

Metabolic susceptibility to agricultural pesticides and non-Hodgkin's lymphoma

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Epidemiologic studies have failed to establish clearly whether agricultural pesticides contribute to the genesis of non-Hodgkin's lymphoma (NHL). Discordant results may be related to variation in susceptibility factors, including metabolism gene polymorphisms that might influence lymphocyte exposures to active pesticide metabolites. Associations between NHL and polymorphisms that may be relevant to pesticide metabolism have been assessed, including CYP1A1 and glutathione S-transferase variants, but the results are not highly informative because estimates were based on small numbers and convenience samples of cases and controls. Butyrylcholinesterase and paraoxonase (PON1) enzyme variants associated with altered activity and acute organophosphate toxicity are strong candidate susceptibility factors for pesticides and NHL, but others may be identified as knowledge of pesticide metabolism and relevant polymorphisms improves. Studies of metabolic susceptibility must be large and include information on specific exposures and subtypes of NHL for results to further the understanding of the relation between agricultural pesticides and NHL.

Key terms butyrylcholinesterase; cytochrome P-450; gene-environment interaction; glucuronosyltransferase; glutathione S-transferase; polymorphism; paraoxonase; review; sulfotransferase.

Farming has been repeatedly associated with non-Hodgkin's lymphoma (NHL) (1), but epidemiologic studies have not provided unequivocal evidence that agricultural pesticides are a cause of the relation (2). Unfortunately, studies also have not convincingly refuted the possibility that pesticides contribute to NHL, because most have lacked detailed exposure information for specific pesticides (3, 4), have failed to address the etiologic heterogeneity of NHL subtypes (5–7), and have not investigated factors that may influence individual susceptibility to pesticide-mediated effects. If susceptibility factors exist they may explain why observed associations vary among different populations (8) and may strengthen evidence of a causal relation by focusing effect estimation on populations at risk (9).

The following three general categories of candidate susceptibility factors can be considered for pesticides and NHL: (i) those that may influence lymphocyte exposures, (ii) those that may influence putative lymphomagenic effects of pesticides once exposure has occurred, and (iii) cofactors that may determine whether the pesticide-mediated effect would contribute to a complete carcinogenic mechanism. This review focuses on

metabolism gene polymorphisms that may affect susceptibility by influencing the rate, persistence, and nature of lymphocyte exposures to active metabolic intermediates of agricultural pesticides (9, 10).

Cytochrome P450 metabolism

Many pesticides are converted to active intermediates via reactions catalyzed by cytochrome P450 (CYP450) (11). CYP1A1 is expressed in peripheral blood lymphocytes (12), and DNA (deoxyribonucleic acid) damage following exposure to carbaryl was increased in cultured lymphoblastoid cells that expressed CYP1A1 compared with CYP1A1 null clones (13). Linked CYP1A1*2A (*MspI*) and CYP1A1*2B (Ile462Val) variants (14) have been shown to be associated with increased activity and inducibility in cultured lymphocytes (15, 16), although the functional relevance of these variants has not been confirmed by other in vitro assays (17). CYP1A1 is highly inducible via (AhR) transcriptional activation mediated by the aryl hydrocarbon receptor (18), and small effects of common polymorphisms

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may be undetectable when variation secondary to induction is pronounced. Two case-control studies evaluated NHL and CYP1A1*2A and reported no association, including a Norwegian study of 143 NHL cases that were compared with 455 unrelated controls (recruited from the staff of the National Institute of Public Health and from residents of senior citizen homes) (19) and an Australian study that compared 169 NHL cases with 205 gender-matched volunteer bone marrow donors (20) [odds ratios (OR) and 95% confidence intervals (95% CI) for any variant allele versus none: OR 0.8, 95% CI 0.4–1.3, and OR 0.8, 95% CI 0.5–1.4, respectively]. Children with acute lymphoblastic leukemia (ALL), a subtype of NHL, were more likely to carry CYP1A1*2A and CYP1A1*2B alleles if exposed to household pesticides during pregnancy than were cases without such exposures, but the case-case effect estimates were imprecise (eg, OR 5.0, 95% CI 1.0–25.1, for any *2A allele with mite or spider pesticides) (21). A study of 177 childhood ALL cases compared with 304 controls from an institutional DNA bank also reported a positive association with CYP1A1*2A (OR 1.8, 95% CI 1.1–3.1, for any *2A allele), but not CYP1A1*2B (OR 0.9, 95% CI 0.4–1.8) (22).

