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Occupational exposure to reproductive toxicant: risk assessment, health surveillance and prevention under Directive (EU) 2022 / 431 and Legislative Decree No. 135 / 2024

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ABSTRACT

This thesis examines the practical implications of recent regulatory reforms on reproductive toxicants for workplace prevention strategies in the European Union, with particular attention to the Italian transposition of Directive (EU) 2022/431 through Legislative Decree No. 135/2024.

The study adopts an interdisciplinary and literature-based methodology integrating legal analysis, occupational health doctrine, toxicological evidence and comparative regulatory models.

The analysis demonstrates that the inclusion of Category 1A and 1B reproductive toxicants within the Carcinogens, Mutagens and Reprotoxicants Directive (CMRD) represents a significant strengthening of the legal architecture of worker protection, marking a transition from a predominantly risk-based approach toward a hazard-oriented and precautionary regulatory model. This shift introduces reinforced obligations for substitution, exposure minimisation, health surveillance and exposure traceability, redefining the standard of care in occupational settings.

However, the findings also show that this regulatory advancement remains only partial. The persistence of a two-tier regulatory structure—whereby suspected reproductive toxicants (Category 2) remain governed by the more flexible framework of Directive 98/24/EC—creates a structural gap that is difficult to reconcile with current scientific evidence.

Reproductive toxicity emerges as a multifactorial, latency-driven and uncertainty-based domain, characterised by low-dose effects, endocrine

disruption, mixture exposure and long-term or transgenerational outcomes, which challenge traditional threshold-based regulatory models.

The study further highlights the limitations of occupational exposure limits as primary tools of protection, as well as the insufficient integration of gender-specific and life-stage vulnerabilities into risk assessment processes.

In this context, effective protection depends not only on formal legal transposition but also on the integration of scientific evidence, institutional capacity and operational risk assessment practices.

Comparative analysis confirms that the practical effectiveness of Directive (EU) 2022/431 varies significantly across Member States, with more advanced systems combining binding exposure limits, technical guidance and precautionary approaches, while the Italian system—although significantly strengthened—remains in a transitional phase of development.

The thesis argues that a further evolution toward an adaptive, science-informed and precautionary regulatory model is required. This includes stronger management of scientific uncertainty, enhanced protection of vulnerable workers, improved integration of biomonitoring and exposome-based approaches, and closer alignment between occupational and environmental exposure assessment.

The study concludes that the effectiveness of Directive (EU) 2022/431 ultimately depends on its operational translation into workplace practice and on the progressive alignment between legal frameworks and evolving toxicological knowledge.

INTRODUCTION

Occupational exposure to hazardous chemicals has long been regulated in European Union law through a dual normative structure.

On the one hand, Council Directive 98/24/EC established the general framework for the assessment and prevention of risks arising from hazardous chemical agents at work¹.

On the other hand, Directive 2004/37/EC introduced a more stringent regime for carcinogens and mutagens, built around the principles of substitution, exposure minimization, health surveillance, and occupational exposure control².

For many years, reproductive toxicants remained outside this stricter framework and were governed, as a rule, by the more flexible logic of the Chemical Agents Directive³.

This asymmetry generated an increasingly problematic regulatory gap, given the seriousness of reproductive and developmental harm and the growing

¹ Directive 98/24/EC of the European Parliament and of the Council of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work

² Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work, as amended.

³ Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding.

body of scientific evidence concerning fertility impairment, pregnancy complications, developmental toxicity, and endocrine disruption⁴⁵⁶.

Directive (EU) 2022/431 represents a decisive turning point in this area.

By amending Directive 2004/37/EC, it extends the stricter CMR regime to reproductive toxicants classified under the CLP Regulation as Category 1A or 1B⁷.

In the Italian legal system, this development was transposed through Legislative Decree No. 135/2024, which amended Legislative Decree No. 81/2008⁸ and formally included such substances within the regime of Title IX, Chapter II.

This reform is not merely terminological. It carries major practical implications for employers, occupational physicians, labour inspectorates, and workers,

⁴ Miller LB, Feuz MB, Meyer RG, Meyer-Ficca ML. *Reproductive toxicology: keeping up with our changing world*. 2024.

⁵ Ramezanifar S, Beyrami S, Mehrifar Y, et al. *Occupational Exposure to Physical and Chemical Risk Factors: A Systematic Review of Reproductive Pathophysiological Effects in Women and Men*. 2024

⁶ Bonde JP. *On endocrine disruption at the workplace – how to get from suggestive to conclusive evidence?* Scand J Work Environ Health. 2020;46(4):335–338. doi:10.5271/sjweh.3897

⁷ European Parliament and Council. (2008). Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP).

⁸ Legislative Decree No. 81 of 9 April 2008. Consolidated Act on occupational health and safety.

because it redefines the level of prevention expected in workplaces where reproductive hazards are present⁹¹⁰¹¹¹².

This thesis investigates the legal and practical significance of that reform. Its main objective is to analyse how recent changes in EU and Italian law reshape workplace prevention strategies for reproductive toxicants and how those reforms interact with current scientific evidence.

A secondary objective is to compare selected national implementation models and to identify areas in which Italy could still strengthen worker protection beyond the minimum required by transposition.

Three research assumptions guide the analysis. First, the extension of the CMR framework to reproductive toxicants reflects a broader shift toward a more precautionary and hazard-based approach in EU occupational health law.

Second, risk assessment remains the central operational tool, but its content and function change significantly when reproductive toxicants enter the stricter CMR regime¹³.

⁹ Claessens, T., Hougaard, K. S., & Ronsmans, S. (2025). Risk assessment and management of chemical hazards for pregnant workers: A qualitative review of guidance from EU member states. *Journal of Occupational Medicine and Toxicology*, 20, 10. <https://doi.org/10.1186/s12995-025-00456-7>

¹⁰ Samardžić T, Žaja R, Babić Ž, Macan J. *Workplace risk assessment criteria for pregnant workers exposed to physical exertion and biological and chemical hazards*. 2025.

¹¹ Schenk, L., Ho, M.-R., Taxell, P., Huuskonen, P., Leite, M., Martinsone, I., Nordby, K.-C., Paegle, L., & Strumylaite, L. (2024). Occupational exposure limits for reproductive toxicants: A comparative analysis. *Reproductive Toxicology*, 128, 108649. <https://doi.org/10.1016/j.reprotox.2024.108649>

¹² Ladeira C. *Environmental and Occupational Exposure to Chemical Agents and Health Challenges I—What Message Can Bring to Regulatory Science?* *Frontiers in Toxicology*. 2024. doi:10.3389/ftox.2024.1456687

¹³ Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.

Third, the effectiveness of formal transposition depends heavily on institutional capacity, national technical standards, and the integration of toxicological evidence into preventive practice.

The thesis adopts a qualitative, literature-based and normative methodology. It analyses EU directives, regulations, and Italian legislation; guidance and technical documents from institutional actors such as ECHA¹⁴, EU-OSHA¹⁵, BAuA¹⁶, INRS¹⁷, and national labour authorities; and selected peer-reviewed literature in occupational medicine, reproductive toxicology, and endocrine disruption.

The comparative section does not claim to provide an exhaustive country-by-country reconstruction of all 27 EU Member States. Rather, it identifies clusters of regulatory practice and examines selected front-runner and intermediate systems that are especially relevant for understanding the implementation of Directive (EU) 2022/431.

The structure of the thesis is as follows. Chapter 1 reconstructs the legal architecture governing chemical and reproductive risks in EU and Italian law. Chapter 2 discusses risk assessment as the core operational tool, highlighting the difficulties involved in assessing reproductive toxicants and the

¹⁴ European Chemicals Agency (ECHA). (2024). Guidance on the application of the CLP criteria. European Chemicals Agency.

¹⁵ EU-OSHA. (2017). State of the art report on reproductive toxicants. Publications Office of the European Union. <https://doi.org/10.2802/53226>

¹⁶ BAuA. (2023). Technical Rules for Hazardous Substances (TRGS). Federal Institute for Occupational Safety and Health.

¹⁷ INRS. (2024). Valeurs limites d'exposition professionnelle (VLEP) and national guidance on hazardous substances. Institut national de recherche et de sécurité.

implications for the Italian “Documento di Valutazione dei Rischi (DVR)”. Chapter 3 examines suspected reproductive toxicants classified as Category 2, emphasizing the persistent regulatory gap and the role of the precautionary principle. Chapter 4 discusses practical implications for employers and outlines policy options for strengthening the Italian system, informed by selected comparative regulatory models that highlight different approaches to implementation across Member States. A final discussion and conclusion synthesize the findings.

METHODOLOGY

This study is based on doctrinal legal research integrated with narrative review methods in occupational health and toxicology.

The legal analysis focuses on the interaction between Directive 98/24/EC, Directive 2004/37/EC, Directive (EU) 2022/431, Regulation (EC) No 1272/2008 (CLP), Regulation (EC) No 1907/2006 (REACH)¹⁸, Directive 92/85/EEC, Legislative Decree No. 81/2008, and Legislative Decree No. 135/2024.

The comparative analysis relies on official legislative and institutional sources for selected Member States, especially where the transposition of reproductive toxicants into occupational safety law is clearly documented.

The scientific literature was selected on the basis of relevance to four themes: reproductive toxicity in occupational settings; endocrine-disrupting mechanisms and low-dose effects; occupational exposure limits and risk assessment models; and protection of pregnant or otherwise vulnerable workers.

Greater weight was attributed to official institutional documents, peer-reviewed reviews, and comparative studies published in 2024–2025 when available. Older sources were retained where they remain foundational, especially in the field of endocrine disruption and reproductive toxicology.

¹⁸ European Parliament and Council. (2006). Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Methodologically, the thesis treats legal categories and scientific uncertainty as interacting variables.

The aim is not only to describe the law as written, but also to examine whether existing legal thresholds and compliance mechanisms are adequate in light of evolving toxicological evidence.

This interdisciplinary approach is particularly important in the field of reproductive risk, where conventional threshold-based occupational risk paradigms are often strained by long latency, multifactorial causation, low-dose effects, and gender-specific vulnerability.

CHAPTER 1

The regulatory framework on chemical and reproductive risks

1.1 Directive 98/24/EC and the general framework for chemical agents

Council Directive 98/24/EC, commonly referred to as the Chemical Agents Directive (CAD), establishes the general framework for protecting workers from risks related to hazardous chemical agents at work.

It requires employers to assess the risks arising from the presence of hazardous substances, taking into account their hazardous properties, exposure conditions, occupational exposure limits, safety data sheets, and the specific circumstances of work.

The Directive is characterized by a flexible and proportionate approach: preventive measures are calibrated according to the nature and magnitude of the identified risk, and health surveillance is required only where appropriate in light of the risk assessment.

This structure has several advantages.

It allows adaptation across sectors, encourages risk-based decision-making, and can respond to diverse industrial contexts.

