Foodborne Disease Handbook

Volume 2: Viruses, Parasites, Pathogens, and HACCP

Second Edition

Edited by
Y. H. Hui, Syed A. Sattar, K. D. Murrell, Wai-Kit Nip and Peggy S. Stanfield
Foodborne Disease Handbook
FOODBORNE DISEASE HANDBOOK

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Volume 1  Bacterial Pathogens
Volume 2  Viruses, Parasites, Pathogens, and HACCP
Volume 3  Plant Toxicants
Volume 4  Seafood and Environmental Toxins
Foodborne Disease Handbook
Second Edition, Revised and Expanded

Volume 2: Viruses, Parasites, Pathogens, and HACCP

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Introduction to the Handbook

The Foodborne Disease Handbook, Second Edition, Revised and Expanded, could not be appearing at a more auspicious time. Never before has the campaign for food safety been pursued so intensely on so many fronts in virtually every country around the world. This new edition reflects at least one of the many aspects of that intense and multifaceted campaign: namely, that research on food safety has been very productive in the years since the first edition appeared. The Handbook is now presented in four volumes instead of the three of the 1994 edition. The four volumes are composed of 86 chapters, a 22% increase over the 67 chapters of the first edition. Much of the information in the first edition has been carried forward to this new edition because that information is still as reliable and pertinent as it was in 1994. This integration of the older data with the latest research findings gives the reader a secure scientific foundation on which to base important decisions affecting the public’s health.

We are not so naive as to think that only scientific facts influence decisions affecting food safety. Political and economic factors and compelling national interests may carry greater weight in the minds of decision-makers than the scientific findings offered in this new edition. However, if persons in the higher levels of national governments and international agencies, such as the Codex Alimentarius Commission, the World Trade Organization, the World Health Organization, and the Food and Agriculture Organization, who must bear the burden of decision-making need and are willing to entertain scientific findings, then the information in these four volumes will serve them well indeed.

During the last decade of the previous century, we witnessed an unprecedentedly intense and varied program of research on food safety, as we have already noted. There are compelling forces driving these research efforts. The traditional food-associated pathogens, parasites, and toxins of forty years ago still continue to cause problems today, and newer or less well-known species and strains present extraordinary challenges to human health.

These newer threats may be serious even for the immunocompetent, but for the immunocompromised they can be devastating. The relative numbers of the immunocompromised in the world population are increasing daily. We include here not just those affected by the human immunodeficiency virus (HIV), but also the elderly; the very young; the recipients of radiation treatments, chemotherapy, and immunosuppressive drugs; pa-
tients undergoing major invasive diagnostic or surgical procedures; and sufferers of debilitat-
ing diseases such as diabetes. To this daunting list of challenges must be added numerous instances of microbial resistance to antibiotics.

Moreover, it is not yet clear how the great HACCP experiment will play out on the worldwide stage of food safety. Altruism and profit motivation have always made strange bedfellows in the food industry. It remains to be seen whether HACCP will succeed in wedding these two disparate motives into a unifying force for the benefit of all concerned—producers, manufacturers, retailers, and consumers. That HACCP shows great promise is thoroughly discussed in Volume 2, with an emphasis on sanitation in a public eating place.

All the foregoing factors lend a sense of urgency to the task of rapidly identifying toxins, species, and strains of pathogens and parasites as etiologic agents, and of determining their roles in the epidemiology and epizootiology of disease outbreaks, which are described in detail throughout the Foodborne Disease Handbook.

It is very fortunate for the consumer that there exists in the food industry a dedicated cadre of scientific specialists who scrutinize all aspects of food production and bring their expertise to bear on the potential hazards they know best. A good sampling of the kinds of work they do is contained in these four new volumes of the Handbook. And the benefits of their research are obvious to the scientific specialist who wants to learn even more about food hazards, to the scientific generalist who is curious about everything and who will be delighted to find a good source of accurate, up-to-date information, and to consumers who care about what they eat.

We are confident that these four volumes will provide competent, trustworthy, and timely information to inquiring readers, no matter what roles they may play in the global campaign to achieve food safety.

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Preface

Much of the thought and action surrounding food safety deals with preventing foodborne bacteria from causing disease—and that is as it should be. But there are other threats that command our attention. These—the viruses and parasites—take center stage in the second volume of the *Foodborne Disease Handbook, Second Edition, Revised and Expanded*.

Viruses play an important role as agents of human diseases, and indeed their relative significance is increasing as we try to prevent and control the spread of common bacterial pathogens. The potential for foodborne spread of viruses is also stronger now than ever because of a combination of many current societal changes. Ongoing changes in demographics, changing lifestyles, faster and more frequent movement of peoples and goods, and rapidly expanding global trade in produce have already had a profound impact on the potential of viruses and other pathogens to spread through foods.

Eight chapters on foodborne viruses, contributed by internationally recognized experts in their respective fields, represent an overview of the most up-to-date information in this area. They cover well-known viral pathogens, as well as those that are less well understood but may acquire greater significance if left unheeded. The chapters, when considered together, represent a valuable resource on the biology of foodborne viruses, clinical diagnosis, and medical management as well as laboratory-based identification of viral infections transmitted through foods, and the epidemiology, prevention, and control of foodborne spread of viral pathogens. Wherever appropriate, the challenges and difficulties of detecting viruses in foods are highlighted and research needs identified. The guidelines for reducing the risk of spread of hepatitis A through foods should be applicable to many other foodborne pathogens.

It is anticipated that the information presented here will assist researchers, epidemiologists, physicians, public health officials and government regulators, and those in the food production and marketing business, to become better informed on the human health impact of foodborne viral infections and to work collectively in making foods safer.

All chapters on parasites from the first edition have been revised and updated. The addition of a chapter on the occurrence of parasites in seafood completes the overall subject of foodborne and waterborne diseases transmitted by parasites.

Although Americans are relatively unfamiliar with parasitic infection, three examples of areas in which diseases have been transmitted by parasites will help us to remember
this important subject: northern Taiwan (from consuming raw or undercooked beef), Asian
countries such as Thailand (undercooked pork), and Japan and Hawaii (undercooked sea-
food). Various chapters in this volume provide detailed description of these types of dis-
eases transmitted by parasites.

There is a gradual movement—sometimes voluntary, sometimes mandated—toward
implementation of HACCP principles in all aspects of the food industry, beginning with
production and harvesting and continuing through the various stages of manufacturing,
warehousing, wholesaling, retailing, and serving, until the food eventually reaches the
consumer’s plate. However, for the moment, at least, it is in the area of food service that
the application of HACCP principles has reached the highest level of achievement. While
much remains to be done even in the food service sector with regard to the implementation
of HACCP, it will be seen from this second volume of the Foodborne Disease Handbook
that the mechanics of implementation have been worked out and fine-tuned, and that this
accomplishment may now serve as a model and a guide for other facets of the food in-
dustry.

The food industry in general seems to be buying into the HACCP system with an
apparent high level of commitment, and this bodes well for the consumer. But rather than
relaxing vigilance and trusting that HACCP will solve all food safety problems, the food
industry must heighten vigilance and redouble efforts to ensure that HACCP programs
are protected on all sides by a secure fortress of state-of-the-art environmental sanitation.

The editors and contributors to this volume have given researchers, microbiologists,
parasitologists, food-industry managers, food analysts, and HACCP managers a wealth
of information on how to detect and identify foodborne parasites and viral pathogens, how
to investigate the disease outbreaks they cause, and, most importantly, how to prevent
foodborne diseases by the practical application of HACCP principles.

Y. H. Hui
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I. EPIDEMIOLOGY

Epidemiological studies aid treatment facilities in determining risk factors, determining who becomes exposed, and establishing the probable outcomes with various treatments. A few toxicology organizations have attempted to gather such information and organize it into yearly reports. The American Association of Poison Control Centers (AAPCC) and some federal agencies work toward obtaining epidemiological information, but the AAPCC also has an active role in assisting with the treatment of potentially toxic exposures. Epidemiological studies assist government and industry in determining package safety, effective treatment measures, conditions of exposure, and frequency of exposure.

Studies on viral exposures provide information on the type of people most commonly involved in exposures. Are they children, adults at home, outdoorsmen, industrial workers, or blue collar workers? Studies can also tell us which viral species are most commonly involved. What symptoms are seen first, what the onset of symptoms is like, and if there are any sequelae may also be determined and compared with current norms.
A. AAPCC

1. What Are Poison Centers and the AAPCC?

The group in the United States that is most concerned on a daily basis with potential poisonings due to household agents, industrial agents, and biologics is the American Association of Poison Control Centers (AAPCC). This is an affiliation of local and regional centers that provides information concerning all aspects of poisoning and refers patients to treatment centers. This group of affiliated centers is often supported by local government, private funds, and industrial sources.

Poison centers were started in the late 1950s; the first were in the Chicago area. The idea caught on quickly and at the peak of the movement there were hundreds of centers throughout the United States. Unfortunately, there were few or no standards as to what might be called a poison center, the type of staff, hours of operation, or information resources. One center may have had a dedicated staff of doctors, pharmacist, and nurses trained specifically in handling poison cases; the next center may just have a book on toxicology in the emergency room or hospital library. In 1993, the Health and Safety Code (Section 777.002) specified that a poison center must provide a 24-hour service for public and health care professionals and meet requirements established by the AAPCC. This action helped the AAPCC to standardize activities and staffs of the various centers.

The federal government does not fund poison centers, even though for every dollar spent on poison centers there is a savings of $2 to $9 in unnecessary medical expenses (1,2). The federal agency responsible for the Poison Prevention Packaging Act is the U.S. Consumer Product Safety Commission (CPSC). The National Clearinghouse for Poison Control Centers initially collected data on poisonings and provided information on commercial product ingredients and biologic toxic agents. For several years the National Clearinghouse provided product and treatment information to the poison centers that handled the day-to-day calls.

At first, most poison centers were funded by the hospital in which they were located. As the centers grew in size and number of calls handled, both city and state governments look on the responsibility of contributing funds. In recent years the local governments have found it difficult to fund such operations and centers have had to look to private industry for additional funding. Government funding may take several forms, either as a line item on a state budget, as a direct grant, or as moneys distributed on a per-call basis. Some states with fewer residents may contract with a neighboring state to provide services to its residents. Some states are so populous that more than one center is funded by the state. Industrial funding also varies—sometimes as a grant, sometimes as payment for handling the company’s poison or drug information—related calls, sometimes as payment for collection of data regarding exposure to the company’s product.

