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Pediatric Safety and Toxicological Evaluation of Chemical and Botanical Household Insect Repellents: A Comprehensive Review

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ABSTRACT: Vector-borne infectious diseases, including dengue, Zika, chikungunya, West Nile fever, and malaria, represent significant worldwide public health challenges. In the absence of universal immunizations for numerous arboviral pathogens, personal chemical prophylaxis via insect repellents serves as a critical defensive measure. However, applying chemical and botanical formulations in pediatric cohorts requires precise toxicological balancing. Infants and young children possess distinctive anatomical and physiological characteristics—such as an elevated body surface area-to-body mass ratio, thinner stratum corneum, increased cutaneous blood flow, developing hepatic cytochrome P450 enzyme activity, and frequent hand-to-mouth behaviors—that alter xenobiotic disposition and heighten vulnerability to adverse reactions. This comprehensive review examines the neurobiology, transdermal pharmacokinetics, toxicological profiles, indoor air emissions, and global regulatory frameworks governing primary synthetic repellents (DEET, picaridin, and IR3535) and botanical agents (para-menthane-3,8-diol [PMD], citronella, and essential oils). Modern clinical evidence demonstrates that synthetic repellents, when utilized within recommended guidelines, offer broad-spectrum efficacy with manageable risk. Picaridin and IR3535 exhibit minimal transdermal penetration (<4%) and high margins of exposure. Botanical alternatives frequently present limited protection windows (<1 hour) due to high volatility and may cause contact sensitization. Furthermore, indoor thermal dispersion devices such as coils and liquid vaporizers release fine particulates and volatile organic compounds, underscoring the need for adequate room ventilation. Pediatric clinical guidelines, tiered risk assessments, and advanced formulation approaches are evaluated to support safe, evidence-based arthropod bite prevention in children.

Keywords: *Pediatric toxicology, insect repellents, DEET, picaridin, dermal absorption, risk assessment.*

1. Introduction

Arthropod-borne infectious diseases present an ongoing challenge to global public health, generating significant illness across tropical, subtropical, and temperate environments (Diaz, 2016; Islam et al., 2017). Emerging and re-emerging viral pathogens transmitted by *Aedes* species (notably *Aedes aegypti* and *Aedes albopictus*), including dengue virus, chikungunya virus, yellow fever, and Zika virus, along with *Anopheles*-transmitted

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malaria, continue to expand their geographical ranges (Debboun et al., 2006; Maia & Moore, 2011). In pediatric populations, young children can experience acute vulnerabilities following vector-borne infections, manifesting accelerated progression to severe dengue hemorrhagic shock syndrome, neurological complications, or cerebral malaria (Sorge et al., 2007; Sorge, 2009). Because universal vaccines remain unavailable for several of these vector-borne pathogens, personal chemical prophylaxis via topical repellents and household interventions serves as an essential preventative strategy (Goodyer et al., 2010; Kendrick, 2006).

Despite the established efficacy of repellents in mitigating mosquito bites, their domestic use in pediatric cohorts introduces distinct toxicological considerations (ATSDR, 2017; Sudakin & Trevathan, 2003). Children exhibit unique anatomical and physiological characteristics compared to adults (Dourson et al., 2002; Scheuplein et al., 2002):

1. **Elevated body surface area-to-weight ratio**: Infants have a surface area-to-mass ratio nearly three times greater than that of adults, resulting in greater relative systemic exposure per unit of topically applied chemical (Plunkett et al., 1992; Sorge, 2009).
2. **Cutaneous barrier characteristics**: In neonates and young infants, the stratum corneum and skin microvascular bed facilitate transcutaneous absorption of lipophilic and amphiphilic active ingredients (Bartelink et al., 2006; Ginsberg et al., 2004).
3. **Hepatic and renal elimination maturity**: Hepatic cytochrome P450 monooxygenases (such as CYP2B6, CYP2C19, and CYP3A4) and phase II conjugating enzymes undergo progressive post-natal development, reaching mature functional activity between infancy and early childhood (Usmani et al., 2002; de Zwart et al., 2004). Neonates and young infants have lower baseline clearance rates, which can alter systemic elimination kinetics (Morselli et al., 1980; Sorge, 2009).
4. **Behavioral dynamics**: Pediatric cohorts demonstrate natural hand-to-mouth exploration and eye-rubbing habits, which can transfer topical dermal residues to oral or ocular mucosal surfaces (Bell et al., 2002; Menon & Brown, 2005).

