

4. SOME ILLUSTRATIVE DATA SETS

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- 4.2 Skin painting experiment with cigarette- and cigar-smoke condensates
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CHAPTER 4

SOME ILLUSTRATIVE DATA SETS

In this chapter we give some detailed data sets which are used as examples in the subsequent chapters.

4.1 Bioassay of 1,2-dichloroethane

The first data set is taken from an NCI (USA) bioassay of 1,2-dichloroethane (National Cancer Institute, 1978). For our purposes, we have considered only data on the occurrence of alveolar/bronchiolar adenomas of the lung in female B6C3F1 mice in three groups – a high-dose group, a low-dose group and a control group, with originally 50, 50 and 40 animals, respectively. Dosage was continued for 78 weeks and terminal sacrifice carried out after 90 weeks. The lungs of all animals, apart from two autolysed animals in the high-dose group, were examined histopathologically; the data are summarized in Table 4.1. Although, in this experiment, no attempt was made to record the context of observation of the tumours, there appears to be agreement that these lung adenomas can be considered as incidental findings, that is, they did not contribute to the deaths of the animals.

4.2 Skin-painting experiment with cigarette- and cigar-smoke condensates

The second data set is taken from a mouse skin-painting study carried out by the Tobacco Research Council, UK (Lee, 1979). This study included six groups of 100 Carworth Swiss female mice, three painted with condensate from standard cigarettes at dose levels of 180, 136 and 103 mg per week and three painted with condensate from standard cigars at dose levels of 103, 78 and 59 mg per week. The dose levels were chosen from past experience so as to give a similar range of responses on a rising part of the dose-response curve, to be at equal steps on a logarithmic scale and to allow some comparison between identical doses of the two carcinogens. Condensates were applied continuously three times per week and continued for 100 weeks, at which time all surviving mice were killed. The data are presented in Table 4.2, giving time to visible skin tumour (if applicable) or time to death or terminal kill for all animals.

4.3 Pituitary tumours in rats treated with various doses of *N*-nitrosodimethylamine (NDMA)

A large animal experiment with a total of 5000 rodents was conducted by the British Industrial Biological Research Association (Peto *et al.*, 1984). The study was designed

Table 4.1 Alveolar/bronchiolar adenomas of the lung in female B6C3F1 mice treated with 1,2-dichloroethane by gavage

Control group			Low-dose group			High-dose group		
Time (weeks)	No. of deaths	No. of animals with tumours	Time (weeks)	No. of deaths	No. of animals with tumours	Time (weeks)	No. of deaths	No. of animals with tumours
22	1		46	1		11	3	
56	1		61	1		12	4	
60	1		66	1		14	1	
65	1		70	1		31	1	
77	1		73	1		36	1	
79	1		78	1		44	1	
85	1		81	1		57	1	
90	33	2	82	2		62	2	1
			86	2		63	2	2
			87	1		65	4	2
			88	3		66	1	
			90	35	7	67	2	1
						68	4	
						69	2	1
						70	3	1
						71	1	
						73	4	2
						74	2	1
						75	2	1
						76	1	1
						77	3	
						79	1	
						80	1	1
						90	1	1
Total	40	2		50	7		48	15

to investigate the dose-response relationship for the carcinogenicity of different nitrosamines administered in drinking-water.

In the main part of the study, for each of the two nitrosamines investigated, *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA), 16 treatment groups were considered: an untreated control group was given 0 ppm (group 1), and the 15 treated groups were given 0.033 ppm (group 2), 0.066 ppm (group 3), 0.132 ppm (group 4), 0.264 ppm (group 5), 0.528 ppm (group 6), 1.056 ppm (group 7), 1.584 ppm (group 8), 2.112 ppm (group 9), 2.640 ppm (group 10), 3.168 ppm (group 11), 4.224 ppm (group 12), 5.280 ppm (group 13), 6.336 ppm (group 14), 8.448 ppm (group 15) and 16.896 ppm (group 16). Inbred Colworth rats were used and, for each compound and each sex, the control group comprised 192 animals and each treated group, 48.

