Changes induced in the human respiratory tract by chronic cigarette smoking can reduce the dose to the lungs from exposure to radon progeny

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Abstract

Chronic cigarette smoking leads to changes in the respiratory tract that might affect the dose received from exposure to radon progeny. In this study, changes induced by cigarette smoking in the respiratory tract were collected from the literature and used for calculation of the dose received by the lungs and organs outside the respiratory tract. Morphological and physiological parameters affected by chronic smoking were implemented in the Human Respiratory Tract Model (HRTM) used by the International Commission of Radiological Protection (ICRP). Smokers were found to receive lung doses 3% smaller than the ICRP reference worker (non-smoking reference adult male) in mines and 14% smaller in indoor workplaces and tourist caves. A similar dose reduction was found for the extrathoracic region of the HRTM. Conversely, kidneys, brain, and bone marrow of smokers were found to receive from 2.3- up to 3-fold of the dose received by the respective organ in the ICRP reference worker, although they remained at least 2 orders of magnitude smaller than the lung dose. These results indicate that the differences in the lung dose from radon progeny exposure in cigarette smokers and non-smokers are smaller than 15%.

1 Introduction

Cigarette smoking and radon exposure are the two leading causes of lung cancer. Radon-attributable lung cancer deaths account for about 3% of the total deaths caused by cancer [1]. Cigarette smoking is recognised as an epidemy, killing more than 8 million people per year [2]. Thus, understanding the synergy between radon exposure and cigarette smoking in inducing lung cancers is highly important [3].

Epidemiological studies consistently demonstrate the excess relative risk of lung cancers associated with radon exposure [4,5]. Initially, an additive nature was suggested for the combined risk from cigarette smoking and radon exposure [6], being later replaced by the proposition of an intermediate model between additive and multiplicative [7], which has since been supported by other independent studies [8–10].

Nevertheless, one of the major drawbacks in understanding the combined risk from cigarette smoking and radon exposure is the lack of knowledge on the dose in the lung of smokers. In a study in which potential changes induced by smoking were considered, the effective dose of cigarette smokers without lung diseases was found to be 21% lower than the effective dose of non-smokers exposed to the same activity [11]. Only the mucus present in the respiratory tract, the breathing rate, and the lung volumes were considered to be affected by smoking. However, in this study a stochastic lung deposition model simulating the air flow was used, not a compartment model as proposed by ICRP, thus a direct comparison with ICRP reference doses is not straightforward. Moreover, doses to other organs than the lungs were not calculated.

A standard methodology for internal dose assessment from inhaled radionuclides in radiological protection is established by the ICRP and includes the reference ICRP Human Respiratory Tract Model (HRTM), Human Alimentary Tract Model (HATM) , models of systemic biokinetics and the ICRP dosimetric models [12–14].

In this study, data from changes induced by chronic cigarette smoking influencing the parameters of the HRTM were collected from the literature and used to calculate the dose from radon progeny to the lungs and extrathoracic (ET) regions of the HRTM for the Reference

Worker. Doses to kidneys, brain and bone marrow are also provided to illustrate the changes induced in doses to other organs.

2 Methods

In the ICRP HRTM morphometric and physiological parameters of the respiratory tract, as well as the deposition of inhaled aerosol particles and their clearance are considered. Parameters from the HRTM that could be affected by chronic cigarette smoking were identified, and data from the literature were collected. Finally, their influence on the dose to the lungs, ET region of HRTM, kidneys, brain, and bone marrow were calculated for the Reference Worker exposed in tourist caves, mines and indoor workplaces.

The influence of cigarette smoking on the respiratory tract was gathered through a literature search on Scopus and Google Scholar platforms and from references included in selected articles. Preference was given to studies where groups of chronic smokers and non-smokers were both included. No animal models or *in vitro* studies were considered.

ICRP Publication 66 indicates that cigarette smoking influences morphological, physiological, and clearance parameters. Morphological and physiological changes may alter the specific absorption fraction (SAF) and aerosol deposition, respectively. The following subsections present the methodology used to calculate specific absorption fractions (SAFs), lung regional deposition fractions, time-dependant content of radionuclides (activity) in various compartments of the ICRP biokinetic models and doses to the dosimetric target tissues and organs.

2.1 SAF calculation

The specific absorbed fraction (SAF) is the amount of radiation of a given energy that is emitted from the source region and absorbed per unit of mass in the target region and depends on the geometry of the target and the source. The influence of cigarette smoking on the morphology of the respiratory tract was used to modify the reference ICRP epithelial thickness. These epithelial changes influence the energy deposited in the target cells of the airways. Thus, SAFs for cigarette smokers were calculated using Monte Carlo simulation (MCNPX)[15]. Source-target regions of the HRTM were modelled as described in ICRP Publication 66 [12] but using the epithelial-adjusted smoking values. In short, concentric cylinders were modelled, each cylinder shell corresponding to a specific layer of the lung epithelial tissue compartment. All epithelial layers were modelled as ICRU 4-element soft tissue, with air filling the luminal volume[16]. Moreover, to account for the narrowing of airways found in smokers [17], the luminal diameter was decreased by 3% in both bronchial (BB) and bronchiolar (bb) compartments.

Given the thickness of the epithelium and its variation caused by chronic cigarette smoking, only the SAFs from alpha particles were considered to be affected. Three alpha energies of 6, 7.5 and 8 MeV, were simulated, so that both potential alpha energies related to radon progeny decay were considered: 6 MeV from ^{218}Po decay and 7.69 MeV from ^{214}Po decay (interpolated between 7.5 and 8 MeV, as done by ICRP[18]). Eight Target <- Source combinations affected by the variation of the epithelial thickness were simulated: ET1_basal <- ET1 surface (ET1_bas <- ET1 sur); BB_basal <- BB_mucociliary (BB_bas <- Bronchi); BB_secretory <- BB_mucociliary (BB_sec <- Bronchi); BB_basal <- BB_bound (BB_bas <- Bronchi-b); BB_secretory <- BB-bound (BB_sec <- Bronchi-b); BB_basal <- BB_sequestered (BB_bas <- Bronchi-q); BB_secretory <-

BB_sequestered (BB_sec <- Bronchi-q) and bb_secretory <- Bronchiole_mucociliary (bb_sec <- Bronchiole). Energy deposition in each target volume was calculated using tally **F8* (MeV/number of particles), then divided by the initial energy and finally normalised by the corrected mass. Statistical uncertainties of the Monte Carlo simulation remained below 5%, and calculations were validated against reference ICRP values.

2.2 Aerosol deposition

Physiological parameters of the HRTM influence aerosol deposition within the airways. Hence, the aerosol deposition was calculated for smokers based on the modified physiological parameters using an in-house developed tool written in Interactive Data Language (IDL), based on the work from Klumpp and Bertelli, *kdep* [19]. This tool calculates the deposition according to the model proposed by ICRP Publication 66 [12]. Lung deposition fractions of unattached and attached radon progeny in indoor workplaces, tourist caves and mines were calculated for cigarette smokers. The IDL tool was validated considering the deposition values provided by ICRP for the Reference Worker and different levels of exercises and differences from ICRP values were smaller than 2%.