Polymorphisms in several other CYP450 enzymes that may influence pesticide metabolism have not yet been evaluated as risk factors for NHL in published studies. CYP1B1 is active in peripheral lymphocytes (23) and is constitutively expressed, but also regulated, via AhR-mediated transcriptional activation. Common polymorphisms include CYP1B1*2 (linked Arg48Gly and Ala119Ser variants) and CYP1B1*3 (Leu432Val), with allele frequencies ranging between 29% and 39% (24, 25). Activity was strongly associated with the CYP1B1*5 (Arg48Gly, Ala119Ser, and Leu432Val) and *6 alleles (CYP1B1*5 plus Asn453Ser), which occurred with frequencies of 6% and 7% in an Ethiopian population (25). CYP3A4 and CYP1A2 metabolize several pesticides, including carbaryl (26), parathion (27), atrazine (11), and methoxychlor (28). Neither enzyme is produced in lymphocytes (12, 23), but both may influence extranodal lymphocyte exposures to pesticide metabolites. There is considerable individual variation in CYP3A4 activity that has not been linked to known polymorphisms (29). The CYP1A2*1C allele has been associated with decreased activity (30), and CYP1A2*1F has been associated with increased inducibility (31), but these findings have not been consistent (32).

Hydrolytic detoxification reactions

Acute toxic effects of organophosphate and carbamate pesticides occur when CYP450 intermediates inhibit

enzymatic degradation of the neurotransmitter acetylcholine (33). Hydrolytic degradation or scavenging by serum butyrylcholinesterase (BChE) may limit exposure of the central nervous system (CNS) (33, 34) and may limit immune system effects that have been tentatively attributed to the pesticide-mediated inhibition of mono-enzyme-specific esterases (35, 36) and serine proteases required for cell-mediated cytotoxicity (37). There is substantial variation in BChE activity that may be largely explained by BChE polymorphisms (38). The BChE-K variant (Ala539Thr) has been associated with a 30% decline in serum BChE activity, and it occurred with an allele frequency of 13% among Americans (39), 18% among healthy Japanese, and 47% among Japanese with low BChE activity (40). BChE-K may be in linkage disequilibrium with other low-activity polymorphisms, including the rare Asp70Gly allele (associated with a 70% reduction in activity) and numerous inactivating mutations (39, 41); thus it is unclear whether the K allele or a linked variant may be causing the low-activity phenotype. BChE-K and other polymorphisms have been associated with Alzheimer's disease (42) and diabetes (43), and insights offered by ongoing studies of these associations will be useful to researchers interested in BChE as a susceptibility factor for pesticides and NHL.

Reactive oxon intermediates of organophosphates are substrates for hydrolytic degradation by phosphotriesterase enzymes, including paraoxonase (PON1) (44). PON1 Arg192Gln and Met55Leu variants have been associated with substrate-dependent effects on activity (45) and acute organophosphate toxicity (46, 47), and Kerridge et al reported that the 192Gln/Gln genotype was more common among NHL cases than among bone marrow donor controls (OR 2.5, 95% CI 1.4–4.6) (20). Recently discovered –108T and –162A promoter variants have been shown to be associated with increased activity, and they occur with allele frequencies of about 50% and 20%. These polymorphisms are in linkage disequilibrium with high activity 55Leu and 192Arg variants (allele frequencies of about 30%) (48). PON1 variants are under investigation because activity may limit damage caused by bacterial endotoxins, prevent lipid oxidation, and possibly decrease the risk of atherosclerosis (49). In theory, PON1 activity may influence lymphomagenesis not only by limiting exposure to toxic organophosphate metabolites, but also by influencing putative effects of pesticides on immune function and oxidative stress.

Conjugation reactions

Glutathione S-transferase (GST) enzymes conjugate reactive metabolic intermediates of many pesticides (50), and they have been investigated as risk factors for NHL.

The common GSTM1 null genotype has not been independently associated with NHL (OR 0.9–1.0) (19, 20, 51) or chronic lymphocytic leukemia (CLL), an NHL subtype (OR 1.3, 95% CI 0.8–1.9) (52). GSTM1 null was associated with ALL in one study (OR 1.8, 95% CI 1.1–3.1) (22), but two others reported no overall association with ALL (21, 53). GSTT1 null genotype was more common among Australian NHL cases than among bone marrow donors (adjusted OR 4.3, 95% CI 2.4–7.6) (20), but it was not increased among Norwegian NHL cases (OR 1.1) (19). There was a slight increase in the GSTT1 null among CLL cases when compared with that of spouses of other cancer patients (OR 1.4, 95% CI 0.9–2.2) (52), but three studies of pediatric ALL reported no association (21, 22, 53). The GSTP1 Ile105Val variant may influence activity (54, 55) and was associated with Hodgkin's lymphoma (OR 2.1, 95% CI 1.1–4.1 based on 76 cases) but not NHL (OR 1.0) in one study (19). The 105 Val variant has also been weakly associated with CLL (OR 1.4 for any Val allele) (52).