The context of observation was recorded for all tumours found. Subsequently, we give the data for the occurrence of pituitary tumours in male rats given NDMA. Table 4.3 lists, for all 16 groups, the time to death for each animal and the context of observation for pituitary tumours. Time to death is recorded in days, whereas the

Table 4.2 Time (in weeks) to skin tumour or death (terminal kill) for six groups of Carworth Swiss female mice

Group A: Cigarette condensate 180 mg/week

(a) 43 animals with skin tumour at:

24	24	29	31	32	34	34	38	41	41
41	41	43	48	48	49	51	57	58	59
61	61	62	62	62	63	64	65	66	66
68	72	72	75	76	79	79	81	84	85
88	88	100							

(b) 57 animals without skin tumour died at:

4	8	8	8	8	8	12	12	12	12
17	17	17	20	20	20	22	28	28	28
33	36	43	47	50	50	51	51	51	52
54	54	56	58	62	62	64	64	65	66
67	68	69	71	71	71	71	72	75	78
81	81	82	86	87	96	96			

Group B: Cigarette condensate 136 mg/week

(a) 36 animals with skin tumour at:

32	38	46	46	50	61	61	63	64	66
67	69	71	71	72	72	75	75	75	79
79	79	80	81	81	81	82	84	84	85
88	88	89	90	93	98				

(b) 64 animals without skin tumour died at:

5	6	8	12	12	12	12	12	16	16
16	17	19	19	20	22	23	28	31	36
36	38	40	40	41	44	47	50	52	53
53	54	59	64	65	66	68	69	70	71
74	74	76	80	84	84	84	86	88	89
91	93	95	95	96	98	98	98	100	100
100	101	101	101						

Group C: Cigarette condensate 103 mg/week

(a) 13 animals with skin tumour at:

20	27	35	47	50	64	65	84	84	88
93	98	100							

(b) 87 animals without skin tumour died at:

7	8	10	11	12	14	16	16	16	16
16	17	17	20	20	23	23	24	25	29
31	34	34	43	45	46	47	48	49	50
55	57	59	60	64	65	66	68	68	72
72	74	74	74	74	75	77	78	79	79
79	80	80	81	82	83	83	84	84	84
84	84	85	88	89	91	91	91	93	94
95	95	95	96	96	97	100	100	101	101
101	101	101	101	101	101	101			

Group D: Cigar condensate 103 mg/week

(a) 37 animals with skin tumour at:

38	43	43	48	49	50	50	50	50	57
57	58	58	58	61	62	64	64	66	66
71	71	72	72	72	75	76	79	79	81
84	84	86	88	93	93	99			

Table 4.2 *Contd.*

(b) 63 animals without skin tumour died at:									
5	6	7	7	8	8	8	8	8	8
8	8	11	11	11	12	16	20	20	20
22	25	25	28	28	28	30	34	35	36
36	38	40	54	55	55	56	57	59	61
61	61	63	63	64	65	68	68	69	73
75	79	81	82	82	84	90	91	92	92
97	100	101							
<i>Group E: Cigar condensate 78 mg/week</i>									
(a) 31 animals with skin tumour at:									
38	41	41	49	54	57	57	58	61	64
64	64	71	71	72	72	75	76	76	76
79	79	82	84	85	86	93	93	93	98
100									
(b) 69 animals without skin tumour died at:									
7	7	7	8	8	8	8	8	8	12
13	14	16	16	17	19	20	20	20	25
25	27	29	33	33	37	39	40	41	43
44	44	47	50	50	50	53	56	57	63
63	66	70	71	75	79	79	81	81	81
82	85	87	88	89	94	96	97	98	98
98	100	100	100	100	101	101	101	101	101
<i>Group F: Cigar condensate 59 mg/week</i>									
(a) 21 animals with skin tumour at:									
24	31	38	39	46	46	53	54	58	66
71	73	75	79	79	80	81	85	93	94
96									
(b) 79 animals without skin tumour died at:									
7	12	12	12	12	12	14	14	16	16
16	16	16	17	19	20	20	25	25	28
33	36	47	48	49	50	50	53	57	57
59	60	62	63	68	69	69	70	78	84
84	84	85	85	86	89	89	89	90	90
90	91	91	92	92	94	97	97	98	98
99	100	100	101	101	101	101	101	101	101
101	101	101	101	101	101	101	101	101	101

context of observation is given as:

- 0 no pituitary tumour found,
- 1 incidental,
- 2 probably incidental,
- 3 probably fatal,
- 4 fatal,
- 3 totally cannibalized or autolysed; cause of death not ascertainable,
- 2 head cannibalized or autolysed; presence or absence of pituitary tumour not ascertainable but death known *not* to be caused by pituitary tumour.

