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Systematic Review

Exposure to Carcinogenic, Mutagenic, and Reprotoxic Chemical Agents in Research Laboratories and the Healthcare Sector: A Systematic Review

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Abstract

Background: Carcinogenic, Mutagenic, and Reprotoxic (CMR) substances are among the most significant occupational health hazards in healthcare and research laboratories. Despite preventive measures and regulations, exposure assessment and risk management remain complex due to varied working practices, mixed exposures, and the lack of harmonized monitoring protocols. This systematic review investigates occupational exposure to CMR substances in laboratory and healthcare environments. **Methods:** Searches were conducted in PubMed, Scopus, and Web of Science up to February 2025 using tailored keyword strategies. Studies published between 2020 and 2025 reporting exposure assessment, monitoring, and/or risk management of CMR chemicals were included; non-English papers and irrelevant studies were excluded. Titles/abstracts and full texts were screened independently by two reviewers with arbitration by a third. Risk of bias was assessed by three authors who independently evaluated each study. A narrative synthesis with frequency tables was performed; no meta-analysis was conducted. **Results:** Of 446 screened records, 50 studies were included. Formaldehyde (25 studies) and antineoplastic drugs (18 studies) were most frequently examined. Healthcare settings—e.g., hospital pharmacies, oncology wards, and pathology laboratories—were predominant, while research laboratories were underrepresented. Inhalation was the main exposure route for formaldehyde, whereas dermal uptake and surface contamination predominated for antineoplastic drugs. Monitoring methods included air sampling, surface wipe testing, and biological assays; preventive strategies varied and were inconsistently applied. Most included studies involved environmental monitoring and did not report participant numbers, so a total number of participants cannot be aggregated; for the main outcomes, participant counts were often not available. Limitations of the evidence include marked heterogeneity across settings, matrices, analytical methods, and reporting units, which precluded meta-analysis, as well as imprecision and incomplete reporting in several studies. **Conclusions:** Findings reveal persistent gaps in harmonized exposure limits, monitoring standards, and long-term health

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surveillance, underscoring the need for comprehensive prevention strategies. This review was not registered and did not receive any external funding.

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1. Introduction

Carcinogenic, mutagenic, and reprotoxic (CMR) substances represent the most hazardous category of toxic chemicals under the European Union (EU) legislation. Carcinogens are linked to cancer development, mutagens can alter genetic material with potential heritability, and reprotoxic chemicals may impair fertility or fetal development. Due to their severe health effects, even minimal exposure levels can pose significant risks, with no universally safe threshold for most CMRs [1]. In occupational environments, CMR substances may be present as reagents, solvents, intermediates, or final products. Exposure routes include inhalation—typically the primary pathway—dermal absorption, and ingestion, depending on the chemical properties and working conditions. This variability complicates risk assessment, necessitating tailored evaluations. The European Directive 2004/37/EC (Carcinogens and Mutagens Directive, CMD) establishes minimum requirements for protecting workers from CMR exposure. Initially covering carcinogens and mutagens, the directive was expanded by Directive (EU) 2022/431 to include reprotoxic substances [2]. It mandates a hierarchy of preventive measures, including substitution, closed systems, and exposure minimization. Employers must implement technical and organizational controls, provide training, and ensure health surveillance, especially when biological limit values are exceeded. Complementing the CMD, the "Classification, Labelling and Packaging" (CLP) Regulation (EC 1272/2008) harmonizes classification, labeling, and packaging of hazardous substances across the EU, adopting the Globally Harmonized System (GHS). The CLP Regulation ensures consistent hazard communication and risk management, particularly for CMRs, through standardized pictograms, precautionary statements, and packaging requirements [3]. Despite the presence of established safety protocols, the assessment of occupational exposure to CMR substances in research laboratories and healthcare settings remains a complex task. This complexity is due to several factors, such as the variability of working procedures, the presence of mixed or intermittent exposures, and the lack of harmonized monitoring practices. For instance, antineoplastic drugs—many of which are CMRs—are frequently handled by healthcare workers, who may still be exposed to these chemicals even when control measures are in place. This is shown by quantifiable concentrations of such hazardous drugs on workplace surfaces and in biological samples collected from exposed personnel [4]. This study aims to conduct a systematic review of the scientific literature on occupational exposure to carcinogenic, mutagenic, and reprotoxic substances in healthcare settings and research laboratories. In this review, we considered two main types of laboratory environments: clinical laboratories within healthcare facilities (such as pathology and anatomy units and hospital pharmacies) and research laboratories in academic and non-academic institutions. Although these workplaces differ in their organizational and regulatory frameworks, they share core features: the handling of relatively small quantities of hazardous and CMR-classified chemicals under controlled laboratory conditions, the use of similar engineering controls and local exhaust devices, and highly standardized workflows. Accordingly, this review focuses on 'laboratory-type' healthcare and research environments that present comparable patterns of CMR use and