Cytosolic sulfotransferases (SULT) may detoxify some pesticide metabolites and increase the activity of others (56). SULT activity is physiologically regulated, but may also be influenced by common polymorphisms, including the SULT1A1*2 Arg213His variant (allele frequency 32% in Caucasians) and SULT1A2*2 alleles with the Asn235Thr variant (frequency 29% in Caucasians). SULT1A1*2 and SULT1A2*2 are located in adjacent genes and may be in linkage disequilibrium with each other and with other less common alleles. Several SULT enzymes are expressed in lymphocytes (57). Glucuronide conjugation is also a major metabolic pathway for pesticide intermediates (58), and several polymorphisms in UDP-glucuronosyltransferase (UGT) genes have been associated with altered activity (59). Organophosphate pesticides were shown to markedly inhibit UGT activities in vitro, and it has been suggested that effects of pesticides and other inhibitory xenobiotics may be related to the altered glucuronide conjugation of endogenous substrates, including steroid hormones (60).

Gene–gene interactions

Enzymes involved in pesticide metabolism have overlapping substrate specificities, and the lack of one-to-one specificity may buffer effects of any single metabolism enzyme variant by providing an alternate catalyst for metabolic transformation. Likewise, effects of “high-risk” polymorphisms affecting a single metabolic step may be diminished by “low-risk” variants acting at subsequent steps, such that consequences of rapid phase I activation may be lessened by rapid phase II detoxification. Therefore, it may be necessary to evaluate joint

effects of multiple functional gene polymorphisms to detect an effect on pesticide metabolism and NHL (61). It may also be important to estimate effects of haplotypes, as well as individual single nucleotide polymorphisms (SNP), when causal variants have not been firmly established, since haplotypes that define an appropriate domain may be more likely to capture the effects of linked causal variants and may also identify alleles where combined effects of multiple SNPs produce the “at risk” phenotype (62).

Studies have had inadequate numbers of participants to reliably assess gene–gene interactions and NHL. Keridge et al (20) reported evidence of a synergistic effect of GSTT1 null and PON1 192Gln/Gln genotypes on NHL in a comparison with bone marrow donor controls, based on an OR of 4.0 for the GSTT1 null alone, an OR of 2.6 for PON1 192Gln/Gln alone, and an OR of 9.1 (95% CI 2.7–30.4) for the GSTT1 null and PON1 192Gln/Gln combined, using the wild type–wild type of genotype as the common reference group. The joint OR was greater than expected for additive risks (OR 5.6) (63), but was based on the findings from only 14 cases and 3 controls. Joint-effect estimates for the GSTM1 null and CYP1A1*2A alleles on pediatric ALL (22), and for the GSTM1 null, GSTT1 null and GSTP1 105Val alleles on CLL (52), were imprecise and did not clearly differ from expectations for additive effects.

Nongenetic influences on metabolism

Nongenetic influences on metabolism are harder to define and measure than gene polymorphisms, but they may be a significant determinate of susceptibility. In general, metabolism varies with age, gender, and comorbid conditions but may also vary because of induction or inhibition by cytokines (64), metabolic byproducts (58), drugs, dietary factors, and xenobiotics (65, 66). Metabolism enzyme induction and inhibition has also been proposed as a mechanism that may indirectly link pesticides and estrogen-associated cancers. For example, there is evidence that preferential CYP1A1 inhibition by estrogenic pesticides may increase the production of carcinogenic 4-hydroxy catechol estrogen metabolites via CYP1B1-mediated pathways, on the basis of metabolic effects of endosulfan and dioxin in a breast cancer cell line (67).

Other candidate susceptibility factors

Metabolic susceptibility may be easier to identify if we could also account for factors that influence whether

additional steps in lymphomagenesis occur after lymphocyte exposure to pesticide metabolites. For example, oxidative damage, which has been associated with pesticide exposures *in vivo* (68) and *in vitro* (69), may be influenced by environmental and dietary oxidants and antioxidants (65). Polymorphisms that influence DNA break repair via homologous recombination and nonhomologous end joining may be particularly relevant to NHL, given the role of translocations in the genesis of hemolymphatic cancers (70, 71). Factors that influence immunity, including age, psychological and physiologic stress, diet, drugs, overall health, and polymorphisms that affect immune function, may also influence susceptibility to pesticides and NHL (72). Immune-mediated mechanisms may also be influenced by agricultural exposures other than pesticides, including sunlight, allergenic plant and animal dusts, and zoonotic infections (3, 4). Direct hormonal effects proposed for pesticides may be influenced by metabolism enzyme polymorphisms that alter the elimination of reactive or functional intermediates of estrogenic pesticides (73).