Table 4.3 Group number, time to death (in days) and context of observation of pituitary tumours in male Colworth rats exposed to *N*-nitrosodimethylamine (NDMA)

1 4-3	1 793 0	1 931 0	1 1029 0
1 50-3	1 795 0	1 932 4	1 1036 0
1 197 0	1 796 0	1 933 4	1 1037 2
1 260 0	1 796 0	1 934 0	1 1039 0
1 297 0	1 797 1	1 937 0	1 1044 4
1 302 0	1 799 1	1 937 0	1 1050 4
1 373 0	1 806 0	1 944 0	1 1050 4
1 415 0	1 812 0	1 944 0	1 1051 1
1 471 0	1 823 1	1 952 0	1 1055 0
1 476-2	1 826-2	1 954 0	1 1058 0
1 496 0	1 835 0	1 955 0	1 1062 0
1 502 0	1 837 0	1 959 0	1 1063 4
1 523 0	1 840 0	1 964 0	1 1066 0
1 534 4	1 840 0	1 965 1	1 1070 0
1 604 0	1 846 4	1 965 1	1 1073 1
1 607-3	1 847 0	1 966 1	1 1075 0
1 617 0	1 848 0	1 966 0	1 1078 1
1 618 0	1 851 0	1 968 0	1 1078 0
1 623 0	1 856 4	1 973 0	1 1079 4
1 637 0	1 858 4	1 973 0	1 1079 0
1 652 0	1 864 0	1 973 1	1 1087 1
1 652-2	1 867 0	1 974 0	1 1092 4
1 672 0	1 871 0	1 975 1	1 1097 0
1 676 0	1 872 0	1 977 0	1 1100 0
1 679 3	1 875 0	1 981 0	1 1101 1
1 688 0	1 881 0	1 981 4	1 1102 0
1 700 0	1 884 4	1 986 0	1 1103 0
1 700 0	1 884 0	1 988 0	1 1113 0
1 713 0	1 885 0	1 989 0	1 1117 0
1 716 0	1 886 4	1 991 0	1 1125 0
1 721 4	1 889 0	1 994 0	1 1135 1
1 723 0	1 895 1	1 995 0	1 1135 1
1 724 4	1 897 0	1 996 0	1 1147 1
1 726 0	1 897 0	1 999 4	1 1149 0
1 727-3	1 902 0	1 999 0	1 1151 0
1 732 0	1 904 0	1 999 0	1 1156 4
1 734 0	1 904 4	1 1003 0	1 1159 0
1 734 0	1 905 0	1 1003 0	1 1165 0
1 747 0	1 908 1	1 1003 0	1 1182 1
1 750 0	1 910 0	1 1006 0	1 1184 0
1 756 0	1 916 1	1 1009 0	1 1187 4
1 764 4	1 918 0	1 1013 0	1 1213 0
1 765 4	1 919 0	1 1015 0	
1 766 0	1 919 0	1 1022 0	
1 773 0	1 919 1	1 1024 0	
1 776 0	1 921 1	1 1024 0	
1 777 4	1 921 4	1 1024 0	
1 778 0	1 922 0	1 1026 0	
1 782 0	1 923 0	1 1027 0	
1 785 0	1 925 1	1 1027 0	

