



Toxicological Profile for Cobalt

October 2024



U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk of acute, intermediate, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Christopher M. Reh, Ph.D.

Associate Director

Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
October 2024	Final toxicological profile released
January 2023	Draft for public comment toxicological profile released
April 2004	Final toxicological profile released
July 1992	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Sam Keith, M.S., C.H.P. (Lead)
Obaid Faroon, D.V.M., Ph.D.

ATSDR, Office of Innovation and Analytics,
Toxicology Section, Atlanta, GA

Rekha C. Balachandran, M.S, Ph.D.
Adriana Antezana, M.P.H.
Hannah Derrick, B.S.
Kerry Diskin, Ph.D.
Andrea Chiger, M.P.H.
Meghan Lynch, Ph.D.

Abt Associates, Cambridge, MA

Kimberly Zaccaria, Ph.D., D.A.B.T.
Frances Belmonte, Ph.D., D.A.B.T.
Christina Coley, M.S.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Office of Community Health Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Sciences; NCEH, Division of Environmental Health Science and Practice; EPA, Office of Research and Development; EPA, Office of Water.

PEER REVIEWERS

1. David Dorman, DVM, PhD, DABVT, DABT, Professor of Toxicology, Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina
2. Katherine Zychowski, PhD, Assistant Professor, College of Pharmacy, The University of New Mexico, Albuquerque, New Mexico
3. Ruth Danzeisen, PhD, DABT, Advisor Toxicology, Albemarle, Germany-NI Langelsheim (LHM)
4. Benoit Nemery, MD, PhD; Emeritus Professor of Toxicology & Occupational Medicine; Centre for Environment and Health; Department of Public Health and Primary Care; Faculty of Medicine; KU Leuven
5. Arne Burzlaff, PhD; Arne Burzlaff, PhD; EBRC Consulting GmbH; Hannover, Germany

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

CONTENTS

DISCLAIMER	ii
FOREWORD	iii
VERSION HISTORY	iv
CONTRIBUTORS & REVIEWERS	v
CONTENTS.....	vii
LIST OF FIGURES	ix
LIST OF TABLES	x
CHAPTER 1. RELEVANCE TO PUBLIC HEALTH	1
1.1 OVERVIEW AND U.S. EXPOSURES	1
1.2 SUMMARY OF HEALTH EFFECTS.....	2
1.3 MINIMAL RISK LEVELS (MRLs)	7
CHAPTER 2. HEALTH EFFECTS.....	11
2.1 INTRODUCTION.....	11
2.2 DEATH	79
2.3 BODY WEIGHT.....	82
2.4 RESPIRATORY.....	85
2.5 CARDIOVASCULAR	99
2.6 GASTROINTESTINAL.....	103
2.7 HEMATOLOGICAL	105
2.8 MUSCULOSKELETAL	111
2.9 HEPATIC.....	112
2.10 RENAL	114
2.11 DERMAL	117
2.12 OCULAR	118
2.13 ENDOCRINE.....	118
2.14 IMMUNOLOGICAL	123
2.15 NEUROLOGICAL.....	128
2.16 REPRODUCTIVE	131
2.17 DEVELOPMENTAL	135
2.18 OTHER NONCANCER.....	136
2.19 CANCER.....	138
2.20 GENOTOXICITY	144
2.21 MECHANISM OF ACTION	156
2.22 COBALT NANOPARTICLES	158
CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS.....	160
3.1 TOXICOKINETICS.....	160
3.1.1 Absorption.....	160
3.1.2 Distribution	167
3.1.3 Metabolism.....	171
3.1.4 Excretion	172
3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	181
3.1.6 Animal-to-Human Extrapolations	185

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	187
3.3 BIOMARKERS OF EXPOSURE AND EFFECT	190
3.3.1 Biomarkers of Exposure.....	191
3.3.2 Biomarkers of Effect	193
3.4 INTERACTIONS WITH OTHER CHEMICALS	193
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION	196
4.1 CHEMICAL IDENTITY	196
4.2 PHYSICAL AND CHEMICAL PROPERTIES	198
CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE	203
5.1 OVERVIEW	203
5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	206
5.2.1 Production	206
5.2.2 Import/Export.....	210
5.2.3 Use	211
5.2.4 Disposal.....	212
5.3 RELEASES TO THE ENVIRONMENT.....	213
5.3.1 Air	213
5.3.2 Water.....	218
5.3.3 Soil	219
5.4 ENVIRONMENTAL FATE	220
5.4.1 Transport and Partitioning.....	220
5.4.2 Transformation and Degradation	224
5.5 LEVELS IN THE ENVIRONMENT	227
5.5.1 Air	229
5.5.2 Water.....	230
5.5.3 Sediment and Soil	234
5.5.4 Other Media	236
5.6 GENERAL POPULATION EXPOSURE	241
5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	255
CHAPTER 6. ADEQUACY OF THE DATABASE	264
6.1 EXISTING INFORMATION ON HEALTH EFFECTS	264
6.2 IDENTIFICATION OF DATA NEEDS	266
6.3 ONGOING STUDIES	272
CHAPTER 7. REGULATIONS AND GUIDELINES	273
CHAPTER 8. REFERENCES	277

APPENDICES

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS	A-1
APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR COBALT	B-1
APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR COBALT	C-1
APPENDIX D. USER'S GUIDE.....	D-1
APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS	E-1
APPENDIX F. GLOSSARY	F-1
APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS.....	G-1

