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METHODOLOGY OF CELLULAR LUNG DOSIMETRY FOR INHALED ALPHA-EMITTING RADIONUCLIDES*

Methodisches zur zellularen Lungendosimetrie für inhalierte alphastrahlende Radionuklide

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Summary

Biological radiation induced effects in the lungs due to inhaled alpha-emitting radionuclides are caused primarily by highly localized energy deposition of alpha particle tracks at the cellular level. In order to establish a dose-effect relationship between macroscopically observable biological effects in the lung tissue, e. g. lung cancer, and the absorbed dose it is necessary to determine the cellular dose for different parts of the lung. The basis of all calculations presented are randomly selected tissue slices and LUMO — a computer model developed for deposition and retention of inhaled radionuclides in the respiratory tract. The dose absorbed in different types of cells hit by alpha particles depends on cellular physiological and alpha particle parameters, e. g. cell size, cell turn-over-rate, track length, linear energy transfer (LET) and hit probability. With the use of these above data the cellular dose was calculated for various cell types in different regions of the lung. Previous results from conventional lung dose calculations with the ICRP-compartment model, neglecting the fine structure of biological target, nuclide deposition and energy absorption, are compared to these individual cellular doses. As an example, several selected cases, such as chronic low-level exposure and short-term therapeutic inhalation of ^{222}Rn and its short-lived decay products are discussed.

Zusammenfassung

Biologische strahleninduzierte Effekte in der Lunge, hervorgerufen durch inhalierte alphastrahlende Radionuklide, beruhen vor allem auf der eng lokalisierten hohen Energieabgabe der Alphateilchen auf zellularer Ebene. Zur Her-

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stellung einer Dosis-Effekt-Beziehung zwischen dem biologischen, makroskopisch beobachtbaren Effekt im Lungengewebe, wie z. B. Lungenkrebs, und der absorbierten Dosis ist es notwendig, die zellularen Dosen in verschiedenen Teilen der Lunge zu bestimmen. Grundlage der vorliegenden Berechnungen sind ausgewählte Gewebeschnitte und LUMO — ein Computermodell zur Berechnung von Deposition und Retention inhalierter Radionuklide im Atemtrakt. Die in den einzelnen Zellen infolge von Bestrahlung mit Alphateilchen absorbierte Dosis hängt von verschiedenen physiologischen Zellparametern, wie Größe der Zelle, Zellteilungsrate und den physikalischen Eigenschaften der Alphastrahlung, z. B. Bahnlänge, linearer Energietransfer (LET) und Trefferwahrscheinlichkeit ab. Unter Verwendung dieser Daten wurden die zellularen Dosen für einige Zelltypen in verschiedenen Lungenabschnitten berechnet. Ergebnisse früherer Lungendosisberechnungen mit dem ICRP-Compartmentmodell, das die Feinstrukturen von biologischem Target, Nuklidablagerung und Energieabsorption nicht berücksichtigt, werden mit den individuellen Zelldosen verglichen. Als Anwendungsbeispiel werden verschiedene ausgewählte Fälle, wie z. B. chronische Bestrahlung mit niedrigen Dosen oder therapeutische Kurzzeitbestrahlung mit ^{222}Rn und seinen kurzlebigen Zerfallsprodukten diskutiert.

Introduction

The initial phase of every biological radiation induced effect is characterized by the primary physical interaction of the ionizing radiation with the biological object at the cellular level. In order to establish a dose-effect relationship between biological effects and the radiation dose it is necessary to know the distribution of energy absorbed in the single cells. The basis for the determination of the energy distribution of inhaled nuclides in the lungs — contrary to external irradiation — is the detailed knowledge of the microdistribution of the deposited radionuclides in relation to the irradiated biological target. Biological effects are then the result of the superposition of the microdistribution and the distribution of the radiation sensitive sites. In particular in the case of the short-range alpha radiation with a highly localized energy deposition over several cellular diameters, any macroscopically observable biological effect, e. g. lung cancer induction depends to a large extent on the degree of this congruence.

