CHAPTER I
INTRODUCTION

1. Background and Rationale

Leukemia is the most common type of childhood cancer. About 2,400 cases of childhood leukemia (age 0-14 years) are diagnosed annually, 78% of these cases are ALL (Zahm *et al.*, 1995; Smith *et al.*, 1999). Confirmed clinical and epidemiologic associations explain less than 10% of childhood leukemia incidence, leaving at least 90% of cases with an unresolved etiologic mechanism. Current evidence suggests that leukemia results from chromosomal alterations and mutations that disrupt the normal process by which lymphoid or myeloid progenitor cells differentiate (Smith *et al.*, 1999). The underlying triggers for molecular damage may be inherited at conception, occur during fetal development, or develop during infancy. Chromosomal translocations are a hallmark genetic event in leukemia. Many leukemia patients have chromosome translocation that is often the only observable cytogenetic event. These abnormalities help categorize leukemia for treatment strategy and prognosis, and they may also delineate specific causal pathways to malignancy (Wiemels *et al.*, 1999).

Leukemia is a heterogeneous disease, characterized by the dysregulated proliferation of blood precursor cells of myeloid or lymphoid origin. It can be classified as acute (low level of differentiation) or chronic (high level of differentiation) and can be further classified by cytogenetic subtype. For example, t(12;21) which generates the *TEL-AML1* fusion gene occurs in 25% of patients with common ALL (cALL). Translocation t(1; 19) and high hyperdiploidy (>50 chromosome) are also common in childhood ALL while various specific chromosome rearrangement, including t(8;21), t(15;17), and inv(16), are found in acute myeloid leukemia (Smith *et al.*, 2005).

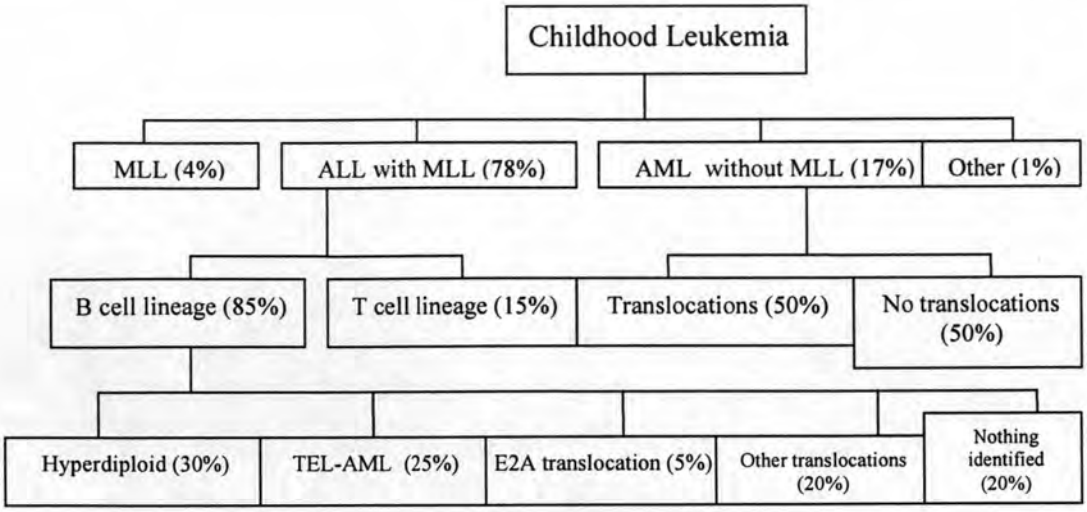


Figure1 Molecular subclassification of childhood leukemia (Greaves *et al.*, 2001)

The incidence of leukemia is 10-fold lower in children than adults. Environment exposures from parental were early suspect in the search for causes of childhood leukemia. In 1974, the first published study on this topic suggested that mortality from childhood leukemia was elevated in children born to fathers with hydrocarbon-related jobs (Buffler *et al.*, 2002). Although a number of investigations have suggested that parental occupational exposure to pesticides may increase risk ALL and lymphoma (Flower *et al.*, 2000). Exposure to household pesticides of maternal in Minnesota has been linked to an increased risk of childhood ALL with Down's syndrome (Alderton *et al.*, 2006). The investigation of parental occupational exposure to pesticides or benzene was not associated with significantly increased risk of childhood lymphoproliferative malignancy, leukemia and lymphoma by match case-control study (Reynolds *et al.*, 2005; McNally *et al.*, 2006)

NCCLs (Northern California Childhood Leukemia), a population-based case-control study begun at the University of California, Berkeley in 1995 with the aim of investigating the relationship between environmental exposures and genetic risk factors for childhood leukemia. Recent findings from the NCCLs emphasize the importance of the time of exposure. For example, use of household insecticides during pregnancy appeared to pose a high risk than exposures after birth (Smith *et al.*, 2005), the

associated between different races and genetic polymorphisms. As the major population in California is white and Hispanic races Asian with relatively few. Thus, the cause of Asian childhood cancer is not clearly. Agriculture is mainly in Thailand, there are many people had been exposed pesticides from occupational or household chemicals. Furthermore, the registry system of the new cases of childhood cancers has recently established in Thailand. This registry system is an opportunity to systematically study the cause of childhood cancer, and it is useful to compare with another country regarding the effect of genetic polymorphisms or environmental exposure on child's risk of leukemia.

