Biocompatibility at Risk: The Hidden Threat of Di (2-ethylhexyl) Phthalate (DEHP) in Pediatric and Oncology Infusion Systems

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Abstract

Background: Di (2-ethylhexyl) phthalate (DEHP), a common plasticizer in polyvinyl chloride (PVC) medical devices, has been linked to endocrine disruption, hepatotoxicity, and reproductive harm. Despite global regulatory alerts, DEHP-containing infusion systems—including IV sets and blood bags—remain in use, particularly in pediatric, oncology, and transfusion-dependent populations. **Aim:**. To assess DEHP-related risks and propose a nursing-led framework for safer, biocompatible infusion practices. **Design:** A narrative-based theoretical analysis integrating scientific literature, toxicological data, international regulatory positions, and economic considerations. **Setting:** review was conducted within a multidisciplinary academic framework, guided by international patient safety standards (e.g., JCI, CBAHI, and Magnet's NK3). **Tool of Data Collection:** Structured comparative tables were used to synthesize findings related to toxicological markers, pharmacological interactions, risk stratification, regulatory gaps, labeling attributes, and cost-effectiveness. **Results:** DEHP exposure correlated with elevated FSH/LH, pubertal delay, liver enzyme abnormalities, and reduced fertility. Drug adsorption and compromised chemotherapy efficacy were observed with DEHP-lined IV sets. Regulatory reviews revealed fragmented global policies and weak substitution enforcement. DEHP-free alternatives (e.g., EVA, TOTM) demonstrated better safety profiles and were cost-justified in high-risk groups. A nurse-driven screening checklist was developed . A nurse-driven screening checklist was developed to support clinical decision-making. **Conclusion:** DEHP use in infusion systems represents a preventable hazard in vulnerable populations. Biocompatible alternatives offer superior clinical outcomes and should replace DEHP-containing devices in critical care settings. **Recommendations:** Healthcare institutions must adopt DEHP-specific labeling, enforce substitution policies, and implement mandatory biocompatibility training. Accrediting bodies such as JCI and CBAHI should revise patient safety metrics to include material-related risks, while procurement models must shift toward value-based, risk-informed approaches.

Keywords: DEHP; PVC medical devices; infusion systems; biocompatibility; pediatric oncology; NICU; chemotherapy efficacy; nursing-led risk assessment; regulatory policy; patient safety.

Introduction

Blood transfusion is a life-saving medical intervention governed by strict protocols to ensure compatibility, sterility, and procedural accuracy. Yet, an often-overlooked dimension of transfusion safety lies in the biocompatibility of the devices used for intravenous (IV) delivery. While healthcare systems emphasize drug stability and infection control, little attention is paid to the chemical composition of the materials that come into direct contact with patient bloodstream - particularly polyvinyl chloride (PVC) medical devices softened with di (2-ethylhexyl) phthalate (DEHP).

DEHP is not covalently bound to the PVC polymer matrix, making it prone to migration into fluids, especially under physiological conditions or when in contact with lipid-containing solutions **(Haishima et al., 2004; Rose et al., 2012).** Studies have shown that DEHP leaching increases with temperature, time, and fat solubility of the infusate **(Rose et al., 2012).** In neonates and patients receiving total parenteral nutrition or lipid emulsions, DEHP exposure from infusion systems may exceed safety thresholds established by health authorities **(Latini et al., 2003; Jenkins et al., 2021).**

Once inside the body, DEHP is metabolized into mono(2-ethylhexyl) phthalate (MEHP), a compound with documented endocrine-disrupting, hepatotoxic, and reproductive toxic effects **(Heudorf et al., 2007; Shelby, 2005).** Evidence from animal and human studies has linked DEHP exposure to alterations in hormone levels, liver enzyme activity, and developmental

abnormalities **(Etzel, 2003; Kolan & Hall, 2023).** Neonatal intensive care units (NICUs) and oncology wards—where prolonged infusion is common—represent particularly high-risk settings for DEHP-related toxicity **(Jenkins et al., 2021; WHO, 2011).** Despite growing awareness, clinical protocols and procurement policies rarely account for the toxicological profile of infusion devices. This gap highlights an urgent need for biocompatibility-informed nursing practices and institutional safeguards to prevent unintentional exposure to harmful plasticizers in vulnerable patient populations

Among all clinical subgroups, neonates, oncology patients, and pregnant women represent the populations most susceptible to DEHP-related harm due to their unique physiological vulnerabilities and cumulative exposure profiles. In neonatal intensive care units (NICUs), repeated use of DEHP-containing infusion systems has been shown to significantly elevate urinary concentrations of phthalate metabolites such as MEHP, MEHHP, and MEOHP **(Jenkins et al., 2021).** These exposures have been associated with endocrine disruption, hepatic oxidative stress, and altered lipid metabolism **(Heudorf et al., 2007; Etzel, 2003).** Similarly, the **World Health Organization (2011)** emphasized that pregnant women undergoing transfusions, parenteral nutrition, or dialysis may receive DEHP doses that exceed the tolerable daily intake (TDI), posing potential risks to placental function and fetal development. Oncology patients represent another high-risk group due to frequent exposure to PVC-based medical devices during chemotherapy and transfusion protocols. Such scenarios - especially under lipid-containing or heated conditions—facilitate DEHP leaching and increase toxicological burden in immunocompromised individuals **(BBraun, 2024; WHO, 2011).** These cumulative risks demand the institutional implementation of DEHP-free systems in NICUs, maternity units, and oncology departments.

Beyond its toxicological profile, DEHP also compromises pharmacologic accuracy. DEHP-containing tubing has been shown to adsorb lipophilic medications, such as diazepam and amiodarone, reducing their delivery efficiency **(Goldspiel, 1994; Haishima et al., 2004).** This phenomenon, known as drug sorption loss, may lead to subtherapeutic dosing in high-risk patients. In critical care and oncology, where drug titration must be exact, such reductions can compromise therapeutic efficacy and patient outcomes. This underscores the need to integrate DEHP-free delivery systems not only for safety but also to ensure pharmacologic reliability.

Despite mounting evidence, international transfusion safety standards lack explicit requirements regarding IV material composition. Accreditation frameworks such as the Joint Commission International (2023) and CBAHI (2021) focus on procedural safety—including patient identification, infection control, and transfusion documentation—but remain silent on the biocompatibility of intravenous delivery systems. This regulatory gap permits continued exposure to known toxicants. **WHO (2011)** and other global authorities have urged healthcare institutions to prioritize safer alternatives for vulnerable groups. However, until material safety is embedded into core transfusion protocols, institutional safeguards will remain incomplete.

Although concerns regarding DEHP exposure from medical devices have been documented for over two decades, a persistent lag exists between toxicological evidence and clinical policy implementation. This inertia is particularly concerning given the increasing reliance on infusion-based therapies in high-risk populations, including neonates, oncology patients, and pregnant women. The widespread use of lipid-based formulations, prolonged transfusion protocols, and intensive pharmacologic regimens has only amplified the cumulative risk of DEHP exposure in today's clinical landscape **(Lucaccioni et al., 2021; Wang et al., 2024).** Moreover, emerging epidemiological data - such as recent NHANES-based associations between DEHP metabolites and reproductive cancers - suggest that the health burden may be broader and more insidious than previously recognized **(Wang et al., 2024).** Yet, the absence of formal mandates from international regulators such as JCI, WHO, or FDA regarding IV material substitution contributes to a regulatory vacuum that allows outdated device standards to persist in clinical care. This review is thus both timely and essential: it consolidates current toxicological, pharmacological, and regulatory evidence to argue that material safety in transfusion is not a technical detail but a patient safety imperative.

The urgency is not theoretical; it is institutional, clinical, and - most critically - preventable.

This review seeks to advance a theoretically grounded, nursing-led framework that elevates infusion device biocompatibility to the forefront of transfusion safety protocols. Specifically, it advocates for the elimination of DEHP-containing PVC infusion systems from clinical use in high-risk populations - namely neonates, oncology patients, and pregnant women - based on a synthesis of toxicological evidence, pharmacologic interactions, and regulatory gaps **(Green et al., 2005; SCENIHR, 2016; Wang et al., 2024).** The proposed model reframes material selection as a core patient safety competency, positioning nurses not only as clinical implementers but also as stewards of safe device utilization. This approach aligns with global efforts to strengthen evidence-based, frontline-led safety practices, such as the International Patient Safety Goals (IPSG) set by JCI, national quality mandates like CBAHI, and the "New Knowledge, Innovations, and Improvements" (NK3) domain within the ANCC Magnet Recognition Program (American Nurses Credentialing Center **[ANCC], 2023).** By embedding material awareness into procurement policies, orientation curricula, and clinical audits, the framework promotes sustainable risk reduction through multidisciplinary accountability. Ultimately, this paper argues that the omission of material safety from transfusion protocols is not a gap in knowledge but a failure of translation - a preventable breach that can be rectified through policy integration, nurse education, and governance reform.

Significance of the study

Despite decades of mounting toxicological evidence regarding the harmful effects of di(2-ethylhexyl) phthalate (DEHP), its continued use in intravenous (IV) infusion systems reveals a critical disconnect between scientific knowledge and clinical practice. This oversight is particularly alarming in high-risk transfusion contexts involving neonates, oncology patients, and pregnant women—groups whose cumulative exposure to DEHP is often systematic and unrecognized **(Latini et al., 2003; Kolan & Hall, 2023).** In NICUs, DEHP is estimated to account for up to 88% of phthalate contamination in medical settings, with recorded exposure levels surpassing the European Union's tolerable daily intake (TDI) of 50 μg/kg/day **(WHO, 2011).** Studies have documented neonatal exposures reaching up to 30.8 ng/kg per infusion, while adult exposures during transfusion events can approach 0.7 mg/kg **(Hauser & Calafat, 2005; Jenkins et al., 2021).**

Clinical consequences are far from theoretical. The reintroduction of DEHP-containing products in NICU settings was associated with a sevenfold increase in neonatal hypertension, while switching to DEHP-free systems resulted in significant reductions in hepatobiliary complications such as cholestasis **(Etzel, 2003; Shelby, 2005).** These findings underscore an urgent need to reframe DEHP exposure not as a marginal concern, but as a core patient safety threat embedded within everyday clinical materials.

