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Review article

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Occupational exposure to genotoxic chemical substances in clinical diagnostic laboratories and cellular mechanisms related to DNA damage: systematic review of observational studies

Exposição ocupacional a substâncias químicas genotóxicas em laboratórios de diagnósticos clínicos e mecanismos celulares relacionados a danos no DNA: revisão sistemática de estudos observacionais

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Abstract

Objectives: To identify the main genotoxic chemical substances used in different clinical diagnostic laboratories and to investigate the cellular mechanisms involved in DNA damage caused by these substances. **Methods:** To identify the genotoxic chemical substances used in diagnostic laboratories, a systematic review was conducted. To investigate the cellular mechanisms associated with DNA damage caused by these substances, systems biology was applied to construct interaction networks between the chemical compounds and proteins. **Results:** A total of 20 full articles were assessed for eligibility. The main genotoxic substances used in laboratories identified in the included studies were: formaldehyde, n-hexane, and methanol. In the systems biology analysis, bioprocesses such as post-translational modification, phosphorylation, response to apoptosis, regulation of cell communication, and cellular response to reactive oxygen species, among others, stood out. **Conclusion:** Twenty-four substances potentially harmful to DNA were identified in clinical analysis laboratories. The bioprocesses associated with these substances may be related to cellular processes that lead to DNA damage.

Keywords: Chemicals; Genotoxicity; DNA; Occupational Exposure; Laboratory; Occupational Health; Systematic Review; Systems Biology.

Resumo

Objetivos: Identificar as principais substâncias químicas genotóxicas utilizadas em diferentes laboratórios de diagnósticos clínicos e investigar os mecanismos celulares envolvidos nos danos ao DNA por essas substâncias. **Métodos:** Para identificar as substâncias químicas genotóxicas utilizadas em laboratórios diagnósticos foi feita uma revisão sistemática. Para investigar os mecanismos celulares associados aos danos ao DNA causados por essas substâncias foi utilizada a biologia de sistemas, constituindo redes de interação entre os compostos químicos e proteínas. **Resultados:** Um total de 20 artigos completos foram avaliados quanto à elegibilidade. As principais substâncias genotóxicas utilizadas em laboratórios identificadas nos estudos incluídos foram: formaldeído, n-hexano e metanol. Na análise de biologia de sistemas, destacaram-se bioprocessos como modificação pós-traducional, fosforilação, resposta à apoptose, regulação da comunicação celular e resposta celular às espécies reativas de oxigênio, entre outros. **Conclusão:** Foram identificadas 24 substâncias potencialmente danosas ao DNA, presentes em laboratórios de análises clínicas. Os bioprocessos identificados para essas substâncias podem estar relacionados a processos celulares que conduzem a danos ao DNA.

Palavras-chave: Produtos Químicos; Genotoxicidade; DNA; Exposição Ocupacional; Laboratório; Saúde do Trabalhador; Revisão Sistemática; Biologia de Sistemas.

Introduction

Occupational exposure refers to the contact of workers, individually or collectively, with chemical, physical, biological, or mechanical risk agents present in the workplace. Occupational health aims to protect and promote the health of workers, through actions to monitor risks, the consequences of exposure, treat symptoms and monitor signs, to reduce and prevent occupational diseases[1].

In the ranking of risks related to the global burden of diseases in Brazil, occupational factors occupy a prominent position compared to other determinants[2,3]. However, exposure to chemical agents in the workplace is still poorly characterized and often underestimated. Most of the available data comes from studies with small samples, restricted to certain economic sectors or specific occupations. It is important to note that the characterization of exposure does not depend exclusively on direct measurements, which are not always feasible; it can also be carried out by observing the work, with the support of qualitative tools and modelling systems[2,4].

The chemical agents present in clinical diagnostic laboratories represent significant health hazards for technicians working in different sectors. Exposure to these substances, which can be present in various forms such as solids, liquids, gases, or vapors, constitutes an occupational risk with the potential to cause temporary and permanent adverse effects on occupational health[3,5].

According to Regulatory Standard No. 26 (NR 26), every chemical product sold in Brazil must have a Safety Data Sheet (SDS), as standardized by the Brazilian Association of Technical Standards (ABNT) in ABNT NBR 14725:2023 (corrected version: 2024)[6]. This document provides essential safety, health, and environmental information, including guidance on hazards, preventive measures, and handling, storage, and disposal procedures. It is the supplier's responsibility to provide adequate information on the hazards associated with the product, ensuring that workers have access to clear instructions on how to avoid accidents and occupational illnesses[6].

Despite the existence of specific regulations, many SDSs, like the old Chemical Safety Data Sheets (CSDS), still contain incomplete, vague, or outdated information, which compromises worker protection. Inconsistent data, such as the identification of hazardous ingredients, exposure limits, or control measures, makes it difficult to systematically collect and compare information from different sources. This prevents the consolidation of reliable data, negatively affecting the preparation of accurate statistics on accidents and occupational diseases related to exposure to chemical agents and, consequently, hindering the planning of preventive actions and worker health surveillance[7].

In Brazil, the safe use of chemical products is regulated by various standards, including: (a) the Resolutions of the Collegiate Board (RDC), issued by the Brazilian National Health Surveillance Agency (ANVISA); (b) the Regulatory Norms (NR) of the Ministry of Labor and Employment, such as NR 26, which deals with the labeling and identification of chemical products[8]; and (c) the Brazilian Standards (NBR), from ABNT, which establish technical safety requirements for different environments, such as clinical laboratories[6] (ABNT, 2024). In this context, chemical safety is an essential strategy for promoting workers' health and preventing occupational accidents[3,7,9].

Among the health problems related to exposure to chemical products, occupational cancer stands out as one of the most common diseases. It is estimated that approximately 19.0% of cancer cases are occupational in origin, accounting for around 4.0% of cancer deaths. Of these, around 12.5% are associated with lung cancer, often linked to the inhalation of organic solvents and other agents present in work environments[10]. This information reinforces the relevance of the topic addressed in this study, which discusses the occupational risks associated with exposure to solvents and their possible health consequences.

As genotoxicity represents one of the initial mechanisms in the development of cancer, especially in chronic exposures to chemical agents such as solvents, its evaluation is essential to understand and prevent the long-term effects on occupational health. Despite this, to date there have been no studies systematizing the main chemical substances used in diagnostic laboratories, the genotoxic effects associated with their exposure, and

the cellular mechanisms involved in this damage[3,10]. This makes it necessary to identify the substances with genotoxic potential present in these environments and to understand their effects, both individually and in mixtures, which reflect more realistic exposures. To this end, the use of systems biology can provide relevant support, allowing us to map the interaction networks between chemical compounds and cellular proteins involved in genotoxicity processes, contributing to an integrated understanding of the molecular mechanisms of DNA damage.

The aim of this study was therefore to identify, through a literature review, the main genotoxic chemical substances used in diagnostic laboratories and, with the support of systems biology, to investigate the cellular mechanisms involved in DNA damage caused by these substances, considering both isolated and complex exposures.

Methods

Literature sources and search strategy

A systematic literature review was conducted, searching the databases PubMed/Medline and SCOPUS, to identify studies on occupational exposure to chemical agents used in laboratories and the induction of DNA damage.

The search strategy was based on the elements of the PEOS acronym (population, exposure, outcome, and study type)[11]. The population was defined as workers of any age, gender, or ethnicity. Exposure was defined as occupational exposure to physical and chemical agents. The main outcomes were the following genetic damage: DNA damage, numerical and/or structural chromosomal abnormalities, micronucleus alterations, carcinogenic effects, and mutations. No additional outcomes were included. The type of study was delimited as observational.

The combinations of search terms were structured using Boolean operators to connect the exposure of interest (occupational exposure to chemical agents) and the adverse health outcome of interest (biomarkers of DNA damage, genetic damage). This resulted in the following strategies: 1. "DNA AND damage AND clinical AND laboratory AND workers"; 2. "DNA AND damage AND pathology AND laboratory AND (workers OR occupational) AND exposure AND chemical".

Selection of studies and data extraction

The literature search was carried out between April 2021 and March 2022. It was limited to studies published from 2002 to 2020, in languages known to the authors (English, Portuguese and Spanish), which indicate genetic damage occurring in workers occupationally exposed to chemical agents in Brazil and worldwide.

The inclusion criteria were: observational studies that investigated whether occupational exposure to physical and chemical agents alters the risk/occurrence of genetic damage in the exposed population. The exclusion criteria were: 1) *in vitro* experimental studies, 2) *in vivo* and *ex-vivo* animal studies, 3) *in silico* studies, 4) studies of the effects on non-target species other than humans, 5) letters, reviews, editorials, reports, commentaries, theses, documents issued by regulatory bodies, and book chapters, 6) complete articles not available or those not available in English, Portuguese, and Spanish.

After the electronic and manual search and the exclusion of duplicates, two reviewers (AB and JS) independently assessed the relevant literature. The first screening was based on titles and abstracts. Relevant references were screened again, basing the decision on full texts. If a disagreement persisted after being thoroughly discussed by the two reviewers, a third investigator (FS) was asked to resolve it. The study selection stages were documented in a flowchart.

For each study included, information was extracted to identify the study (title, authors, year of publication, journal, DOI); information on the study design (type of study, location, year and period in which it was carried out); information on studies identifying genetic damage from occupational exposure; the quality of the studies; the occupations related to the appearance of genetic damage; the most studied exposures, e.g.: organic solvents; the types of genetic tests used in occupational exposure studies to assess DNA damage; the test methods used, staining, how many points were assessed (comet and micronucleus tests): the most common biological samples; and the biological samples used to assess DNA damage caused by occupational exposure.

The data was extracted manually by two independent reviewers (AB and JS), that registered the information in electronic spreadsheets (Microsoft Excel), previously structured with the fields of interest. The data was categorized descriptively according to the objectives of the review. Divergences in extraction were resolved by consensus, with the help of the third reviewer (FS) when necessary.