2.3 Biokinetic and dosimetric calculations

Finally, radon doses to the Reference Worker were calculated using the Internal dose Calculation for Radionuclide Exposure (ICARE)[20]. This software solves biokinetic models and calculates dose coefficients for any radionuclide, it implements ICRP biokinetic and dosimetric models and also allows modification of these models. The modified lung regional deposition fractions, SAFs, and clearance rates were directly used as inputs for ICARE. Doses were calculated taking into account the exposure conditions (aerosol size distribution and density)[21]. Validation of the effective and equivalent organ doses from the reference radon exposure at indoor workplaces, tourist caves, and mines indicated a perfect agreement with ICRP data for the Reference Worker.

3 Results

The parameters varied in the HRTM from cigarette smoking influenced only the dose from radon progeny, which accounts for at least 98% of the equivalent dose to the lungs and 95% of the effective dose. Dose from radon gas depends on the transfer coefficient from air to arterial blood [21], and was kept the same in all calculations, thus, maintaining the dose from radon gas invariable. In the following sections, the influence from the changes in the HRTM from cigarette smoking in the dose from radon progeny is presented.

3.1 Changes in the HRTM induced by cigarette smoking

3.1.1 SAF

Cigarette smoking was found to alter significantly the epithelium of smokers, leading to the enlargement of secretory cells [22], loss of ciliated cells [23], and an abnormal increase in the number of basal cell layers [24]. In comparison with the HRTM data for the Reference Worker, heavy cigarette smokers (> 5 pack-years) were found to have 85% thicker epithelium in the anterior extrathoracic compartment (ET1) of the HRTM [25]. For the bronchi (BB) compartment, light smokers had 17% thicker epithelium, while in heavy smokers, it increased by 31% [22,23,26]. As for the cilia, light smokers had a 14% decrease in their length at the BB region, whilst for heavy smokers, the reduction was 32% [22,23,26]. The cilia in the bronchiole (bb) compartment were also found to be affected by smoking, leading to a 9% reduction in their length [27].

The ICRP HRTM reference morphological values and the cigarette-smoking adjusted parameters are shown in Table 1. For consistency and due to the lack of literature values, a light smoker's profile was added for the ET1 compartment, considering an increase in epithelial thickness of about half (40%) of the one observed in heavy smokers (85%). Similarly, a heavy smoker profile was added for the cilia length in the bb compartment by considering a 20% decrease in its length, about twice the 9% decrease observed in light smokers. No literature data was available from morphological variations in the posterior nasal passages, oral and nasal parts of the pharynx and larynx (ET2 compartment), or epithelial thickness variations in the bb compartment. Thus, they were kept the same as the ICRP reference values.

Table 1: Reference ICRP morphological values and cigarette-induced epithelial changes

Compartment	Epithelial layer and target cells	Layer thickness and target depth (µm)		
		ICRP Reference Worker[12]	Smokers	
			Light	Heavy
ET1	keratin layer	8	11.2	14.8 [25]
	epithelial cells	32	44.8	59.2 [25]
	target basal cells	10	14	18.5 [25]
BB [22,23,26]	mucus	5	5.0	5.0
	cilia	6	5.2	4.1
	target secretory cells	30	35.1	39.3

	target basal cells	15	17.6	19.7
	depth secretory cells	10	11.7	13.1
	depth basal cells	35	41.0	45.9
bb	cilia	4	3.6 [27]	3.2

Table 2 presents the SAF calculated for the male individual using the cigarette-smoking adjusted epithelial thicknesses from Table 1 and the SAF ratio between the male smoker and the male non-smoker (Reference Worker). Overall, smokers were found to have smaller SAFs than the ICRP Reference Worker. This is because of the increase in the epithelial thickness of their respiratory tract, which increases the path that alpha particles must follow before reaching the target layer, combined with the increased mass of the target layer (SAF = AF/mass). SAFs for the ET1 were the most affected by cigarette smoking, with heavy smokers having almost no absorbed fraction from alpha particles. The only exception with increased SAFs was found for the bronchiole compartment, for which no data on the epithelial thickness was found but only the decrease in the cilia length. This decreases the source distribution height in the mucociliary layer, and overall brings the source closer to the target cells, thus, increasing the SAFs.

Table 2: Specific Absorbed Fractions (SAFs) calculated for the male light and heavy smoker for the relevant radon alpha progeny energies. SAFs ratios between the male smoker and Reference Worker (non-smoker) ($R_{SAFs/ns}$) are also presented.

SAFs for a male cigarette smoker (Ratio of SAFs male Smoker/ICRP Reference Worker)												
	Light Smokers						Heavy Smokers					
Target <-Source	6 MeV		7,5 MeV		8 MeV		6 MeV		7,5 MeV		8 MeV	
	SAF	$R_{SAF(s/ns)}$	SAF	$R_{SAF(s/ns)}$	SAF	$R_{SAF(s/ns)}$	SAF	$R_{SAF(s/ns)}$	SAF	$R_{SAF(s/ns)}$	SAF	$R_{SAF(s/ns)}$

ET1_bas <- ET1 sur	0.0	0.00	884	0.21	1884	0.41	0.0	0.00	0.0	0.00	25	0.01
BB_bas <- Bronchi	4.5	0.14	110	0.60	160	0.69	0.1	0.00	66	0.36	115	0.50
BB_sec <- Bronchi	239	0.79	359	0.89	373	0.91	205	0.68	328	0.81	348	0.85
BB_bas <- Bronchi-b	422	0.90	368	0.92	349	0.93	387	0.83	345	0.87	329	0.87
BB_sec <- Bronchi-b	440	0.91	393	0.92	380	0.93	406	0.84	369	0.86	358	0.87
BB_bas <- Bronchi-q	276	0.85	270	0.91	261	0.92	236	0.73	248	0.84	242	0.85
BB_sec <- Bronchi-q	67	0.57	140	0.78	152	0.82	41	0.35	107	0.59	125	0.67
bb_sec <- Bronchiole	113	1.02	93	1.02	87	1.02	115	1.03	94	1.03	88	1.03

3.1.2 Deposition

Chronic cigarette smoking affects physiological parameters. Cigarette smokers were found to have from 3% to 8% smaller tracheobronchial tree diameter [17,28]. For the present study, a reduction of 3% was used because of the larger cohort from which it was drawn (more than five thousand individuals [17] in contrast to 39 individuals [28]). The forced vital capacity (FVC) - used to estimate the tidal volume (V_T) [29], volumetric flow rate ($\dot{V}$) and ventilation rate (B) [12] - was also found to be reduced in cigarette smokers by 8% on average, varying from 2% to 23% [30–34]. Finally, the relative functional residual capacity (FRC) was found to increase in smokers by around 6% [35–37]. Given that the FRC refers to the volume of air remaining in the lungs after a passive exhalation, the relative FRC used in the present study was calculated as the FRC normalised by the Total Lung Capacity (TLC) reported for the same cohorts [35–37].