Every year the AAPCC reports a summary of all kinds of exposures.

2. Regional Centers

As the cost of providing this service has risen, the number of listed centers has dropped significantly since its peak of 600-plus. Many centers have been combined into regional organizations. These regional poison centers provide poison information, offer telephone management and consultation, collect pertinent data, and deliver professional and public education. Cooperation between regional poison centers and poison treatment facilities is crucial. The regional poison information center, assisted by local hospitals, should determine the capabilities of the treatment facilities of the region. They should also have a
working relationship with their analytical toxicology, emergency and critical care, medical transportation, and extracorporeal elimination services. This should be true for both adults and children.

A “region” is usually determined by state authorities in conjunction with local health agencies and health care providers. Documentation of these state designations must be in writing unless a state chooses (in writing) not to designate any poison center or accepts a designation by other political or health jurisdictions. Regional poison information centers should serve a population base of greater than 1 million people and must receive at least 10,000 human exposure calls per year.

The number of certified regional centers in the United States is now under 50. Certification as a regional center requires the following.

1. Maintenance of a 24 hour-per-day, 365-days-per-year service.
2. Provision of service to both health care professionals and the public.
3. Availability of at least one specialist in poison information in the center at all times.
4. Having a medical director or qualified designee on call by telephone at all times.
5. Service should be readily accessible by telephone from all areas in the region.
6. Comprehensive poison information resources and comprehensive toxicology information covering both general and specific aspects of acute and chronic poisoning should be available.
7. The center is required to have a list of on-call poison center specialty consultants.
8. Written operational guidelines that provide a consistent approach to evaluation, follow-up, and management of toxic exposures should be obtained and maintained. These guidelines must be approved in writing by the medical director of the program.
9. There should be a staff of certified professionals manning the phones (at least one of the individuals on the phone has to be a pharmacist or nurse with 2000 hours and 2000 cases of supervised experience)
10. There should be a 24 hour-per-day physician (board-certified) consultation service.
11. The regional poison center shall have an ongoing quality assurance program.
12. Other criteria, determined by the AAPCC, may be established with membership approval.
13. The regional poison information center must be an institutional member in good standing of the AAPCC. Many hospital emergency rooms still maintain a toxicology reference such as the POISINDEX® system to handle routine exposure cases but rely on regional centers to handle most of the calls in their area.

B. Poison Center Staff

The staffing of poison centers varies considerably from center to center. The three professional groups most often involved are physicians, nurses, and pharmacists. Who answers the phones is somewhat dependent on the local labor pool, monies available, and the types of calls being received. Others personnel used to answer the phone include students in
medically related fields, toxicologists, and biologists. Persons responsible for answering the phones are either certified by the AAPCC or are in the process of obtaining certification. Passage of an extensive examination on toxicology is required for initial certification, with periodic recertification required.

Regardless of who takes the initial call, there is a medical director and other physician back-up available. These physicians have specialized training or experience in toxicology, and are able to provide in-depth consultations for health care professionals calling a center.

1. Medical Director
A poison center medical director should be board-certified in medical toxicology or be board-certified in internal medicine, pediatrics, family medicine, or emergency medicine. The medical director should be able to demonstrate ongoing interest and expertise in toxicology as evidenced by publications, research, and meeting attendance. The medical director must have a medical staff appointment at a comprehensive poison treatment facility and be involved in the management of poisoned patients.

2. Managing Director
The managing director must be a registered nurse, pharmacist, physician, or hold a degree in a health science discipline. The individual should be certified by the American Board of Medical Toxicology (for physicians) or by the American Board of Applied Toxicology (for nonphysicians). He or she must be able to demonstrate ongoing interest and expertise in toxicology.

3. Specialists in Poison Information
These individuals must be registered nurses, pharmacists, or physicians, or be currently certified by the AAPCC as specialists in poison information. Specialists in poison information must complete a training program approved by the medical director and must be certified by the AAPCC as specialists in poison information within two examination administrations of their initial eligibility. Specialists not currently certified by the Association must spend an annual average of no fewer than 16 hours per week in poison center–related activities. Specialists currently certified by the AAPCC must spend an annual average of no less than 8 hours per week. Other poison information providers must have sufficient background to understand and interpret standard poison information resources and to transmit that information understandably to both health professionals and the public.

4. Consultants
In addition to physicians specializing in toxicology, most centers also have lists of experts in many other fields as well. Poison center specialty consultants should be qualified by training or experience to provide sophisticated toxicology or patient care information in their area(s) of expertise. In regard to viral exposures, the names and phone numbers of persons in infectious disease at nearby hospitals might be helpful. Funding is usually a crucial issue, so these experts should be willing to donate their expertise in identification and handling cases within their specialty. Poison centers usually do not have specific specialists in viral diseases. Local hospital departments are most often contacted and the patient referred to the specialist.

C. What Types of Calls Are Received?
All types of calls are received by poison centers, most of which are handled immediately while others are referred to more appropriate agencies. Which calls are referred depends
Poison Centers and Viral Exposure

on the center, its expertise, its consultants, and the appropriateness of a referral. Below are lists of calls that generally fall into each group. Remember there is considerable variation between poison centers; if there is doubt, call the poison center and they will tell you if your case is more appropriately referred. Poison centers do best on calls regarding acute exposures. Complicated calls regarding exposure to several agents over a long period of time, which produces nonspecific symptoms, are often referred to another medical specialist, to the toxicologist associated with the center, or to an appropriate government agency. The poison center will often follow up on these cases to track outcome and type of service given.

Types of Calls Usually Accepted

Drug identification
Actual acute exposure to a drug or chemical
Actual acute exposure to a biologic agent (e.g., plants, mushrooms, various animals)
Information regarding the toxic potential of an agent
Possible food poisonings

Types of Calls Often Referred

Questions regarding treatment of a medical condition (not poisoning)
Questions on common bacterial, viral, or parasitic infections
General psychiatric questions
Proper disposal of household agents such as batteries, bleach, insecticides
Use of insecticides (which insecticide to use, how to use it) unless related to a health issue, e.g., a person allergic to pyrethrins wanting to know which product does not contain pyrethrins)

Records of all calls/cases handled by the center should be kept in a form that is acceptable as a medical record. The regional poison information center should submit all its human exposure data to the Association’s National Data Collection System. The regional poison information center shall tabulate its experience for regional program evaluation on at least an annual basis.

1. AAPCC Toxic Exposure Surveillance System

In 1983 the AAPCC formed the Toxic Exposure Surveillance System (TESS) from the former National Data Collection System. Currently, TESS contains nearly 16.2 million human poison exposure cases. Sixty-five poison centers, representing 181.3 million people, participate in the data collection. The information has various uses to both governmental agencies and industry, providing data for product reformulations, repackaging, recalls, bans, injury potential, and epidemiology.

The summation of each year’s surveillance is published in the American Journal of Emergency Medicine late each summer or fall.

D. How Calls Are Handled

Most poison centers receive requests for information via the telephone. Calls come from both health care professionals and consumers. Only a few requests are received by mail or in person, and these are often medicolegal or complex cases. Most centers can be reached by a toll-free phone number in the areas they serve, as well as a local number.
Busy centers will have a single number that will ring on several lines. Calls are often direct referrals from the 911 system. In most cases, poison center specialists are unable to determine the virus involved, so the caller is referred to a infectious disease physician.

Poison information specialists listen to the caller, recording the history of the case on a standardized form developed by AAPCC. Basic information such as the agent involved, amount ingested, time of ingestion, symptoms, previous treatment, and current condition are recorded, as well as patient information such as sex, age, phone number, who is with the patient, relevant medical history, and sometimes patient address. All information is considered a medical record and is therefore confidential.

The case is evaluated (using various references) as:

1. Information only, no patient involved
2. Harmless and not requiring follow-up
3. Slightly toxic, no treatment necessary but a follow-up call is given
4. Potentially toxic, treatment given at home and follow-up given to case resolution
5. Potentially toxic, treatment may or may not be given at home, but it is necessary for the patient to be referred to a medical facility
6. Emergency—an ambulance and/or paramedics are dispatched to the scene

Cases are usually followed until symptoms have resolved. In cases where the patient is referred to a health care facility, the hospital is notified, the history relayed, toxic potential discussed, and suggestions for treatment given.

E. What References Are Used?

References used also vary from center to center, but virtually all centers use a toxicology system called POISINDEX®, which contains lists of products, their ingredients, and suggestions for treatment. The system is compiled using medical literature and editors throughout the world. Biologic products such as plants, insects, mushrooms, animal bites, and so forth are handled similarly. Viral infections are not listed in the system. An entry for an individual household product or plant might contain a description, potentially toxic agent, potential toxic amounts, and so forth. The physician or poison information specialist is then referred to a treatment protocol that may apply to a general class of agents. Using plants as an example, an exposure to a philodendron would be referred to a protocol on oxalate-containing plants. An unknown skin irritation or potential infection would deserve a consult with an infectious disease specialist. POISINDEX is available on microfiche, a CD-ROM, over a network, or on a mainframe. It is updated every 3 months.

Various texts are also used, especially when the exposure agents, like viruses, are usually not in POISINDEX. It is very difficult to identify infectious cases over the phone, so often the assistance of an epidemiologist and an infectious disease specialist is used. Some poison centers have more experience with certain types of poisonings, so often one center will consult another on an interesting case. These are often more complex cases, or cases involving areas within both centers’ regions.

A recent trend has been for various manufacturers not to provide product information to all centers via POISINDEX but to contract with one poison center to provide for poison information services for the whole country. Product information is given to only that center and cases throughout the country are referred to that one center.
F. How Poison Centers Are Monitored for Quality

Most poison centers have a system of peer review in place. One person takes a call, another reviews it. Periodic spot review is done by supervisor and physician staff. General competence is assured by certification and recertification via examination of physicians and poison information specialists. The review process helps the poison control specialists to be consistent.

G. Professional and Public Education Programs

The regional poison information center is required to provide information on the management of poisoning to the health professionals throughout the region who care for poisoned patients. Public education programs aimed at educating both children and adults about poisoning concerns and dangers should be provided.

