparison, the dose from a diagnostic chest x ray is on the order of 0.1 mSv.)

The BEIR V cancer risk estimates are several times higher than those published a decade earlier by the BEIR III committee.¹⁷ (Table 5 compares the BEIR V estimates with those from several earlier studies.) There are three main reasons for this:

▷ revised estimates of the radiation doses received by the A-bomb survivors

▷ increase with time in the annual excess cancer mortality in the A-bomb survivors, especially those irradiated at young ages

▷ evidence that mortality from cancers other than leukemia in the A-bomb survivors has increased more steeply with dose than envisaged previously⁶ (that is, as a linear function rather than as a linear-quadratic function).

However, the new estimates do not differ greatly from those that the United Nations Scientific Committee on the Effects of Atomic Radiation and the BEIR I committee derived through the use of risk models analogous to the one used by the BEIR V group. It remains to be seen whether the relative risk of cancer will remain as persistently elevated in those irradiated at young ages as the BEIR V model projects. If it does not remain elevated to the extent projected, as some studies predict, then the smaller lifetime risk estimates projected by models of the additive type (see table 5) may ultimately prove to be more accurate.

Pending a more complete understanding of the biological effects of low-level ionizing radiation, the risk estimates of the United Nations Scientific Committee on the Effects of Atomic Radiation and the BEIR V committee provide a reasonable basis for public health policy. They reaffirm the wisdom of two basic tenets of radiation protection:

▷ Because exposure to any amount of radiation may carry some risk of harm, no exposure can be considered permissible unless it is associated with a commensurate benefit.

▷ The dose to any exposed person should be kept as low as is reasonably achievable, all relevant social and economic factors considered.¹⁸

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