Quality assessment

The methodological quality of the studies was assessed manually by two independent reviewers (AB and JS), based on criteria previously defined by the authors, taking into account the clarity of the description of the study population, the characterization of occupational exposure, the methods used to assess genetic damage, the adequacy of the analyses, and the coherence of the results presented.

Systems biology

Systems biology involves the integration of substance data with computer programs[12]. The *in silico* evaluation of the interaction of substances with *Homo sapiens* proteins was carried out by constructing and analyzing interaction networks. To do this, the substances that appeared most frequently in the review were evaluated. In this way, networks were built with formaldehyde, methanol, and n-hexane using interaction search tools. STITCH 5.0 (http://stitch.embl.de)[13] performed the search for chemical-protein interactions, and the search tool for protein-protein interactions was STRING 11.5 (http://string-db.org)[14,15,16]. In STITCH chemical compounds are connected to proteins by means of evidence derived from experiments, databases and available literature[15]. The subnetworks formed in STITCH were imported using the following parameters: no more than 50 interactions, medium confidence score (0.400); and network depth equal to 2; prediction methods activated except text mining. The subnetworks created were augmented in STRING 10.5. This search tool predicts protein interactions that can be directly (physically) and indirectly (functionally) associated[16]. In STRING 11.5, protein-protein interactions were imported using the parameters: no more than 50 interactions, medium confidence score (0.400); and network depth equal to 2; prediction methods activated except for text mining. The different subnetworks generated in these two processes were joined individually using the Advanced Merge Network tool in the Cytoscape 3.8.2[17] program, generating the METHANOL, FORMALDEHYDE, and N-HEXANE networks.

Funrich 3.1.4 was used to perform a general analysis of the biological processes present in each interaction network. Funrich is open-access software that facilitates the analysis of proteomic data, providing tools for functional enrichment and analysis of gene and protein interaction networks[18].

The networks were analyzed using the Molecular Complex Detection (MCODE) plug*in* in the Cytoscape 3.8.2 program, to identify the modules (clusters) - strongly connected regions - which suggest physically and/or functionally related protein complexes. The Biological Network Gene Ontlogy (BiNGO) plugin was also used to analyze the main bioprocesses associated with the clusters generated by MCODE, which is very useful for directing the analysis of the network with its compounds and proteins. To analyze the centrality of the network, the Centiscape 2.2 plugin was used to identify the nodes (protein-compound) that have central positions. The centralities analyzed were node degree, which refers to the number of adjacent nodes directly connected to another node, and betweenness, which refers to the number of "shortest" paths that pass through a single node, making it possible to estimate the relationship between them[19] .

Hubs are proteins and/or compounds (nodes) with a high node degree value, i.e. with a large number of connections to other nodes or hubs with fewer connections, while nodes with a relatively high betweenness value are known as "bottlenecks" (hub-bottleneck: HG), due to their high capacity to interact with other proteins or bioprocesses[19]. This is why hub-bottlenecks are so essential in the network and, once disturbed or removed, can trigger failures within it.

Results

Systematic review

The electronic searches identified 116 records relating to occupational exposure. Ninety-six records were excluded because they were not articles related to the topic studied. A total of 20 articles were included in the review (**Figure 1**).

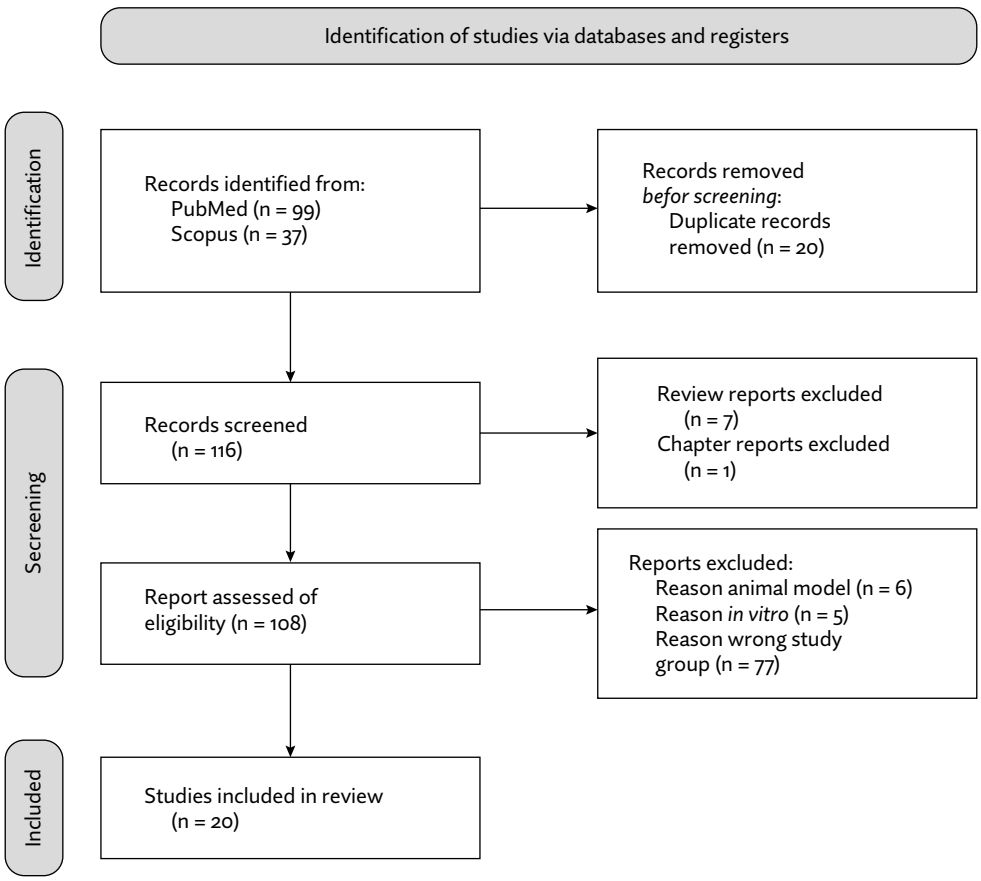

Figure 1 Flowchart of the study

Table 1 details the studies identified in this review investigating occupational exposure to organic solvents and their genotoxic effects. The articles included evaluated genotoxicity using cytogenetic tests widely used in human biomonitoring, with a focus on detecting genotoxic effects resulting from occupational exposure. Among the most frequent tests are the micronucleus test, structural and numerical chromosome aberrations, sister chromatid exchanges (SCE), nucleoplasmic bridges (NPB), nuclear budding (NBUD), and the comet assay. All the studies analyzed reported a significant increase in genotoxicity in the exposed individuals compared to the control groups. Formaldehyde was the most investigated agent, with 18 studies specifically addressing its exposure in occupational contexts. In addition, most of the studies evaluated exposure to mixtures of chemical agents rather than isolated compounds, reflecting the complexity of occupational environments.

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Table 1 Manuscripts from this review evaluating occupational exposure to chemical agents and their relationship with genotoxicity (N=20)

Study	Exposure (country)	Smoking (%)	Genotoxicity (exposed/ control)	Use of protective equipment	Substance of occupational exposure	Conclusion	Reference
1	Pathology laboratory (Tunisia)	10.00%	Micronucleus: ↑3,58	80% wore gloves; 6% wore lab coats	Formaldehyde (FA exposure level was 3.4 ppm)	Exposure induced genotoxicity (increase in mutations)	21
2	Research laboratory (Brazil)	13.90%	Chromosomal aberrations: ↑4,10	Gloves, masks and goggles	Substances detected by colorimetric testing in the air analyzed by health personnel: Hydrochloric acid; Methanol; Isopropyl alcohol; Chloroform; Formaldehyde; Carbon tetrachloride; Ethyl acetate. Questionnaire: Before the study, each person completed a questionnaire about their lifestyle, professional history, exposure to known genotoxic agents and medical history, including recent illnesses and treatments received	Exposure induced genotoxicity (increase in mutations)	22
3	Pathology laboratory (Portugal)	41.00%	Micronucleus: ↑0,71	Not used	n-hexane, toluene, methyl, ethyl, acetone and formaldehyde	Exposure induced genotoxicity (increase in mutations)	23
4	Hospital anatomy laboratory pathological (Portugal)	20.00%	Micronucleus: ↑2.5; SCE: ↑1,3	Disposable face masks	Formaldehyde	Exposure induced genotoxicity (increase in DNA damage and mutations)	24

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Continuation

5	Histopathology laboratory (India)	45.00%	Micronucleus: ↑2,54	Not used	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	25
6	Pathology laboratory (Brazil)	0%	Comet assay (blood cells): ↑3.16; Buccal micronucleus cytome assay: Micronucleus: ↑1.5; Binucleated cells: ↑1.05; Kariolytic cells: ↑2.66; Apoptotic cells: ↑2.12; Condensed chromatin: ↑2.24	100% wore only lab coats; 50% wore gloves; and no use of masks or safety glasses	Xylene	Exposure induced genotoxicity (increased DNA damage and mutations) and cell death	26
7	Pathology laboratory (Portugal)	30.90%	Micronuclei (peripheral blood lymphocytes): ↑2.33; Micronuclei (oral cavity epithelial cells): ↑7,34	Masks	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	27
8	Pathology laboratory (Hungary)	25.80%	Chromatid-type aberration: ↑2.61; and aneuploidy: ↑1,66	Not specified	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	28
9	Hospital laboratory of pathology (Portugal)	25.00%	Micronucleus: ↑1.67; SCE: ↑1.37; Comet assay (comet tail length): ↑1,43	Not specified	Formaldehyde	Exposure induced genotoxicity (increase in DNA damage and mutations)	29
10	Pathology laboratory (Portugal)	30.95%	Micronucleus (peripheral blood lymphocytes): ↑3.16; Micronuclei (buccal epithelial cells): ↑4,92	Ventilation in the environment	Formaldehyde	Exposure induced genotoxicity (increased mutations)	30

