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Pesticide Information Leaflet

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No. 30: Cholinesterase Monitoring – A Guide for the Health Professional

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BACKGROUND

Cholinesterase is an enzyme necessary for proper nerve impulse transmission. If the activity of this enzyme is reduced below a critical level, nerve impulses to the muscles can no longer be controlled, resulting in serious consequences and even death. This leaflet describes for physicians or other health care providers how to set up a monitoring schedule for persons exposed regularly or seasonally to cholinesterase inhibitors.

Which pesticides inhibit cholinesterase?

Two classes of insecticides, the organophosphates (OP) and the carbamates, act as cholinesterase inhibitors. One OP herbicide (Betasan) and the desiccant DEF, or Folex, can also have this effect. OP and carbamate insecticides are used in the United States and worldwide on many fruit, field, and vegetable crops; in greenhouses, forests, and marshes; inside structures; and on home landscapes. Occupational exposures to these insecticides may occur during manufacture, distribution, mixing and loading, application, or reentry into treated areas. Most are available for use without special training in the U.S., and it is not uncommon to find them handled by homeowners or by unskilled, temporary laborers.

Applicators sometimes know only the brand names or, at best, the common names of the pesticides they use. They may not be aware of which classes of pesticides they use, as this information has not generally been required to appear on the pesticide label. The

labels of newer products, however, identify pesticides that act as cholinesterase inhibitors. The last page of this leaflet presents a list of brand and common names of organophosphate and carbamate insecticides.

How does cholinesterase inhibition happen?

Synaptic acetylcholine (ACh) is released from vesicles in cholinergic nerve endings and binds to nicotinic and muscarinic receptors on the postsynaptic membrane. Acetyl cholinesterase (AChE), in close proximity to ACh receptors on the postsynaptic membrane, then hydrolyzes ACh in a 3-step process involving binding to the enzyme, acetylating the enzyme, and reacting with water to produce acetic acid and the reconstituted enzyme. The reaction is completed rapidly, freeing the esterase for the next molecule of ACh. However, if OP or carbamate compounds are present, they bind to the cholinesterase, resulting in release of the organic moiety of the OP or carbamate and phosphorylation or carbamyl-ation of the enzyme at the esteratic site. With AChE no longer available to hydrolyze ACh, the neurotransmitter saturates the receptors and accumulates in the synapses, causing overstimulation and, later, blockage of further nerve impulse transmission. The rate of dephosphorylation of the esterase-OP complex is so slow that OPs are referred to as irreversible inhibitors. Carbamates form less stable complexes, and are referred to as reversible inhibitors. This is an important concept in monitoring, as carbamates have often lost their affinity for the enzyme by the time a cholinesterase assay is performed.

What are the consequences of cholinesterase inhibition?

Depression of cholinesterase activity below a critical level may occur from a single large exposure, such as spilling the concentrate insecticide, or from a series of small exposures over a long period of time, such as applying these materials throughout an entire growing season. An applicator may exhibit symptoms within 48 hours after an application, after which the symptoms may disappear until the next exposure. Symptoms of overexposure to cholinesterase inhibitors include headaches, dizziness, blurred vision, nausea and vomiting, stomach cramps, and tightness of the chest. Signs of overexposure include diarrhea, excessive salivation and sweating, tightness of the chest, muscle twitching, and pinpoint pupils. Acute overexposure can be fatal.

Decreases in cholinesterase activity, when compared to the individual's own baseline, generally parallel the potential severity of toxicity. Clinical symptoms requiring hospitalization are usually not associated with depletions of less than 50% of cholinesterase activity.

How can cholinesterase monitoring help the pesticide applicator?

When used properly, cholinesterase monitoring helps protect workers from acute poisoning, increases hazard awareness, and can form an initial step in identifying unsafe work practices. If overexposure does occur, cholinesterase monitoring can assist clinical management. By following recommendations, pesticide applicators can reduce their overall exposure to cholinesterase inhibitors, thereby preventing acute overexposures as well as potential chronic or delayed effects.

Who should be monitored?

Cholinesterase monitoring is appropriate only for occupational users of OPs and, perhaps, carbamates. Applicators who use

herbicides (except Betasan), fungicides, rodenticides, other pesticides, or only other classes of insecticides are not appropriate subjects for cholinesterase monitoring. Also, persons only occasionally exposed to cholinesterase-inhibiting insecticides through residues in and around structures, landscapes, treated crops, or through residues on foods are not considered to be at risk for significant cholinesterase inhibition. Pesticide applicators who work frequently with OPs and carbamates may benefit from surveillance of their cholinesterase levels.