A common assumption among consumers is that natural or plant-derived products are inherently harmless, whereas synthetic compounds carry greater hazard (Diaz, 2016; Maia

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& Moore, 2011). Consequently, caregivers often select botanical formulations over synthetic active ingredients like N,N-diethyl-meta-toluamide (DEET). However, pharmacological assessments demonstrate that unrefined botanical preparations contain complex mixtures of terpenes, phenols, and aldehydes with variable irritancy, contact sensitization potential, and short protection durations (<1 hour) due to rapid evaporation (Barnard, 1999; Nerio et al., 2010; Trongtokit et al., 2005).

Beyond topical sprays and lotions, household mosquito defense frequently employs thermal dispersal systems, such as smoldering coils, electric mats, and liquid vaporizers (Jo & Lee, 2009). While effective at dispersing pyrethroid insecticides, these devices can emit volatile organic compounds (VOCs) and fine particulate matter into domestic environments, creating sustained inhalation exposure pathways for young children (Dubey et al., 2014; Jo & Lee, 2009).

Regulatory policies for pediatric repellent application also vary across jurisdictions. The United States Environmental Protection Agency (US EPA) and Centers for Disease Control and Prevention (CDC) allow DEET use in infants older than two months at concentrations up to 30%, whereas Health Canada restricts concentrations to a maximum of 10% for children aged 2 to 12 years and discourages use below six months (Health Canada, 2002, 2012; US EPA, 1998, 2014). In France, regulatory bodies have historically maintained conservative age boundaries, while specialized pediatric panels advocate pragmatic protocols for high-risk endemic environments (Sorge et al., 2007, 2009).

This review provides a toxicological, neurobiological, and clinical synthesis of chemical and botanical household insect repellents in pediatric care. By evaluating synthetic agents (DEET, picaridin, IR3535), botanical compounds (PMD, citronella, essential oil terpenes), olfactory receptor mechanisms, indoor air dispersion, and formulation technologies, this article provides an integrated framework to optimize pediatric bite prevention while minimizing chemical exposure risks.

2. Methods and Review Framework

A systematic evaluation of the literature was conducted across the compiled scientific records, regulatory monographs, and clinical trial datasets. The analysis encompassed technical records and toxicological monographs, focusing on five primary evaluative areas:

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1. **Synthetic Chemical Repellents**: Technical data and clinical evaluations for registered compounds, including DEET, picaridin (icaridin/KBR 3023), and IR3535.

2. **Botanical and Biopesticidal Active Ingredients**: Data on plant-derived agents, including para-menthane-3,8-diol (PMD/Citriodiol from *Corymbia citriodora*), citronella oil (*Cymbopogon* species), lemon eucalyptus oil, and specific terpenes (linalool, linalyl acetate, carvacrol, thymol, elemol, and nepetalactone).

3. **Pediatric Toxicokinetics and Systemic Dynamics**: Quantitative parameters including transdermal absorption rates, peak plasma intervals, metabolic pathways, urinary excretion profiles, no-observed-adverse-effect levels (NOAELs), acceptable exposure levels (AELs), margins of exposure (MOEs), and minimal risk levels (MRLs).

4. **Epidemiological Surveillance and Clinical Studies**: Human observational datasets, including reports from poison control registries, clinical case series, dermal patch testing, and hypersensitivity reports.

5. **Indoor Dispersion Dynamics and Environmental Inhalation**: Headspace analyses, environmental chamber testing, and gas chromatography-mass spectrometry (GC-MS) assessments of volatile organic emissions from domestic mosquito coils, electric mats, and liquid vaporizers.

The compiled evidence was synthesized using standard toxicological benchmarks, international regulatory evaluation reports, and pediatric clinical recommendations.

3. Results: Toxicological Profiles, Efficacy, and Pediatric Exposure Dynamics

3.1. Synthetic Chemical Repellents

3.1.1. DEET (N,N-Diethyl-meta-toluamide)

DEET (*N,N*-diethyl-3-methylbenzamide) has served as the reference standard in chemical insect repellency for over six decades (Brown & Hebert, 1997; Debboun et al., 2006). Registered for consumer use in 1957, DEET is commercially available in concentrations ranging from 4% to 100% across multiple formulations, including sprays, lotions, gels, and towelettes (ATSDR, 2017; Fradin, 1998).

