

Table of contents

List of contributors

1 Introduction

| | |
|--|----|
| 1.1 Background | 13 |
| 1.2 The <i>N</i> -nitroso compounds as model carcinogens | 13 |
| 1.3 Interest in the role of <i>N</i> -nitroso compounds | 14 |
| 1.4 The structure of this book | 15 |
| References | 15 |

2 Analysis of *N*-nitroso compounds in foods and human body fluids

| | |
|---|----|
| 2.1 Introduction | 16 |
| 2.2 General analytical considerations | 17 |
| 2.2.1 Contamination during analysis | 17 |
| 2.2.2 Artefact formation | 17 |
| 2.2.3 Accuracy and precision | 18 |
| 2.3 Volatile <i>N</i> -nitrosamines | 19 |
| 2.3.1 Extraction and sample work-up procedures | 19 |
| 2.3.2 Gas chromatographic determination | 20 |
| 2.3.3 Collaborative studies | 21 |
| 2.4 Non-volatile <i>N</i> -nitroso compounds | 22 |
| 2.4.1 High performance liquid chromatography detectors | 22 |
| 2.4.2 <i>N</i> -nitrosoamino acids | 24 |
| 2.4.3 Heterocyclic <i>N</i> -nitrosoamino acids | 25 |
| 2.4.4 <i>N</i> -terminal <i>N</i> -nitrosoamino acid residues | 26 |
| 2.4.5 Hydroxylated <i>N</i> -nitroso compounds | 26 |
| 2.4.6 <i>N</i> -nitrosoureas and related compounds | 27 |
| 2.4.7 Other <i>N</i> -nitroso compounds | 27 |
| 2.5 Apparent total <i>N</i> -nitroso compounds | 28 |
| 2.5.1 Analytical methods | 28 |
| 2.5.2 False-positive interference | 30 |

| | |
|--|----|
| 2.5.3 False-negative interference | 32 |
| 2.5.4 Gastric juice | 33 |
| 2.6 Conclusions | 34 |
| 2.7 Abbreviations | 35 |
| References | 35 |
| 3 The chemistry of <i>N</i>-nitrosation | |
| 3.1 Introduction | 48 |
| 3.1.1 Introduction to the chemistry of <i>N</i> -nitrosation | 48 |
| 3.1.2 Literature of <i>N</i> -nitrosation chemistry | 49 |
| 3.2 <i>N</i> -nitrosation in solution | 49 |
| 3.2.1 Formation of <i>N</i> -nitrosating agents | 49 |
| 3.2.2 Reactions under acidic conditions | 50 |
| 3.2.3 <i>N</i> -nitrosation under neutral and alkaline conditions | 56 |
| 3.3 Modifiers of <i>N</i> -nitrosation | 59 |
| 3.3.1 Catalysts or enhancers of <i>N</i> -nitrosation | 59 |
| 3.3.2 Inhibitors of <i>N</i> -nitrosation | 60 |
| 3.4 Relevance of <i>N</i> -nitrosation chemistry to the formation of <i>N</i> -nitroso compounds <i>in vivo</i> | 61 |
| References | 62 |
| 4 Mechanisms of endogenous <i>N</i>-nitrosation | |
| 4.1 Introduction | 69 |
| 4.2 Precursors to endogenous <i>N</i> -nitrosation | 72 |
| 4.3 Potential mechanisms of endogenous formation | 72 |
| 4.3.1 Chemical mechanisms | 74 |
| 4.3.2 Biologically mediated <i>N</i> -nitrosation reactions | 75 |
| 4.4 Assessment of the relevance of the proposed mechanisms to <i>in vivo</i> <i>N</i> -nitrosation | 81 |
| 4.5 Conclusions | 83 |
| References | 84 |
| 5 <i>N</i>-nitroso compounds and their precursors in the human environment | |
| 5.1 Introduction | 88 |
| 5.2 Preformed environmental nitrosamines | 89 |
| 5.2.1 Cured meat products | 89 |
| 5.2.2 Fish and sea food | 91 |
| 5.2.3 Cheese and dairy products | 92 |
| 5.2.4 Vegetables and cereal products | 92 |
| 5.2.5 Other food products | 93 |
| 5.2.6 Beer and alcoholic beverages | 94 |
| 5.2.7 Tobacco and tobacco products | 95 |
| 5.2.8 Cosmetics and toiletries | 97 |
| 5.2.9 Pharmaceutical products | 98 |
| 5.2.10 Agricultural chemicals: pesticides and herbicides | 99 |