Reference physiological parameters influencing the deposition of radon progeny within the airways are presented in Table 3, along with the modified cigarette smoking values for light smokers. Cigarette smoking was found to decrease the physical volume available in the lungs and to increase the functional residual capacity. Thus, smaller volumes of air are exchanged with each breath. This seems to agree with studies showing that smoking leads to decreased oxygen uptake [38]. Because literature data was available only for light smokers, an additional variation was considered, for which heavy smoking led to 10% to 25% further changes to the physiological parameters, Table 3.

Table 3: Reference physiological parameters and cigarette-induced changes for male light and heavy-smoking individuals

Parameter		Male values		
		ICRP Reference Worker [12]	Smokers	
			Light	Heavy
Scaling Factor	SF_t	1.00	1.03 [17]	1.10
	SF_b	1.00	1.03 [17]	1.10
	SF_A	1.00	1.03 [17]	1.10
Functional Residual Capacity (FRC), ml		3301	3499 [35–37]	3961
Anatomical dead space, ml	V_D_ET	50	50	50
	V_D_BB	49	46 [17]	42
	V_D_bb	47	44 [17]	40
	V_D_TOTAL	146	140	132
Tidal Volume (V_T), ml	Sleep*	625	575 [30–34]	531
	Sitting	750	690 [30–34]	638
	Light Ex	1250	1150 [30–34]	1063
	Heavy Ex*	1920	1766 [30–34]	1632
Volumetric flow rate ($\dot{V}$), ml/s	Sleep*	250	210 [30–34]	188
	Sitting	300	252 [30–34]	225
	Light Ex	833	700 [30–34]	625
	Heavy Ex*	1670	1403 [30–34]	1253
Ventilation rate (B), m^3/h	Sleep*	0.45	0.38 [30–34]	0.34
	Sitting	0.54	0.45 [30–34]	0.41
	Light Ex	1.50	1.26 [30–34]	1.13

	Heavy Ex*	3.00	2.52 [30–34]	2.25

*data not used for the calculation of deposition for the standard worker

The fraction of inhaled radon progeny deposited within the airways of light and heavy smokers calculated using the physiological parameters from Table 3 are presented in Table 4.

Table 4: Percentage of inhaled radon progeny deposited within the airways of light and heavy smokers in different workplaces (indoor, mine and cave) and for different radon progeny aerosol modes. Reference deposition values for workers (Non-smokers) and definition of radon aerosol modes are given in ICRP Publication 137 [21].

Radon deposition – male (%)						
Light Smokers	ET1	ET2	BB	bb	AI	Total
Rn-222_unattached	52.31	28.17	8.26	9.38	0.43	98.55
Rn-222_indoor_nuc	3.85	2.07	1.01	6.93	29.14	43.01
Rn-222_indoor_acc	9.95	5.36	0.57	1.54	9.86	27.28
Rn-222_mine_acc	2.96	1.59	0.43	2.33	10.67	17.98
Rn-222_cave_acc	3.22	1.73	0.50	2.81	12.76	21.02
Heavy Smokers	ET1	ET2	BB	bb	AI	Total
Rn-222_unattached	52.42	28.23	8.63	8.94	0.33	98.55
Rn-222_indoor_nuc	3.82	2.06	1.07	7.30	30.61	44.85
Rn-222_indoor_acc	10.49	5.65	0.59	1.60	10.57	28.91
Rn-222_mine_acc	3.10	1.67	0.46	2.48	11.49	19.19
Rn-222_cave_acc	3.36	1.81	0.53	2.98	13.70	22.38

ET1= anterior nasal passage, ET2= posterior nasal passage, pharynx, and larynx, BB= bronchial, bb= bronchiolar and AI= alveolar-interstitial compartments. Radon aerosol modes as defined by the ICRP [21]: Nuc= nucleation mode, acc= accumulation mode

Total deposition remained the same compared to the Reference Worker for the unattached fraction, both for light and heavy smokers. The total deposition increased up to 11% for other aerosol modes and workplaces. However, a greater variation in the deposition was observed in specific regions, with the largest impact obtained for the unattached fraction deposited within the alveolar region. Light and heavy smokers had 26% and 42% less unattached radon progeny deposited in their alveolar compartments and 6% and 11% less in their bronchioles, respectively.

3.1.3 Clearance

One challenge in distinguishing between absorption and particle transport clearance is that they occur simultaneously, with few studies reporting one of the phenomena while also controlling for the absence of the other. Clearance due to absorption and particle transport was found to be affected by cigarette smoking in opposite manners: while the absorption rate increased in smokers, the particle transport rate decreased. Table 5 shows the modifying factors for the absorption rate in smokers from literature, which was overall found to happen on average 3-fold faster than in non-smokers. A small correlation ($r^2 = 0.3$) was found between cigarette consumption and relative absorption rate. Studies in which not only the disappearance of the tracer from the lungs was followed but its consequent appearance in the blood was identified also supports the conclusion that the faster clearance observed was due to absorption. O'Byrne *et al*. found a strong correlation (r^2=0.9) between lung clearance half time and the peak in blood concentration [39]. Similarly, Kennedy *et al.* found that the radionuclide-tagged aerosol signal from the lungs of smokers disappeared 2.6-fold faster than in non-smokers. In addition, the signal in their blood appeared 2.2-fold faster than non-smokers [40]. Even though most studies reported on Tc-DTPA, smokers were found to also show faster absorption than non-smokers for other aerosols. Schmekel *et al.* reported an 8.7-fold faster absorption rate, measured by the appearance in the bloodstream when smokers inhaled terbutaline [41]. The much higher absorption rate than in other studies could be due to terbutaline being a vasodilator. Thus, based on available data, and taking into account only these studies in which the appearance of the radionuclide in the blood stream was also accounted for [39–41], smokers' absorption rate was considered to be four times faster than for the Reference Worker (non-smoker), for all progeny dissolution and uptake rates, Table 6. The increased absorption rate observed in smokers has been attributed to changes in the lining fluid of the lungs caused by smoking [42].

Table 5: Clearance modifying factor in smokers due to absorption

Reference	Aerosol	Absorption rate ratio (smokers/non-smokers)
Minty 1984 [43]	Tc-DTPA	1.6
Nolop 1987 [44]	In-DTPA	1.8
Nolop 1987 [44]	Tc-DTPA	2.2
Bhure 2009 [45]	Tc-DTPA	2.4
Kennedy 1984 [40]	Tc-DTPA	2.6
Inoue 1995 [32]	Tc-DTPA	2.7
Taylor 1988 [46]	Tc-DTPA	2.9
Schmekel 1992 [47]	Tc-DTPA	3.1
Thunberg 1989 [48]	Tc-DTPA	3.1
O'Byrne 1984 [39]	Tc-DTPA	3.2
Schmekel 1991 [41]	Tc-DTPA	3.4
Minty 1981 [49]	Tc-DTPA	3.7
Coates 1986 [50]	Tc-DTPA	4.0

Scherrer-Crosbie 1996 [51]	Tc-DTPA	4.1
Mason 2001 [52]	Tc-DTPA	4.3
Morrison 1999 [53]	Tc-DTPA	5.1
Mason 2001 [52]	In-DTPA	5.2
Mason 1983 [54]	Tc-DTPA	5.4
Schmekel 1991 [41]	terbutamine	8.7
	Geometric Average	3.4