^{222}Rn and its short-lived decay products RaA (^{218}Po), RaB (^{214}Pb) and RaC (^{214}Bi), resp. RaC′ (^{214}Po) play an important role in the natural radiation burden of a population (POHL et al. 1976). Ocurring anywhere in the atmosphere of our environment, indoors as well as outdoors, they are inhaled and — in the case of decay products — deposited throughout the respiratory tract. The radiation effects of these nuclides are caused primarily by the alpha radiation emitted by RaA and RaC′ The most important cells in the lungs from a radiation protection point of view are the basal cells of the bronchial epithelium which are regarded as the critical cells for the initiation of bronchial carcinoma. Receiving high doses even in a normal natural radioactive environment the radiation risks are com-

paratively higher for people living in elevated areas, e. g. in radon spas (POHL 1979).

Dosimetric method

Conventional lung dosimetry is based primarily on the ICRP-compartmental lung model as proposed by the ICRP Task Group on Lung Dynamics (1966). This model takes into account deposition for different particle sizes and defines three classes of retention reflecting the chemical form of the aerosol. The respiratory tract is divided into three regions, nasopharyngeal, tracheobronchial and pulmonary compartment. In the recent ICRP publication 30 (1979) the commission considers that in adults, for the purpose of radiological protection, this model will be useful for research in view of the many uncertainties involved, e. g. the precise location of the cells at risk. For the induction of malignant disease it is supposed that the hazard of radioactive particles deposited inhomogeneously in the lung is likely to be less than of the same amount of nuclides distributed uniformly. Therefore, according to the theory of compartmental systems this model neglects the fine structure of nuclide deposition on the airway surfaces, the specific location of the radiation sensitive target and the inhomogeneity of the energy deposition along the particle track through different cell structures.

In order to reveal subtile biological cellular effects as a function of the absorbed dose it is, however, necessary to refine the existing ICRP dose calculations. Therefore, a dosimetric method for inhaled alpha-emitting nuclides in the lung was developed, based on cellular dosimetry (Fig. 1). The basis of these dose calculations are randomly selected tissue slices and LUMO — a computer

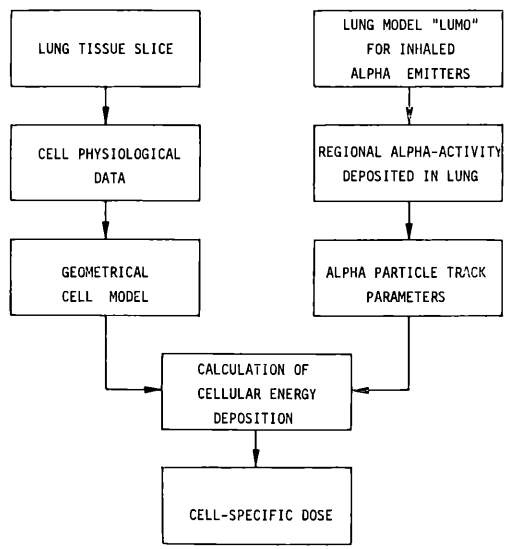


Fig. 1: Scheme for cellular lung dosimetry after inhalation of alpha emitting radionuclides

lung model for deposition and retention of inhaled radionuclides in the human respiratory tract (HOFMANN et al., 1977). Cell physiological data for a geometrical cell model were derived from the quantitative analysis of tissue slices by light microscopy. The regional alpha activity deposited in different parts of the lung was determined with the aid of the lung model LUMO, defining the number and physical properties of alpha particle tracks emitted by the nuclides deposited. With these two data pools the energy deposited in the single cells and the resulting cell-specific doses were calculated.