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Pharmacokinetics and Cutaneous Absorption

Following topical application, DEET permeates the stratum corneum through passive diffusion. In human clinical studies administering radiolabeled technical DEET to the forearm, systemic dermal absorption ranged between 5.6% and 8.4% of the applied dose, with earlier studies reporting absorption up to 16.7% (Feldmann & Maibach, 1970; Selim et al., 1995; Sudakin & Trevathan, 2003). Peak plasma levels are reached within two to six hours (Robbins & Cherniack, 1986). The formulation vehicle markedly influences cutaneous penetration: ethanol-based carriers enhance transdermal flux by altering stratum corneum barrier lipids, whereas microencapsulation, lipospheres, and polyethylene glycol vehicles attenuate cutaneous penetration, keeping the active ingredient localized on the skin surface (Domb et al., 1995; Qiu et al., 1997, 1998; Stinecipher & Shah, 1997).

Systemically absorbed DEET is biotransformed in the liver primarily via cytochrome P450 monooxygenases, with CYP2B6 playing a central role and minor contributions from CYP2C19, CYP3A4, and CYP2A6 (Usmani et al., 2002). The primary human urinary metabolites are 3-(diethylcarbamoyl)benzoic acid (DCBA) and *N,N*-diethyl-3-(hydroxymethyl)benzamide (DHMB), along with monodeethylated derivatives (ATSDR, 2017; Calafat et al., 2016; Wu et al., 1979). Excretion is rapid, with more than 90% of absorbed compound eliminated through the kidneys within 24 hours (Selim et al., 1995).

Pediatric biomonitoring indicates age-dependent metabolic differences. In a study comparing children aged 5 to 7 years with adults aged 23 to 25 years following standardized 12% DEET application, children demonstrated a higher proportion of urinary DCBA (78.2% versus 46.1% in adults) and greater total metabolite recovery over eight hours (1,116 µg versus 446 µg DEET equivalents), reflecting efficient metabolic turnover and higher relative dermal loading per unit body weight (Tian & Yiin, 2014).

Systemic Toxicology and Margin Assessment

In mammalian toxicological assays, technical DEET demonstrates low acute oral and dermal toxicity in adult animals, with oral LD50 values of 2,000 to 3,429 mg/kg in adult rats and dermal LD50 values above 3,167 mg/kg in rabbits (Ambrose, 1959; Carpenter et al., 1974; Schoenig et al., 1999). However, age-related susceptibility was observed in animal studies: Verschoyle et al. (1992) found an oral LD50 of 667 mg/kg in 11-day-old

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neonatal rats, approximately five-fold lower than in mature adult rats, indicating lower metabolic clearance and greater blood-brain barrier permeability in neonatal rodents (ATSDR, 2017).

Subchronic dermal testing in rats exposed to 1,000 mg/kg/day over 90 days showed no systemic organ pathology (Schoenig et al., 1993, 1999). Regimens involving high daily dermal doses (40 mg/kg/day) alone or paired with permethrin reported histological changes in Purkinje cells and motor pathways in adult rats (Abdel-Rahman et al., 2001, 2002; Abou-Donia et al., 2001). The ATSDR established an intermediate-duration oral Minimal Risk Level (MRL) of 1.0 mg/kg/day based on a developmental NOAEL of 100 mg/kg/day in continuous rodent feeding studies, using an uncertainty factor of 100 (ATSDR, 2017; US EPA, 1989). Dermal exposure during human pregnancy in the second and third trimesters did not lead to adverse outcomes in birth weight, physical development, or infant neurological progress during one-year follow-up (McGready et al., 2001).

Historically, rare pediatric reports of neurobehavioral symptoms were documented following extensive, repeated overapplications of high-concentration preparations (up to 75%–95%) over extended periods (Briassoulis et al., 2001; Roland et al., 1985; Zadikoff, 1979). In one notable case involving an infant, metabolic encephalopathy occurred due to an undiagnosed underlying metabolic inborn error, ornithine transcarbamylase deficiency (OTD), which impaired ammonia handling under high chemical exposure (Heick et al., 1980; Sudakin & Trevathan, 2003). Clinical toxicologists observe that afebrile seizures occur in 3% to 5% of young children from various etiologies; given that millions of children use DEET annually, random temporal overlap can occur without established causal connection (ATSDR, 2017; US EPA, 1998). When applied according to label instructions, the incidence of systemic adverse reactions remains low (Osimitz & Murphy, 1997).

3.1.2. Picaridin (Icaridin / KBR 3023)

Picaridin (sec-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate; trade names Bayrepel, Saltidin) is an acylated 1,3-aminopropanol derivative developed by Bayer AG in the 1990s as a structural alternative to DEET (Boeckh et al., 1996; Debboun et al., 2006). Approved

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across Europe, Australia, and registered by the US EPA in 2005, picaridin is formulated in concentrations of 5% to 20% (Kendrick, 2006; MedPartner, 2017).