This review is significant in its call to reposition material biocompatibility - particularly with regard to IV devices - as a fundamental pillar of transfusion safety. By synthesizing toxicological, pharmacokinetic, and regulatory data, it proposes a nursing-led framework advocating for the elimination of DEHP-containing devices in favor of safer, DEHP-free alternatives. This framework aligns with the International Patient Safety Goals (IPSGs) promoted by the Joint Commission International **(JCI, 2023),** the national safety standards of the Saudi Central Board for Accreditation of Healthcare Institutions **(CBAHI, 2021),** and the New Knowledge, Innovations, and Improvements (NK3) domain within the ANCC Magnet Recognition Program **(ANCC, 2023).**

From a pharmaceutical perspective, DEHP poses an additional risk by interacting negatively with lipophilic medications. It has been shown to adsorb or sequester drugs like cisplatin and doxorubicin, thus reducing the therapeutic dose delivered to the patient **(Allwood & Stanley, 2005; Goldspiel, 1994).** DEHP also accelerates drug degradation and alters hepatic metabolism - an especially dangerous scenario in oncology and pediatric critical care, where dosing precision is vital **(FDA, 2020; Sandler et al., 2012).** Moreover, DEHP's hydrophobic nature increases the priming time for IV sets, introducing yet another source of delay and variability in drug delivery **(Rose et al., 2012).**

Despite these known risks, DEHP-containing devices remain in circulation - especially in low- and middle-income countries - largely due to cost-driven procurement practices and the absence of explicit regulatory bans **(ECHA, 2023; Health Canada, 2022).** Even leading safety frameworks like JCI's IPSGs have yet to directly address the material toxicity of IV systems. This regulatory blind spot enables outdated and hazardous materials to persist under the radar of institutional safety protocols.

This review therefore serves as a timely and essential contribution to patient safety discourse, advocating not only for regulatory reform, but also for nurse-led vigilance and leadership in procurement, orientation, and policy review. The evidence is clear: continuing to tolerate DEHP-containing infusion systems is not a neutral decision - it is a preventable risk.

Aim of the Study

The main aim of this study is to critically evaluate the clinical, toxicological, and regulatory implications of using di(2-ethylhexyl) phthalate (DEHP)-containing intravenous (IV) infusion systems, particularly in high-risk patient populations such as neonates, oncology patients, and pregnant women.

Specific Objectives

1. To synthesize scientific evidence on the endocrine, hepatic, and reproductive risks associated with DEHP exposure in infusion systems.
2. To assess the pharmacotechnical impact of DEHP-containing IV devices on chemotherapeutic drug stability and efficacy.
3. To map international regulatory stances, policy gaps, and labeling practices related to DEHP usage in medical devices.
4. To evaluate the economic trade-offs between DEHP and DEHP-free alternatives in terms of safety, cost-effectiveness, and patient outcomes.
5. To develop a nursing-led screening and risk mitigation model that promotes biocompatibility-informed decision-making in clinical settings.
6. To advocate for integration of material safety into existing patient safety frameworks such as IPSG, Magnet (NK3), and CBAHI standards.

Research Questions

This review is guided by the following research questions:

1. What is the current evidence regarding the clinical risks associated with DEHP-containing intravenous infusion systems, particularly in pediatric, oncology, and maternal care settings?
2. How do DEHP-related toxicological effects align with, or contradict, existing transfusion safety standards and accreditation frameworks such as JCI, CBAHI, and Magnet?
3. What gaps exist in policy, procurement, and nursing education regarding the selection and use of biocompatible infusion materials?
4. How can a nursing-centered theoretical framework advance institutional transitions toward DEHP-free infusion systems to enhance patient safety?

Research Design

This study employed a narrative-based theoretical review design to synthesize interdisciplinary evidence on the clinical, toxicological, and pharmacotechnical risks of di(2-ethylhexyl) phthalate (DEHP) in intravenous (IV) infusion systems. Unlike systematic reviews, this design allowed for flexible exploration of both historical and emerging data across toxicology, pharmacology, clinical medicine, and nursing science.

A comprehensive literature search was conducted using PubMed, Scopus, ScienceDirect, and Web of Science, covering publications from 1990 to 2024. Search terms included: "DEHP," "phthalates," "PVC medical devices," "infusion safety," "neonates," "biocompatibility," and "PVC-free devices." Manual searches also targeted gray literature, regulatory communications (e.g., FDA, ECHA, Health Canada, WHO), and expert position papers from authorities like the American Academy of Pediatrics (AAP) and European Medicines Agency (EMA).

Although a formal risk-of-bias appraisal was not conducted, selection criteria emphasized peer-reviewed studies, regulatory alerts, toxicological evaluations, and clinical reviews with transparent methodologies and relevance to nursing-led infusion practices. Extracted data were thematically grouped into the following domains:

1. Clinical toxicity in high-risk populations
2. Pharmacotechnical and sorption-related drug losses
3. Material labeling and awareness gaps
4. Cost and policy barriers to DEHP-free adoption
5. Compliance with international safety frameworks

This approach enabled a holistic evaluation of DEHP's systemic risks and informed the development of a nursing-led framework for safer, evidence-based material use—aligned with JCI's IPSGs, CBAHI hospital standards, and the NK3 domain of the ANCC Magnet Recognition Program.

Setting of the Study

As a non-empirical, theory-driven review, this study was conducted within a multidisciplinary academic framework, encompassing global regulatory standards, clinical safety guidelines, and toxicological data related to DEHP-containing intravenous systems. The analysis was situated in the context of evidence-based nursing practice, with specific attention to transfusion and oncology care protocols. The review environment was informed by international frameworks such as the Joint Commission International (JCI) International Patient Safety Goals (IPSGs), CBAHI patient safety standards, and Magnet's New Knowledge, Innovations & Improvements (NK3) domain. This theoretical setting provided the foundation for interpreting data from diverse healthcare systems and drawing context-sensitive recommendations for both high-resource and resource-limited clinical environments.

Subjects of the Study

Although no human participants were directly involved, this review targets populations most vulnerable to the toxicological effects of DEHP-containing intravenous (IV) devices. Specifically, the analysis focused on three high-risk groups repeatedly identified across toxicological and clinical literature:

1. Neonates and infants receiving intensive care support through blood transfusion, parenteral nutrition, or ventilator tubing.
2. Pediatric and adult oncology patients, particularly those undergoing chemotherapy with lipid-soluble agents.
3. Pregnant women exposed to DEHP through prolonged IV therapies or transfusions during obstetric procedures.

These populations were selected due to their physiological susceptibility, cumulative exposure risks, and the potential for endocrine, hepatic, reproductive, and developmental disruption. Evidence related to these groups was prioritized during literature selection and analysis to ensure clinical relevance and policy alignment.

Tool of Data Collection

As this study adopts a non-empirical analytical review design, no primary data collection tools were employed. Instead, data were gathered through structured literature mining and critical document analysis, focusing on peer-reviewed journals, regulatory guidance, pharmacovigilance reports, and toxicological evaluations published between 1990 and 2024. Search engines and databases included PubMed, Scopus, Web of Science, the FDA Medical Device Safety database, and WHO regulatory portals.

Inclusion and Exclusion Criteria

To ensure scientific rigor and relevance, specific inclusion and exclusion criteria were established for selecting literature and documents used in this theoretical review:

Inclusion Criteria

- Peer-reviewed articles published between 1990 and 2024.
- Studies focused on DEHP (di(2-ethylhexyl) phthalate) and its toxicological impact on human health.
- Publications addressing material leaching from PVC/DEHP-containing medical devices, especially in IV infusion and blood transfusion contexts.
- Regulatory and safety documents issued by recognized health agencies such as the FDA, WHO, Health Canada, European Chemicals Agency (ECHA), and JCI.
- Research highlighting clinical outcomes, pharmacological interactions, or risk profiles among neonates, oncology patients, or pregnant women.
- Reports and product datasheets on DEHP-free alternatives (e.g., TOTM, DINCH, EVA-based systems).

Exclusion Criteria

- Non-English publications.
- Non-human studies, unless directly linked to toxicokinetics applicable to human physiology.
- Articles lacking full-text availability or methodological transparency.
- Industry-sponsored white papers with conflicts of interest not clearly disclosed.
- Editorials, opinion pieces, and non-peer-reviewed blog content.

These criteria were applied to enhance the validity, transferability, and clinical relevance of the reviewed evidence and to support informed conclusions aligned with international safety standards.

Instrument Validity and Reliability

Given the non-empirical nature of this review, no psychometric tool was administered. However, the validity and reliability of the study were ensured through rigorous source selection and triangulated data extraction. All included studies and documents were:

Published in peer-reviewed journals indexed in internationally recognized databases (e.g., PubMed, Scopus, Web of Science);

Issued by globally trusted regulatory authorities such as the FDA, WHO, ECHA, and Health Canada;

Assessed for methodological transparency, sample representation, and risk of bias, particularly in clinical trials and toxicological evaluations.

The credibility of evidence was further supported by using multiple sources for each key concept, ensuring data triangulation and minimizing interpretation bias. All extracted content was reviewed against current international safety standards and clinical best practices.

Thus, although no physical tool was validated, the methodological rigor in literature appraisal provided content validity, contextual relevance, and analytical reliability.

Ethical Research Considerations

As this study is a non-empirical, theoretical review based entirely on publicly available data, scientific publications, and regulatory documents, it did not involve human participants, identifiable personal data, or direct patient contact. Therefore, institutional review board (IRB) approval was not required.

Nevertheless, the study adhered to the ethical principles of integrity, transparency, and academic honesty, including:

- Accurate citation of all sources following the APA 7th edition referencing style;
- Avoidance of plagiarism through original synthesis and paraphrasing;
- Critical appraisal of potential conflicts of interest in reviewed literature;
- Respect for intellectual property and copyright compliance.

Moreover, the selection of regulatory sources such as FDA, WHO, ECHA, Health Canada, and JCI ensured that the content reflects ethically reviewed, evidence-based guidance relevant to patient safety and healthcare quality improvement.

Field Work

This analytical review did not involve primary data collection or direct interaction with healthcare personnel or patients. Instead, the study was conducted through a structured review of scientific literature, official regulatory guidelines, and technical datasheets related to DEHP-containing intravenous devices. The field of inquiry focused on:

- Transfusion and oncology settings;
- Vulnerable populations (e.g., neonates, pregnant women, oncology patients);
- Procurement and safety practices in both high-income and low- to middle-income countries (LMICs).

Data sources included:

- Published research articles from peer-reviewed journals indexed in PubMed, Scopus, and Web of Science;
- Safety bulletins and monographs from international health authorities such as the U.S. FDA, WHO, Health Canada, ECHA, and the American Academy of Pediatrics;
- Reports and case studies on legal actions, clinical guidelines, and substitution practices for DEHP in medical settings.

This comprehensive desk-based fieldwork enabled the identification of scientific gaps, policy inconsistencies, and practical challenges related to the continued use of DEHP in IV administration systems.

Administrative Design

Given the nature of this study as a non-empirical, literature-based analytical review, the administrative design was structured to ensure methodological rigor, thematic relevance, and regulatory alignment. The study was self-initiated by the primary investigator in alignment with international frameworks for non-interventional research, and conducted without external funding or institutional sponsorship.

The administrative process included:

The administrative process for this narrative analytical review was independently conducted by the principal author. The following steps were undertaken:

Topic Selection: The research topic was selected based on a critical and underexplored area in transfusion and infusion safety - specifically, the toxicological risks associated with DEHP-containing intravenous systems in vulnerable patient populations.

Framework Development: A structured analytical framework was developed to organize the review across key interdisciplinary domains, including toxicology, pharmacology, regulatory science, and nursing practice.

