

# MEDICAL TOXICOLOGY OF NATURAL SUBSTANCES

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## **Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals**

**DONALD G. BARCELOUX, MD, FAACT, FACMT, FACEP**

CLINICAL PROFESSOR OF MEDICINE, DEPARTMENT OF EMERGENCY MEDICINE  
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STAFF PHYSICIAN, DEPARTMENT OF EMERGENCY MEDICINE  
POMONA VALLEY HOSPITAL MEDICINE CENTER  
POMONA, CALIFORNIA



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# FOREWORD

Men and women live in a miraculous world, surrounded by natural beauty, diverse environmental conditions and habitats, and evolutionary marvels. Within this intricate assembly of flora and fauna, many plant and animals have evolved that are more than passive inhabitants of this planet. They are endowed with substances both offensive and defensive, namely, potent toxins capable of slowly poisoning or rapidly subduing very large animals, including humans. In addition, modern man utilizes plant and animal products and extracts for commercial, medical, religious, and other purposes. These exposures range from naturopathic cures to a casual encounters with cactus spines during a wilderness expedition, from a diver's encounters with the needles of sea urchins to covert politically motivated assassinations utilizing ricin from castor beans. Wild mushroom foragers grow old only if they are not too bold, while amateur aquarists who reach into their saltwater tanks learn about the toxicity under the cover of lionfish plumage.

We can never learn or know too much about how best to deal with natural toxins, whether we seek to eliminate them from our immediate food supply or treat acutely intoxicated victims. Furthermore, from the

understanding of syndromes and therapies, we are offered insights into their possible therapeutic value. No matter what the ultimate fate of man, the seeds, spores, fangs, and venom glands will survive. While the relationship of toxins to humans may not be always be characterized as symbiotic, there will remain a coexistence that is predicted, yet always in part unpredictable.

The medical toxicology of natural substances is predicated upon their existence, which will diminish as humans continue to erode and consume their environment. Until then, we should continue to catalogue, record, evaluate, and teach. Medical practitioners and toxicologists should accept the responsibility to perpetuate these traditions because the wisdom of indigenous shamans is being lost as rapidly as the rainforests in which they reside.

What we do not seek to protect may soon disappear. It is my fervent wish that this book not only serve as a superb medical reference for those who seek to cure, but that all who read it are inspired to preserve the landscapes and seascapes that support the origination of everything that is natural and sustainable upon this Earth.

PAUL S. AUERBACH, MD, MS, FACEP, FAWM

*Division of Emergency Medicine, Department of Surgery,  
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# PREFACE

*Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* is designed to provide in-depth, evidence-based coverage of the most important natural toxins. This book is the first of a four volume series in Medical Toxicology, which will include drugs of abuse and psychoactive plants, occupational and environmental exposures, and pharmaceutical overdoses. Scientific knowledge in the field of Medical Toxicology increased considerably since I co-authored the First Edition of *Medical Toxicology: Diagnosis and Treatment of Human Poisoning* with the late Matthew J. Ellenhorn, published in 1988. That book was designed as an authoritative, concise volume for the immediate treatment of poisoning including natural toxins, pharmaceutical agents, and occupational exposures. In the last 20 years, sufficient interest has developed in natural toxins, food contamination, medicinal herbs, chronic occupational exposures, and bioterrorism to justify coverage of the field of Medical Toxicology by a book series rather than a single volume. *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* retains the consistent, formatted style I developed for the First Edition of *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. Once the reader is familiar with the templates used in my book series, the consistency of the organization allows the reader quickly to locate the appropriate information necessary for informed decisions regarding the sources, effect, regulation, recognition, and management of toxic exposures.

Conversions for length and temperature in metric and imperial systems are provided to ease the use of this book by an international readership, whereas the metric system for mass and concentrations are retained to limit any confusion about doses in the United States.

The following provides organizational details on the material under the headings for each toxin:

**History** provides interesting historical facts involving the use and recognized effects of the toxicity of natural substances.

**Identifying Characteristics and Botanical Descriptions** helps the reader identify the characteristics and geographic distribution of the specific toxin (e.g., venomous animal, toxic plant).

**Exposure** discusses the sources, uses, and regulation of exposures to these toxins.

**Principal Toxins** identifies the main toxins in the natural substances and provides data on the chemistry, structure, and physical properties of the toxin that are important for the reader's understanding of the clinical response to the toxin. This part discusses the basic science and the composition of the toxins along with factors that affect the delivery of the toxin including discussions of the venom apparatus and seasonal variation in the locations of the toxins. Additionally, this part covers the biochemical and pathophysiological basis for the toxic responses.