Cutaneous Absorption and Metabolic Disposition

Picaridin possesses favorable cosmetic characteristics: it is colorless, non-greasy, nearly odorless, and compatible with synthetic fabrics and plastics (Diaz, 2016; Kendrick, 2006). Human dermal penetration studies using radiolabeled compound demonstrated absorption of less than 4% (2% for undiluted technical substance and 4% for a 15% formulation) over eight hours (European Commission Competent Authority Report [CAR], 2011). In rats, dermal absorption was 17% to 23% over 8 hours and 47% over 24 hours. Excretion is rapid, with greater than 93% of absorbed material eliminated in human urine within 24 hours (CAR, 2011).

The principal mammalian metabolic pathway involves oxidation of the hydroxyethyl terminal carbon, forming 2-(2-hydroxyethyl)piperidine-1-carboxylic acid sec-butyl ester oxidation derivatives, designated as Bayrepel acid (CAR, 2011). Recent investigations in rat models identified Bayrepel acid as the major urinary and hepatic biomarker for systemic picaridin exposure (Taiwan National Central Library Thesis Repository, 2018).

Toxicology and Risk Characterization

Picaridin displays low acute toxicity: the rat oral LD50 exceeds 4,743 mg/kg and dermal LD50 exceeds 2,000 mg/kg (Category IV) (Debboun et al., 2006). Subchronic 90-day dermal studies in rats determined a systemic NOAEL of 500 mg/kg/day, with minor liver weight adjustments reflecting reversible metabolic adaptation (CAR, 2011). A one-year dermal study established a chronic NOAEL of 100 mg/kg/day, defining an Acceptable Daily Intake (ADI) of 1.0 mg/kg/day and a medium-term Acceptable Exposure Level (AEL) of 2.4 mg/kg/day (CAR, 2011). Teratogenicity and two-generation reproductive assays showed no developmental anomalies or reproductive deficits up to 200 mg/kg/day (Astroff et al., 1999, 2000).

In the European regulatory exposure assessment for a representative 20% pump spray, realistic refined exposure scenarios (Tier III) for a 3-year-old child (13.2 kg) yielded an internal dose of 1.2 mg/kg/day, consuming 50% of the medium-term AEL and providing an

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acceptable Margin of Exposure (MOE) of 196 (CAR, 2011). The addition of a bittering agent (such as denatonium benzoate) is recommended to prevent oral ingestion by toddlers. Surveillance data from poison control registries between 2000 and 2015 identified no major systemic toxicities associated with cutaneous picaridin use (Charlton et al., 2016).

3.1.3. IR3535 (Ethyl Butylacetylaminopropionate)

IR3535 (ethyl butylacetylaminopropionate; CAS No. 52304-36-6) is a synthetic amino acid derivative based on beta-alanine (Diaz, 2016; Sorge et al., 2007). Utilized in Europe for over thirty years in 10% to 30% lotions and sprays, it provides protection against *Aedes*, *Culex*, and *Anopheles* mosquitoes, as well as ticks and biting midges (Carroll, 2008; Costantini et al., 2004; Thavara et al., 2001). Field trials demonstrate that 20% IR3535 provides 4 to 8 hours of complete protection against *Aedes albopictus* and *Aedes aegypti* (Liu et al., 2003, 2008).

Pharmacokinetically, IR3535 is absorbed through the skin but undergoes rapid enzymatic hydrolysis to free IR3535 acid, peaking in serum within 2 to 6 hours and undergoing swift renal excretion (Broschard et al., 2013). Acute oral LD50 in rats exceeds 5,000 mg/kg, and dermal LD50 exceeds 2,000 mg/kg (Debboun et al., 2006). It demonstrates good cutaneous tolerance, though contact with eyes can induce transient ocular discomfort. Reproduction and developmental studies in rodents have shown no teratogenic effects (FDA Pregnancy Category B) (Diaz, 2016).

3.2. Botanical Repellents and Essential Oils

3.2.1. PMD (Para-Menthane-3,8-diol / Citriodiol)

Para-menthane-3,8-diol (PMD; C10H20O2) is obtained from the distillation by-product of lemon eucalyptus foliage (*Corymbia citriodora*, formerly *Eucalyptus maculata citriodora*, Myrtaceae) or produced synthetically from citronellal (Debboun et al., 2006; Maia & Moore, 2011). In traditional use, it is known as *Quwenling* (Moore et al., 2007).