In the past, several centers provided stickers or logos such as Officer Ugh, Safety Sadie, and Mr. Yuck that could be placed on or near potentially toxic substances. While the intent was to identify potentially toxic substances from which children should keep away, the practice has been much curtailed on the new assumption that in some cases the stickers actually attracted the children to the products.

In the spring of every year there is a poison prevention week. National attention is focused on the problem of potentially toxic exposures. During this week many centers run special programs for the public. This may include lectures on prevention, potentially toxic agents in the home, potentially toxic biologic agents, or general first-aid methods using during a poisoning. Although an important time for poison centers, public and professional education is a year-round commitment. Physicians are involved with medical toxicology rounds, journal clubs, and lectures by specialty consultants. Health fairs, school programs, and various men’s and women’s clubs are used to educate the public. The extent of these activities is often determined by the amount of funding from government, private organizations, and public donations.

H. Related Professional Toxicology Organizations

ACGIH  American Conference of Governmental and Industrial Hygienists
Address: Kemper Woods Center, Cincinnati, OH, 45240
Phone: 513-742-2020
FAX: 513-742-3355

ABAT  American Board of Applied Toxicology
Address: Truman Medical Center, West, 2301 Holmes St., Kansas City, MO, 64108
Phone: 816-556-3112
FAX: 816-881-6282

AACT  American Association of Clinical Toxicologists
Address: c/o Medical Toxicology Consultants, Four Columbia Drive, Suite 810, Tampa FL, 33606

AAPCC  American Association of Poison Control Centers
Address: 3201 New Mexico Avenue NW, Washington, DC, 20016
Phone: 202-362-7217
FAX: 202-362-8377
ABEM  American Board of Emergency Medicine  
Address: 300 Coolidge Road, East Lansing, MI, 48823  
Phone: 517-332-4800  
FAX: 517-332-2234

ACEP  American College of Emergency Physicians (Toxicology Section)  
Address: P.O. Box 619911, Dallas, TX, 75261-9911  
Phone: 800-798-1822  
FAX: 214-580-2816

ACMT  American College of Medical Toxicology (formerly ABMT)  
Address: 777 E. Park Drive, P.O. Box 8820, Harrisburg, PA, 17105-8820  
Phone: 717-558-7846  
FAX: 717-558-7841E-mail: lkoval@pamedsoc.org (Linda L. Koval)

ACOEM  American College of Occupational and Environmental Medicine  
Address: 55 West Seegers Road, Arlington Heights, IL, 60005  
Phone: 708-228-6850  
FAX: 708-228-1856

ACS  Association of Clinical Scientists, Dept. of Laboratory Medicine, University of Connecticut Medical School  
Address: 263 Farmington Ave., Farmington, CT, 06030-2225  
Phone: 203-679-2328  
FAX: 203-679-2328

ACT  American College of Toxicology  
Address: 9650 Rockville Pike, Bethesda, MD, 20814  
Phone: 301-571-1840  
FAX: 301-571-1852

AOEC  Association of Occupational and Environmental Clinics  
Address: 1010 Vermont Ave., NW, #513, Washington, DC, 20005  
Phone: 202-347-4976  
FAX: 202-347-4950  
E-mail: lo478x@gwis.circ.gwu.edu

ASCEPT  Australian Society of Clinical and Experimental Pharmacologists and Toxicologists  
Address: 145 Macquarie St., Sydney N.S.W. 2000, Australia  
Phone: 61-2-256-5456  
FAX: 61-2-252-3310

BTS  British Toxicology Society, MJ Tucker, Zeneca Pharmaceuticals  
Address: 22B11 Mareside; Alderley Park, Macclesfield, Cheshire, Sk10 4TG, United Kingdom  
Phone: 0428 65 5041

CAPCC  Canadian Association of Poison Control Centers, Hopital Sainte-Justine  
Address: 3175 Cote Sainte-Catherine; Montreal, Quebec, H3T1C5  
Phone: 514-345-4675  
FAX: 514-345-4822

CSVVA (CEVAP)  Center for the Study of Venoms and Venomous Animals  
Address: UNESP, Alameda Santos, N 647, CEP 01419-901, Sao Paulo, SP; Brazil  
Phone: 55 011 252 0233  
FAX: 55 011 252 0200
Poison Centers and Viral Exposure

I. International AAPPC Affiliations

The AAPCC and its members attend various world conferences to learn of toxicology problems and new methods used by these agencies. An especially close relationship has formed between the American and Canadian poison center associations. Once a year the
AAPCC and CAPCC hold a joint scientific meeting and invite speakers and other toxicology specialists from around the world. Some international affiliated organizations are listed with the North American groups above.

J. Toxicology and Poison Center Web sites

**Association of Occupational and Environmental Clinics**  This group is dedicated to higher standards of patient-centered, multidisciplinary care emphasizing prevention and total health through information sharing, quality service, and collaborative research.
Address: lo478x@gwis.circ.gwu.edu

**Finger Lakes Regional Poison Center**
Address: pwax@ed.urmc.rochester.edu

**Medical/Clinical/Occupational Toxicology Professional Groups**  A list of primarily U.S. professional groups interested in toxicology. There is a description of each group, the address, phone numbers, and contact names.
Keyword: poison centers, toxicology
Address: http://www.pitt.edu/~martint/pages/motoxorg.htm

**Poison Net**  A mailing list dedicated to sharing information, problem solving, and networking in the areas of poisoning, poison control centers, hazardous materials, and related topics. The list is intended for health care professionals, not the lay public. The moderators do not encourage responses to individual poisoning cases from the public:
Keyword(s): poisoning, poison control centers

II. U.S. POISON INFORMATION CENTERS

The following poison control center telephone numbers and addresses are thought to be accurate as of the date of publication. Poison control center telephone numbers or addresses may change. The address and phone number of the poison control center nearest you should be checked frequently. If the number listed does not reach the poison center, contact the nearest emergency service, such as 911 or local hospital emergency rooms. The authors disclaims any liability resulting from or relating to any inaccuracies or changes in the phone numbers provided below. An asterisk indicates a regional center designated by the American Association of Poison Control Centers. This information should NOT be used as a substitute for seeking professional medical diagnosis, treatment, and care.

**ALABAMA**

_Birmingham_

Regional Poison Control Center*
Children’s Hospital of Alabama
1600 Seventh Avenue, South Birmingham,
AL 35233-1711
(800) 292-6678 (AL only)
(205) 933-4050

_Tuscaloosa_

Alabama Poison Control System, Inc.
408 A Paul Bryant Drive, East
Tuscaloosa, AL 35401
(800) 462-0800 (AL only)
(205) 345-0600
Poison Centers and Viral Exposure

ALASKA

Anchorage
Anchorage Poison Center
Providence Hospital
P.O. Box 196604
3200 Providence Drive
Anchorage, AK 99519-6604
(800) 478-3193 (AK only)

Fairbanks
Fairbanks Poison Center
Fairbanks Memorial Hospital
1650 Cowles St.
Fairbanks, AK 99701
(907) 456-7182

ARIZONA

Phoenix
Samaritan Regional Poison Center*
Good Samaritan Medical Center
1130 East McDowell Road, Suite A-5
Phoenix, AZ 85006
(602) 253-3334

Tucson
Arizona Poison and Drug Information Center*
Arizona Health Sciences Center, Room 1156
1501 N. Campbell Ave
Tucson, AZ 85724
(800) 362-0101 (AZ only)
(602) 626-6016

ARKANSAS

Little Rock
Arkansas Poison & Drug Information Center
University of Arkansas College of Pharmacy
4301 Wes Markham, Slot 522
Little Rock, AR 77205
(800) 482-8948 (AR only)
(501) 661-6161

CALIFORNIA

Fresno
Fresno Regional Poison Control Center*
Fresno Community Hospital & Medical Center
2823 Fresno Street
Fresno, CA 93721
(800) 346-5922 (CA only)
(209) 445-1222

Los Angeles
Los Angeles County
University of Southern California Regional Poison Center*
1200 North State, Room 1107
Los Angeles, CA 90033
(800) 825-2722
(213) 222-3212

Orange
University of California
Irvine Medical Center Regional Poison Center*
101 The City Drive, South
Route 78
Orange, CA 92668-3298
(800) 544-4404 (CA only)
(714) 634-5988

Richmond
Chevron Emergency Information Center
15299 San Pablo Avenue
P.O. Box 4054
Richmond, CA 94804-0054
(800) 457-2202
(510) 233-3737 or 3738

Sacramento
Regional Poison Control Center*
University of California at Davis Medical Center
2315 Stockton Boulevard Rm HSF-124
Sacramento, CA 95817
(800) 342-3293 (northern CA only)
(916) 734-3692

San Diego
San Diego Regional Poison Center*
University of California at San Diego Medical Center
225 West Dickinson Street
San Diego, CA 92013-8925
(800) 876-4766 (CA only)
(619) 543-6000
San Francisco
San Francisco Bay Area Poison Center*
San Francisco General Hospital
1001 Potrero Avenue Rm 1E86
San Francisco, CA 94122
(800) 523-2222
(415) 476-6600

San Jose
Regional Poison Center
Santa Clara Valley Medical Center
751 South Bascom Avenue
San Jose, CA 95128
(800) 662-9886, 9887 (CA only)
(408) 299-5112, 5113, 5114

COLORADO
Denver
Rocky Mountain Poison Center*
1010 Yosemite Circle
Denver, CO 80230
(800) 332-3073 (CO only)
(303) 629-1123

CONNECTICUT
Farmington
Connecticut Poison Control Center
University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030
(800) 343-2722 (CT only)
(203) 679-3456

DELWARE
Wilmington
Poison Information Center
Medical Center of Delaware
Wilmington Hospital
501 West 14th Street
Wilmington, DE 19899
(302) 655-3389

DISTRICT OF COLUMBIA
Washington
National Capital Poison Center*
Georgetown University Hospital
3800 Reservoir Road, North West
Washington, DC 20007
(202) 625-3333

FLORIDA
Jacksonville
Florida Poison Information Center
University Medical Center
655 West Eighth Street
Jacksonville, FL 32209
(904) 549-4465 or 764-7667