potential exposure. In line with the laboratory-type environments considered, we describe exposure scenarios, routes, and monitoring approaches for CMR substances and provide an overview of the main strategies currently adopted for the prevention and protection of workers exposed to these agents.

2. Materials and Methods

This systematic review is based on a selection of scientific articles gathered from three databases: Scopus, PubMed and Web of Science. Specific keyword combinations were used for each database to target studies related to our topic (Table S1; Supplementary Materials); the last search was completed on 6 February 2025. Specific search queries were tailored for each database to identify relevant studies published since 2020 concerning occupational exposure to CMR agents in healthcare and research laboratory settings. Studies were included if they: (i) reported original data on occupational exposure, risk assessment, or management of CMR substances; (ii) focused on healthcare or research laboratory settings; and (iii) were published in English in peer-reviewed journals. Exclusion criteria were non-English papers, book chapters, and studies with insufficient relevance. A total of 446 articles were initially found across all databases (Scopus: 187, PubMed: 64, Web of Science: 195). After checking for duplicates, a total of 137 articles were removed. The remaining articles (n = 309) underwent a two-step screening process based on (i) title (219 articles excluded) and (ii) abstract (30 articles excluded). At the end of the selection process, the remaining articles (n = 60) were read in full text. Ten of them were excluded: one because it was written in French, one because it was part of a book, and eight due to insufficient relevance to the topic (Figure S1, Supplementary Materials). Titles/abstracts and full texts were screened independently by two reviewers with arbitration by a third; no automation tools were used. Risk of bias was assessed by three authors who independently evaluated each study. In the end, a total of 50 articles were included in this study; the analysis of the selected articles focused on the typology of CMR chemicals, scenarios, exposure routes, monitoring (environmental and biological), and risk management measures. Two reviewers independently extracted data using a piloted form. Extracted items included CMR agent(s); setting (e.g., hospital pharmacy, oncology ward, pathology/anatomy laboratory, research laboratory); study design; exposure route(s); monitoring approach (environmental, surface, and/or biological); sampling and analytical methods (including matrix, device, analytical technique); units and reported statistics; LOD/LOQ; reference values (OELs/BLVs); risk management measures (engineering controls, administrative controls, PPE); and participant numbers where applicable. Discrepancies were resolved by consensus or, if needed, by a third reviewer. No automation tools were used, and study authors were not contacted for additional information. Primary outcomes were: (i) type of CMR agent; (ii) occupational exposure routes; (iii) quantitative exposure metrics from environmental, surface, and/or biological monitoring; (iv) occurrence of exceedances against applicable occupational exposure limits (OELs) or biological limit values (BLVs); and (v) presence and typology of risk management measures (engineering controls, administrative controls, personal protective equipment, cleaning and decontamination procedures, and health surveillance). Secondary outcomes included country/region and setting; sampling and analytical techniques; LOD/LOQ; and study design. We sought all compatible results for each outcome across included studies. We also collected the study year(s), monitoring matrix (air, surface, biological), sampled area/volume where reported, PPE and engineering/administrative controls, and the specific OELs/BLVs referenced. For values reported as "<LOD/<LOQ", we recorded them qualitatively and did not impute numerical values. When units differed across studies, harmonization procedures are described below. When participant numbers were not applicable (e.g., environmental or surface monitoring only) or not reported, this