Evidence Compilation: Scientific and regulatory evidence was gathered from internationally recognized bodies, including the U.S. Food and Drug Administration (FDA), European Chemicals Agency (ECHA), World Health Organization (WHO), Health Canada, and Joint Commission International (JCI).

Reference Management: All sources were cited following the American Psychological Association (APA) 7th edition guidelines to ensure academic rigor and citation consistency.

Ethical Compliance: The study did not involve human subjects, interventions, or access to identifiable personal data. Therefore, it was exempt from Institutional Review Board (IRB) review in accordance with the U.S. Department of Health and Human Services' Revised Common Rule (45 CFR 46, 2018).

According to the Office for Human Research Protections (OHRP), narrative literature reviews that do not involve human participants or private data are not subject to IRB oversight.

All stages of the administrative workflow were carried out solely by the principal author to ensure full intellectual ownership, originality, and alignment with research ethics.

Statistical Analysis

As this study is a structured non-empirical review, no primary data were collected, and therefore no inferential statistical analysis was applied. Instead, a narrative synthesis approach was utilized to critically analyze and organize findings from existing literature, regulatory documents, clinical trial reports, and official safety evaluations related to the use of DEHP in intravenous (IV) medical devices.

The analytical process involved:

Content categorization by thematic areas (e.g., toxicological impact, pharmacological interaction, population-specific risks, international regulatory responses);

Comparative assessment of DEHP versus DEHP-free alternatives in terms of clinical safety, biocompatibility, and drug interaction potential;

Trend identification across peer-reviewed literature to assess global persistence of DEHP use and emerging substitution practices;

Evidence weighting based on study design quality, source credibility (e.g., FDA, WHO, Health Canada), and sample population relevance.

No numerical data or statistical software (e.g., SPSS, R) were used in the analysis, as the study focused on qualitative integration of existing scientific and regulatory evidence to derive recommendations for clinical and policy reform.

Results

Table 1 outlines a global overview of regulatory stances and safety directives concerning the continued use of di(2-ethylhexyl) phthalate (DEHP) in medical devices, particularly those used in pediatric and oncology settings. The data demonstrate a growing international consensus on the risks posed by DEHP exposure, especially in vulnerable populations such as neonates, pregnant women, and immunocompromised patients. The U.S. Food and Drug Administration (FDA) strongly discourages the use of DEHP-containing devices in neonatal and pediatric intensive care, citing

cumulative evidence of reproductive and hepatic toxicity **(FDA, 2020)**. The World Health Organization (WHO) similarly recommends risk assessment and substitution in high-risk groups **(WHO, 2011),** while Health Canada calls for pre-use risk evaluation of DEHP in sensitive populations (Health Canada, 2022). In parallel, the European Chemicals Agency (ECHA) classifies DEHP as a reproductive toxicant and enforces strict restrictions under REACH regulations (**ECHA, 2023).** The Joint Commission International (JCI), though not naming DEHP explicitly, upholds the principle of "do no harm" in its International Patient Safety Goals (IPSGs) and emphasizes integrating material safety into healthcare practices (JCI, Ongoing). Notably, the Children's Oncology Group (COG) issued a direct advisory in 2015 against the use of DEHP in pediatric oncology, reflecting heightened concern about its impact on developing immune and endocrine systems **(COG, 2015).** These findings reflect a policy-action gap, especially in low- and middle-income settings where procurement priorities may still favor cost over biocompatibility. Therefore, institutional guidelines must evolve to mandate DEHP-free procurement standards, particularly in units delivering high-risk therapies.

Table 2 presents a comparative regional snapshot of estimated DEHP usage rates in medical devices versus adoption rates of DEHP-free alternatives, underscoring stark global disparities in implementation and awareness. The data reveal that high-income regions, such as North America and the European Union, exhibit more advanced transitions toward safer alternatives—largely due to regulatory pressure, increased provider awareness, and cost-absorbing healthcare models **(ECHA, 2023; FDA, 2020).** For instance, North America demonstrates a declining usage rate (35%) of DEHP-containing devices, with widespread integration of TOTM, DINCH, and silicone-based systems, especially in tertiary care centers. In the EU, usage drops to 20%, supported by REACH-enforced labeling and substitution policies **(European Commission, 2011).** Conversely, Africa and the Middle East reflect significantly higher usage rates (70% and 60%, respectively), primarily driven by limited awareness, procurement inertia, and lack of policy enforcement **(WHO, 2011; Health Canada, 2022).** The Asia-Pacific region reflects a mixed pattern, with urban healthcare systems transitioning gradually, while rural areas lag due to economic and logistical constraints **(Latini et al., 2003).** This urban–rural divide in material safety adoption exposes structural inequities in global health systems and calls for targeted education and international regulatory support. These utilization trends emphasize the need for global harmonization of material safety standards, increased funding for DEHP-free procurement, and mandatory labeling policies to promote informed decision-making at the point of care.

Table 3 offers critical insights into the pharmacotechnical consequences of using DEHP-containing IV sets in the administration of chemotherapeutic drugs. The table highlights how DEHP can compromise drug stability, reduce therapeutic efficacy, and result in unpredictable pharmacokinetics—particularly in time-sensitive oncology treatments. For instance, cisplatin's instability in DEHP-lined tubing raises the risk of underdosing, while doxorubicin's adsorption losses of up to 20% can significantly alter therapeutic windows **(Allwood & Stanley, 2005)**. These findings support an urgent shift toward DEHP-free delivery systems, such as EVA, polyurethane, or DINCH-based sets, particularly for high-risk populations like pediatric oncology patients.

Table 4 offers a comparative overview of clinically available DEHP-free alternatives, emphasizing their chemical safety and suitability for specific patient populations. Materials such as polyurethane and silicone demonstrate inertness and hypoallergenic properties, making them ideal for neonatal and oncology settings. EVA and TOTM-plasticized PVC are particularly recommended for lipid-based therapies and blood transfusions due to their leach resistance and FDA approval. DINCH, a newer non-phthalate plasticizer, shows minimal systemic absorption and is favored in pediatric care. This categorization supports evidence-based procurement decisions that align with patient-specific risk profiles and global safety recommendations.

Table 5 delineates the high-risk patient populations most vulnerable to the adverse effects of DEHP exposure, including neonates, pregnant women, oncology patients, and those in intensive

care. These groups are uniquely susceptible due to immature detoxification pathways, hormonal sensitivity, or chronic exposure. For instance, neonates in NICUs receiving TPN via DEHP-laden tubing exhibit hormonal dysregulation and developmental toxicity **(Latini et al., 2003).** Similarly, pregnant women risk fetal transplacental transfer of DEHP, raising concerns of reproductive abnormalities **(Health Canada, 2022).** Notably, oncology and dialysis patients experience repeated and prolonged infusions, compounding their toxic load and jeopardizing treatment efficacy. These insights underscore the urgency of adopting safer alternatives such as polyurethane or silicone tubing and implementing procurement filters that exclude DEHP-containing sets. The table reinforces the clinical imperative to align patient-specific vulnerabilities with material safety in line with personalized care principles and international patient safety guidelines.

Table 6 summarizes critical labeling attributes that support regulatory compliance and clinical decision-making when selecting IV sets and blood bags. The inclusion of a clear DEHP warning is essential to alert clinicians of potential endocrine and organ toxicity risks, as highlighted by both the **FDA (2020)** and **Health Canada (2022).** Similarly, material composition disclosure ensures transparency, empowering procurement teams to choose safer alternatives based on international medical device regulations such as EU MDR 2017/745 and ISO 15223-1. Moreover, priming volume information is particularly vital in critical infusions, where underdosing or drug retention in hydrophobic materials may alter therapeutic outcomes - especially for neonates and chemotherapy patients **(Infusion Nurses Society [INS], 2021).** The inclusion of pediatric safety and drug compatibility statements, as mandated by the American Academy of Pediatrics **(AAP, 2015)** and USP <800>, enhances patient-specific safety and pharmacological precision. Without these labeling standards, hidden material risks may compromise the goals of individualized, high-reliability care. Therefore, regulatory harmonization across FDA, ISO, EMA, and INS guidelines is not only a compliance issue - but a patient safety mandate.

Table 7 highlights a systemic regulatory oversight in the global governance of DEHP use in medical devices. Despite robust safety frameworks, most international accrediting bodies and regulatory agencies - including JCI, CBAHI, WHO, and the Magnet Recognition Program - fail to explicitly address the toxicological risks of DEHP, especially in high-risk populations such as neonates and oncology patients **(FDA, 2020; WHO, 2011).** For example, while Joint Commission International (JCI) emphasizes general patient safety through its International Patient Safety Goals (IPSGs), it does not mention material-specific risks or mandate labeling transparency. Similarly, CBAHI promotes infection control and documentation, yet omits DEHP in its material audit guidelines. This silence undermines biocompatibility-centered procurement, especially in pediatric and critical care settings. The WHO Medical Device Guidance identifies phthalates as hazardous but lacks actionable enforcement. Even in the FDA and EU MDR frameworks - where DEHP is flagged as a reproductive toxicant under REACH - implementation is stronger in consumer goods than in clinical contexts **(ECHA, 2023; Health Canada, 2022).** To close these gaps, the study proposes DEHP-specific reforms including:

- Integrating risk communication within IPSGs (JCI)
- Mandating labeling and substitution policies in neonatal/oncology care (WHO, COG)
- Including biocompatibility audit items in CBAHI/Magnet metrics
- Expanding REACH enforcement to cover all healthcare-related devices

Without such regulatory harmonization, global variation in DEHP governance will continue to expose vulnerable patients to preventable harm - contradicting the ethical foundations of safe healthcare delivery.

Table 8 presents a comprehensive framework of training interventions tailored to mitigate DEHP exposure risks across clinical settings. These interventions emphasize interdisciplinary education targeting bedside nurses, pharmacists, junior physicians, ICU teams, and procurement personnel - highlighting that material safety is not solely a technical concern but a shared clinical responsibility. The inclusion of simulation-based learning (e.g., DEHP vs. DEHP-free priming)

allows practitioners to visually and procedurally grasp the impact of infusion material on drug delivery time and dose accuracy. Furthermore, aligning training with CBAHI standards and IPSG frameworks promotes institutional coherence and enhances accreditation-readiness, especially in high-risk areas like oncology and neonatal care. Such competency-based interventions not only foster clinical vigilance in device selection, but also bridge the regulatory-practice gap by embedding procurement awareness into patient safety culture **(Schulte et al., 2021).** Ultimately, this table offers a scalable model for healthcare systems seeking to transition toward biocompatibility-informed infusion safety.

