Prenatal Pesticide Exposure and Acute Myeloid Leukemia: Epidemiological Evidence, Molecular Mechanisms, & Research Gaps

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Abstract

Pediatric acute myeloid leukemia (AML) is a hematologic malignancy that is characterized by uncontrolled proliferation and impaired differentiation of myeloid progenitor cells. Although chromosomal abnormalities and genetic mutations contribute to leukemogenosis, growing evidence shows that environmental exposures are a potential contributor to childhood leukemia.This review examines the relationship between prenatal pesticide exposure and pediatric AML, focusing on potential biological mechanisms that involve placental transfer, oxidative stress, DNA damage, as well as epigenetic dysregulation. Epidemiological studies have reported associations between prenatal exposure to certain agricultural pesticides and pediatric AML. Differing human and experimental studies have indicated a possible association with changes in DNA methylation as well as other molecular processes. In addition, promoter hypermethylation of CDKN2B/p15INK4B has been reported in pediatric AML, while pesticide-associated CDKN2B methylation has been observed in pediatric acute lymphoblastic leukemia (ALL). These findings provide a biologically plausible framework for further investigation; however, the available literature does not establish a direct pathway linking prenatal pesticide exposure, CDKN2B hypermethylation, and pediatric AML. Further research integrating exposure assessment with molecular profiling of developmentally relevant hematopoietic cells is needed. [1–3]

Introduction

Pediatric acute myeloid leukemia (AML) is hematologic malignancy characterized by the uncontrolled proliferation and impaired differentiation of the myeloid progenitor cells. Though Pediatric AML represents approximately 15% - 20% of childhood acute leukemia, its molecular characteristics differ significantly from those of adult AML. [4] Pediatric AML contains distinct patterns of gene fusions, structure alterations, mutations, as well as epigenetic abnormalities, which is suggestive that childhood leukemogenesis involves both developmental and molecular processes that differ from adult AML.[5] Epigenetic regulation is relevant due to hematopoietic stem and progenitor cells requiring tightly controlled gene expression during both proliferation and differentiation, as well as the disruption of regulatory processes that may contribute to leukemic transformation.[6,7]

Environmental exposures have increasingly been investigated as potential contributors to childhood leukemia.[8] Pesticides are a diverse group of substances utilized to prevent, destroy, repel, or control pests. Pesticides constitute a diverse group of toxicants rather than a single chemical agent. Insecticides, herbicides, fungicides, and rodenticides all possess distinct chemical properties, toxicological effects, and have different biological targets.[9] It is noted however, that several pesticide classes have contributed to genotoxic, oxidative, endocrine disrupting or epigenetic effects providing biological plausibility for its involvement in

leukemogenesis. [10,11] Although, biological plausibility does not establish that pesticide exposure contributes to pediatric AML. Evidence that prenatal exposure is associated with pediatric AML is necessary before examining certain biological mechanisms. This distinction is important because prenatal pesticide exposure generally is a mixture of pesticides rather than exposure to a single compound. Exposure of pesticides prenatally has been linked to developing leukemogenesis. These mechanisms provide biological plausibility when investigating pesticide exposure and its possible contributions to childhood leukemia, although biological plausibility alone can not establish causation.

Timing of exposure may be particularly important; Fetal development is vulnerable to the susceptibility of environmental toxicants due to rapid cellular proliferation, differentiation, and organogenesis occurring during this period. Environmental toxicants encountered during this period may interfere with the developmental process that are actively being established [12] , [13] The placenta provides an important interface between maternal and fetal circulation, but does not completely prevent the environmental chemicals from reaching the developing fetus. Placental transfer is dependent on characteristics that include molecular size, lipid solubility, protein binding, placental metabolism, and membrane transporter activity. [14] Research on the prenatal origins of childhood leukemia has proposed that some leukemias may originate from abnormal events that occur during fetal hematopoiesis, with additions that occur later before clinically detectable disease develops [15]. Hematopoiesis occurs through sequential developmental stages that involve certain populations of hematopoietic stem and progenitor cells, and alterations during these stages may influence certain cellular populations through which possibility of child leukemias could rise [16]