Genetic polymorphisms have become an increasingly recognized as important risk factors for childhood leukemia. Xenobiotic-metabolizing enzymes (Detoxification enzymes) such as cytochrome P-450 (*CYP*) and glutathione-S-transferase (*GST*) biotransform and eliminate environment toxicants from an individual's body. A few studies suggested that polymorphisms at the loci of *CYP1A1*, NAD(P)H: quinine oxidoreductase (*NQO1), GSTM1, GSTP1* genes are associated with the risk of childhood leukemia (Kadlubar *et al.*, 1987; Guengerich *et al.*, 1991; Bell *et al.*, 1995; Cascorbi *et al.*, 1996; Errico *et al.*, 1996., Rebbeck *et al.*, 1997; Wiernels *et al.*, 1999). Specifically, the *GSTM1* null and *CYP1A1**2A genotypes were shown to be significant predictors of ALL risk in childhood acute lymphoblastic leukemia (Krajinovic *et al.*, 1999). Ethnicity is also an important factor to consider when evaluating the relationship between genetic polymorphisms and disease risk. It has been observed that the frequency of *GSTT1* and *GSTM1* "double-null" genotype was a risk factor for ALL in African-American childhood, but not in white children (Chen *et al.*, 1997).

In the past study, most of them had been studied only genetic factors, that it can not explain obviously the root cause of cancer. The cause of cancer is not only genetic but also environmental factors such as pesticides, dietary, immunology and chemicals. Combining environmental and genetic may demonstrate interactive between the two factors, a study of genetic polymorphisms of xenobiotic-metabolizing enzymes and patients dietary intake in China, they found associated between high calories

dietary intake and *GSTT* null genotype increased risk of esophageal squamous cell carcinoma (Wang *et al.*, 2006). A number of other study found maternal exposure to insecticides during pregnancy and *CYP1A1**2A, *2B genetic polymorphisms to be associated with the risk of childhood leukemia (Rivard *et al.*,1999). Due to relatively of pesticides exposure and the genetic polymorphisms of xenobiotic-metabolizing enzymes from previous studies, this study will be evaluated together the role of xenobiotic-metabolizing genetic polymorphisms with environment exposure, especially pesticides. Therefore, study of gene-environment interactions is important for improving accuracy and precision in the assessment of genetic and environmental influences.

Even though the childhood cancers can be cured, the treatment are costly and take 6 months – 3 years to complete. Thus, if we know the root cause of childhood cancer, it might be possible to make specific recommend action on prevention of cancer risk, chemical and environmental in order to reduce childhood cancers risk which it can be save treatment cost.

2. Research questions

Whether the polymorphisms in genes encoding xenobiotic-metabolizing enzymes and/or the pesticides exposure associated with risk of ALL in Thai children?

3. Objectives

Primary

To assess the relationship between genetic polymorphisms of xenobiotic-metabolizing enzymes and risk of childhood acute lymphoblastic leukemia.

To assess the relationship between and pesticides exposure and risk of childhood acute lymphoblastic leukemia.

Secondary

To determine interaction between pesticides exposure and genetic polymorphisms of xenobiotic-metabolizing enzymes as risk for childhood acute lymphoblastic leukemia.

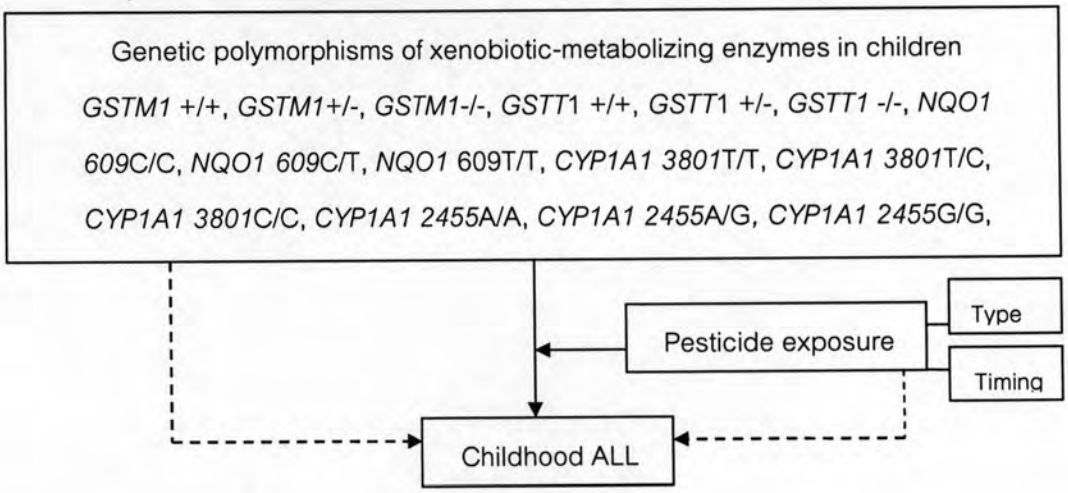
4. Hypothesis

The risk of Thai childhood acute lymphoblastic leukemia associate with polymorphisms of xenobiotic-metabolizing enzymes and pesticides exposure.

5. Keywords

Acute lymphoblastic leukemia, Xenobiotic- metabolizing enzymes or detoxification enzymes, pesticides

6. Conceptual Framework



7. Expected benefit

The prevalence of genetic polymorphisms for xenobiotic-metabolizing enzyme of childhood acute leukemia and relationship between genetic polymorphisms and pesticide exposure in Thailand is unknown. This knowledge would be a direct benefit. Furthermore, when evaluation the role of genetic polymorphisms and pesticides exposure in risk for childhood acute leukemia is understood, the relationship between gene and risk of acute lymphoblastic leukemia, and the relationship between pesticide exposure and risk of acute lymphoblastic leukemia. Thus, if we know the root cause of childhood acute lymphoblastic leukemia, it might be possible to make specific recommend action on prevention of acute lymphoblastic leukemia risk.