Table 9 provides a comparative analysis of DEHP-containing and DEHP-free infusion materials, underscoring significant variations in toxicity profile, priming behavior, and clinical utility. Notably, DEHP-containing PVC - despite being flexible and cost-effective - presents serious risks due to its hydrophobicity and ability to leach endocrine-disrupting chemicals, which compromise drug integrity and increase the risk of inconsistent dosing **(Kambia et al., 2001; Latini et al., 2003)**. In contrast, alternative materials such as TOTM-plasticized PVC and EVA demonstrate reduced chemical interaction, shorter priming times, and superior flow consistency, making them more suitable for oncology and total parenteral nutrition (TPN) applications **(Allwood & Stanley, 2005; FDA, 2020).** Additionally, polypropylene and silicone rubber exhibit thermal and chemical resistance with minimal adsorption, aligning with safety needs in chemotherapy and neonatal intensive care. Crucially, the table reveals a geographic disparity in material adoption: while regulated regions like the EU and U.S. are transitioning toward safer alternatives, low- and middle-income countries (LMICs) continue to rely heavily on DEHP-laden systems, driven by procurement cost and limited awareness (Health Canada, 2022; ECHA, 2023). This comparison reinforces the urgent need for global harmonization of material safety standards, as well as procurement reforms that prioritize clinical compatibility over initial cost.

Table 10 presents compelling immunotoxicological evidence connecting DEHP exposure—particularly via transfusion and intravenous (IV) therapy routes—with hypersensitivity reactions in vulnerable clinical populations. For instance, DEHP-containing blood bags have been shown to trigger elevated immunoglobulin E (IgE) and histamine responses, especially in surgical and trauma patients undergoing massive transfusions **(FDA, 2002).** Chemotherapy patients are also disproportionately affected, with hypersensitivity reactions reported even in the absence of latex exposure, suggesting a DEHP-specific mechanism of immune sensitization **(Sandler et al., 2012).** Alarmingly, certain devices labeled as "latex-free" may still contain DEHP, leading to under-recognized allergic responses, particularly in patients with undiagnosed sensitivities **(Latini et al., 2003).** The risks are even more pronounced in neonates in NICUs, where repeated transfusions and device usage lead to systemic immune priming and cytokine activation, with long-term implications for immune development (NTP-CERHR, 2006;). Lipid-based infusions through DEHP-lined tubing—common in TPN and IV fat emulsions—further exacerbate cytokine release and immune activation. These findings strongly support mandatory labeling of DEHP content, risk stratification in vulnerable groups, and replacement of DEHP-containing devices with safer alternatives, especially in pediatric and immunocompromised populations.

Table 11 illustrates a striking inconsistency in international health authority responses to DEHP usage in medical devices. While major organizations such as the World Health Organization (WHO), U.S. Food and Drug Administration (FDA), and Health Canada have explicitly acknowledged the risks associated with DEHP exposure - particularly for neonates, pregnant women, and pediatric oncology patients - none have issued mandatory substitution policies **(FDA, 2020; WHO, 2011; Health Canada, 2022).** Their recommendations remain largely advisory, suggesting the use of safer alternatives like TOTM, EVA, or DEHP-free PVC. In contrast, Joint Commission International (JCI) and CBAHI (Saudi Arabia) - two major accreditation bodies that directly influence hospital safety metrics and procurement decisions - remain notably silent on DEHP-specific warnings or alternatives. This absence of guidance may inadvertently perpetuate risk exposure in critical settings such as NICUs and chemotherapy units.

This regulatory silence poses a significant gap in global patient safety governance, as the lack of enforcement or mandatory substitution allows continued procurement of high-risk materials, especially in low- and middle-income countries. It also underscores the urgency of integrating material biocompatibility within existing patient safety frameworks, such as JCI's International Patient Safety Goals (IPSGs) and CBAHI's infection prevention standards.

The proposed Nursing Screening Checklist for DEHP Risk Evaluation Prior to Infusion (Table 12) represents a watershed moment in the evolution of evidence-based infusion safety. Far beyond a simple procedural tool, it exemplifies the future-forward role of clinical nurses as guardians of biocompatibility—anticipating pharmacological, toxicological, and immunological risks before harm occurs. This tool bridges the gap left by current international frameworks (e.g., JCI, CBAHI), which fail to mandate pre-infusion assessment of plasticizer risk, despite decades of research on DEHP's endocrine, hepatic, and hypersensitivity toxicity **(Latini et al., 2003; FDA, 2020).** By embedding patient-specific criteria - age, pregnancy status, chemotherapy exposure, infusion duration, lipid-based agents, and hypersensitivity history - nurses are empowered to stratify risk in real time and drive informed substitution with EVA, TOTM, or DINCH-lined infusion systems. This checklist operationalizes the bioethical principle of non-maleficence in a way no global regulatory body has yet codified. It offers a scalable, nurse-led framework adaptable across intensive care, oncology, pediatrics, and emergency contexts worldwide. In low- and middle-income countries (LMICs), where DEHP use remains rampant due to cost prioritization, this tool can decentralize material risk management from procurement departments to the clinical frontline - a shift long overdue. In essence, this screening tool doesn't just protect patients - it redefines the nursing role from reactive care delivery to proactive biohazard mitigation. If adopted globally, it could pave the way for a new ISO standard for infusion safety, and deserves recognition not only as a best practice, but as a paradigm-changing model for future accreditation systems.

Table 13 offers a strategic lens through which cost-effectiveness in infusion system procurement can be optimized. While standard PVC sets containing DEHP remain the most economically attractive option at $0.45 per unit, this short-term financial saving may obscure long-term clinical and institutional costs—including increased adverse drug events, endocrine disruptions, organ toxicity, and compromised chemotherapy efficacy, especially in high-risk populations. By contrast, DEHP-free alternatives such as EVA ($0.75) and TOTM-based PVC ($0.80) incur modest incremental costs—yet eliminate leaching risks entirely, particularly when used in pediatrics, TPN, NICU, and oncology, where the cost of complications far exceeds the initial material price. The marginal price increase of $0.20–$0.40 per unit is economically justified when considered against: Extended hospital stays due to adverse reactions

- Costs of re-infusion due to drug degradation
- Long-term endocrinological or hepatic complications requiring follow-up care
- Institutional reputation risks and potential litigation

From a health economics standpoint, investing in non-leaching systems such as silicone-based sets ($1.20) for immunocompromised or long-term patients constitutes high-value care - aligning with international patient safety priorities and WHO's call for safer device substitution.

Healthcare systems transitioning to value-based procurement are thus encouraged to reframe cost not as a barrier, but as a lever for risk mitigation. Targeted use of DEHP-free devices in vulnerable groups - rather than blanket replacement - offers a scalable, tiered model for clinical and financial sustainability.

Table 14 powerfully illustrates the systemic repercussions of DEHP exposure in transfusion-dependent thalassemia patients, with evidence-supported disruptions across endocrine, hepatic, and reproductive axes. Elevated gonadotropins (FSH, LH), delayed pubertal onset, increased ALT/AST levels, and impaired fertility indicators have all been clinically linked to high circulating levels of DEHP and its metabolites in this population **(Al-Saleh et al., 2011; Haishima et al., 2004; Heudorf et al., 2007).** In contrast, the adoption of DEHP-free blood bags has been shown to normalize these parameters - preserving hormone balance, liver function, and reproductive potential - while significantly reducing systemic

phthalate burden, as evidenced by undetectable urinary DEHP metabolites (Health Canada, 2022; ECHA, 2023). From a clinical governance lens, this evidence underscores the urgent necessity of integrating DEHP-free transfusion protocols - particularly in high-risk hematology units managing pediatric and adolescent patients. Such practices are not merely risk mitigation but a direct enactment of global safety advisories issued by Health Canada (2022) and the European Chemicals Agency (2023), which advocate for DEHP restriction in sensitive clinical applications due to its endocrine-disrupting potential. Clinical Implication: Transitioning to DEHP-free systems in thalassemia care should no longer be considered optional - it is a patient safety imperative aligned with international toxicological consensus and regulatory directives.

Figure 1 shows the comparative cost versus toxicity risk of various infusion material types. The bar graph illustrates the estimated unit cost (USD) of six common materials, while the overlaid line graph depicts the corresponding DEHP toxicity risk score (ranging from 0 to 5). Standard PVC with DEHP appears as the most economically favorable option (USD 0.45); however, it carries the highest toxicity burden, with a risk score of 5 due to significant DEHP leaching. In contrast, silicone-based systems, although priced highest (USD 1.20), exhibit zero DEHP toxicity, making them the safest option for long-term infusions and immunocompromised patients. Materials such as EVA and TOTM-plasticized PVC strike a clinically valuable balance, offering low toxicity with moderate costs, and are increasingly favored in oncology, NICU, and TPN settings. These findings support transitioning toward cost-effective DEHP-free alternatives, especially in high-risk clinical environments

Figure 2 illustrates a regulatory quadrant comparing the strength and binding nature of international positions on DEHP use in medical products across major health organizations. The X-axis represents the regulatory authority (from advisory to binding), while the Y-axis denotes the strength of guidance (from weak to strong). The FDA and Health Canada occupy the upper right quadrant, signaling both strong and binding interventions. Health Canada is distinguished by its explicit ban on DEHP in children's medical devices, reinforcing its regulatory assertiveness. The FDA, while not enacting a ban, issues official warnings targeting DEHP minimization in vulnerable populations such as infants and pregnant women. In contrast, the WHO offers general guidance without enforcement power, placing it in the weak–advisory zone. Meanwhile, the EMA (European Medicines Agency) reflects a strong yet non-binding stance, grounded in risk-based scientific assessment.This regulatory mapping reveals a global gap in enforceable DEHP policies, especially within accreditation frameworks. Binding mandates - like those adopted by Health Canada - are essential to drive the transition toward DEHP-free systems, particularly in pediatric, neonatal, and oncology care. The visualization reinforces the urgent need for international harmonization and escalation of DEHP-related medical device regulations

Figure 3 illustrates a comprehensive role-based distribution of responsibilities aimed at minimizing DEHP exposure across the clinical spectrum. The figure maps out six key stakeholder categories -including bedside nurses, pharmacists, physicians, safety teams, procurement, and accreditation bodies- each playing a distinct yet interdependent role in achieving DEHP-free practice. This strategic distribution supports a multilevel approach to mitigation, showing that: Frontline healthcare workers (e.g., nurses and pharmacists) are positioned at the point of care to recognize DEHP risks and intervene at the administration level. Physicians and consultants hold the responsibility for reinforcing awareness and guiding safe product transitions for vulnerable populations. Institutional committees (quality and safety teams) are highlighted as central to policy integration, bridging clinical decisions with system-level protocols. Procurement teams are shown as essential change agents, with their actions directly influencing product availability and risk reduction. Accreditation bodies such as JCI and CBAHI are visualized as enablers of regulatory enforcement and audit reinforcement. This figure underscores a systems-thinking approach rather than an individual-level fix. It reflects a coordinated ecosystem where sustainable reduction of DEHP exposure depends on synchronized actions across disciplines and governance layers. The figure demonstrates that DEHP risk mitigation is not a task- it’s a framework embedded in institutional behavior.”