Because PMD has a lower vapor pressure (0.017 Pa at 20°C) than lighter monoterpenes, it provides extended repellency (Barasa et al., 2002; Islam et al., 2017). Field evaluations in Bolivia showed that 30% PMD formulations conferred 6 to 8 hours of protection against *Anopheles* malaria vectors, comparable to 30% DEET (Hill et al., 2007; Moore et al.,

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2002). PMD also provides protection against tick species (*Ixodes scapularis* and *Dermacentor andersoni*) (Carroll & Loye, 2006).

Systemic toxicity of technical PMD is low: rat oral LD50 is 2,408 mg/kg and dermal LD50 is greater than 2,000 mg/kg (Debboun et al., 2006). Transdermal penetration is low, measured at 1% to 3% in human skin (Sorge et al., 2007). A developmental neurotoxicity study in rats receiving dermal doses up to 1,000 mg/kg/day during gestation and lactation revealed no neurobehavioral or morphological alterations in offspring (Barnett et al., 2004).

However, concentrated PMD and Oil of Lemon Eucalyptus (OLE) cause notable eye irritation and can cause contact sensitization (Diaz, 2016; US EPA, 2000). Major regulatory agencies—including the US EPA, US CDC, AAP, and Health Canada—mandate that **PMD and OLE must not be applied to children younger than 3 years of age** (AAP, 2015; CDC, 2015; Health Canada, 2012). This restriction reflects the absence of extensive clinical trials in children under 36 months and the potential for ocular irritation from uncoordinated facial rubbing (Debboun et al., 2006; Sorge, 2009).

3.2.2. Volatile Terpenes and Essential Oils

Botanical repellents containing citronella oil (*Cymbopogon nardus*, *Cymbopogon winterianus*), lemongrass, eucalyptus, clove, and lavender oils are widely marketed for pediatric use (Islam et al., 2017; Nerio et al., 2010).

While pure components (such as citronellal, geraniol, eugenol, and carvacrol) show repellent activity in membrane feeding bioassays—with 50% feeding inhibition doses (ID50) ranging from 14.4 µg/cm² for citronellal to 23.8 µg/cm² for eugenol (compared to 1.62 µg/cm² for DEET)—their high vapor pressures cause rapid evaporation (Chia-Nan University Thesis, 2016; Fradin, 1998; Trongtokit et al., 2005). Unformulated citronella products typically provide complete protection for less than one hour (Maia & Moore, 2011; MedPartner, 2017).

Furthermore, natural essential oils contain terpene hydrocarbons, alcohols, and aldehydes that can oxidize into reactive hydroperoxides, serving as skin sensitizers (Barnard, 1999; Nerio et al., 2010). Citronellol, eugenol, and linalool are recognized contact allergens that

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can induce localized dermatitis in young children (European Parliament, 2009; Reutemann & Ehrlich, 2008).

3.3. Olfactory Receptor Mechanisms

Mosquitoes detect human hosts via antennal and maxillary palp olfactory sensory neurons (OSNs) that recognize host odorants such as carbon dioxide, lactic acid, and (R)-(−)-1-octen-3-ol (Bohbot & Dickens, 2009; Davis & Sokolove, 1976). These neurons express heteromeric receptor complexes consisting of a variable ligand-binding subunit (ORx) and a conserved core subunit, Orco (Ditzen et al., 2008; Sato et al., 2008; Wicher et al., 2008).

Electrophysiological analyses reveal distinct molecular targets among repellent classes (Bohbot & Dickens, 2010; Tsitoura et al., 2015):

1. **DEET**: Acts as a dual-action agent. It inhibits odorant-evoked inward currents in specific receptor complexes (such as AaOR8 paired with Orco responding to octenol), effectively masking host emanations (Bohbot & Dickens, 2010; Ditzen et al., 2008). Simultaneously, it stimulates specific avoidance receptors, including CquiOR136 in *Culex quinquefasciatus* (Syed & Leal, 2008; Xu et al., 2014).
2. **Picaridin and IR3535**: Function as non-competitive allosteric inhibitors that target the conserved Orco core subunit, dampening sensory neuron responses across divergent odorant receptor types without acting as direct agonists (Bohbot & Dickens, 2010; Tsitoura et al., 2015).
3. **Botanical Terpenoids**: Sesquiterpenes (e.g., elemol) and bicyclic monoterpenes (e.g., nepetalactone) provide variable spatial and contact repellency. Spatial protection correlates with lower volatility, allowing sustained vapor concentration gradients around the treated host (Paluch et al., 2009; Schultz et al., 2006).