Table 6: Absorption rates for smokers

Radon Progeny	Rapid dissolution rate s_r (d^{-1})		Slow dissolution rate s_s (d^{-1})		Bound uptake rate s_b (d^{-1})	
	ICRP reference [21]	Smoker	ICRP reference [21]	Smoker	ICRP reference [21]	Smoker
Polonium	3	12	-	-	-	-
Lead	100	400	1.7	6.8	1,7	6.8
Bismuth	1	4	-	-	-	-

The particle transport rate in cigarette smokers was found to vary from 0.1 to 0.8 of the rate observed in non-smokers. Again, because of potential confounding between particle transport and absorption, studies assessing clearance using millimetric particles are deemed as purely particle transport assessments. By placing 1 mm Teflon discs in the trachea of smokers and non-smokers and following its movement using fluoroscopy, Goodman *et al.* found that the tracheal velocity in smokers was only 30% of the velocity in non-smokers (BB -> ET2) [55]. Similarly, using a bronchoscope, Toomes *et al.* found that the particle transport rate of millimetric discs placed in the trachea of smokers was 40% of the rate observed in non-smokers (BB -> ET2) [56]. These values agree with the geometric average from all studies reporting from BB -> ET2 particle transport. Hence, the particle transport rate in smokers was considered to happen at 40% of the rate from the Reference Worker (non-smokers) between

BB-> ET2 and bb -> BB [12]. Indeed, an assumption of impaired particle transport is supported by the fact that cigarette smoking leads to shorter cilia and loss of ciliated cells[22,23,27]. Clearance modifying factors due to particle transport are shown in Table 7 and varies, on average, from 0.3 between ALV -> bb compartments and 0.6 between bb -> BB compartments. Previous modification factors proposed by ICRP Publication 66 [12] to account for cigarette smoking, and later withdrawn in Publication 130 [14] were: 0.5 between BB -> ET2, 1 between bb -> BB and 0.7 between AI -> bb.

Table 7: Clearance modifying factor in smokers due to particle transport

Reference	Aerosol	Compartments	Particle Transport rate ratio (smokers/non-smokers)
Lourenço 1971 [35]	Fe3O4-Au	BB -> ET2	0.1
Goodman 1978 [55]	Teflon	BB -> ET2	0.3
Toomes 1981 [56]	Teflon	BB -> ET2	0.4
Foster 1985 [57]	Fe2O3-Tc	BB -> ET2	0.4
Camner 1972 [58]	Tc-Teflon	BB -> ET2	0.7
Agnew 1986 [59]	Tc	BB -> ET2	0.7
Vastag 1985 [60]	Tc-erythrocytes	BB -> ET2	0.8
		Geometric average	**0.4**
Foster 1985 [57]	Fe2O3-Tc	bb -> BB	**0.6**
Cohen 1979 [61]	Fe3O4	ALV -> bb	0.2
Moller 2001 [62]	Fe3O4	ALV -> bb	0.4
Moller 2001 [62]	Fe3O4	ALV -> bb	0.6
		Geometric average	**0.4**

Kathren 1993 [63]	Pu/AM	ALV -> LN	**0.4**

Due to the short-lived nature of radon progeny, the variation in the particle transport rate from ALV -> bb or ALV -> LN was not considered to affect lung dose since radon progeny deposited in the alveoli are cleared at a slower rate than their physical decay.

3.2 Doses in indoor workplaces, tourist caves and mines

Changes in the respiratory tract caused by cigarette smoking ultimately influence the lung dose. Figure 1a-d shows the relative dose (ratio dose smoker/dose non-smoker) in the lungs due to the variation induced by smoking in the SAF, deposition, absorption and particle transport separately, for the indoor workplace, tourist cave and mine.

Increase in the epithelial thickness of the respiratory tract caused by cigarette smoking affects the SAF, resulting in smokers receiving down to 14% lower doses to their lungs than the Reference Worker (non-smoker). Conversely, the smoking-induced changes in the physiological parameters that altered aerosol deposition within the airways led to an increase in the lung dose of smokers up to 13%. The faster clearance rate by absorption makes the relative dose decrease, whilst the slower clearance from particle transport has the opposite effect, increasing the lung dose. Overall, lung dose was found to vary linearly with clearance, and even for the highest variations in heavy smokers (modifying factors of 6 for absorption and 0.1 for particle transport), the lung dose in smokers varied within ± 20% of the lung dose from non-smokers.

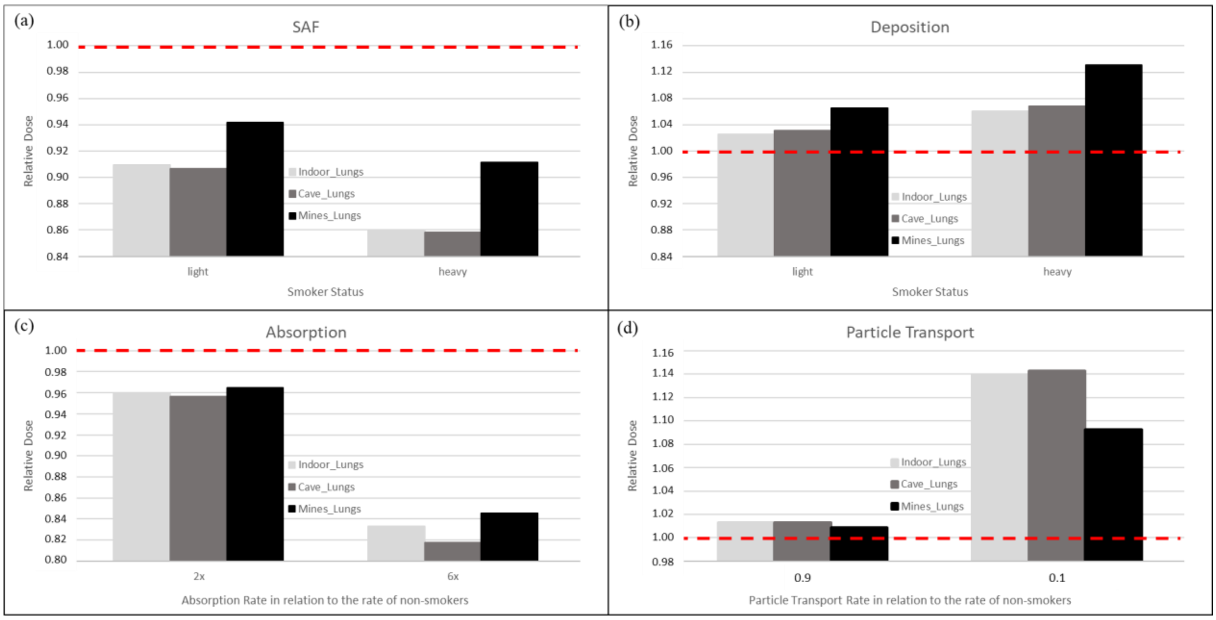

Figure 1: Smoker's lung dose relative to the Reference Worker (non-smoker) due to variation from (a) SAF, (b) deposition, (c) absorption and (d) particle transport, separately. The horizontal dashed line indicates the relative dose equal to unit.