Table 4.3 *Contd.*

2 380 0	3 529 0	4 343 -3	5 317 0
2 447 0	3 646 0	4 458 -2	5 619 0
2 454 0	3 646 0	4 493 0	5 621 0
2 512 0	3 677 0	4 520 0	5 626 0
2 552 4	3 679 0	4 559 0	5 632 0
2 623 0	3 693 0	4 623 0	5 677 -2
2 696 0	3 714 0	4 664 0	5 688 4
2 703 4	3 724 0	4 680 0	5 706 0
2 748 0	3 728 0	4 709 0	5 709 0
2 753 0	3 751 4	4 714 0	5 733 0
2 785 0	3 764 0	4 761 0	5 736 1
2 835 0	3 766 0	4 767 4	5 742 0
2 837 0	3 783 4	4 779 0	5 749 0
2 844 0	3 784 0	4 808 1	5 776 0
2 863 4	3 819 4	4 828 0	5 791 4
2 873 0	3 824 0	4 833 4	5 798 0
2 901 0	3 828 0	4 848 1	5 804 0
2 907 4	3 830 0	4 852 0	5 809 0
2 913 4	3 835 0	4 879 4	5 826 0
2 916 4	3 854 0	4 908 0	5 828 0
2 917 4	3 874 0	4 928 0	5 828 0
2 926 0	3 874 0	4 939 1	5 832 4
2 967 0	3 882 4	4 945 1	5 842 0
2 974 0	3 917 0	4 952 0	5 843 0
2 982 0	3 924 1	4 966 0	5 895 0
2 984 0	3 935 0	4 969 0	5 900 0
2 985 0	3 960 0	4 973 0	5 903 0
2 996 0	3 960 0	4 980 4	5 915 0
2 997 0	3 962 0	4 986 1	5 923 4
2 997 0	3 987 1	4 999 0	5 960 4
2 1002 1	3 988 0	4 1003 1	5 967 0
2 1010 3	3 989 4	4 1003 0	5 976 0
2 1016 0	3 995 1	4 1004 0	5 986 0
2 1029 1	3 996 4	4 1018 0	5 988 4
2 1033 1	3 1013 4	4 1020 0	5 1007 0
2 1036 0	3 1021 0	4 1021 1	5 1015 1
2 1048 1	3 1044 1	4 1023 0	5 1046 0
2 1065 0	3 1045 0	4 1029 0	5 1049 0
2 1081 0	3 1048 1	4 1056 4	5 1065 1
2 1085 3	3 1059 0	4 1068 0	5 1071 0
2 1095 1	3 1066 4	4 1071 0	5 1084 0
2 1102 0	3 1077 0	4 1084 0	5 1086 4
2 1110 0	3 1088 0	4 1084 0	5 1092 0
2 1118 1	3 1126 0	4 1090 0	5 1101 0
2 1130 3	3 1132 0	4 1095 1	5 1110 4
2 1135 0	3 1162 0	4 1114 1	5 1162 0
2 1148 0	3 1166 1	4 1121 0	5 1167 0
2 1234 0	3 1178 0	4 1188 0	5 1234 0