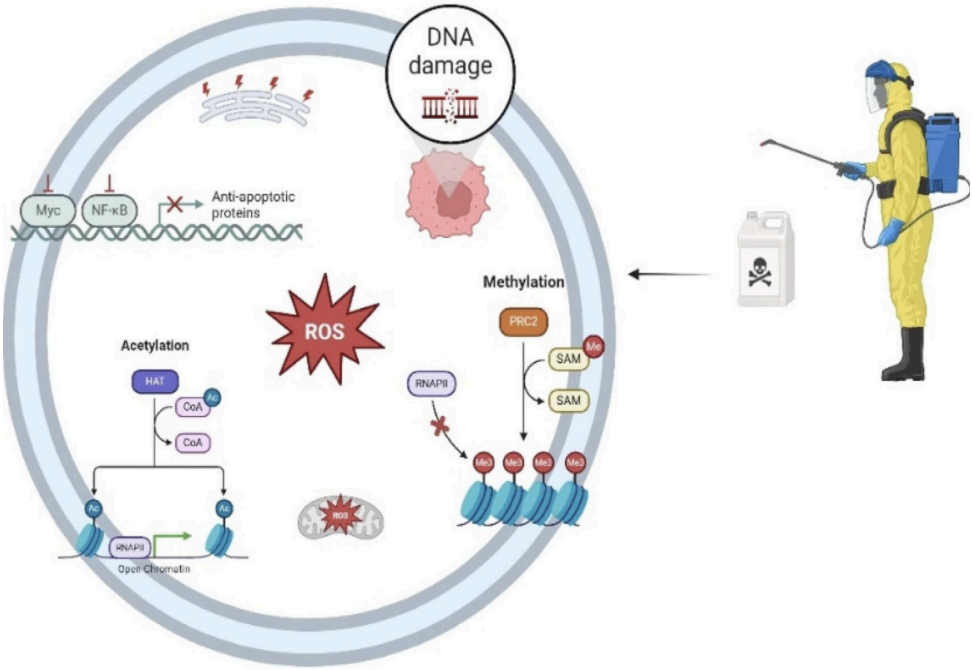

Figure 1. Proposed relationship between prenatal pesticide exposure and pediatric acute myeloid leukemia (AML). Certain pesticides may cross the placenta and reach the developing fetus. During fetal development, pesticide exposure may contribute to oxidative stress, DNA damage, and epigenetic alterations that could affect hematopoietic stem and progenitor cell development. These processes may contribute to abnormal cellular

regulation associated with leukemogenesis. However, the complete pathway from prenatal pesticide exposure to pediatric AML has not been directly established.[1–3, 10–13]

A possible pathway that connects pesticide exposure with leukemia development is through oxidative stress and DNA damage. Pesticide exposure has been associated with increased oxidative stress as well as alteration in cellular pathways that involve inflammation, DNA damage, and DNA repair. A recent systematic review of early - life pesticide exposure had found evidence of DNA damage and changes in pathways that are related to oxidative stress and DNA repair, though magnitude and biological significance of such effects have varied across exposure and populations [17] Moreover, damage that occurs during fetal development could be relevant due to disruption of developing hematopoietic cells that may impact its ability to maintain proper, normal growth and differentiation.

Moreover, pesticides may influence epigenetic regulation, which impacts gene expression without necessarily changing the underlying DNA sequence.[18] DNA methylation is one major epigenetic mechanism and is commonly involved in the addition of methyl groups to cytosine residues at CpG sites. Alterations in DNA methylation can change expression of genes involved in certain processes such as DNA repair, cell - cycle regulation, as well as cellular differentiation. A systematic review of human studies had found that pesticide exposure was associated with global and gene specific changes in DNA methylation, demonstrating that pesticides have influence on the peigenhttps:ome, although specific direction and location of these changes do vary by pesticide and population.[19] Most importantly, these findings again, do not establish that pesticide exposure produces the same methylation changes that are observed in pediatric AML.