Pre-existing somatic mutations may influence susceptibility. t(14;18) translocations are common NHL mutations that are believed to contribute to lymphomagenesis via bcl-2-mediated inhibition of apoptosis (5). These translocations are also prevalent among peripheral blood lymphocytes of healthy adults (74–76) and may increase susceptibility by preventing programmed cell death when adverse somatic mutations occur during antigen-stimulated clonal expansion (5, 77). Studies have reported an increase in chromosome aberrations in pesticide applicators and producers (78, 79), including breaks at locations involved in t(14;18) rearrangements (80), and there is preliminary evidence that chromosome aberrations in peripheral lymphocytes may be increased in association with GSTM1 and GSTT1 null genotypes (81).

Study design

There is little reason to believe that all types of NHL would be causally associated with pesticides, given the widely accepted evidence of etiologic diversity among NHL subtypes (6, 7). Studies that evaluate associations between risk factors and all NHL combined ignore this diversity and may mask associations if they are relevant only to specific subtypes of NHL (82). The importance of accounting for potential etiologic differences among NHL outcomes in epidemiologic research has been stressed (5, 7, 83), and studies of pesticides and NHL have demonstrated stronger associations with NHL subtypes than NHL in the aggregate (84–86). Unfortunately, these studies have used a variety of NHL classification

schemes, and findings are difficult to summarize. Improved understanding of lymphomagenesis may suggest etiologically relevant classifications for future research, including NHL subtypes defined by common somatic mutations or other potential markers of common etiologic mechanisms (5, 86, 87).

Criteria for selecting candidate gene polymorphisms and appropriate study designs to assess them have been reviewed elsewhere (8, 88–90). Metabolism gene polymorphisms should be relevant to the specific exposure and target tissue of interest and should ideally include only common variants with evidence of functional effects. Currently, these criteria do little to narrow the list of candidates for pesticides and NHL, since information regarding specific metabolic pathways for individual products is limited, pesticide exposures are often mixed, and lymphocytes may be exposed to a wide array of tissue-level metabolic environments. New information on the relevance of specific polymorphisms for pesticides and NHL should be utilized, if and when it becomes available.

Adequate sample size is a critical problem for all studies of genetic susceptibility (8, 89). In theory, data from small studies could be pooled to increase precision, but this approach is never valid if the individual study data are biased (91). Previous studies of metabolism genes and NHL have relied on convenience samples of controls such as nursing home residents (19), anonymous blood or bone marrow donors (20, 53), and spouses of other cancer patients (52), and information on individual exposures has been limited, at best. Studies that fail to ensure that cases and controls are sampled from the same population can produce biased gene-disease effect estimates if environmental cofactors differ between cases and controls (8, 92) or there is substantial population stratification (93). Case eligibility criteria have also been poorly specified, and studies may have included prevalent cases that would bias effect estimates if metabolic susceptibility factors influence treatment response and survival (8).

Concluding remarks

We cannot expect to improve our understanding of NHL etiology by ignoring its complexity, but we are also unlikely to advance the field through studies that attempt to address complexity one cofactor at a time. An alternative approach is to evaluate potential risk factors in the context of plausible biological models of NHL etiology that account for joint effects of candidate cofactors, including pesticides and metabolism gene polymorphisms relevant to specific types of pesticides and putative mechanisms of effect. These conceptual models

must be developed based on information from multiple sources, including both experimental and observational studies, and they must be allowed to develop and mature as new information becomes available. Over time, studies of metabolic susceptibility to pesticides and NHL may clarify whether some agricultural pesticides are an important causal cofactors for NHL, but only if they are well-designed, collect high-quality exposure data for specific types of pesticides, and include analyses of NHL subtypes relevant to proposed etiologic mechanisms. Metabolism gene polymorphisms that have been associated with acute pesticide toxicity, particularly PON1 and BChE variants, are particularly attractive candidate susceptibility factors for pesticides and NHL, but accumulating information may also support future studies of CYP450 and phase II enzyme polymorphisms that may influence pesticide metabolism.