Because smoking affects the different aspects of the HRTM simultaneously, four smoking profiles were then defined for dose calculation, Table 8. Light and heavy smoking profiles were established based on literature data. In addition, the two extra profiles – very light and very heavy - were included to consider further changes in the clearance rate.

Relative equivalent doses from radon progeny to the lungs, ET of HRTM, kidneys, brain, and bone marrow for a male individual exposed at the indoor workplace are shown in Table 9 for the four smoking profiles. Dose to organs outside the respiratory tract were also included for completeness purposes, given that they are at least two orders of magnitude smaller than those received by the respiratory tract.

Table 8: Parameters from the smoking profiles used in the dose calculation

Cigarette consumption profile	**Modifying parameter**			
	Very light	**Light**	**Heavy**	**Very heavy**
SAF	light	light	heavy	heavy
Deposition	light	light	heavy	heavy
Absorption	3x	4x	4x	6x
Particle transport	0.7	0.4	0.4	0.1

Table 9: Relative dose for different organs according to the smoking profile

Relative dose – male (dose smokers/dose non-smokers)				
Smoking Profile	Indoor Workplace only			
	Very light	Light	Heavy	Very heavy
Lungs	0.89	0.89	0.86	0.83
ET of HRTM	0.81	0.81	0.78	0.78
Kidneys	2.25	2.79	2.92	3.95
Brain	2.01	2.44	2.56	3.38
Bone marrow	1.94	2.33	2.44	3.19

Cigarette smokers exposed to radon were found to receive from 11% to 17% smaller doses to their lungs, depending on their smoking profile. The reduction in doses to the ET region of the respiratory tract in smokers compared with non-smokers was even greater, at 19% to 22%. Conversely, equivalent doses to the kidneys, brain and bone marrow were 2- to 4-times greater in smokers than non-smokers. Despite this increase, such doses were at least two orders of magnitude smaller than the lung dose. Moreover, doses to systemic organs are mostly due to radon gas, hence, the increase in the total equivalent dose (from radon gas plus progeny) for a heavy smoker was of 5% for the bone marrow, 24% for the brain and 67% for the kidneys.

By varying cigarette consumption profile from very light to light, as well as from heavy to very heavy, no difference in the dose is observed in the ET of the HRTM, and only a 3% variation in lung dose between heavy and very heavy smokers is observed. As shown in Figure 1, the increased absorption rates and slower particle transport rates of smokers counteract each other so that the overall effect on lung doses is reduced. The lung's net dose was affected mainly by SAF and deposition variations, *i.e.*, morphological and physiological changes, as illustrated in Figure 1. Given that variation in the SAF decreased the relative dose, while variation in the deposition increased it (see Figure 1), it is reasonable to consider that the major factor altering the dose received by the lung of smokers exposed to radon are due to the changes that cigarette smoking causes to the epithelium of their respiratory tract, in particular its thickening. As for the increase in the dose to organs outside the respiratory tract, these are likely caused by the radon progeny aerosol being absorbed faster in smokers, hence entering the systemic circulation and being available to deposit their energy in other organs before their decay.

Finally, the relative dose to the lungs, ET of the HRTM, kidneys, and brain of light and heavy smokers is shown in Table 10 for indoor workplaces, tourist caves, and mines. The variation in doses received by light and heavy smokers was found to be similar at indoor workplaces and tourist caves. However, the lung dose received by miners seemed to be less influenced by smoking than in other workplaces. This is likely related to the variation in the deposition within the airways of cigarette smokers. For miners, the deposition of radon progeny in accumulation mode accounts for more than 90% of the total lung dose [21]. Thus, even though the deposition from the accumulation mode varied at the same rate for mines and tourist caves due to smoking, the final impact was more relevant for miners because of its larger contribution. Therefore, when all the effects from SAF, deposition, absorption, and particle clearance are considered for miners, the net effect is more strongly affected by the deposition, which increases the relative dose to the lungs (Figure 1), thus bringing the smokers' lung dose closer to the dose received by non-smokers.

Table 10: Relative organ dose for light and heavy smokers exposed to radon progeny at the indoor workplace, tourist cave, and mine

Relative dose (dose smokers/dose non-smokers)						
Exposure	Indoor workplace		Tourist cave		Mine	
Smoking status	Light	Heavy	Light	Heavy	Light	Heavy
Lungs	0.89	0.86	0.88	0.86	0.94	0.97
ET of HRTM	0.81	0.78	0.80	0.74	0.81	0.78
Kidneys	2.79	2.92	2.84	2.97	2.84	3.04
Brain	2.44	2.56	2.53	2.66	2.62	2.81
Bone Marrow	2.33	2.44	2.39	2.51	2.36	2.53

The relative doses received by organs outside the respiratory tract were found to not largely vary among workplaces, 2 – 3-fold higher than in non-smokers, depending on cigarette consumption.

4 Discussion

In this study, changes induced by cigarette smoking collected from the literature were applied in the Human Respiratory Tract Model from ICRP, and the equivalent dose due to radon exposure to the lungs, extrathoracic region of the HRTM, kidneys, brain and bone marrow were calculated. Cigarette smoking was reported to increase the epithelial thickness in the respiratory tract while decreasing cilia length, diminish the physical volume available in the lungs and affect aerosol clearance by reducing the particle transport rate whilst increasing the absorption rate. As a summary, increased absorption to blood and reduced particle transport tend to compensate each other so that the available radioactive content in the lungs is not so strongly affected by chronic smoking. The lung dose is thus mostly affected by variations from aerosol deposition and morphological changes in the epithelial thickness. These changes result in smokers receiving between 3% to 14% less dose to their lungs than non-smokers under the same exposure conditions, depending on the smoking profile and exposure conditions. Similarly, doses to the ET of HRTM were also smaller by 19% to 26% in smokers. The increase in the lung to blood absorption rate, caused by chronic cigarette smoking, was found to affect the radiation doses received by organs outside of the respiratory tract. Although they remained at least two orders of magnitude smaller than the lung dose, the equivalent dose received by the kidneys, brain, and bone marrow of cigarette smokers were from 2.3- to 3-fold higher than in non-smokers, again depending on smoking profile and environment. Nevertheless, because dose to systemic organs are mostly due to radon gas, even a 3-fold increase in the dose to the kidneys from radon progeny results in only a 67% increase in the kidney total equivalent dose (radon gas plus progeny).

In the only other study available where changes in the respiratory tract caused by cigarette smoking were considered to influence the dose due to radon, the effective dose for healthy light long term smokers exposed in mines was 21% smaller than in non-smokers[11]. This is a more substantial reduction in the dose than the maximum 6% reduction found in this study for the same environment. One potential explanation is the difference in the target <- source distance considered in both studies: while Baias *et al.* increased the mucus thickness by 28%, in this present study, the epithelial thickness was increased by 17% to 31% in the BB compartment, for light and heavy smokers, respectively, with the cilia length decreasing by 14% and 32% as well. Furthermore, a decrease of 9% in the cilia length at the bb compartment was also considered. Additionally, we considered simultaneously the aerosol deposition and clearance, which probably contributed to the difference in result from that obtained by Baias *et al*. Further comparison between other smoking profiles from Baias *et al.* is not possible since in our study only healthy smokers were considered – thus, a thicker layer of mucus usually present in conditions such as chronic obstructive pulmonary disease (COPD) was not analysed. In Baias *et al*. a heavy long term smoker profile was defined. For this profile it was calculated that the lung dose would increase by 85%, as compared to a non-smoker. This trend was mainly attributed to obstructive lung disease and particularly impaired lung functions and airway obstructions. While it is possible to take into account impaired lung function through ICRP deposition model, it is not clear at present how airway obstruction can be implemented in the HRTM.