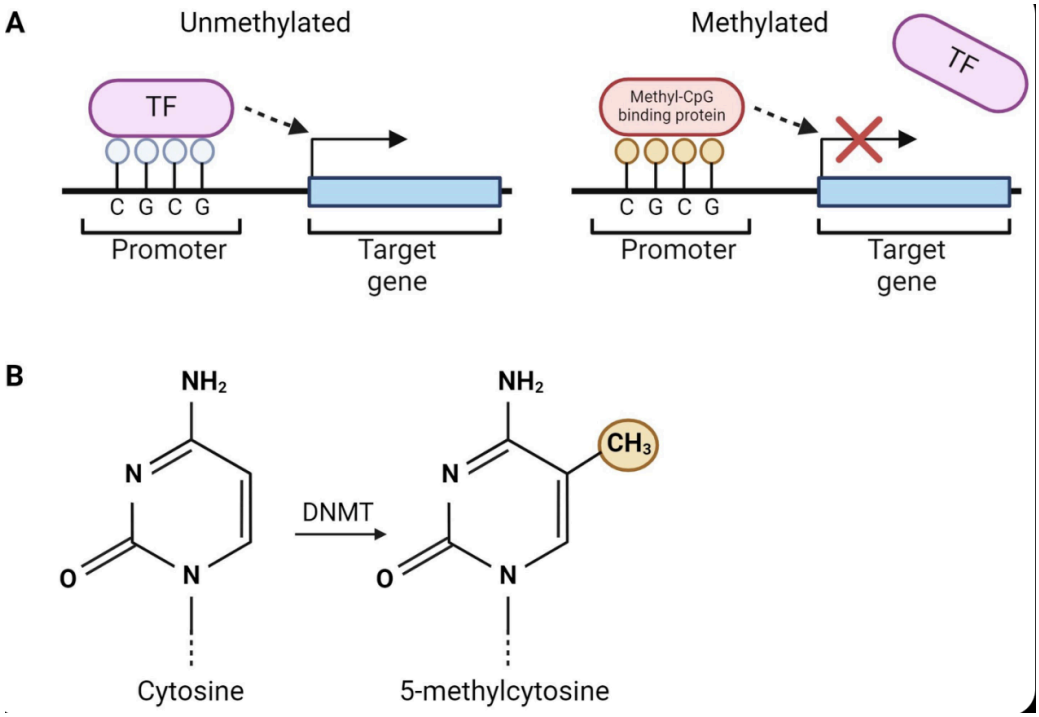

Figure 2. Simplified mechanism of DNA methylation at a gene promoter. Shows DNMT-mediated addition of methyl groups to CpG sites and the potential association between promoter hypermethylation and reduced transcription. However, Methylation does not always silence a gene.

Methods

Eligibility Criteria

Studies had to specifically investigate the correlation between pesticides exposure and risk of diagnosis for Pediatric Acute Myeloid Leukemia. Any studies that had focused on the development of pediatric tumors, other diseases, or did not properly assess pesticide exposure leading to pediatric AML were excluded.

Search Strategy

Terms such as, “Pediatric Acute Myeloid Leukemia”, “Pesticide exposure”, “Prenatal”, “Epigenetics” were all used.

Results

Sheif et al. (2026) investigated prenatal pesticide exposure utilizing California agricultural pesticide use records rather than reliance on parental recall. The study had children younger than the age of 6 who were born in California between 1998 and 2011 and used pesticide use and land use within a 4,000 meter buffer around residential areas at birth. Exposure to any of the 59 carcinogenic pesticides during pregnancy was associated with elevated odds of AML (OR = 3.75, 95% CI: 0.97 - 11.57), although the confidence interval included 1.00. Analyzing individual pesticides, it was seen that exposure to metam sodium was associated with increased AML odds (OR = 2.56, 95% CI: 1.19-5.49) whereas paraquat dichloride was too associated with increased odds (OR = 3.38, 95% CI: 1.23 - 9.27), Chlorpyrifos exposure was also similarly exposed AML odds (OR=3.05, 95% CI: 1.09 - 8.52) These findings provided additional evidence of association between agricultural pesticide exposure during pregnancy and childhood AML, but relatively few AML cases led to wide confidence intervals for several estimates.

Though epidemiological studies demonstrated an association between prenatal pesticide exposure and AML, it does not solely establish how pesticide exposure could contribute to leukemogenosis. Rusiecki et al. (2017) examined 695 male pesticide applicators from the Agricultural Health Study and compared DNA methylation patterns with results reporting unusually high pesticide exposure events. 142 participants reported a high pesticide exposure event. These individuals showcased significantly increased methylation in the GSTP1 promoter, including at CpG7 and across measured CpG sites. Applicators older than the age of 59, showed high pesticide exposure was associated with reduced methylation in several CpG sites within the MGMT promoter. In addition, Reduce LINE - 1 methylation was observed with lower plasma folate concentrations. These results then show that pesticide exposure is associated with changes in DNA methylation in humans, although the study did not establish whether or not the alterations contribute to cancer development.