References

- Khuder SA, Schaub EA, Keller-Byrne JE. Meta-analyses of non-Hodgkin's lymphoma and farming. *Scand J Work Environ Health* 1998;24(4):255–61.
- Zahm S, Blair A. Pesticides and non-Hodgkin's lymphoma. *Cancer Res* 1992;52s:5485s–8s.
- Pearce N, Reif J. Epidemiologic studies of cancer in agricultural workers. *Am J Ind Med* 1990;18:133–48.
- Blair A, Hoar Zahm S, Pearce N, Heineman EF, Fraumeni JF Jr. Clues to cancer etiology from studies of farmers [review]. *Scand J Work Environ Health* 1992;18:209–15.
- Magrath I. Molecular basis of lymphomagenesis. *Cancer Res* 1992;52s:5529s.
- Herrinton L. Epidemiology of the revised European-American lymphoma classification subtypes. *Epidemiol Rev* 1998;20:187–203.
- Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* 2000;92(15):1240–51.
- Little J, Bradley L, Bray MS, Clyne M, Dorman J, Ellsworth DL, et al. Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. *Am J Epidemiol* 2002;156(4):300–10.
- Vineis P, Martone T. Genetic-environmental interactions and low-level exposure to carcinogens. *Epidemiology* 1995;6(4):455–7.
- Hirvonen A. Polymorphisms of xenobiotic-metabolizing enzymes and susceptibility to cancer. *Environ Health Perspect* 1999;107 suppl 1:37–47.
- Lang DH, Rettie AE, Bocker RH. Identification of enzymes involved in the metabolism of atrazine, terbuthylazine, ametryne, and terbuthryne in human liver microsomes. *Chem Res Toxicol* 1997;10(9):1037–44.
- Spatzenegger M, Horsmans Y, Verbeeck RK. CYP1A1 but not CYP1A2 proteins are expressed in human lymphocytes. *Pharmacol Toxicol* 2000;86(5):242–4.
- Delescluse C, Lédirac N, Li R, Piechocki MP, Hines RN, Gidrol X, et al. Induction of cytochrome P450 1A1 gene expression, oxidative stress, and genotoxicity by carbaryl and thiabendazole in transfected human HepG2 and lymphoblastoid cells. *Biochem Pharmacol* 2001;61(4):399–407.
- Hayashi S, Watanabe J, Nakachi K, Kawajiri K. Genetic linkage of lung cancer-associated MspI polymorphisms with amino acid replacement in the heme binding region of the human cytochrome P450IA1 gene. *J Biochem (Tokyo)* 1991;110(3):407–11.
- Landi MT, Bertazzi PA, Shields PG, Clark G, Lucier GW, Garte SJ, et al. Association between CYP1A1 genotype, mRNA expression and enzymatic activity in humans. *Pharmacogenetics* 1994;4(5):242–6.
- Crofts F, Taioli E, Trachman J, Cosma GN, Currie D, Toniolo P, et al. Functional significance of different human CYP1A1 genotypes. *Carcinogenesis* 1994;15(12):2961–3.
- Persson I, Johansson I, Ingelman-Sundberg M. In vitro kinetics of two human CYP1A1 variant enzymes suggested to be associated with interindividual differences in cancer susceptibility. *Biochem Biophys Res Commun* 1997;231(1):227–30.
- Kawajiri K. CYP1A1. In: Book AS, editor. *Metabolic polymorphisms and susceptibility to cancer*. Lyon: International Agency for Research on Cancer; 1999.
- Sarmanova J, Benesova K, Gut I, Nedelcheva-Kristensen V, Tynkova L, Soucek P. Genetic polymorphisms of biotransformation enzymes in patients with Hodgkin's and non-Hodgkin's lymphomas. *Hum Mol Genet* 2001;10(12):1265–73.
- Kerridge I, Lincz L, Scorgie F, Hickey D, Granter N, Spencer A. Association between xenobiotic gene polymorphisms and non-Hodgkin's lymphoma risk. *Br J Haematol* 2002;118(2):477–81.
- Infante-Rivard C, Labuda D, Krajcinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 1999;10(5):481–7.
- Krajcinovic M, Labuda D, Richer C, Karimi S, Sinnett D. Susceptibility to childhood acute lymphoblastic leukemia: influence of CYP1A1, CYP2D6, GSTM1, and GSTT1 genetic polymorphisms. *Blood* 1999;93(5):1496–501.
- Raunio H, Hakkola J, Hukkanen J, Pelkonen O, Edwards R, Boobis A, et al. Expression of xenobiotic-metabolizing cytochrome P450s in human pulmonary tissues. *Arch Toxicol Suppl* 1998;20:465–9.
- Stoilov I, Akarsu AN, Alozie I, Child A, Barsoum-Homsy M, Turacli ME, et al. Sequence analysis and homology modeling suggest that primary congenital glaucoma on 2p21 results from mutations disrupting either the hinge region or the conserved core structures of cytochrome P4501B1. *Am J Hum Genet* 1998;62(3):573–84.
- Aklillu E, Oscarson M, Hidestrand M, Leidvik B, Otter C, Ingelman-Sundberg M. Functional analysis of six different polymorphic CYP1B1 enzyme variants found in an Ethiopian population. *Mol Pharmacol* 2002;61(3):586–94.
- Tang J, Cao Y, Rose RL, Hodgson E. In vitro metabolism of carbaryl by human cytochrome P450 and its inhibition by chlorpyrifos. *Chem Biol Interact* 2002;141(3):229–41.
- Mutch E, Blain PG, Williams FM. The role of metabolism in determining susceptibility to parathion toxicity in man. *Toxicol Lett* 1999;107(1–3):177–87.
- Hu Y, Kupfer D. Metabolism of the endocrine disruptor pesticide-methoxychlor by human P450s: pathways involving a novel catechol metabolite. *Drug Metab Dispos* 2002;30(9):1035–42.
- Lamba JK, Lin YS, Thummel K, Daly A, Watkins PB, Strom S, et al. Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. *Pharmacogenetics*.