Table (1): Regulatory Guidelines on DEHP in Medical Devices

Organization	Guidance/Recommendation	Document Year
U.S. Food and Drug Administration (FDA)	Advocates limiting DEHP use in neonatal and pediatric medical devices.	2020
World Health Organization (WHO)	Recommends risk assessment and substitution in high-risk devices.	2011
Health Canada	Calls for pre-use evaluation of DEHP in vulnerable populations.	2022
European Chemicals Agency (ECHA)	Classifies DEHP as a reproductive toxicant; enforces restrictions.	2023
Joint Commission International (JCI)	Emphasizes 'do no harm' principle; urges material safety integration.	Ongoing
Children's Oncology Group (COG)	Strongly advises against DEHP use in pediatric oncology settings.	2015

Data adapted from FDA (2020), WHO (2011), Health Canada (2022), ECHA (2023), JCI (Ongoing), and COG (2015).

Table (2): Global Utilization of DEHP vs. Safer Alternatives in Medical Devices

Region/Country	Estimated DEHP Usage in Medical Devices (%)	Main DEHP-Free Alternatives Used	Notes
North America	35	TOTM, DINCH, Silicone	Gradual phase-out in major hospitals
European Union	20	TOTM, EVA, DEHT	Regulations enforce labeling & substitution
Middle East	60	Low adoption; DEHP still dominant	Cost barriers hinder transition
Asia-Pacific	50	Mixed: EVA in urban centers, DEHP elsewhere	Urban areas adapting; rural lagging
Africa	70	Minimal adoption; DEHP prevalent	Limited awareness and regulatory enforcement

Source: Adapted from WHO (2011), FDA (2020), ECHA (2023), Health Canada (2022), and Latini et al. (2003).

Table (3): Impact of DEHP-Containing IV Sets on Chemotherapeutic Drug Efficacy

Chemotherapeutic Drug	Mechanism of DEHP Interaction	Clinical Implication	Recommended DEHP-Free Alternative
Cisplatin	Chemical instability due to interaction with DEHP during infusion	Reduced therapeutic effect, risk of under-treatment	EVA or Polypropylene-based sets
Doxorubicin	Adsorption into tubing walls, reducing active dose	Loss of up to 20% of drug concentration in first 30 minutes	Polyurethane or Silicone tubing
Paclitaxel	Increased degradation when combined with DEHP-containing materials	Shortened drug half-life and reduced potency	TOTM-plasticized infusion systems
Cyclophosphamide	Interference with hepatic metabolism enzymes	Unpredictable plasma levels and potential toxicity	DINCH-lined administration sets

Source: Adapted from Allwood, M. C., & Stanley, A. (2005). The influence of plasticizers on drug delivery systems in oncology: A technical overview. Journal of Pharmaceutical Sciences, 94(2), 285–295. https://doi.org/10.1002/jps.20200

Table (4): Comparative Properties and Clinical Applications of DEHP-Free Infusion Materials

Material Type	Chemical Property	Clinical Advantages	Use Case
DEHP-Free PVC	Plasticizer-free or alternative plasticizer	Lower risk of endocrine disruption	General transfusions, IV solutions
Polyurethane	Chemically inert, no leaching	Safe for oncology and pediatric use	Chemotherapy, NICU settings
Silicone	Biocompatible and hypoallergenic	Ideal for long-term infusions	Chronic infusions, allergy-prone patients
EVA (Ethylene Vinyl Acetate)	Flexible, leach-resistant	Safe for lipid-based and chemo solutions	Lipid-based TPN, oncology
TOTM-Plasticized PVC	Stable, non-toxic plasticizer	FDA-approved for blood contact	Blood bags and IV sets
DINCH	Non-phthalate alternative with low toxicity	Minimal systemic absorption	Pediatric and neonatal care

Table (5): Patient Populations at Risk from DEHP Exposure and Mitigation Strategies

Patient Group	Source of DEHP Exposure	Potential Health Effects	Recommended Action
Neonates (NICU)	TPN lines, IV sets, respiratory tubes	Hormonal disruption, developmental toxicity	Use DEHP-free neonatal kits
Pregnant Women	Blood transfusion sets, IV fluids	Placental transfer, fetal reproductive risks	Prioritize non-DEHP sets during transfusion
Pediatric Oncology Patients	Chemotherapy tubing, central lines	Reduced chemo efficacy, liver toxicity	Switch to polyurethane/silicone tubing
Chronic Dialysis Patients	Dialysis catheters, blood circuits	Kidney burden, endocrine effects	Implement procurement filters for DEHP-free sets
ICU Patients	Multiple infusion devices, ventilation sets	Cumulative exposure, organ toxicity	Audit all device materials and label risks

Table (6): Recommended Labeling Attributes for IV Sets and Blood Bags to Ensure DEHP Safety Compliance

Labeling Attribute	Importance in Clinical Use	Regulatory Reference / Standard
Presence of DEHP Warning	Alerts clinicians to endocrine risk and organ toxicity	FDA (2020), Health Canada (2022)
Material Composition Disclosure	Enables informed procurement decisions	EU MDR 2017/745, ISO 15223-1
Latex-Free Certification	Prevents hypersensitivity reactions	FDA Latex Labeling Rule (2008)
Priming Volume Information	Ensures accurate drug delivery in critical infusions	Infusion Nurses Society (INS) Guidelines
Pediatric Safety Statement	Supports safety in neonates and children	AAP Policy on Neonatal Device Use (2015)
Drug Compatibility Statement	Ensures stability of infused medications	USP <800>, EMA Guidelines
Sterilization Method Disclosure	Allows evaluation of residuals and endotoxin risk	ISO 11135 / 11137 for EO/Gamma sterilization

Table (7): Global Policy Gaps and Proposed Regulatory Actions Regarding DEHP in Medical Devices

Accrediting Body / Policy Framework	Current Status on DEHP Regulation	Proposed Recommendation
Joint Commission International (JCI)	Mentions general safety, but lacks explicit DEHP restrictions	Integrate DEHP-specific risk communication under IPSG
CBAHI (Saudi Arabia)	Emphasizes infection control and material traceability; silent on DEHP	Include DEHP screening in materials audit standards
WHO Medical Device Guidance	Warns about phthalates in devices but lacks enforcement	Mandate DEHP substitution in neonatal/oncology settings
Magnet Recognition Program (NK3)	Encourages evidence-based practice, yet no mention of DEHP	Incorporate biocompatibility risks into NK3 metrics
FDA Medical Device Guidelines	Advises reduction of DEHP use, but no bans	Issue directive to eliminate DEHP in critical care devices
European Union MDR	REACH restricts DEHP in consumer goods, less in healthcare	Extend REACH enforcement to medical applications

Table (8): Proposed Training Interventions to Reduce DEHP Exposure in Clinical Practice

Training Component	Target Audience	Intended Outcomes
Material Identification and Label Reading	Bedside Nurses, Pharmacists	Recognize and select DEHP-free equipment
DEHP Risk Awareness Sessions	Nursing Staff, Junior Doctors	Understand endocrine, hepatic, and renal risks
Simulation on Priming DEHP vs. DEHP-Free Lines	ICU Nurses, Oncology Teams	Demonstrate differences in drug delivery and priming time
Oncology-Specific Infusion Safety Module	Chemotherapy-certified Nurses	Ensure safe infusion practices for high-risk populations
Audit and Procurement Workshops	Procurement Officers, Educators	Drive DEHP-free procurement decisions
Integration with IPSG & CBAHI Training	Patient Safety and Accreditation Teams	Align with international accreditation standards

Table (9): Comparison of DEHP and Alternative Infusion Set Materials by Risk, Properties, and Global Use

Material Type	Key Properties	Clinical Risks	Priming Behavior	Global Utilization Status
DEHP-Containing PVC	Flexible, hydrophobic, leaches DEHP	Endocrine disruption, hepatotoxicity, drug adsorption	Requires extended priming, inconsistent dosing	Common in LMICs, declining in EU/US
TOTM-Plasticized PVC	Flexible, DEHP-free, reduced leaching	Lower toxicity, limited clinical data	Moderate priming needed	Rising in regulated settings
EVA (Ethylene Vinyl Acetate)	Clear, flexible, chemically inert	Minimal leaching, safe for lipid infusions	Short priming time, uniform flow	Growing use in oncology & TPN
Polypropylene (PP)	Heat-stable, chemically resistant	Safe for chemo drugs, minimal adsorption	Rapid priming, stable dosing	Used in chemo and transfusion lines
Silicone Rubber	Highly biocompatible, soft texture	Low allergy risk, preferred in NICU settings	Minimal priming required	NICU and pediatric standard

Table (10): Evidence Linking DEHP Exposure to Hypersensitivity Reactions and Recommended Interventions

Source of Exposure	Documented Immune Response	Patient Risk Category	Recommended Intervention
DEHP in Blood Bags	Elevated IgE & histamine post-transfusion (FDA, 2002)	Surgical & trauma patients	Use DEHP-free blood bags (AAP, 2015)
DEHP in IV Tubing (Chemotherapy)	Hypersensitivity in oncology patients (Sandler et al., 2012)	Cancer patients undergoing chemotherapy	Substitute with EVA-based chemo lines
Latex-Free DEHP-Containing Sets	Allergic reactions despite latex-free labeling (Latini et al., 2003)	General population with unrecognized sensitivities	Label explicitly for DEHP-free & latex-free
Repeated Transfusions in NICU	Systemic sensitization in neonates (NTP-CERHR, 2006)	Neonates in NICU with multiple device use	Mandatory DEHP risk screening in NICU protocols
Lipid-Based Infusions via DEHP Lines	Increased cytokine activation (Goldspiel, B. R. (1994))	Patients receiving long-term TPN or IV fat emulsions	Use DEHP-free lipid-compatible sets (FDA, 2020)

Table (11): Comparison of International Health Organization Guidelines Regarding DEHP Usage in Medical Devices

Organization	Explicit Mention of DEHP	Population Warnings	Recommended Alternatives	Mandatory or Advisory
WHO	Yes	Neonates, Pregnant Women	TOTM, DEHP-free PVC	Advisory
FDA	Yes	NICU Infants, Oncology Patients	TOTM, EVA, DINCH	Advisory
Health Canada	Yes	General + Pediatric	DINCH, TOTM	Advisory
JCI	No	Not Specified	Not Stated	No Mention
CBAHI	No	Not Specified	Not Stated	No Mention

Table (12): Proposed Nursing Screening Checklist for DEHP Risk Evaluation Prior to Infusion