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Continuation

11	Pathology and anatomy laboratory (France)	22.00%	Micronuclei:↑1.52; Micronuclei with centromeres: ↑1.67; Monocentromeric micronuclei: ↑3.54; Acentromeric micronuclei: ↑0,9	Not informed	Formaldehyde	Exposure induced genotoxicity (increased DNA damage and mutations)	31
12	Clinical laboratory (molecular biology, histology, immunology and microbiology) (France)	0%	Micronucleus: ↑1,4	Personal protective equipment, no specifications	Complex mixture of chemical products (not specified in the study)	Exposure induced genotoxicity (increased DNA damage and mutations)	32
13	Histopathology laboratories (Portugal)	24.50%	Micronuclei (lymphocytes): ↑4.88; NPB (nucleoplasmic bridges): ↑16.8; NBUD (nuclear sprouts): ↑14; Micronuclei in buccal cells: ↑6	Use of protective measures, no specifications	Formaldehyde	Exposure induced genotoxicity (increased DNA damage and mutations)	33
14	Pathology laboratories (Portugal)	25.00%	Chromosomal aberrations: ↑1,91	Not informed	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	34
15	Pathology laboratories (Italy)	26.20%	M1dG: ↑2.37	Not informed	Formaldehyde	Exposure induced DNA adducts	35
16	Pathology laboratories (Turkey)	57.50%	Micronucleus: ↑1,65	None	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	36

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Continuation

17	Pathology laboratories (Portugal)	20.00%	Micronuclei (peripheral blood lymphocytes): ↑2.05; Micronuclei (buccal mucosa cells): ↑5,91	Not informed	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	37
18	Pathology laboratories (Portugal)	25.00%	Micronucleus: ↑1.55; SCE: ↑1.27; MNB: ↑4.08; NBud: ↑2.88; TCR-Mf: ↑1.03	Disposable face masks for biological hazards and formaldehyde vapors	Formaldehyde	Exposure induced genotoxicity (increased DNA damage and mutations)	38
19	Pathology laboratories (Germany)	Not informed	Micronucleus: ↑1,50	Not reported	Formaldehyde	Exposure induced genotoxicity (increase in mutations)	39
20	Laboratory of urinalysis and biochemistry (Brazil)	0%	Urine tested on *Salmonella typhimurium* strain YG1024 with S9mix: ↑revertants	Full protective equipment is only used for acetonitrile	Ethanol; benzene; dichloromethane; n-hexane; dimethylsulfoxide; β-nicotinamide adenine dinucleotide hydrate sodium phosphate salt; D-glucose-6-phosphate disodium; L-histidine monohydrate; sodium azide; 4-nitro-o-phenylenediamine; D-biotin; Formaldehyde; ethyl acetate; acetonitrile; methanol; acetone; propylene oxide; ethylene	Exposure induced genotoxicity (increased mutations)	40

Notes: Upward arrows mean a significant increase compared to the control group. Sister chromatid exchange (SCE); binucleated cells in the micronucleus test (MNB); nuclear buds (NBud); reciprocal chromosome exchange/fragment mutations (TCR-Mf).

Table 2 presents the list of 24 chemical substances identified in the different laboratories described in the selected articles, the number of studies that reported them, and their classification according to the GHS (Globally Harmonized System)[6,20]. All chemical agents reported in the articles were associated with chemical exposure in clinical analysis laboratories, including urinalysis, biochemistry, pathology, immunology, microbiology, histology, and clinical chemistry sectors, as well as in research laboratories handling chemical and biological substances. It is noteworthy that 18 studies cited formaldehyde as the main chemical agent, followed by methanol (2 studies) and n-hexane (2 studies).

Table 2 Chemical substances used in different laboratories, its CAS number, GHS classification, and articles in which they were identified

Substance (CAS)	GHS classification	References
Formaldehyde (CAS: 50-00-0)	Flam. Liq. 4; Acute Tox. 3 (oral); Acute Tox. 3 (inh); Skin Corr. 1B; Eye Dam. 1; Resp. Sens. 1; Skin Sens. 1; Muta. 2; Carc. 1B; STOT SE 3	21 to 25, 27 to 31, 33 to 40
Acetone (CAS: 67-64-1)	Flam. Liq. 2; Eye Irrit. 2; STOT SE 3	23
Ethylene (CAS: 74-85-1)	Flam. Gas 1; Press. Gas	40
Benzene (CAS: 71-43-2)	Flam. Liq. 2; Carc. 1A; Muta. 1B; STOT RE 1; Asp. Tox. 1	40
Propylene oxide (CAS: 75-56-9)	Flam. Liq. 1; Acute Tox. 3 (oral, dermal, inh); Eye Irrit. 2; STOT SE 3; Muta. 1B; Carc. 1B	40
n-hexane (CAS: 110-54-3)	Flam. Liq. 2; STOT RE 2; Asp. Tox. 1; STOT SE 3	23, 40
Toluene (CAS: 108-88-3)	Flam. Liq. 2; Repr. 2; STOT RE 2; Asp. Tox. 1; STOT SE 3	23
Methyl ethyl ketone (CAS: 78-93-3)	Flam. Liq. 2; Eye Irrit. 2; STOT SE 3	23
Ethyl acetate (CAS: 141-78-6)	Flam. Liq. 2; Eye Irrit. 2; STOT SE 3	22
Carbon tetrachloride (CAS: 56-23-5)	Acute Tox. 3 (oral, dermal, inh); Carc. 2; STOT RE 1; Aquatic Chronic 3; Ozone 1	22
Chloroform (CAS: 67-66-3)	Acute Tox. 4 (oral); Acute Tox. 3 (inh); Carc. 2; STOT RE 2	22
Isopropyl alcohol (CAS: 67-63-0)	Flam. Liq. 2; Eye Irrit. 2; STOT SE 3	22
Methanol (CAS: 67-56-1)	Flam. Liq. 2; Acute Tox. 3 (oral, dermal, inh); STOT SE 1	22, 40
Hydrochloric acid (CAS: 7647-01-0)	Press. Gas; Acute Tox. 3 (inh); Skin Corr. 1A	22
Xylene (CAS: 1330-20-7)	Flam. Liq. 3; Acute Tox. 4 (inh); Skin Irrit. 2; Eye Irrit. 2; STOT SE 3; STOT RE 2; Asp. Tox. 1	26

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Ethanol (CAS: 64-17-5)	Flam. Liq. 2; Eye Irrit. 2	40
Dichloromethane (CAS: 75-09-2)	Carc. 2; STOT SE 3	40
Dimethylsulfoxide (CAS: 67-68-5)	Not classified as hazardous according to GHS	40
β-Nicotinamide adenine dinucleotide phosphate sodium salt hydrate (NADP dinucleotide; CAS: 1184-16-3)	Not classified as hazardous according to GHS	40
Disodium D-glucose-6-phosphate (CAS: 3645-24-7)	Not classified as dangerous according to GHS	40
L-histidine monohydrate (CAS: 5934-29-6)	Not classified as dangerous according to GHS	40
Sodium azide (CAS: 26628-22-8)	Acute Tox. 2 (oral); Aquatic Acute 1; Aquatic Chronic 1	40
4-Nitro-o-phenylenediamine (CAS: 100-01-6)	Acute Tox. 3 (oral); Skin Sens. 1; Eye Irrit. 2	40
D-biotin (CAS: 58-85-5)	Not classified as hazardous according to GHS	40

Notes: GHS classifications (Globally Harmonized System; ABNT, 2024) include categories such as: Flam. Liq.: Flammable liquid; Acute Tox.: Acute toxicity; Skin Corr.: Skin corrosion; Skin Irrit.: Skin irritation; Skin Sens.: Skin sensitization; Eye Irrit.: Eye irritation; Eye Dam.: Serious eye damage; Resp. Sens.STOT SE: Specific target organ toxicity - single exposure; STOT RE: Specific target organ toxicity - repeated exposure; Carc.: Carcinogenicity; Muta.: Mutagenicity; Repr.: Reproductive toxicity; Asp. Tox.: Aspiration hazard; Press. Gas: Gas under pressure; Ozone: Hazardous to the ozone layer; Aquatic Acute/Chronic: Hazardous to the aquatic environment. The information was obtained from sources such as ECHA and ChemRadar. List of the chemical substances used in different laboratories, and how they are related to toxicity according to the GHS (Globally Harmonized System) classifications.[6,20]

Systems biology

The FORMALDEHYDE network has 597 nodes and 17,602 connectors, the N-HEXANE network has 561 nodes and 18,974 connectors, and the METHANOL network has 548 nodes and 12,403 connectors (**Appendix A, Supplementary Figures 1, 2 and 3**). A general analysis of the biological processes of each network was carried out using FunRich, where it is possible to observe repair proteins, anti-apoptotic proteins and cell communication proteins connected to formaldehyde ($p < 0.05$). Regarding the N-HEXANE network, more than 45% of the genes are associated with cell communication pathways, while for the METHANOL network, the energy metabolism and signal transduction bioprocesses stand out (**Appendix A, Supplementary Figures 4, 5 and 6**).