was recorded as "not available". No effect measures were planned. Given the heterogeneity in settings, agents, matrices, units, and analytical methods, no effect measures were planned, and no meta-analysis was feasible. We performed a narrative synthesis with frequency tables. Studies were grouped a priori by agent (e.g., formaldehyde, antineoplastic drugs), setting (healthcare vs. research sub-settings), exposure route (inhalation, dermal/hand-to-mouth), and monitoring technique (environmental air sampling, surface wipe testing, biological monitoring). Allocation rules were defined before synthesis; studies could contribute to multiple groups if relevant. Where necessary, units were harmonized for qualitative comparison (e.g., ng/cm^2 to µg/m^2 for surface contamination; ng/m^3 to ppm for formaldehyde using standard conversion at reported temperature/pressure when available). Values reported as "<LOD" or "<LOQ" were retained as such and treated qualitatively; no quantitative imputation was performed. Because of inconsistent statistics across studies (e.g., ranges vs. means/medians), we did not compute pooled estimates. Study identification, selection, and reporting followed the PRISMA guidelines [5]. We did not formally assess publication or selective-reporting bias because no statistical syntheses were performed and the required assumptions would not be met. No formal quantitative analyses of heterogeneity were planned. We qualitatively compared results across settings, countries/regions, monitoring matrices, and analytical methods. No sensitivity analyses were planned or conducted. We did not apply formal certainty grading due to the descriptive nature of the evidence and the absence of statistical synthesis.

3. Results

This systematic review included 50 studies [6–55] published between 2020 and February 2025 that investigated occupational exposure to CMR substances in healthcare and research laboratory settings. Results are presented in six subsections. Section 3.1 introduces the typology of CMR agents considered in the selected studies. Section 3.2 summarizes the occupational scenarios, including setting and geographical distribution. Section 3.3 focuses on exposure routes and methods for exposure characterization. Section 3.4 reviews environmental and biological monitoring practices. Preventive measures and corrective strategies are examined in Section 3.5, which synthesizes the risk management approaches described in the included studies. Section 4 provides an overall discussion, addressing strengths, limitations, and implications for occupational health practice. No sensitivity analyses were conducted. No statistical syntheses (meta-analyses) were performed due to substantial methodological and reporting heterogeneity. Qualitatively, exposure levels and detection frequencies varied by setting (e.g., higher formaldehyde in pathology/anatomy areas vs. other clinical labs), monitoring approach (air vs. surface vs. biological), and country/analytical method (differences in LOD/LOQ and units). These differences limited cross-study comparability. Potential publication or selective-reporting biases could not be assessed in the absence of statistical synthesis. Overall, risk of bias was generally low, with occasional concerns related to measurement methods (heterogeneous sampling/analytics) and incomplete reporting of LOD/LOQ and other design elements. Environmental and surface monitoring reports were more likely to lack participant information, while several studies documented methods comprehensively. We did not apply formal certainty grading due to the descriptive, heterogeneous evidence base. Quantitative results at the individual-study level are not tabulated due to substantial heterogeneity in reporting formats (e.g., ranges vs. means/medians, incompatible units, and non-comparable LOD/LOQ thresholds) and because many included articles focus on environmental/surface monitoring without participants. These features precluded a meaningful like-for-like display and would risk misinterpretation. Accordingly, we provide a structured narrative synthesis by

agent, setting, exposure route, and monitoring technique, highlighting recurring patterns and outliers where consistently reported.

3.1. Typology of CMR Substances

Because this review was not restricted to a specific geographical area, the original studies relied on different carcinogenic classification systems (e.g., CLP/GHS, IARC, or national lists). We therefore did not reclassify agents against a single scheme a priori (such as Regulation (EC) No. 1272/2008). Instead, we retained the CMR status as reported in each article and subsequently grouped substances into four broad categories (formaldehyde, antineoplastic drugs, other specified CMR chemicals, and unspecified/other CMR chemicals), as presented in Table 1. As reported in Table 1, most of the studies included in this review focused primarily on the exposure to formaldehyde (25 studies), mainly in pathology and anatomy laboratories [7–11,15,17–20,22,23,26,27,30,39,42,44–46,49–51,54,55] and antineoplastic drugs (ANDs) (17 studies) [8,12,15,16,26,27,30,31,33–36,38,40,47,54,55]. Only a limited number of studies addressed other CMR substances (2 studies), including solvents and reagents (e.g., benzene, chloroform, or acrylates) [37,41]. 5 studies fell under the category "Unspecified/Other CMR chemicals", covering anesthetic gases, ethyl methanesulfonate (EMS), or heterogeneous exposures [16,21,40,43,48].

Table 1. Typology of CMR agents investigated across the included studies.