Tallahassee
Tallahassee Memorial Regional Medical Center
1300 Miccosukk Road
Tallahassee, FL 32308
(904) 681-5411

Tampa
Tampa Poison Information Center*
Tampa General Hospital
Davis Islands
P.O. Box 1289
Tampa, FL 33601
(800) 282-3171 (FL only)
(813) 253-4444

GEORGIA
Atlanta
Georgia Regional Poison Control Center*
Cerady Memorial Hospital
80 Butler Street South East
Box 26066
Atlanta, GA 30335-3801
(800) 282-5846 (GA only)
(404) 616-9000

Macon
Regional Poison Control Center
Medical Center of Central Georgia
777 Hemlock Street
Macon, GA 31208
(912) 744-1146, 1100 or 1427
### Poison Centers and Viral Exposure

**Savannah**
- Savannah Regional Poison Control Center
- Memorial Medical Center Inc.
- 4700 Waters Avenue
- Savannah, GA 31403
- (912) 355-5228 or 356-5228

**HAWAII**

**Honolulu**
- Kapiolani Women’s and Children’s Medical Center
- 1319 Punahou Street
- Honolulu, HI 96826
- (800) 362-3585, 3586 (HI only)
- (808) 941-441

**IDAHO**

**Boise**
- Idaho Poison Center
- St. Alphonsus Regional Medical Center
- 1055 North Curtis Road
- Boise, ID 83706
- (800) 632-8000 (ID only)
- (208) 378-2707

**ILLINOIS**

**Chicago**
- Chicago and NE Illinois Regional Poison Control Center
- Rush Presbyterian—St. Luke’s Medical Center
- 1653 West Congress Parkway
- Chicago, IL 60612
- (800) 942-5969 (Northeast IL only)
- (312) 942-5969

**Normal**
- Bromenn Hospital Poison Center
- Virginia at Franklin
- Normal, IL 61761
- (309) 454-6666

**Springfield**
- Central and Southern Illinois Poison Resource Center
- St. John’s Hospital
- 800 East Carpenter Street
- Springfield, IL 62769
- (800) 252-2022 (IL only)
- (217) 753-3330

**Urbana**
- National Animal Poison Control Center
- University of Illinois Department of Veterinary Biosciences
- 2001 South Lincoln Avenue, 1220 VMBSB
- Urbana, IL 61801
- (800) 548-2423 (Subscribers only)
- (217) 333-2053

**INDIANA**

**Indianapolis**
- Indiana Poison Center*
- Methodist Hospital
- 1701 North Senate Boulevard
- Indianapolis, IN 46202-1367
- (800) 382-9097
- (317) 929-2323

**IOWA**

**Des Moines**
- Variety Club Drug and Poison Information Center
- Iowa Methodist Medical Center
- 1200 Pleasant Street
- Des Moines, IA 50309
- (800) 362-2327
- (515) 241-6254

**Iowa City**
- University of Iowa Hospitals and Clinics
- 200 Hawkins Drive
- Iowa City, IA 52246
- (800) 272-6477 or (800) 362-2327 (IA only)
- (319) 356-2922

**Sioux City**
- St. Luke’s Poison Center
- St. Luke’s Regional Medical Center
- 2720 Stone Park Boulevard
- Sioux City, IA 51104
- (800) 352-2222 (IA, NE, SD)
- (712) 277-2222
KANSAS

Kansas City
Mid America Poison Center
Kansas University Medical Center
39th and Rainbow Boulevard Room B-400
Kansas City, KS 66160-7231
(800) 332-6633 (KS only)
(913) 588-6633

Topeka
Stormont Vail Regional Medical Center
Emergency Department
1500 West 10th
Topeka, KS 66604
(913) 354-6100

Wichita
Wesley Medical Center
550 North Hillside Avenue
Wichita, KS 67214
(316) 688-2222

MAINE

Portland
Maine Poison Control Center
Maine Medical Center
22 Bramhall Street
Portland, ME 04102
(800) 442-6305 (ME only)
(207) 871-2950

MARYLAND

Baltimore
Maryland Poison Center
University of Maryland School of Pharmacy
20 North Pine Street
Baltimore, MD 21201
(800) 492-2414 (MD only)
(410) 528-7701

MASSACHUSETTS

Boston
Massachusetts Poison Control System
The Children’s Hospital
300 Longwood Avenue
Boston, MA 02115
(800) 682-9211 (MA only)
(617) 232-2120 or 735-6607

LOUISIANA

Houma
Terrebonne General Medical Center Drug and Poison Information Center
936 East Main Street
Houma, LA 70360
(504) 873-4069

Monroe
Louisiana Drug and Poison Information Center
Northeast Louisiana University School of Pharmacy, Sugar Hall
Monroe, LA 71209-6430
(800) 256-9822 (LA only)
(318) 362-5393

MICHIGAN

Adrian
Bixby Hospital Poison Center
Emma L. Bixby Hospital
818 Riverside Avenue
### Poison Centers and Viral Exposure

<table>
<thead>
<tr>
<th>Location</th>
<th>Address</th>
<th>Phone Numbers</th>
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<tbody>
<tr>
<td>Adrian, MI</td>
<td>49221</td>
<td>(517) 263-2412</td>
</tr>
<tr>
<td>Detroit</td>
<td>Poison Control Center</td>
<td>Children’s Hospital of Michigan 3901 Beaubien Boulevard Detroit, MI 48201 Outside metropolitan Detroit; (800) 462-6642 (MI only) (313) 745-5711</td>
</tr>
<tr>
<td>Grand Rapids</td>
<td>Blodgett Regional Poison Center 1840 Wealthy Street, South East Grand Rapids, MI 49506 Within MI: (800) 632-2727</td>
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<tr>
<td>Kalamazoo</td>
<td>Bronson Poison Information Center 252 East Lovell Street Kalamazoo, MI 49007 (800) 442-4112 616 (MI only) (616) 341-6409</td>
<td></td>
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<tr>
<td>Minneapolis</td>
<td>Hennepin Regional Poison Center* 701 Park Avenue South Minneapolis, MN 55415 (612) 347-3144 (612) 347-3141 (Petline)</td>
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</tr>
<tr>
<td>St. Paul</td>
<td>Minnesota Regional Poison Center* St. Paul-Ramsey Medical Center 640 Jackson Street St. Paul, MN 55101 (800) 222-1222 (MN only) (612) 221-2113</td>
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<tr>
<td>Hattiesburg</td>
<td>Forrest General Hospital 400 S. 28th Avenue Hattiesburg, MS#39402 (601) 288-4235</td>
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<tr>
<td>Jackson</td>
<td>University of Mississippi Medical Center 2500 North State Street Jackson, MS 39216 (601) 354-7660</td>
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<tr>
<td>Las Vegas</td>
<td>Humana Hospital—Sunrise* 3186 Maryland Parkway Las Vegas, NV 89109 (800) 446-6179 (NV only)</td>
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### MISSOURI

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<td>Kansas City</td>
<td>Poison Control Center</td>
<td>Children’s Mercy Hospital 2401 Gillham Road Kansas City, MO 64108-9898 (816) 234-3000 or 234-3430</td>
</tr>
<tr>
<td>St. Louis</td>
<td>Regional Poison Center* Cardinal Glennon Children’s Hospital 1465 South Grand Boulevard St. Louis, MO 63104 (800) 392-9111 (MO only) (800) 366-8888 (MO, West IL) (314) 772-5200</td>
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### MINNESOTA

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<tr>
<td>St. Paul</td>
<td>Minnesota Regional Poison Center* St. Paul-Ramsey Medical Center 640 Jackson Street St. Paul, MN 55101 (800) 222-1222 (MN only) (612) 221-2113</td>
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### MONTANA

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<tr>
<td>Denver</td>
<td>Rocky Mountain Poison and Drug Center Denver, CO 80204 (800) 525-5042 (MT only)</td>
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### NEBRASKA

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<tbody>
<tr>
<td>Omaha</td>
<td>The Poison Center* Children’s Memorial Hospital 8301 Dodge Street Omaha, NE 68114 (800) 955-9119 (WY, NE) (402) 390-5400, 5555</td>
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### MISSISSIPPI

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<th>Location</th>
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<tbody>
<tr>
<td>Jackson</td>
<td>University of Mississippi Medical Center 2500 North State Street Jackson, MS 39216 (601) 354-7660</td>
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### NEVADA

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<tbody>
<tr>
<td>Las Vegas</td>
<td>Humana Hospital—Sunrise* 3186 Maryland Parkway Las Vegas, NV 89109 (800) 446-6179 (NV only)</td>
<td></td>
</tr>
</tbody>
</table>
Reno
Washoe Medical Center
77 Pringle Way
Reno, NV 89520
(702) 328-4144

NEW HAMPSHIRE

Lebanon
New Hampshire Poison Center
Dartmouth-Hitchcock Medical Center
1 Medical Center Drive
Lebanon, NH 03756
(800) 562-8236 (NH only)
(603) 650-5000

NEW JERSEY

Newark
New Jersey Poison Information and Education Systems*
201 Lyons Avenue
Newark, NJ 07112
(800) 962-1253 (NJ only)
(973) 923-0764

Phillipsburg
Warren Hospital Poison Control Center
185 Rosberg Street
Phillipsburg, NJ 08865
(800) 962-1253
(908) 859-6768

NEW MEXICO

Albuquerque
New Mexico Poison and Drug Information Center*
University of New Mexico
Albuquerque, NM 87131
(800) 432-6866 (NM only)
(505) 843-2551

NEW YORK

Buffalo
Western New York Poison Control Center
Children’s Hospital of Buffalo
219 Bryant Street
Buffalo, NY 14222
(800) 888-7655 (NY only)
(716) 878-7654

Mineola
Long Island Regional Poison Control Center*
Winthrop University Hospital
259 First Street
Mineola, NY 11501
(516) 542-2323, 2324, 2325

New York City
New York City Poison Control Center*
455 First Avenue, Room 123
New York, NY 10016
(212) 340-4494
(212) 764-7667

Nyack
Hudson Valley Regional Poison Control Center
Nyack Hospital
160 North Midland Avenue
Nyack, NY 10920
(800) 336-6997 (NY only)
(914) 353-1000

Rochester
Finger Lakes Regional Poison Control Center
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, NY 14642
(800) 333-0542 (NY only)
(716) 275-5151