3.4. Domestic Inhalation Hazards: Thermal Dispersion Devices

Domestic mosquito abatement frequently uses thermal dispersal systems, including smoldering coils, electric mats, and liquid vaporizers, which release synthetic pyrethroids (e.g., d-allethrin, prallethrin, transfluthrin) (Diaz, 2016; Jo & Lee, 2009).

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Chamber tests and indoor bedroom monitoring demonstrate marked differences in secondary pollutant emissions across devices (Jo & Lee, 2009):

- **Mosquito Coils**: Emitted the highest levels of combustion-derived pollutants, generating benzene (0.45 mg/h), toluene (0.82 mg/h), ethylbenzene (0.31 mg/h), and xylenes (0.64 mg/h), along with fine particulate matter (PM2.5). In bedroom studies, coil use increased ambient benzene and ethylbenzene concentrations by 1.8- to 1.9-fold over baseline (Jo & Lee, 2009).
- **Liquid Vaporizers**: Did not emit combustion particulates but released naphthalene from organic hydrocarbon solvents at a rate of 2.4 mg/h, elevating closed-bedroom levels by up to 4.2-fold (Jo & Lee, 2009).

Because infants spend extended periods asleep indoors and possess higher resting ventilation rates relative to body weight, continuous nightly exposure to coil smoke or solvent vapor presents potential respiratory risks, including airway irritation and aggravated bronchospasm (Jo & Lee, 2009).

3.5. Formulation Interventions and Dermal Interactions

3.5.1. Co-Application with Sunscreens

In outdoor environments, children are frequently exposed to both sunscreens and insect repellents. In vitro and in vivo studies indicate that the organic UV filter oxybenzone (benzophenone-3) acts as a penetration enhancer for both DEET and picaridin (Fediuk et al., 2010, 2011; Ross et al., 2004). Applying sunscreen immediately prior to repellent significantly increases systemic dermal uptake in animal models, while simultaneously lowering sunscreen SPF by up to 33% (Hexsel et al., 2008; Taiwan National Central Library Thesis Repository, 2018; Wang et al., 2014). Regulatory agencies advise against fixed combination products; when both are required, sunscreen should be applied first, allowed to absorb for 20 minutes, followed by repellent application (CDC, 2017; Sorge et al., 2007).

3.5.2. Advanced Delivery Formulations

Modern carrier technologies can reduce percutaneous absorption while preserving protection times. Encapsulation of active ingredients in solid lipid nanoparticles (SLNs),

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microcapsules, or cyclodextrin matrices reduces transdermal migration, keeping the repellent on the outer stratum corneum (Barradas et al., 2015; Iscan et al., 2006; Proniuk et al., 2002). Furthermore, microencapsulated finishes applied directly to children's outerwear can provide multi-hour protection without direct cutaneous chemical contact (Miro Specos et al., 2010; Sorge et al., 2007).

3.6. Comparative Synthesis of Repellent Toxicokinetics and Pediatric Regulatory Boundaries

As quantitatively synthesized in the comparative evaluation (Table 1 / Section 4.2), distinct divergence exists across synthetic and plant-derived repellent compounds regarding their pharmacokinetics, barrier permeability, and pediatric safety margins:

1. **Dermal Absorption Dynamics and Internal Dose**: Among the evaluated active ingredients, picaridin (icaridin) demonstrates the most favorable toxicokinetic profile for pediatric application, exhibiting human transdermal absorption of less than 4% (as low as 2% in undiluted forms). In contrast, topical DEET displays significantly higher systemic penetration (5.6%–8.4%, increasing up to 16.7% when co-formulated with volatile ethanol vehicles), necessitating prudent restriction of concentrations in pediatric populations. While IR3535 exhibits rapid dermal permeation (~10%–15%), its systemic burden is mitigated by immediate in vivo enzymatic ester hydrolysis into inert free acid metabolites before complete renal excretion.

2. **Metabolic Fate and Organ Clearance**: Both synthetic dialkylamides and piperidines undergo primary hepatic transformation followed by rapid and exhaustive renal clearance (>90% within 24 hours). DEET depends primarily on cytochrome P450 oxidation (predominantly CYP2B6) generating DCBA and DHMB, whereas picaridin undergoes Phase II conjugation and side-chain oxidation yielding stable, non-reactive urinary biomarkers (notably Bayrepel acid). These rapid clearance kinetics prevent cumulative tissue bioaccumulation under normal dosing regimens.

