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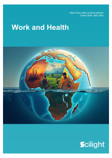

*Article*

# Assessment of Potential Exposure to Research Chemicals in Academic Laboratories: Challenges and Opportunities for Scientists' Health Protection

Federico Maria Rubino

Department of Health Sciences, Università degli Studi di Milano, v. A. di Rudinì 8, 20122 Milano, Italy; Federico.rubino@unimi.it

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**Abstract:** Academic chemical research, especially in the laboratories that prepare very small quantities of novel chemical compounds, potentially exposes faculty, staff and students to several substances, in special conditions of manual work, for which the established methods of industrial hygiene monitoring and of medical health protection are not entirely adequate. Academic careers in chemistry develop over several decades, entailing workers' mobility through research projects, institutions, and countries, especially in the early phase of researchers' lives, when important life choices, such as pregnancy and childbearing, may be strongly influenced by occupational exposure to chemicals. This pilot study explores using the experimental section of published articles as proxy of activity recording in researcher's laboratory logbook to record individual and group occupational exposure to research chemicals. Chemical researchers use substances with complete safety information, including occupational exposure limits, substances without occupational exposure limits but with safety assessment, including hazard classification, and produce completely new, original substances as the epistemological object of chemical research, the hazards of which may not be anticipated. A pilot example exemplifies data extraction from experimental descriptions and open-source safety information. Hazard indexes for the employed substances can be used to classify and rank individual experiments, such as chemical preparations, by hazard type and semi-quantitative hazard level, with more hazardous substances having higher Hazard index. However, hazards from original new substances cannot be anticipated. This approach can be shared by researchers to keep track of past occupational exposures throughout their professional lives.

**Keywords:** chemical preparation; chemical reagent; chemical risk assessment; gravity index; hazard index; solvent

## 1. Introduction

Chemical researchers in industrial or academic institutions, imagine, prepare, test and develop all kinds of new materials for aims of fundamental knowledge, new applications and process development. Unlike chemical professionals employed in plants and chemical-related services, research chemists face unique occupational scenarios, where hazards may be unforeseen, due to the novelty of the field they explore. This emerging environment should now be considered a distinctive workplace, given its overlap with the specific professions, such as that of the chemist, practiced by academic employees, while at the same time encompassing activities and organizations that differ from those of industrial employment. These specific features influence multiple dimensions of occupational life and of life-work balance, including the management of occupational safety and health risk.

Accidents in the chemical laboratory, even serious and deadly, are a long-time part of the professional folklore, up to Edgard Lee Master's "*Trainor, the druggist*" *Killed while making an experiment* [1]. However, the prevention of accidents in the chemical laboratory was the concern of the classical textbooks, such as Ludwig Gatterman's *Anleitung fur das organisch-chemisten Praktikum* [2].

More recent accidents in academic chemical laboratories have prompted growing interest [3–5], directed not only towards improving safety, but, more importantly, at understanding how the recommendation of safe practices [6] and the enhancement of the specific academic organizational climate may reduce the likelihood of accidents [7–9]. Acute, deadly intoxications have demonstrated that in some cases the safety information available to even expert researchers is not sufficient to ensure protection [10–12]. Besides, when management is inadequate and communication is ineffective, a lifetime of work may result in health threatening chronic exposure of academic staff, faculty and students to chemicals used in preparations and experiments, as well as to produced chemical waste [13,14].

The toxic properties of novel substances—the very epistemological object of chemical research- may be unforeseen, partly because of the difficulty in locating relevant literature in fields distant from those typically consulted by chemists. One such case involved an Italian experienced chemist, who was studying a class of niche molecules for fundamental research. Following a mild inhalation episode that resulted in serious lung oedema, he discovered that several years of prior exposures had already caused substantial lung damage [15]. An English translation of his brief published alert is reported in Appendix A.

A brief description of the main working phases, potential operators' exposures, and possible risk scenarios in academic chemical laboratories is reported in Table 1 [16].

The need to protect academic chemical researchers from this professional hazard is far from adequately addressed. Existing methods of occupational health prevention, including workplace monitoring, were developed mainly for protection of industrial workers in chemical plants and manufacturing facilities that use chemical substances [17]. These monitoring and control strategies are often insufficient to address the unique exposure circumstances of the academic chemical laboratories. Key differences include: the reliance on predominantly manual techniques, often applied to very small amounts of materials [16], the frequent use of substances with poorly known properties, the preparation of entirely novel compounds, the potential for exposure through multiple routes, and the simultaneous performance of diverse laboratory and office tasks, often within shared laboratory and office facilities.

