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) proposed 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 touristic 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 same radon exposure results in changes smaller than 15% in the dose received by the lungs of cigarette smokers and non-smokers.

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]. However, when cigarette smoking and radon exposure are combined, the resulting risk is less clear. Initially, an additive nature was suggested [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 the 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 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 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 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 IDL tool, 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 the difference with ICRP values was 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

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 decretory 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 brings the source in the mucociliary layer closer to the target cells, thus, increasing the SAFs. Interestingly, even a 20% decrease in the cilia length resulted in only a 3% increase in 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)												
Target <-Source	Light Smokers						Heavy Smokers					
	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

Radon progeny deposition within the airways of light and heavy smokers calculated using the physiological parameters from Table 3 are presented in Table 4.

Table 4: Radon progeny deposition within the airways of light and heavy smokers in different workplaces (indoor, mine and cave) and for different radon progeny aerosol modes.

Radon deposition - male						
Light Smokers	ET1	ET2	BB	bb	AI	Total
Rn-222_unattached	0.5231	0.2817	0.0826	0.0938	0.0043	0.9855
Rn-222_indoor_nuc	0.0385	0.0207	0.0101	0.0693	0.2914	0.4301
Rn-222_indoor_acc	0.0995	0.0536	0.0057	0.0154	0.0986	0.2728
Rn-222_mine_acc	0.0296	0.0159	0.0043	0.0233	0.1067	0.1798
Rn-222_cave_acc	0.0322	0.0173	0.0050	0.0281	0.1276	0.2102
Heavy Smokers	ET1	ET2	BB	bb	AI	Total

Rn-222_unattached	0.5242	0.2823	0.0863	0.0894	0.0033	0.9855
Rn-222_indoor_nuc	0.0382	0.0206	0.0107	0.0730	0.3061	0.4485
Rn-222_indoor_acc	0.1049	0.0565	0.0059	0.0160	0.1057	0.2891
Rn-222_mine_acc	0.0310	0.0167	0.0046	0.0248	0.1149	0.1919
Rn-222_cave_acc	0.0336	0.0181	0.0053	0.0298	0.1370	0.2238

ET1= anterior nasal passage, ET2= posterior nasal passage, pharynx, and larynx, BB= bronchial, bb= bronchiolar and AI= alveolar-interstitial compartments. 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. In studies where not only the disappearance of the tracer from the lungs was followed but its consequent appearance in the blood was identified also supports the indication 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 contrast, 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). 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

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 6 and varies, on average, from 0.3 between ALV -> bb compartments and 0.6 between bb -> BB compartments.

Table 6: 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	**0.3**
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 at indoor workplace, tourist cave and mine

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.