Syracuse
Central New York Poison Control Center
SUNY Health Science Center
750 E Adams Street
Syracuse, NY 13210
(800) 252-5655
(315) 476-4766

NORTH CAROLINA

Ashville
Western North Carolina Poison Control Center
Memorial Mission Hospital
Poison Centers and Viral Exposure

509 Biltmore Avenue
Ashville, NC 28801
(800) 542-4225 (NC only)
(704) 255-4490 or 258-9907

Charlotte
Carolinias Poison Center
Carolinias Medical Center
100 Blythe Boulevard
Charlotte, NC 28232-2861
(800) 848-6946
(704) 355-4000

Durham
Duke Regional Poison Control Center
P.O. Box 3007
Durham, NC 27710
(800) 672-1697 (NC only)
(919) 684-8111

Greensboro
Triad Poison Center
Moses H. Cone Memorial Hospital
1200 North Elm Street
Greensboro, NC 27401-1020
(800) 953-4001 (NC only)
(919) 574-8105

Hickory
Catawba Memorial Hospital Poison Control Center
810 Fairgrove Church Road, South East
Hickory, NC 28602
(704) 322-6649

NORTH DAKOTA

Fargo
North Dakota Poison Center
St. Luke’s Hospital
720 North 4th Street
Fargo, ND 58122
(800) 732-2200 (ND only)
(701) 234-5575

Akron
Akron Regional Poison Center
281 Locust Street
Akron, OH 44308
(800) 362-9922 (OH only)
(216) 379-8562

Canton
Stark County Poison Control Center
Timken Mercy Medical Center
1320 Timken Mercy Drive, North West
Canton, OH 44667
(800) 722-8662 (OH only)
(216) 489-1304

Cincinnati
South West Ohio Regional Poison Control System and Cincinnati Drug and Poison Information Center*
University of Cincinnati College of Medicine
231 Bethesda Avenue ML #144
Cincinnati, OH 45267-0144
(800) 872-5111 (Southwest OH only)
(513) 558-5111

Cleveland
Greater Cleveland Poison Control Center
2074 Abington Road
Cleveland, OH 44106
(216) 231-4455

Columbus
Central Ohio Poison Center*
700 Children’s Drive
Columbus, OH 43205
(800) 682-7625 (OH only)
(614) 228-1323

Dayton
West Ohio Regional Poison and Drug Information Center
Children’s Medical Center
One Children’s Plaza
Dayton, OH 45404-1815
(800) 762-0727 (OH only)
(513) 222-2227

Lorain
County Poison Control Center
Lorain Community Hospital
3700 Kolbe Road
Lorain, OH 44053
(800) 821-8972 (OH only)
(216) 282-2220

OHIO
**Sandusky**
Firelands Community Hospital Poison Information Center
1101 Decatur Street
Sandusky, OH 44870
(419) 626-7423

**Toledo**
Poison Information Center of Northwest Ohio
Medical College of Ohio Hospital
3000 Arlington Avenue
Toledo, OH 49614
(800) 589-3897 (OH only)
(419) 381-3897

**Youngstown**
Mahoning Valley Poison Center
St. Elizabeth Hospital Medical Center
1044 Belmont Avenue
Youngstown, OH 44501
(800) 426-2348 (OH only)
(216) 746-2222

**Zanesville**
Bethesda Poison Control Center
Bethesda Hospital
2951 Maple Ave
Zanesville, OH 43701
(800) 686-4221 (OH only)
(614) 454-4221

**OKLAHOMA**

**Oklahoma City**
Oklahoma Poison Control Center
Children’s Memorial Hospital
940 Northeast 13th Street
Oklahoma City, OK 73104
(800) 522-4611 (OK only)
(405) 271-5454

**RHODE ISLAND**

**Providence**
Rhode Island Poison Center*
593 Eddy Street
Providence, RI 02903
(401) 444-5727

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**PENNSYLVANIA**

**Hershey**
Central Pennsylvania Poison Center*
Milton Hershey Medical Center
Pennsylvania State University
P.O. Box 850
Hershey, PA 17033
(800) 521-6110
(717) 531-6111

**Lancaster**
Poison Control Center
St. Joseph Hospital and Health Care Center
250 College Avenue
Lancaster, PA 17604
(717) 299-4546

**Philadelphia**
Philadelphia Poison Control Center*
One Children’s Center
34th and Civic Center Boulevard
Philadelphia, PA 19104
(215) 386-2100

**Pittsburgh**
Pittsburgh Poison Center*
One Children’s Place
3705 Fifth Avenue at DeSoto Street
Pittsburgh, PA 15213
(412) 681-6669

**Williamsport**
The Williamsport Hospital Poison Control Center
777 Rural Avenue
Williamsport, PA 17701
(717) 321-2000

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**OREGON**

**Portland**
Oregon Poison Center
Oregon Health Sciences University
3181 South West Sam Jackson Park Road
Portland, OR 97201

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Poison Centers and Viral Exposure

SOUTH CAROLINA

Charlotte
Carolinas Poison Center
Carolinas Medical Center
1000 Blythe Boulevard
Charlotte, NC 28232-2861
(800) 848-6946

Columbia
Palmetto Poison Center
University of South Carolina
College of Pharmacy
Columbia, SC 29208
(800) 922-1117 (SC only)
(803) 765-7359

SOUTH DAKOTA

Aberdeen
Poison Control Center
St. Luke’s Midland Regional Medical Center
305 S. State Street
Aberdeen, SD 57401
(800) 592-1889 (SD, MN, ND, WY)
(605) 622-5678

Rapid City
Rapid City Regional Poison Control Center
835 Fairmont Boulevard
P.O. Box 6000
Rapid City, SD 57709
(605) 341-3333

Sioux Falls
McKennan Poison Center
McKennan Hospital
800 East 21st Street
P.O. Box 5045
Sioux Falls, SD 57117-5045
(800) 952-0123 (SD only)
(800) 843-0505 (IA, MN, NE)
(605) 336-3894

TENNESSEE

Knoxville
Knoxville Poison Control Center
University of Tennessee Memorial Research Center and Hospital
1924 Alcoa Highway
Knoxville, TN 37920
(615) 544-9400

Memphis
Southern Poison Center, Inc.
Lebanheur Children’s Medical Center
848 Adams Avenue
Memphis, TN 38103-2821
(901) 528-6048

Nashville
Middle Tennessee Regional Poison Center, Inc.
501 Oxford House
1161 21st Avenue South B-101VUII
Nashville, TN 37232-4632
(800) 288-9999 (TN only)
(615) 322-6435

TEXAS

Conroe
Montgomery County Poison Information Center
Medical Center Hospital
504 Medical Center Blvd.
Conroe, TX 77304
(409) 539-7700

Dallas
North Central Texas Poison Center*
Parkland Memorial Hospital
5201 Harry Hines Boulevard
P.O. Box 35926
Dallas, TX 75235
(800) 441-0040 (TX only)
(214) 590-5000

El Paso
El Paso Poison Control Center
Thomas General Hospital
4815 Alameda Avenue
El Paso, TX 79905
(915) 533-1244

Galveston
Texas State Poison Control Center
University of Texas Medical Branch
8th and Mechanic Street
Galveston, TX 77550-2780
(800) 392-8548 (TX only)
(713) 654-1701 (Houston)
(409) 765-1420 (Galveston)

Lubbock
Methodist Hospital Poison Control
3615 19th Street
Lubbock, TX 79413
(806) 793-4366

UTAH

Salt Lake City
Utah Poison Control Center*
Intermountain Regional Poison Control Center
410 Chipeta Way, Suite 230
Salt Lake City, UT 84108
(800) 456-7707 (UT only)
(801) 581-2151

VERMONT

Burlington
Vermont Poison Center
Medical Center Hospital of Vermont
111 Colchester Avenue
Burlington, VT 05401
(802) 658-3456

VIRGINIA

Charlottesville
Blue Ridge Poison Center*
University of Virginia Health Sciences Center
Box 67
Charlottesville, VA 22901
(800) 451-1428 (VA only)
(804) 924-5543

Richmond
Virginia Poison Center
Virginia Commonwealth University
MCV Station Box 522
Richmond, VA 23298-6522

WASHINGTON

Washington
Washington Poison Center
P.O. Box 5371
Seattle, WA 98105-0371
Within WA: (800) 732-6985
(206) 526-2121

WEST VIRGINIA

Charleston
West Virginia Poison Center*
West Virginia University
3110 MacCorkle Avenue, South East
Charleston, WV 25304
(304) 348-4211
(800) 642-3625 (WV only)

PARKERSBURG
St. Joseph’s Hospital Center
19th Street and Murdoch Avenue
Parkersburg, WV 26101
(304) 424-4222

VIRGINIA

Madison
Regional Poison Control Center
University of Wisconsin Hospital
600 Highland Avenue
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**REFERENCE**

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Hepatitis A and E Viruses

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I. INTRODUCTION

Our knowledge of the disease that was initially called infectious hepatitis has increased greatly since the 1950s when hepatitis A became reportable in the United States (1). Studies in human volunteers showed that hepatitis A was transmitted primarily by the fecal-oral route, and distinguished this disease from serum hepatitis, or hepatitis B (2). However, it was not until after hepatitis A virus (HAV) was identified and diagnostic tests were developed that the full epidemiological spectrum of the disease was appreciated, and this has led to the development of an approach to its control and potential eradication.

In the United States, the most common source of infection is contact with an HAV-
infected person. The importance of food and water in the transmission of hepatitis A has been well established; however, food and waterborne outbreaks contribute only 3–8% of the total cases reported in any year (3). Hepatitis A virus infection is highly endemic in developing countries where children become infected at a young age (4). Detection of HAV by polymerase chain reaction (PCR) in clinical and environmental samples combined with nucleotide sequence analysis has expanded our understanding of the epidemiology of virus transmission (5–12). New approaches and methods for detection of HAV in clinical and environmental samples will be important for further understanding of the epidemiology of HAV transmission (13–18). The ability to grow HAV in cell culture has culminated in the development of inactivated vaccines that have been shown to effectively prevent hepatitis A (19–21). Vaccine use in selected populations may reduce disease, but only routine childhood vaccination will have significant and long-term impact on total disease burden in developed countries. Genetic engineering is being used to develop an attenuated vaccine (22,23), but it remains to be determined as to whether such a vaccine would be better than the current inactivated ones.

