

**A Practical Approach to
Pesticide Illness:
Chronic Neurologic Effects**

Prepared for
Office of Environmental Health Hazard Assessment

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Welcome

Welcome to the Clinical Approach to Pesticide Exposure (CAPE) series of online learning modules. The purpose of this series is to provide primary care providers, through case presentations, a practical approach for addressing pesticide exposures and illnesses. The overwhelming majority of pesticide-related cases can be handled in primary care settings with simple diagnostic and supportive measures and without the need for hospitalization or specialists. Our approach emphasizes:

- Using your traditional skills and clinical common sense
- A practical approach to confirming the diagnosis
- A practical approach to therapy
- Reporting confirmed cases

DISCLOSURE

- Office of Environmental Health Hazard Assessment, Grants/Research Support
- NIOSH Agricultural Health & Safety grant 5 U50 OH007550-07, Research Support

Welcome

This module utilizes a case-based approach similar to that used in any clinical encounter:

- Obtain a focused history
- Conduct a focused examination
- Identify a likely diagnosis within a reasonable differential
- Perform appropriate laboratory studies
- Institute appropriate treatment
- Post-case discussion

Welcome

Clinical practice is frequently portrayed in strict linear fashion: history, physical examination, laboratory studies, diagnosis, and finally therapy. In practice, however, physicians often begin formulating a list of possible diagnoses and instituting therapy from the very beginning. We attempt to incorporate this aspect of practice in these case studies.

Our last step, a post-case discussion, has a long and respected history in medicine. It is all too often left out because of our busy schedules, yet it is critical for learning. Accordingly, we include this as an essential element of each case.

Let's get started . . .

A Case of Peripheral Neuropathy

History of present illness: Your patient is a middle-aged man who complains of a three-month history of shooting pains in his back, generalized muscle weakness, and evanescent numbness and tingling involving the hands and feet. He is otherwise healthy, a nonsmoker and nondrinker.

Comment: *Your clinical common sense is pointing toward a possible peripheral neuropathy. The evanescent numbness and tingling in a "stocking-glove" distribution is especially suggestive of this. Accordingly, you ask for more history. . .*

	A Case of Peripheral Neuropathy
	<p>The medical and family histories provide no clues for an underlying cause. In particular, he is not diabetic and drinks no alcohol. He is married with three grown children. He has no unusual hobbies or known heavy-metal exposures, and no one else in his household is ill.</p> <p>His occupational history is of interest: he has worked for approximately six months as an animal technician in a local veterinary hospital. He uses a variety of dips and shampoos on the animals, and many of these contain pesticide agents. He uses no gloves or other protective equipment.</p>

	A Case of Peripheral Neuropathy
	<p><i><u>Comment:</u> This again raises your suspicion that he may have a toxic condition related to pesticide exposure. Many pesticide agents are fat-soluble and thus well absorbed through the skin. He uses pesticide-containing products frequently without gloves or other protective clothing.</i></p>

	A Case of Peripheral Neuropathy
	<p><u>Physical examination:</u></p> <p>Vital signs and general appearance are unremarkable. Cranial nerves: Difficulty in maintaining upward gaze. Motor: Mild generalized weakness. Sensory: Reduced sensation for light touch below knees. Examination otherwise unremarkable.</p>

	A Case of Peripheral Neuropathy
	<p><i><u>Comment:</u> At this point it is likely that the general practitioner will obtain some laboratory studies and refer to a neurologist for further evaluation. Your consultation request will likely include your concern about possible toxic neuropathy related to pesticide exposures at work.</i></p>

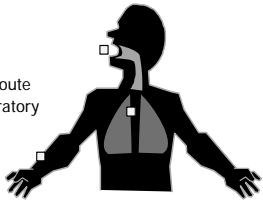
	A Case of Peripheral Neuropathy
	<p><u>Laboratory examination:</u></p> <ul style="list-style-type: none"> ▪ Complete blood count ▪ B₁₂ and folate ▪ Metabolic panel ▪ Blood lead and zinc protoporphyrin (ZPP) ▪ Urine heavy metal screen ▪ Consider HIV testing ▪ Plasma cholinesterase ▪ RBC-acetylcholinesterase ▪ "Hold-it" tubes of blood and urine