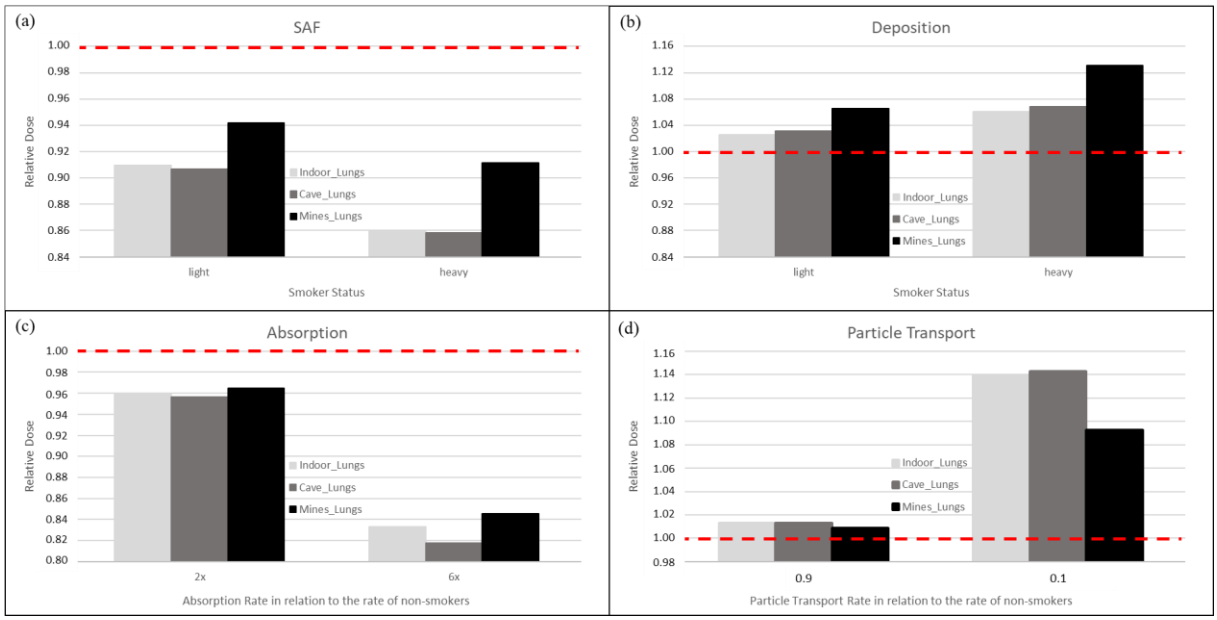

Figure 1: Smoker's lung dose relative to the Reference Worker (non-smoker) due to variation from (a) SAF, (b) deposition, (c) absorption and (d) particle transport, separately. The horizontal dashed line indicates the relative dose equal to unit.

Because smoking affects the different aspects of the HRTM simultaneously, four smoking profiles were then defined for dose calculation, Table 7. Light and heavy smoking profiles were established based on literature data. In contrast, the two extra profiles – very light and very heavy - were included to consider further changes in the clearance rate.

Relative equivalent doses to the lungs, ET of HRTM, kidneys, brain, and bone marrow for a male individual exposed at the indoor workplace are shown in Table 8 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 7: 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 8: 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 ET of HRTM received even lower doses, from 19% to 22% smaller. Conversely, equivalent doses to the kidneys, brain and bone marrow increased from 2- to almost 4-fold, even though they remained at least two orders of magnitude smaller than the lung dose.

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. These results and those of Figure 1 indicate that smokers' faster absorption rate and slower particle transport rate

compensate for each other. 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 9 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 9: 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 found 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.

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, contrary to Baias *et al.*, which probably contributed to the difference in both results. 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, radon exposure has also been related to an increased risk for extrathoracic [66,67] and brain cancers [68,69], as well as 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. However, since separate risk analysis is rarely made between smokers and non-

smokers, the significance of a reduced dose to the ET of HRTM of smokers is still to be established. The 2 to 3-fold higher doses to brain and bone-marrow in smokers is of concern regarding the potential risk of radon induced brain cancer and leukaemia. Indeed smoking could in this case be a significant risk factor, even if the magnitude of the doses remain two order of magnitude smaller than the dose to the lungs. The increased dose in smokers' brain and bone marrow is caused by faster aerosol absorption into blood, likely due to damage induced by cigarette consumption in the lining fluid of the lungs [42]. Because no effect from cigarette smoking was considered outside the respiratory tract, once the aerosol entered the systemic circulation, its availability was unaffected, resulting in higher doses to organs such as bone marrow and the brain.

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 [14,73]. While our study does not propose re-introducing modifying factors for occupational dose calculation, distinguishing between the doses received by smokers and non-smokers might still be necessary for epidemiological assessment of the separate risk of each group. Regarding the organ doses that should be attributed to individuals considered in epidemiological studies, chronic cigarette smoking might play a small role as compared with other factors: inter-individual variabilities of real-life biokinetic processes or source-target geometries, variations on aerosol parameters and on working conditions, etc.

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 [74]. No changes from electronic cigarettes were considered. Little information was available correlating modifications to the respiratory tract, cigarette consumption, age, and sex. 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. Regarding the organ doses that should be attributed to individuals considered in epidemiological studies, chronic cigarette smoking might play a small role as compared with other factors. 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 from radon exposure for both profiles.

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