Following the introduction of serological tests for acute HAV and hepatitis B virus (HBV) infection, epidemics of viral hepatitis were identified that were not due to HAV but that had a fecal-oral route of transmission. This second type of viral hepatitis was initially designated enterically transmitted non-A, non-B (ETNANB) hepatitis. In the 1980s, virus-like particles were identified in patients, and this new virus, named hepatitis E virus (HEV), was cloned and partially sequenced in 1990 (24). Reagents for the serological diagnosis of HEV infection have been developed, and epidemiological studies have suggested that a substantial proportion of acute viral hepatitis in developing countries may be due to HEV (25,26). Detection of HEV requires amplification by PCR since antigen detection assays with adequate sensitivity have not been developed. Hepatitis E virus replication in several cell culture systems has been reported; however, the degree of replication appears limited and does not produce enough antigen for detection, and detailed replication studies have not been performed in these systems (27–30). In most outbreaks of this disease, fecally contaminated water has been identified as the source. However, several aspects of the epidemiology of hepatitis E could be explained by zoonotic transmission. Recently, HEV infection has been identified in several species (26,31–33). In addition, a swine HEV has been identified in the United States (34), which is similar to HEV isolated from several cases not associated with travel (35). A number of important questions concerning the epidemiology and natural history of HEV infections must be answered before prevention strategies can be devised. Evaluation of a recombinant vaccine in animal models indicated protection against disease although virus excretion occurred (36).

II. HEPATITIS A

A. Clinical Features

1. Disease Pattern

Acute hepatitis caused by infection with HAV is generally self-limited and infrequently causes fulminant disease that results in death. The degree of clinically evident illness is best predicted by the age of the infected individual (37,38). Among children younger than 6 years, less than 10% develop jaundice and fewer than 50% have any symptoms associated with acute viral hepatitis (37). In older children and adults, icterus is present in 40–80% and almost all have some signs or symptoms associated with viral hepatitis (38).
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Typically a symptomatic infection begins as a mild illness characterized by malaise, nausea, low-grade fever, and headache and progresses to more severe symptoms that include vomiting, diarrhea, right upper quadrant discomfort, maculopapular rashes, arthritis, and pruritus. In most cases these symptoms are accompanied by jaundice, and the illness usually lasts for 2–6 weeks. Death from fulminant hepatitis A is a rare event. In the United States, the reported case-fatality rate is 0.3% and varies from 0.004% in persons 5–14 years old to 2.7% in persons older than 49 years (4). Underlying chronic liver disease or concomitant infection with HBV has often been found in persons dying from hepatitis A and may predispose to a more severe outcome from this infection.

Hepatitis A virus has not been shown to cause a persistent infection and has not been associated with chronic liver disease. However, 3–20% of persons with hepatitis A have been shown to have a relapse of symptoms, liver enzyme elevations, or jaundice that occurs 1–3 months after resolution of their initial liver enzyme abnormalities (39,40). These relapses have been associated with reactivation of viral shedding, and in some instances extrahepatic manifestations of disease have been observed (39–41).

The average incubation period for HAV infection is 28 days, but can range from 2 to 6 weeks (2,42–44). The patterns of virus replication and excretion have been best defined using experimental infection of nonhuman primates (chimpanzees and tamarins) by the oral-gastric route (44,45) (Fig. 1A). Viremia, as measured by extraction of RNA from chimpanzee serum followed by RT-PCR, begins approximately 1 week after inoculation and continues up to 12 weeks (W. Bower, et al., manuscript in preparation). The duration of HAV RNA in serum was dependent on dose; RNA was detected up to 5 weeks when one infectious dose was administered and up to 13 weeks with 10^6 infectious doses. Approximately 1 week prior to the onset of liver enzyme elevations, HAV antigen is detected in hepatocytes surrounding the portal region. At the peak of liver enzyme elevations, most hepatocytes have become infected, and several weeks after the resolution of disease HAV antigen is no longer detected. Hepatitis A virus detected by enzyme immunoassay is excreted in feces soon after it can be detected in the liver. Cyclical shedding may occur, and excretion measured by antigen detection usually ceases once liver enzymes return to normal.

In humans, the duration of virus shedding may be age-related. In adults, 22–50% have detectable HAV antigen in stool specimens within a week of the onset of jaundice, and virus shedding measured by immunoassay may continue for another 2 weeks in about 20% of patients (46,47). Infants and children appear to shed virus for longer periods than adults, perhaps accounting for the high rates of infection observed among young children and their contacts (7,47,48). Detection of HAV RNA in human stool samples from outbreaks has demonstrated shedding for as long as 2–3 months after the onset of symptoms (11,49) (B. H. Robertson et al., in preparation). Whether HAV RNA is excreted for prolonged periods has not been evaluated fully in adults. However, the presence of HAV RNA does not prove the presence of infectious virus in persons with prolonged excretion.

The diagnosis of acute HAV infection can only be confirmed through serological testing; no combinations of signs or symptoms are predictive of the diagnosis. IgM antibody to HAV (anti-HAV IgM) is first detected 7–10 days after infection and is usually present at the time patients present with clinical illness. An IgM capture assay is commercially available for the detection of anti-HAV IgM as either a radioimmunoassay (RIA) or an enzyme immunoassay (EIA) (50,51). Although anti-HAV IgM may be present for long periods of time, the diagnostic assays are configured in such a manner that they usually do not produce a positive result 4–6 months after acute infection. Anti-HAV IgM
Figure 1  Viral replication and excretion: (A) virological, immunological, and biochemical events during the course of experimental hepatitis A virus (HAV) infection in chimpanzees inoculated intravenously with human HAV, strain HLD-2. (B) Virolological, immunological, and biochemical events during the course of hepatitis E virus (HEV) infection in experimentally infected cynomolgus macaques and humans. ALT, alanine aminotransferase; IgG, immunoglobulin G; IgM, immunoglobulin M. (Fig. 1A adapted from Ref. 59; Fig. 1B adapted from Refs. 392, 449, 455, 457).

is quickly followed by the appearance of IgG antibody (anti-HAV IgG) that appears to confer lifelong immunity. Competitive inhibition immunoassays that detect both IgG and IgM anti-HAV (total anti-HAV) are commercially available. The presence of total anti-HAV and the absence of anti-HAV IgM indicates that the person had a prior HAV infection and is not currently infected.

There is no specific therapy for hepatitis A. In the case of fulminant disease, orthotopic liver transplantation has been used successfully, although persistent infection has been reported infrequently (52,53).

2. Pathogenesis
Hepatitis A virus is primarily hepatotropic, although limited data suggest that the virus may replicate in cells other than hepatocytes. Whether limited infection of some intestinal
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cells occurs is unclear. Using antigen and nucleic acid detection methods, tamarins inoculated intragastrically had no evidence of intestinal replication (54), whereas nucleic acid detection methods suggested that there is intestinal replication in both experimentally infected monkeys and tamarins (55,56). In experimentally infected chimpanzees, saliva obtained 18 days after inoculation was found to contain viral RNA (57), and transmission by oropharyngeal secretions has been suggested in one foodborne outbreak (58).

In the chimpanzee model of HAV infection, the virus can be recovered from blood during a viremic phase that begins early and lasts until up to 13 weeks after inoculation of chimpanzees (Fig. 1A)(W. Bower et al., in preparation). Circulating virus is probably contained in immune complexes (59). During infection, virus is released from hepatocytes into the bile and is then shed in feces (60). The exact routes by which virus enters the liver after ingestion and passage into the small intestine are not known. Experimental infections can be initiated by intravenous inoculation of fecal material (44), and hepatitis A has been transmitted by blood transfusion (7,61) showing that the gastrointestinal tract and/or oral ingestion are not required for HAV infection.

Hepatitis A virus antigen can be detected in hepatocytes by immunofluorescence microscopy within a week of experimental inoculation, and its distribution in cells near the portal tract during the initial phase of infection suggests delivery by the portal blood supply. The histopathological picture of acute hepatitis A does not differ significantly from acute hepatitis B in terms of the cellular infiltrates and pathomorphological changes. Unlike hepatitis B, HAV can be identified in Kupffer cells (liver macrophages) and other sinusoidal cells from the period of peak liver enzyme elevation onward (44,62).

Vesicular structures containing virus particles have been seen in hepatocytes and Kupffer cells of infected animals (63,64), and similar structures have been identified in cell culture where HAV produces no cytopathic effect (65). In cell culture, HAV can replicate and be released without cell damage, and the virus does not appear to produce the hepatocellular injury observed in human or nonhuman primates. Several studies have suggested that cytotoxic T cells are involved in the resolution of HAV infection and may contribute to the observed hepatocellular injury (66,67). Clonal analysis has shown that at the site of inflammation in the liver, CD8 interferon-producing cytotoxic T lymphocytes are enriched (68). Peripheral blood lymphocytes have been shown to produce interferon in response to exposure to HAV-infected cells (69), and γ-interferon production by T lymphocytes has been found during acute infection (70). Although serum complement levels drop during infection and complement has been shown to bind to HAV capsid proteins (44,59), it is not clear as to whether complement-mediated cellular injury occurs (71).

B. Epidemiology

1. Distribution of Infection and Disease

Worldwide, infection with HAV is very common. In many developing countries (e.g., most of Africa and much of Asia) more than 90% of children may be infected by 6 years of age, with most infections being asymptomatic (4). However, in countries where there has been significant improvement in the standard of living, a noticeable decrease has been reported in early childhood infections (72–76). These changes in age-specific infection rates have resulted in a large proportion of the childhood and adult population being susceptible to infection. When HAV is introduced into these populations (e.g., through con-
taminated food and/or water, or from person-to-person contact) large outbreaks of disease have occurred.

An example of the impact of the changing epidemiology of HAV infection occurred in 1988 in Shanghai, China. Seroprevalence studies had shown low rates of infection among young children and young adults (74). However, in 1988, a very large epidemic of hepatitis A occurred over several months (more than 300,000 cases) because adults ate partially cooked clams that were harvested from areas contaminated with raw sewage (77,78).