However, precisely because it is highly flexible, it may provide insufficient protection when the hazard is severe, when the scientific basis for threshold

setting is incomplete, or when effects may occur at low or cumulative exposures.

These limitations become especially visible in the area of reproductive toxicants, where adverse outcomes may involve fertility, pregnancy, embryofetal development, and long-term developmental effects, often with complex causal pathways.

Before Directive (EU) 2022/431, reproductive toxicants were generally regulated under this CAD framework. As a result, even substances capable of causing severe reproductive harm were not automatically subject to substitution obligations, mandatory health surveillance, or exposure registration comparable to those required for carcinogens and mutagens.

This differential treatment was one of the main weaknesses of the previous system.

1.2 Directive 2004/37/EC and the stricter regime for high-hazard substances

Directive 2004/37/EC originally established a special regime for workers exposed to carcinogens or mutagens at work.

Its logic is markedly stricter than that of Directive 98/24/EC. Rather than merely requiring a proportionate response to identified risk, it imposes a hierarchy of mandatory preventive measures triggered by the presence of substances falling within its scope.

The key elements are substitution wherever technically feasible, use of closed systems where substitution is not possible, reduction of exposure to the lowest technically possible level, mandatory health surveillance, and the keeping of records of workers exposed to such hazards.

This regime reflects a hazard-oriented model.

In other words, the classification of the substance itself activates a set of enhanced legal obligations, irrespective of whether exposure remains below an existing limit value.

Compliance with occupational exposure limits does not exhaust the employer's duties; rather, exposure must still be reduced as far as technically possible. This normative structure is especially important in situations where scientific uncertainty prevents the identification of a genuinely safe threshold. The architecture of Directive 2004/37/EC became the normative reference point for later reform.

Once the EU legislator accepted that serious reproductive harm should receive protection analogous to that of carcinogenic and mutagenic harm, extending the Directive's scope became a logical next step.

1.3 Directive (EU) 2022/431 and the extension to reproductive toxicants

Directive (EU) 2022/431 amended Directive 2004/37/EC by extending its scope to reprotoxic substances classified under the CLP Regulation as Category 1A or 1B.

This is one of the most consequential developments in recent EU occupational safety and health law. The reform expressly recognizes that certain reproductive toxicants warrant the same higher level of protection already applicable to carcinogens and mutagens.

The amended framework therefore subjects those substances to substitution obligations, exposure minimization, binding or otherwise relevant occupational exposure limit mechanisms, mandatory health surveillance, and exposure registers.

The reform also has a conceptual significance. It acknowledges that worker protection cannot remain organized solely around traditionally recognized severe endpoints such as carcinogenesis and mutagenesis when reproductive harm may be equally serious, potentially transgenerational, and socially consequential.

In this sense, the Directive reflects a wider evolution in EU occupational health law toward greater integration of scientific evidence concerning reproductive and developmental toxicity.

At the same time, the Directive does not eliminate all regulatory problems. It applies only to Category 1A and 1B reproductive toxicants. Suspected reproductive toxicants classified as Category 2 remain outside the stricter CMRD regime. The result is an improved but still incomplete system, marked by a two-tier model of protection.

1.4 Legislative Decree No. 81/2008 and the Italian dual system

The Italian legal system implements the European Union framework on occupational exposure to hazardous substances primarily through Legislative Decree No. 81/2008, the Consolidated Act on Occupational Health and Safety. This legislative instrument represents the central normative structure governing workplace prevention in Italy and is explicitly designed to transpose and operationalise the principles established by EU occupational safety directives. Within this system, Title IX plays a pivotal role, as it regulates risks arising from exposure to hazardous chemical agents and structurally mirrors the dual architecture of EU law.

More specifically, Title IX, Chapter I (“Protection from hazardous chemical agents”) governs dangerous chemical agents in general and reflects the logic and regulatory philosophy of Directive 98/24/EC (Chemical Agents Directive). This chapter is based on a risk-oriented and proportional model, in which preventive measures are calibrated according to the results of risk assessment, taking into account exposure levels, duration, frequency, hazardous properties of substances, and available technical and organisational controls. Under this framework, employer obligations are flexible and context-dependent, allowing adaptation to different sectors and exposure scenarios, but also leaving a significant margin of discretion in determining the appropriate level of protection.

By contrast, Title IX, Chapter II (“Protection from risks related to exposure to carcinogens, mutagens and, following recent reforms, reprotoxic substances”)

establishes a distinctly stricter regime, originally applicable only to carcinogens and mutagens and now extended—following Legislative Decree No. 135/2024—to include reproductive toxicants classified as Category 1A and 1B under the CLP Regulation. This chapter embodies a hazard-based regulatory model, in which the classification of a substance as particularly dangerous automatically activates a set of enhanced legal obligations, independently of the specific level of exposure measured in the workplace.

This dual structure is doctrinally and practically significant because it determines the intensity and nature of the preventive obligations imposed on employers.

Under Chapter I, prevention is primarily driven by risk assessment and proportionality: the employer must evaluate risks and adopt measures that are adequate in relation to the identified level of exposure. Under Chapter II, however, the mere presence of a high-hazard substance triggers a hierarchy of mandatory controls, including substitution where technically feasible, reduction of exposure to the lowest technically possible level, implementation of closed systems where appropriate, mandatory health surveillance, and the maintenance of exposure registers.

The reform introduced by Legislative Decree No. 135/2024 represents a crucial turning point in this architecture. By incorporating reproductive toxicants (Category 1A and 1B) into Chapter II, the Italian system formally shifts these substances from a “chemical agents” model (Chapter I / Annex XXXVIII) to a “CMR–reprotoxicants” model (Chapter II / Annex XLIII). This transition is not

merely classificatory but reflects a profound transformation in the underlying regulatory logic: reproductive risks are no longer treated as ordinary chemical hazards subject to proportional management, but as high-consequence risks requiring precautionary, structured and traceable prevention.

From an analytical perspective, the Italian system provides a particularly valuable case study for examining how the dual architecture of EU occupational risk regulation is translated into national law. It illustrates how supranational legal principles—such as hazard classification, substitution hierarchy and precaution—are operationalised through concrete legal categories, procedural obligations and preventive instruments within a domestic legal framework.

At the same time, it reveals the points of tension between formal transposition and practical implementation, especially in areas characterised by scientific uncertainty and evolving evidence, such as reproductive toxicology.

Furthermore, the coexistence of Chapter I and Chapter II within the same legislative structure highlights the persistence of a two-tier regulatory model, in which different categories of substances are subject to different levels of protection depending on their classification. This raises important questions regarding the adequacy of the system in addressing emerging or suspected risks, particularly those associated with Category 2 reproductive toxicants, which remain outside the stricter regime.

From a medico-legal standpoint, the dual system also has significant implications. The classification of a substance under Chapter II increases the

standard of care expected from employers and strengthens the evidentiary framework for assessing compliance and liability. The presence of mandatory documentation, health surveillance and exposure registers enhances traceability and facilitates the reconstruction of exposure histories, which is crucial in cases involving long-latency outcomes such as reproductive or developmental effects.

In this sense, Legislative Decree No. 81/2008, as amended, should be understood not only as a transposition instrument but as a dynamic regulatory platform, within which evolving scientific knowledge, European legal developments and national preventive practices interact.

The Italian dual system thus embodies both the strengths and the limitations of current occupational health regulation: it provides a structured and legally coherent framework, but it also reflects the ongoing challenge of aligning legal categories with the complexity and uncertainty of real-world exposure and biological response.

1.5 Legislative Decree No. 135/2024 and the Italian transposition of Directive (EU) 2022/431

Legislative Decree No. 135 of 4 September 2024 transposed Directive (EU) 2022/431 into Italian law.

Published in the Gazzetta Ufficiale on 26 September 2024 and entering into force on 11 October 2024, the Decree amends Legislative Decree No. 81/2008 by

integrating reproductive toxicants into the stricter regime of Title IX, Chapter II.

The reform is best understood as an updating and strengthening measure, not as a complete rewrite of the pre-existing system.

It extends the notion of substances of particular concern to include reproductive toxicants in CLP Category 1A and 1B, reinforces substitution and exposure minimization, requires more explicit and specific risk assessment in the DVR, extends mandatory health surveillance, and broadens exposure registration to cover workers exposed to reproductive toxicants.

A particularly significant aspect of the reform lies in the systematic reallocation of substances within the annex structure of Legislative Decree No. 81/2008, which concretely operationalises the shift introduced at EU level.

Several substances previously included in Annex XXXVIII (Title IX, Chapter I, Protection from the risks related to chemical agents)—and therefore governed by the general chemical agents regime—have been transferred to Annex XLIII (Title IX, Chapter II, Protection from the risks related to exposure to carcinogens, mutagens and reprotoxic substances at work), thus becoming subject to the stricter regime applicable to carcinogens, mutagens and reproductive toxicants.

This transition reflects a deeper structural transformation: the passage from a “chemical agents” model (Title IX, Chapter I / Annex XXXVIII), based on proportional risk assessment and exposure thresholds, to a “CMR-

reprotoxicants” model (Title IX, Chapter II / Annex XLIII), grounded in hazard classification and precautionary prevention.

In this sense, the Italian transposition gives concrete legal expression to the core innovation of Directive (EU) 2022/431, by translating the extension of the CMRD framework into a redefinition of regulatory categories, preventive obligations and organisational responsibilities at workplace level.

From a conceptual standpoint, the reform therefore marks a decisive shift in regulatory logic.

While the previous framework relied predominantly on a risk-based model, centred on exposure assessment and compliance with occupational exposure limits, the new regime reflects a hazard-based and precautionary approach, in which the classification of a substance itself activates enhanced preventive obligations, independently of quantitative risk estimation.

This transformation is structurally embedded in the dual architecture of Legislative Decree No. 81/2008, which now differentiates more sharply between the general chemical agents regime (Title IX, Chapter I) and the stricter CMR regime (Title IX, Chapter II). From a legal perspective, this distinction is coherent with the architecture of EU chemical classification.

From a preventive and scientific perspective, however, it introduces a potential asymmetry, as the activation of stronger protective measures depends on the achievement of a high level of evidentiary certainty, which may not always be aligned with the evolving nature of toxicological knowledge. From a practical standpoint, the Decree raises the level of expected organisational diligence.

Employers who were already formally compliant with Legislative Decree No. 81/2008 must now revise their procedures, documentation and preventive strategies to reflect the new legal status of reproductive toxicants.

The significance of the reform therefore lies not only in legal harmonisation with EU law, but also in its capacity to redefine the standard of preventive care, anticipating a broader evolution toward more precautionary and science-informed models of occupational risk governance.

The reform also has implications for pregnancy and breastfeeding protection¹⁹, requiring coordination with the framework governing pregnant and breastfeeding workers.

