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A SURVEY OF THE JANUS MOUSE SKIN-PAINTING EXPERIMENTS

REPORT NO: RD.773-R

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Research & Development Establishment

Southampton

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AUTHOR: E.B. Wilkes

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The key to understanding the reasons for such things as the negative dose-response relationship in the observed response rates in B6 is to be found in Table 3 and Graph 3, where is shown plotted the number of animals dying before the appearance of the first tumour in each of the experiments. Now two distinct patterns of events can be seen. Experiments B2, B3 and B4 show little change in the number of deaths prior to first tumour as the dose level increases; on the other hand in experiments B0, B6, and B7, the deaths increase sharply with dose level. Comparison of Graphs 2 and 3 shows that it is the experiments with this sharp increase of early deaths with dose rate (B0, B6, B7) which exhibit the most anomalous behaviour.

This high initial mortality is (usually) due to the toxicity of the condensate, and it has the effect of reducing the number of animals at risk of producing a tumour; if the increase of death rate with dose level is high enough, the number of animals producing tumours will decrease with dose level, rather than increase. This is what happened in B6. Age standardisation is aimed at removing effects such as these, and generally speaking it does so quite well; the anomalous effects that remain in the standardised data are not primarily due to toxicity effects.

Cigarette smoke condensate does not produce instant tumours. The earliest tumours produced at Battelle have occurred about the 20th week of an experiment, and usually the time is about 28 to 32 weeks. Now consider B0. In the age standardised experiment 95½% of the animals survive to about the 28th week, so that even if every animal then became tumour bearing, the standardised response rate would be 95½%. In fact, the age standardised

rate for B0 (50 mg) is 80%, i.e. only 15% of the animals escaped becoming tumouring-bearing during the remainder of the experiment. This 15% represents the maximum amount by which any increase of the dose level above 50 mg no matter how great, can increase the standardised response. It is no surprise that under these circumstances an increase to 75 mg can only produce a rise to 84% in the standardised rate; this is about 25% of the maximum possible increase. Thus it is unrealistic to hope that when the 50 mg dose is producing a 70-80% response, the 75 mg dose will produce an effect that is proportionally greater. To do so in B0, for example, the standardised response at 75 mg would have to be 94%, i.e. virtually every animal after about 28 weeks must become tumour bearing; the 75 mg dose must absorb 100% of the available increase. And of course, this means that a further increase in dose level from 75 mg to 100 mg could produce no increase in the standardised rate at all; an equally anomalous situation.

The remedy for these high dose anomalies in the standardised experiments is now obvious; the dose levels must be reduced. The problem is to estimate the magnitude of this reduction. If the dose levels are too low, the tumour rates at the lowest doses will be so low as to be subject to great uncertainty, and requiring many animals to produce reasonable confidence levels. The consequences of the dose levels being too high are already quite apparent. The ideal situation is one where we have a linear dose-response relationship coupled with a reasonably high tumour yield even at the lowest dose levels.

APPENDIX

A short description of the cigarettes used in Experiments B0 to B7 is as follows:

B0 Flue-cured blend (CN102), lamina only.

B2 "Typical" U.S. K.S.F.T. cigarette.

B3 PCL, based on CN102 lamina and Canadian stem binder.

B4 Flue-cured lamina (CN102) and Canadian Stem (as CRS), in equal portions.

B6 Yeast treated flue-cured lamina (CN102), strand widths 30, 60 and 120 c.p.i.

B7 Flue-cured lamina (CN102) control for B6; strand widths 30, 60 and 120 c.p.i.

K0 groups are control groups of mice which are not treated.

KLm groups are control groups of mice which are treated with solvent only.

TABLE 1

Standardised values	Dose Levels		
	25	50	75
B0	47.7	79.9	83.8
B2	33.6	76.0	79.6
B3	16.9	54.9	65.2
B4	31.1	68.2	75.8
b6	59.1	81.2	80.7
B7	62.2	84.9	83.7

TABLE 2

Observed values	Dose Levels		
	25	50	75
B0	41.3	64.5	47.9
B2	33.4	68.9	69.8
B3	17.3	55.4	67.8
B4	28.4	62.5	65.9
B6	57.8	43.1	24.3
B7	56.2	57.9	43.8