3. **Efficacy-Duration Profiles Against Vectors**: Protection longevity scales positively with concentration for modern synthetic agents: 20% formulations of picaridin deliver 8 to 12 hours of complete protection against anthropophilic *Aedes* vectors, exceeding equivalent concentrations of DEET (~5 hours) and IR3535 (~6–8 hours). Conversely,

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unprocessed botanical essential oils (such as citronella) suffer from severe volatility limitations, failing to provide sustained protection beyond 30 to 60 minutes. This marked drop-off introduces potential vulnerability to vector bites unless combined with advanced sustained-release technologies.

4. **Pediatric Toxicological Hazards and Global Age Harmonization**: The clinical safety margins highlighted in the comparative matrix underline critical regulatory age thresholds:

    - **DEET and Picaridin**: Both are endorsed by the US EPA and CDC down to 2 months of age (with DEET concentration capped at 10%–30%), though jurisdictions like Health Canada and Taiwan maintain more conservative tiers (e.g., restricting picaridin to children ≥2 years of age).

    - **Botanical PMD / OLE**: Despite being naturally derived from *Corymbia citriodora*, PMD presents marked ocular irritation and contact sensitization hazards, driving a strict regulatory consensus across the US EPA, CDC, AAP, and Health Canada that strictly prohibits its use in children younger than 3 years (36 months).

    - **Essential Oils**: Despite widespread public perception of botanical safety, pure essential oils pose documented risks of allergic contact dermatitis and unpredictable purity without conferring dependable vector protection.

4. Discussion: Comparative Safety and Clinical Guidelines

Managing insect bite protection in children requires weighing the potential risks of chemical exposure against the clinical consequences of vector-borne infections (Kendrick, 2006; Sorge, 2009). The subsequent analytical matrix outlines the comparative metrics of primary personal protectants.

4.1. The "Natural vs. Synthetic" Misconception

The belief that plant-derived products are intrinsically safer than synthetic compounds is contradicted by toxicological testing (Diaz, 2016; Maia & Moore, 2011). While raw essential oils have low acute systemic toxicity, their volatile components oxidize into reactive cutaneous allergens (Nerio et al., 2010; Reutemann & Ehrlich, 2008). In addition,

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their short protection duration (<1 hour) creates an unrecognized exposure risk in disease-endemic areas. In contrast, well-studied synthetic agents like picaridin and microencapsulated DEET provide consistent multi-hour defense with low dermal absorption (<4%) and high margins of safety (CAR, 2011; Sudakin & Trevathan, 2003).

4.2. Comparative Summary of Repellent Active Ingredients

The clinical and toxicological characteristics of the major active ingredients are summarized in Table 1 below:

Active Ingredient	Chemical Classification	Standard Formulations (%)	Mean Protection Duration against *Aedes*	Human Dermal Absorption (%)	Primary Elimination Route & Metabolites	Key Pediatric Toxicological Considerations	International Regulatory Age Guidance
DEET	Synthetic dialkylamide (*N,N*-diethyl-*m*-toluamide)	5%–30% (up to 100% in adult formulas)	10%: ~3 h 20%: ~5 h 30%: ~6–8 h	5.6%–8.4% (up to 16.7% in ethanol)	Hepatic CYP oxidation (CYP2B6); renal excretion (>90% in 24 h); main urinary metabolites DCBA and DHMB	Neurobehavioral alterations in massive overdose; cutaneous irritation; mucosal stinging; solvent damage to plastics	**US EPA/CDC/AAP**: ≥2 months (max 30%) **Health Canada**: ≥6 months (10% max for 6 mo–12 yr) **France (Afssaps)**: ≥30 months; **GPTrop**: ≥6 months (1x/day)
Picaridin (Icaridin)	Synthetic piperidine carboxylate (KBR 3023)	7%–20%	10%: ~5–6 h 20%: ~8–12 h	<4% (2% undiluted; 4% in 15% solution)	Hepatic Phase II conjugation & side-chain oxidation; renal (>93% in 24 h); biomarker	Negligible systemic toxicity; lacks neurotoxic potential; non-irritating to skin; bittering	**US EPA/CDC**: ≥2 months **Europe/WHO**: Approved for general public; national labels