1.6 The role of CLP and REACH

The regulation of reproductive toxicants cannot be understood without considering the interaction between occupational safety law and the broader EU chemicals framework, especially the CLP and REACH Regulations.

Regulation (EC) No 1272/2008 (CLP) provides the harmonized criteria for classifying substances as toxic to reproduction in Categories 1A, 1B, and 2.

This classification is not merely informative; it determines whether a substance enters the stricter occupational regime established by the amended CMRD.

CLP therefore functions as the gateway between scientific hazard identification and legal consequence.

¹⁹ Clark KL, et al. *Environmental and occupational risks to reproductive health in women service members and veterans*. 2025.

Regulation (EC) No 1907/2006 (REACH), by contrast, governs registration, evaluation, authorization, and restriction of chemical substances placed on the EU market. Reproductive toxicants classified as Category 1A or 1B may be identified as substances of very high concern (SVHCs) and become subject to authorization or restriction.

However, REACH does not automatically restrict every reproductive toxicant. Regulatory action depends on prioritization and on the procedural pathways of EU chemicals governance.

This means that a substance may be recognized as seriously hazardous in occupational settings without necessarily being removed from the market.

CLP and REACH are thus complementary but not interchangeable.

CLP identifies and communicates hazard; REACH manages market access and use, occupational safety law governs workplace prevention.

Their interaction is essential, yet it also reveals a structural limitation: a substance may trigger strong downstream workplace obligations without a corresponding upstream restriction, thereby leaving much of the practical burden on employers and national prevention systems.

1.7 The emergence of reproductive risk as a regulatory priority

The inclusion of reproductive toxicants within the CMRD framework reflects a broader normative and epistemic shift.

Reproductive risk has become a regulatory priority because the underlying scientific evidence increasingly shows that occupational exposures can affect

fertility, pregnancy outcomes, fetal development, and later-life health in offspring.

In addition, endocrine-disrupting mechanisms and low-dose effects complicate traditional toxicological assumptions that have long underpinned occupational exposure limit setting.

The new regulatory attention to reproductive toxicants also responds to growing concern for vulnerable groups, especially workers who are pregnant, breastfeeding, or of reproductive age.

EU law is gradually moving from a narrow model of reproductive protection centered on pregnancy toward a broader model that includes fertility and developmental endpoints.

This development remains incomplete, but the trend is clear: scientific evidence is increasingly reshaping the boundaries of occupational risk regulation.

CHAPTER 2

Risk assessment as the core operational tool

2.1 Risk assessment under Directive 98/24/EC

Risk assessment constitutes the central operational mechanism of European Union occupational safety and health law, functioning as the primary interface between legal obligations and workplace prevention practices.

Under Directive 98/24/EC, employers are required to assess risks arising from hazardous chemical agents by systematically considering a range of factors, including the intrinsic hazardous properties of substances, the level, duration and frequency of exposure, the existence of occupational exposure limits (OELs), and the information provided through safety data sheets and other technical sources.

This framework is designed to be flexible and context-sensitive, allowing adaptation across different industrial sectors and exposure scenarios. It performs effectively in situations where the relationship between hazard and exposure can be reasonably characterised and where threshold-based control strategies are scientifically robust and operationally feasible.

At the same time, this model reflects a regulatory paradigm grounded in the assumption that risk can be adequately managed through the identification of exposure thresholds and the implementation of proportionate control measures.

While this approach remains appropriate for many classes of chemical agents, its limitations become increasingly evident in the field of reproductive toxicology.

Reproductive toxicants introduce a level of biological and epistemological complexity that challenges several of the underlying assumptions of traditional risk assessment models.

In particular, reproductive outcomes are often multifactorial, latency-driven and highly sensitive to critical windows of exposure. Adverse effects may involve fertility impairment, pregnancy complications, embryofetal development and long-term or even transgenerational health consequences. These outcomes are not only difficult to detect and attribute in human populations, but may also be influenced by cumulative exposures, mixture effects and interactions between occupational and environmental determinants.

Moreover, susceptibility varies significantly according to sex, reproductive stage, pregnancy status and route of exposure, requiring a more differentiated and life-stage-sensitive analytical approach.

Recent scientific developments further complicate the assessment process. Evidence relating to endocrine-disrupting chemicals has demonstrated the existence of low-dose effects and non-monotonic dose-response relationships, which undermine the traditional toxicological assumption that “the dose makes the poison” in a linear and predictable manner.

In addition, growing attention to internal dose variability, biomonitoring data and exposome-based approaches highlights the limitations of relying solely on external exposure metrics. These developments suggest that risk assessment cannot be confined to static, substance-by-substance evaluation, but must instead evolve toward more integrated and dynamic models capable of capturing real-world exposure complexity.

Within this context, the risk assessment model established by Directive 98/24/EC remains a necessary foundation for occupational prevention, but is often insufficient when applied in isolation to reproductive toxicants.

Its effectiveness depends on its interaction with more precautionary regulatory frameworks—such as that introduced by Directive (EU) 2022/431—and on its capacity to incorporate emerging scientific knowledge into practical decision-making. This implies a shift from a purely compliance-oriented exercise toward a more interpretative, evidence-responsive and precaution-informed process, in which uncertainty is not treated as a limitation but as a central parameter guiding preventive action.

2.2 Risk assessment under Directive 2004/37/EC

Under Directive 2004/37/EC, as amended by Directive (EU) 2022/431, risk assessment remains a central legal requirement, but its function and normative significance are fundamentally transformed.

Unlike the framework established by Directive 98/24/EC, where risk assessment primarily serves to determine whether and to what extent

preventive measures are necessary, within the CMRD system it operates within a pre-defined hierarchy of obligations that are triggered by the intrinsic hazardous properties of the substance.

In this context, risk assessment no longer acts as the sole gateway to action, but rather as a structured instrument for characterising exposure and supporting the implementation of already binding preventive duties.

More specifically, once a substance is classified as a carcinogen, mutagen or reproductive toxicant of Category 1A or 1B, the regulatory logic shifts from a risk-based to a hazard-oriented model. The presence of the hazard itself activates a set of mandatory measures, including substitution where technically feasible, the use of closed systems where substitution is not possible, and the reduction of exposure to the lowest technically achievable level.

Risk assessment, therefore, does not determine whether these obligations apply, but instead informs how they are to be operationalised in specific workplace contexts.

In this framework, the role of risk assessment becomes both technical and evidentiary. Employers are required to determine the nature, degree and duration of worker exposure through all relevant routes, including inhalation, dermal absorption and, where appropriate, ingestion.

Particular attention must be paid to exposure scenarios, process characteristics, and the identification of tasks associated with higher risk. The assessment must be regularly updated to reflect changes in working conditions, technological

developments or new scientific evidence, ensuring that preventive measures remain aligned with evolving knowledge.

This transformation also reflects a deeper epistemological shift in occupational risk regulation. The CMRD framework acknowledges that for certain categories of substances—particularly those associated with carcinogenic, mutagenic or reproductive effects—it may not be possible to identify a safe exposure threshold with sufficient scientific certainty.

As a result, compliance with occupational exposure limits, where they exist, does not exhaust the employer's obligations. Instead, exposure must be minimised as far as technically possible, even below established limit values. This approach is particularly relevant in the context of reproductive toxicants, where emerging evidence highlights the importance of low-dose effects, cumulative exposure and complex biological mechanisms.

Furthermore, the integration of reproductive toxicants into the CMRD system following Directive (EU) 2022/431 extends this precautionary logic to a domain characterised by high uncertainty and variability.

As discussed in the broader scientific analysis of this thesis, reproductive outcomes may depend on critical windows of exposure, gender-specific susceptibility, and interactions between occupational and environmental determinants.

In this context, risk assessment must move beyond a purely quantitative exercise and incorporate qualitative, task-based and life-stage-sensitive

considerations, including the identification of vulnerable groups such as pregnant workers and workers of reproductive age.

From an operational perspective, this means that risk assessment becomes a central component of compliance documentation, closely linked to other legal instruments such as health surveillance programmes, exposure registers and workplace monitoring systems.

It must provide a transparent and traceable justification of preventive choices, including the feasibility of substitution, the adequacy of engineering controls and the residual level of exposure. In medico-legal terms, this significantly strengthens its evidentiary value, as it serves not only as a tool for prevention but also as a record of the employer's fulfilment of the duty of care.

In comparison with the CAD model, the CMRD approach therefore represents a shift from a reactive and proportionate system to a more anticipatory and precaution-driven framework. Risk assessment remains indispensable, but it is no longer the determinant of whether action is required; rather, it structures and substantiates a set of obligations that arise independently from the classification of the hazard.

This reconfiguration is particularly significant in the field of reproductive toxicology, where scientific uncertainty and evolving evidence require a regulatory approach capable of acting in advance of definitive proof.

2.3 Scientific limitations in assessing reproductive toxicants

The assessment of reproductive toxicants faces significant methodological and scientific difficulties that challenge the adequacy of traditional occupational risk paradigms.

Adverse reproductive outcomes—including infertility, miscarriage, fetal growth restriction, developmental abnormalities, and endocrine-mediated dysfunctions—are often the result of complex, multifactorial processes that unfold over long temporal scales.

These outcomes may arise from chronic, low-level or cumulative exposures and are frequently influenced by non-occupational confounders, such as lifestyle factors, environmental exposures, genetic susceptibility, and socio-demographic variables.

As a result, establishing clear causal relationships in occupational settings is inherently difficult, particularly in human epidemiological studies.

A further layer of complexity derives from the biological specificity of reproductive toxicity. Effects may vary significantly depending on sex, reproductive stage, pregnancy status, timing of exposure and route of absorption.

Critical windows of susceptibility—such as gametogenesis, early embryonic development or fetal organogenesis—introduce temporal variability that is not easily captured by conventional exposure assessment models. In addition, reproductive effects may manifest long after exposure, or even across

generations, through epigenetic mechanisms, thereby further complicating both risk assessment and attribution.

Traditional occupational risk assessment frameworks are largely grounded in assumptions of threshold-based toxicity and monotonic dose–response relationships. However, the scientific literature on endocrine-disrupting chemicals has repeatedly challenged these assumptions.

A growing body of evidence demonstrates that certain substances may exert biologically significant effects at very low doses and may exhibit non-monotonic dose–response relationships, in which the direction or magnitude of the effect changes across exposure levels.

These phenomena undermine the reliability of classical toxicological models and call into question the validity of identifying safe exposure thresholds for certain categories of substances.

This does not imply that occupational exposure limits (OELs) are devoid of regulatory value. On the contrary, OELs remain essential tools for structuring exposure assessment and guiding preventive strategies.

However, they cannot be treated as exhaustive or definitive indicators of safety in the context of reproductive toxicants.