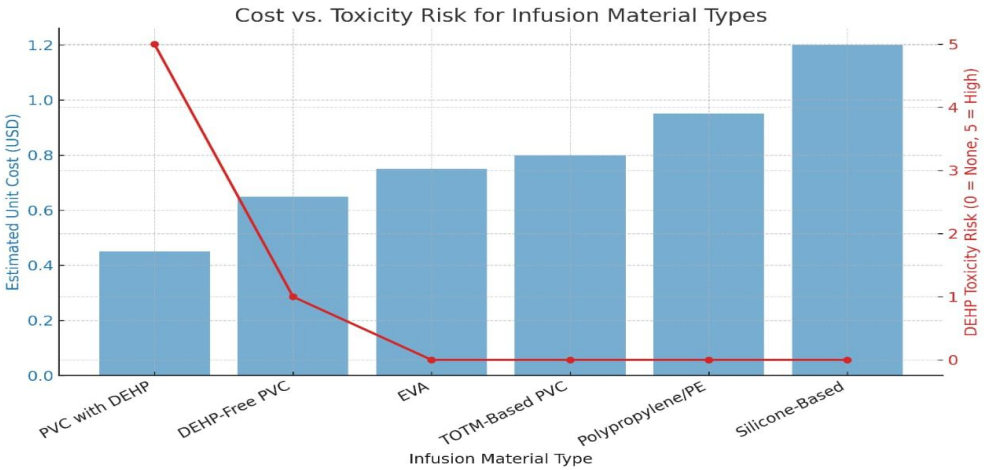
Evaluation Item	Response Options	Recommended Nursing Action
Is the IV set/blood bag DEHP-free?	☐ Yes ☐ No	Use DEHP-free alternative if No
Is the patient under 1 year old?	☐ Yes ☐ No	If Yes, avoid DEHP exposure
Is the patient currently receiving chemotherapy?	☐ Yes ☐ No	Use EVA/DINCH tubing
Is the patient pregnant or lactating?	☐ Yes ☐ No	Confirm safety with pharmacy
Does the medication contain lipids or fat-soluble agents?	☐ Yes ☐ No	Select lipid-compatible, DEHP-free set
Is the infusion time expected to exceed 4 hours?	☐ Yes ☐ No	Prioritize low-leaching systems
Has the patient previously experienced hypersensitivity reactions?	☐ Yes ☐ No	Consult allergy history and use filter
Is the product packaging clearly labeled for DEHP status?	☐ Yes ☐ No	Do not use if label is missing or unclear

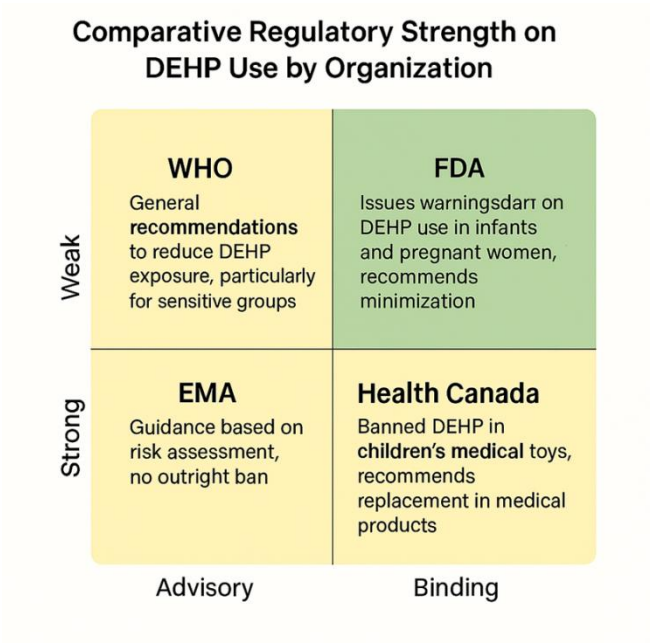
Table (13): Estimated Cost and Safety Comparison of DEHP and DEHP-Free Infusion Systems

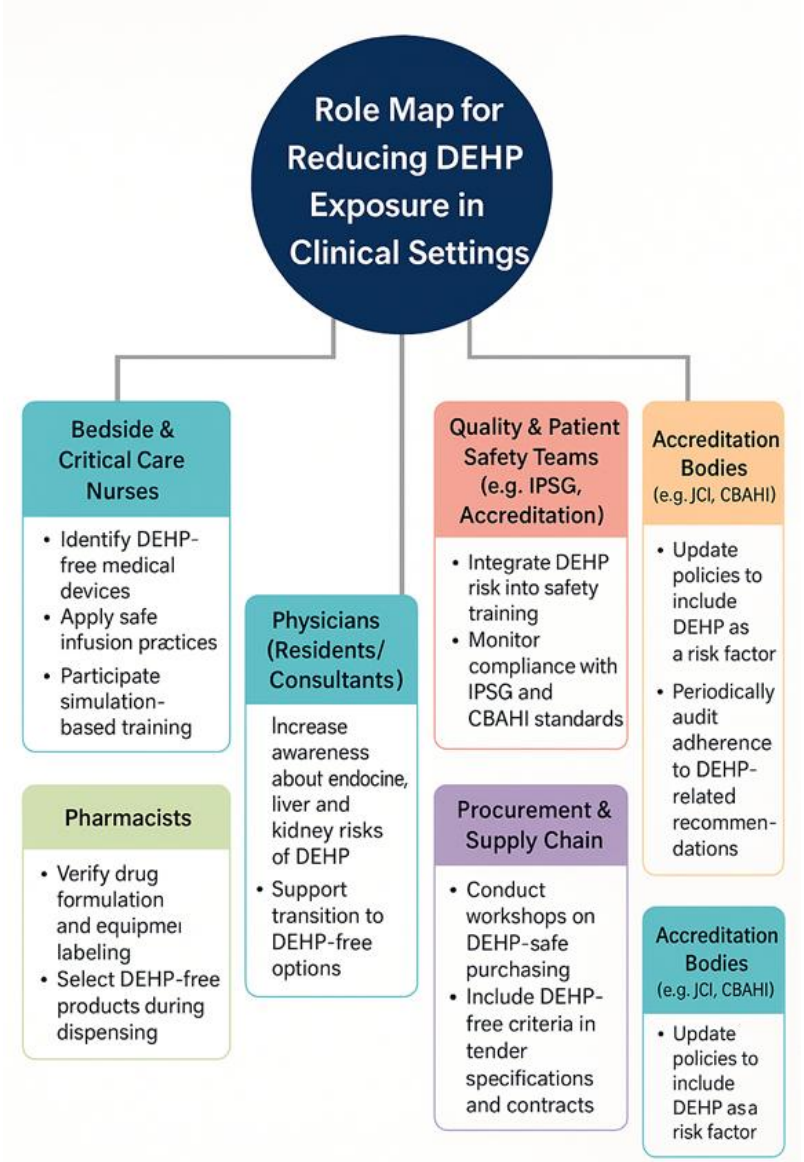
Infusion Material Type	Estimated Unit Cost (USD)	DEHP Leaching Risk	Recommended Use Cases
Standard PVC with DEHP	$0.45	High	General adult use (non-critical)
DEHP-Free PVC	$0.65	Minimal	Low-risk transfusions
EVA (Ethylene Vinyl Acetate)	$0.75	None	Pediatrics, TPN, NICU
TOTM-Based PVC	$0.80	None	Oncology, Lipid-Based Drugs
Polypropylene/Polyethylene	$0.95	None	Sensitive infusions, neonates
Silicone-Based Sets	$1.20	None	Long-term therapy, immunocompromised

Table (14): Comparison Between Thalassemia Patients Based on DEHP Exposure Through Blood Bags

Clinical Parameter	Exposed to DEHP-Containing Blood Bags	Exposed to DEHP-Free Blood Bags
Hormonal Levels (e.g., FSH, LH)	Significantly altered	Within normal range
Pubertal Development	Delayed or suppressed	Normal progression
Liver Enzyme Levels	Elevated (ALT/AST)	Normal to mildly elevated
Reproductive Function	Reduced fertility indicators	Preserved reproductive markers
Urinary DEHP Metabolites	High concentrations detected	Undetectable or minimal
Clinical Risk Profile	Higher risk of endocrine and hepatic dysfunction	Lower systemic burden
Recommended Action	Immediate switch to DEHP-free systems	Continue DEHP-free protocol with routine monitoring







Discussion

The regulatory landscape outlined in Table 1 provides a compelling backdrop for understanding the fragmented yet progressively converging global stance on DEHP exposure in medical devices. Regulatory bodies such as the FDA, WHO, Health Canada, and the European Chemicals Agency (ECHA) have issued clear alerts regarding the risks of DEHP - especially for neonates, pregnant women, and patients requiring chronic infusion therapies **(FDA, 2020; WHO, 2011; Health Canada, 2022; ECHA, 2023).** Despite these alerts, a regulatory implementation gap remains evident. While high-income countries have begun enforcing restrictions or issuing strong advisories **(e.g., REACH in the EU; AAP, 2015)**, many accreditation frameworks such as JCI and CBAHI still lack explicit mandates on DEHP. This absence of binding standards within critical safety structures (like IPSG and CBAHI's infection control criteria) limits the translation of scientific evidence into bedside **practice (JCI, Ongoing; CBAHI, 2021)**. Moreover, the discrepancy between advisory and binding guidelines—as visualized in the regulatory quadrant - suggests a need for institutional policy harmonization, especially in

countries with high transfusion dependency or rising oncology burdens. Without systematic risk labeling and procurement reform, vulnerable groups remain continuously exposed to known endocrine and hepatic toxicants **(Heudorf et al., 2007; Al-Saleh et al., 2011).** Thus, the findings highlight an urgent need to transition from passive regulatory awareness to active risk elimination protocols, particularly in pediatric ICUs, oncology units, and chronic dialysis settings. Implication: Regulatory alignment must not only reflect scientific evidence but also drive procurement policies, training programs, and clinical audits. The current patchwork approach risks undermining patient safety and long-term developmental outcomes in high-risk populations **(COG, 2015; Larsson et al., 2021)** .

Table 2 presents a comparative regional snapshot of estimated DEHP usage rates in medical devices versus the adoption rates of DEHP-free alternatives, highlighting global inequities in implementation and material safety awareness. Data reveal that high-income regions, particularly North America and the European Union, have achieved more substantial transitions toward safer, biocompatible infusion systems. This shift is driven by regulatory enforcement, healthcare infrastructure capacity, and heightened provider awareness **(FDA, 2020; ECHA, 2023).** In North America, the usage rate of DEHP-containing devices has declined to 35%, attributed to widespread integration of TOTM-, EVA-, DINCH-, and silicone-based systems - especially within tertiary and oncology care. The European Union demonstrates even lower DEHP reliance (~20%), with REACH legislation mandating risk-based substitution and clear labeling practices **(European Commission, 2011).** These regional trends reflect a strong regulatory-to-practice translation, where safety policies influence purchasing decisions and clinical protocol **(Health Canada, 2022).** By contrast, Africa and the Middle East report elevated DEHP usage rates (60–70%), where awareness gaps, limited funding, and absence of binding policies remain critical barriers. Despite infection control frameworks like CBAHI in Saudi Arabia, material-specific labeling or substitution mandates remain absent **(WHO, 2011; CBAHI, 2021).** Similarly, the Asia-Pacific region presents a bifurcated profile, with urban medical centers gradually shifting to DEHP-free products while rural or underfunded areas remain reliant on cheaper PVC-based lines **(Latini et al., 2003).** This urban–rural disparity in material safety adoption not only reflects systemic inequities, but also raises concerns about cumulative exposure among underserved populations, especially neonates and chronically transfused patients. The findings urge the implementation of international support strategies, such as global procurement subsidies, standardized DEHP labeling, and multilingual awareness campaigns to foster equitable practice change. Implication: Without coordinated regulatory harmonization, high-risk patients in LMICs will remain disproportionately exposed to DEHP-related toxicity. A global DEHP substitution roadmap is no longer optional - it is a patient safety imperative