Because it is necessary to obtain baseline data, the best candidates for cholinesterase monitoring are workers who apply pesticides on a seasonal basis, with a period of months when they are not exposed. Many applicators who work in agriculture, nurseries, turf production, golf courses, and lawns and landscapes apply cholinesterase- inhibiting pesticides seasonally. Applicators who work indoors, such as structural pest control operators; pet groomers and veterinary workers; and applicators treating indoor plant pests in restaurants, malls or greenhouses often use these pesticides year-round, with no significant non-exposed period. In such cases, a baseline is best obtained at the time of hiring, assuming the individual has not recently worked with cholinesterase inhibitors in a previous job. For those already working with cholinesterase inhibitors, an attempt should be made to obtain a baseline during a period of least exposure, preferably at least 30 days after last exposure.

California has set guidelines that require testing for those who handle cholinesterase inhibitors for more than 6 days within a 30-day period. The state of Washington uses a similar guideline, but also recommends testing those handling cholinesterase inhibitors on any 3 consecutive days.

What test(s) should be used?

While it is the inhibition of AChE in the nervous system that is responsible for toxicity, similar types of cholinesterase exist in the blood and can be used as markers of exposure to OPs and carbamates. OPs and carbamates bind to both AChE, found in the synapses and attached to red blood cells, and to butyryl cholinesterase, also called plasma cholinesterase (PChE), found in plasma. Pesticides can have different affinities for AChE and PChE; thus, potency as an inhibitor varies with the particular pesticide.

Levels of inhibition of AChE and PChE provide slightly different information, and both assays should be done for each patient. Red blood cell cholinesterase is identical to the enzyme found in the nervous system, and it is thought to be a good indicator of actual neuronal activity. The turnover rate for red blood cells is slow (about 3 months), and AChE measurements reflect this slow replacement rate. Thus, AChE is typically used as a marker of chronic exposure. In contrast, PChE turnover is much quicker. PChE is a better short-term indicator due to its more rapid response to exposure; it is used as an indicator of recent, acute exposure. When an individual's exposure ceases, both enzymes recover to their normal activity levels as turnover occurs.

There are several different methods available for conducting cholinesterase assays. It is important to use the same laboratory throughout the monitoring period and to ensure that the laboratory does not change methodologies during the course of the monitoring. If different methods are used, the values cannot be compared throughout the season. Also, be aware that not all laboratories perform cholinesterase assays well. A quality assurance program with periodic blinded spiked split samples should

be part of any monitoring system.

How often should testing be done for monitoring purposes?

Non-exposed, baseline values differ significantly between individuals. The "normal" range is wide enough that an individual might exhibit a significant drop in available cholinesterase while remaining within the normal range for a given laboratory; however, this is an abnormal condition for that individual. Therefore, it is important to perform a baseline measure-ment of both AChE and PChE during a non-exposed period. Preferably, the assay should be performed when the applicator has not handled OPs for 3 months in order for red blood cells, and their AChE, to be regenerated. An average derived from 2 baseline readings is optimal, and a baseline should be developed yearly. Once the application season has started, testing should be done every 3-4 weeks during intensive application periods, preferably within 3 days after application of an OP.

Inhibition of cholinesterase by carbamates, while potentially serious, is less persistent and probably will not be detected by regular monitoring. If an applicator is exposed only to carbamates and not OPs, cholinesterase monitoring may provide a false sense of security because the extent of inhibition from each exposure will likely not show up in the test results. However, obtaining a baseline on those exposed only to carbamates can be helpful in case of a subsequent incident of severe overexposure necessitating a cholinesterase assay as part of the diagnostic work-up.

How should monitoring results be used?

Each time testing is done throughout the season, AChE and PChE levels should be compared to the respective baselines for the patient. California critical threshold levels identify an overexposure as a drop of 40% in PChE or a drop of 30% in AChE. Some employers use a decrease of 25-30% in either AChE or PChE as the threshold. In the event of such a decrease from baseline, the individual should be told to stop working with OPs and carbamates until values return to at least 80% of baseline. A decrease of 20% or greater in either AChE or PChE should precipitate an evaluation of work practices to minimize further exposure.

Can other factors affect the results of cholinesterase tests?

Pregnancy and liver disease can contribute to false positive test results, as can caffeinated foods and certain medications including anticholinergics, hormones, INH, and chloroquine. Factors that can contribute to false negative test results include depressed baseline values, testing errors, and certain anemias.

What about acute poisoning?

Cholinesterase testing can provide limited information about the condition of a patient if baseline values are not available. If OP or carbamate poisoning is suspected, a clinical evaluation (physical examination and review of symptoms) should be performed, and cholinesterase testing of both AChE and PChE should be ordered. If baseline values have been obtained, results should be compared as with individuals in monitoring programs. Comparisons should be interpreted using the same guidelines presented for comparisons in monitoring programs. If no baseline exists, and the initial test reading during the illness episode is within the laboratory's normal range, the possibility of poisoning cannot be excluded. Follow-up testing should be done at 1-2 week

intervals until a stable value is evident. If the values show an increasing trend, but eventually reach a stable value 30% or more above the first AChE level or 40% or more above the first PChE value, it is evidence that an overexposure did occur.

What practices are likely to contribute to a drop in cholinesterase level?