As highlighted by Schenk et al. (2024), OEL coverage for reproductive toxicants remains incomplete and inconsistent across jurisdictions, and many existing limits are not specifically designed to capture reproductive endpoints or endocrine-mediated mechanisms. Moreover, OELs typically address single

substances and do not adequately account for mixture effects, cumulative exposure or internal dose variability.

Additional limitations arise from the gap between external exposure metrics and internal biological dose. Conventional risk assessment models rely primarily on environmental or workplace measurements, whereas emerging scientific approaches increasingly emphasise the importance of biomonitoring and internal dose assessment.

These approaches can provide a more accurate representation of actual biological exposure, particularly in complex scenarios involving multiple routes of absorption or variable individual susceptibility.

In this context, the assessment of reproductive toxicants cannot rely solely on traditional risk-based paradigms. Instead, it requires a more integrated and dynamic approach that incorporates uncertainty, biological plausibility and evolving scientific evidence into preventive decision-making.

A precautionary interpretation of risk assessment becomes particularly relevant where evidence is suggestive but not yet conclusive, and where the potential consequences of exposure are severe, long-term or irreversible.

From both a regulatory and medico-legal perspective, these limitations have important implications. They reinforce the need to interpret compliance with exposure limits as a minimum requirement rather than a guarantee of safety, and they support a broader conception of the employer's duty of care, encompassing anticipatory and precautionary measures in the presence of plausible reproductive hazards.

2.4 Advanced models: TRGS and exposure-based approaches

Several advanced national systems have sought to address the methodological and scientific limitations inherent in the assessment of reproductive toxicants by developing more sophisticated, exposure-oriented and technically detailed regulatory models.

These approaches aim to bridge the gap between evolving toxicological knowledge and operational workplace prevention, moving beyond simplified and purely threshold-based paradigms.

The German system, in particular, represents one of the most advanced examples in this regard. The Technical Rules for Hazardous Substances (TRGS), developed under the coordination of BAuA, provide a dynamic interface between scientific evidence and regulatory practice.

Rather than functioning as static legal provisions, TRGS documents integrate classification, exposure characterisation and preventive decision-making into a coherent and continuously updated framework.

Instruments such as TRGS 905 (classification of carcinogenic, mutagenic and reprotoxic substances) and TRGS 910 (risk-based exposure concepts) explicitly recognise uncertainty, variability and the absence of clear thresholds for certain substances, thereby allowing preventive strategies to be adapted in light of evolving scientific knowledge.

These models move beyond rigid reliance on occupational exposure limits as sole decision-making criteria and instead incorporate a more nuanced understanding of hazard, exposure and risk.

In particular, they reflect a shift toward exposure-based and process-oriented assessment, in which attention is directed not only to the presence of a substance, but also to how, when and to what extent workers are actually exposed in real-world conditions.

Exposure-based approaches emphasise several key methodological tools. Biomonitoring allows the assessment of internal dose and provides a more accurate representation of biologically relevant exposure, especially in cases involving multiple exposure routes or individual variability.

Process analysis and task-based assessment enable the identification of specific operational phases associated with higher exposure, rather than relying on average or static measurements.

Route-specific evaluation—considering inhalation, dermal and, where relevant, ingestion pathways—further refines risk characterisation.

In addition, these approaches increasingly account for real-world variability, including intermittent exposures, maintenance activities, accidental releases and combined occupational and environmental exposures.

In the context of reproductive toxicants, these methodological advances are particularly valuable. They enhance the sensitivity of risk assessment by allowing the identification of critical exposure scenarios, hidden or underestimated pathways, and susceptible groups, including pregnant

workers and workers of reproductive age. They also facilitate the detection of exposure patterns that may be relevant for low-dose, cumulative or endocrine-mediated effects, which are often missed by conventional monitoring strategies.

At the same time, these advanced models are not without limitations. Their effective implementation requires a high level of technical expertise, access to specialised measurement and analytical tools, and strong institutional support. They also depend on organisational maturity within enterprises, including the capacity to integrate occupational hygiene, medical surveillance and risk management into a coherent preventive system.

For small and medium-sized enterprises, in particular, these requirements may represent a significant barrier, potentially leading to uneven levels of protection across sectors and jurisdictions.

From a broader regulatory perspective, these approaches exemplify the transition toward a more adaptive and science-informed model of occupational risk governance, in which prevention is guided not only by formal classification and fixed thresholds, but also by a dynamic interpretation of exposure, uncertainty and biological plausibility. As such, they provide an important reference point for the future evolution of EU regulatory frameworks in the field of reproductive toxicants.

2.5 The DVR in Italian workplace implementation

In Italy, risk assessment is formally documented through the *Documento di Valutazione dei Rischi* (DVR), which constitutes the central operational and evidentiary instrument of occupational prevention. The DVR is not merely a descriptive document but a legally binding framework through which the employer identifies hazards, evaluates risks, and defines the preventive and protective measures to be implemented within the workplace.

Following Legislative Decree No. 135/2024, the DVR must explicitly and systematically address reproductive toxicity where Category 1A or 1B reproductive toxicants are present. This entails a more structured and analytically demanding approach to risk assessment. In particular, the DVR must identify the substances involved and their classification under the CLP Regulation, describe exposure scenarios in a task-specific and process-oriented manner, justify the continued use of hazardous substances where substitution is not technically feasible, and document in detail the technical, organisational and procedural measures adopted to minimise exposure.

This expanded content requirement reflects a shift from a generic and often standardised form of risk assessment toward a more substantive, evidence-based and context-sensitive evaluation. Exposure assessment must go beyond nominal presence of substances and include duration, frequency, routes of exposure and variability across different tasks and worker groups. Where possible, it should incorporate quantitative data, but also qualitative analysis

capable of capturing complex or uncertain exposure scenarios, including maintenance activities, accidental releases and mixed exposures.

The quality of the DVR is therefore decisive for the effectiveness of the reform. If it functions merely as a formal administrative document—based on generic templates or minimal compliance logic—it cannot achieve the preventive goals of the legislative framework.

In contrast, an effective DVR must be specific, dynamic, task-oriented and regularly updated, reflecting both changes in workplace organisation and evolving scientific knowledge. It should also be closely integrated with occupational medical surveillance, ensuring that risk assessment and health monitoring operate as mutually reinforcing components of prevention.

A particularly critical aspect concerns the documentation of substitution decisions. The DVR must clearly demonstrate whether safer alternatives have been evaluated and, where substitution is not feasible, provide a reasoned justification supported by technical and organisational considerations.

This requirement has direct regulatory and medico-legal implications, as it allows retrospective evaluation of the employer's decision-making process and the adequacy of preventive measures adopted.

Furthermore, the DVR must explicitly address the protection of vulnerable groups, including pregnant workers and workers of reproductive age. This involves identifying potentially incompatible tasks, defining exposure thresholds for reassignment, and ensuring that preventive measures are adapted to specific biological and life-stage conditions.

From a medico-legal perspective, the DVR acquires increasing importance as a document of proof. Its content may be used to assess compliance with legal obligations, to reconstruct exposure scenarios, and to evaluate the adequacy of preventive measures in the event of occupational disease or reproductive harm. In this sense, the reform strengthens not only the preventive function of the DVR, but also its evidentiary role within the broader framework of occupational liability.

2.6 Vulnerable workers and gender-based risk

A central issue in the assessment and management of reproductive risk is the identification and protection of vulnerable workers. While this category traditionally includes pregnant and breastfeeding workers, it extends more broadly to encompass workers of reproductive age, whose susceptibility may vary according to sex, biological function, hormonal status and life stage.

Directive 92/85/EEC establishes a specific legal framework for the protection of pregnant and breastfeeding workers, requiring employers to assess risks, adapt working conditions where necessary, and provide reassignment to safer tasks when exposure cannot be adequately controlled.

However, the scope of reproductive risk extends beyond pregnancy alone and includes potential effects on fertility, gametogenesis and long-term developmental outcomes in offspring. This broader perspective requires a more comprehensive and anticipatory approach to vulnerability.

The scientific literature has increasingly highlighted the limitations of traditional gender-neutral models of occupational risk assessment. These models often assume homogeneous exposure and response patterns, thereby overlooking relevant differences in both exposure conditions and biological susceptibility.

Occupational segregation, task allocation, differences in work organisation, and disparities in access to protective equipment can all contribute to differentiated exposure profiles between men and women. In addition, personal protective equipment is often designed based on male anthropometric standards, potentially reducing its effectiveness for female workers.

Biological differences further complicate risk assessment. Reproductive physiology, hormonal regulation and metabolic pathways may influence both exposure and response to chemical agents. Moreover, critical windows of susceptibility—such as early pregnancy or specific phases of the reproductive cycle—introduce temporal variability that is rarely captured by standard assessment models. These factors underscore the need for a gender-sensitive and life-stage-specific approach to occupational risk evaluation.

Claessens et al. (2025) further demonstrate that guidance for the protection of pregnant workers remains heterogeneous across EU Member States, both in terms of risk assessment criteria and in the operationalisation of preventive measures. This variability suggests that formal legal obligations are not always

matched by coherent and practical tools for implementation, leading to differences in the level of protection afforded in practice.

In the context of reproductive toxicants, the identification of vulnerable workers must therefore move beyond a reactive model based solely on pregnancy status toward a more proactive and inclusive framework, capable of addressing potential reproductive risks across the entire working population. This includes the integration of reproductive endpoints into risk assessment, the adaptation of exposure scenarios to account for biological variability, and the development of clear criteria for task modification or reassignment.

From a regulatory and medico-legal standpoint, failure to adequately identify and protect vulnerable workers may constitute a critical weakness in the prevention system. As scientific evidence continues to highlight differential susceptibility and complex exposure patterns, the duty of care imposed on employers must be interpreted in a broader and more dynamic sense, encompassing not only formal compliance with legal provisions but also the effective anticipation and management of reproductive risks.

2.7 Emerging scientific evidence and its implications for risk assessment

Recent scientific developments in the field of reproductive toxicology increasingly indicate that traditional toxicological paradigms based on

threshold-dose relationships are insufficient to adequately capture the complexity of reproductive risk.

In particular, the growing body of evidence on endocrine-disrupting chemicals (EDCs) highlights that adverse reproductive outcomes may occur at low doses, through non-monotonic dose-response relationships, and as a result of cumulative and combined exposures. These mechanisms challenge the scientific assumptions underpinning conventional occupational exposure limits (OELs) and call into question their adequacy as primary tools for risk control in the context of reproductive health.

Current research identifies EDCs—including per- and polyfluoroalkyl substances (PFAS), phthalates, bisphenols, pesticides, and emerging contaminants such as microplastics—as major contributors to reproductive dysfunction. These substances have been associated with impaired fertility, altered gametogenesis, pregnancy complications, developmental abnormalities, and long-term or transgenerational effects mediated by epigenetic mechanisms. Recent studies have also demonstrated the presence of microplastics in human reproductive tissues, including the placenta, testicular tissue and follicular fluid, suggesting new pathways of exposure and toxicity that are not yet fully addressed within existing regulatory frameworks.