Tissue and cell characteristics

Cellular lung dosimetry is based on tissue slices of the lung. For the determination of the dose in a defined region of interest the respective tissue slices have to be selected. Since no slices of a healthy human lung were available for this simulation procedure, the relevant information was taken from the literature (STÖHR et al., 1969). Fig. 2 shows as an example of the cellular arrangement in tracheobronchial and alveolar parts of the human lung a tissue slice selected for all following calculations. It represents the region of the human lung where the transition occurs from terminal bronchus (1) to respiratory bronchus. Also the end of the respiratory epithelium (2) at the beginning of the

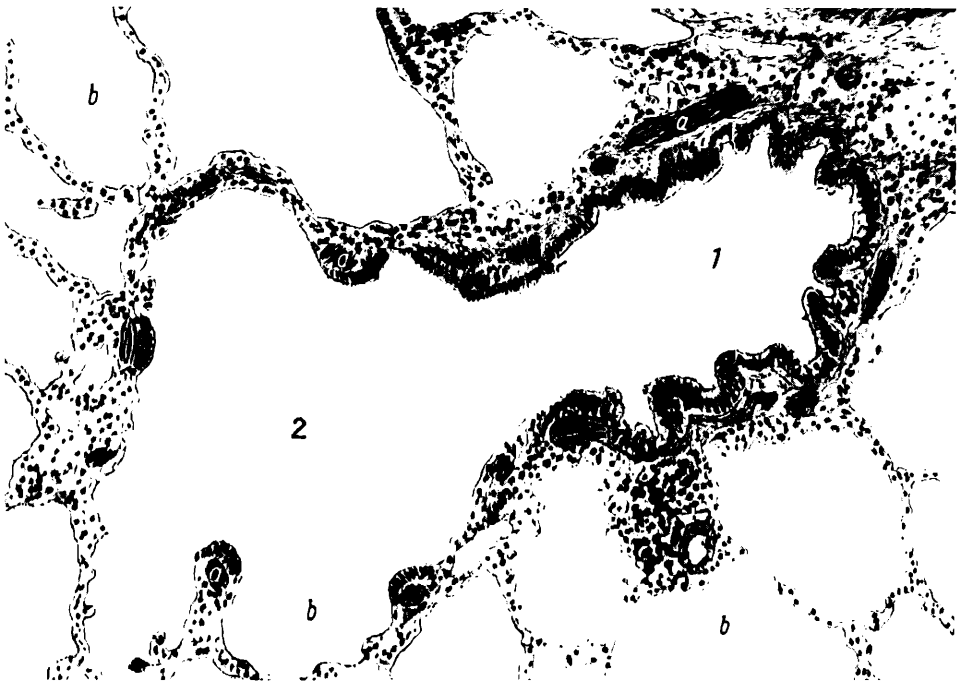
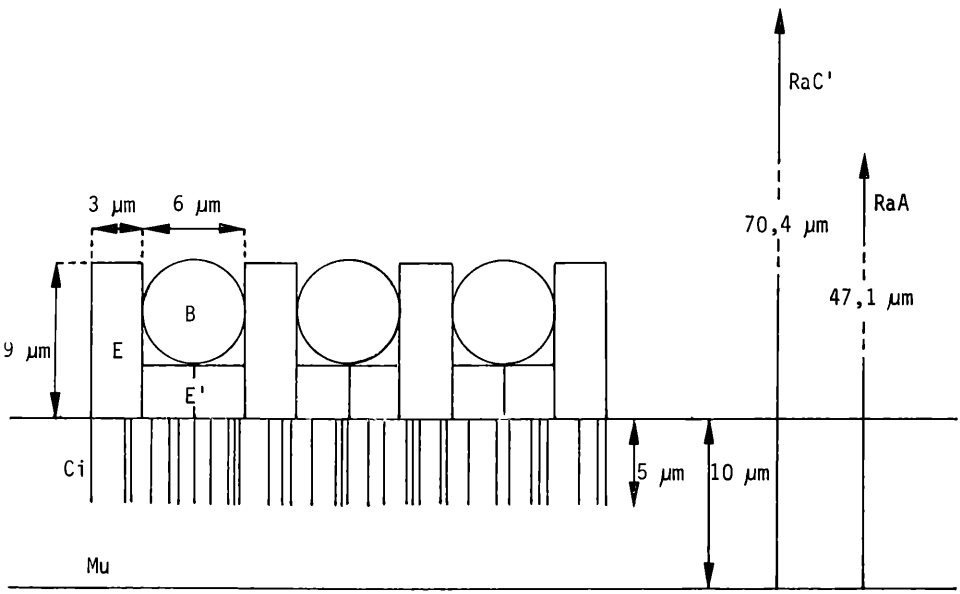


Fig. 2: Human lung (magnifaction 110 1). Transition from terminal bronchus (1) to respiratory bronchus. (2) End of respiratory epithelium at the beginning of alveoli (b)

alveoli can be seen in this figure. Numbers 1 and 2 indicate the regions for which the dose was calculated.