We applied cluster analysis to each network using the MCODE plugin. Clustering can provide relevant information on large sets of nodes, as it shows which clusters have more common characteristics with each other than with nodes in another group. The FORMALDEHYDE and N-HEXANE networks each generated four clusters (score > 10) and the METHANOL network generated six clusters (score > 10) (data not shown). The cluster with the highest score for each network was submitted to functional enrichment analysis in the BiNGO program, revealing how many and which categories were enriched, and which were the main biological processes associated with the proteins studied. In

this analysis, bioprocesses such as post-translational modification, phosphorylation, response to apoptosis, regulation of cell communication and the MPKK signaling cascade stood out in cluster 1 of the FORMALDEHYDE network. In cluster 1 of the N-HEXANE network, the highlights were the cell communication pathways, RAS protein signal transduction, negative regulation of apoptosis, and neurogenesis. The METHANOL network presented significant biological processes in cluster 1, such as regulation of the fatty acid metabolic process, organization of the peroxisome, aerobic respiration, and cellular response to oxygen-restricted species (**Appendix A, Supplementary Table 1**).

The centrality analysis revealed HB proteins in each network, which are the representation of key proteins in a given metabolic pathway. Some important parameters of the topological analysis are the betweenness and the degree of connectivity of each of the nodes (proteins). A greater flow of information passes through nodes with a high relative centrality value. The HBs with the highest node degree and betweenness values are shown in **Supplementary Figures 7, 8 and 9** in **Appendix A**. Among the main HBs nodes are: (a) FORMALDEHYDE network: MAPK1, MAPK3, MAPK14, MAPK11, SRC, Formaldehyde, AKT1, CREBBP, UBC, CASP3, and formaldehyde itself (**Appendix A, Supplementary Figure 7**); (b) N-HEXANE network: HRAS, KRAS, NRAS, SRC, GRB2, EGFR, UBA52, and SOS1 (**Appendix A, Supplementary Figure 8**); (c) METHANOL network: PRKACA, PRKACB, PRKACG, RPS27A, HSP90AA1, CAT, AKT1, and methanol (**Appendix A, Supplementary Figure 9**).

Discussion

In this systematic review, we identified 20 studies that evaluated occupational exposure to chemical agents with genotoxic potential in laboratory environments. Among the agents investigated in the mixtures, formaldehyde was the most frequently reported, with 18 studies specifically addressing its genotoxic effects. The predominance of this agent can be explained by its widespread use in pathology and clinical analysis laboratories, despite its classification as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC). From an occupational point of view, this combination reinforces the need for continuous monitoring of formaldehyde to protect workers' health and guide appropriate preventive measures[21-25, 27-31, 33-42].

Although various compounds have been investigated, such as benzene, xylene, ethanol, hydrochloric acid, and n-hexane, we observed that most studies have focused on complex mixtures of solvents. Benzene is a compound widely recognized for its genotoxicity, acting through the formation of reactive metabolites that cause chromosomal breaks, the formation of micronuclei and genetic mutations, and is strongly associated with the development of leukaemias[43]. Although xylene shows less robust evidence of genotoxicity, it can induce genetic alterations at high exposures, and causes toxic effects on the central nervous system[44]. Ethanol, on the other hand, has low direct genotoxic potential, but its metabolite acetaldehyde is highly reactive, forming adducts in DNA and promoting mutations, as well as increasing the risk of various types of cancer[45]. Hydrochloric acid is predominantly cytotoxic, causing severe tissue damage due to its corrosive nature. Although it is not a primary genotoxicant, it can cause indirect damage to DNA through oxidative stress[46]. On the other hand, n-hexane, known for its neurotoxicity, also shows limited evidence of genotoxicity, especially related to the formation of chromosomal aberrations[47].

In general, occupational exposure to these chemicals can trigger oxidative stress processes, promoting the generation of reactive oxygen species (ROS) which, in turn, induce DNA damage, contributing to genomic instability and increasing the risk of developing chronic diseases, including cancer. The characteristic of these exposures, involving mixtures of various chemical substances, reinforces the importance of understanding the combined effects, since synergistic interactions between the different agents can potentiate DNA damage[3]. The main mechanisms proposed to explain the genotoxic effects observed involve oxidative stress, especially the production of ROS, associated with chronic exposure to these chemical mixtures[3,48].

Of the studies included, only three were conducted in Brazil[22,26,40], which limits the generalization of our findings in the national context. Despite this, we observed that, historically, cytogenetic tests, especially the micronucleus test, have been the most widely used in the country. This choice seems to be related to the simplicity and low cost of these methods, which makes them accessible even in contexts with limited resources. However, it is not possible to say that these tests are the most widely used in Brazil, given the small number of national studies. In relation to other occupational exposures to complex mixtures, both the micronucleus test and the comet assay are the most widely used for detecting

DNA damage[3]. The scarcity of local investigations also compromises the assessment of relevant occupational exposures, such as those associated with the intense use of pesticides or solvents in public and private laboratories[3].

The analysis of the studies also revealed the absence of quantitative data on exposure levels as a recurring limitation. Most of the studies were based on questionnaires and qualitative approaches, without the support of biomonitoring or environmental monitoring (such as air analysis). The absence of this data compromises the accuracy of the correlation between exposure levels and the genotoxic outcomes observed. Future studies should incorporate more robust exposure assessment strategies, such as specific biomarkers and instrumental environmental quantification methods, as well as considering confounding factors such as age, gender, lifestyle and diet, which can interfere with biomonitoring results.

The application of systems biology in some studies has brought relevant contributions by allowing the integrated analysis of different biomarkers and molecular pathways associated with genetic damage. This enables a more comprehensive understanding of the mechanisms involved, especially in contexts of multiple exposure. However, its use is still incipient and often not critically explored. Systems biology could be more widely applied in assessing the effects of chemical mixtures, contributing to the mapping of affected cell signaling networks, the identification of target genes and the metabolic pathways altered by occupational exposure. In the analysis carried out using systems biology tools, bioprocesses such as post-translational modification, phosphorylation, response to apoptosis, regulation of cell communication, and the MPKK signaling cascade were highlighted for formaldehyde. For hexane, the focus was on cell communication pathways, RAS protein signal transduction, negative regulation of apoptosis and neurogenesis. For methanol, the regulation of the fatty acid metabolic process, peroxisome organization, aerobic respiration, and the cellular response to reactive oxygen species were highlighted.

All these bioprocesses may be related in some way to the cellular processes that lead to DNA damage, as demonstrated in the literature review. Many hub proteins in the three networks generated are kinases, which play critical roles in telomere maintenance and DNA repair[49]. Ontology analysis of cluster 1 of the FORMALDEHYDE and N-HEXANE networks also revealed processes such as phosphorylation, while cluster 1 of the METHANOL network identified processes related to peroxisome organization and the response to reactive oxygen species. Studies have shown that catalase is actively transported out of peroxisomes during periods of oxidative stress, conferring a greater protective effect to the cell[50,51], and this oxidative stress may be being caused by ethanol exposure, also impacting genetic stability.

Our findings reinforce the need for more robust experimental designs that integrate classical genotoxicity approaches with molecular and omics tools. In addition, it is essential that future studies incorporate more sophisticated statistical analyses to assess correlations between exposure levels and biological effects, considering multiple and chronic exposures. From this, it will be possible to advance in the construction of more realistic exposure profiles and in the development of more effective preventive policies. By mapping the molecular and cellular damage resulting from these exposures, science should serve as a basis for formulating regulatory actions and strengthening occupational health surveillance.

Conclusion

The analysis of the studies included in this review identified 24 potentially genotoxic substances used in diagnostic laboratories. Formaldehyde was the most frequently detected substance in the workplace, followed by n-hexane and methanol. Benzene, xylene, organic solvents in general, and strong acids (such as hydrochloric acid) were also identified. These substances demonstrated genotoxicity and were frequently associated with carcinogenicity. The main genotoxic effects observed included micronucleus formation, DNA strand breaks, and an increase in chromosomal aberrations, indicative of genomic instability and potential initiating events in neoplastic processes. Although these agents are already widely recognized for their adverse effects, there remains a lack of studies that robustly integrate exposure profiling with molecular tools capable of elucidating the underlying mechanisms involved.

In the systems biology analysis, processes such as post-translational modification, phosphorylation, response to apoptosis, regulation of cell communication, and cellular response to reactive oxygen species were highlighted, among others. The identified bioprocesses may be related to cellular pathways that lead to DNA damage, as demonstrated in the reviewed literature. Although the application of systems biology was not explored in the analyzed studies,

it may, in the future, contribute to the identification of gene networks and affected metabolic pathways, offering a more integrated understanding of cellular effects in the context of multiple and complex exposures.

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Information on academic work: Article derived from the master's thesis entitled "*Exposição ocupacional em laboratórios de diagnósticos clínicos a substâncias químicas genotóxicas e os principais mecanismos celulares relacionados aos danos ao DNA*" (Occupational exposure in clinical diagnostic laboratories to genotoxic chemicals and the main cellular mechanisms related to DNA damage), presented by Ana Kamila Figueira Burlamaqui to the Postgraduate Program in Health and Human Development, La Salle University, in 2022.

