Table II: Observed numbers of lung-cancer cases by dose categories, compared with those predicted by the descriptive and multi-stage models (in brackets: excess cases). As a reference, we also give the person years (py).

Doses (Gy)	py	Cases	TSCE	3SCE(A)	3SCE(B)	3SCE(C)	descriptive
$0-0.01$	$188,995$	204	198 (0.5)	203 (0.2)	205 (0.2)	204 (0.3)	194 (0.6)
$0.01-0.03$	$18,888$	32	50 (3)	49 (1)	50 (1)	50 (1)	49 (4)
$0.03-0.1$	$15,843$	58	51 (9)	47 (4)	47 (4)	48 (4)	52 (11)
$0.1-0.3$	$7,091$	41	37 (15)	31 (8)	30 (23)	31 (7)	39 (17)
$0.3-1$	$3,153$	29	33 (24)	34 (25)	31 (21)	31 (21)	32 (23)
>1	738	24	18 (16)	24 (21)	25 (22)	25 (22)	22 (20)
total	$234,708$	388	388 (67)	388 (59)	388 (56)	388 (56)	388 (75)

rate, note that α-particle hits of a cell nucleus are independent and rare. Thus the number of hits, N, is Poisson-distributed, $P_N = e^{-\bar{N}}\bar{N}^N/N!$, which means the fraction of cells *not* hit is $P_{N=0} = e^{-\bar{N}}$. Assuming (i) a linear dose response, $\bar{N} = n\,D$, with $n \sim 4/\mathrm{Gy}$ [56], and (ii) delivery of the dose $D \equiv d\,\tau$ over a characteristic time of order the interval between cell cycles ($\tau \sim 1$a for basal stem cells [57]), we have $P_{N=0}(d) = e^{-nd\tau}$. At the characteristic dose rate, d_s, about one out of, say, six nearest neighbors would be hit, such that $P_0(d_s) = 1-p$, $p \equiv 1/6$, yielding a characteristic dose rate of

$$d_s \simeq \frac{p}{n\tau} \sim 0.04\frac{\mathrm{Gy}}{\mathrm{a}}. \tag{3}$$

This is on the same order of magnitude as the value found in this study, $d_* \sim (0.03-0.06)\mathrm{Gy/a}$. In this light, the model results presented here and the repopulation mechanism may be interpreted to be compatible. However, it is important bearing in mind that these estimates are naturally crude. Matters are further complicated by the spatially inhomogeneous energy deposition within different spots in the lungs, an effect not reflected in whole-lung doses used here [58].

As an alternative mechanism, a radiation-induced disturbance of cell communication has been suggested [9, 59]. This may lead to, e.g., up-regulated growth signals or a reduction of apoptosis [60, 61], with a higher effect on intermediate cells because those tend to evade homeostatic control. It has even been proposed that a proliferation enhancement, mediated by such a bystander signaling, might be the generic mechanism for the response to densely ionizing radiation [62]. However, no mechanistic model has been put forward explaining in detail how this might lead to a dose-rate response, $\gamma(d)$.

Even so, should the radiation response indeed be governed by the bystander effect, then a similar behavior ought to be expected as for bystander-mediated mutation induction [63]. In microbeam experiments [64, 65], it has been found that for low doses—corresponding to less than $\sim 10\%$ of cells being hit—the mutagenic yield was strongly amplified as bystander cells also received signals. (A similar pattern has been found for intercellular induction of apoptosis [66].) For much higher doses, in turn, the response essentially saturated. Along the lines leading to Eq. (3), we can estimate the characteristic dose rate d_s by assuming the crossover to occur at a fraction $p = 0.1$ of cells being hit. This yields $d_s \approx p/n\tau \sim 0.025\mathrm{Gy/a}$, under the same caveats as mentioned above. From this standpoint, both bystander signaling and the repopulation hypothesis appear compatible with the dose-rate response found in this study.

B. Comparison with previous studies

As discussed earlier on, for mechanistic models, the risk is essentially determined by its structure, particularly, the radiation response. A dose-rate dependent proliferation rate, $\gamma(d)$, saturating for larger dose rates (as in Eq. 2) is found in many studies applying the two-stage model to α-particle-induced lung cancer. In particular, this response quantitatively agrees with that of the preferred two-stage model by Jacob *et al.* for the Mayak cohort, both for Plutonium and smoking [32]. Concordantly, their risk estimates are similar to those of the present TSCE model – such as a cohort-averaged excess risk of $\mathrm{ERR}(t = 60\mathrm{a})/D \sim 4/\mathrm{Gy}$, a nonlinear dose dependence $\mathrm{ERR}(D)$ for larger doses, and sub-multiplicity of smoking and radiation risks.

In a recent descriptive analysis of the Mayak data, Gilbert *et al.* found a linear dose response, modified significantly only by a drop-off with attained age ([37], see also Appendix). The value at age 60, $\mathrm{ERR}(t = 60\mathrm{a}) \sim 7D/\mathrm{Gy}$, is somewhat higher than for the cohort average of the mechanistic models presented here. By contrast, the multi-stage models exhibit a strongly nonlinear dose dependence especially for higher doses. Furthermore, they typically display a decrease with attained age only for large enough ages, most pronounced after the end of exposure. Initially, an increase with age is seen due to exponential clonal growth, at least for high enough doses.

In contrast to descriptive models, where an exposure modifier may not be significant when parametrized explicitly, mechanistic models implicitly make predictions for the risk dependence on any exposure scenario. This is exemplified by the age-at-exposure dependence or the inverse dose-rate effect shown by (at least some) mechanistic models (Fig. 5). Furthermore, a non-significant trend in Ref. [37] indicated a sub-multiplicative interaction be-