Cyclical epidemics of hepatitis A have been shown to occur in populations where HAV infection is considered highly endemic (79,80). In many Native American populations, epidemics of hepatitis A occur every 5–7 years. Prior to one such epidemic, 40% of very young children and over 80% of adults had serological evidence of previous infection (80). However, inapparent person-to-person transmission among younger children was the most likely source of the epidemic, and resulted in a 10–40% attack rate of hepatitis A among older children and adolescents.

In the United States, epidemics of hepatitis A have occurred with almost regular periodicity until the 1980s (Fig. 2) and are probably related to the age-specific proportion of the population that is susceptible to infection and the degree to which HAV is circulating in the general population or in selected risk groups. The highest rates of hepatitis A have consistently been in the western part of the country and are primarily in counties with a low population density and large Hispanic or Native American populations (3). In addition, these epidemic periods have been associated with extended, community-wide epidemics that occur among children and young adults of low socioeconomic status via person-to-person transmission (81,82).

In 1988, approximately 28,500 cases of hepatitis A were reported to the Centers for Disease Control (CDC) and this number increased to 35,800 in 1989, reflecting a country-

![Figure 2](image.png)

**Figure 2** Rates of hepatitis A (per 100,000 population) by year in the United States, 1952–1996. (Adapted from Refs. 458 and 459.)
wide epidemic that lasted through 1991 (Fig. 2). Although the actual number of cases was probably several times higher because of underreporting, it has been shown that health care providers report hepatitis A better than other types of viral hepatitis (84,88). Among reported cases, the primary risk factors associated with hepatitis A include contact with an infected person (24–30% of cases); attending, working in, or having a child in a day care center (15% of cases); international travel (5% of cases); injection drug use (2% of cases); and food- or waterborne outbreaks (5–7%). In addition, approximately 15% of cases are associated with the presence of a child less than 5 years of age in the household who is not in day care (CDC, unpublished data). However, in all surveillance studies, 20–35% of the cases of hepatitis A have no known source for their infection (3,8) (CDC, unpublished data).

The distribution of risk factors associated with hepatitis A since 1983 is shown in Fig. 3. Injection drug use as a risk factor for infection has only been recognized since the early 1980s, and a number of outbreaks of hepatitis A have been observed in this risk group (86). Whether transmission occurs primarily through needle sharing or whether this risk factor is a surrogate for poor hygiene is not clear; both factors probably play a role in disease transmission.

The risk of infection among persons traveling to countries where HAV is highly endemic has been well documented (87). Risk factors include the region of the world being visited and the length of stay in that country. When traveling in these areas, it is recommended that hepatitis A vaccine be administered 4 weeks prior to travel; immune globulin (IG) should be administered if travel is to commence within 4 weeks of immunization. It is recommended for travelers under the age of 2 (88). Although vaccination will provide protection from HAV, travelers should take precautions to minimize ingestion of other enteric pathogens.

Epidemiological studies have also identified other settings in which HAV infection has been transmitted. These include outbreaks among persons working with nonhuman primates (89), high rates of infection among personnel during military operations in countries with a high endemicity of infection (21,90), rare instances of transmission by blood transfusion with secondary transmission to health care workers or other caregivers.

![Figure 3](image)

**Figure 3** Distribution of risk factors for hepatitis A in the United States since 1983, mutually exclusive groups. (Adapted from Refs. 458 and 459.)
(7,91,92), and high rates of infection among homosexual men (93–95). Transmission by clotting factor concentrates has also been described (96). Some investigators have suggested that sewage workers are at risk of HAV infection; however, more evaluation of this potential risk factor in different geographic locations with appropriate control groups is needed (97).

2. Modes of Transmission
Hepatitis A virus is transmitted by the ingestion of feces on contaminated objects, as fomites, or in food or water. The most important source of infection is transmission from person to person. This is shown by the high rates of transmission among young children in developing countries, in populations with a high degree of crowding or poor sanitation, as well as within households, day care settings, and institutions for the developmentally disabled (4). In almost all settings, secondary infections occur among 4–20% of household or sexual contacts of persons involved in outbreaks of hepatitis (58,81,98). Investigation of transmission in the hospital setting has confirmed that poor handwashing practices and eating in an environment where HAV is present were risk factors for infection (7).

Compared with other picornaviruses, HAV has been shown to be more resistant to low pH, heat (99–101) and drying (102), and probably allows the virus to persist in the environment for months. Hepatitis A virus can survive on human hands and be transmitted to environmental surfaces (103), a characteristic that may allow transmission from sources that are not apparent or readily traceable.

Common source outbreaks due to contaminated food or water have been well documented. When they occur they attract a great deal of public attention and concern. However, in countries such as the United States they contribute to a very small proportion of the total disease burden. Even in developing countries, foodborne transmission is probably not the primary source of HAV infection. Outbreaks may be due to contamination of the food where it is grown or harvested, or to contamination from infected food handlers. In both cases the food is usually not cooked adequately, has been eaten raw, or has been contaminated after being cooked. The food most often contaminated at its origin has been shellfish. Filter-feeding shellfish may concentrate virus up to 100-fold from large volumes of water (104,105), thus permitting the accumulation of HAV from fecally contaminated water. Although outbreaks from contaminated shellfish are usually small, an outbreak in China resulted in over 300,000 cases (77), and the degree of low-level endemic transmission from this source has not been quantified. One study has suggested that in Italy hepatitis A is mainly foodborne and that shellfish consumption is the most frequently reported risk factor (106). Other foods contaminated at the source include fruits and vegetables that may be consumed raw or fresh-frozen. These agricultural products are most likely contaminated by infected agricultural workers. Reclaimed wastewater used for irrigation is a potential source of contamination if sprayed on the plants or if contaminated soil remains on produce. Contamination at the processing and packaging plants is also possible, and it can be difficult to determine whether the contamination occurred in the agricultural field or in a processing plant. Certain preparative processes including freezing do not inactivate HAV and the usual washing procedures do not always remove virus from the produce. Some authors have suggested that foodborne outbreaks could be an increasing problem in populations with low immunity due to the increased use of imported fresh food from countries where disease is endemic (10).

Uncooked food or food handled after cooking has been the usual source of infection transmitted by food handlers. The major risk factor in these outbreaks has been poor
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personal hygiene prior to the recognition that the food handler has hepatitis A (58,107). The attack rate among patrons of the involved eating establishment has usually been low, although some notable exceptions have been reported (58). In addition, the potential exists for widespread transmission when commercial facilities prepare food that is distributed to geographically distant locations. Recently, outbreaks possibly due to contamination by agricultural field workers prior to retail food distribution have been associated with fresh lettuce (108) and frozen strawberries (5,12).

Hepatitis A virus has been shown to be transmitted by water, and fecally polluted water used in food processing can be a source of contamination. Epidemiological studies have shown an association between HAV infection and consumption of defined groundwater sources that were subsequently shown to have been fecally contaminated using bacterial indicators (109–111). In addition, outbreaks of hepatitis A and viral or bacterial gastroenteritis have been associated with contaminated groundwater. Ingestion of water while swimming in a chlorinated pool or in a lake has been associated with disease (112,113). Most convincing has been the isolation of HAV from groundwater sources associated with outbreaks of hepatitis (110,111). In one recent outbreak HAV was isolated from the source of the groundwater contamination, the implicated groundwater, and the infected individuals, with molecular confirmation of the chain of transmission (11). In a recent analysis of 139 groundwater concentrates from different geographic locations in the United States, 8.6% of samples were HAV RNA positive (114). If confirmed, this would suggest there has been a relatively high level of contamination of groundwater sources, although RNA detection does not necessarily reflect presence of infectious virus.

Viable HAV has been detected in groundwater as long as 17 months after the original contamination of wells associated with outbreaks of HAV (11,110,111) (Cromeans et al., in preparation). The significance of HAV RNA detection in groundwater needs to be established, including its potential infectivity.

C. Hepatitis A Virus Biology

1. Isolation and Characterization

For decades it was known that hepatitis was an infectious disease, but it was not until World War II that it became apparent that two epidemiologically distinct forms existed (115). Early studies in human volunteers demonstrated the intestinal-oral route of infection for the disease that has now become known as hepatitis A (42). Later, studies in human volunteers distinguished infectious hepatitis (hepatitis A) and serum hepatitis (hepatitis B) by their incubation period, primary source of the virus in the patient, and route of transmission. For hepatitis A, these studies identified fecal shedding of the virus, the viremic phase of the infection, and the effect of antibody on disease expression (42,116). However, attempts to culture the virus associated with hepatitis A were unsuccessful for almost three decades.

In 1973, Feinstone and co-workers used immune electron microscopy to visualize, in feces of patients, the 27-nm virus particles that reacted with serum of persons known to have recovered from infectious hepatitis (117). After an experimental model of infection was established in chimpanzees and tamarins (43,118), the virus was characterized further, along with the events that occurred in the host from time of infection to the resolution of disease. Initially, cell culture of HAV was only achieved after virus was passaged multiple times in marmosets (tamarins) (119), but subsequently HAV was cultivated directly from
human stools without animal passage (120–124). Whether the inoculum was human- or animal-derived, long periods of growth ranging from 4 to 10 weeks have been required for detection of significant amounts of HAV antigen in infected cells. However, no cytopathic effect (CPE) typical of many picornaviral infections was observed in any of these culture systems.

Hepatitis A virus has an RNA genome (125), is a 27- to 32-nm icosahedral particle with 32 capsomeres on the surface, has a buoyant density of 1.33–1.34 g/mL, a sedimentation coefficient of 156–160S, and contains four polypeptides based on genomic sequence, although the fourth has not been isolated (126,127). Based on its early characterization, HAV was classified as an enterovirus in the Picornavirus family (128,129). However, when compared to other enteroviruses, HAV replicated much more slowly, had greater heat stability (100), had essentially no nucleotide and amino acid sequence identity, and did not appear to have a primary intestinal tract phase of replication. Thus, HAV has been reclassified in a separate genus, the Hepatovirus in the Picornavirus family (131,132).