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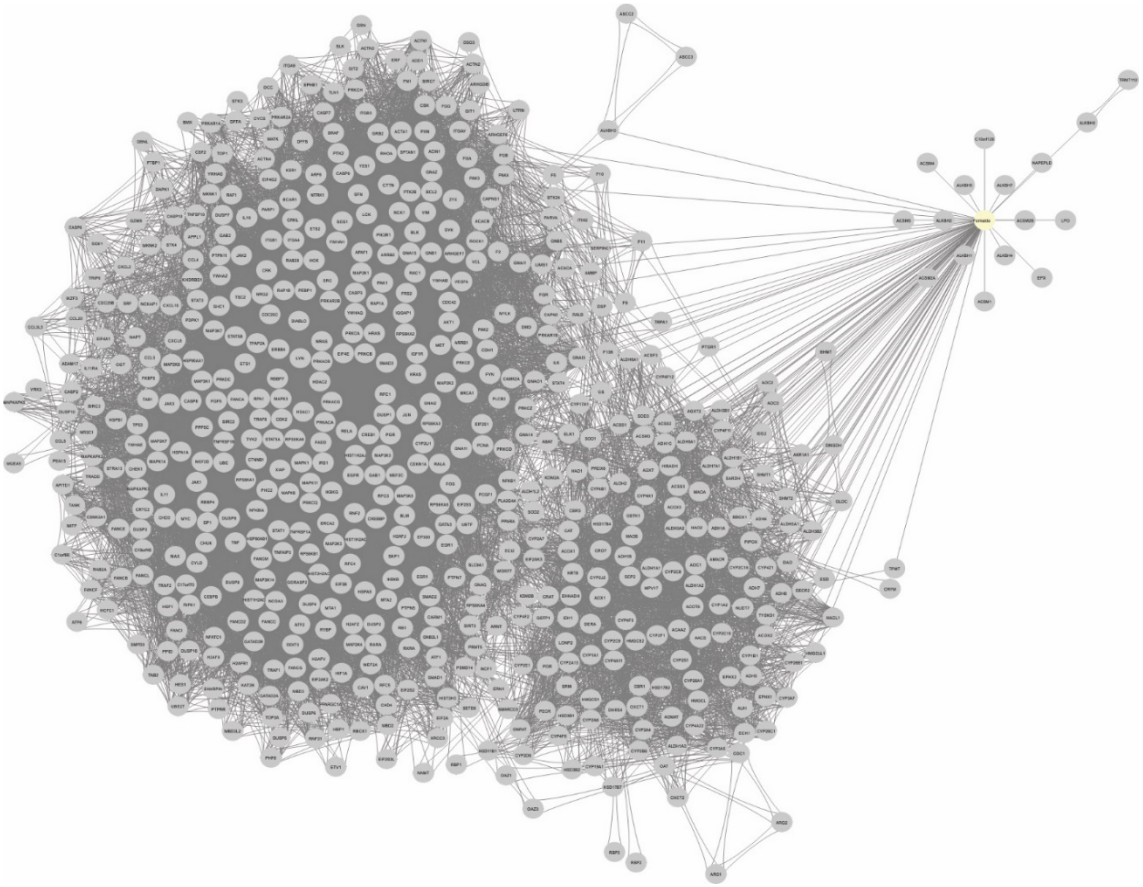
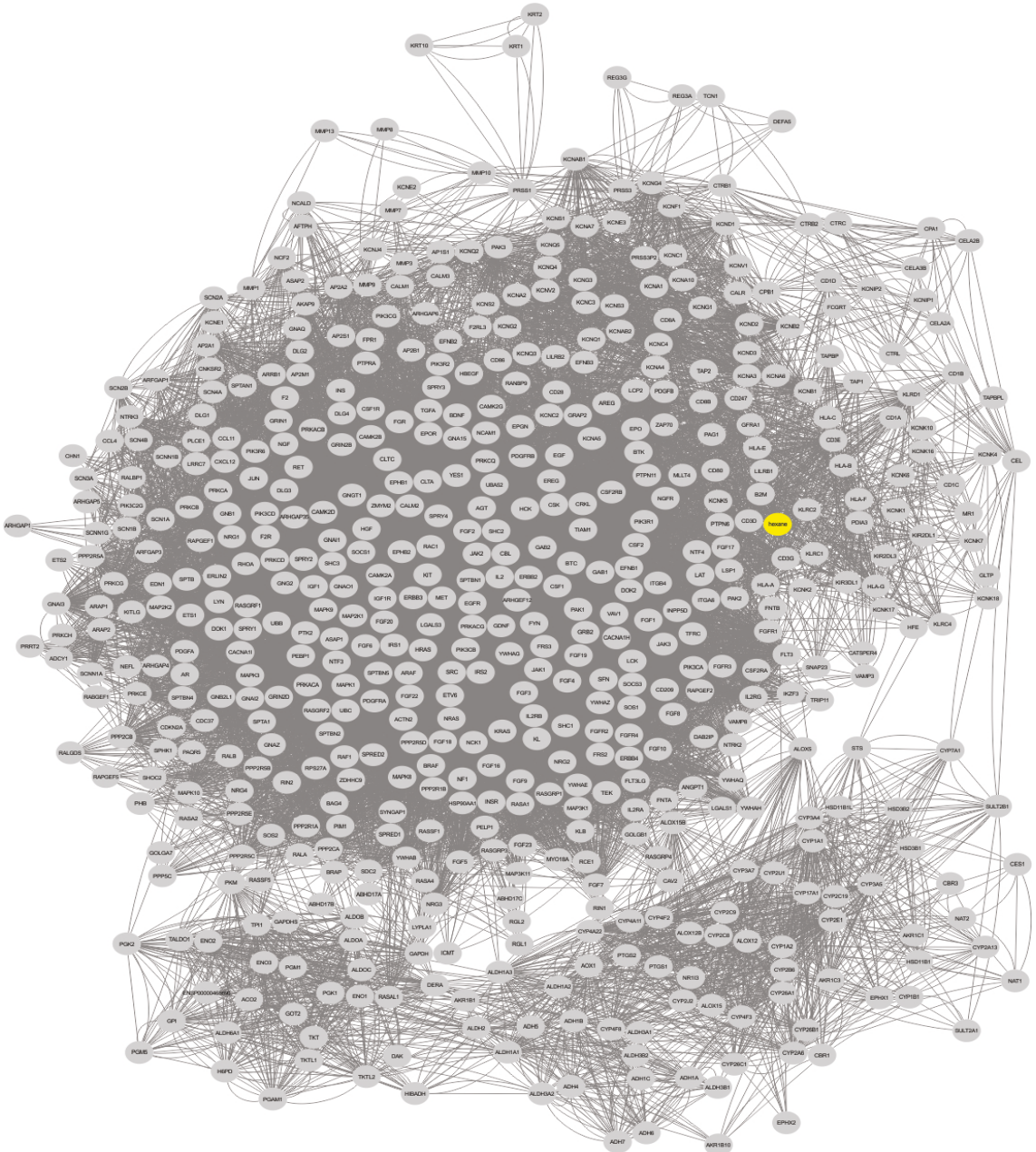
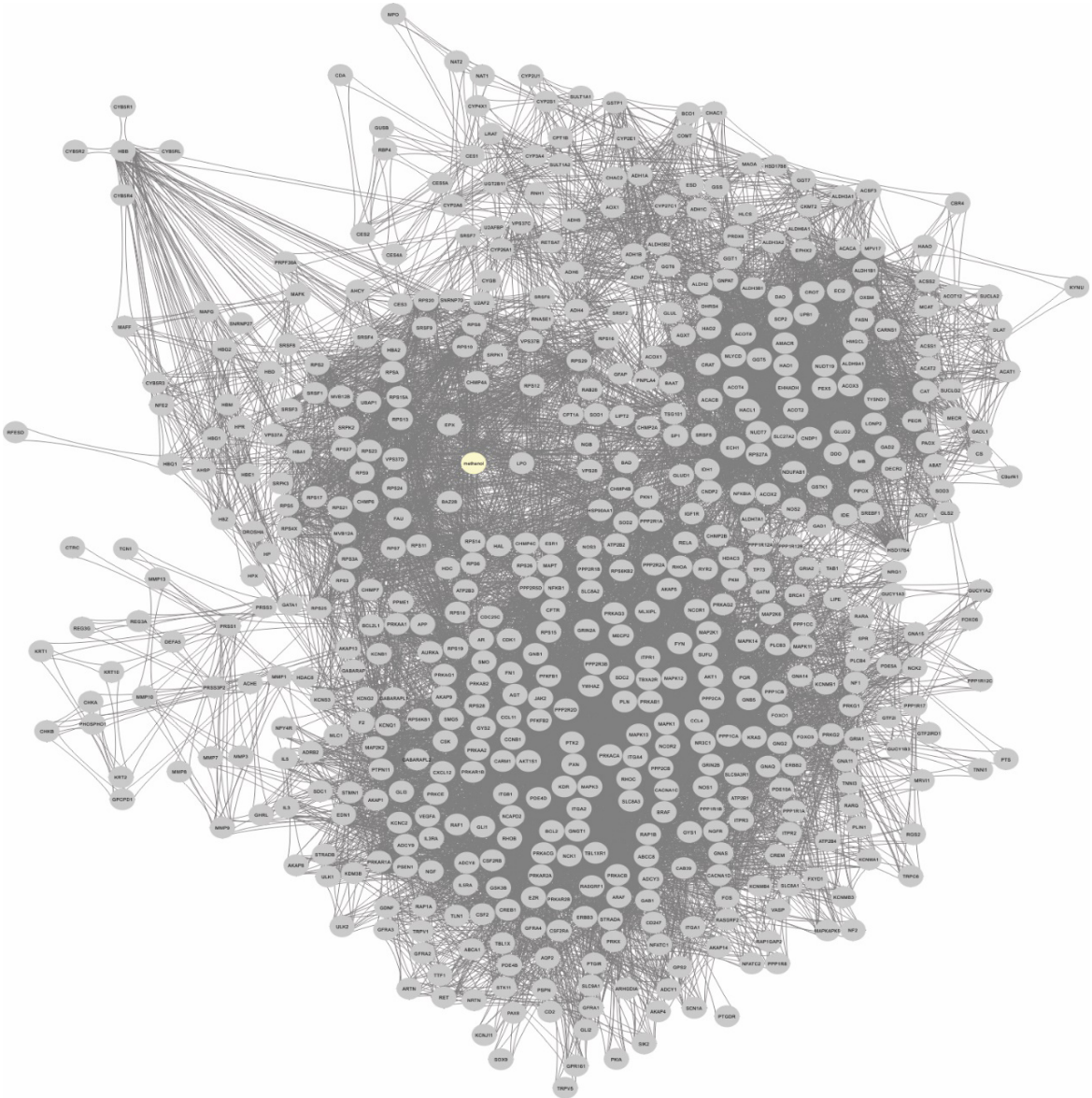
Appendix A



