## **CONTENTS**

1.

2.

## ENVIRONMENTAL HEALTH CRITERIA FOR MORPHOLINE

| SUI   | MMARY AND EVALUATION, CONCLUSIONS                                 |    |  |  |
|---|---|----|--|--|
| AN  | DRECOMMENDATIONS  | 19 |  |  |
|   |   |    |  |  |
| 1.1   | Physical and chemical properties                                  | 19 |  |  |
| 1.2   | Analytical methods  | 19 |  |  |
| 1.3   | .3 Sources of human and environmental exposure                    |    |  |  |
| 1.4 Environmental transport, distribution and     |   |    |  |  |
|   | transformation  | 20 |  |  |
| 1.5   | Environmental levels and human exposure                           | 21 |  |  |
| 1.6 Kinetics and metabolism in laboratory animals |   |    |  |  |
|   | and humans  | 22 |  |  |
| 1.7   | Effects on laboratory mammals and in vitro                        |    |  |  |
|   | test systems  | 23 |  |  |
| 1.8   | Effects on humans   | 25 |  |  |
| 1.9   | Effects on other organisms in the laboratory and field            | 25 |  |  |
| 1.10  | ) Evaluation of human health risks and effects                    |    |  |  |
|   | on the environment  | 26 |  |  |
|   | 1.10.1 Evaluation of effects on human health                      | 26 |  |  |
|   | 1.10.2 Evaluation of effects on the environment                   | 28 |  |  |
| 1.11  | Conclusions and recommendations                                   | 28 |  |  |
|   | 1.11.1 Recommendations for protection of                          |    |  |  |
|   | human health  | 28 |  |  |
|   | 1.11.2 Recommendations for protection of                          |    |  |  |
|   | the environment   | 29 |  |  |
|   | 1.11.3 Recommendations for further research                       | 29 |  |  |
| IDE<br>AN   | ENTITY, PHYSICAL AND CHEMICAL PROPERTIES,<br>D ANALYTICAL METHODS |    |  |  |
| 2.1   | Identity  | 31 |  |  |
|   | 2.1.1 Technical product   | 31 |  |  |
|   | 2.1.2 Impurities  | 32 |  |  |
| 2.2   | Physical and chemical properties                                  | 32 |  |  |
|   | 2.2.1 Physical properties of morpholine                           | 32 |  |  |
|   | 2.2.1.1 Storage of morpholine                                     | 33 |  |  |
|   |   |    |  |  |

Chemical properties of morpholine 2.2.2 34 2.3 Conversion factors for morpholine 35 35

## 2.4 Analytical methods

2.4.1 Determination of morpholine in air 35 Determination of morpholine in water 2.4.2 40

|    |                    | 2.4.3  | Determi    | nation of morpholine in soil                      | 10 |
|----|--------------------|--------|------------|---|----|
|    |                    | 2.4.4  | Determi    | ments<br>nation in biological and other materials | 40 |
|    |                    |        | ~~ ···· ·  |   |    |
| 3. | SOU                | RCES   | OF HUM     | IAN AND ENVIRONMENTAL                             | 41 |
|    | EXF                | OSUR   | E          |   | 41 |
|    | 3.1                | Natura | al occurre | ence  | 41 |
|    | 3.2                | Anthro | opogenic   | sources   | 41 |
|    |                    | 3.2.1  | Product    | ion levels and processes                          | 41 |
|    |                    |        | 3.2.1.1    | World producers                                   | 41 |
|    |                    |        | 3.2.1.2    | Production figures                                | 41 |
|    |                    |        | 3.2.1.3    | Production processes                              | 42 |
|    |                    |        | 3.2.1.4    | Losses to the environment                         |    |
|    |                    |        |            | during normal production                          | 43 |
|    |                    |        | 3.2.1.5    | Methods of transport                              | 43 |
|    |                    |        | 3.2.1.6    | Accidental release                                | 43 |
|    |                    | 3.2.2  | Uses       |   | 43 |
|    |                    |        | 3.2.2.1    | Rubber chemicals                                  | 44 |
|    |                    |        | 3.2.2.2    | Anticorrosion agent                               | 44 |
|    |                    |        | 3.2.2.3    | Waxes and polishes                                | 45 |
|    |                    |        | 3.2.2.4    | Optical brighteners                               | 45 |
|    |                    |        | 3.2.2.5    | Catalysts   | 45 |
|    |                    |        | 3.2.2.6    | Pharmaceuticals                                   | 45 |
|    |                    |        | 3.2.2.7    | Bactericides, fungicides and                      | _  |
|    |                    |        |            | herbicides  | 46 |
|    |                    |        | 3.2.2.8    | Food additive applications                        | 46 |
|    |                    |        | 3.2.2.9    | Cosmetics   | 46 |
| 1  | EN                 | VIRON  | MENTA      | I. TRANSPORT. DISTRIBUTION                        |    |
| 4. | AND TRANSFORMATION |        |            |   |    |
|    |                    |        |            |   |    |
|    | 4.1                | Trans  | port and   | distribution between media                        | 48 |
|    |                    | 4.1.1  | Volatili   | zation  | 48 |
|    | 4.2                | Trans  | formation  | n   | 48 |
|    |                    | 4.2.1  | Biodegi    | radation  | 48 |
|    |                    |        | 4.2.1.1    | Batch biodegradation tests                        | 49 |
|    |                    |        | 4.2.1.2    | Biodegradation in laboratory-scale                |    |
|    |                    |        |            | wastewater treatment plants                       | 50 |
|    |                    | 4.2.2  | Abiotic    | degradation                                       | 52 |
|    |                    |        | 4.2.2.1    | Hydrolytic degradation                            | 52 |
|    |                    |        | 4.2.2.2    | Photochemical degradation                         | 52 |
|    |                    |        | 4.2.2.3    | Degradation by physico-chemical                   |    |
|    |                    |        |            | processes   | 53 |