Epidemiological studies indicate that smokers might be at a lower risk of lung cancer from radon exposure than non-smokers [1,7,8]. The lower doses received by the lungs of smokers exposed to the same activity than non-smokers indicate one potential reason for this finding, even though they cannot account for all differences in risk observed in epidemiological studies[10]. Previous studies had attributed the smaller dose in smokers to an increased mucus thickness [9,11], often associated with COPD [64,65], which would shield the radiosensitive cells of the respiratory system. Our study has shown that even healthy smokers, *i.e.*, those with normal spirometry, lack of COPD, and unchanged mucus thickness, are already subject to smaller lung doses. Such a decrease is mostly caused by the elongation of epithelial cells in the respiratory tract, which ultimately affects the SAFs similarly to a thicker mucus layer. Nevertheless, whilst a thicker mucus layer would decrease the SAFs only for sources distributed in the mucociliary layer, a thicker epithelium also affects the SAFs from sequestered and bound source distributions.

Besides lung cancer, it has also been suggested that radon exposure increases the risk of cancers of the extrathoracic region [66,67], of the brain [68,69], and the risk of leukaemia [70,71]. In our study, equivalent doses to the ET of HRTM in smokers were found to be 19% to 26% smaller than in non-smokers, while dose to the brain and bone marrow increased by up to 3-fold. However, since separate risk analysis is rarely made between smokers and non-smokers the significance of these changes is still to be established. Moreover, for organs like brain and bone-marrow, the doses are still at least two orders of magnitude smaller than the lung doses.

ICRP Publication 66 introduced modifying factors to account for changes in the HRTM caused by cigarette smoking that could affect the dose from inhaled radioactive aerosol [12]. These modifying factors were later withdrawn due to the lack of support from long-term studies that failed to provide a clear influence from cigarette smoking to the long-term retention of inhaled aerosol particles [14,72]. Although this study does not propose re-introducing modifying factors for occupational dose calculation, it does provide a basis for more accurate determination of doses separately for smokers and non-smokers for assessment of risks in epidemiological studies. Regarding the organ doses that should be attributed to individuals considered in epidemiological studies, chronic cigarette smoking might play a small role as compared to other factors, as for example, inter-individual variabilities of biokinetic processes, source-target geometries, variations on aerosol parameters and on working conditions.

This study had several limitations. The availability of data on the changes to the respiratory tract caused by cigarette smoking was far from being complete, with information from morphological and physiological changes caused by smoking not always available. Moreover, cigarette composition has changed over the years, and the influence on the respiratory tract estimated in older studies might not be the same as for currently available cigarettes [73]. No changes from electronic cigarettes were considered. Little information was available correlating modifications to the respiratory tract, cigarette consumption, age, and sex. No effect from cigarette smoking was considered outside the respiratory tract, thus once the aerosol entered the systemic circulation, its availability was unaffected. Despite the large amount of data available concerning the effect of cigarette smoking, much of this information cannot be quantitatively related to the parameters used in the ICRP models. Finally, the presence of cigarette smoke affects the aerosol distribution of radon progeny and thus the lung dose, however, apart from exceptional conditions, it is a transient effect. It was thus assumed, based on the potential duration of such an effect, that it could be neglected as compared with permanent effect induced by chronic cigarette smoking.

5 Conclusion

This study assessed the impact of cigarette smoking on the radon progeny dose to the lungs, ET region of the ICRP HRTM, kidneys, brain, and bone marrow of the occupationally exposed ICRP reference adult male individual (ICRP Reference Worker). Lungs and ET region of the HRTM of cigarette smokers were found to receive from 3% – 26% less dose than their non-smoking counterparts exposed to the same time-integrated activity concentrations. Considering organs outside the respiratory tract, smokers can receive from 2 to 3-fold higher doses to their kidneys, brain and bone marrow. These results highlight that the same exposure does not lead to the same dose for cigarette smokers and non-smokers. Ultimately, this might impact the risk assessment for the lungs from radon exposure for both profiles.

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7 References

[1] Gaskin J, Coyle D, Whyte J and Krewksi D 2018 Global Estimate of Lung Cancer Mortality Attributable to Residential Radon.pdf *Environ. Health Perspect.* **126** 057009

[2] World Health Organization 2022 Tobacco

[3] Madas B G, Boei J, Fenske N, Hofmann W and Mezquita L 2022 Effects of spatial variation in dose delivery: what can we learn from radon-related lung cancer studies? *Radiat. Environ. Biophys.* **61** 561–77

[4] Richardson D B, Rage E, Demers P A, Do M T, Fenske N, Deffner V, Kreuzer M, Samet J, Bertke S J, Kelle-Reif K, Schubauer-Berigan M K, Tomasek L, Zablotska L B, Wiggins C and Laurier D 2022 Lung Cancer and Radon: Pooled Analysis of Uranium Miners Hired in 1960 or Later *Environ. Health Perspect.* **130** 057010

[5] Rage E, Vacquier B, Blanchardon E, Allodji R S, Marsh J W, Car-Lorho S, Acker A and Laurier D 2012 Risk of lung cancer mortality in relation to lung doses among french

uranium miners: Follow-up 1956-1999 *Radiat. Res.* **177** 288–97

[6] Saccomanno G, Huth G C, Auerbach O and Kuschner M 1988 Relationship of radioactive radon daughters and cigarette smoking in the genesis of lung cancer in uranium miners *Cancer* **62** 1402–8

[7] Lubin J H, Boice J D, Edling C, Hornung R W, Howe G R, Kunz E, Kusiak R A, Morrison H I, Radford E P, Samet J M, Tirmarche M, Woodward A, Yao S X and Pierce D A 1995 Lung cancer in radon-exposed miners and estimation of risk from indoor exposure *J. Natl. Cancer Inst.* **87** 817–27

[8] Tomasek L 2011 Interaction of radon and smoking among czech uranium miners *Radiat. Prot. Dosimetry* **145** 238–42

[9] Leuraud K, Schnelzer M, Tomasek L, Hunter N, Timarche M, Grosche B, Kreuzer M and Laurier D 2011 Radon, smoking and lung cancer risk: Results of a joint analysis of three European case-control studies among uranium miners *Radiat. Res.* **176** 375–87

[10] United Nations Scientific Committee on the Effects of Atomic Radiation 2020 *Sources, effects and risks of ionizing radiation. United Nations Scientific Committee on the Effects of Atomic Radiation.*