	A Case of Peripheral Neuropathy
	<p><u>Treatment:</u> In view of your concern over pesticide exposure, you restrict the patient from using these at work until your evaluation is complete. You also decide to refer him to a neurologist for further evaluation, including electromyography and nerve conduction studies.</p>

	<h3>A Case of Peripheral Neuropathy</h3>
	<p><u>Treatment:</u> Several days later your laboratory studies return as normal, including plasma cholinesterase and RBC-acetylcholinesterase.</p> <p>You await the results of your neurological referral.</p>

	<h3>A Case of Peripheral Neuropathy: Post-Case Discussion: History</h3>
	<p><u>Differential diagnosis:</u> When you first saw your patient, you began formulating a differential diagnosis. Your history and physical examination pointed toward a peripheral neuropathy. As a clinician, you will think of the most common causes for this, including diabetes and alcohol abuse. You may also consider HIV, although there are no evident risk factors.</p> <p>In this case these were not in evidence, and the history of unprotected exposures to pesticides raised suspicion of a toxic neuropathy related to these agents.</p>

	<h3>A Case of Peripheral Neuropathy: Post-Case Discussion: History</h3>
	<p>Physicians naturally want to know the agent involved, but this is often not possible, especially at the first visit.</p>

	<h3>A Case of Peripheral Neuropathy: Post-Case Discussion: History</h3>
	<p>There are three main routes of exposure to pesticides:</p> <ul style="list-style-type: none"> ▪ Ingestion ▪ Dermal ▪ Respiratory <p>In this case, the most likely route is dermal, although the respiratory route may also contribute.</p> 

	<h3>A Case of Peripheral Neuropathy: Post-Case Discussion: History</h3>
	<p><u>History of Present Illness:</u> How can we get information on the specific pesticide agent?</p> <ul style="list-style-type: none"> ▪ Ask the patient. (Often the patient does not know.) ▪ Contact the employer. The employer should have Material Safety Data Sheets (MSDS) for all chemicals used in the establishment.

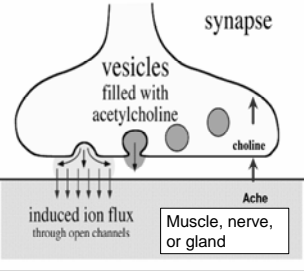
	<h3>A Case of Peripheral Neuropathy: Post-Case Discussion: History</h3>
	<p><u>History of Present Illness:</u> How can we get information on the specific pesticide agent?</p> <ul style="list-style-type: none"> ▪ County health officer ▪ Poison Control Center (800-222-1222) ▪ National Pesticide Information Center (npic.orst.edu) <p>Fortunately, we are usually able to treat properly even without knowing what agent is involved. <i>Removal from exposure and supportive care are the mainstays of therapy.</i></p>

A Case of Peripheral Neuropathy: Post-Case Discussion: History

Mechanism and Historical Background:

- Organophosphate agents most common class of pesticide
- Acute effects related to inhibition of acetylcholinesterase

A Case of Peripheral Neuropathy: Post-Case Discussion: History



This figure shows an impulse coming down the nerve axon. This releases acetylcholine into the synapse, which stimulates the "downstream" muscle, nerve, or gland.

Acetylcholinesterase is also released into the synapse to neutralize the acetylcholine and prevent over stimulation.

Source: Medscape General Medicine v.8(4); 2006

A Case of Peripheral Neuropathy: Post-Case Discussion: History

Mechanism and Historical Background:

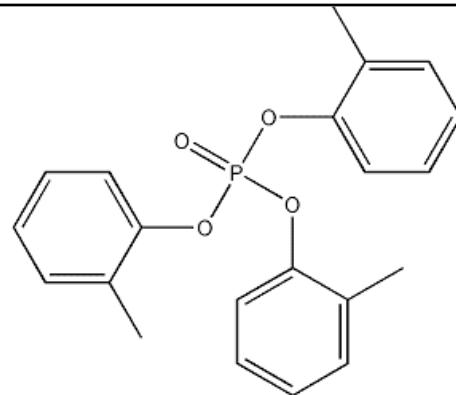
- Neuropathic effects due to inhibition of neuropathy target esterase (NTE); affects nutrient transport
 - Not related to acetylcholinesterase inhibition
 - Not all organophosphates affect NTE
 - Examples include methamidophos, leptophos, fenthion, merphos
 - Causes axonopathy; also affects upper motor neurons
 - Leads to Organophosphate-Induced Delayed Neuropathy (OPIDN) with latency of 1-3 weeks