A further critical development concerns the increasing recognition that real-world exposure scenarios are characterised by chronic, low-dose, multi-agent exposures rather than isolated substances. This has led to a growing emphasis on mixture toxicity, cumulative exposure assessment and exposome-based

approaches, which aim to capture the totality of environmental and occupational exposures across the life course. Within this perspective, the traditional focus on single-substance evaluation appears increasingly inadequate for the prevention of reproductive harm.

Methodologically, significant advances are being made through the development of New Approach Methodologies (NAMs), including in vitro human-based models, organ-on-chip systems, placental and gonadal models, and computational toxicology tools. European research initiatives such as PARC and EURION are actively contributing to the refinement of developmental and reproductive toxicity (DART) testing, with the aim of improving early hazard identification and reducing reliance on animal models²⁰.

Taken together, these scientific developments reinforce the need for a precautionary and adaptive regulatory approach.

Increasingly, the literature supports the view that uncertainty should not justify regulatory inertia where plausible reproductive hazards exist. Instead, preventive strategies should incorporate early intervention, conservative exposure assessment, biomonitoring, and enhanced protection of vulnerable populations, including workers of reproductive age and pregnant workers.

In this context, Directive (EU) 2022/431 represents an important step toward a more hazard-based regulatory model. However, the persistence of a two-tier system—whereby only Category 1A and 1B reproductive toxicants fall within

²⁰ OECD. Developmental and reproductive toxicity testing: emerging approaches. Paris: OECD; 2022

the stricter CMR regime — appears only partially aligned with current scientific knowledge.

Emerging evidence suggests that suspected reproductive toxicants (Category 2) and unclassified substances may also pose significant risks, supporting calls for a more precautionary and science-informed evolution of occupational health regulation.

CHAPTER 3

Suspected reproductive toxicants, scientific uncertainty and the limits of the current regulatory framework

3.1 Category 2 reproductive toxicants under CLP

Under Regulation (EC) No 1272/2008 (CLP), reproductive toxicants are classified into Category 1A, Category 1B, and Category 2, reflecting different levels of evidentiary certainty regarding their effects on human reproductive health.

Category 1A includes substances known to impair fertility or cause developmental toxicity in humans, based primarily on human evidence, whereas Category 1B includes substances presumed to have such effects, largely on the basis of animal studies supported by mechanistic data.

Category 2, by contrast, identifies substances suspected of causing reproductive toxicity, for which the available evidence is limited, inconsistent or not yet conclusive.

From a regulatory standpoint, this classification system represents a structured translation of scientific evidence into legal categories. However, it is essential to emphasise that the distinction between categories does not reflect a binary opposition between “hazard” and “no hazard.”

Rather, it reflects graduated levels of epistemic certainty, influenced by the availability, quality and interpretability of toxicological and epidemiological data. In the field of reproductive toxicology, where human data are often scarce, confounded or ethically difficult to obtain, this distinction becomes particularly critical.

Indeed, reproductive toxicity is frequently characterised by complex causal pathways, long latency periods, and sensitivity to timing of exposure. Outcomes such as reduced fertility, miscarriage, developmental abnormalities and endocrine-mediated effects may arise from chronic, low-dose exposures and may be influenced by both occupational and non-occupational factors. As a result, the evidentiary threshold required for classification in Categories 1A or 1B may not be reached until substantial harm has already occurred or become detectable at population level.

The classification of a substance as Category 2 should therefore not be interpreted as indicating negligible risk, but rather as signalling scientific uncertainty in the presence of plausible hazard.

This interpretation is supported by ECHA guidance, which explicitly recognises that Category 2 substances may warrant precautionary consideration in risk management, particularly in occupational settings characterised by repeated or mixed exposures.

From the perspective of occupational health regulation, this raises a fundamental issue: whether preventive strategies should be strictly aligned with formal classification thresholds, or whether they should incorporate a

broader, uncertainty-oriented approach capable of addressing suspected hazards before they are fully established. This question lies at the core of the regulatory tensions explored in the present thesis.

3.2 The two-tier regulatory structure

Directive (EU) 2022/431 significantly strengthens the protection of workers exposed to reproductive toxicants by extending the scope of Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work, as amended—to include substances classified as Category 1A and 1B under the CLP Regulation.

As a result, these substances are now subject to a stricter regulatory regime based on substitution, exposure minimisation, mandatory health surveillance and exposure traceability.

However, substances classified as Category 2 remain generally governed by Directive 98/24/EC, the Chemical Agents Directive, which is based on a more flexible, risk-oriented approach.

This regulatory differentiation gives rise to a two-tier structure, in which confirmed or presumed reproductive toxicants are subject to stringent, hazard-based control measures, while suspected reproductive toxicants are managed within a more discretionary framework.

From a formal legal perspective, this distinction is coherent with the logic of EU hazard classification, which links regulatory obligations to levels of

evidentiary certainty. However, from a preventive and scientific standpoint, it raises significant concerns.

The classification process is inherently dynamic: substances may be reclassified over time as new evidence emerges, moving from Category 2 to Category 1B or 1A. A regulatory system that conditions the application of stricter preventive measures on the attainment of higher certainty may therefore lag behind the evolution of scientific knowledge, resulting in delayed protection. This issue is particularly relevant in the field of endocrine disruption and developmental toxicity, where causal relationships are difficult to establish conclusively in human populations due to latency, multifactorial exposure and methodological constraints. The scientific literature increasingly emphasises that waiting for conclusive evidence may be incompatible with effective prevention, especially in the presence of plausible and potentially irreversible harm.

The two-tier structure thus reflects a deeper structural tension between legal certainty and scientific uncertainty. While the law seeks clear thresholds for the activation of obligations, the underlying science often operates in a domain of probabilistic evidence, evolving knowledge and incomplete data.

This mismatch can result in a regulatory gap, whereby substances that present credible reproductive risks remain subject to weaker preventive regimes.

In this context, the two-tier system should not be interpreted as a stable equilibrium, but rather as a transitional configuration, reflecting an ongoing adaptation of occupational health law to emerging scientific evidence.

The persistence of this structure highlights the need for more flexible and precautionary approaches capable of bridging the gap between classification-based regulation and real-world exposure scenarios.

3.3 Examples and practical management of suspected reproductive toxicants

A number of widely used industrial chemicals classified as Category 2 reproductive toxicants remain relevant to occupational prevention due to their widespread use and potential for exposure.

Substances such as styrene, ethylbenzene, acetone, cumene and tetrahydrofuran are frequently cited in the literature as examples of agents for which evidence of reproductive toxicity is suggestive but not yet sufficient for higher classification.

In many cases, these substances are subject to occupational exposure limits (OELs) at EU or national level, providing a quantitative benchmark for exposure control. While OELs play an important role in structuring risk assessment, their protective value in the context of reproductive toxicity is inherently limited.

As highlighted in recent analyses, OELs are often derived from systemic toxicity endpoints and may not adequately capture reproductive or endocrine-specific effects, particularly at low doses or in the presence of mixture exposures.

Moreover, OELs do not account for cumulative exposure across multiple agents, variability in individual susceptibility, or internal dose dynamics. Compliance with an exposure limit therefore does not necessarily ensure effective protection, especially in complex occupational environments characterised by chronic, low-level exposure and multiple concurrent hazards. For employers, this implies that the management of Category 2 reproductive toxicants cannot be reduced to formal compliance with numerical thresholds. Instead, it requires a multi-layered preventive strategy grounded in the principles of anticipation and precaution.

Exposure minimisation should be pursued through engineering controls, process redesign, ventilation systems, containment measures and, where feasible, substitution with less hazardous alternatives. Organisational measures—including task rotation, exposure time reduction and safe work procedures—also play a crucial role.

In addition, targeted information and training of workers are essential, particularly in relation to reproductive risks that may not be immediately apparent.

Occupational physicians should be actively involved in identifying potential reproductive hazards, advising on risk management and integrating reproductive endpoints into health surveillance.

In settings characterised by continuous, low-dose or mixed exposures, a precautionary approach is especially justified. This includes considering the combined effects of multiple substances, even where individual exposures

remain below established limits, and paying particular attention to vulnerable groups such as workers of reproductive age.

From a broader perspective, the management of Category 2 reproductive toxicants represents a test case for the evolution of occupational risk regulation. It illustrates the limitations of strictly classification-based approaches and highlights the need for more flexible, science-informed and preventive models capable of addressing uncertainty and complexity in real-world exposure scenarios.

3.4 Scientific uncertainty and the precautionary principle in reproductive risk regulation

The scientific literature increasingly supports a more precautionary approach in the field of occupational reproductive risk, and this perspective is fully consistent with the broader body of evidence emerging from recent interdisciplinary research.

Pan et al. (2024)²¹ review the wide range of reproductive impacts associated with endocrine-disrupting chemicals, while foundational work by Vandenberg et al. (2012)²² and Gore et al. (2015)²³ demonstrates why low-dose and non-

²¹ Pan, J., Liu, P., Yu, X., Zhang, Z., & Liu, J. (2024). The adverse role of endocrine disrupting chemicals in the reproductive system. *Frontiers in Endocrinology*, 14, 1324993. <https://doi.org/10.3389/fendo.2023.1324993>

²² Vandenberg, L. N., Colborn, T., Hayes, T. B., Heindel, J. J., Jacobs, D. R. Jr., Lee, D.-H., Shioda, T., Soto, A. M., vom Saal, F. S., Welshons, W. V., Zoeller, R. T., & Myers, J. P. (2012). Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. *Endocrine Reviews*, 33(3), 378-455. <https://doi.org/10.1210/er.2011-1050>

²³ Gore, A. C., Chappell, V. A., Fenton, S. E., Flaws, J. A., Nadal, A., Prins, G. S., Toppari, J., & Zoeller, R. T. (2015). EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocrine Reviews*, 36(6), E1-E150. <https://doi.org/10.1210/er.2015-1010>

monotonic dose–response effects challenge conventional toxicological assumptions. Schenk et al. (2024) further highlights the structural limitations of occupational exposure limit systems for reproductive toxicants, reinforcing the conclusion that traditional regulatory tools are not sufficient to ensure effective protection.

In parallel, the current body of scientific literature on occupational reproductive risks—encompassing studies by Claessens et al., Samardžić et al., Schenk et al., Ladeira, Clark et al., Miller et al., and Ramezanifar et al., together with the conceptual contribution from the *Scandinavian Journal of Work, Environment & Health* (2020)—converges toward a unified conclusion: the traditional paradigm of occupational risk regulation is structurally insufficient to address reproductive toxicity, and this limitation directly affects the implementation and effectiveness of Directive (EU) 2022/431.

