

SUBJECT INDEX

A

- Abelson–Tukey test, 174
- Acceleration
 - definition, 7
 - fatal tumours, 13
 - incidental tumours, 14–15
 - test for, with fatal tumours, 87
- 2-Acetylaminofluorine (2-AAF), 43, 49, 109–10, 119
- Adaptive internal selection method, 89–90
- Additive model, 158
- Adjustment for intercurrent mortality, 8, 13, 15
- Age-specific hazard rates, 160
- Age-specific incidence rates, 127
- Analysis of variance, 171–80
 - nonparametric, 177
 - parametric, 172
- Animal carcinogenesis experiments, 6–20, 70–106
- Animal selection, 24
- Armitage–Doll model, 112
- Armitage test, 174
- Association among tumour types, 165
- Asymptotic approximations
 - 2×2 table, 77
 - $2 \times k$ table, 82, 97
 - rank tests with censored data, 71
- Auxiliary data, 170

B

- Background response, 111
- Benzo[*a*]pyrene (BP), 50, 132–35
- Bias
 - due to intercurrent mortality, 8, 13–15
 - due to lack of randomization, 30
 - in analysis of fatal tumours, 13–14
 - in analysis of incidental tumours, 14–15
- Blind pathology, 51
- Bonferroni correction, 87

- Bonferroni method (*see* Multiple comparisons)
- Breslow-modified Wilcoxon test, 101

C

- Cage effects (*see* Randomization)
- Carcinogenesis mechanism studies, 47–50, 54
- Carcinogenic potency, estimation, 120, 121
- Carcinogenic potential, 41
- Carcinogenicity bioassay, 23, 27
- Carcinogenicity evaluation, 19–20
- Chi-squared statistics, 71, 79, 83, 97
- Cigar-smoke condensate, 95–100, 129, 130, 135
- Cochran–Armitage trend test, 83, 86
- Combining evidence from several experiments
 - analysis of crude tumour rates, 75–87
 - analysis of tumour incidence curves, 96–98
 - contexts of observation, 15
 - rationale, 10
- Competing risks, 124–25
- Computer programs, 212–13
- Concomitant information, 19
- Conditional maximum likelihood estimator, 81
- Conditional point estimates, 81
- Confidence intervals
 - nonparametric for percentile, 73
 - odds ratio for crude tumour rates, 81, 82
 - quantiles for low-dose extrapolation, 117
- Contexts of observation, 15–17
 - definition, 12
 - use in analysis, 15–16, 101
- Contingency tables, 70, 90
- Continuity correction
 - for 2×2 table, 79
 - for $2 \times k$ table, 86

- Control group, 81–82
 positive control, 34–35
 rationale, 34–35
 vehicle control, 35
- Cornfield's method, 78
- Cornish–Fisher skewness correction, 83
- Crude tumour rate
 comparison of more than two crude rates, 81, 82
 comparison of two crude rates, 77, 80
 definition, 17, 76
 modification of denominator for early mortality, 76
 potential for bias in analysis of, 8–9, 17
- D**
- Data recording, 51–53, 55
- Data sets, 58–67
- DDT, 167
- 1,2-Dichloroethane, 58, 76, 82, 89–91, 93
- Dieldrin, 117
- 7,12-Dimethylbenz[*a*]anthracene, 151
- Dose-response, 23, 54, 143
 design considerations, 43
 general power considerations, 11
 models for crude tumour rates, 109
 pharmacokinetic models, 112–16
- Dose selection, 26, 45
- Druckrey's relationship, 135
- Dunn–Sidák method, 175
- Duration of experiment, 25
- E**
- Error rates
 control of false-positive rate for multiple comparisons, 87
 design considerations, 36
 effect of heterogeneity in test animals, 42
 sequential designs to reduce error rates, 42–43
- Estimation, 131–32
- Exact or conditional analysis, 80, 85
- Experimental design, 22–55
 considerations for low-dose extrapolation, 46
 criteria evaluation, 35–36
 factorial, 49
 for determination of dose-response, 43
 for screening experiment, 36
 general considerations, 28–36
 optimal, 36
 principles of, 28–36
 sequential, 42–43
- Experimental unit, 54
 importance of determining, 28–29
- F**
- False-positive rate (*see* Nominal significance level)
- Fatal context
 definition, 13
 likelihood contribution when fitting models, 124
 nonparametric comparison of tumour death rates, 94
- Fisher–Irwin exact test, 80
 approximate formula for, 37
 extension to $2 \times k$ table, 85
 for 2×2 table, 80
- Formaldehyde, 110
- G**
- Generalized Savage test (*see* Log-rank test)
- GLIM, 132
- Graded responses, analysis when lesions graded, 153
- Growth curve models, 182–83
- H**
- Histopathological analysis, 50
- Historical control data, 8, 167
- Homogeneity chi-squared tests, 97
- I**
- Incidence, difficulty in evaluating for occult tumours, 12–16
- Incidental context
 definition, 13
 nonparametric comparison of tumour prevalence rates, 87
- Incidental tumours, 14, 15
- Initiation/promotion study, 48

Integrated models, 141–42
 Intercurrent mortality, 8
 Interdisciplinary decision process, 19
 Internal tumours, 137 (*see also* Occult tumours)

J

Jonckheere statistic, 179

K

Kaplan–Meier curve
 for observable or fatal tumours, 95
 to summarize survival, 73–75, 141
 Kaplan–Meier estimate, 96, 127
 Kinetic rate constants, 128, 134, 136–37
 Kruskal–Wallis test, 177, 178