**Dose Response** covers data on the lethality and clinical effects of the toxin both in animals and in humans as well as factors that affect the potency of the toxin. The emphasis is on dose-related effects, but important adverse and idiosyncratic reactions are also discussed.

**Toxicokinetics** discusses the disposition of the principal toxins in the body including the distribution, absorption, and elimination of the principal toxins. The emphasis is on human data, but animal data may be included when human data are sparse.

## PREFACE

**Clinical Response** provides data on the clinical features of poisoning following exposure to the toxin including the onset, duration, and type of clinical effects.

**Diagnostic Testing** covers information important to the interpretation of the clinical significance of the laboratory data. This section includes current laboratory methods to determine the presence of the toxin, effects of storage, biomarkers of exposure in blood, urine, and postmortem material, and the laboratory abnormalities detected by imaging studies and ancillary tests.

**Treatment** provides details on current methods to treat the poisoning including information important for first responders, life-threatening problems associated with the poisoning, the use of antidotes, and measures of supportive care.

*Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* focuses on scientifically validated facts about specific toxins based on clinical experience and the medical literature. References are documented to validate the statements and to provide sources for further inquiry. The interdisciplinary, evidence-based approach is designed to reach beyond clinical settings to increase the scientific understanding of those in associated fields (analytical laboratories, universities, regulatory agencies, coroner's offices) involved with decisions regarding toxic exposures. My hope is that increased scientific communication between the fields aligned with Medical Toxicology will inspire more inquiry into the pathophysiology, clinical effects, biomarkers, treatment, and prevention of toxic exposures.

DONALD G. BARCELOUX, MD

*June 12, 2008*

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## Review Panel

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## **PART 1**

# **FOODBORNE and MICROBIAL TOXINS**

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## PART 1   FOODBORNE and MICROBIAL TOXINS

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# I Chemical Contamination and Additives

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## Chapter 1

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# FOOD CONTAMINATION

CYRUS RANGAN, MD, FAAP

Records of outbreaks of human illness caused by toxic contaminants in foods appeared at least several centuries BC, when mad honey poisoning was associated with an illness among troops under the command of the Greek historian and mercenary, Xenophon.<sup>1</sup> One of the first recorded foodborne outbreaks of ergotism occurred in Limoges, France during the Capetian Dynasty in 994 AD.<sup>2</sup> The ingestion of rye bread contaminated with ergot alkaloids during this epidemic caused the deaths of approximately 20,000–50,000 victims. Numerous episodes of ergotism have occurred throughout history. Although ergotism is a possible explanation for the bizarre behavior that occurred before and during the Salem Witch Trials of 1692, there is no definite evidence that ergotism was a contributing factor.<sup>3</sup> In the 1950s, mining operations in the Toyama region of Japan released cadmium into the Jinzu River. The use of this water for drinking and for irrigation of nearby rice fields resulted in a disease called *itai-itai* (translation: “ouch-ouch”), manifest by osteoporosis and renal dysfunction primarily in middle-aged women.<sup>4</sup> In the same decade, numerous neonates born near Minamata Bay, Japan, developed birth defects and neurological abnormalities after pregnant women were exposed to seafood contaminated by methyl mercury released into the bay from a local factory. A methyl mercury-based fungicide caused an outbreak of mercury poisoning in Iraq in 1971 after grain seeds treated with the fungicide were inadvertently used for food manufacturing instead of plant-

ing.<sup>5</sup> Prominent outbreaks of illnesses associated with chemical contamination of cooking oils include tri-*ortho*-cresyl phosphate-induced neuropathy (Morocco, 1959),<sup>6</sup> yusho (“rice oil disease,” Japan, 1968), yu-cheng (“oil disease,” Taiwan, 1979), toxic oil syndrome (Spain, 1981), and epidemic dropsy (India, 1998). Some contaminants are unavoidable in food manufacturing. In the United States, the Food and Drug Administration (FDA) imposes “Current Good Manufacturing Practices” (CGMP) on food manufacturers. These mandatory codes enable the FDA to cite food products as *unfit* if an unavoidable contaminant poses a risk of harm by violating a standard or action level for that unavoidable contaminant (e.g., aflatoxin). Food products are considered *adulterated* when concentrations of avoidable contaminants (e.g., pesticides) exceed established standards, sometimes prompting food recalls after sale and distribution.