The results from statistical analysis of all tissue and cell parameters, such as cell diameter and cell volume, using light microscopy were used for the development of a geometrical model for different cell types of interest (Fig. 3). For a simplified description of the tissue structure for modelling purposes the terminal bronchial epithelium was defined to consist of cylindrical epithelial cells and spherical basal cells (BYKHOVSKII et al. 1972, STÖHR et al. 1969). The basal cells are of special importance for the radiation protection of man, since they are regarded as the critical cells for lung carcinogenesis. The remaining cells of this tissue section, including ciliated and nonciliated cells, e. g. ciliated epithelial, goblet and Clara cells, are all summarized as epithelial cells. Mucus layer thickness for the terminal bronchial region was assumed to be 10 µm, derived from a mean, distance of the basal cells from the mucus layer surface of about 20 µm (JACOBI and SCHRAUB 1974). For a better comparison of the linear dimensions of tissue structure and particle tracks the ranges of alpha particles emitted by RaA (6.0 MeV) and RaC′ (7.69 MeV) are also included in this figure.



E, E'	EPITHELIAL CELLS	Ci	CILIA
B	BASAL CELLS	Mu	MUCUS LAYER

Fig. 3: Simplified geometrical model of the bronchial epithelial tissue (terminal bronchus)

In the alveolar region a matrix of spherical cells in a close-packed structure was assumed (TISLJAR-LENTULIS et al. 1976). From the tissue slices described above a mean cellular diameter of 13 μm was derived for those cells.

For the determination of the cell turn-over-rate data in the literature compiled by BURRI and WEIBEL (1977) were used. From these data a mean turnover-rate of 100 days for an adult was calculated for all cells investigated.

Nuclide deposition and track formation

Deposition and retention of inhaled particles in the human respiratory tract are functions of various superimposed and interacting anatomical, physiological and aerosol-specific parameters. In order to simulate their mutual influence on the resulting particle distribution a multiparameter deposition and retention model for inhaled alpha-emitting radionuclides, called LUMO, was developed (HOFMANN et al. 1977, HOFMANN 1978, HOFMANN et al. 1979). The anatomical basis for this computer model is the model of an adult lung as proposed by WEIBEL (1963), denoted as model A for regular dichotomy. In this model the respiratory tract is divided into 24 generations, starting with the trachea as generation O up to the alveolar sacs as the 23rd generation. For modelling purposes the spherical alveoli, lining the respiratory airways from generation 17 to 23 were considered as generation 24. The single airways are represented as cylindrical tubes of specified diameters and lengths, branching at fixed angles into two further tubes. The regions of interest in the selected tissue slice can be identified now as generation 16 (region 1) and generation 23 (region 2). These anatomical data together with physiological parameters, such as respiratory frequency and tidal volume, show a significant dependence of age, sex, weight, body length and physical activity, influencing particle deposition to a large extent.

Table 1

Particle size distribution of radon decay products attached to the natural aerosol

Range of particle radius r (μm)	Mean particle radius r (μm)	Fraction of aerosol (%)	Mean diffusion constant ($cm^2\ s^{-1}$)
0.006—0.02	0.013	22	$8.0\ 10^{-5}$
0.020—0.04	0.030	26	$1.6 . 10^{-5}$
0.040—0.06	0.050	18	$7.5\ 10$
0.060—0.08	0.070	11	$4.0\ 10^{-6}$
0.080—0.10	0.090	8	$2.7\ 10^{-6}$
0.100—0.20	0.150	12	$1.2 . 10^{-6}$
> 0.2	0.300	3	$5.0\ 10^{-7}$
Free ions	0.0005	—	$5.4\ 10^{-2}$

Fractions of free ions: RaA: 20 %, RaB: 2 %, RaC: all attached.