- 2002;12(2):121–32.
30. Nakajima M, Yokoi T, Mizutani M, Kinoshita M, Funayama M, Kamataki T. Genetic polymorphism in the 5'-flanking region of human CYP1A2 gene: effect on the CYP1A2 inducibility in humans. *J Biochem (Tokyo)* 1999;125(4):803–8.
 31. Sachse C, Brockmoller J, Bauer S, Roots I. Functional significance of a C-A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol* 1999;47(4):445–9.
 32. Landi M, Sinha R, Lang N, Kadlubar F. Human cytochrome P4501A2. In: Book AS, editor. *Metabolic polymorphisms and susceptibility to cancer*. Lyon: International Agency for Research on Cancer; 1999.
 33. Sogorb MA, Vilanova E. Enzymes involved in the detoxification of organophosphorus, carbamate and pyrethroid insecticides through hydrolysis. *Toxicol Lett* 2002;128(1–3):215–28.
 34. Lockridge O, Masson P. Pesticides and susceptible populations: people with butyrylcholinesterase genetic variants may be at risk. *Neurotoxicology*. 2000;21(1–2):113–26.
 35. Lee MJ, Waters HC 3rd. Inhibition of monocyte esterase activity by organophosphate insecticides. *Blood* 1977;50(5):947–51.
 36. Newcombe D. Immune surveillance, organophosphorus exposure, and lymphomagenesis. *Lancet* 1992;339:539–41.
 37. Li Q, Nagahara N, Takahashi H, Takeda K, Okumura K, Minami M. Organophosphorus pesticides markedly inhibit the activities of natural killer, cytotoxic T lymphocyte and lymphokine-activated killer: a proposed inhibiting mechanism via granzyme inhibition. *Toxicology* 2002;172(3):181–90.
 38. Barta C, Sasvari-Szekely M, Devai A, Kovacs E, Staub M, Enyedi P. Analysis of mutations in the plasma cholinesterase gene of patients with a history of prolonged neuromuscular block during anesthesia. *Mol Genet Metab* 2001;74(4):484–8.
 39. Bartels CF, Jensen FS, Lockridge O, van der Spek AF, Rubinstein HM, Lubrano T, et al. DNA mutation associated with the human butyrylcholinesterase K-variant and its linkage to the atypical variant mutation and other polymorphic sites. *Am J Hum Genet* 1992;50(5):1086–103.
 40. Maekawa M, Sudo K, Dey DC, Ishikawa J, Izumi M, Kotani K, et al. Genetic mutations of butyrylcholine esterase identified from phenotypic abnormalities in Japan. *Clin Chem* 1997;43(6 Pt 1):924–9.
 41. Primo-Parmo SL, Bartels CF, Wiersema B, van der Spek AF, Innis JW, La Du BN. Characterization of 12 silent alleles of the human butyrylcholinesterase (BCHE) gene. *Am J Hum Genet* 1996;58(1):52–64.
 42. Wiebusch H, Poirier J, Sevigny P, Schappert K. Further evidence for a synergistic association between APOE epsilon4 and BCHE-K in confirmed Alzheimer's disease. *Hum Genet* 1999;104(2):158–63.
 43. Hashim Y, Shepherd D, Wiltshire S, Holman RR, Levy JC, Clark A, et al. Butyrylcholinesterase K variant on chromosome 3 q is associated with Type II diabetes in white Caucasian subjects. *Diabetologia*. 2001;44(12):2227–30.
 44. Costa LG, Li WF, Richter RJ, Shih DM, Lusi A, Furlong CE. The role of paraoxonase (PON1) in the detoxication of organophosphates and its human polymorphism. *Chem Biol Interact* 1999;119–120:429–38.
 45. Humbert R, Adler DA, Disteché CM, Hassett C, Omiecinski CJ, Furlong CE. The molecular basis of the human serum paraoxonase activity polymorphism. *Nat Genet* 1993;3(1):73–6.