Sherif et al. (2026) conducted a systematic review and a meta analysis of 28 studies examining prenatal and early childhood exposure in relation to DNA damage, DNA methylation, and gene expression. The review found DNA damage amongst pesticide exposed populations and identified changes in DNA methylation that varied according to pesticide class. The analysis identified alterations in pathways that related to oxidative stress, cell signalling, inflammation, while gene expression analysis have demonstrated downregulation of genes that were involved in DNA damage and repair. These conclusions provide broader evidence that pesticide exposure during sensitive development periods can lead to epigenetic alterations.

Evidence from experimental studies suggests that pesticide exposure may alter DNA methylation through disruption of enzymes such as DNA methyltransferases (DNMT), DNMTS catalyze the transfer of methyl groups from S - adenosylmethionine to cytosine residues, specifically at CpG sites. DNMT1 maintains existing methylation patterns during DNA replication whereas enzymes such as DNMT3A and DNMT3B contribute to de novo DNA methylation during cellular development and differentiation. Because DNA methylation regulates gene expression, disruption of DNMT activity or expression could contribute to abnormal promoter methylation and genes involved in cellular regulation. Zhang et al (2012) examined the effects of three organophosphate pesticides: fonofos, parathion, and terbufos on DNA methylation in human cells. It was identified that pesticide associated methylation changes in genes were involved in DNA methylation and included DNMT3A and DNMT3B. Specifically DNMT methylation increased when exposed to fonofos and parathion, whereas DNMT3B methylation decreased when exposed to fonofos and terbufos.The study had identified pesticide associated changes in genes that were involved in oxidative stress and cellular regulation. [20] These findings ultimately, were suggestive that organophosphate exposure can interfere with components of DNA methylation machinery, although the studies did not establish that these changes had directly altered DNMT enzyme activity or caused leukemia.

Zhang et. al (2012) further invested organophosphate pesticide associated DNA methylation and identified changes at 1,069 CpG sites across 984 genes following exposure to fonofos, parathion, and terbufos. Several affected genes were involved in cancer related pathways such as: TP53INP1 and PTEN, genes that are involved in both cellular growth and tumor suppression. These findings help demonstrate that pesticide exposure can produce gene - specific changes in DNA methylation; however, the study was conducted in an experimental cellular model. Thus, the findings can not establish whether the same methylation changes occur during fetal hematopoiesis or contribute to pediatric AML.

Juhl - Christeren et al. (2012) compared genetic mutations and promoter methylations patterns in 70 pediatric AML patients and 383 adult AML patients. Amongst the pediatric AML cases promoter hypermethylation occurred in several genes: p15/CDKN28 (47%), CDH1 (64%), MDR1 (8%), estrogen receptor (62%), and RARB2 (22%). This comparison provides evidence that DNA methylation abnormalities occur in pediatric AMl could configure a connection between pesticide associated epigenetic alteration and the development of childhood leukemia. Frequency of p15/CDKN28 promoter hypermethylation demonstrates that epigenetic modification of the cell cycle is a frequent occurrence in pediatric AML.

Previous research has shown that there is a relative low incidence of p15INK4B promoter hypermethylation in pediatric AML. For instance, in a study by Moschovi et al. (2005), out of 32 patients diagnosed with AML, 18.8% showed signs of p15INK4B promoter hypermethylation. Even though the incidence was lower compared to that reported by Tsellou et al. (2005), this study demonstrates the presence of p15INK4B promoter hypermethylation in pediatric AML. It is also interesting to note that the researchers noticed significantly higher incidences of p15INK4B promoter hypermethylation in T-cell acute lymphoblastic leukemia (T-ALL). Thus, it can be inferred that p15INK4B methylation might be more relevant in T-cell ALL than AML.

Direct proof linking pesticide exposure to the methylation of CDKN2B in pediatric acute myeloid leukemia (AML) is currently sparse. However, Rafeeinia et al. (2022) provide supportive data in pediatric acute lymphoblastic leukemia (ALL). Specifically, the authors have measured the concentration of organochlorine pesticides and studied the methylation level of promoters of CDKN2B, CDKN2A, and MGMT. CDKN2B promoters were found to be highly methylated in 76.2% of children suffering from ALL compared to the controls, while 85.1% of MGMT promoters were highly methylated. [21] Increased organochlorine pesticides were related to the methylation of the promoters of CDKN2B and MGMT and to decreased gene expression. Histone modification was also observed, including a decreased level of H4K16ac and H3K4me3. Even though the study involved pediatric ALL patients rather than AML patients, it provides a good mechanistic basis for the association of pesticide exposure with epigenetic alteration of CDKN2B and decreased gene expression.