Continued

Table 4.3 *Contd.*

6 460 0	7 410 0	8 296 0	9 554 0
6 548 0	7 566 0	8 586 0	9 561 0
6 577 0	7 568 0	8 623 4	9 576 0
6 679 0	7 575 0	8 650 0	9 596 1
6 707 0	7 579 0	8 656 0	9 646 0
6 708 0	7 638 4	8 702 -2	9 671 0
6 713 0	7 656 0	8 728 0	9 683 0
6 750 0	7 678 0	8 736 0	9 684 0
6 777 4	7 680 0	8 737 4	9 709 4
6 786 4	7 708 0	8 740 0	9 730 0
6 821 0	7 712 0	8 767 0	9 742 4
6 825 0	7 714 4	8 771 0	9 743 0
6 838 0	7 719 0	8 771 4	9 744 0
6 848 0	7 723 0	8 776 0	9 766 0
6 874 4	7 742 0	8 779 0	9 773 0
6 898 4	7 777 0	8 800 0	9 821 0
6 898 4	7 797 4	8 802 0	9 823 0
6 901 1	7 805 0	8 811 4	9 838 0
6 916 4	7 806 4	8 816 4	9 861 0
6 929 0	7 830 0	8 838 0	9 864 0
6 948 0	7 842 0	8 843 3	9 870 0
6 951 4	7 844 0	8 851 4	9 880 4
6 952 4	7 846 0	8 858 1	9 891 0
6 953 4	7 858 4	8 872 4	9 921 0
6 961 0	7 863 4	8 889 0	9 925 1
6 961 0	7 888 0	8 892 1	9 930 0
6 966 0	7 909 4	8 895 0	9 936 4
6 973 0	7 917 0	8 897 0	9 940 0
6 994 0	7 937 0	8 901 0	9 947 0
6 1009 0	7 953 0	8 903 0	9 953 0
6 1010 0	7 954 0	8 908 0	9 955 0
6 1034 0	7 955 0	8 912 1	9 961 4
6 1041 1	7 956 0	8 932 0	9 970 0
6 1046 0	7 980 0	8 933 0	9 992 0
6 1053 0	7 982 1	8 946 0	9 996 1
6 1056 0	7 996 1	8 950 0	9 1009 1
6 1059 0	7 998 0	8 956 4	9 1028 0
6 1064 0	7 1000 4	8 994 0	9 1030 0
6 1073 1	7 1001 0	8 1003 4	9 1035 1
6 1073 1	7 1047 0	8 1020 1	9 1041 1
6 1085 1	7 1052 0	8 1028 0	9 1047 1
6 1092 4	7 1055 0	8 1037 0	9 1056 0
6 1094 1	7 1081 4	8 1045 0	9 1058 0
6 1120 0	7 1115 0	8 1063 0	9 1073 0
6 1126 1	7 1122 0	8 1071 4	9 1082 0
6 1127 1	7 1174 0	8 1078 0	9 1101 0
6 1137 0	7 1183 0	8 1082 1	9 1117 0
6 1218 0	7 1204 1	8 1089 1	9 1119 0

Table 4.3 *Contd.*

10 254 0	11 331 0	12 87 0	13 345 0
10 264 0	11 441 0	12 265 0	13 371 0
10 411 0	11 467 0	12 267 0	13 387 0
10 495 0	11 485 0	12 289 0	13 407 0
10 495 -2	11 526 0	12 393 0	13 412 0
10 516 0	11 527 0	12 419 0	13 435 0
10 554 0	11 533 0	12 470 0	13 442 0
10 569 0	11 559 0	12 499 0	13 470 0
10 601 0	11 596 4	12 506 0	13 476 0
10 627 0	11 600 0	12 516 0	13 477 0
10 633 0	11 614 0	12 539 0	13 483 0
10 660 4	11 645 4	12 555 0	13 483 0
10 660 4	11 651 0	12 581 0	13 485 0
10 663 -2	11 676 0	12 610 0	13 488 0
10 681 1	11 690 0	12 621 0	13 518 0
10 686 0	11 695 0	12 632 0	13 519 0
10 698 4	11 707 0	12 633 0	13 522 0
10 708 0	11 709 0	12 646 0	13 525 0
10 716 0	11 716 0	12 661 0	13 525 0
10 716 1	11 731 0	12 665 0	13 534 0
10 720 0	11 732 0	12 667 4	13 534 0
10 724 0	11 764 0	12 676 0	13 539 0
10 729 4	11 768 0	12 690 0	13 540 0
10 751 0	11 771 0	12 696 0	13 546 0
10 759 0	11 775 0	12 707 0	13 549 0
10 770 1	11 783 0	12 710 0	13 556 0
10 777 0	11 796 0	12 715 0	13 564 0
10 778 0	11 802 0	12 720 0	13 581 0
10 786 0	11 814 0	12 720 1	13 581 0
10 788 0	11 833 0	12 729 0	13 586 0
10 795 0	11 838 0	12 729 0	13 589 0
10 812 4	11 840 0	12 736 0	13 591 0
10 864 0	11 855 0	12 736 0	13 597 0
10 880 0	11 857 0	12 741 0	13 598 0
10 884 0	11 864 0	12 779 0	13 604 0
10 884 4	11 867 0	12 795 0	13 604 0
10 903 0	11 868 1	12 804 0	13 618 1
10 911 0	11 868 4	12 808 0	13 628 0
10 918 0	11 879 0	12 814 0	13 651 0
10 931 1	11 883 0	12 863 0	13 656 0
10 938 1	11 894 0	12 872 0	13 663 0
10 944 0	11 894 4	12 880 0	13 665 0
10 946 0	11 898 0	12 893 0	13 677 0
10 966 0	11 914 0	12 894 0	13 684 0
10 986 0	11 919 0	12 897 0	13 687 0
10 1015 0	11 919 4	12 904 0	13 700 0
10 1043 0	11 947 0	12 933 0	13 706 1
10 1086 0	11 957 0	12 1019 0	13 778 0