Typology of CMR Agent	References	N Studies
Antineoplastic drugs (general/unspecified)	[12,35,47]	3
Antineoplastic drugs (specified)	[8,15,16,26,27,30,31,33,34,36,38,40,54,55]	14
Formaldehyde	[7–11,15,17–20,22,23,26,27,30,39,42,44–46,49–51,54,55]	25
Other CMR chemicals	[37,41]	2
Unspecified CMR chemicals	[16,21,40,43,48]	5

Specific ANDs were analyzed in 15 studies [6,13,14,24,25,28,29,31–34,36,38,52,53], particularly cyclophosphamide, platinum compounds (cisplatin carboplatin, oxaliplatin), antimetabolites (5-FU, methotrexate, cytarabine, gemcitabine), anthracyclines (doxorubicin, epirubicin), vinca alkaloids (vincristine, vinblastine), and others. General or unspecified ANDs were investigated in 3 studies [12,35,47], often referring to "antineoplastic", "cytotoxic" or "antiblastic" categories without naming any specific compound. This distribution reflects the prominent role that Formaldehyde and ANDs have in healthcare and laboratory contexts.

3.2. Occupational Scenarios

The selected studies were grouped on the basis of the occupational settings and their geographical distribution. Table 2 reports the number of investigations carried out in healthcare environments and research laboratories. Most of the studies (37 out of 50) were conducted in healthcare settings, mainly within hospital pharmacies, oncology wards and pathology departments [6–15,17–19,21,23–29,31–33,35,36,38,40,42,47,49–55]. Approximately one-fifth (10 out of 50) addressed research laboratories, including academic and biomedical facilities [20,22,30,34,37,39,43,44,46,48]. Overall, these findings indicate that exposure assessment and prevention studies are particularly concentrated in hospital-based oncology/pharmacy and pathology/anatomy activities, while research laboratories remain

comparatively less investigated, even though they present similar risks due to mixed and irregular exposures. This imbalance highlights the importance of expanding systematic assessments in research laboratory contexts, where task heterogeneity and non-routine operations can make risk evaluation and monitoring a difficult operation. Beyond those presented, 3 studies did not provide a clear description of the investigated setting [16,41,45]. Regarding geographical coverage, Italy (12 studies) [11,13,17,18,22–24,32,44,45,49,50] and Iran (10 studies) [7,9,19,21,26–28,37,42,46] were the most represented countries. Other contributions came from France (4) [25,36,38,40], Germany (3) [14,29,52], Portugal (3) [51,54,55], and China (3) [8,12,35]. A smaller number of studies originated from Canada [31], Morocco [30], Thailand [16,20], Turkey [43], Denmark [48], Hungary [47], the Netherlands [39], Finland [41] and the USA [34]. Four studies did not clearly report the country of origin [6,10,15,53].

Table 2. Occupational scenarios distribution and counts of studies (N studies) for each type (Healthcare, Research laboratory, Unspecified).

Type of Scenario	References	N Studies
Healthcare laboratory	[6–15,17–19,21,23–29,31–33,35,36,38,40,42,47,49–55]	37
Research laboratory	[20,22,30,34,37,39,43,44,46,48]	10
Not specified/Not reported	[16,41,45]	3

3.3. Exposure Routes

This section presents the exposure routes described in the studies included. Table 3 provides an overview of the main pathways of occupational exposure to CMR substances, including inhalation, dermal absorption, ingestion, surface contamination, and biological uptake. Among the pathways of exposure reported, inhalation represented the most frequently investigated route (19 studies), particularly in relation to formaldehyde and airborne cytotoxic agents [24–27,34,36–42,45,46,49–51,54,55]. Dermal contact was also commonly highlighted (14 studies), often linked to contamination of work surfaces and drug vials in the handling of ANDs [14,24,25,31–34,36,38–41,52,53]. A smaller number of studies (n = 4) mentioned ingestion, usually as an indirect consequence of surface contamination or inadequate handling practices [25,30,31,40]. A substantial proportion of studies did not specify the route of exposure, here categorized as "unspecified", which likely reflects the absence of detailed assessment or a general focus on occupational risk without characterization of specific pathways [6–13,15–23,28,29,35,43,44,47,48]. Overall, the findings suggest that healthcare professionals, particularly pharmacists, nurses and technicians involved in drug preparation and administration, are the most frequently studied groups. Research laboratory staff appear less represented, even though both healthcare and laboratory environments face similar challenges related to mixed or intermittent exposures, which complicate the definition of standard exposure scenarios.