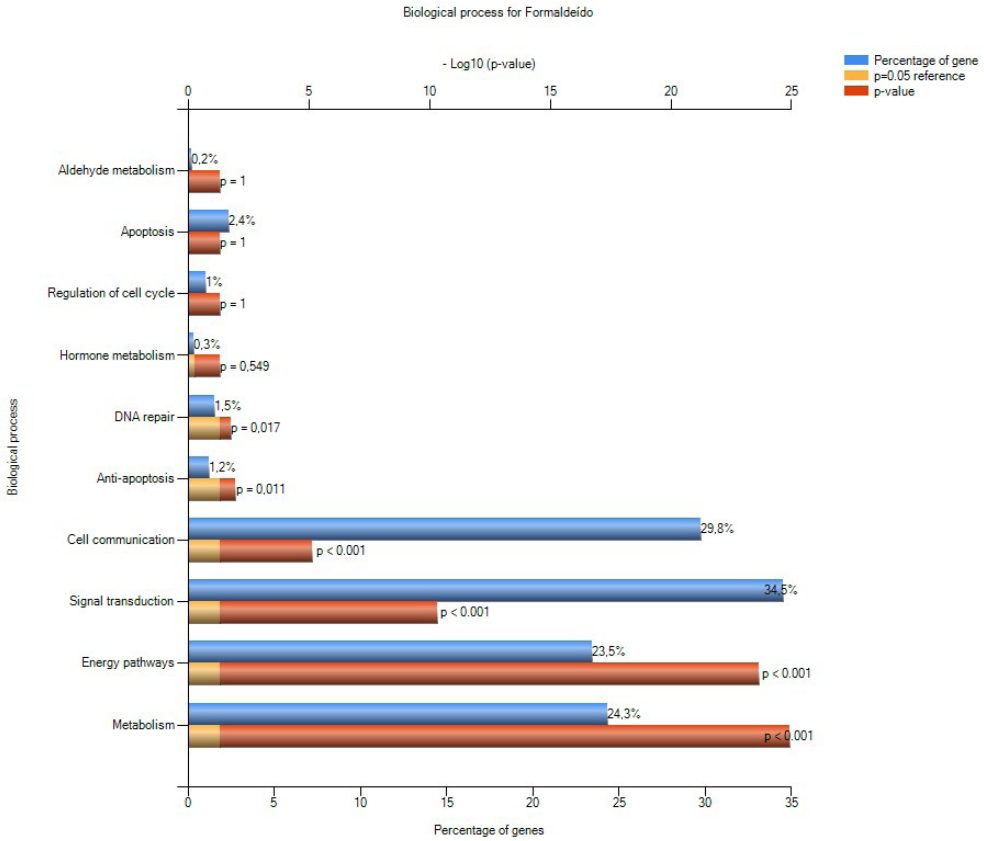
Supplementary Figure 1 Interaction networks prospected from formaldehyde connected to their respective proteins. The nodes in gray represent proteins and the nodes in yellow represent the chemical compound



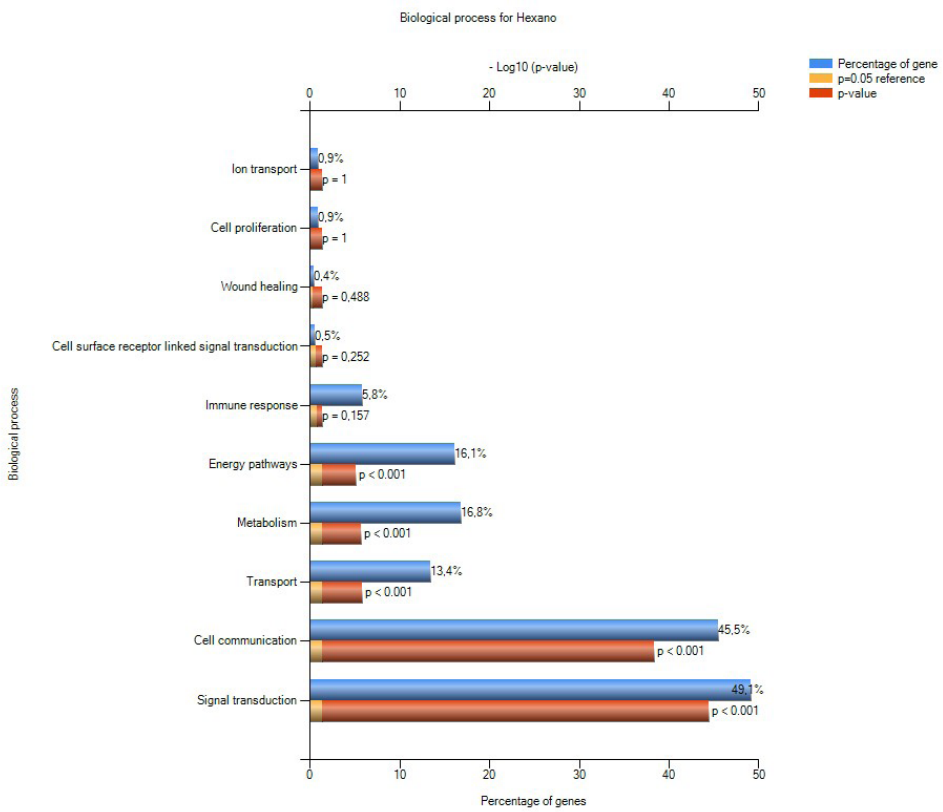
Supplementary Figure 2 Interaction networks prospected from n-hexane connected to their respective proteins. The nodes in gray represent proteins and the nodes in yellow represent the chemical compound



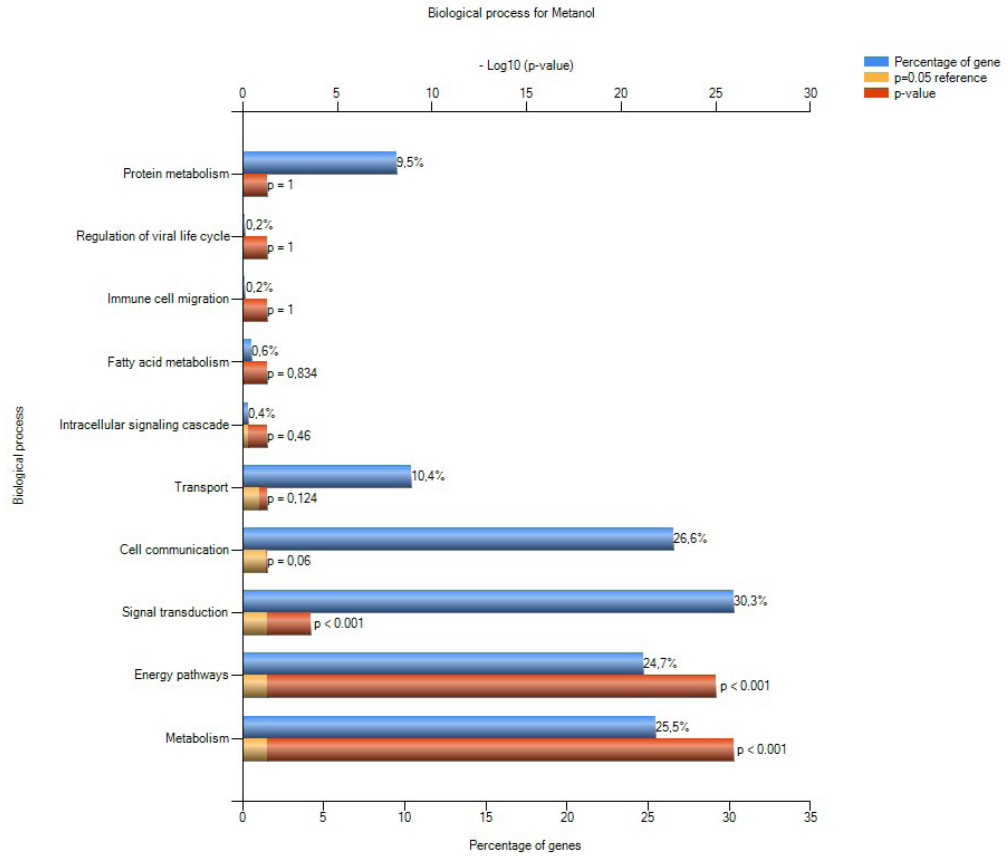
Supplementary Figure 3 Interaction networks prospected from methanol connected to their respective proteins. The nodes in gray represent proteins and the nodes in yellow represent the chemical compound



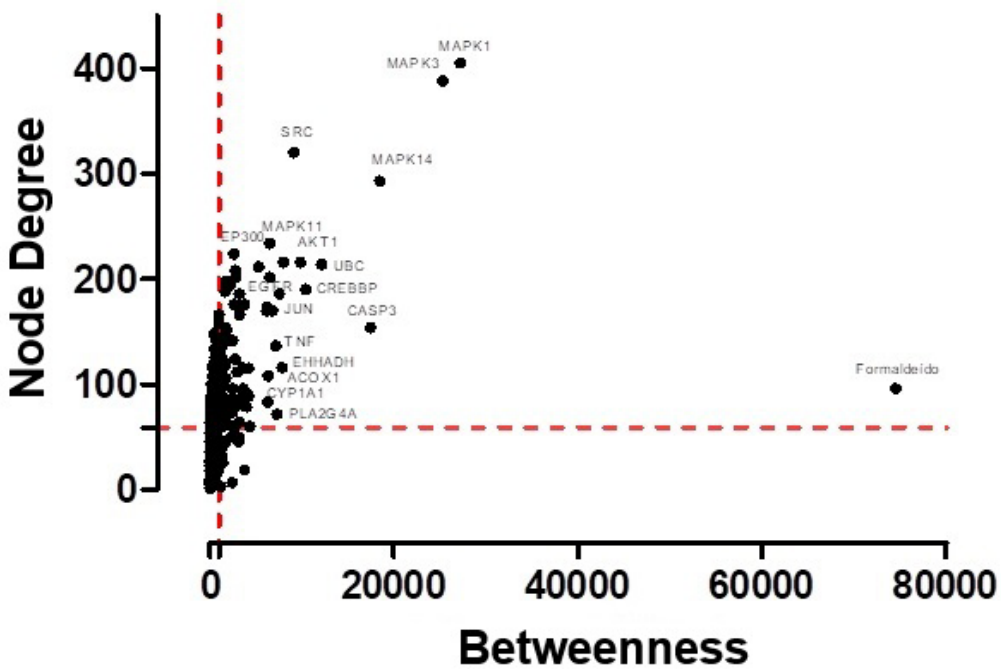
Supplementary Figure 4 Main biological processes of the FORMALDEHYDE network