Across the literature, reproductive toxicity emerges as a multifactorial, latency-driven and biologically complex phenomenon, in which causal relationships are difficult to establish with certainty, particularly in human populations.

The epistemological challenge highlighted in the SJWEH editorial—namely the transition from “suggestive” to “conclusive” evidence in endocrine disruption—reflects a structural mismatch between scientific knowledge and regulatory thresholds. This gap is further amplified by the recognition that occupational exposures rarely occur in isolation, but rather as chronic, low-dose, multi-agent exposures, often involving endocrine-disrupting chemicals capable of producing non-monotonic dose–response effects, epigenetic

modifications and transgenerational outcomes. Such findings, consistently supported by toxicological and epidemiological studies, fundamentally challenge regulatory models based on single-substance assessment and threshold-dependent safety concepts.

Together, this literature supports a core thesis: uncertainty should not be interpreted as a reason for regulatory inertia where plausible reproductive hazards exist.

A precautionary approach, in this context, does not require abandoning evidence-based regulation; rather, it entails recognising that, in the face of plausible severe harm, prevention may need to move ahead of complete certainty.

In occupational settings, this can be operationalised through conservative exposure assessment, preference for substitution, stricter engineering controls, and enhanced protection of vulnerable workers even where a substance has not yet entered the stricter CMRD regime.

3.5 Structural Limits of Directive (EU) 2022/431 and Implications for Occupational Prevention

Within this framework, Directive (EU) 2022/431 represents a significant legal advancement by extending the stricter regime of Directive 2004/37/EC to include reproductive toxicants classified as Category 1A and 1B under Regulation (EC) No 1272/2008. This shift introduces a hazard-based and precautionary logic, whereby the presence of a high-risk classification

automatically triggers enhanced preventive obligations—such as substitution, exposure minimisation, health surveillance and exposure registers—independently of quantitative risk estimation. In this respect, the Directive aligns with the scientific literature’s call for earlier intervention in the face of uncertainty and long-term health effects.

However, the same body of evidence also reveals that the Directive remains partially misaligned with contemporary scientific knowledge. A critical limitation lies in its reliance on formal hazard classification as the trigger for enhanced protection.

As demonstrated across the cited studies, a substantial number of substances with suspected or emerging reproductive effects—particularly those classified as Category 2 or not yet classified—remain outside the scope of the strengthened CMR regime and continue to be regulated under the more flexible framework of Directive 98/24/EC. This results in a two-tier regulatory structure, in which only well-established hazards are subject to strict control, while uncertain but potentially harmful exposures receive comparatively weaker protection.

The literature also highlights a second major limitation: the inadequacy of occupational exposure limits (OELs) as a primary tool for protecting reproductive health. Comparative analyses show that OEL coverage for reproductive toxicants is incomplete, inconsistent across Member States, and often not specifically designed to address reproductive endpoints. Moreover,

OELs do not account for cumulative exposure, mixture effects or internal dose variability.

As a result, compliance with exposure limits does not necessarily equate to effective protection, particularly in environments characterised by chronic, low-level exposure and complex exposure scenarios.

A further critical dimension emerging from the integrated evidence concerns vulnerable workers, especially pregnant workers, workers of reproductive age and, more broadly, gender-specific susceptibility. The studies collectively demonstrate that traditional occupational risk models have been largely based on male populations, leading to systematic underestimation of female reproductive risks and insufficient integration of pregnancy-related vulnerabilities into risk assessment processes. Although Directive (EU) 2022/431 strengthens protection for workers exposed to reprotoxic substances, its effectiveness depends on its interaction with Directive 92/85/EEC and on the availability of clear, harmonised criteria for risk assessment and management, which currently remain fragmented across Member States, resulting in variability in practical implementation.

In addition, the literature emphasises the need to move beyond purely external exposure assessment toward a more comprehensive model incorporating biomonitoring, internal dose evaluation and exposome-based approaches. This perspective, strongly supported by regulatory science contributions, suggests that effective prevention of reproductive risk requires integration between

occupational and environmental exposure, as well as closer alignment between toxicological research and regulatory decision-making.

Taken together, these findings reveal a fundamental tension between the static, classification-driven structure of current regulation and the dynamic, evolving nature of scientific evidence. Directive (EU) 2022/431 constitutes a decisive step toward a more precautionary model, but it remains anchored in a framework that is still partly reactive, intervening primarily when hazards reach a high level of evidentiary certainty, whereas the scientific literature consistently supports a proactive and uncertainty-oriented approach capable of addressing emerging risks before they are fully established.

From a regulatory and medico-legal perspective, this implies that the duty of care imposed on employers should be interpreted in an expanded and dynamic manner, extending beyond formal compliance with classification and exposure limits. In particular, effective implementation should include precautionary management of suspected reproductive toxicants, integration of mixture and cumulative exposure assessment, adoption of gender-sensitive and life-stage-specific risk criteria, and strengthening of health surveillance systems with specific attention to reproductive endpoints.

In conclusion, while Directive (EU) 2022/431 represents a crucial evolution in EU occupational health law, the integrated scientific evidence demonstrates that full protection of reproductive health in the workplace requires a further shift toward an adaptive, science-informed and precautionary regulatory model, without which the Directive's formal legal innovation risks remaining

only partially translated into effective and equitable protection for all workers, particularly those most biologically and occupationally vulnerable.

3.6 Future perspectives

Future EU and national developments are likely to evolve along trajectories that reflect the growing tension between the static, classification-based structure of current regulation and the dynamic, uncertainty-driven nature of scientific evidence on reproductive toxicity. In this context, regulatory evolution cannot be limited to incremental adjustments but should move toward a more adaptive, precautionary and science-integrated framework.

One key direction concerns the progressive strengthening and conceptual redefinition of occupational exposure limits (OELs). Rather than functioning as isolated compliance thresholds, OELs should be integrated into a broader preventive architecture capable of addressing low-dose effects, cumulative exposures, mixture toxicity and internal dose variability. This implies not only expanding OEL coverage for reproductive toxicants, but also rethinking their epistemological role in light of endocrine disruption and non-monotonic dose-response relationships.

Closer integration between REACH, CLP and occupational safety law is therefore essential, in order to reduce the current fragmentation between hazard identification, market regulation and workplace prevention.

A second major development concerns the extension of precautionary approaches beyond substances formally classified as Category 1A and 1B. As

highlighted in the previous sections, the persistence of a two-tier regulatory structure leaves suspected reproductive toxicants (Category 2) and emerging hazards insufficiently addressed. Future regulatory strategies should therefore incorporate more explicit precautionary criteria for uncertain risks, particularly in high-exposure sectors, moving from a reactive model based on established hazard toward a more anticipatory approach capable of managing scientific uncertainty.

A third direction involves the development of harmonised, operational and gender-sensitive guidance for the protection of vulnerable workers, including pregnant workers and workers of reproductive age. This requires stronger coordination between Directive (EU) 2022/431 and Directive 92/85/EEC, as well as the establishment of clearer and more consistent criteria for workplace risk assessment, task adaptation and exposure management across Member States. Particular attention should be paid to overcoming the historical bias toward male-centred risk models and to integrating reproductive endpoints more systematically into occupational health surveillance.

A fourth and increasingly central area of development concerns the transition toward more advanced exposure assessment models. The literature strongly supports the integration of biomonitoring, internal dose evaluation and exposome-based approaches, which allow a more accurate representation of real-world exposure scenarios. This shift would enable occupational risk assessment to move beyond simplified external exposure metrics and toward a more comprehensive understanding of cumulative and life-course exposure

patterns, including the interaction between occupational and environmental determinants.

Finally, future perspectives should include the strengthening of medico-legal and organisational dimensions of prevention. In light of the evolving scientific evidence, the duty of care imposed on employers is likely to be interpreted in a more dynamic and expanded manner, extending beyond formal compliance with classification systems and exposure limits. This will require more robust documentation, enhanced traceability of exposure, improved health surveillance systems focused on reproductive outcomes, and greater integration between occupational physicians, risk assessment processes and preventive decision-making.

Taken together, these directions point toward a necessary transformation of the current regulatory model. Bridging the gap between scientific knowledge and legal protection will require not only technical updates, but also a conceptual shift toward a precautionary, adaptive and evidence-responsive system of occupational risk governance. Only through such evolution can the objectives of Directive (EU) 2022/431 be fully realised in practice, ensuring effective and equitable protection of reproductive health in the workplace.

CHAPTER 4

Practical implications for employers and policy perspectives for Italy

4.1 The organizational impact of the reform

Directive (EU) 2022/431 and Legislative Decree No. 135/2024 substantially increase employers' obligations in workplaces where Category 1A or 1B reproductive toxicants are present.

The practical consequences are significant.

Companies must re-examine their inventories of hazardous substances, update classification checks, review production processes, revise the DVR, strengthen engineering and organizational controls, involve the occupational physician more closely, and establish or update exposure registration systems.

These changes increase operational complexity and compliance costs. Yet they should not be understood solely as burdens. They also reflect a redefinition of good occupational governance.

By moving reproductive toxicants into the stricter CMR regime, the law signals that protection of fertility, pregnancy, and developmental health is not ancillary but central to modern workplace prevention.

4.2 Substitution and exposure minimization

The strengthened duty of substitution represents one of the most consequential and structurally transformative elements of the revised regulatory regime introduced by Directive (EU) 2022/431. Within this framework, substitution is no longer a merely recommended preventive option, but becomes a primary legal obligation, triggered by the presence of substances classified as Category 1A or 1B reproductive toxicants.

Employers are now required to actively verify whether less hazardous alternatives are technically feasible, and this assessment must be concrete, documented and periodically updated. The obligation is not satisfied by abstract or generic considerations: it requires a demonstrable analysis of available technological, chemical and organisational alternatives, including substitution of substances, modification of formulations, or redesign of processes. Where substitution is not feasible, the employer must provide a reasoned justification, supported by technical and economic evidence, which is subject to scrutiny by supervisory authorities and, where relevant, judicial evaluation.

In practical terms, compliance with the substitution requirement may entail profound organisational and technological changes. These include redesign of production processes, modification of supply chains and procurement policies, reformulation of mixtures, adoption of alternative materials, and investment in cleaner or less hazardous technologies. In some sectors, particularly those involving complex chemical processes or hazardous medicinal products,

substitution may require long-term strategic planning and significant capital investment.

Where substitution cannot be achieved, the regulatory focus shifts to exposure minimisation to the lowest technically possible level, a standard that goes beyond simple compliance with occupational exposure limits. This principle reflects a hazard-based approach, under which the presence of a high-risk substance justifies the continuous reduction of exposure irrespective of measured levels.

Operationally, this entails a strict hierarchy of control measures, prioritising collective and engineering interventions over individual protection. Ventilation systems, local exhaust ventilation, closed or semi-closed systems, process isolation, automation, remote handling, safe storage and transport procedures, and process redesign become central instruments of compliance. Personal protective equipment (PPE) retains an important role, but is clearly positioned as a residual protective measure, to be used where risks cannot be eliminated or adequately controlled by upstream interventions.