 46. Cherry N, Mackness M, Durrington P, Povey A, Dipnall M, Smith T, et al. Paraoxonase (PON1) polymorphisms in farmers attributing ill health to sheep dip. *Lancet* 2002;359(9308):763–4.
 47. Sozmen EY, Mackness B, Sozmen B, Durrington P, Girgin FK, Aslan L, et al. Effect of organophosphate intoxication on human serum paraoxonase. *Hum Exp Toxicol* 2002;21(5):247–52.
 48. Brophy VH, Jampsa RL, Clendenning JB, McKinsty LA, Jarvik GP, Furlong CE. Effects of 5' regulatory-region polymorphisms on paraoxonase-gene (PON1) expression. *Am J Hum Genet* 2001;68(6):1428–36.
 49. La Du BN, Billecke S, Hsu C, Haley RW, Broomfield CA. Serum paraoxonase (PON1) isozymes: the quantitative analysis of isozymes affecting individual sensitivity to environmental chemicals. *Drug Metab Dispos* 2001;29(4 Pt 2):566–9.
 50. Eaton DL. Biotransformation enzyme polymorphism and pesticide susceptibility. *Neurotoxicology* 2000;21(1–2):101–11.
 51. Lemos MC, Cabrita FJ, Silva HA, Vivan M, Placido F, Regateiro FJ. Genetic polymorphism of CYP2D6, GSTM1 and NAT2 and susceptibility to haematological neoplasias. *Carcinogenesis* 1999;20(7):1225–9.
 52. Yuille M, Condie A, Hudson C, Kote-Jarai Z, Stone E, Eeles R, et al. Relationship between glutathione S-transferase M1, T1, and P1 polymorphisms and chronic lymphocytic leukemia. *Blood* 2002;99(11):4216–8.
 53. Chen CL, Liu Q, Pui CH, Rivera GK, Sandlund JT, Ribeiro R, et al. Higher frequency of glutathione S-transferase deletions in black children with acute lymphoblastic leukemia. *Blood* 1997;89(5):1701–7.
 54. Zimniak P, Nanduri B, Pikula S, Bandorowicz-Pikula J, Singhal SS, Srivastava SK, et al. Naturally occurring human glutathione S-transferase GSTP1-1 isoforms with isoleucine and valine in position 104 differ in enzymic properties. *Eur J Biochem* 1994;224(3):893–9.
 55. Ali-Osman F, Akande O, Antoun G, Mao JX, Buolamwini J. Molecular cloning, characterization, and expression in *Escherichia coli* of full-length cDNAs of three human glutathione S-transferase Pi gene variants: evidence for differential catalytic activity of the encoded proteins. *J Biol Chem* 1997;272(15):10004–12.
 56. Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases- molecular mechanisms and clinical significance. *Drug Metab Dispos* 2001;29(4 Pt 2):522–8.
 57. Glatt H, Boeing H, Engelke CE, Ma L, Kuhlow A, Pabel U, et al. Human cytosolic sulphotransferases: genetics, characteristics, toxicological aspects. *Mutat Res* 2001;482(1–2):27–40.
 58. Krieger R. *Handbook of pesticide toxicology*; vol 2. San Diego (CA): Academic Press; 2001.
 59. Burchell B, Soars M, Monaghan G, Cassidy A, Smith D, Ethell B. Drug-mediated toxicity caused by genetic deficiency of UDP-glucuronosyltransferases. *Toxicol Lett* 2000;112–113:333–40.
 60. Grancharov K, Naydenova Z, Lozeva S, Golovinsky E. Natural and synthetic inhibitors of UDP-glucuronosyltransferase. *Pharmacol Ther* 2001;89(2):171–86.
 61. Garte S. Metabolic susceptibility genes as cancer risk factors: time for a reassessment? *Cancer Epidemiol Biomarkers Prev* 2001;10(12):1233–7.
 62. Judson R, Stephens JC. Notes from the SNP vs. haplotype front. *Pharmacogenomics* 2001;2(1):7–10.
 63. Pearce N. Analytical implications of epidemiological concepts of interaction. *Int J Epidemiol* 1989;18:976–80.
 64. Ke S, Rabson AB, Germينو JF, Gallo MA, Tian Y. Mechanism