A Case of Peripheral Neuropathy: Post-Case Discussion: History

19th Amendment ("Prohibition," Volstead Act)

Jamaican Ginger extract used as alcoholic beverage
 US Treasury Department responded by requiring doubling of dissolved ginger solids
 Assumed these would render it undrinkable
 Harry Gross, Max Reisman of Boston chose to adulterate instead with tri-ortho cresyl phosphate (TOCP), an organophosphate agent
 Tasteless, thought to be harmless



tri-ortho-cresyl phosphate

A Case of Peripheral Neuropathy: Post-Case Discussion: History

Estimated 50,000 victims in 1930-31
Mostly poor men
Gave rise to popular music:

I can't eat, I can't talk
Been drinkin' mean jake,
Lord, now can't walk
Ain't got nothin' now to lose
Cause I'm a jake walkin' papa
with the jake walk blues.
Allen Brothers, "Jake Walk Blues" (1930)

Jake-Based Songs of the 1930s

Date	Writer	Song
1928	Lemuel Turner	"Jake Bottle Blues"
1930	Allen Brothers	"Jake Walk Blues"
1930	Ray Brothers	"Jake Leg Wobble" - instrumental
1930	Byrd Moore	"Jake Leg Blues"
1930	Ray Brothers	"Got The Jake Leg Too"
1930	Narmour and Smith	"Jake Leg Rag - instrumental"
1930	Tommy Johnson	"Alcohol and Jake Blues"
1930	Ishman Bracey	"Jake Liquor Blues"
1930	Mississippi Sheiks	"Jake Leg Blues"
1930	Daddy Stovepipe	"Jake Leg Blues"
1933	Asa Martin	"Jake Walk Papa"
1934	Willie Lofton	"Jake Leg Blues"

A Case of Peripheral Neuropathy: Post-Case Discussion: Physical Exam

Although initially thought to be a peripheral neuritis with hope of recovery, long-term evaluation showed it involved anterior horn cells and corticospinal tracts, leading to an upper-motor neuron syndrome. Axonal degeneration also occurs.

Functional recovery was best in the upper extremities. For most, flaccidity was replaced by spasticity and was permanent.

A Case of Peripheral Neuropathy: Post-Case Discussion: Physical Exam

Physical examination: Your physical examination focused on the neurological system. The stocking-glove distribution is suggestive of a toxic or metabolic neuropathy.

Long axons are metabolically vulnerable. Hence many metabolic conditions (e.g., alcohol, diabetes) can yield similar pictures with a "stocking-glove" involvement due to axonopathy, or "dying back" of axons.

A Case of Peripheral Neuropathy: Post-Case Discussion: Laboratory

Laboratory Examination: Choice of laboratory studies should be guided by your clinical common sense.

- A CBC, B₁₂, and folate are appropriate because these may indicate a megaloblastic anemia or alcoholism.
- Metabolic screen may show hypercalcemia (suggestive of cancer and paraneoplastic syndrome) or indicate diabetes or alcoholism.
- Consider also HIV, which can present as neuropathy.

A Case of Peripheral Neuropathy: Post-Case Discussion: Laboratory

Laboratory Examination:

- Plasma cholinesterase and acetylcholinesterase may indicate exposure to cholinesterase-inhibiting pesticide, such as organophosphate or carbamate.
- Whole-blood lead and zinc protoporphyrin may indicate lead poisoning.
- Urine heavy metal screen may indicate other metals.
- "Hold-it" tubes may be useful in future investigations

	<p>A Case of Peripheral Neuropathy: Post-Case Discussion: Treatment</p>
	<p><u>Treatment:</u> One must often treat the patient without laboratory confirmation of pesticide intoxication.</p> <p>In this case your suspicion of a work exposure leads to a pesticide agent lead to restrictions against working with these. This comports with our therapeutic mainstays: supportive care and removal from exposure.</p>