Evidence from experimental human placental models showcase that some pesticides can cross the placenta.[22] examined transplacental transport of pesticides such as pyrethroid insecticide: cypermethrin and fungicides: propiconazole and bitertanol using human placental perfusion and BeWO trophoblast cell models. Propiconazole and bitertanol demonstrated relatively rapid transfer whereas cypermethrin crossed placental cell layers more slowly. Researchers have also configured pesticide metabolites in both fetal and maternal compartments, showcasing that the placenta can metabolize these compounds while being transferred.[22] These findings however, do not demonstrate that every pesticide that can cross the placenta or that prenatal exposure necessarily produces leukemia. Although, they play a fundamental role in understanding how certain pesticides reach a fetus prenatally during development.

Limitations

There are several limitations present in both the review and existing literature that should be considered when interpreting the correlation between prenatal pesticide exposure and pediatric AML. The most significant limitation would be the lack of studies that directly examine a completely proposed pathway from prenatal pesticide exposure to epigenetic alteration in Pediatric AML. Though epidemiological studies have reported associations between prenatal pesticide exposure and childhood AML (Bailey et al, 2014; Bailey et al. 20215, Park et al, 2020) as well as molecular studies identifying pesticide associated changes in DNA methylation (Rusiecki et al, 2017; Roihr et al; 2024) these pieces of evidences have been investigated separately. Unfortunately, current literature does not have a direct establishment on whether prenatal pesticide exposure produces specific epigenetic alterations in fetal hematopoietic cells that would then contribute to the developmenting risk of pediatric AML.

An important gap to note are the CDKN2B/p15INK4B genes. Promoter hyperinflation of DNKN2B/ p15INK4B have been observed in pediatric AML, in which supports potential relevance to abnormal cell - cycle regulation [23,24] However, direct evidence that connects pesticide exposure to CDKN2B/ p15INK4B methylation in pediatric AML is limited. Evidence provided from Rafeeini et al. (2022) gives a potentially relevant mechanism in which reports the association between organochlorine pesticide exposure and increases methylation of CDKN2B and MGMT promoters in children with acute lymphoblastic leukemia (ALL), However ALL and AML are biologically distinct disease, so findings from ALL can not be assumed to be applicable directly to pediatric AML. Thus, a major limitation of current literature is the absence of human studies that measure prenatal pesticide exposure, DNA methylation of CDKN2B/p15INK4B, as well as the subsequent development of pediatric AML.

Another limitation to be considered is how pesticide exposure has been measured. Epidemiological studies have used parental occupation. Residential proximity to agricultural application, pesticide use records, and other indirect exposure measures. [1,3,25] However, these approaches may not accurately represent concentration, duration, or specific combination of pesticides reaching the fetus. In addition, prenatal exposure commonly involves the mixture of multiple pesticides rather than a single compound, in which makes it extremely difficult when determining what specific chemical, combination of chemicals, or biological pathway holds responsibility for the observed association . [9,19] Therefore, differences in exposure assessment make results difficult to compare across studies and may lead to inconsistent findings.

Moreover, with the relatively small sample sizes and overall number of pediatric AML cases in many epidemiological studies, it too provides statistical precision. Pediatric AML is uncommon, and several studies have consequently reported wide confidence intervals around risk estimates [1,25]. Small sample size reduces ability to examine individual pesticides, specific exposure windows, genetic or epigenetic subtypes, and potential difference in accordance to its developmental stage. It's also important to note that studies may lack sufficient statistical power to distinguish associations caused by individual pesticides from correlated exposures or pesticide mixtures. More studies targeted towards would be necessary to investigate these relationships, as it would allow greater precision and accuracy.

Another limitation to be considered is the difficulty in determining both timing and biological persistence of epigenetic changes. DNA methylation can vary according to developmental stage, tissue type, age, nutritional status, as well as environmental exposure [19,26] Many human studies of pesticide associated methylation have examined blood or accessible tissues rather than fetal hematopoietic cells.[19] Consequently, methylation patterns measured after birth may not accurately represent methylation changes that occurred during fetal hematopoiesis. This is important for the proposed relationship between prenatal exposure and pediatric AML as relevant epigenetic alterations could occur during specific developmental windows.

Evidence for both oxidative stress and DNA damage too has its limitations. Both experimental and observational studies showcase the ability of certain pesticides to induce oxidative stress and genotoxic impacts, but these effects vary in accordance to pesticide type, dose, exposure duration, and biological system [17,27]This demonstrates how pesticides can generate reactive

oxygen species or dna establish but not establish the magnitude of damage that occur during human fetal development being sufficient to initiate and/ or promote pediatric AML. Furthermore, oxidative stress, DNA damage, and epigenetic alterations may interact with one another, making it difficult to determine whether one represents an initiating event or a parallel response to exposure.