L

Latent failure times, 124
 Lethal tumours, 94, 160
 Life-table analysis, 98–100 (*see also* Kaplan–Meier curve; Log-rank test)
 Litters
 design considerations, 28–32
 statistical methods, 160
 Liver tumours, 117, 119
 Logistic model
 estimation of logistic slope, 83–84
 fitting regression models with prevalence data, 141–42
 for crude tumour rates, 81–82
 prevalence analysis of incidental tumours, 87–94
 Logistic regression, 19, 97
 Log-likelihood function, 126, 130–32
 Log-rank test, 96–97
 analysis of observable or fatal tumours, 94
 analysis of survival data, 73–75
 Low-dose extrapolation
 design considerations, 43
 quantile estimation, 117
 Lung tumour, 82

M

Mann–Whitney test, 178, 179
 Mantel–Haenszel estimator, 97

Mantel–Haenszel procedure, 86
 Markov model, 142
 Maximum likelihood estimation, 116–17, 129
 Maximum tolerated dose (MTD), 26, 45–46, 53
 Michaelis–Menten kinetics, 113, 115
 Model fitting, 108–45
 Monotonicity, 174, 178–80
 Multi-factorial design
 definition, 49
 methods of analysis, 155
 Multi-generation studies
 design considerations, 39, 47–50
 importance of identifying experimental units, 28–29
 Multi-hit models, 111
 Multiple comparisons, 87, 101, 180
 comparisons at several dose levels, 77, 171, 174
 inference at several organ sites, 148
 multiple test statistics, 101
 Multiplicative model, 158
 Multivariate linear models, 181
 Multi-stage experiments (*see* Sequential designs)
 Multi-stage models, 112, 127, 138
 Multi-strain experiments, 41–42, 54

N

N-Nitrosodimethylamine, 58–67, 103
 Nested analysis of variance model, 176
 Newton–Raphson method, 140
 Nominal significance level, definition, 36, 149
 Non-continuous exposure, 136
 Nonparametric methods, 70–106, 177–78, 182
 general form of rank test statistics, 70–71
 survival and tumour incidence curve estimator, 73–75, 94
 Nonparametric test statistics, 70–73

O

Observable tumours, 160
 analysis of incidence curves, 94
 definition, 11
 fitting time-to-tumour models, 122

- Occult tumours, 14, 87–94, 126
 analysis, 101–105
 definition, 12
 general, 12–15
 likelihood for time-to-tumour models, 125
- Odds ratio, 81, 84, 85
 approximate confidence interval, 78
 conditional maximum likelihood estimator, 80–81
 definition, 78
 exact confidence interval, 81
 unconditional maximum likelihood estimator, 78
- One-way analysis of variance, 175–77
- P**
- Pairwise group comparisons, 174–75
- Parametric methods, 172
- Parametric model, 127
- Peto–Prentice-modified Wilcoxon statistics
 96, 101
- Pharmacokinetic models, 112–16, 143
- Pituitary tumours, 58–67, 104
- [²³⁹Pu]-Plutonium oxide, 50
- Potency index, 120, 121
- Power
 definition, 35
 effect of genetic heterogeneity, 42
 effect of intralitter correlation, 39–40
 for Cochran–Armitage trend test, 38
 for Fisher–Irwin exact test, 37, 39
- Prevalence analysis, for incidental occult tumours, 87–94
 fitting logistic regression models, 141
 models with planned interim sacrifices, 141–42
 significance tests, 131–32
- Proportional hazards model, 139–41
- Q**
- Quantile estimation, 117, 143
- R**
- Randomization, 24, 54, 80, 154, 171, 175
 general importance, 29–32
 of animals to treatment, 29–32
 of cage location, 30–32
- Regression analysis, 171
- Regression coefficients, 132
- Regression models, 141
- Relative risks, 159
- Repeated measures, 180
 definition, 180
 multivariate linear models, 181
 nonparametric and robust methods, 182
- Replication, 33
- Reticuloendothelial tumours, 29
- S**
- Sample size
 approximate formula for
 Cochran–Armitage trend test, 39
 approximate formula for Fisher–Irwin exact test, 37
 table for Cochran–Armitage trend test, 40
 tables for Fisher–Irwin exact test, 37, 38, 39
- Screening studies, 23, 26, 36–43, 53
- Sequential designs, 42–43
- Significance testing, 131–32
- Skin-painting experiment, 58, 95, 128, 130, 135
- Skin tumours, 136
- Stratification, 33–34, 54
 combining results from several strata, 10, 86
- Survival analysis, general, 170 (*see also* Kaplan–Meier curve; Log-rank test)
- Survival curves, 73–75, 96
- Systematic designs, 31
- T**
- Tests for departure from trend, 71, 86
- Tests for heterogeneity, 71, 83
- Tests for trend, 83, 85, 86, 101, 174, 178–80
- 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD), 120
- Time-to-tumour models, 122–42, 144
- Tolerance distribution
 definition, 110
 incorporation of background rates, 111
ortho-Toluenesulfonamide, 181

Tumorigenic ratio, 135
Tumour multiplicity
 general, 6–8
 methods of analysis, 150
Two-generation studies, 39

V

Vinyl chloride, 109
'Virtually safe' dose, 119
Visible tumours, 125, 128

W

Weibull distribution, 127, 128, 131, 132, 134,
 136, 137
Weibull models, 119, 129
 derivation from multi-stage theory, 127
 fitting model to observable or fatal
 tumours, 128 *et seq.*
 fitting model to occult tumours, 137
Wilcoxon test, 75, 96, 178