	<p>A Case of Peripheral Neuropathy: Post-Case Discussion: Treatment</p>
	<p><u>Follow-up:</u> The neurologist confirmed your findings, and subsequent electromyography and nerve conduction studies demonstrated a peripheral neuropathy with axonopathy.</p> <p>Suspicion centered on a topical flea-control agent containing 20% fenthion, an organophosphate. Further investigation by NIOSH led to four more cases among the eight employees at the veterinary hospital.</p> <p>Morb Mortal Wkly Rpt 1985; 34:402-403</p>

	<p>A Case of Peripheral Neuropathy: Post-Case Discussion: Treatment</p>
	<p><u>Follow-up:</u> Fenthion is very fat soluble, facilitating skin absorption.</p> <p>Limited studies showed it to be neurotoxic in hens.</p> <p>OPIDN typically is a mixed motor and sensory neuropathy, typically beginning in the legs.</p> <p>Note normal plasma cholinesterase and RBC-acetylcholinesterase results--peripheral neuropathy is not related to anticholinesterase activity.</p>

	<p>A Case of Forgetfulness: History</p>
	<p>Mr. Jacobs is a 43-year-old residential pesticide applicator who enters clinic because of memory difficulties. Over the past year he has noted increasing forgetfulness. This has affected him at work in that he has had to write down addresses and telephone numbers that he previously could remember. He sleeps poorly, and characterizes his mood as sad.</p>

	<p>A Case of Forgetfulness: History</p>
	<p>His past medical history is unremarkable. He is a nonsmoker, but drinks "several beers" every night after returning from work. He is divorced and living alone, but sees his children every other weekend.</p> <p><i>Comment: The history suggests several possibilities at this point: alcoholism, depression, toxic effect from pesticides, among others. These will inform your diagnostic approach.</i></p>

	<p>A Case of Forgetfulness: History</p>
	<p>He has worked as a residential pesticide applicator for eight years. He uses a variety of chemicals, including organophosphates and pyrethroids. He wears a half-face mask and cloth overalls when he sprays. His coveralls frequently become moist when he sprays, and he washes them weekly. He has not had any episodes of acute illness from his work exposures.</p>

	<p>A Case of Forgetfulness: Physical Examination</p>
	<p>On physical examination VS: BP 148/92 HR 80 Wt 220 lb. Ht 70" BMI 31.6 He is in no acute distress. Mental status: Able to remember a 7-digit telephone number, but only 3 digits in reverse. Serial sevens show about 50% accuracy. Proverb interpretation is concrete. He recalls one of three objects after 5 minutes.</p>

	<p>A Case of Forgetfulness: Laboratory</p>
	<p>Chemistry panel, including liver function tests CBC Plasma cholinesterase RBC-acetylcholinesterase Consider HIV testing Consider neuropsychiatric testing</p>

	<p>A Case of Forgetfulness: Laboratory</p>
	<p>Obtain further information on exposures: Material Safety Data Sheets (MSDS) (by law employers must have these available.) Poison Control Center</p>

	<p>A Case of Forgetfulness: Potential Underlying Causes</p>
	<p>Broad at this point Alcoholism Depression Metabolic disorder (e.g., hypercalcemia) Toxic effect of pesticides</p>

	<p>A Case of Forgetfulness: Treatment</p>
	<p>Stop alcohol consumption Use protective equipment at work Exercise regimen Encourage social engagement</p>

	<p>A Case of Forgetfulness: Post-Case Discussion: History</p>
	<p>The physician and patient are best served by first focusing on the illness rather than potentially causative exposures. Otherwise, one risks missing easily diagnosed and treatable conditions because of a premature focus on an exposure. In this case, we focus on his clinical syndrome of forgetfulness and consider a broad set of underlying causes, including but not limited to pesticide exposures.</p>

	<p>A Case of Forgetfulness: Post-Case Discussion: History</p>
	<p>Relevant points from the history include</p> <ul style="list-style-type: none"> ■ Gradual onset of memory difficulties ■ Alcohol use ■ Divorce and “loner” status ■ Poor sleep and mood ■ Poor hygiene with work clothes

	<p>A Case of Forgetfulness: Post-Case Discussion: History</p>
	<p>Information on work exposures</p> <ul style="list-style-type: none"> ■ Patient ■ Workplace (Material Safety Data Sheets) ■ Poison Control Center