| | |
|--|-----|
| 5.2.11 Rubber products | 100 |
| 5.2.12 Air | 101 |
| 5.2.13 Water | 102 |
| 5.3 Occupational nitrosamine exposure | 102 |
| 5.3.1 Amine producing and using factories | 102 |
| 5.3.2 Leather tanning industry | 104 |
| 5.3.3 Rubber industry | 104 |
| 5.3.4 Metal working industries (machine shops) | 105 |
| 5.3.5 Other industries | 106 |
| 5.4 Abbreviations | 106 |
| References | 107 |
| | |
| 6 The toxicology of <i>N</i>-nitroso compounds | |
| 6.1 Introduction | 117 |
| 6.2 Types of <i>N</i> -nitroso compounds | 118 |
| 6.3 Metabolism | 118 |
| 6.3.1 Pharmacokinetics | 119 |
| 6.3.2 Metabolism of nitrosamines | 120 |
| 6.3.3 Species and organ differences in <i>N</i> -nitrosamine activation | 122 |
| 6.4 Acute toxicity | 124 |
| 6.5 Carcinogenicity | 125 |
| 6.5.1 Structure–activity relationships in carcinogenesis | 126 |
| 6.5.2 Species differences in carcinogenesis and organotropy | 126 |
| 6.5.3 Carcinogenicity of <i>N</i> -nitroso compounds in young animals | 128 |
| 6.5.4 Dose–response carcinogenicity studies | 129 |
| 6.6 Mutagenicity | 130 |
| 6.6.1 Bacterial mutagenicity assays | 130 |
| 6.6.2 Other genetic toxicity assays | 132 |
| 6.7 Teratogenicity | 132 |
| 6.8 Toxicological properties of nitrosopeptides and nitrosated bile salts | 133 |
| 6.8.1 Nitrosopeptides | 133 |
| 6.8.2 Nitrosated bile acid conjugates | 133 |
| 6.9 Summary and conclusions | 134 |
| 6.10 Abbreviations | 134 |
| References | 134 |
| | |
| 7 <i>N</i>-nitroso compounds and human cancer | |
| 7.1 Introduction | 142 |
| 7.2 Exposure of humans to <i>N</i> -nitroso compounds | 142 |
| 7.3 The relation between <i>N</i> -nitroso compound exposure and human carcinogenesis | 145 |
| 7.3.1 Exogenous <i>N</i> -nitroso compounds | 145 |
| 7.3.2 Endogenous <i>N</i> -nitroso compounds | 147 |
| 7.4 Conclusions | 158 |
| References | 158 |

8 Prospects for the future

| | |
|--|------------|
| 8.1 Introduction | 163 |
| 8.2 The risk to health of non-volatile <i>N</i> -nitroso compounds | 163 |
| 8.2.1 Analytical problems | 163 |
| 8.2.2 Assessment of exposure. | 164 |
| 8.2.3 Assessment of risk | 164 |
| 8.3 Methods to decrease the risk of <i>N</i> -nitroso carcinogenesis | 164 |
| 8.3.1 Minimising nitrate exposure | 165 |
| 8.3.2 Minimising exposure to nitrosatable nitrogen compounds | 165 |
| 8.3.3 Intervention with inhibitors of <i>N</i> -nitrosation | 165 |
| References | 167 |
| Index | 168 |