Furthermore, personal and hierarchic relationships in academia are strongly influenced by organizational level and scientific authority ranging from young students with limited experience and initial training, to seasoned professionals and faculty members [18]. Academic workers often hold fixed-time appointments and progress through their career by changing research topics, techniques and exposure conditions. Consequently, the long-term reconstruction of past exposure—essential for assessing causality in ~~the~~ case of late-onset health impairment- may prove difficult or even impossible, especially when records are unavailable. Retrieving information from routinely maintained laboratory logbooks may help address this difficulty. For example, the examination of personal laboratory records following the UCLA fire case revealed the chemical reaction involving a pyrophoric reagent that ignited and set the technician's clothing on fire [19]. Similarly, colleagues caring for Dr Wetterhahn, after the onset of her neurological symptoms, suspected intoxication as a possible cause and reviewed her meticulously kept laboratory logbook, demonstrating that, a few months earlier, she had handled dimethylmercury, and confirming the causal link [20,21].

However, laboratory logbooks are rarely accessible due to the confidential nature of information, aiming to reclaim novelty or priority, or enforce research ethics. For this explanatory study, a reasonable proxy is the published descriptions of laboratory chemical preparations. This article explores that possibility by analyzing a representative example of a typical activity involving the handling of hazardous chemicals to assess its potential value for preventive planning and establishing a long-term record of work-related health risks. Some specific issues refer to the Italian normative situation, which is country-specific, but can also be used as reference for countries with systems of Occupational Health Protection that are based on comparable general principles.

**Table 1.** Preparation of chemical substances in the research laboratory: main working phases and circumstances for potential operators' exposure.

| Activity | Circumstances for Potential Operators' Exposure |
|---|---|
| 1. **Preparing the necessary ingredients and equipment.** Once the work schedule (daily or multi-day) for the activity has been established, which includes calculating the quantities of materials required, the operator prepares the chemicals to be used, the work equipment to be employed, and the spaces available for the various phases of the activity. Generally speaking, the equipment is assembled inside the work hood whenever operations involve heating or cooling or involve substances capable of appreciably dispersing into the air, such as volatile organic solvents, flammable or reactive substances. The substances are weighed according to the calculated quantities, in powder form using a scale or by volumetric measurement if liquid. The dispensing of gaseous reagents, less frequently, occurs mainly from cylinders, and requires a more complex work organization phase, including the safety measures to be adopted. | • Weighing solid reagents may result in trace amounts being spilled on the scale (closed compartment, which must be cleaned after each operation), during transfers, and in surrounding areas.<br>• Liquid reagents can be sampled directly and transferred with syringes or pipettes (dripping may occur) or measured more accurately by weighing, which may result in spillage in affected areas of the workspace.<br>• Even if the operator wears gloves, it must be borne in mind that operations may need to be interrupted, requiring the gloves to be removed. The outer surface of these gloves may already be contaminated and may constitute a source of uncontrolled dispersion of trace amounts of the handled products, even at a distance from the source (the original containers, reaction vessels, auxiliary equipment), throughout the duration of operations. |
| 2. **Mixing and preparation.** Typically, the main substances are dissolved in an appropriate solvent, in the quantity needed to achieve the reaction in the shortest possible time. The reaction occurs through heating or cooling, or at room temperature, in previously assembled and tested equipment. Reagents, solvents, and other auxiliary materials can be added in a single step at the beginning or progressively over time. Some specific techniques are adopted to work with substances with particularly high reactivity in ambient conditions (presence of humidity, contact with oxygen in the air), which require the exclusion of air and traces of humidity by operating in closed circuits, in an inert atmosphere (usually nitrogen from a distribution network), at sub-ambient pressure or under vacuum, and in refrigerated conditions. To continuously and safely use the most complex of these techniques, laboratories are equipped with dedicated work lines manned by specifically trained and qualified personnel. | • Risk of material spilling and projecting into the surrounding space even under "calm" conditions. Reactions conducted in solution and under heating result in the emission of volatile solvent vapors, which may not be fully condensed and captured by the refrigeration system and must be efficiently extracted by the fume hood's localized extraction system.<br>• Throughout the course of operations, microdroplets or droplets of the solution can escape confinement and settle on surfaces in the surrounding environment, where the solvent evaporates and the solids crumble into particles that resuspend and are transported into the environment by occasional air flows. This continuous resuspension-sedimentation pattern plays a significant role in the poorly controlled and ubiquitous dispersion of the chemicals used throughout the work environment, even at great distances from the source and in unsuspected locations, such as corridors, offices, restrooms, and elevators.<br>• The extent of chemicals dispersion depends on the concentration in the reaction mixture and the fraction that escapes confinement. It represents one of the main sources of contamination of workspaces and of "secondary" exposure of workers present and those passing through. This occurs both in operations carried out of the chemical fume hood and, even more so, in subsequent operations, performed on lab benches. |
| 3. **At the end of the preparation: isolation procedures**. At the end of the reaction, the reaction mixture is prepared for the subsequent steps, using various procedures that depend on the nature of the chemicals involved. Among the most used procedures are "quenching" by adding water, separation or extraction of the reaction products with an organic solvent, and subsequent evaporation of the extraction solvent in a "rotary evaporator" to obtain a "crude" product for subsequent fractionation and purification steps. | • At this stage, the procedures result in a laboratory waste 5 to over 10 times greater than the reaction mixture. Spills and spread of material into the surrounding ambient are possible especially when operating, even partially, outside the hood. Therefore, this phase represents a major source of workspace contamination and direct and indirect exposure for workers and bystanders. The disposal of spent reactions and contaminated wastewater represents a potential source of contamination of the work environment and potential exposure for workers and bystanders, particularly when lab waste cannot be immediately and permanently removed and is temporarily held in waste tanks inside the laboratories. |