Table 3. Exposure characterization by main routes of exposure and their frequencies in studies.

Assessed Exposure Route	References	Number of Studies (n)
Dermal	[14,24,25,31–34,36,38–41,52,53]	14
Ingestion	[25,30,31,40]	4
Inhalation	[24–27,34,36–42,45,46,49–51,54,55]	19
Not specified/Not reported	[6–13,15–23,28,29,35,43,44,47,48]	24

3.4. Monitoring

For this section, there are two subsections: one covering environmental monitoring (e.g., air sampling, surface wipe testing, environmental contamination surveys) and the other covering methods of biological monitoring (e.g., urinary metabolite analysis, comet assay, micronucleus test).

3.4.1. Environmental Monitoring

Most studies reported at least one method of environmental monitoring (Table 4), adapting to the agents investigated. Air sampling and surface wipe tests were the most frequently reported techniques. Air sampling was applied mainly in studies on formaldehyde in pathology and anatomy laboratories [8,9,11,15,16,20–24,26,27,30,39,42,46,50,54], primarily following established NIOSH protocols (e.g., Methods 3500, 2541, 3800). Some studies involved active sampling using personal pumps connected to solid sorbents coated with 2,4-dinitrophenylhydrazine (DNPH) for efficient aldehyde collection [15,20,23,39], followed by laboratory analysis via High-Performance Liquid Chromatography with ultraviolet detection (HPLC-UV/VIS) or Gas Chromatography. Studies often employed both stationary area sampling (positioned at 1.5 m height in room centers or near specific hazard sources [21] or biological safety cabinets [24]) to assess background room concentration and personal sampling in the breathing zone to estimate individual worker exposure [16,20,39,42,54].

Table 4. Environmental monitoring techniques and their frequencies in studies.

Environmental Monitoring Techniques	References	Number of Studies (*n*)
Air sampling	[8,9,11,15,16,20–24,26,27,30,39,42,46,50,54]	18
Continuous environmental sensors	[49]	1
Other environmental monitoring	[7,14,17,19,31,34,35,37,38,41,44,45,47,48,51,55]	16
Review/multiple methods	[10]	1
Surface wipe sampling	[6,13,25,28,29,32,33,36,40,43,52,53]	12
Not specified/Not reported	[12,18]	2

Surface wipe sampling was common in studies of ANDs in oncology and pharmacy units, where contamination of workbenches and preparation areas was quantified [6,13,25,28,29,32,33,36,40,43,52,53].

A study adopted continuous environmental sensors [49], while another one applied mixed methods [10]. Sixteen studies were grouped under "Other environmental monitoring", which includes heterogeneous approaches, like environmental surveys and laboratory-specific protocols [7,14,17,19,31,34,35,37,38,41,44,45,47,48,51,55]. Three of these studies used real-time equipment, like photoionization detectors, that can show the changes in exposure levels with a one-minute time resolution, capturing short-term peaks during specific tasks [17,19,55].

3.4.2. Biological Monitoring

Biological monitoring was less frequently reported and more heterogeneous than environmental monitoring (Table 5). Urinary metabolite analysis was the most common approach, particularly for cyclophosphamide and other ANDs [25,29,32–35,38,51,53]. This often involved pre- and post-shift sampling [29] or full 24 h collection [32] and was analyzed

with techniques like LC-MS/MS [25,34]. Blood-based biomarkers were applied in six studies [12,18,46,47,50,55], often relying on cytogenetic markers of genotoxicity such as the Cytokinesis-Block Micronucleus (CBMN) assay [12], chromosomal aberrations [50], and the comet assay to measure DNA damage [12,54]. These were often complemented by analysis of genetic susceptibility or immunotoxicity markers [51,54]. Fourteen studies were labeled as "Other biological monitoring", which included broad biomarker panels and exploratory methods [26,27,31,36,37,39–42,44,45,48]. A substantial number of studies (26 out of 50) did not specify biological monitoring, focusing solely on environmental or descriptive risk assessment [6–11,13–17,19–24,28,30,36,37,39–42,49].

Table 5. Biological monitoring methods and their frequencies in studies.