[11] Baias P F, Hofmann W, Winkler-Heil R, Cosma C and Duliu O G 2010 Lung dosimetry for inhaled radon progeny in smokers *Radiat. Prot. Dosimetry* **138** 111–8

[12] International Commission of Radiological Protection (ICRP) 1994 *ICRP Publication 66 - Human Respiratory Tract Model for Radiological Protection*

[13] International Commission of Radiological Protection (ICRP) 2006 ICRP Publication 100 - Human Alimentary Tract Model for Radiological Protection *Ann. ICRP*

[14] International Commission of Radiological Protection (ICRP) 2015 *ICRP Publication 130 - Occupational Intakes of Radionuclides: Part 1*

[15] Pelowitz D B 2011 MCNPX Users Manual Version 2.7.0 LA-CP-11-00438

[16] Pacific Northwest National Laboratory 2011 *Compendium of Material Composition Data for Radiation Transport Modeling*

[17] Donohue K M, Hoffman E A, Baumhauer H, Guo J, Budoff M, Austin J H M, Kalhan R, Kawut S, Tracy R and Graham Barr R 2012 Cigarette smoking and airway wall thickness on CT scan in a multi-ethnic cohort: The MESA Lung Study *Respir. Med.* **106** 1655–64

[18] International Commission on Radiological Protection 2016 *The ICRP Computational Framework for Internal Dose Assessment for Reference Adults: Specific Absorbed Fractions. ICRP Publication 133* vol 45

[19] Klumpp J and Bertelli L 2017 KDEP: A resource for calculating particle deposition in the respiratory tract *Health Phys.* **113** 110–21

[20] Blanchardon E, Davesne E, Bohand S and Lorache P 2019 ICARE software for calculation of dose coefficients and retained/excreted fractions of intake *BIO Web Conf.* **14** 03016

[21] International Commission of Radiological Protection (ICRP) 2017 *ICRP Publication 137: Occupational Intakes of Radionuclides: Part 3* vol 46

[22] Chang S C 1957 Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and nonsmokers *Cancer* **10** 1246–62

[23] Ide G, Suntzeff V and Cowdry E V. 1959 A comparison of the histopathology of

tracheal and bronchial epithelium of smokers and non-smokers *Cancer* **12** 473–84

[24] Auerbach O, Cuyler Hammond E and Garfinkel L 1979 Changes in bronchial epithelium in relation to cigarette smoking, 1955 - 1960 vs 1970 - 1977 *N. Engl. J. Med.* **300** 381–6

[25] Hadar T, Yaniv E, Shvili Y, Koren R and Shvero J 2009 Histopathological changes of the nasal mucosa induced by smoking Smoking-induced nasal mucosa changes *Inhal. Toxicol.* **21** 1119–22

[26] Innes A L, Woodruff P G, Ferrando R E, Donnelly S, Dolganov G M, Lazarus S C and Fahy J V. 2006 Epithelial mucin stores are increased in the large airways of smokers with airflow obstruction *Chest* **130** 1102–8

[27] Hessel J, Heldrich J, Fuller J, Staudt M R, Radisch S, Hollmann C, Harvey B G, Kaner R J, Salit J, Yee-Levin J, Sridhar S, Pillai S, Hilton H, Wolff G, Bitter H, Visvanathan S, Fine J, Stevenson C S, Crystal R G and Tilley A E 2014 Intraflagellar transport gene expression associated with short cilia in smoking and COPD *PLoS One* **9** e85453

[28] Hale K A, Ewing S L, Gosnell B A and Niewoehner D E 1984 Lung disease in long-term cigarette smokers with and without chronic air-flow obstruction *Am. Rev. Respir. Dis.* **130** 716–21

[29] Hoftman N, Eikermann E, Shin J, Buckley J, Navab K, Abtin F, Grogan T, Cannesson M and Mahajan A 2017 Utilizing forced vital capacity to predict low lung compliance and select intraoperative tidal volume during thoracic surgery *Anesth. Analg.* **125** 1922–30

[30] Chatterjee S, Kumar Nag S and Kumar Dey S 1988 Spirometric Standards for Non-Smokers and Smokers of India (Eastern Region) *Jpn. J. Physiol.* **38** 283–98

[31] Dicpinigaitis P V. 2003 Cough reflex sensitivity in cigarette smokers *Chest* **123** 685–8

[32] Inoue T, Shigeta M, Mochizuki H, Shimizu T, Morikawa A, Suzuki H, Watanabe N, Tateno M, Oriuchi N, Hirano T, Tomiyoshi K and Endo K 1995 Effect of Inhaled Furosemide on Lung Clearance of Technetium-99m-DTPA *J. Nucl. Med.* **36** 73–7

[33] Morton A R and Holmik E V 1985 The effects of cigarette smoking on maximal oxygen consumption and selected physiological responses of elite team sportsmen *Eur. J. Appl. Physiol.* **53** 348–52

[34] Sekulic D and Tocilj J 2006 Pulmonary function in military divers: Smoking habits and physical fitness training influence *Mil. Med.* **171** 1071–5

[35] Lourenço R V., Klimek M F and Borowski C J 1971 Deposition and clearance of 2 micron particles in the tracheobronchial tree of normal subjects--smokers and nonsmokers. *J. Clin. Invest.* **50** 1411–20

[36] Melville G N, Kumar M, Ismail S and Mills J L 1982 Response of the central and peripheral airways to cigarette smoking in humans and rats *Respiration* **43** 29–34

[37] Tashkin D P, Coulson A H, Clark V A, Simmons M, Bourque L B, Duann S, Spivey G H and Gong H 1987 Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers *Am. Rev. Respir. Dis.* **135** 209–16

[38] Ingemann-Hansen T and Halkjær-Kristensen J 1977 Cigarette smoking and maximal oxygen consumption rate in humans *Scand. J. Clin. Lab. Invest.* **37** 143–8

[39] O'Byrne P M, Dolovich M, Dirks R, Roberts R S and Newhouse M T 1984 Lung epithelial permeability: Relation to nonspecific airway responsiveness *J. Appl. Physiol.*

Respir. Environ. Exerc. Physiol. **57** 77–84

[40] Kennedy S M, Elwood R K, Wiggs B J R, Paré P D and Hogg J C 1984 Increased airway mucosal permeability of smokers. Relationship to airway reactivity *Am. Rev. Respir. Dis.* **129** 143–8

[41] Schmekel B, Borgstrom L and Wollmer P 1991 Difference in pulmonary absorption of inhaled terbutaline in healthy smokers and non-smokers *Thorax* **46** 225–8

[42] Wollmer P and Evander E 1994 Biphasic pulmonary clearance of 99mTc-DTPA in smokers *Clin. Physiol.* **14** 547–59

[43] Minty B D, Royston D, Jones J G and Hulands G H 1984 The effect of nicotine on pulmonary epithelial permeability in man *Chest* **86** 72–4

[44] Nolop K B, Maxwell D L, Fleming J S, Braude S, Hughes J M B and Royston D 1987 A comparison of 99mTc-DTPA and 113mIn-DTPA aerosol clearances in human. Effects of smoking, hyperinflation, and in vitro oxidation *Am. Rev. Respir. Dis.* **136** 1112–6