Finally, the present review is limited by the small amount of literature that is specifically focused on prenatal pesticide exposure and pediatric AML that is compared with childhood leukemia in a broader scope. Some evidence included in the mechanistic discussion derives from studies of adult pesticide exposed populations, experimental models, or pediatric ALL than pediatric AML. These studies are relevant as they help establish biological plausibility, but cannot substitute for disease specific evidence. Current evidence should be interpreted as supporting a plausible mechanistic framework rather than it being framed as a casual pathway.

Thus, future research should address these gaps by having more multicenter studies that measure pesticide exposure during pregnancy that use multiple approaches, including environmental monitoring, biomonitoring of maternal and fetal compartments that are ethically feasible and are detailed records of both occupational and residential exposure. Studies should examine pesticide mixtures rather than focusing exclusively on individual compounds as real world exposure often involves several chemicals. Longitudinal designs following children from pregnancy through diagnosis could too help establish a possible temporal relationship between exposure, molecular alterations, and disease development. Integrating exposure measurement with genome - wide DNA methylation, DNMT expression, oxidative DNA damage, as well as leukemia specific molecular profiling could further determine whether pesticide exposure is associated with epigenetic alterations that have characteristics of pediatric AML. In particular, future studies directly examining certain genes such as the CDKN2B/p15INK4B methylation in children exposed prenatal to pesticide would be both relevant and valuable for testing specific mechanistic pathways proposed in this review.

Discussion

The evidence reviewed in the paper support a biologically plausible relationship between prenatal pesticide exposure and pediatric AML, but the strength of evidence varies across the proposed pathway. Epidemiological studies provide the strongest evidence for an association between prenatal pesticide exposure and pediatric AML, whereas molecular and experimental studies provide evidence for potential mechanisms that involve placental transfer, oxidative stress, DNA damage, and epigenetic regulation. [1–3] However it’s important to note that these findings derive from separate bodies of research. Current literature supports a plausible connection between prenatal pesticide and pediatric AML, but does not establish a complete pathway.

An important consideration when interpreting the epidemiological evidence is whether pesticides associated with pediatricAML are capable of reaching the fetus. Experimental human placental models have demonstrated that pesticides such as cypermethrin, propiconazole, and bitertanol can be transported across the placental tissue, although the rate of transfer varies among the compounds. [22] This provides evidence that maternal exposure can result in fetal exposure to at

least some pesticide compounds. Although, placental transfer does not solely demonstrate that a sufficient concentration reaches fetal hematopoietic tissues to cause molecular alterations that are associated with AML. The transfer rates do vary according to the chemical properties of individual pesticides and their metabolic and transport functions of the placenta.[14] The important gap in current literature is currently determining whether pesticides associated with increased pediatric AML risk are also capable of reaching the fetus reaching fetal tissues, developing hematopoietic cells, at a biologically relevant concentration. Thus, placental transfer should be considered an important component of biological plausibility rather than evidence of leukemogenicity.

Epidemiological evidence helps support the need to investigate the relationship. Studies have reported associations between maternal or prenatal pesticide exposure and childhood AML. Findings from the Childhood Leukemia International Consortium as well as studies that utilize agricultural pesticide use data [2,25]. Park et al (2020) reported elevated odds of AML associated with exposure to several agricultural pesticides during the window of pregnancy. Although confidence intervals for some estimates were high, reflecting the relatively small number of pediatric AML sampled and available for analysis, exposure was estimated by using residential proximity and pesticide usage records rather than direct measurement of pesticide concentrations within maternal or fetal tissues. With these limitations, it is difficult to determine the dose actually received by individual pregnancies, complicating comparison across studies. Therefore, epidemiological findings demonstrate an association that supports the need for further investigation but do not independently establish causation.

Proposed biological mechanisms provide further context for epidemiological observations. Pesticide exposure has been associated with oxidative stress as well as DNA damage in human and experimental research. [17,27] Excess reactive oxygen species can damage DNA repair. In the process of fetal hematopoiesis, such damage would be considered relevant as hematopoietic stem and progenitor cells undergo substantial proliferation and differentiation [16]. DNA alterations that occur within these populations could potentially be retained in descendent cells if not accurately repaired. Research on prenatal origins of childhood leukemia showcase how abnormal cellular events may occur during fetal development, with additional alterations that accumulate before clinical leukemia becomes apparent [15]. However, available evidence and literature does not demonstrate that pesticide induced oxidative damage directly initiates pediatric AML. Oxidative stress is interpreted as a possible mechanism that could contribute to genomic instability within a much larger process.