4

|    | 43  | 4.2.3 Bioaccumulation                         | 53 |  |  |
|----|-----|---|----|--|--|
|    | ч.5 | hiological factors                            |    |  |  |
|    | 44  | Ultimate fate following use                   | 56 |  |  |
|    | 4.4 | 4.4.1 Fate of morpholine in various products  | 56 |  |  |
|    |     | 4.4.2 Waste disposal                          | 57 |  |  |
|    |     | 4.4.2 Waste disposal                          | 51 |  |  |
| 5. | EN  | VIRONMENTAL LEVELS AND HUMAN EXPOSURE         | 58 |  |  |
|    | 5.1 | Environmental levels                          | 58 |  |  |
|    |     | 5.1.1 Ambient air                             | 58 |  |  |
|    |     | 5.1.2 Water                                   | 58 |  |  |
|    |     | 5.1.2.1 River water                           | 58 |  |  |
|    |     | 5.1.2.2 Wastewater                            | 58 |  |  |
|    |     | 5.1.3 Sediment                                | 58 |  |  |
|    |     | 5.1.4 Soil                                    | 59 |  |  |
|    | 1   | 5.1.5 Terrestrial and aquatic organisms       | 59 |  |  |
|    | 5.2 | General population exposure                   | 59 |  |  |
|    |     | 5.2.1 Indoor air                              | 59 |  |  |
|    |     | 5.2.2 Drinking-water and food                 | 59 |  |  |
|    |     | 5.2.3 Tobacco                                 | 64 |  |  |
|    |     | 5.2.4 Cosmetics and toiletry articles         | 66 |  |  |
|    |     | 5.2.5 Rubber articles                         | 69 |  |  |
|    | 5.3 | Occupational exposure during manufacture,     |    |  |  |
|    |     | formulation or use                            | 69 |  |  |
|    |     | 5.3.1 Exposure to morpholine                  | 70 |  |  |
|    |     | 5.3.2 Exposure to <i>N</i> -nitrosomorpholine | 70 |  |  |
| 6. | KIN | NETICS AND METABOLISM IN LABORATORY           |    |  |  |
|    | AN  | IMALS AND HUMANS                              | 75 |  |  |
|    |     |   |    |  |  |
|    | 6.1 | Absorption                                    | 75 |  |  |
|    | 6.2 | Distribution                                  | 75 |  |  |
|    | 6.3 | Metabolic transformation                      | 75 |  |  |
|    | 6.4 | Elimination and excretion                     | 80 |  |  |
|    |     | 6.4.1 Expired air                             | 80 |  |  |
|    |     | 6.4.2 Urine                                   | 80 |  |  |
|    |     | 6.4.3 Faeces                                  | 81 |  |  |
|    | 6.5 | Retention and turnover                        | 81 |  |  |
|    |     |   |    |  |  |
| 7. | EFF | FECTS ON LABORATORY MAMMALS AND               |    |  |  |
|    | IN  | VITRO TEST SYSTEMS                            | 82 |  |  |
|    |     |   |    |  |  |
|    | 7.1 | Single exposure                               | 82 |  |  |
|    |     |   |    |  |  |