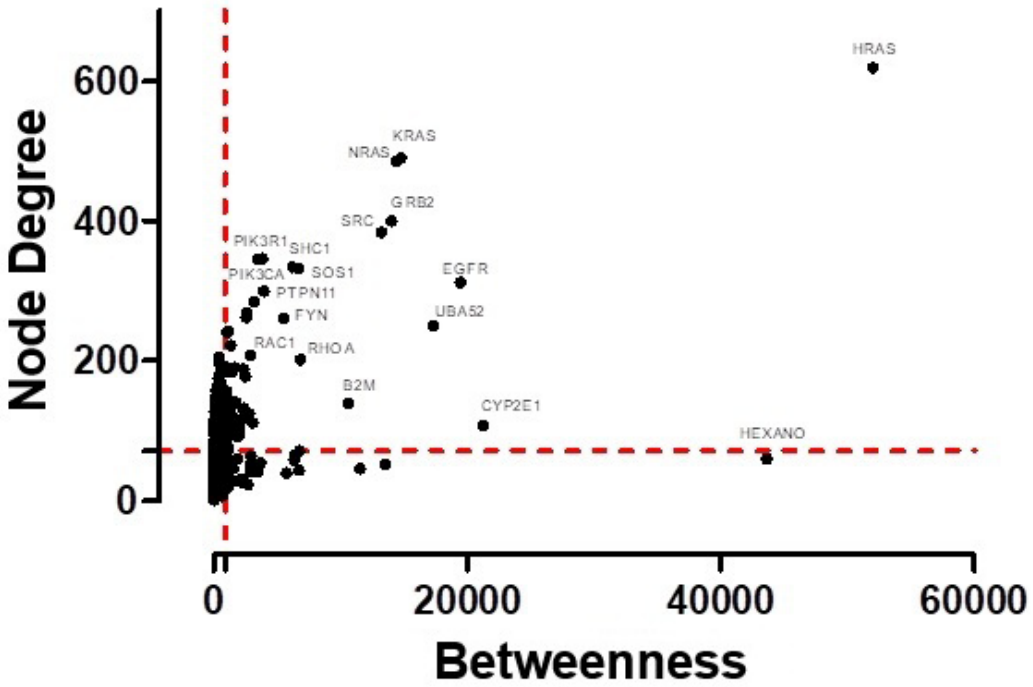
Supplementary Figure 5 Main biological processes of the N-HEXANE network



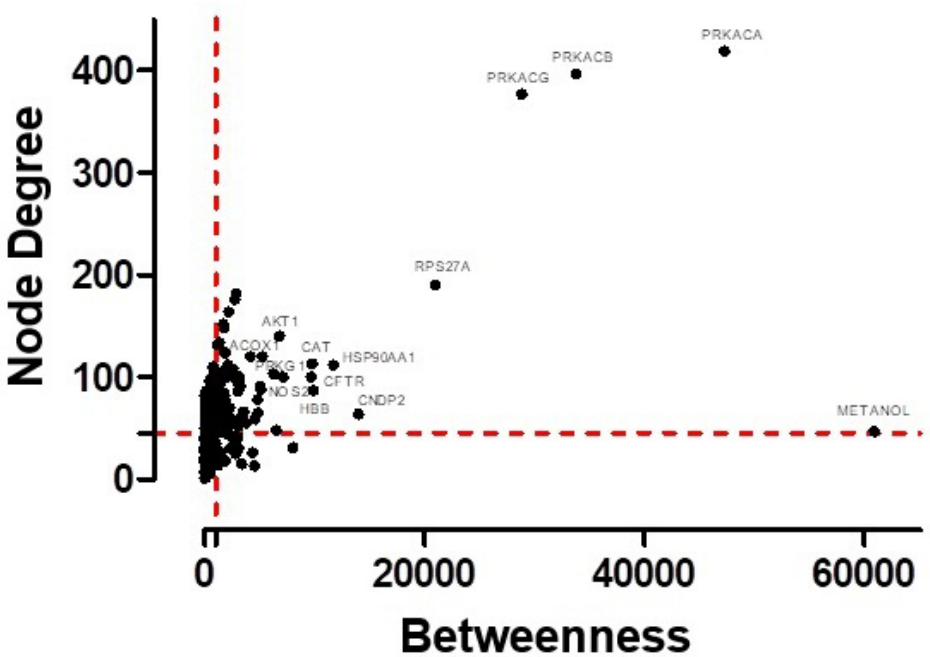
Supplementary Figure 6 Main biological processes of the METHANOL network



Supplementary Figure 7 Hub-bottleneck graph with the most relevant nodes in the FORMALDEHYDE network. The x-coordinate shows the betweenness values, while the y-coordinate shows the node degree. The line above 100 node degree represents the above-average nodes (hubs-bottlenecks), which have a high capacity for interaction and/or signaling with other biological processes



Supplementary Figure 8 Hub-bottleneck graph with the most relevant nodes in the N-HEXANE network. The x-coordinate shows the betweenness values, while the y-coordinate shows the node degree. The line above 100 node degree represents the above-average nodes (hubs-bottlenecks), which have a high capacity for interaction and/or signaling with other biological processes



Supplementary Figure 9 Hub-bottleneck graph with the most relevant nodes in the METHANOL network. The x-coordinate shows the betweenness values, while the y-coordinate shows the node degree. The line above 100 node degree represents the above-average nodes (hubs-bottlenecks), which have a high capacity for interaction and/or signaling with other biological processes

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Supplementary Table 1 Functional enrichment analysis in the BiNGO program

Cluster 1	Corrected p-value	Bioprocesses	Genes/Proteins
Formaldehyde	4.52 X 10-48	Post-translational modification	TNF|MYLK|IGF1R|RPS6KA4|RPS6KA5|SLK|PRKACG|RPS6KA2|CHEK1|AKT1|EP300|PRKACA|PRKACB|EPHB1|MAP3K7|SKP1|MAP3K5|MAP2K3|MAP2K4|MAP2K1|PRKCH|MAP2K2|CSNK2A1|PRKCB|PRKCE|PRKCD|FRS2|PRKCA|CDC25C|CDC25B|PRKAR1B|MAPKAPK3|MAPKAPK2|PRKCQ|RAF1|BLK|SHC1|PRKCZ|STK3|MAP2K7|MAP2K6|LYN|SMAD2|SMAD1|CREBBP|YES1|AMBP|FN1|BRAF|PTK2|PPP5C|GNAQ|BCL2|MAP3K14|CDKN1A|TNFAIP3|ILK|ARRB1|BRCA1|ARRB2|PHF8|IKBKB|JAK2|JAK3|JAK1|PRMT5|PARP1|SYK|KSR1|CHUK|DUSP1|PDPK1|GAB1|TYK2|F2|FGR|KAT2B|HCK|CREB1|LCK|TRAF6|RARA|SGK1|MET|HDAC2|ROCK1|HDAC1|SRC|CAMK2A|EGFR|RNF2|GNA14|PAK1|GNA15|MAPK8|GNA11|STAT4|PTK2B|MAPK1|CSK|FYN|PAK3|PAK2|PAK4|MAPK3|MBD3|NTRK1|MAP3K3|MAP3K1|PTPN11|MAPK14|SOD1|MAPK11|RPS6KB1|CARM1
	2.52 X 10-42	Phosphorylation	CDKN1A|ILK|TNF|MYLK|IGF1R|RPS6KA4|IKBKB|RPS6KA5|SLK|PRKACG|RPS6KA2|CHEK1|AKT1|PRKACA|JAK2|PRKACB|EPHB1|JAK3|MAP3K7|JAK1|MAP3K5|MAP2K3|MAP2K4|MAP2K1|PRKCH|MAP2K2|CSNK2A1|SYK|KSR1|CHUK|PRKCB|PDPK1|PRKCE|PRKCD|FRS2|PRKCA|TYK2|F2|FGR|HCK|CREB1|PRKAR1B|MAPKAPK3|LCK|MAPKAPK2|RARA|PRKCQ|SGK1|RAF1|MET|BLK|ROCK1|SHC1|SRC|CAMK2A|PIK3R1|PRKCZ|EGFR|STK3|PAK1|MAPK8|STAT4|PTK2B|MAPK1|CSK|FYN|PAK3|MAP2K7|PAK2|PAK4|MAP2K6|MAPK3|LYN|SMAD2|NTRK1|MAP3K3|SMAD1|YES1|MAP3K1|BRAF|PTPN11|MAPK14|PTK2|SOD1|MAPK11|RPS6KB1|BCL2|MAP3K14
	2.52 X 10-28	Regulation of apoptosis	ATF1|YWHAE|ATF2|CDKN1A|YWHAB|TNFAIP3|ILK|BRCA1|ELK1|ETS1|TNF|IGF1R|IKBKB|CASP8|CDH1|AKT1|RAC1|IKBKG|PRKACA|JAK2|HRAS|MAP3K7|MAP3K5|MEF2C|ACTN3|ACTN2|DUSP1|DCC|PRKCE|ACTN1|PLA2G4A|PRKCA|ACTN4|F2|YWHAZ|RHOA|CREB1|LCK|DDIT3|TRAF6|SOS1|TP53|CEBPB|ROCK1|HDAC1|XIAP|PRKCZ|EGFR|RELA|STK3|NRAS|MAPK8|RXRA|MAPK1|SFN|PAK3|MAP2K6|NTRK1|JUN|MAP3K1|SMAD3|HSPA5|BRAF|SOD2|ESR1|NFKB1|VEGFA|SOD1|NFKBIA|RPS6KB1|BCL2|CTNNB1|KRAS|BCAR1|HSPA1A
	1.12 X 10-23	Regulation of cell communication	ATF1|ATF2|HSP90AB1|IRS1|ITGB3|PEBP1|TNFAIP3|ILK|ARRB1|ARRB2|TNF|IGF1R|IKBKB|CASP8|AKT1|STRA13|RAC1|IKBKG|PRKACA|JAK2|HRAS|MAP3K7|GIT1|YWHAG|MAP3K5|YWHAH|MAP2K1|SYK|CHUK|PRKCB|DCC|NCOA3|PRKCD|GAB1|TSC2|ARNT|FRS2|PRKCA|RHOA|CREB1|LCK|TRAF6|SOS1|TP53|CRK|ARF6|SHC1|IQGAP1|HIF1A|PRKCZ|EGFR|RELA|STK3|PAK1|NRAS|PTK2B|PAK3|MAP2K6|LYN|EGR1|MAP3K3|MAP3K1|SMAD3|F10|AMBP|HSPA5|CAV1|MBD2|BRAF|PTPN11|ESR1|VEGFA|SOD1|NFKBIA|PPP5C|SP1|CTNNB1|GRB2|KRAS|MAP3K14
	3.14 X 10-23	Regulation of kinase activity	RB1|CDKN1A|BLM|IRS1|SHC1|ITGB3|ILK|PRKCZ|TNF|EGFR|PAK1|PRKAR2B|PRKACG|PRKAR2A|CHEK1|AKT1|PTK2B|SFN|IKBKG|PRKACA|JAK2|PRKACB|PAK2|MAP3K7|YWHAG|MAP3K5|MAP2K6|MAP2K3|MAP2K1|MAP3K1|SYK|HSPA5|DUSP1|PDPK1|CAV1|TSC2|FRS2|PRKCA|PTPN11|CDC25C|SOD1|PRKAR1B|PRKAR1A|GNAQ|TRAF6|KRAS|TAB1
	5.63 X 10-18	MPKK signaling cascade	SHC1|TNF|EGFR|CRKL|PAK1|MAPK8|PTK2B|MAPK1|PRKACA|JAK2|MAP2K7|MAP3K7|MAP3K5|MAP2K6|MAP3K3|MAP2K4|SMAD1|MAP2K1|MAP3K1|MAP2K2|SYK|CAV1|FRS2|PRKCA|BRAF|PTPN11|SOD1|TRAF6|MAPKAPK2|TAB1