Continued

Table 4.3 *Contd.*

14 248 0	15 177 0	16 92 0
14 284 0	15 297 0	16 140 0
14 285 0	15 303 0	16 160 -2
14 372 0	15 309 0	16 164 0
14 376 0	15 316 0	16 168 0
14 421 0	15 362 0	16 169 0
14 428 0	15 364 0	16 170 0
14 432 0	15 365 0	16 180 0
14 441 0	15 371 -2	16 188 -2
14 471 0	15 383 0	16 189 0
14 474 0	15 388 0	16 194 0
14 477 0	15 390 0	16 200 0
14 482 0	15 399 0	16 200 0
14 498 0	15 399 0	16 205 0
14 498 0	15 405 0	16 206 0
14 498 0	15 416 0	16 208 0
14 499 0	15 417 0	16 210 0
14 505 0	15 423 0	16 210 0
14 507 0	15 433 0	16 211 0
14 518 0	15 445 0	16 211 0
14 526 0	15 462 0	16 214 0
14 527 0	15 462 0	16 215 0
14 527 0	15 468 0	16 222 0
14 539 0	15 469 0	16 223 0
14 539 0	15 470 0	16 223 0
14 539 0	15 471 0	16 225 0
14 540 0	15 471 0	16 228 0
14 540 0	15 475 0	16 232 0
14 546 0	15 477 0	16 236 0
14 551 0	15 483 0	16 236 -2
14 562 0	15 488 0	16 238 0
14 567 0	15 492 0	16 239 0
14 568 0	15 497 0	16 244 0
14 569 0	15 499 0	16 245 0
14 575 0	15 505 0	16 252 0
14 576 0	15 505 0	16 252 0
14 602 0	15 511 0	16 254 0
14 602 0	15 516 0	16 255 0
14 603 0	15 520 0	16 261 0
14 606 0	15 526 0	16 266 0
14 609 0	15 527 0	16 266 0
14 609 0	15 533 0	16 267 0
14 632 0	15 540 0	16 267 0
14 633 0	15 553 0	16 275 0
14 648 0	15 555 0	16 281 0
14 672 0	15 557 0	16 290 0
14 694 0	15 562 0	16 310 0
14 757 0	15 570 0	16 311 0

How these different types of observations are used in the analysis will be outlined in the respective sections of Chapter 5.

4.4 An artificial teaching example

In order to illustrate the different methods that will be given in the next chapter with a smaller example for which the computations required can be done by hand, a constructed example is given here. The hypothetical experiment comprises three groups of 15 animals; group 1 may be considered an undosed control group, group 2 a low-dose group, and group 3 a high-dose group. Time to death is given for each animal (scale unimportant), and the context of observation of each tumour is recorded as follows:

- 0 tumour not present,
- 1 incidental,
- 2 probably incidental,
- 3 probably fatal,
- 4 fatal.

The data are given in Table 4.4; a detailed solution to this example can be found in Appendix I.

Table 4.4 Time to death and context of observation for animals in three groups (hypothetical example)

Group 1		Group 2		Group 3	
Time	Context	Time	Context	Time	Context
140	2	100	2	80	0
140	0	110	0	90	4
140	0	110	0	100	0
150	0	120	0	110	0
150	0	130	3	130	2
160	0	140	2	140	1
165	2	150	2	140	3
170	4	150	0	140	0
180	0	160	4	150	0
185	4	165	0	150	4
200	1	170	0	150	1
200	1	180	3	160	4
200	0	200	1	170	0
200	0	200	0	190	3
200	0	200	1	200	0