	<p>A Case of Forgetfulness: Post-Case Discussion: PEx</p>
	<p>Points to note:</p> <ul style="list-style-type: none"> ■ Elevated weight and blood pressure ■ Potential intermediate and short-term memory deficit ■ Potential concentration deficit with poor serial sevens (may be confounded by educational background) ■ Concrete proverb interpretation (may be confounded by educational background)

	<p>A Case of Forgetfulness: Post-Case Discussion: Laboratory</p>
	<p>Chemistry panel and CBC helpful for alcoholism, electrolyte disorders</p> <p>Plasma cholinesterase for organophosphate exposures over past several weeks</p> <p>RBC-acetylcholinesterase for organophosphate exposures over past 2-3 months</p> <p>Consider HIV testing</p>

	<p>A Case of Forgetfulness: Post-Case Discussion: Laboratory</p>
	<p>Consider neuropsychiatric testing</p> <ul style="list-style-type: none"> ■ Characterizes cognitive function ■ Shows function, not cause ■ Expensive and time consuming ■ USUALLY NO PREMORBID BASELINE AVAILABLE FOR COMPARISON <ul style="list-style-type: none"> - I.e., are findings new? <p>Interpretation can therefore be difficult. . .</p>

	<p>A Case of Forgetfulness: Post-Case Discussion: Diagnosis</p>
	<p>Main considerations</p> <ul style="list-style-type: none"> ■ Depression ■ Alcohol ■ Pesticide toxicity

	<p>A Case of Forgetfulness: Post-Case Discussion: Diagnosis</p>
	<p>Several studies show dose-related effects on chronic central nervous system function: mood, memory, attention.</p> <p>Many persons with pesticide exposures also report central and peripheral neurologic symptoms with increased frequency.</p>

	<p>A Case of Forgetfulness: Post-Case Discussion: Treatment</p>
	<p>Mainstay of treatment is removal from exposure and supportive care</p> <ul style="list-style-type: none"> ■ Cease alcohol ■ Daily exercise regimen ■ Social engagement ■ Consider counseling ■ Sleep hygiene ■ Proper use of protective equipment and hygiene at work

	<p>Pesticide-Related Conditions: Post-Case Discussion: Reporting</p>
	<p><u>Reporting:</u> Pesticide illness cases must be reported to State and local agencies.</p> <ul style="list-style-type: none"> • Requirement of CA Health and Safety Code • Reports serve as an early warning system system--County and state can alert physicians and the public, reducing the extent of an epidemic • State agencies may assist County officers • Identify and characterize trends • Assist State in writing pesticide regulations

	<p>Pesticide-Related Conditions: Post-Case Discussion: Reporting</p>
	<p><u>By telephone:</u> Report pesticide illnesses to County Health Officer. Phone numbers available at: www.dhs.ca.gov/hisp/chs/OVR/LocalRegistrar/default.htm</p> <p><u>By the internet:</u> Coming soon to a URL near you!</p> <p><u>By mail:</u></p> <ul style="list-style-type: none"> - Pesticide Illness Report Form (PIR) available from the CA Environmental Protection Agency - Work-related cases also require a Doctor's First Report Form (within 5 days of visit)

	<p>Clinical Approach to Pesticide Exposure: Cultural Competency Resources</p>
	<p>"With the increasing diversity of the US population, physicians are more and more likely to encounter situations that require the delivery of culturally competent care, access to a vast array of language services, and supportive healthcare organizations." (U.S Dept. of Health and Human Services).</p> <p>Cultural competency is key for communicating with a diverse patient population.</p>

	<p>Clinical Approach to Pesticide Exposure: Cultural Competency Resources</p>
	<p>For patients with limited English ability, options include:</p> <ul style="list-style-type: none"> ■ The Health Care Provider (if proficient in the patient's language) ■ Staff proficient in the patient's language ■ A trained interpreter ■ A family member of the patient (except children) Always use the method with which the patient feels most comfortable.