Metal contaminants such as lead, mercury, arsenic, and cadmium come from factory emissions, mining operations, and metal-containing industrial products used in food production. Methyl mercury found in commercially sold seafood is deemed an unavoidable contaminant because contamination preexists in the raw material; therefore, the contamination does not result from food processing or distribution. Fish and shellfish acquire methyl mercury primarily from microorganisms that methylate environmental inorganic mercury compounds released primarily from industrial sources.

# YUSHO and YU-CHENG

## HISTORY

The first known case of yusho (rice oil disease) involved a 3-year-old girl in northern Kyushu, Japan, who had an acute onset of an acneiform rash (chloracne) in June, 1968. Her family members, followed by other familial clusters, presented to a single clinic with complaints of acneiform rash, hyperpigmentation, and eye discharge over the next 2 months. By January 1969, 325 cases were reported. After a small minority of patients initially identified rice oil as the causative agent of yusho, Kyushu University convened the *Study Group for Yusho* to investigate yusho; about 2,000 afflicted patients were subsequently identified. The clinical features of yusho included fatigue, headache, cough, abdominal pain, peripheral numbness, hepatomegaly, irregular menstrual cycles, nail deformities, and hypersecretion of sebaceous glands. A field survey of canned rice oil associated the disease with the use of “K Rice Oil” produced or shipped by the K Company on February 5–6, 1968.<sup>7</sup> The yu-cheng epidemic involved over 2,000 individuals in Taiwan in 1979, when an accidental leakage of thermal exchange fluid resulted in the contamination of rice-bran oil with polychlorinated biphenyls (PCBs), dibenzofurans (PCDFs), and quaterphenyls (PCQs).<sup>8</sup> The clinical features of yu-cheng and yusho were similar.

## EXPOSURE

### Source

Polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) are thermal heat exchanger compounds used in food processing machinery. Leakage of these compounds into rice oils during manufacturing led to the yusho and yu-cheng outbreaks.

### YUSHO

Epidemiological studies revealed that 95.7% ( $p < 0.01$ ) of surveyed patients recalled consumption of rice oil from K Company in Western Japan.<sup>7</sup> A case-control study revealed rice oil as the only associated etiologic factor, and a cohort study demonstrated a 64% risk of yusho in K rice oil consumers compared with no risk for nonexposed individuals.<sup>7</sup> Food engineers confirmed the leakage of dielectric thermal exchange fluid (Kanechlor

400) containing PCBs into the rice oil. This contaminant contained PCB compounds, primarily tetra-chlorinated biphenyls. In 1969, the Study Group initially concluded that PCBs caused yusho.<sup>9</sup> However, a lack of similar symptoms (besides chloracne) in PCB workers who had significantly higher tissue burdens (mean blood PCB level: 45 ppb) contradicted this conclusion. Furthermore, the dermatological lesions could not be reproduced in animals following the oral administration of PCB compounds or by Kanechlor 400, and the severity of the clinical features of yusho did not correlate to serum concentrations of PCB compounds. Therefore, other compounds (e.g., polychlorinated dibenzofurans) in the adulterated rice oil probably contributed to the development of yusho.<sup>10,11</sup>

### YU-CHENG

As with the yusho incident, the suspected causative agents of yu-cheng were PCDFs rather than PCBs.<sup>12</sup> Contamination of the cooking oil occurred when PCBs used for the indirect heating of rice-bran oil leaked into the cooking oil. Repeated heating of the partially degraded PCBs produced PCDFs, as well as polychlorinated terphenyl and polychlorinated quaterphenyl compounds.<sup>13</sup>

## Food Processing

High temperatures ( $>200^{\circ}\text{C}$ ) in dielectric thermal exchange fluid during the deodorization step of oil refining contributed to the development of yusho and yu-cheng by degrading PCBs in the contaminated rice oil to PCDFs, PCDDs (polychlorinated dibenzo dioxins), and PCQs (polychlorinated quaterphenyls).<sup>14</sup>

## DOSE RESPONSE

Exposure to toxic contaminants in the rice oil from the yusho and yu-cheng epidemics was assessed by recording the lot numbers of purchased oil containers and comparison of the volume of oil purchased to the volume of oil remaining in the containers retrieved from affected households. Consumption of the contaminated rice oil by household members was estimated by proportional distribution to each family member. Positive relationships were observed between estimated individual oil consumption and incidences of yusho and yu-cheng.<sup>15,16</sup> The mean concentrations of PCBs, polychlorinated quaterphenyls (PCQs), and PCDFs in five samples of contaminated cooking oil from the yu-cheng outbreak were 62 ppm, 20 ppm, and 0.14 ppm, respectively.<sup>17</sup> The congeners of these compounds were similar in the cooking oils from these two outbreaks, but yu-cheng cooking oil