Epigenetic dysregulation provides another possible connection between environmental exposure and pediatric AML. Human studies have identified associations between pesticide exposure and alterations in global and gene specific DNA methylation in which it is suggestive that some pesticides can influence epigenetic regulation [16,19] . This is relevant to Pediatric AML as abnormal DNA methylation is a recognized feature of the disease, including methylation changes impacting genes involved in cell cycle regulation as well as cellular differentiation Although, an important distinction must be made between demonstrating that pesticides can alter DNA methylation and demonstrating that they produce the specific methylation patterns that are associated with Pediatric AML. The current literature available unfortunately does not establish this connection directly.

CDKN2B/ p15INK4B is particularly important for the evidence gap. Promoter hypermethylation of CDKN2B / p15INK4B has been identified in pediatric AML, suggesting that epigenetic suppression of the cell cycle regulator may occur during leukemogenesis. [24] Because p15INK4B participates in regulation of cell cycle progression, abnormal promoter methylation could reduce its expression, potentially weakening mechanisms that restrict inappropriate cellular proliferation. In addition, frequency of the CDKN2B/p15INK methylation differs across pediatric AML studies, which is demonstrative that it's not a universal molecular feature of the disease [23,24]

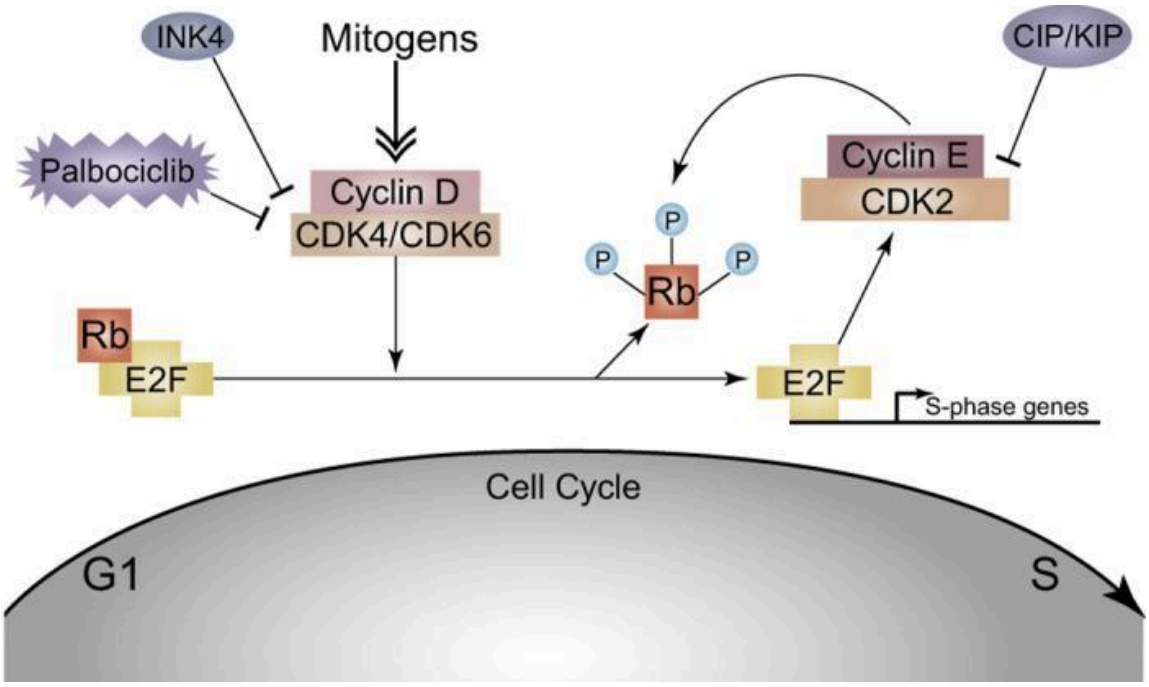

Figure 3: This figure illustrates a proposed molecular mechanism and does not establish that prenatal pesticide exposure causes CDKN2B hypermethylation or pediatric AML.