**Table 1.** *Cont.*

| Activity | Circumstances for Potential Operators' Exposure |
|---|---|
| 4. **At the end of the preparation: fractionation and purification procedures**. The final stages of chemical preparation aim to prepare the expected products from the reaction mixture in the purest form possible, separating them from incompletely transformed starting products, "unwanted" reaction products, and products of secondary reactions or decomposition. Different techniques can be employed depending on the needs, the availability of equipment, the quantities of products handled, the known or expected characteristics of the products, and mixtures complexity. Most techniques use large volumes of other chemicals, including organic solvents for crystallization, selective extraction, and manual or instrumental preparative chromatography. | • These procedures also generate even greater laboratory waste, especially when using preparative chromatography techniques for separation. The evaporation of chromatographic fractions causes a fraction of the volatile solvent to be dispersed into the air and widespread contamination of the equipment (rotary evaporator), which contributes to the further dispersion of low-volatile chemical compounds into the environment, again through secondary transport mechanisms. |
| 5. **Analytical characterization of the products.** In this final stage, small samples of purified products are subjected to analytical and spectroscopic measurements to demonstrate their chemical identity. Modern techniques use few milligrams quantities of products and are often non-destructive. | • The potential for material spill and splash into the surrounding space persists during sample transfers to various instruments, the execution of certain tests, and sample recovery after measurements. The samples provided for analysis are essentially pure, though often in minute quantities. Depending on organization, different operators may be involved, with varying levels of awareness of the physical and chemical properties of the sample and its potential known hazards. |
| 6. **Workplace maintenance and waste disposal**. Workspaces are typically manually cleaned or sanitized at the end of operations, through household procedures. Personal protective equipment such as gloves, lab coats, and aprons is often, but not consistently, used. | • Cleaning and decontamination of laboratory workspaces can be a source of inadvertent but sometimes significant contamination for operators, especially if lacking personal protective equipment and unaware of the operations performed and the products used. Cleaning and decontamination with chemical agents can result in incidents due to unintentional and uncontrolled exposure. Receiving laboratory wastewater for disposal can result in the unintentional exposure of operators, unaware of the nature of the substances handled. |

## 2. Materials and Methods

The block scheme of Figure 1 describes the main phases of the work.