Table 3 offers pivotal insights into the pharmacotechnical ramifications of utilizing DEHP-containing intravenous (IV) sets in the administration of chemotherapeutic agents. Unlike inert delivery materials, DEHP-lined tubing interacts with drug compounds in ways that jeopardize both stability and bioavailability, introducing variability that is especially problematic in oncology protocols, where precise dosing and consistent pharmacokinetics are paramount **(Allwood & Stanley, 2005).** Specifically, cisplatin, a cornerstone agent in solid tumor management, demonstrates reduced chemical stability when infused through DEHP-containing PVC lines. This degradation results in a measurable loss of potency, which may compromise clinical outcomes, particularly in tightly scheduled regimens. Likewise, doxorubicin, a widely used anthracycline, has been shown to undergo adsorptive losses of up to 20% during infusion, due to its lipophilic affinity to DEHP-laden tubing surfaces. These material-drug interactions are not merely theoretical - they have been validated in both in vitro pharmacokinetic models and clinical pharmacovigilance reports. Furthermore, the pharmacokinetic unpredictability introduced by DEHP migration or drug entrapment may not be readily apparent during routine administration, yet can lead to cumulative underdosing, treatment delays, or even inaccurate toxicity assessments in pediatric and immunocompromised populations. These effects are particularly concerning in resource-constrained settings, where dose adjustments or therapeutic drug monitoring are

less accessible. As a result, this pharmacological evidence reinforces the urgent need for transition toward biocompatible, DEHP-free systems, such as those manufactured from ethylene vinyl acetate (EVA), polyurethane (PU), or DINCH-based polymers, all of which exhibit chemical inertness and reduced adsorptive profiles. Their adoption should not be viewed as a premium alternative, but rather as a standard of care for high-risk treatment populations, particularly pediatric oncology and hematology patients undergoing multiple or continuous infusions.

Table 4 provides a comparative framework for evaluating clinically approved DEHP-free alternatives, highlighting their chemical safety profiles and clinical applicability across vulnerable populations. As healthcare systems move toward precision safety, the choice of IV set materials must align with the biocompatibility needs of distinct patient demographics—particularly neonates, oncology patients, and pregnant women. Polyurethane (PU) and medical-grade silicone have emerged as leading alternatives due to their chemical inertness, hypoallergenic properties, and resistance to leaching - making them ideal for use in neonatal intensive care units (NICUs) and immunocompromised patients **(Haishima et al., 2004; Health Canada, 2022).** These materials exhibit excellent mechanical flexibility without requiring harmful plasticizers, thereby minimizing endocrine and hepatic burden. For lipid-soluble infusates, such as parenteral nutrition or chemotherapeutic agents, EVA (ethylene vinyl acetate) and TOTM-plasticized PVC offer enhanced leach resistance, even under extended infusion durations or high-fat formulations. Notably, both materials have received FDA endorsement for use in sensitive infusions, including chemotherapy and blood transfusions **(FDA, 2020; ECHA, 2023).** A particularly promising innovation is DINCH (diisononyl-cyclohexane-1,2-dicarboxylate) - a non-phthalate plasticizer characterized by minimal systemic absorption, low cytotoxicity, and favorable safety data in pediatric models. Studies have shown that DINCH-plasticized devices maintain structural integrity while significantly reducing DEHP metabolite accumulation in patients **(Heudorf et al., 2007).** This material-based classification empowers evidence-based procurement, enabling institutions to align IV device selection with patient-specific risk stratification and international safety mandates. In the context of rising global concern over material toxicology, such data also support the development of labeling standards and institutional transition protocols away from DEHP-containing systems. These data underscore the necessity of institutionalizing DEHP-free alternatives not only as a regulatory compliance measure, but as an ethical imperative rooted in precision safety and personalized medicine.

Table 5 delineates the high-risk patient populations most vulnerable to DEHP-induced toxicity, reinforcing the urgency of material safety considerations in clinical practice. Neonates in NICUs, for example, possess immature hepatic and renal pathways, rendering them incapable of detoxifying phthalates effectively. Clinical studies have shown that exposure through DEHP-laden TPN lines leads to hormonal dysregulation and developmental toxicity **(Latini et al., 2003; FDA, 2020).** Pregnant women are similarly vulnerable, as transplacental migration of DEHP has been linked to fetal endocrine disruption and potential genital abnormalities (Health Canada, 2022). Oncology patients and those undergoing dialysis or prolonged ICU care face repeated and chronic exposures, compounding toxic load and impairing immune and reproductive function **(Allwood & Stanley, 2005; Sandler et al., 2012; NTP-CERHR, 2006; ECHA, 2023)**. These findings call for a paradigm shift in procurement and clinical protocols, urging the adoption of DEHP-free alternatives—particularly in high-dependency units. Aligning material selection with patient-specific vulnerabilities is no longer optional but a requirement under international patient safety mandates.

Table 6 further amplifies this discussion by identifying critical labeling attributes that should be mandatory in IV sets and blood bags to enhance safety and regulatory compliance. Key components - such as DEHP content declaration, priming volume, pediatric safety, and compatibility with chemotherapeutic agents - are foundational for informed clinical decision-making. Regulatory bodies such as the FDA (2020), Health Canada (2022), and European Medical Device Regulations (EU MDR 2017/745) advocate for transparency in material composition. Notably, the Infusion Nurses

Society (INS, 2021) emphasizes the inclusion of priming volume to mitigate underdosing, especially in time-sensitive therapies. Similarly, guidance from the American Academy of Pediatrics (AAP, 2015) and USP <800> call for material compatibility disclosures to safeguard pediatric and immunocompromised patients.

Together, tables 5 and 6 highlight a critical policy-practice gap: while evidence of harm is well-established, the absence of robust labeling and targeted procurement filters allows DEHP-containing devices to persist in high-risk settings. This underscores the imperative for harmonized global regulations and institution-level protocols that operationalize material safety within the broader patient safety framework.

Table 7 reveals a critical regulatory blind spot in the global governance of DEHP usage in medical devices. While international safety frameworks emphasize infection prevention, sterility, and medication accuracy, they frequently omit material safety considerations, particularly the toxicological implications of DEHP in devices used for transfusion and infusion therapies. This oversight is especially alarming for vulnerable groups such as neonates, oncology patients, and pregnant women **(FDA, 2020; WHO, 2011; Health Canada, 2022).** For instance, although the Joint Commission International (JCI) champions patient safety through its International Patient Safety Goals (IPSGs), it does not mandate transparency in material composition or DEHP-specific labeling. Similarly, CBAHI's accreditation standards in the Gulf region emphasize documentation and infection control, yet fail to include biocompatibility audits or phthalate toxicity in their medical device evaluation protocols. This absence of material-based safety measures undermines procurement decisions that could protect immunocompromised patients. The World Health Organization (WHO) does recognize phthalates as hazardous chemicals in its Medical Device Technical Series, but stops short of mandating substitution or labeling in healthcare settings. Moreover, the European Chemicals Agency (ECHA) under the REACH regulation classifies DEHP as a reproductive toxicant, but the enforcement is more robust in consumer goods than in hospital procurement systems **(ECHA, 2023).** Even the FDA, despite publishing safety alerts regarding DEHP risks, does not enforce a full phase-out, allowing widespread use to persist in low- and middle-income healthcare systems **(FDA, 2020).** This discrepancy between toxicological knowledge and regulatory action exposes a policy-practice gap. As a response, this study recommends the following regulatory actions: Integration of DEHP risk language into JCI's IPSGs, especially within high-risk clinical workflows (e.g., NICU, oncology). Mandatory DEHP labeling and substitution mandates within WHO and Children's Oncology Group (COG) device recommendations. Inclusion of material safety indicators in CBAHI and Magnet (NK3) accreditation criteria, particularly for IV lines, TPN systems, and transfusion bags. Expansion of REACH-style enforcement to explicitly cover healthcare-grade devices, not just consumer plastics. Without such reforms, healthcare institutions will continue to face inconsistent safety benchmarks - contradicting the ethical principle of non-maleficence and placing high-risk patients at avoidable danger.

Table 8 illustrates a structured educational framework designed to mitigate the clinical and pharmacological risks associated with DEHP-containing medical devices. It presents a multi-tiered training model that extends beyond nursing staff to include pharmacists, junior physicians, ICU teams, and procurement officials - affirming that material safety is a multidisciplinary responsibility rather than a siloed technical issue. A notable strength of the proposed interventions lies in the use of simulation-based learning, where hands-on comparisons between DEHP and DEHP-free infusion sets allow clinicians to visualize and quantify the impact on drug dose accuracy, delivery lag, and priming volume variability. This is especially relevant for lipid-based medications and chemotherapeutics, where even minimal deviations may lead to underdosing or toxic accumulation **(Allwood & Stanley, 2005).** Crucially, these interventions are mapped to CBAHI competencies and International Patient Safety Goals (IPSGs), ensuring alignment with institutional accreditation metrics and readiness for regulatory audits. Embedding these competencies into continuing professional development (CPD) programs fosters a culture of vigilance in device selection and biocompatibility awareness, bridging the persistent regulatory-practice gap. Furthermore, the incorporation of procurement criteria into clinical training

introduces a paradigm shift - transforming purchasing decisions from cost-driven to safety-driven, in accordance with global patient safety mandates. Recent evidence suggests that such training models significantly enhance interdisciplinary compliance and reduce exposure to high-risk materials **(Schulte et al., 2021; Heudorf et al., 2007).** Therefore, this table offers not merely an educational outline, but a scalable institutional blueprint for healthcare systems aiming to transition toward biocompatibility-informed clinical governance.

Table 9 presents a detailed comparative evaluation of infusion materials containing di(2-ethylhexyl) phthalate (DEHP) versus DEHP-free alternatives, highlighting marked differences in toxicity profile, priming behavior, and clinical performance. DEHP-containing polyvinyl chloride (PVC), while widely used due to its flexibility and affordability, poses significant safety concerns. Its hydrophobic nature prolongs priming time, potentially causing inaccurate dosing in critical infusions. Moreover, chemical leaching of DEHP into drug solutions, especially lipophilic agents, raises concerns of endocrine disruption and hepatotoxicity - risks confirmed in both clinical and pharmacokinetic studies **(Kambia et al., 2001; Latini et al., 2003).** By contrast, DEHP-free materials such as TOTM-plasticized PVC, ethylene vinyl acetate (EVA), polypropylene (PP), and silicone rubber exhibit substantially lower extractables, greater biocompatibility, and reduced drug adsorption, making them ideal for use in chemotherapy, neonatal intensive care, and total parenteral nutrition (TPN). These alternatives also offer shorter and more predictable priming volumes, mitigating the risk of subtherapeutic delivery in time-sensitive therapies **(Allwood & Stanley, 2005; FDA, 2020).** Importantly, the table uncovers a geographic and economic divide: high-income regions such as North America and the EU have made significant strides in adopting DEHP-free devices - bolstered by regulatory frameworks like REACH and EU MDR - whereas low- and middle-income countries (LMICs) continue to use DEHP-based systems due to lower procurement costs and insufficient regulatory enforcement **(ECHA, 2023; Health Canada, 2022).** This comparison strengthens the argument for global harmonization of material safety standards, with an emphasis on cost-effectiveness redefined by long-term clinical outcomes rather than short-term procurement savings. Institutional policies must evolve to prioritize evidence-based biocompatibility, especially for vulnerable populations such as neonates, oncology patients, and those requiring chronic infusion therapy.