Clinical Approach to Pesticide Exposure: Cultural Competency Resources
<p>Online training in Cultural Competency:</p> <p>https://cccm.thinkculturalhealth.org/ http://www.familydocs.org/assets/Multicultural_Health/ http://www.omhrc.gov</p> <p>Useful phrases in non-English languages:</p> <p>futurehealth.ucsf.edu/TheNetwork/Portals/3/CommonSentences.pdf</p>

Clinical Approach to Pesticide Exposure: Cultural Competency Resources
<p>TIP: Working with trained interpreters, on-site</p> <ul style="list-style-type: none"> ■ Greet the patient first, not the interpreter. ■ During the medical interview, speak directly to the patient, not to the interpreter: "Tell me why you came in today" instead of "Ask her why she came in today." ■ A professional interpreter will use the first person in interpreting, reflecting exactly what the patient said, e.g. "My stomach hurts" instead of "She says her stomach hurts." This allows you to hear the patient's "voice" most accurately and deal with the patient directly. ■ Speak at an even pace in relatively short segments; pause often to allow the interpreter to interpret. You do not need to speak especially slowly; this actually makes a competent interpreter's job more difficult. ■ Don't say anything that you don't want interpreted. It is the interpreter's job to interpret everything. ■ If you must address the interpreter about an issue of communication or culture, let the patient know first what you are going to be discussing with the interpreter. ■ Speak in: Standard English (avoid slang) Layman's terms (avoid medical terminology and jargon) Straightforward sentence structure Complete sentences and ideas ■ Ask one question at a time. ■ Ask the interpreter to point out potential cultural misunderstandings that may arise. Respect an interpreter's judgment that a particular question is culturally inappropriate and either rephrase the question or ask the interpreter's help in eliciting the information in a more appropriate way. ■ Do not hold the interpreter responsible for what the patient says or doesn't say. The interpreter is the medium, not the source, of the message. ■ Avoid interrupting the interpretation. Many concepts you express have no linguistic, or conceptual equivalent in other languages. The interpreter may have to paint word pictures of many terms you use. This may take longer than your original speech. ■ Don't make assumptions about the patient's education level. An inability to speak English does not necessarily indicate a lack of education. ■ Acknowledge the interpreter as a professional in communication. Respect his or her role. <p>Source: California Academy of Family Physicians</p>

On-Line Sources of Information
<ul style="list-style-type: none"> ■ Recognition and Management of Pesticide Poisonings, by Reigart and Roberts, U.S. EPA <ul style="list-style-type: none"> - http://www.epa.gov/oppfead1/safety/healthcare/handbook/handbook.htm - Hardcopies are available in English or Spanish ■ National Pesticide Information Center <ul style="list-style-type: none"> - http://npic.orst.edu ■ Pesticide Illness compact disc by Association of Occupational and Environmental Clinics <ul style="list-style-type: none"> - http://www.aoec.org/LLDIR.htm#PowerPoint

On-Line Sources of Information
<ul style="list-style-type: none"> ■ California Department of Pesticide Regulation, Pesticides and Human Health Information <ul style="list-style-type: none"> - http://www.cdpr.ca.gov/docs/quicklinks/humanhea.htm ■ Pesticide Labels and MSDSs <ul style="list-style-type: none"> - http://www.pested.psu.edu/resources/web/labels.shtml

Resources for Reporting
<p><i>How to report: 4 options:</i></p> <ol style="list-style-type: none"> 1. Call the local health officer or designated county contact See http://www.oehha.ca.gov/pesticides/pdf/pestnums.pdf for list of phone numbers 2. Fax or mail a report to local health officer You may use one of the following forms: <ul style="list-style-type: none"> - PIR: Confidential Report of Known or Suspected Pesticide-Related Illness http://www.oehha.ca.gov/pesticides/pdf/PIR_99.pdf - CMR: Confidential Morbidity Report - DFR: Doctor's First Report of Occupational Injury or Illness

Resources for Reporting
<p><i>How to report: 4 options:</i></p> <ol style="list-style-type: none"> 3. Call California Poison Control System at 1-800-222-1222 For health care providers requesting help with pesticide toxicology information and medical management. Center staff will offer to report on your behalf to your local health officer. 4. File an electronic CMR/pesticide illness report Contact your county health department for instructions (available soon in Los Angeles, San Diego, Sacramento, Orange, Monterey, Stanislaus, and Yolo counties.)

	<p>Resources for Reporting</p>
	<p><i>When to report:</i> Within 24 hours – <i>known or suspected</i> pesticide-related illness or injury</p> <p><i>What to report:</i> See PIR form at http://www.oehha.ca.gov/pesticides/pdf/PIR_99.pdf</p> <p><i>Confidentiality:</i> Reporting of pesticide illness does not violate HIPAA or state laws.</p>

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