LIST OF FIGURES

1-1. Health Effects Found in Humans and Animals Following Inhalation Exposure to Cobalt	3
1-2. Health Effects Found in Humans and Animals Following Oral Exposure to Cobalt	4
1-3. Summary of Sensitive Targets of Cobalt – Inhalation.....	8
1-4. Summary of Sensitive Targets of Cobalt – Oral.....	9
2-1. Overview of the Number of Studies Examining Cobalt Health Effects	15
2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m ³).....	33
2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day).....	64
2-4. Mechanistic Events Associated with Cobalt Toxicity and Carcinogenicity	156
3-1. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 0.8 µm Porous Cobalt Tetraoxide	162
3-2. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 1.7 µm Porous Cobalt Tetraoxide	163
3-3. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 0.9 µm Solid Cobalt Tetraoxide	163
3-4. Structure of ICRP (2016) Cobalt Systemic Model	183
3-5. Structure of Unice et al. (2014b) Cobalt Systemic Model.....	184
3-6. Updated Model Inhalation	186
5-1. Number of NPL Sites with Cobalt Contamination	203
6-1. Summary of Existing Health Effects Studies on Cobalt by Route and Endpoint.....	265

LIST OF TABLES

1-1. Minimal Risk Levels (MRLs) for Cobalt	10
2-1. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m ³)	16
2-2. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day).....	45
2-3. Levels of Significant Exposure to Cobalt – Dermal	77
2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects	86
2-5. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cardiovascular Effects.....	100
2-6. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Hematological Effects.....	105
2-7. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Thyroid Effects	119
2-8. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Immunological Effects.....	124
2-9. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cancer	139
2-10. Genotoxicity of Cobalt <i>In Vitro</i>	144
2-11. Genotoxicity of Cobalt <i>In Vivo</i>	151
3-1. Peak Translocation and Average Mechanical Clearance Rates (%) After Inhalation of Cobalt Oxide for 180 Days.....	173
3-2. Initial (Day 3) Lung Deposits of Cobalt Oxide and Summary of Lung Retention at 90 and 180 Days	174
3-3. Retention of Cobalt (Cobalt Chloride) in Whole Blood and Serum in Humans after Oral Dosing.....	176
3-4. Summary of Retention and Excretion After Intragastric Administration of Cobalt Tetraoxide Particles (Mean Percentage of Recovered Activity at 7 Days Post Administration).....	176
3-5. Pharmacokinetic Parameters for Orally Administered Cobalt in Rats	177
3-6. Cobalt Levels in Urine and Feces in Rats Following Oral Exposure to Cobalt	178
3-7. Summary of Retention and Excretion of Cobalt Following Injection of Cobalt Nitrate Solution (Mean Percent Recovery).....	180
3-8. ICRP (2016) Absorption Parameter Values for Cobalt	182
4-1. Chemical Identity of Cobalt and Selected Cobalt Compounds	196
4-2. Physical and Chemical Properties of Cobalt and Selected Cobalt Compounds	199

5-1. Facilities that Produce, Process, or Use Cobalt	208
5-2. Facilities that Produce, Process, or Use Cobalt Compounds	209
5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt.....	213
5-4. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds.....	215
5-5. Lowest Limit of Detection for Cobalt Based on Standards	228
5-6. Summary of Environmental Levels of Cobalt	228
5-7. Cobalt Levels in Water, Soil, and Air of National Priorities List (NPL) Sites.....	228
5-8. Percentile Distribution of Annual Mean Cobalt (TSP) Concentrations ($\mu\text{g}/\text{m}^3$) Measured in Ambient Air Locations Across the United States.....	229
5-9. Summary of Annual Concentration of Cobalt (ppbv) Measured in Ambient Air Samples at Locations Across the United States	229
5-10. Summary of Concentrations of Cobalt (ppb) Measured in Surface and Groundwater Samples Across the United States	230
5-11. Summary of Concentrations of Cobalt (ppb) Measured in Surface and Groundwater Samples at Superfund Sites	231
5-12. Summary of Concentrations of Cobalt (ppb) Measured in Wastewater Samples Across the United States.....	232
5-13. Summary of Concentrations of Cobalt (ppb) Measured in Sediment Samples Across the United States.....	236
5-14. Summary of Concentrations of Cobalt (ppb) Measured in Soil Samples Across the United States	236
5-15. Summary of Concentrations of Cobalt (ppb) Measured in Soil and Sediment Samples at Superfund Sites.....	236
5-16. Summary of Concentrations of Cobalt (ppb) Measured in Biota Samples Across the United States	238
5-17. Reasonable Maximum Exposure of Cobalt for Daily Administered Dermal Dose in $\mu\text{g}/\text{kg}/\text{day}$ for the Target Person	242
5-18. Geometric Mean and Selected Percentiles of Urinary Cobalt (in $\mu\text{g}/\text{L}$) for the U.S. Population from NHANES.....	247
5-19. Geometric Mean and Selected Percentiles of Urinary Cobalt (Creatinine Corrected) (in $\mu\text{g}/\text{g}$ of Creatinine) for the U.S. Population from NHANES	250
5-20. Geometric Mean and Selected Percentiles of Blood Cobalt (in $\mu\text{g}/\text{L}$) for the U.S. Population from NHANES.....	253

6-1. Ongoing Studies on Cobalt.....	272
7-1. Regulations and Guidelines Applicable to Cobalt.....	273