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					Bayrepel acid	agent recommended to prevent ingestion	recommend ≥2 to 3 years **Taiwan EPA**: ≥2 years
IR3535	Synthetic amino acid derivative (ethyl butylacetylaminopropionate)	10%–20%	10%: ~3–4 h 20%: ~6–8 h	Rapidly absorbed (~10%–15%) but quickly cleared	Rapid ester hydrolysis to free acid; renal elimination	Excellent skin tolerance; transient conjunctival irritation upon direct eye contact; plastic-dissolving potential	**US EPA/CDC**: Approved for all ages **France (GPTrop)**: ≥12 months (20% formula)
PMD (Citriodiol / OLE)	Botanical monoterpene diol (*Corymbia citriodora* extract/synthetic)	10%–40%	10%: ~2 h 30%: ~6 h	1%–3% (minimal systemic loading)	Hepatic glucuronidation; renal excretion	Moderate to severe eye irritation; potential contact sensitization; lack of infant trial data	**US EPA/CDC/AAP**: Strictly forbidden <3 years **Health Canada**: Forbidden <3 years
Citronella & Essential Oils	Natural volatile monoterpenes & sesquiterpenes	5%–15%	<1 h (frequently <30 min)	Highly volatile; variable dermal penetration	Hepatic metabolism; renal excretion	Very short protection time; high risk of allergic contact dermatitis; unstandardized impurities	**US EPA**: FIFRA 25(b) exempt; not recommended by AAP or CDC for disease endemic zones

4.3. Harmonized Pediatric Clinical Recommendations

To optimize safety and efficacy when using repellents on children, healthcare providers and parents should observe the following guidelines (AAP, 2015; CDC, 2017; Kendrick, 2006; Sorge, 2009):

1. **Infants under two months of age**: Topical chemical or botanical insect repellents should not be used. Protection should rely on mechanical controls, including fine

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netting (<1.2 mm mesh) over strollers, cribs, and infant carriers, along with protective clothing (Sorge et al., 2007).

2. **Infants aged two to six months**: Where significant vector-borne disease transmission risks exist, low-concentration DEET (<=10%) or picaridin (<=10%) may be applied once daily to limited exposed extremities, avoiding hands and face (CDC, 2015; Sorge, 2009).

3. **Children aged six months to two years**: Picaridin (10% to 20%) or DEET (<=10%) may be applied once daily for routine exposure, or twice daily in high-risk transmission zones. Botanical PMD/OLE is not recommended under age three (Health Canada, 2012; Sorge, 2009).

4. **Children aged 2 to 12 years**: Formulations of 10% to 20% picaridin, <=30% DEET, or 20% IR3535 may be applied up to two or three times daily. Children aged 3 years and older may use 30% PMD for sustained protection (AAP, 2015; Diaz, 2016).

5. **Application Techniques**: Repellents should always be applied by an adult. The caregiver should dispense the product onto their own hands first and gently rub it onto the child's exposed arms, legs, and neck, strictly avoiding the eyes, mouth, and hands to prevent inadvertent ingestion (Bell et al., 2002; Menon & Brown, 2005).

6. **Indoor Air Hygiene**: Smoldering mosquito coils and continuous solvent vaporizers should be avoided in poorly ventilated bedrooms where infants sleep, due to combustion particulates, benzene, and naphthalene emissions. Physical window screens, bed nets, and air circulation should be prioritized (Jo & Lee, 2009).

5. Conclusion and Future Perspectives

Personal insect repellents are essential tools in preventing vector-borne diseases in pediatric cohorts. Developing evidence-based safety guidance requires accounting for children's distinct physiological characteristics, including elevated surface area-to-mass ratios and developing metabolic pathways.

Decades of surveillance demonstrate that DEET maintains an acceptable safety record when applied according to regulatory instructions. However, modern alternatives such as picaridin and IR3535 offer comparable multi-hour protection with minimal dermal

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penetration (<4%), negligible neurotoxic risk, and favorable skin tolerance, making them excellent primary options for pediatric use.

Conversely, plant-derived essential oils are limited by high volatility, resulting in short protection windows (<1 hour) and risks of contact sensitization. While PMD provides long-lasting repellency, regulatory restrictions appropriately exclude its use in children under three years of age due to potential mucosal and ocular irritation. Indoors, thermal coils and vaporizers generate significant VOC and particulate emissions, necessitating caution in children's living spaces.

Future advances should focus on controlled-release carrier technologies, such as solid lipid nanoparticles and repellent-treated textiles, which prolong protective efficacy while minimizing dermal absorption. Establishing harmonized pediatric age guidelines and standardized testing for all repellent products will ensure effective, safe protection for children worldwide.

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