- of suppression of cytochrome P-450 1A1 expression by tumor necrosis factor- α and lipopolysaccharide. *J Biol Chem* 2001;276(43):39638–44.
65. Sinha R, Caporaso N. Diet, genetic susceptibility and human cancer etiology. *J Nutr* 1999;129(2S Suppl):556S–9S.
66. Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying children's susceptibility to environmental toxicants. *Environ Health Perspect* 2000;108 suppl 1:13–21.
67. Coumoul X, Diry M, Robillot C, Barouki R. Differential regulation of cytochrome P450 1A1 and 1B1 by a combination of dioxin and pesticides in the breast tumor cell line MCF-7. *Cancer Res* 2001;61(10):3942–8.
68. Kannan K, Holcombe RF, Jain SK, Alvarez-Hernandez X, Chervenak R, Wolf RE, et al. Evidence for the induction of apoptosis by endosulfan in a human T-cell leukemic line. *Mol Cell Biochem* 2000;205(1–2):53–66.
69. Banerjee BD, Seth V, Bhattacharya A, Pasha ST, Chakraborty AK. Biochemical effects of some pesticides on lipid peroxidation and free-radical scavengers. *Toxicol Lett* 1999;107(1–3):33–47.
70. Difilippantonio MJ, Zhu J, Chen HT, Meffre E, Nussenzweig MC, Max EE, et al. DNA repair protein Ku80 suppresses chromosomal aberrations and malignant transformation. *Nature* 2000;404(6777):510–4.
71. Papavasiliou FN, Schatz DG. Cell-cycle-regulated DNA double-stranded breaks in somatic hypermutation of immunoglobulin genes. *Nature* 2000;408(6809):216–21.
72. Banerjee BD. The influence of various factors on immune toxicity assessment of pesticide chemicals. *Toxicol Lett* 1999;107(1–3):21–31.
73. Kristensen VN, Kure EH, Erikstein B, Harada N, Borresen-Dale A. Genetic susceptibility and environmental estrogen-like compounds. *Mutat Res* 2001;482(1–2):77–82.
74. Bell D, Liu Y, Cortopassi G. Occurrence of bcl-2 oncogene translocation with increased frequency in the peripheral blood of heavy smokers. *J Natl Cancer Inst* 1995;87:223–4.
75. Fuscoe J, Setzer R, Collard D, Moore M. Quantification of t(14;18) in the lymphocytes of healthy adult humans as a possible biomarker for environmental exposures to carcinogens. *Carcinogenesis* 1996;17:1013–20.
76. Limpens J, Stad R, Vos C, Vlaam Cd, deJong D, Ommen G-JBv, et al. Lymphoma-associated translocation t(14;18) in blood B cells of normal individuals. *Blood* 1995;85:2528.
77. Liu Y, Cortopassi G, Steingrimsdottir H, Waugh AP, Beare DM, Green MH, et al. Correlated mutagenesis of bcl2 and hprt loci in blood lymphocytes. *Environ Mol Mutagen* 1997;29(1):36–45.
78. Lander F, Knudsen LE, Gamborg MO, Järventaus H, Norppa H. Chromosome aberrations in pesticide-exposed greenhouse workers. *Scand J Work Environ Health* 2000;26(5):436–42.
79. Kiraly J, Szentesi I, Ruzicska M, Czeize A. Chromosome studies in workers producing organophosphate insecticides. *Arch Environ Contam Toxicol* 1979;8:309–19.
80. Garry VF, Tarone RE, Long L, Griffith J, Kelly JT, Burroughs B. Pesticide applicators with mixed pesticide exposure: G-banded analysis and possible relationship to non-Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers* 1996;5:11–16.
81. Norppa H. Cytogenetic markers of susceptibility: influence of polymorphic carcinogen-metabolizing enzymes. *Environ Health Perspect* 1997;105 suppl 4:829–35.
82. Weiss NS, Liff JM. Accounting for the multicausal nature of disease in the design and analysis of epidemiologic studies. *Am J Epidemiol* 1983;117(1):14–8.
83. Weisenburger D. Pathological classification of non-Hodgkin's lymphoma for epidemiological studies. *Cancer Res* 1992;52s:5456s.
84. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001;10(11):1155–63.
85. Cantor K, Blair A, Everett G, Gibson R, Burmeister L, Brown L, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;52:2447.
86. Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, et al. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology* 2001;12(6):701–9.
87. Schroeder JC, Olshan AF, Baric R, Dent RB, Weinberg CR, Yount B, et al. A case-control study of tobacco use and other non-occupational risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma (United States). *Cancer Causes Control* 2002;13(2):159–68.
88. Williams JA. Single nucleotide polymorphisms, metabolic activation and environmental carcinogenesis: why molecular epidemiologists should think about enzyme expression. *Carcinogenesis* 2001;22(2):209–14.
89. Rothman N, Wacholder S, Caporaso NE, Garcia-Closas M, Buetow K, Fraumeni JF Jr. The use of common genetic polymorphisms to enhance the epidemiologic study of environmental carcinogens. *Biochim Biophys Acta* 2001;2(10):C1–10.
90. Boffetta P, Pearce N. Epidemiological studies on genetic polymorphism: study design issues and measures of occurrence and association. In: Vineis P, Malats N, Lang M, d'Errico A, Caporaso N, Cuzik J, et al, editors. *Metabolic polymorphisms and susceptibility to cancer*. Lyon: International Agency for Research on Cancer; 1999.
91. Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol* 1994;140(9):783–7.
92. Elbaz A, Alperovitch A. Bias in association studies resulting from gene-environment interactions and competing risks. *Am J Epidemiol* 2002;155(3):265–72.
93. Wacholder S, Rothman N, Caporaso N. Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. *J Natl Cancer Inst* 2000;92(14):1151–8.