This regulatory logic is not confined to EU law in the abstract, but is increasingly reflected in national implementation measures. The Spanish reform, for example, explicitly clarifies that compliance with occupational exposure limits does not exhaust the employer's duty of prevention and that exposure must in any case be reduced as far as technically possible (BOE-A-2024-13419, lines 249–271). This reinforces the interpretation that OELs

function as reference values rather than safety thresholds, particularly in the context of reproductive toxicants.

From a broader perspective, the strengthened substitution and minimisation obligations signal a transition toward a more anticipatory and prevention-oriented model of occupational risk governance, in which the burden of managing scientific uncertainty is placed on organisational and technical decision-making rather than deferred until definitive evidence becomes available.

4.3 Documentation, surveillance, and traceability

A further major consequence of the revised regulatory framework is the substantial intensification of documentation, health surveillance and exposure traceability obligations.

Under the stricter CMRD regime, risk assessment is no longer merely a procedural requirement but becomes a central evidentiary and operational instrument, requiring a higher degree of specificity, transparency and auditability.

The risk assessment must explicitly identify reproductive toxicants present in the workplace, describe exposure scenarios in detail, justify the continued use of hazardous substances where substitution is not feasible, and document the technical and organisational measures adopted to control exposure.

This transformation reflects a shift from a generalised and descriptive approach toward a structured, task-oriented and evidence-based assessment model, capable of supporting both preventive action and regulatory oversight. Health surveillance also acquires a more prominent and mandatory role. For workers exposed to substances falling within the scope of the Directive, surveillance is no longer discretionary but constitutes a legal obligation.

In the context of reproductive toxicants, this implies not only general clinical monitoring but also increased attention to reproductive endpoints, including fertility, pregnancy outcomes and developmental effects. Although the precise modalities of surveillance may vary across Member States, the overall trend is toward greater integration between occupational medicine and risk assessment processes.

Exposure registers represent another key element of the strengthened regime. The systematic recording of workers exposed to carcinogens, mutagens and reproductive toxicants enhances the long-term traceability of exposure, which is essential given the latency and multifactorial nature of many reproductive outcomes. These registers facilitate retrospective reconstruction of exposure in medico-legal contexts, support epidemiological research and enable more effective monitoring of occupational health trends.

The medico-legal implications of these developments are particularly significant. Enhanced documentation and traceability increase the capacity to identify non-compliance, attribute responsibility and evaluate causation in cases of occupational disease. At the same time, they raise the standard of

expected diligence, making it more difficult for employers to rely on generic or formal compliance arguments. In this sense, the reform contributes to redefining the standard of care in occupational health, aligning it more closely with principles of precaution and accountability.

For occupational physicians, the reform expands both responsibilities and opportunities. Their role becomes more central in the identification of reproductive risks, the design of surveillance protocols, the interpretation of clinical findings and the integration of medical evidence into the broader prevention system. This requires closer coordination between the physician, the employer, the prevention and protection service, and the DVR process, reinforcing the need for interdisciplinary collaboration.

Overall, the intensification of documentation, surveillance and traceability obligations reflects a broader shift toward a more transparent, accountable and evidence-based system of occupational prevention, in which compliance is increasingly measured not only by outcomes but also by the quality and robustness of underlying processes.

4.4 Hazardous medicinal products and the healthcare sector

One of the most illustrative and practically relevant areas of application of the new regulatory framework concerns hazardous medicinal products, particularly antineoplastic drugs used in oncology and other specialised healthcare settings.

These substances frequently fall within the broader category of CMR hazards and are characterised by high intrinsic toxicity, complex handling requirements and significant potential for occupational exposure.

The preparation, administration, transport and disposal of such medicinal products require highly controlled procedures, including the use of specialised equipment, containment systems, dedicated facilities and trained personnel. Exposure may occur through multiple routes, including inhalation, dermal contact and accidental ingestion, and may affect not only pharmacists and nurses directly involved in handling the drugs, but also ancillary staff responsible for cleaning, waste management and logistics.

Directive (EU) 2022/431 explicitly recognises the need to strengthen protection in relation to hazardous medicinal products, reflecting growing awareness of occupational risks in healthcare settings. National implementation measures, such as the Spanish reform, further reinforce this approach by linking preventive obligations to specific training requirements, procedural standards and surveillance measures in contexts where such agents are used.

The healthcare sector is particularly significant for several reasons. First, it demonstrates that the regulation of reproductive toxicants is not limited to traditional industrial environments but extends to sectors characterised by complex organisational structures and high professional specialisation. Second, it highlights the convergence between chemical safety, occupational health and clinical practice, requiring integration of regulatory compliance with patient care processes.

Third, and perhaps most importantly, the healthcare workforce often includes a high proportion of women of reproductive age, making issues of pregnancy, fertility and reproductive health especially salient. Exposure to hazardous medicinal products in this context raises critical questions regarding task allocation, temporary reassignment, workplace accommodation and the practical implementation of protective measures under Directive 92/85/EEC.

The management of hazardous medicinal products therefore represents a paradigmatic example of the challenges associated with reproductive toxicants: high intrinsic hazard, complex exposure pathways, vulnerable worker populations and significant medico-legal implications. It also illustrates the need for sector-specific guidance, targeted training and integrated prevention strategies, capable of translating general legal obligations into concrete and effective workplace practices.

More broadly, the healthcare example underscores the importance of moving toward a context-sensitive and operationally grounded model of regulation, in which the effectiveness of legal norms depends on their capacity to interact with real-world organisational dynamics, professional practices and exposure scenarios.

4.5 What Italy could still do beyond Legislative Decree No. 135/2024

A comparative perspective on selected European regulatory models provides a useful benchmark for evaluating the strengths and limitations of the Italian system in implementing Directive (EU) 2022/431.

While the Directive establishes a harmonised minimum framework, its practical effectiveness varies significantly across Member States depending on the density of technical standards, institutional capacity and the degree of integration between scientific evidence and preventive practice.

In this regard, several advanced national systems offer relevant points of reference.

The French model is characterised by a strong emphasis on legal formalisation, traceability and binding occupational exposure limits, ensuring a high level of documentation and retrospective reconstructability of exposure, which is particularly important for reproductive outcomes with long latency²⁴.

The German system, by contrast, relies heavily on the integration of scientific knowledge into technical standards, particularly through the TRGS framework, allowing a dynamic and evidence-responsive approach to risk assessment and prevention.

The Dutch model adopts a strongly precautionary orientation, placing the burden on the employer to minimise exposure even in conditions of

²⁴ Ministère du Travail (France). Décret n° 2024-307 du 4 avril 2024 relatif à la protection des travailleurs exposés à des agents CMR. Journal Officiel de la République Française. 2024

uncertainty, especially where non-exposure cannot be conclusively demonstrated²⁵.

Spain, following the recent reform, provides a clear example of explicit normative integration of reproductive toxicants within the classical CMR prevention model, reinforcing substitution, exposure minimisation and the irrelevance of mere compliance with exposure limits²⁶.

Compared with these systems, the Italian framework — although significantly strengthened by Legislative Decree No. 135/2024 — still appears as an integrated but not yet fully mature model.

The reform successfully aligns national law with the expanded CMR regime at a formal level, but the operational dimension remains more dependent on general legal obligations and less supported by detailed technical guidance, harmonised exposure criteria and centralised preventive infrastructures.

This comparative gap is particularly relevant in the field of reproductive toxicants, where scientific uncertainty and complex exposure scenarios require not only legal compliance but also advanced interpretative and technical tools. These comparative insights confirm that formal transposition alone is insufficient to ensure effective worker protection. Rather, the quality of prevention depends on the interaction between legal norms, scientific knowledge and institutional practice.

²⁵ Government of the Netherlands. Working Conditions Decree (Arbeidsomstandighedenbesluit) and national occupational exposure limit system (Grenswaarden). The Hague; updated version

²⁶ Gobierno de España. Real Decreto 612/2024 por el que se modifica la normativa sobre agentes cancerígenos, mutágenos y reprotóxicos en el trabajo. BOE-A-2024-13419

In this sense, the Italian system should be understood not as incomplete, but as undergoing a transition phase from a predominantly compliance-based model toward a more integrated and precautionary approach.

Against this background, several lines of development emerge as particularly relevant for strengthening the Italian system beyond the minimum required by law.

A first priority concerns the need to accelerate the updating of occupational exposure and biological limit values in line with evolving European standards and emerging toxicological evidence, especially for substances of particular concern such as lead and diisocyanates.

At the same time, greater emphasis should be placed on the development of sector-specific technical guidance capable of translating general legal obligations into operational tools, particularly in high-risk contexts such as healthcare, battery manufacturing, laboratory settings and small-scale chemical processing.

A further area of improvement lies in the strengthening of institutional coordination and technical support, including the development of dedicated national guidance for hazardous medicinal products through collaboration between the Ministry of Health, INAIL, regional authorities and scientific bodies.

In parallel, the establishment of centralised digital systems for the registration of exposures to carcinogens, mutagens and reproductive toxicants would significantly enhance traceability and facilitate epidemiological monitoring.

From a preventive perspective, greater attention should also be devoted to the qualitative improvement of occupational health surveillance, with more explicit integration of reproductive endpoints and, where appropriate, the use of biological monitoring.

In addition, the persistence of a two-tier regulatory structure suggests the need for a more precautionary approach to the management of Category 2 reproductive toxicants, particularly in sectors characterised by high or complex exposure scenarios, even in the absence of formal inclusion within the CMRD framework.

Finally, a more coherent integration between reproductive toxicant regulation and broader systems of maternity and paternity protection appears essential. This includes clearer criteria for task adaptation, temporary reassignment and the identification of incompatible exposures during pregnancy and breastfeeding, ensuring that legal obligations are effectively translated into workplace practice.

GENERAL DISCUSSION

The findings of this thesis support a coherent and multidimensional interpretation of the recent evolution of EU occupational health law in relation to reproductive toxicants. Directive (EU) 2022/431 is best understood as a paradigm shift rather than a simple extension of the scope of Directive 2004/37/EC. It expands a specific regulatory logic—based on substitution, exposure minimisation, health surveillance and traceability—to a domain of harm that had long been comparatively under-protected despite its severity. This evolution reflects a broader transformation in EU occupational risk governance, increasingly oriented toward precaution and hazard-based regulation.

At the same time, the analysis demonstrates that formal legal transposition is necessary but not sufficient to ensure effective worker protection. Comparative evidence shows that the practical impact of Directive (EU) 2022/431 depends heavily on national institutional capacity, the availability of technical standards, the development and operationalisation of occupational exposure limits, and the effectiveness of enforcement mechanisms.