Deposition in the single regions of the respiratory system is a function of the particle size of the inhaled aerosol. Table 1 shows the particle size distribution of the radon decay products attached to the natural aerosol used for these calculations. For the computational procedure this distribution was divided into seven particle ranges, represented by a mean particle radius and a mean diffusion constant. The uncombined fractions were assumed as 20 % for RaA and 2 % for RaB whereas all RaC nuclides are attached to the aerosol.

With these data on lung anatomy, lung physiology and defined radioactive aerosol characteristics deposition in the single generations of the respiratory tract was calculated for diffusion, sedimentation and impaction. For particle sizes as they are given in Table 1 diffusion is the main physical process governing particle deposition. After the deposition of the aerosol and the beginning of clearance processes dynamic equilibrium conditions are reached determining the amount of material retained in the various generations. This equilibrium results from activity deposited, radioactive decay, mucus transport and biological clearance into blood and lymph system. The surface activities of the decay products in the single generations, especially generations 16 and 23 of the tissue slice can be described mathematically by a set of interlinked linear differential equations assuming first order kinetics in the compartmental lung model.

In the case of heavy ionizing particles, such as alpha particles, radiation energy is deposited in form of straight tracks of defined range with a high ionization density. The LET of the alpha particles emitted by RaA and RaC′ as well as their ranges in tissue equivalent material (47.1 μm, resp. 70.4 μm) were derived from data of WALSH (1970). For a 5 MeV-alpha particle the track radius, defined by the range of the most energetic δ-electrons, is about 130 nm.

Dose calculations

From the activity deposited on the surface of the defined lung regions the number of cells hit by alpha particles emitted was determined. Together with the data on tissue and cell structure the probability for single- and multiple cell hits for each alpha particle was calculated. For the spherical basal cells a mean chord length in the cell of 4/3 radius was assumed according to the Cauchy theorem (KELLERER 1978). Similar considerations were applied also to the cylindrical epithelial cells. Using a mean nuclide specific LET the energy deposited and the resulting absorbed dose were determined for the cells investigated.

As an example Fig. 4 shows the frequency distribution of the hit probability for epithelial cells from RaA deposited on the mucus layer surface. It can be seen that most frequently each alpha particle hits two epithelial cells.

Based on extensive investigations of the natural radioactive environment in urban areas, radon spas and underground mines (POHL 1979, STEINHÄUSLER et al. 1976, STEINHÄUSLER et al. 1978), the resulting doses from inhalation of radon and decay products were calculated with the method described above. Table 2 represents the absorbed doses for a 100-day-exposure, the assumed mean