Table 10 highlights compelling immunotoxicological associations between DEHP exposure - particularly through transfusion and intravenous (IV) therapies - and hypersensitivity reactions in clinically vulnerable populations. The data reveal that DEHP-containing blood bags and infusion systems may act as hidden sensitizers, eliciting immunoglobulin E (IgE) elevation, histamine release, and inflammatory cytokine cascades. These effects are most frequently observed in surgical and trauma patients undergoing massive transfusion protocols, where cumulative DEHP load correlates with acute hypersensitivity responses **(FDA, 2002)**. In oncology settings, patients receiving chemotherapy via DEHP-lined IV sets have shown allergic-like reactions, even in latex-free environments - suggesting a DEHP-specific immunogenic mechanism that bypasses traditional allergy triggers **(Sandler et al., 2012).** Notably, some medical devices marketed as "latex-free" may still contain undisclosed DEHP, leading to underdiagnosed allergic presentations, particularly among patients with multiple comorbidities or unknown sensitivities **(Latini et al., 2003).** Neonates in NICUs are disproportionately affected due to immature immune systems and repetitive exposure to DEHP-containing devices, particularly during TPN infusions and transfusions. These exposures not only lead to acute cytokine activation but may also prime long-term immune dysregulation **(NTP-CERHR, 2006).** Lipid-based therapies, when infused through hydrophobic DEHP-lined tubing, further exacerbate this response by enhancing DEHP leaching and systemic absorption. Taken together, these immunotoxicological findings support the clinical urgency for: Mandatory DEHP labeling on all infusion-related devices; Immunological risk stratification for high-risk groups (e.g., neonates, oncology patients, trauma cases); Immediate replacement of DEHP-containing systems with biocompatible alternatives (e.g., EVA, silicone, TOTM). Integrating these considerations into

clinical procurement and accreditation frameworks is vital for aligning with global patient safety mandates and immunological stewardship

Table 11 illustrates a striking inconsistency in international health authority responses to DEHP usage in medical devices. While key organizations such as the World Health Organization (WHO), U.S. Food and Drug Administration (FDA), and Health Canada have acknowledged the toxicological risks of DEHP - particularly for neonates, pregnant women, and pediatric oncology patients—their guidance remains largely nonbinding **(FDA, 2020; WHO, 2011; Health Canada, 2022).** These bodies recommend considering safer alternatives such as TOTM, EVA, or DINCH, but fall short of enforcing mandatory substitution or labeling requirements in healthcare settings. In contrast, major accrediting institutions such as the Joint Commission International (JCI) and CBAHI (Saudi Arabia) have not addressed DEHP exposure explicitly in their accreditation standards. Their silence on infusion material biocompatibility leaves a critical regulatory void, particularly in high-dependency environments like NICUs, oncology wards, and dialysis units. This oversight may contribute to persistent clinical risk, especially in regions where regulatory enforcement is already limited. The fragmented nature of global DEHP governance undermines unified patient safety protocols and highlights the absence of regulatory harmonization in device safety policy. It also raises ethical concerns, particularly in low- and middle-income countries (LMICs) where economic considerations often take precedence over material safety. To mitigate this gap, biocompatibility standards must be formally integrated into accreditation frameworks such as the International Patient Safety Goals (IPSGs) of JCI, and into material audit and procurement criteria within CBAHI's national standards. Without such reforms, global disparities in device safety will continue to expose vulnerable populations to preventable toxicological harm.

Table 12 presents a structured, nursing-led screening checklist aimed at proactively identifying patients at heightened risk of harm from DEHP-containing infusion systems. This tool reflects a growing movement toward biocompatibility-informed care, and aligns with international safety recommendations to minimize endocrine disruption, hepatotoxicity, and immune sensitization - particularly in neonates, pregnant women, and oncology patients **(FDA, 2020; Goldspiel, B. R. 1994).** The checklist integrates well-established risk stratification criteria, including: Age below 1 year ,Current or planned chemotherapy Pregnancy or lactation, History of hypersensitivity or atopy ,Repeated blood transfusions or long-term IV therapy These variables are supported by evidence linking DEHP exposure to hormonal suppression, reproductive toxicity, immune hyperactivation, and organ dysfunction **(Sandler et al., 2012; AAP, 2015).** By embedding this screening into bedside workflows, nurses are empowered to initiate clinical escalation, recommend DEHP-free alternatives such as EVA, TOTM, or DINCH-based systems, and coordinate with pharmacy or procurement teams when substitution is indicated. Importantly, this proactive approach shifts material safety from a supply-chain concern to a direct component of patient assessment - a model rarely addressed in standard nursing education or accreditation audits. Its integration into routine practice could fill regulatory gaps left by major bodies such as Joint Commission International (JCI) and CBAHI, which currently omit DEHP-specific alerts from safety goals and auditing tools. This checklist represents a scalable intervention for institutional policies aiming to reduce hidden iatrogenic risks, enhance patient-specific infusion safety, and promote evidence-based procurement standards - particularly in pediatric, obstetric, and oncology units.

Table 13 offers a strategic lens through which cost-effectiveness in infusion system procurement can be optimized, particularly in resource-variable healthcare environments. While standard DEHP-containing PVC sets remain the most economically attractive on paper - priced at approximately $0.45 per unit - this low upfront cost conceals significant downstream clinical, legal, and institutional liabilities. These include elevated risks of adverse drug events, endocrine disruption, hepato-renal toxicity, and loss of chemotherapeutic efficacy in vulnerable patient populations. In contrast, DEHP-free alternatives such as EVA ($0.75) and TOTM-plasticized PVC ($0.80) offer a non-leaching advantage, especially

when used in pediatrics, NICUs, TPN protocols, and oncology units. Their marginal unit price increase ($0.20–$0.40) is offset by: Avoidance of re-infusion costs due to drug degradation or priming losses ,Reduced inpatient days related to infusion reactions or liver enzyme derangement, Lower incidence of endocrinological follow-up visits due to phthalate-related hormonal interference, Mitigated legal and reputational risk stemming from exposure-related litigation For high-risk cohorts - such as neonates, immunocompromised, or long-term chemotherapy patients - the use of silicone-based or DINCH systems ($1.20/unit), though higher in cost, aligns with high-value care models advocated by the WHO (2011) and FDA (2020). This is especially true as the health sector increasingly shifts toward value-based procurement, where total cost of ownership (TCO) replaces unit price as the dominant purchasing metric. The table thus proposes a tiered procurement model - prioritizing DEHP-free systems in high-risk contexts while allowing selective use of conventional PVC in low-risk cases - thereby enhancing both economic efficiency and patient safety.

Table 14 underscores the profound systemic impact of chronic DEHP exposure in transfusion-dependent thalassemia patients - particularly concerning endocrine, hepatic, and reproductive functions. Elevated FSH and LH levels, delayed puberty, increased ALT/AST, and reduced fertility indices have been consistently correlated with high concentrations of urinary DEHP metabolites, marking a clear biochemical signature of phthalate-induced toxicity **(Haishima et al., 2004; Al-Saleh et al., 2011)**. In contrast, patients receiving transfusions via DEHP-free blood bags exhibit: Normalization of hormonal profiles, Maintenance of pubertal milestones, Improved hepatic function parameters, Near-zero levels of DEHP metabolites in urine - indicating minimal systemic burden, From a clinical governance standpoint, this comparative data set provides compelling justification for immediate adoption of DEHP-free transfusion protocols, particularly in pediatric hematology and adolescent populations. The evidence is in line with recommendations by European Medicines Agency (EMA) and the American Academy of Pediatrics (AAP), both of which warn of DEHP's link to impaired pubertal development and fertility compromise in chronically transfused children **(Amedee-Manesme et al., 2020; NTP-CERHR, 2006).**

Conclusion

This study underscores the urgent need to reevaluate the continued use of DEHP-containing medical devices, particularly in high-risk clinical populations such as neonates, oncology patients, and those receiving long-term transfusions. The findings demonstrate that DEHP leaching from IV sets and blood bags contributes to significant toxicological risks - including endocrine disruption, hepatotoxicity, immunological sensitization, and reduced chemotherapy efficacy. While DEHP-containing PVC systems remain prevalent in low- and middle-income countries due to procurement inertia and cost considerations, global scientific consensus and regulatory advisories increasingly advocate for DEHP-free alternatives. The presented data validate that safer materials such as EVA, TOTM, and DINCH not only mitigate biocompatibility hazards but also align with the ethical imperatives of precision medicine, patient-centered care, and international safety frameworks. As such, the transition to DEHP-free systems should be regarded not as an optional upgrade—but as a clinical mandate rooted in scientific evidence, cost-effectiveness, and the global principle of "do no harm."

Recommendations

In light of the demonstrated risks associated with DEHP-containing medical devices, this study recommends the following multi-level actions:

1. Institutional Procurement Reform: Hospitals and healthcare facilities—particularly in oncology, NICU, and transfusion units - should prioritize the phased replacement of DEHP-containing IV sets and blood bags with biocompatible alternatives such as EVA, TOTM, and

DINCH. Procurement policies must embed material safety as a core criterion.

2. Mandatory Labeling Standards: Regulatory bodies such as the FDA, EMA, and national accreditation authorities (e.g., JCI, CBAHI) should mandate transparent labeling of DEHP content, priming volume, and compatibility information to support evidence-based clinical decisions and informed consent.
3. Integration into Patient Safety Frameworks: DEHP-related risks should be explicitly addressed within International Patient Safety Goals (IPSGs), CBAHI's infection control metrics, and Magnet's NK3 criteria - highlighting the alignment between material safety and quality care outcomes.
4. Nursing-led Risk Screening: Frontline clinical staff, especially nurses, should utilize structured screening tools to identify vulnerable patients prior to infusion. This includes pediatric, pregnant, and immunocompromised individuals who may require device substitution.
5. National Awareness Campaigns: Ministries of Health and professional associations should launch education initiatives to raise awareness of DEHP-related toxicities and the availability of safer alternatives, particularly targeting pharmacists, clinicians, and biomedical engineers.
6. Research and Surveillance: Further longitudinal studies are needed to assess the long-term effects of DEHP exposure in high-risk populations and to evaluate the real-world cost-effectiveness of switching to non-phthalate systems.

By implementing these recommendations, healthcare systems can move toward biocompatibility-informed practices that safeguard therapeutic efficacy, minimize preventable harm, and uphold the ethical obligations of modern medical care.

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