In a study done by Rafeenia et al (2022) , it recognizes a potentially relevant relationship between pesticide exposure and CDKN2B methylation, but findings can be interpreted with caution. The researchers identified associations between organochlorine pesticide exposure and increased promoter methylation of CDKN2B and MGMT in children with ALL. Although findings support the possibility that pesticide exposure may influence methylation of genes relevant to leukemia, the study examined pediatric ALL rather than AML. Because AML and ALL arise from different hematopoietic lineages, having distinct molecular characteristics, results can not be directly generalized to pediatric AML. Instead, the study provides mechanistic support for further investigation of CDKN2B methylation in pediatric AML rather than direct evidence of the proposed pathway.

When put together, evidence can be organized into a series of both related but incompletely connected observations. Epidemiological studies have identified associations between prenatal

pesticide exposure and childhood AML. Experimental placental studies have demonstrated that certain pesticides can cross the placenta, reaching the fetus. Third, human and experimental studies have indicated that pesticide exposure can be associated with oxidative stress, DNA damage, and epigenetic alterations. Finally, CDKN2B/p15INK4B prompt hypermethylation has been identified in pediatric AML, whereas pesticide exposure has been associated with CDKN2B methylation in pediatric ALL. The findings provided would be evidence for a plausible mechanism.

Limitations of the available literature are also important to consider when interpreting this framework; pediatric AML is rare, making large epidemiological studies difficult to conduct. Studies differ in how pesticide exposure is both defined and measured, with many relying on indirect exposure estimates rather than biomarkers of internal dose [2,25] In addition, pesticide exposure often involves the mixture of chemicals in which makes it significantly difficult to identify what expat compounds or combinations are biologically relevant [19] Molecular studies presents an additional challenge as methylation measurements are often performed using accessible tissue rather than fetal hematopoietic cells.[28] Consequently, observed methylation patterns may not represent the molecular changes occurring in specific cell populations relevant to leukemogenesis.

These limitations indicate several directions for future research. More studies would significantly improve statistical power, enabling researchers to characterize pesticide exposure before disease developments. Utilization of residential and occupational exposure records with maternal biomonitoring could help provide more accurate estimates of internal pesticide exposure than relying on geographic proximity or solely parental recall. Studies could, too, investigate pesticide mixtures rather than examining individual compounds, isolating them – which would capture the complexity of real world exposure. Longitudinal studies that collect biological samples during pregnancy and track child development over time could help establish the relationship between exposure and molecular changes.

Future studies that focus on certain mechanisms would also directly help examine proposed epigenetic pathways in pediatric AML. Studies that combine pesticide exposure measures and DNA methylation that profiling DNMT expression, oxidative DNA damager, and leukemia specific genomic characterization could determine whether exposed individuals develop molecular alterations that overlap with those observed in pediatric AML. Specifically, by directly measuring CDKN2B/p15INK4B methylation methylation in relation to prenatal pesticide exposure could help determine whether the relationship observed in pediatric ALL is also present in AML. More experimental models of fetal hematopoietic and progenitor cells could help further investigate and observe whether pesticide exposure alters proliferation, differentiation, DNA damage, or epigenetic programming in cells that are relevant to AML development.

The evidence present supports the need for continuing investigation of prenatal pesticide exposure as a potentially preventable risk factor while recognizing the uncertainty surrounding causation. Current evidence is still not enough to determine pediatric AMl and its correlation to pesticide exposure alone, as leukemia development is likely influenced by multiple interacting genetic, developmental, and environmental factors. Nonetheless, improving exposure

assessment and understanding potentially sensitive development windows could help clarify whether specific pesticide exposure represents modifiable risk factors. Whereas more precise evidence would enable future risk selection strategies based on demonstrated exposure response observed rather than utilizing assumptions that derive from biological plausibility alone.

Overall, the review indicates that the relationship between prenatal pesticide exposure and pediatric AML is supported by merging evidence from epidemiological, placental, and epigenetic research, but there are still important gaps that remain between these areas of evidence. The strongest unresolved question is whether pesticide exposure during fetal development produces specific molecular changes within developing hematopoietic cells that either persist or contribute to the emergence of pediatric AML. The proposed relationship between pesticide exposure, CDKN2B /p15INKB methylation, and abnormal cell cycle regulation are still insufficiently studied. By addressing this gap, it enables the call for further research to integrate exposure measurement, fetal or developmentally relevant biological models, epigenetic profiling, and pediatric AML molecular characterization with the same investigative research study.

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