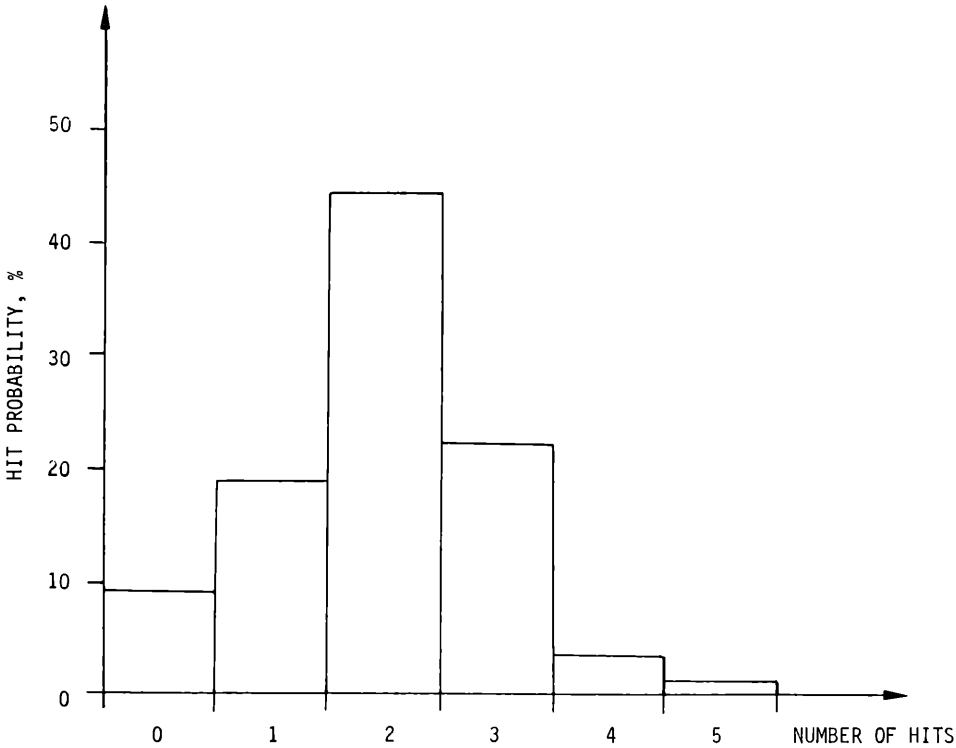


Fig. 4: Hit probability of epithelial cells for each alpha particle emitted from RaA (^{218}Po)

interval required for complete cell renewal as well as for annual exposure for the three cell types investigated. These calculations were carried out for very favourable conditions in an urban environment, represented by very low radon concentrations indoors and outdoors together with light physical activities of people inhaling radon and decay products (HOFMANN et al. 1979). For comparison the results obtained with the ICRP compartmental lung model are included into this table. For the 100-day-exposure the cellular doses exceed the compartmental doses up to a factor 2.5. In the case of annual exposure — due to the influence of the cell turn-over-rate — the cellular doses are about half the compartmental doses. This shows the importance of this dose reducing effect in all those cases where the exposure time exceeds the cell turn-over-time. Due to the pronounced inhomogeneity of both the occuring cellular structures and the nuclide deposition pattern in the tracheobronchial region the differences between cellular and compartmental doses are larger for this region as compared to the more homogeneous alveolar region.

Table 3 shows the resulting doses after a two-hour-exposure in a radon therapy station with an elevated content of radon and decay products in the

Table 2

Comparison of dose values for continuous inhalation of radon and decay products an an urban environment under very favourable conditions (^{222}Rn: 0.1 pCi/l; RaA RaB RaC = 0.9 : 0.6 : 0.4)

Cell type	Absorbed dose (mrad)			
	100 d exposure		1 year exposure	
	Cellular	ICRP-Compartment	Cellular	ICRP-Compartment
Alveolar cells	0.9	0.8	0.9	2.6
Basal cells	4.1	2.1	4.1	7.7
Epithelial cells	5.2	2.1	5.2	7.7

Table 3

Comparison of dose values for short-term inhalation (2 hours) of radon and decay products in a radon therapy station (^{222}Rn 3000 pCi/l; RaA RaB RaC = 0.9 : 0.7 0.6)

Cell type	Absorbed dose (mrad)	
	Cellular	ICRP-Compartment
Alveolar cells	14	12
Basal cells	48	33
Epithelial cells	61	33

atmosphere, e. g. for patients or members of the medical staff. The activities used for this calculation represent mean values of numerous measurements carried out in the thermal gallery of Badgastein (POHL 1979). Since the period required for cell renewal exceeds largely the exposure time this dose modifying effect has no influence on the resulting dose. However, again it can be seen that the cellular doses in the tracheobronchial region are higher than the compartmental doses by a factor 2.

From these results it can be concluded that lung dosimetry based on the ICRP-compartmental model is sufficient for coarse health physics assessments, where speed and ease of use are important. However, whereever a detailed dose-effect relationship in radiobiology has to be investigated, it is necessary to use cellular dosimetry for lung dose assessments. Studies are in progress substituting the geometrical cell model by the real cell structure as represented in a tissue slice and taking into account the stochastic nature of alpha particle tracks interacting with different cells (BERNROIDER et al. 1979, HOFMANN et al. 1979). This statistical method will then permit a more realistic picture of the interaction of ionizing particles with human organs and tissues.

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