Biological Monitoring Method	References	Number of Studies (*n*)
Blood-based biomarker (genotoxicity)	[12,18,46,47,50,55]	6
Comet assay	[54]	1
Other biological monitoring	[26,27,31,43–45,48,52]	8
Urinary metabolite analysis	[25,29,32–35,38,51,53]	9
Not specified/Not reported	[6–11,13–17,19–24,28,30,36,37,39–42,49]	26

3.5. Risk Management and Corrective Actions

The review identified a wide range of preventive and corrective interventions implemented to reduce occupational exposure to CMR substances in laboratory and healthcare settings (Table 6). Their implementation, however, was often inconsistent across studies, due to heterogeneity across workplace environments, available resources, and national regulatory requirements. Engineering controls were mentioned in 11 studies [6,7,16,20,21,23,39,42,44,46,51]. Concerning formaldehyde, fume hoods, laminar flow devices, and biosafety cabinets were commonly employed in pathology and anatomy laboratories. For ANDs, closed-system drug transfer devices (CSTDs) and isolators were highlighted as effective tools to reduce contamination during preparation and administration. Ventilation systems and local exhaust solutions were also described, but their performance appeared strongly dependent on maintenance and compliance with technical standards. Personal protective equipment (PPE) was mentioned in eight studies [7,16,20,26,34,36,38,52], typically including double gloving, gowns or lab coats, respirators (N95, FFP2/FFP3), and protective eyewear. Despite being the last line of defense in the hierarchy of controls, evidence from several studies suggested inconsistent adherence. Incorrect glove use or limited adoption of respiratory protection was associated with measurable contamination on surfaces and in biological samples, pointing to a lack of implementation. Administrative controls were the most reported interventions (21 studies) [6–11,13,21,25,28,30,31,35–37,40,43,46,49,51,52]. They included the establishment of written standard operating procedures (SOPs), mandatory training programs, routine audits, and structured risk assessment methods such as Failure Mode and Effect Analysis (FMEA) or Failure Mode, Effects and Criticality Analysis (FMECA). These kinds of interventions were primarily reported in studies from Italy, Iran and France, where formaldehyde and ANDs underwent structured risk assessment methods. Cleaning and decontamination measures were reported in six studies [21,24,25,36,50,52]. Wipe-down protocols of work surfaces, disinfection of biological safety cabinets, and management of accidental spills were described. Some studies reported that, even after cleaning, surface

contamination was still present; that indicates variability in effectiveness, often linked to the frequency of procedures, the quality of cleaning products, and the adherence to established protocols. Six studies [6,7,16,26,33,41] referred to occupational exposure limits (OELs) or biological exposure indices (BEIs) as benchmarks for evaluating exposures, most commonly national OELs for formaldehyde (e.g., in Italy and Iran) and BEIs for selected antineoplastic drugs adopted from international guidance. However, the absence of harmonized international thresholds for many CMR agents and the limited number of studies reporting explicit values and jurisdictions constrain cross-country comparability and reduce the effectiveness of these references for risk management. Health surveillance was mentioned in seven studies [16,21,28,32,35,46,51], typically being periodic medical check-ups, occupational health evaluations, and biomonitoring for genotoxic markers in exposed workers. Health surveillance is a great tool for the early detection of health effects, but the variability of practices and the lack of long-term follow-up limit its potential for workers' protection. Overall, the findings confirm the need for a multilayered prevention strategy that combines engineering controls, consistent PPE use, effective administrative frameworks and cleaning protocols, and organized health surveillance. The observed heterogeneity across countries and workplaces further underlines the importance of harmonized guidelines.

Table 6. Risk Management Measures and their frequencies in studies.

Risk Management Category	References	Number of Studies (*n*)
Engineering controls	[6,7,16,20,21,23,39,42,44,46,51]	11
PPE	[7,16,20,26,34,36,38,52]	8
Administrative controls	[6–11,13,21,25,28,30,31,35–37,40,43,46,49,51,52]	21
Cleaning/ Decontamination	[21,24,25,36,40,52]	6
Not specified/Not reported	[6,7,16,26,33,41]	6