| 7.1.2Inhalation827.1.3Dermal827.1.4Intraperitoneal837.2Short-term exposure837.2.1Oral837.2.2Inhalation887.3Dermal887.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation937.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity93 |
|---|
| 7.1.3Dermal827.1.4Intraperitoneal837.2Short-term exposure837.2.1Oral837.2.2Inhalation887.2.3Dermal887.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity93                                      |
| 7.1.4Intraperitoneal837.2Short-term exposure837.2.1Oral837.2.2Inhalation887.2.3Dermal887.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity93   |
| 7.2Short-term exposure837.2.1Oral837.2.2Inhalation887.2.3Dermal887.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation937.4.2Skin irritation937.5Reproductive toxicity, embryotoxicity93   |
| 7.2.1Oral837.2.2Inhalation887.2.3Dermal887.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation937.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity   |
| 7.2.2Inhalation887.2.3Dermal887.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation927.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity  |
| 7.2.3 Dermal887.3 Long-term exposure897.3.1 Oral897.3.2 Inhalation897.3.3 Dermal927.4 Skin and eye irritation; sensitization927.4.1 Eye irritation927.4.2 Skin irritation937.4.3 Sensitization937.5 Reproductive toxicity, embryotoxicity   |
| 7.3Long-term exposure897.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation927.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity  |
| 7.3.1Oral897.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation927.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity   |
| 7.3.2Inhalation897.3.3Dermal927.4Skin and eye irritation; sensitization927.4.1Eye irritation927.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity  |
| 7.3.3 Dermal927.4 Skin and eye irritation; sensitization927.4.1 Eye irritation927.4.2 Skin irritation937.4.3 Sensitization937.5 Reproductive toxicity, embryotoxicity   |
| 7.4Skin and eye irritation; sensitization927.4.1Eye irritation927.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity  |
| 7.4.1Eye irritation927.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity   |
| 7.4.2Skin irritation937.4.3Sensitization937.5Reproductive toxicity, embryotoxicity  |
| 7.4.3Sensitization937.5Reproductive toxicity, embryotoxicity  |
| 7.5 Reproductive toxicity, embryotoxicity   |
|   |
| and teratogenicity 94   |
| 7.6 Mutagenicity and related end-points 94  |
| 7.6.1 Mutagenicity of morpholine 94   |
| 7.6.1.1 Bacteria 94   |
| 7.6.1.2 Yeast 94  |
| 7.6.1.3 Mammalian cells in vitro 94   |
| 7.6.1.4 In vivo studies in mammals 96   |
| 7.6.2 Mutagenicity of morpholine in the   |
| presence of nitrite and nitrate 97  |
| 7.6.3 Mutagenicity of N-Nitrosomorpholine 97  |
| 7.7 Carcinogenicity 97  |
| 7.7.1 Morpholine 98   |
| 7.7.1.1 Oral studies 98   |
| 7.7.1.2 Inhalation studies 100  |
| 7.7.2 Morpholine and nitrite 100  |
| 7.7.2.1 Oral studies 100  |
| 7.7.3 Carcinogenicity of <i>N</i> -nitrosomorpholine 101  |
| 7.8 Factors modifying toxicity; toxicity of metabolites 101   |
| 7.8.1 Factors modifying toxicity 101  |
| 7.8.2 Morpholine metabolites 102  |
| 7.9 Mechanisms of toxicity - mode of action 103   |
| EFFECTS ON HUMANS 104   |
| 8.1 General population exposure 104   |
| 8.1.1 Controlled human studies 104  |
| 8.1.1.1 Organoleptic effects 105  |

8.

|  |                                   | 8.1.2                  | Epidem    | iological studies         | 105 |  |
|--|-----------------------------------|------------------------|-----------|---------------------------|-----|--|
|  | 8.2                               | Occupational exposure  |           | 106                       |     |  |
| 9.   | EFFECTS ON OTHER ORGANISMS IN THE |                        |           |                           |     |  |
|  | LAI                               | BORATORY AND FIELD     |           |                           | 107 |  |
|  | 9.1                               | Laboratory experiments |           |                           | 107 |  |
|  |                                   | 9.1.1 Microorganisms   |           |                           | 107 |  |
|  |                                   |                        | 9.1.1.1   | Microorganisms in water   | 107 |  |
|  |                                   |                        | 9.1.1.2   | Microorganisms in soil    | 108 |  |
|  |                                   |                        | 9.1.1.3   | Pathogenic microorganisms | 108 |  |
|  |                                   | 9.1.2                  | Other ad  | quatic organisms          | 110 |  |
|  |                                   |                        | 9.1.2.1   | Monocellular green algae  | 110 |  |
|  |                                   |                        | 9.1.2.2   | Invertebrates             | 110 |  |
|  |                                   |                        | 9.1.2.3   | Vertebrates               | 113 |  |
|  |                                   | 9.1.3                  | Terrestr  | ial organisms             | 116 |  |
|  |                                   |                        | 9.1.3.1   | Plants                    | 116 |  |
|  | ~                                 |                        | 9.1.3.2   | Animals                   | 116 |  |
|  | 9.2                               | Field c                | bservatio | ons                       | 116 |  |
| 10   | DDI                               |                        | EVALL     | ATIONS BY INTERNATIONAL   |     |  |
| BODIES   |                                   |                        |           |                           | 117 |  |
| REF  | FERE                              | ENCES                  |           |                           | 118 |  |
| DEC  | TINA                              | C ET E                 | VALITAT   | FION CONCLUSIONS ET       |     |  |
| RESUME ET EVALUATION, CONCLUSIONS ET<br>RECOMMANDATIONS 13 |                                   |                        |           |                           |     |  |
| DEC  |                                   |                        |           |                           |     |  |
| KES<br>DEC   | UMI                               | EN YE                  | VALUA     | CION, CONCLUSIONES Y      | 151 |  |
| KE(  | JUM.                              | ENDAC                  | IUNES     |                           | 131 |  |