2. Replication in Cell Culture

Since no CPE was observed in HAV-infected cultures, virus was detected by immunofluorescent localization of HAV antigen in the cytoplasm (119,124). Upon initial isolation, HAV antigen accumulates slowly, but with increasing passage the time required for maximum antigen production can be shortened (133,134). However, in all instances maximum yields of virus were not obtained before 3 weeks post infection. The lack of CPE resulted in the establishment of persistently infected cell cultures which have been used to produce large quantities of virus (135–139). Some investigators found HAV to be only cell-associated (119,124,134), whereas others have found infectious virus and/or antigen in the cell culture fluid (133,135,140–142). HAV isolate and passage level and type of cell substrate and passage level (134,138,141,142) influence the degree of viral replication and may influence virus release.

A radioimmunofocus assay (RIFA) for the detection of infectious virus developed by Lemon and co-workers (143) made analysis of HAV replication kinetics possible. The maximum virus titer under one-cycle conditions occurred 5 days after infection, and the block in HAV replication was postulated to be at the uncoating phase (144). The synthesis of HAV RNA and depletion of the RNA pool required for replication due to encapsidation have also been suggested as rate-limiting steps for strains HM-175 and GBM (145–147). In addition, asynchronous virus replication has been suggested as a reason for the slow rate of growth (148,149). Asynchronous replication of HAV as a rate-limiting factor can also be inferred from kinetic studies with cytopathic HM-175 (142). Recent studies have also suggested that the inefficient translation initiation due to the unusual internal ribosome entry site in the 5'-NTR contributes to the slow replication (150,151). The reason(s) for the slow replication cycle of HAV as compared to other picornaviruses is not yet well defined.

Cytopathic variants of HAV have been isolated in several laboratories (152–154), and the specificity of this effect has been shown by neutralization with antibody to HAV, thus eliminating the possibility of adventitious viruses. Generally, these variants have been obtained from persistently infected cells and were subsequently serially (or acutely) passaged (152–154). Cytopathic isolates have also been obtained from serially passaged virus (141,155–157), although HAV was not shown by neutralization to be the only cause of CPE in all of these reports (141,155). The CPE is similar to other picornavirus-induced CPE. The replication cycle of these cytopathic isolates is shortened to 2–3 days and the
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yield is 20–560 infectious virions per cell, depending on the cell type employed (152,158). In studies of morphogenesis, replication has been shown to be in close association with cytoplasmic membranes for both cytopathic (157) and noncytopathic strains (65,159). A cytopathic variant has been shown to increase the number of annulate lamellae in infected cells examined by electron microscopy (160). In addition, studies of noncytopathic (161) as well as cytopathic HAV (162) show no overall effect on host cell metabolism.

Strains of HAV that have been adapted to grow efficiently in cell culture appear to have mutations in the 2B and 2C areas of the P2 region (Fig. 4) that codes for nonstructural proteins (163). Genomic analysis of cytopathic HAV variants has revealed mutations in the P2 region as well as in the P3 region and the 5′- and 3′-NTR regions (164). Although the specific changes associated with the cytopathic effect were not identified, these studies suggested that genetic recombination of HAV strain HM-175 occurred during passage in persistently infected cells. The involvement of multiple genomic regions was shown using infectious cDNA clones of a rapidly replicating variant (165). In another cytopathic strain, mutations in the 5′-NTR, P2, and P3 appear to contribute to the cytopathic phenotype (166). In addition, a cytopathogenic variant with mutation sites similar to those described in other cytopathic variants has produced an apoptotic reaction in infected cells (167). Mutations in the 5′-NTR, 2B, 2C, 3A, 3B, 3D, and 3′-NTR regions of noncytopathic HM-175 have been shown to enhance replication in cell culture (168–170). No consistent pattern of mutation has been observed following adaptation to different cell lines or among different HAV isolates, indicating a role of host factors in replication and adaptation of HAV to cell culture (22,142,168–172).

Hepatitis A virus has been shown to replicate in nonprimate as well as primate cell lines, indicating the presence of cell surface receptor(s) and other host factor(s) required for HAV replication (173). Viral attachment has been shown to be pH- and calcium ion–dependent, and inhibited by fetal calf serum (174–176). A surface glycoprotein on two different cell types has been identified as a receptor for HAV (177,178). Further studies

![Figure 4](image)

Figure 4  HAV genomic organization and proposed cleavage products. (Adapted from Ref. 455.)
have shown that this receptor is expressed in several human tissues including liver, and that the receptor is HAV binding and possibly functional in replication (179,180).

3. Molecular Biology

a. Genomic Organization

Hepatitis A virus has a single-stranded RNA genome of positive polarity that is approximately 7500 nucleotides long (Fig. 4). Genomic structure and replication scheme of HAV are similar to that of poliovirus and other members of the Picornaviridae family. HAV genome contains a single open reading frame (ORF) of 6500 nucleotides encoding a single polyprotein that is cleaved by virus-specific proteases, has a poly-A tract at its 3' terminus, and has no 5'-cap structure (181). VPg, a viral protein linked to the 5' end of the genome, has a lower isoelectric point than that of other picornaviruses (182). Although the genomic organization of HAV and other picornaviruses are similar, there is little similarity in their nucleotide sequences (131,183,184), or amino acid composition (131).

Hepatitis A virus appears to have the same translational strategy as that of other picornaviruses and proteins identified following in vitro translation were related immuno-biologically to the structural proteins (185). Locarnini et al. (186) detected 11 virus-specific proteins in cells infected with wild-type HAV, a pattern similar to that found in cells infected with poliovirus type 1. However, other investigators found only structural proteins of the mature virion in infected cells (185,187), which may be due to low protein stability or the slow growth rate of HAV and its failure to inhibit host protein synthesis. Using various recombinant in vivo and in vitro expression systems, the 3C proteinase (3Cpro) was shown to cleave all structural and nonstructural proteins from the primary translation product (188-194). P1-2A has been proposed as the functional precursor of structural proteins (192,195,196). Transient expression of a nested set of 3Cpro-containing proteins also has been reported (197,198) and suggests that these intermediate products may be involved in promoting viral assembly.

The HAV capsid is composed of three major structural proteins—VP1, VP2 and VP3—with sizes of 33, 27, and 29 kDa, respectively (137). Based on the nucleotide sequence, a fourth capsid protein VP4, of approximately 2.5 kDa, should be encoded (199) but has not been identified in mature virions.

The entire nucleotide sequence and derived amino acid sequence has been obtained from cDNA clones for strains HM-175, HAS-15, LA, and MBB (183,200–202). When the sequence of wild-type human HAV (HM-175) in marmosets was compared to the partial sequence of three other cell culture-adapted human HAV strains (HM-175, LA, CR326 and HAS-15), the majority of amino acid changes were located in the capsid region, mostly in VP1 (184). Nucleotide changes have also been shown to occur following cell culture adaptation and attenuation of HM-175 (203). Twenty-four nucleotide changes distributed throughout the genome were present in the cell culture-adapted virus compared with its wild-type parent. The changes found in the cell culture-adapted isolates do not appear specific for the adaptative process, and some may be cell-specific mutations (170). Studies by Emerson et al. (163) indicate that mutations in the P2 region, specifically in the 2B and 2C areas, resulted in increased growth of the virus in cell culture.

b. Antigenic Sites

Members of the Picornavirus family are distinct from each other antigenically (204,205). These differences are reflected, to a large extent, in the detailed molecular
topography of the virion with most of their antigenic sites contained on the exposed outer surface of the capsid structure (206,207). Because x-ray crystallographic data are not yet available for HAV, information concerning its surface structure and potential antigenic sites comes from several sources. Hepatitis A virus exists as a single serotype, and neutralizing monoclonal antibodies that identify overlapping epitopes of cell culture–adapted strains of HAV generally recognize wild-type isolates from all parts of the world (208). Surface labeling studies have identified VP1 as the major exposed protein (209–211), as is the case for other picornaviruses. Alignments of VP1 sequences of poliovirus type 1 and HAV have identified three peptides with potential cross-reactive antigenicity, and a synthetic peptide from one of these sequences has been used to generate antibodies in rabbits that neutralized HAV in cell culture (212). Ostermayr et al. (213) produced a recombinant VP1 fusion protein, expressed in *Escherichia coli*, that reacted with rabbit anti-HAV serum. However, chimpanzees immunized with this recombinant protein produced antibodies that only reacted with VP1 of denatured virus and not with intact virus. Similarly, chimpanzees immunized with recombinant VP1 produced high titer antibody, but were not protected when challenged with wild-type HAV (Margolis et al., unpublished data).

Virus mutants selected for resistance to neutralization by monoclonal antibodies, as well as competitive antibody binding studies, suggest that HAV has a single conformational immunogenic epitope composed of several sites located on VP1 and VP3 (208,214–216). Under antibody selection, amino acid changes occur in both sites simultaneously, which further supports the concept that these two sites interact to form a single neutralization epitope (216). However, findings from HAV strains isolated from Old World monkeys suggest that sites other than those identified by the escape mutants may be involved in protecting the host from infection. These viruses have been shown to be genetically distinct from human HAV (see section below); they generally are not recognized by monoclonal antibodies produced against human HAV (217, 218, Nainan et al., unpublished data), but they bind polyclonal antibody to human HAV. In these viruses, the specific amino acids in VP1 and VP3 associated with the binding of neutralizing monoclonal antibodies differ from those found in human HAV, and probably explains their poor binding by monoclonal antibodies to human HAV (216). However, chimpanzees immunized with an HAV isolated from an Old World monkey (*Cynomolgus macaques*) induced an antibody response that usually protected them from human HAV infection, suggesting that additional antibody sites may be involved in aborting HAV infection (Nainan et al., unpublished data). In a recent study, a continuous epitope of HAV in VP3, 12 amino acids long, has been identified and antibodies generated against this peptide were found to be capable of binding intact HAV and neutralizing its infectivity (219).

A three-dimensional structure of HAV has been developed using amino acid sequence alignments of the known structures of Mengo virus and human rhinovirus (220). However, these models have not always accurately predicted the structure of other viruses (221). The escape mutant data (214–216) suggest that this may be the case for HAV, since only 6 of the 11 amino acids associated with antibody binding are located on the outer surface. Although the data suggest that the sites in VP1 and VP3 interact to form a single antigenic determinant, they are located too far apart to fit under a single immunoglobulin binding site. However, it is possible that amino acid changes at one site affect primary antibody binding at a distant site, as has been found with foot-and-mouth disease virus (FMDV) (221a). Thus, the true nature of the neutralization epitope(s) of HAV probably will not be resolved without a crystallographic structure.