Continue

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Continuation

N-Hexane	4.87 X 10-64	Signaling via membrane receptor tyrosine kinase	RET|KLB|IRS1|FLT3|IRS2|FGF1|CD3E|AREG|FGF2|FGF3|FGF4|IGF1R|FGF5|FGF6 |FGF7|FGF8|FGF9|PLCE1|JAK2|EPHB2|EPHB1|NCK1|PDGFRB|PDGFRA|HGF|GAB1| FRS2|NRG1|NGF|FRS3|EREG|AR|TIAM1|DOK1|DOK2|CD8B|CD8A|KIT|RAPGEF1| LCP2|SOS1|HBEGF|CSF1R|SHC3|SHC1|SRC|PDGFB|PDGFA|PIK3R1|CBL|EGFR| RASGRP4|EFNB3|ERBB3|ERBB4|ERBB2|FGF20|SHOC2|FGF23|FGF22|KL|NTRK2| ANGPT1|EGF|NTRK3|INSR|PTPN11|PTK2|FGF17|FGF16|PTPRA|FGF19|FGF18|GRB2| TEK|FGFR4|FGFR3|FGFR2|FGF10|FGFR1
	1.39 X 10-47	Regulation of cell communication	KLB|CSF2|CSF1|EPO|IRS1|CD80|PEBP1|IRS2|FGF2|FGF4|IGF1R|SYNGAP1|LGALS1| FGF9|PPP2R1A|PLCE1|PRKACA|EPHB2|MAP2K1|RALBP1|PRKCB|HGF|PRKCD| F2R|FRS2|PRKCA|EREG|AR|TIAM1|CD8A|KCNQ1|CDC37|KCNQ4|SHC1|PDGFB| FPR1|TGFA|RASAL1|RASGRP1|RASGRP4|RASGRP3|SOCS3|SOCS1|INPP5D|RALGDS |FGF23|LYN|BRAP|NGFR|KL|ICMT|BDNF|CAV2|INSR|BRAF|IGF1|GRIN2B|IL2|PPP5C |GDNF|FGF19|FGF18|NF1|GRB2|RGL1|RGL2|MAP3K11|FGF10|FGFR1|RASGRF2| RASGRF1|ARRB1|PIK3CB|CD3E|SPRED2|SPRED1|RAC1|JAK2|HRAS|YWHAG| YWHAH|EDN1|ARHGEF12|SPHK1|GAB1|ARAP2|ARAP1|ARFGAP3|NGF|ARFGAP1| VAV1|RHOA|CNKSR2|ZAP70|LCK|RASA4|RASA1|KIT|RASA2|RAPGEF1|RAPGEF2| RAPGEF5|SOS1|SOS2|HBEGF|CCL11|GNAI3|ASAP1|ASAP2|EGFR|GNAI2|INS| PPP2CA|PPP2CB|NRAS|PAK1|ERBB3|ERBB4|NTF3|ERBB2|SHOC2|NCAM1|PAK3| MAP3K1|ANGPT1|CDKN2A|EGF|SPRY4|DAB2IP|PTPN11|AGT|KITLG|EPGN|SPRY3| SPRY2|SPRY1|KRAS|TEK
	3.06 X 10-33	RAS protein signal transduction	SHC2|RALA|SHC3|RALB|SHC1|SRC|YWHAB|ARHGAP1|ARHGAP5|ARHGAP6 |FGF2|RASGRP1|ARHGAP4|CRKL|RASGRP3|NRAS|RASSF1|GRAP2|PLCE1|MAPK1| SHOC2|RALGDS|HRAS|MAPK3|BRAP|MAP2K1|MAP2K2|CDKN2A|HGF|IGF1|NGF| RHOA|DOK1|DOK2|GNB1|NF1|GRB2|KRAS|SOS1|RAF1|RGL2|LAT
	1.22 X 10-26	Phosphorylation	RET|FLT3|ARAF|PIK3CD|PIK3CB|FGF2|PIK3CG|IGF1R|PRKACG|PIM1|PLCE1| PRKACA|JAK2|EPHB2|PRKACB|JAK3|EPHB1|JAK1|PRKCG|PDGFRB|PDGFRA|MAP2K1| PRKCH|MAP2K2|PRKCB|PRKCE|HGF|PRKCD|F2R|FRS2|PRKCA|F2|FGR|HCK|ZAP70| PIK3CA|LCK|KIT|BTK|PRKCQ|RAF1|MET|CAMK2B|CSF1R|CAMK2D|CCL11|SHC1|SRC| CAMK2A|FPR1|TGFA|PIK3R1|EGFR|GNAI2|MAPK9|PAK1|MAPK8|ERBB3|ERBB4 |ERBB2|MAPK1|FYN|CSK|PAK3|PAK2|CAMK2G|SPTBN1|MAPK3|LYN|NTRK2|YES1| MAP3K1|EGF|NTRK3|INSR|BRAF|PTPN11|PTK2|MAPK10|EPGN|PTPRA|TEK|FGFR4| FGFR3|MAP3K11|FGFR2|FGF10|FGFR1
	4.68 X 10-11	Neurogenesis	RET|YWHAE|EPO|RASGRF1|FGF2|IGF1R|FGF5|GNGT1|FGF8|LGALS1|NEFL|PRKACA |JAK2|EPHB2|EPHB1|YWHAG|YWHAH|PDGFRA|MAP2K1|SPHK1|HGF|FRS2|PRKCA |F2|NGF|RHOA|TIAM1|KIT|PRKCQ|SPTBN4|SDC2|EGFR|EFNB1|EFNB3|ERBB3|NTF3 |ERBB2|FGF20|FYN|PAK3|NGFR|BDNF|KCNIP2|NTRK3|PTPN11|IGF1|AGT|PTK2 |GRIN1|GNAO1|GDNF|GNAQ|NF1|FGFR1
Methanol	3.17 X 10-37	Regulation of the fatty acid metabolic process	PECR|PRKAA1|PRKAA2|PRKAG1|PRKAG2|HSD17B4|CROT|ACACB|ACACA|PRKAG3 |HAO1|HACL1|MLYCD|HAO2|GGT5|ACOT8|CPT1A|PRKAB2|MECR|ECH1|ACOT12| BAAT|PRKAB1|ACSF3|MCAT|GNPAT|ACOX2|ACOX1|FASN|EHHADH|PEX5|ACOT2| ACOX3|SLC27A2|CRAT|ACOT4
	1.41 X 10-5	Organization of the peroxisome	ACOT8|SCP2|PEX5|LONP2|AGXT
	1.11 X 10-4	Aerobic respiration	CS|SUCLA2|IDH1|CAT|SUCLG2
	1.70 X 10-4	Cellular response to reactive oxygen species	CAT|MPV17|SOD2|PRDX6|SOD1