Countries such as Germany, France and the Netherlands illustrate different but converging approaches to bridging the gap between legal requirements and operational practice, while Italy—despite having taken a decisive legislative step forward through Legislative Decree No. 135/2024—still requires further development in technical guidance, exposure governance and health surveillance systems.

A deeper level of analysis emerges when the regulatory framework is examined in light of recent scientific developments.

The regulation of reproductive toxicants reveals structural limitations within the current paradigm of occupational risk assessment, particularly when confronted with the complexity of contemporary toxicological evidence. The integration of recent interdisciplinary literature provides a critical lens through which the Directive itself can be evaluated, showing that the underlying scientific assumptions of occupational risk regulation are increasingly under strain.

The current body of scientific literature on occupational reproductive risks—encompassing studies by Claessens et al., Samardžić et al., Schenk et al., Ladeira, Clark et al., Miller et al. and Ramezanifar et al., together with the conceptual contribution from the *Scandinavian Journal of Work, Environment & Health* (2020)—converges toward a unified conclusion: the traditional paradigm of occupational risk regulation is structurally insufficient to address reproductive toxicity, and this limitation directly affects the implementation and effectiveness of Directive (EU) 2022/431.

Across the literature, reproductive toxicity emerges as a multifactorial, latency-driven and biologically complex phenomenon, in which causal relationships are difficult to establish with certainty, particularly in human populations. As further elaborated in Chapter 3.7, this complexity is not merely empirical but epistemological. The challenge identified in the SJWEH contribution—namely the transition from “suggestive” to “conclusive” evidence in endocrine

disruption—reflects a structural mismatch between scientific knowledge and regulatory thresholds. This gap is further amplified by the recognition that occupational exposures rarely occur in isolation, but rather as chronic, low-dose, multi-agent exposures, often involving endocrine-disrupting chemicals capable of producing non-monotonic dose–response effects, epigenetic modifications and transgenerational outcomes.

These emerging scientific insights fundamentally challenge regulatory models based on single-substance assessment and threshold-dependent safety concepts, which still underpin much of EU occupational risk regulation.

In particular, the evidence discussed highlights the growing relevance of internal dose variability, cumulative exposure, mixture toxicity and exposome-based approaches, all of which require a rethinking of how occupational risk is conceptualised, measured and managed.

Within this framework, Directive (EU) 2022/431 represents a significant legal advancement by extending the stricter regime of Directive 2004/37/EC to include reproductive toxicants classified as Category 1A and 1B under the CLP Regulation. This shift introduces a hazard-based and precautionary logic, whereby the classification of a substance itself triggers enhanced preventive obligations—independently of quantitative risk estimation—and therefore aligns with the scientific literature’s call for earlier intervention in the face of uncertainty.

However, the same body of evidence also reveals that the Directive remains only partially aligned with contemporary scientific knowledge. A key

limitation lies in its reliance on formal hazard classification as the threshold for activating stricter protection. As highlighted both in Chapter 4 and in the scientific analysis of Chapter 3.7, a substantial number of substances with suspected or emerging reproductive effects—particularly those classified as Category 2 or not yet classified—remain outside the scope of the strengthened CMR regime and continue to be regulated under the more flexible framework of Directive 98/24/EC. This creates a two-tier regulatory structure, in which well-established hazards receive stringent protection, while uncertain but potentially harmful exposures are subject to weaker preventive obligations.

A second major limitation concerns the role of occupational exposure limits (OELs). The literature consistently shows that OEL coverage for reproductive toxicants is incomplete, heterogeneous across Member States, and often not specifically designed to capture reproductive endpoints. As further emphasised in Chapter 3.7, OELs also fail to adequately account for cumulative exposure, mixture effects and internal dose variability, particularly in the context of endocrine-disrupting mechanisms and low-dose effects. Consequently, compliance with exposure limits does not necessarily ensure effective protection, particularly in contexts characterised by chronic, low-level exposure and complex exposure scenarios.

A further critical dimension relates to vulnerable workers. The literature highlights that traditional occupational risk models have been largely based on male populations, resulting in systematic underestimation of female reproductive risks and insufficient integration of pregnancy-related

vulnerabilities into risk assessment processes. More recent evidence reinforces the need for gender-sensitive and life-stage-specific approaches, capable of capturing differential susceptibility and exposure patterns.

Although Directive (EU) 2022/431 strengthens protection for workers exposed to reprotoxic substances, its effectiveness depends on its interaction with Directive 92/85/EEC and on the availability of harmonised operational criteria for risk assessment and management, which currently remain fragmented across Member States.

In addition, scientific contributions increasingly emphasise the need to move beyond traditional external exposure assessment toward more integrated models incorporating biomonitoring, internal dose evaluation and exposome-based approaches. This shift represents not only a technical refinement but a conceptual transformation in occupational risk assessment, requiring closer integration between occupational and environmental exposure, as well as stronger alignment between toxicological evidence and regulatory decision-making.

Taken together, these findings reveal a fundamental tension between the static, classification-driven structure of current regulation and the dynamic nature of evolving scientific evidence. Directive (EU) 2022/431 represents a decisive step toward a more precautionary regulatory model, but it remains partly reactive, intervening primarily when hazards reach a high level of evidentiary certainty. In contrast, the scientific literature consistently supports a proactive and

uncertainty-oriented approach capable of addressing emerging risks at earlier stages and under conditions of incomplete knowledge.

From a regulatory and medico-legal perspective, this implies that the duty of care imposed on employers must be interpreted dynamically and expansively. Compliance cannot be reduced to formal adherence to classification and exposure limits; rather, it must encompass precautionary management of suspected reproductive toxicants, consideration of cumulative and mixed exposures, gender-sensitive and life-stage-specific risk assessment, and strengthened health surveillance systems focused on reproductive endpoints. In this sense, the integration of emerging scientific evidence directly reshapes the interpretation of legal obligations, extending the scope of preventive responsibility beyond formal compliance.

Overall, the thesis suggests that reproductive risk regulation represents a critical testing ground for the future evolution of EU occupational health law. It highlights the need for a more integrated, adaptive and science-informed regulatory model capable of bridging the gap between legal standards and biological complexity, and of translating evolving scientific knowledge into effective and equitable workplace protection.

CONCLUSION

This thesis has examined the practical implications of recent regulatory reforms on reproductive toxicants within the European Union, with particular focus on Directive (EU) 2022/431 and its transposition into Italian law through Legislative Decree No. 135/2024. The analysis demonstrates that the inclusion of Category 1A and 1B reproductive toxicants within the Carcinogens, Mutagens and Reprotoxicants Directive (CMRD) represents a significant strengthening of the legal architecture of worker protection, aligning reproductive risk with other high-consequence health hazards such as carcinogenicity and mutagenicity.

At a normative level, the Directive marks a clear transition from a predominantly risk-based approach toward a more hazard-oriented and precautionary regulatory model. As discussed, this shift has important practical consequences: employers are now required to prioritise substitution, minimise exposure beyond mere compliance with limit values, implement mandatory health surveillance, and ensure long-term traceability through exposure registers. These obligations redefine the standard of care in occupational health, particularly in contexts where reproductive hazards are present and where scientific uncertainty remains significant.

However, the thesis also demonstrates that this regulatory advancement remains only partial. Central limitation lies in the persistence of a two-tier system of protection, whereby only substances classified as Category 1A and 1B under the CLP Regulation fall within the stricter CMR regime, while

suspected reproductive toxicants (Category 2) continue to be governed by the more flexible framework of Directive 98/24/EC. This distinction is difficult to reconcile with current scientific evidence, as discussed in Chapter 3 and in the expanded analysis of scientific uncertainty in Chapter 4.4, which shows that reproductive toxicity is often characterised by uncertainty, delayed manifestation and evolving classification. As a result, the existing framework risks under-protecting workers precisely in those contexts where precaution would be most justified.

Furthermore, the analysis highlights structural weaknesses in the current reliance on occupational exposure limits (OELs) as primary tools of risk control. The literature consistently demonstrates that OELs for reproductive toxicants are incomplete, unevenly distributed across Member States, and not always tailored to reproductive endpoints or low-dose endocrine mechanisms. Consequently, compliance with exposure limits cannot be equated with effective protection, particularly in complex exposure scenarios involving mixtures, cumulative effects and long-term biological interactions.

The thesis also underscores the importance of addressing vulnerability and gender-specific risk. As contextualised by recent scientific evidence, traditional occupational risk models have often failed to adequately capture differences in susceptibility related to sex, reproductive status and life stage, leading to gaps in protection for pregnant workers and workers of reproductive age. Although Directive (EU) 2022/431 strengthens the legal framework, its effectiveness ultimately depends on its interaction with Directive 92/85/EEC and on the

development of harmonised and operational risk assessment criteria across Member States.

From a comparative perspective, the research confirms that the effectiveness of EU legislation is strongly mediated by national implementation. While countries such as Germany, France and the Netherlands have developed advanced systems characterised by strong integration of scientific evidence, binding exposure limits and precautionary approaches, Italy—despite its formal compliance through Legislative Decree No. 135/2024—still requires further development in terms of technical guidance, surveillance systems and operational tools. This highlights a broader structural issue within EU occupational health law: harmonisation at the level of legal principles does not necessarily translate into uniform levels of protection in practice.

Taken together, these findings point toward a broader conclusion. The regulation of reproductive toxicants is not merely an incremental extension of existing chemical risk frameworks but it represents a fundamental challenge to the underlying logic of occupational health regulation. As discussed, reproductive toxicity—characterised by low-dose effects, endocrine disruption, multifactorial causation and transgenerational impact—requires a more adaptive, integrative and precautionary approach, capable of operating under conditions of scientific uncertainty.

In this context, Directive (EU) 2022/431 should be understood as a crucial but transitional step: future regulatory developments at both EU and national level should aim to reduce the gap between scientific evidence and legal protection

by strengthening the role of precaution in the management of suspected reproductive toxicants, expanding and harmonising occupational exposure limits, integrating biomonitoring and exposome-based approaches into risk assessment, and developing clearer and more consistent criteria for the protection of vulnerable workers.

For Italy, this implies moving beyond formal transposition toward a more mature and operational system of prevention. This could include the development of sector-specific technical guidance, the establishment of centralised exposure registers, the strengthening of occupational health surveillance protocols with specific attention to reproductive endpoints, and the adoption of precautionary measures for Category 2 substances in high-exposure contexts.

In conclusion, reproductive toxicants have emerged as a central issue in the evolution of EU occupational health law. Directive (EU) 2022/431 represents a decisive advancement, but the integrated scientific evidence analysed throughout this thesis demonstrates that full and effective protection of reproductive health in the workplace requires a further shift toward a dynamic, science-informed and precautionary regulatory model. Only through such an approach can the law adequately respond to the complexity of reproductive risks and ensure equitable protection for all workers, particularly those most biologically and occupationally vulnerable.

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