Failure to use personal protective equipment (PPE) identified on the pesticide label; sloppy handling during mixing, loading, application, or disposal; neglect of personal hygiene; and exposure from non-work-related sources such as use of OPs or carbamates around the home increase exposure. Applicators should wash their hands and face frequently throughout the work day, especially before eating, drinking, smoking, or using the toilet; wash thoroughly (preferably, shower) at the end of the work day; properly clean and maintain work clothes and PPE; and avoid wearing any leather items such as belts, hats or inner hat bands, gloves, and boots because leather absorbs pesticides and cannot be decontaminated. ***Pesticide Information Leaflet No. 11: Practices for Safe Use*** and ***Pesticide Information Leaflet No. 18: Pesticide Applicator Checklist*** provide more specific information for the applicator on the proper handling of pesticides and measures to reduce exposure.

CHOLINESTERASE MONITORING GUIDELINES

Adapted from guidelines adopted by the states of Washington and California.

Utilize cholinesterase monitoring for individuals who apply OP pesticides occupationally on more than 3 consecutive days, or for 30 or more hours within any 30-day period.

Measure both acetylcholinesterase (red blood cell cholinesterase) and butyryl cholinesterase (plasma cholinesterase). Use the same laboratory and the same methodology for all testing so that results may be accurately compared.

Obtain a baseline reading of both measures during the non-exposed period, at least 30 days since the last exposure to OP pesticides.

Repeat testing every 3-4 weeks during intensive OP and carbamate application periods.

Test within 3 days of any 30-day period in which the individual has met or exceeded the handling hours threshold.

Compare each reading to the individual's baseline. Take action as specified in the following table.

Thresholds for cholinesterase decision-making

Decrease from baseline	Action
20% decrease in AChE or PChE	Evaluate work practices
30% decrease in AchE *or* 40% decrease in PChE	Remove worker from exposure to organophosphates and carbamates until levels return to within 80% of baseline

CHOLINESTERASE-INHIBITING PESTICIDES

Cholinesterase-inhibiting pesticides are listed by common name, with trade names in parentheses. Check the active ingredient statement on the label of the pesticide to see if it contains one of the common names listed since not all trade names may be included. Newly registered active ingredients or those not commonly used may not be listed here.

Organophosphates

acephate (Orthene, Payload)
azinphos-methyl (Guthion, Sniper)
bensulide (Betasan, Prefar)
carbophenothion (Trithion)
chlorethoxyfos (Fortress)
chlorfenvinphos (Birlane, Supona)
chlorpyrifos (Dursban, Lorsban)
chlorpyrifos-methyl (Reldan)
coumaphos (Co-Ral)
demeton (Systox)
diazinon (D-Z-N)
dichlorvos (DDVP, Vapona)
dicrotophos (Bidrin)
dimethoate (Cygon, Rebelate)
dioxathion (Delnav)
disulfoton (Di-Syston)
EPN
ethion (Tomahawk)
ethoprop (Mocap)
ethyl parathion (Orthophos, Parathion, PhosKil)
famphur (Warbex)
fenamiphos (Nemacur)
fenitrothion (Sumithion, Rothion)
fensulfothion (Dasanit)
fenthion (Baycid, Baytex, Tiguvon)
fonofos (Dyfonate)
isazophos (Miral, Triumph)
isofenphos (Amaze, Lighter, Oftanol, Pryfon)
malathion (Cythion)
methamidophos (Monitor)
methidathion (Supracide)
methyl parathion (Penncap-M)
mevinphos (Phosdrin)
monocrotophos (Azodrin)
naled (Dibrom, Legion)
omethoate (Folimat)
oxydemeton-methyl (MetaSystox-R)
parathion (see ethyl parathion)
phorate (Thimet)
phosmet (Imidan)
phosphamidon (Dimecron)
phostebupirim (see tebupirimiphos)
pirimiphos-ethyl (Primicid)
pirimiphos-methyl (Silosan, Actellic)
profenofos (Curacron)
propetamphos (Safrotin)
sulfotepp (Bladafum)
sulprofos (Bolstar)
tebupirimiphos (Aztec)
temephos (Abate)
terbufos (Counter)
tetrachlorvinphos (Rabon, Gardona)
tribufos (DEF 6, Folex)
trichlorfon (Dipterex, Dylox, Proxol)

Carbamates

aldicarb (Temik)
aldoxycarb (Standaz)
bendiocarb (Ficam, Garvox, Turcam)
carbaryl (Sevin)
carbofuran (Furadan)
carbosulfan (Advantage)
fenoxycarb (Logic)
formetanate (Carzol)
methiocarb (Mesurol)
methomyl (Lannate, Nudrin)
mexacarbate (Zectran)
oxamyl (Vydate)
pirimicarb (Pirimor)
promecarb (Carbamult)
propathrin (Danitol)
propoxur (Baygon)
thiodicarb (Larvin)
trimethacarb (Broot, Landrin)

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