[45] Bhure U N, Bhure S U, Bhatt B M, Mistry S, Pednekar S J, Chari V V., Desai S A, Joshi J M and Paidhungat A J 2009 Lung epithelial permeability and inhaled furosemide: Added dimensions in asthmatics *Ann. Nucl. Med.* **23** 549–57

[46] Taylor R G, Agnew J E, Francis R A, Pavia D and Clarke S W 1988 Respiratory epithelial permeability is unrelated to bronchial reactivity and small airway function in young smokers and nonsmokers *Eur. Respir. J.* **1** 319–23

[47] Schmekel B, Bos J A H, Khan A R, Wohlfart B, Lachmann B and Wollmer P 1992 Integrity of the alveolar-capillary barrier and alveolar surfactant system in smokers *Thorax* **47** 603–8

[48] Thunberg S, Larsson K, Eklund A and Blaschke E 1989 99mTc-DTPA clearance measured by a dual head gamma camera in healthy subjects and patients with sarcoidosis. Studies of reproducibility and relation to bronchoalveolar lavage findings *Eur. Nucl. J. Med.* **15** 71–7

[49] Minty B D, Jordan C and Jones J G 1981 Rapid improvement in abnormal pulmonary epithelial permeability after stopping cigarettes *Br. Med. J.* **282** 1183–6

[50] Coates G and O'Brodovich H 1986 Measurement of Pulmonary epithelial permeability with 99mTc-DTPA aerosol *Semin. Nucl. Med.* **26** 275–84

[51] Scherrer-crosbie M, Paul M, Meignan M, Dahan E, Lagrue G, Atlan G and Lorino A M 1996 *Pulmonary clearance and lung function: influence of acute tobacco intoxication and of vitamin E* vol 81

[52] Mason G R, Peters A M, Bagdades E, Myers M J, Snook D and Hughes J M B 2001 Evaluation of pulmonary alveolar epithelial integrity by the detection of restriction to diffusion of hydrophilic solutes of different molecular sizes *Clin. Sci.* **100** 231–6

[53] Morrison D, Rahman I, Lannan S and MacNee W 1999 Epithelial permeability, inflammation, and oxidant stress in the air spaces of smokers *Am. J. Respir. Crit. Care Med.* **159** 473–9

[54] Mason G R, Uszler J M, Effros R M and Reid E 1983 Rapidly reversible alterations on pulmonary epithelial permeability induced by smoking *Chest* **83** 6–11

[55] Goodman R M, Yergin B M, Da J F L, Golinvaux M H and Sackner M A 1978 Relationship of Smoking History and Pulmonary Function Tests to Tracheal Mucous Velocity in Nonsmokers, Young Smokers, Ex-smokers, and Patients with Chronic

Bronchitis *Am. Rev. Respir. Dis.* **117** 205–14

[56] Toomes H, Vogt-Moykopfl I, Heller W D and Ostertag H 1981 Measurement of Mucociliary Clearance in Smokers and Nonsmokers Using a Bronchoscopic Video-Technical Method *Lung* **159** 27–34

[57] Foster W M, Langen Back E G and Bergofsky E H 1985 Disassociation in the Mucociliary Function of Central and Peripheral Airways of Asymptomatic Smokers *Am. Rev. Respir. Dis.* **132** 633–9

[58] Camner P and Philipson K 1972 Tracheobronchial clearance in smoking-discordant twins *Arch. Environ. Health* **25** 60–3

[59] Agnew J E, Lopez-Vidriero M T, Pavia D and Clarke S W 1986 Functional small airways defence in symptomless cigarette smokers *Thorax* **41** 524–30

[60] Vastag E, Matthys H, Kohler D, Gronbeck L and Daikeler G 1985 Mucociliary Clearance and Airways Obstruction in Smokers, Ex-Smokers and Normal Subjects Who Never Smoked *Eur J Respir Dis* **66** 93–100

[61] Cohen D, Ara S F and Brain J D 1979 Smoking Impairs Long-Term Dust Clearance from the Lung *Science (80-.).* **204** 514–7

[62] Moller W, Barth W, Kohlhaufl M, Haussinger K, Stahlhofen W and Heyder J 2001 HUMAN ALVEOLAR LONG -TERM CLEARANCE OF FERROMAGNETIC IRON OXIDE MICROPARTICLES IN HEALTHY AND DISEASED SUBJECTS *Exp. Lung Res.* **27** 547–68

[63] Kathren R L, Strom D J, Sanders C L, Filipy R E, McInroy J F and Bistlinell R E 1993 Distribution of plutonium and americium in human lungs and lymph nodes and relationship to smoking status *Radiat. Prot. Dosimetry* **48** 307–15

[64] Thorley A J and Tetley T D 2007 Pulmonary epithelium, cigarette smoke, and chronic obstructive pulmonary disease *Int. J. COPD* **2** 409–28

[65] Aghapour M, Raee P, Moghaddam S J, Hiemstra P S and Heijink I H 2018 Airway epithelial barrier dysfunction in chronic obstructive pulmonary disease: Role of cigarette smoke exposure *Am. J. Respir. Cell Mol. Biol.* **58** 157–69

[66] Kreuzer M, Dufey F, Marsh J W, Nowak D, Schnelzer M and Walsh L 2014 Mortality from cancers of the extra-thoracic airways in relation to radon progeny in the Wismut cohort, 1946-2008 *Int. J. Radiat. Biol.* **90** 1030–5

[67] Kelly-Reif K, Sandler D P, Shore D, Schubauer-Berigan M, Troester M, Nylander-French L and Richardson D B 2022 Lung and extrathoracic cancer incidence among underground uranium miners exposed to radon progeny in the Příbram region of the Czech Republic: a case-cohort study *Occup. Environ. Med.* **79** 102–8

[68] Ruano-Ravina A, Aragonés N, Kelsey K T, Pérez-Ríos M, Piñeiro-Lamas M, López-Abente G and Barros-Dios J M 2017 Residential radon exposure and brain cancer: An ecological study in a radon prone area (Galicia, Spain) *Sci. Rep.* **7** 1–7

[69] Bräuner E V., Andersen Z J, Andersen C E, Pedersen C, Gravesen P, Ulbak K, Hertel O, Loft S and Raaschou-Nielsen O 2013 Residential Radon and Brain Tumour Incidence in a Danish Cohort *PLoS One* **8**

[70] Řeřicha V, Kulich M, Řeřicha R, Shore D L and Sandler D P 2006 Incidence of leukemia, lymphoma, and multiple myeloma in Czech Uranium Miners: A case-cohort study *Environ. Health Perspect.* **114** 818–22

[71] Laurier D, Valenty M and Tirmarche M 2001 Radon exposure and the risk of leukemia:

A review of epidemiological studies *Health Phys.* **81** 272–88

[72] Gregoratto D, Bailey M R and Marsh J W 2010 Modelling particle retention in the alveolar-interstitial region of the human lungs *J. Radiol. Prot.* **30** 491–512

[73] Jarvis M J 2001 Trends in sales weighted tar, nicotine, and carbon monoxide yields of UK cigarettes *Thorax* **56** 960–3