4. Discussion

This systematic review synthesized recent evidence on occupational exposure to carcinogenic, mutagenic and reprotoxic chemicals across healthcare and research laboratory environments and highlights both convergences and persistent gaps in exposure assessment and prevention. In line with the study objective, we interpret the exposure and monitoring findings described in Sections 3.1–3.4 in terms of their implications for prevention and protection strategies, which are summarized in Section 3.5 and further elaborated below. The predominance of studies on formaldehyde and antineoplastic drugs confirms that these agents remain priority hazards for laboratory and hospital personnel. Formaldehyde exposure typically occurs via inhalation during tissue fixation and gross dissection, whereas ANDs exposure is frequently mediated by surface contamination and subsequent dermal uptake during drug preparation, transport, administration, and spill management. These exposure patterns, repeatedly observed in the included studies, are consistent with the intrinsic physicochemical properties of the substances and the workflows in which they are used. A first overarching message concerns the imbalance of evidence across settings. Most studies were conducted in hospital-based units (pharmacy compounding services, oncology wards, pathology/anatomy laboratories), whereas research laboratories—despite comparable or greater task variability—remain underrepresented. This skew may relate to stronger regulatory oversight in clinical environments and to the relative ease of defining SOPs compared with academic labs, where non-routine experiments, one-off procedures, and

mixed chemical inventories complicate exposure characterization. Future research should therefore prioritize task-based and scenario-specific assessments in research laboratories, explicitly capturing intermittent, peak, and multi-agent exposures that are insufficiently reflected by time-weighted averages or area sampling alone. Second, our findings emphasize the fragmentation of monitoring approaches. Environmental assessments for formaldehyde commonly use active personal or area sampling with DNPH cartridges analyzed by HPLC-UV, while AND monitoring relies heavily on surface wipe tests and, less frequently, on air sampling in compounding areas. Biological monitoring is heterogeneous: urinary metabolites (e.g., cyclophosphamide) are the most frequent markers for ANDs exposure, while genotoxicity endpoints (micronuclei, comet assay, chromosomal aberrations) are used variably for both formaldehyde and ANDs. The uneven uptake of personal sampling, the variability in wipe sampling protocols (surface area, solvents, recovery corrections), and differences in analytic limits of detection hamper cross-study comparability. There is a clear need to harmonize sampling strategies and reporting standards, including: (i) detailed descriptions of sampling locations and tasks; (ii) standardized wipe templates and extraction procedures; (iii) calibration, recovery, and uncertainty reporting; and (iv) paired environmental–biological measurements to enable exposure–dose inference. Without such harmonization, pooling data across studies to support meta-analyses or benchmark setting will remain challenging. Third, while compliance with the hierarchy of controls is widely advocated, its deployment is inconsistent. Engineering controls (e.g., biological safety cabinets, isolators, CSTDs) are associated with lower measurable contamination, but their real-world effectiveness depends on maintenance, certification, correct airflow patterns, and user behavior. PPE, as the last line of defense, is frequently used suboptimally (e.g., inadequate glove change frequency, skin exposure at wrist/neck, inconsistent respirator use). Administrative measures (SOPs, audits, training, FMEA/FMECA) are prominent in several studies and appear to drive measurable improvement when consistently implemented. However, implementation fidelity is rarely quantified. Future work should adopt implementation science frameworks to measure adoption, fidelity, and sustainability of controls and to identify organizational determinants (leadership, safety culture, staffing, workload) that influence exposure outcomes. A fourth theme concerns exposure metrics and health relevance. For CMRs with no safe threshold, the "As Low As Reasonably Achievable" (ALARA) principle is appropriate, yet prevention still benefits from quantitative targets. For formaldehyde, short-term peak exposures during specific tasks (container opening, tissue trimming, spill response) may drive risk more than full-shift means. For ANDs, low but persistent surface contamination can produce chronic dermal uptake with cumulative dose concerns. Studies rarely report peak characterization, task-specific short-term exposure limits, or dermal flux estimates. Integrating high-resolution task logging with real-time or semi-continuous monitoring (where feasible) and using physiologically based pharmacokinetic modeling for representative markers could improve exposure–dose interpretation and help set task-level control performance indicators. The evidence base for control technologies also warrants nuanced interpretation. While multiple reports suggest CSTDs reduce contamination relative to safe-handling practices alone, head-to-head comparisons differ in design quality, analytic endpoints, and confounder control (e.g., training recency, workload, cleaning frequency). Similarly, ventilation retrofits and enclosure strategies show variable results depending on room pressurization, sash use discipline for chemicals used in fume hoods, and maintenance. We recommend that future evaluations include standardized before–after designs with concurrent controls, blinded laboratory analyses, and cost-effectiveness endpoints relevant to hospital decision-makers (e.g., contamination reductions per euro invested, maintenance burden, device failure rates). Another gap concerns vulnerable worker groups and life-course considerations. Only a minority of studies

explicitly addressed workers of reproductive age, pregnant personnel, or genetic susceptibility, and relatively few incorporated early-effect biomarkers alongside exposure metrics; our recommendations in these areas are therefore framed as priorities for future research and practice rather than as conclusions supported by extensive evidence. Given the reprotoxic properties of several agents and the genotoxicity endpoints measured in some cohorts, there is a rationale to incorporate risk-based job task allocation, enhanced medical surveillance for high-risk groups, and informed consent/communication frameworks aligned with privacy and non-discrimination principles. Longitudinal surveillance—ideally linking exposure metrics, early-effect biomarkers, and clinical outcomes—remains rare but is critical to clarify latency-affected endpoints. From a policy perspective, the recent extension of the EU CMD to include reprotoxic substances underscores the regulatory momentum but also exposes practical challenges: heterogeneous national OELs/BLVs, differing enforcement capacities, and varying resource levels across institutions. Our review supports the development of internationally harmonized technical standards for: (i) environmental and biological monitoring protocols; (ii) validation and Quality Assurance/Quality Control requirements; (iii) minimum performance specifications for engineering controls; and (iv) training with competency assessments. Such standards would facilitate benchmarking, surveillance, and transnational learning. Methodologically, future studies should expand beyond cross-sectional snapshots to adopt study designs enabling causal inference, including stepped-wedge trials of control implementations, repeated-measures biomonitoring across task changes, and interrupted time-series analyses following policy or engineering upgrades. In research labs, task inventories and process maps can guide sampling campaigns toward high-variability, high-uncertainty operations. Moreover, integrative "exposome" approaches—combining targeted assays with non-targeted high-resolution mass spectrometry and multi-omics early-effect markers—could illuminate low-dose, mixture effects typical of laboratory settings. Ethical considerations (e.g., data protection and return of results) will be essential as personal biomonitoring expands. Finally, we note an opportunity for prevention by design. Substitution with less hazardous reagents, adoption of prefilled/closed formaldehyde alternatives for fixation where histological quality permits, automation/robotics for repetitive compounding steps, and ergonomic redesign to minimize splash/aerosol generation can all reduce baseline risk. These interventions should be evaluated alongside behavioral and administrative controls, acknowledging that layered, system-level strategies are most likely to achieve durable risk reduction. In sum, the literature shows progress—especially in the breadth of monitoring tools and in the institutionalization of administrative controls—yet underscores persistent heterogeneity in practice, limited attention to research laboratories, and insufficient longitudinal evidence. Addressing these issues requires coordinated efforts spanning technical standardization, implementation quality, worker engagement, and regulatory alignment. It is worth noting that the review was limited to English-language studies published between 2020 and 2025. No meta-analysis or formal publication-bias assessment was feasible due to heterogeneity and reporting patterns. The review had no registered protocol, which may increase the risk of undocumented methodological changes; however, the main analytical decisions were pre-specified and transparently reported.

5. Conclusions

Occupational exposure to CMR substances remains a salient risk in healthcare and research laboratory environments. Across the evidence reviewed, formaldehyde and ANDs dominate the exposure landscape, with inhalation and dermal pathways, respectively, shaping the principal risk profiles. Environmental and biological monitoring tools are available but heterogeneously applied, and only a subset of studies reports early-effect biomarkers

or explicitly considers vulnerable worker groups. In light of these findings, policy-makers, employers, occupational health professionals, worker representatives, and researchers should prioritize: (i) harmonized protocols for environmental and biological monitoring, including uncertainty reporting and task linkage; (ii) robust implementation of the hierarchy of controls, with engineering solutions supported by maintenance, competency-based training, and audits; (iii) task-based risk management, capturing short-term peaks and dermal pathways; (iv) integrated surveillance that links exposure, early-effect biomarkers, and clinical follow-up, with special attention to vulnerable worker groups; and (v) prevention by design, including substitution, enclosure, and selective automation. Looking ahead, internationally aligned standards and collaborative surveillance networks will be essential to operationalize the ALARA principle for CMRs in real-world laboratories. By combining harmonized monitoring, rigorous evaluation of controls, and sustained workforce engagement, institutions can build resilient systems that consistently reduce exposures, ultimately improving worker health and safety while preserving the quality and continuity of healthcare and research activities.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/hygiene6010013/s1, Table S1. Search queries; Figure S1. Flowchart of the literature search and review process.

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