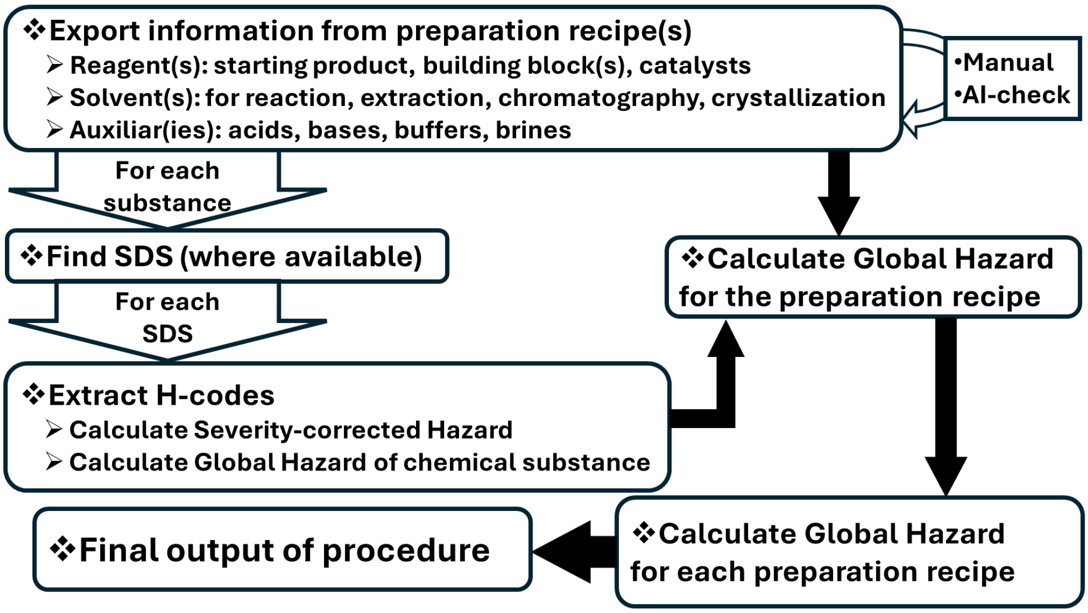

**Figure 1.** Block scheme of data extraction and elaboration.

### *2.1. Selection Criteria for the Article*

One recent scientific article was randomly selected, based on evaluation of its title [22]. The specific scope of the compounds described in the article was not relevant, nor were other details. Due to the public nature of the information, there was no contact with the chemists who had performed the examined work.

The article describes the preparation and purification, in the millimole and sub-millimole range, of 54 compounds, including 17 final compounds and the intermediates, obtained through multiple steps from commercially available chemical "research-grade" reagents and commonly available organic solvents, inorganic salts, chromatography materials, and water.

### *2.2. Stepwise Data Extraction from the Article*

The first step of this proof-of-principle test examined the preparation of one, randomly selected, single reaction, reported as example in the Results section. The second step was considering the preparation of a final product, achieved through 7 passages that led from the earliest, usually, commercial product to the desired target molecule. The third step extended the data extraction to all 54 reactions reported in the experimental section of the article. In 7 cases, the described reaction was a two-step process, where an intermediate product was not isolated, but the raw material directly employed for the last and final reaction of the sequence. In these cases, anyway, two separate assessments were performed for the two steps.

Due to the obviously prohibitive time and effort, and possibility of inadvertent errors, several coordinated approaches combined text mining with the "Search" tool of the word processor and IA (ChatGPT) query, in the lack of available professional tools adapted for this task [23–26]. The extracted information was: the names of the employed substances, the roles of each in the preparation, the employed quantities, the reaction yield, where reported. The retrieved information was copy-and-pasted in an Excel spreadsheet.

The substances were classified into four groups, as Reagents, Solvents, Auxiliaries and Products.

### *2.3. Acquisition of Toxicological and Normative Information*

The chemical, toxicological and normative characteristics of the commercially available products were retrieved from the respective publicly available Safety Data Sheets (SDS), whenever available, while those of the original products are limited to information reported in the article. Manually retrieved information was added to the custom spreadsheets.

The existence of Occupational Exposure Limits, in at least one country, for the commercially available products was checked in the GESTIS—International limit values database (https://ilv.ifa.dguv.de/substances (accessed on 30 November 2025)) both by substance name and by CAS number identifier.

### *2.4. Substance Classification for Data Analysis*

Based on the available information, the substances are classified in three classes, as follows.

- **Class A** substances are those for which both there is a SDS and regulatory exposure limits are issued.
- **Class B** substances are those for which there is a SDS, with hazard classification and coded phrases, but no regulatory exposure limits.
- **Class C** substances are those for which neither information is available. Original research compounds, intermediates, and final products alike, belong to this group.

Other information necessary to further the elaborations was locally obtained from regulatory and authoritative sources, such as the models that are issued by the Italian OSH services to perform chemical Risk Assessment in the Small-Size Enterprises.

### *2.5. Hazard Assessment of the Employed Substances*

The chemical substances employed in the syntheses were assessed for work safety and occupational health according to the Hazard codes assigned to each in the respective SDS documents. [27].

Substances to which multiple health hazard codes have been assigned are considered posing higher hazard for users than substances with less (or no) codes, separately considered, for general Safety ("200" codes), for operator's Health ("300" codes), for the Environment (safe disposal and accidental release, "400" codes). For group "300" of Hazard codes, a further tier of classification ranks severity of consequences in five classes, coded from 1 (most severe) to 5 (less severe) [27–29].

The Italian technical and administrative document for reference is the latest release (February 2025 draft) of the Manuals for the Chemical Risk Assessment tools (MoVaRisCh [28,29]), which reports the updated tables of the Gravity (or Severity) P-scores, according to the Regolamento 1272/2008/CE (CLP) [30] (pp. 12–14 of document). The reported P-scores are used to calculate the Gravity-corrected Hazard Index (GcHI) for each health hazard presented by a substance, according to Equation (1).

$$\mathrm{cHI} = 1\ (\text{if "300" health Hazard code is present}) * \mathrm{GI}\ (x) \tag{1}$$

Table S1 reports the P-scores assigned to the H-300 codes according to the most recent release of the MoVaRisCh document [28,29].

The global Gravity-corrected health Hazard Index (GGcHI; Equation (2)) of each compound is calculated as the sum of the GcHIs of the compound.

$$\text{global GcHI} = \Sigma\ \mathrm{GcHI(H300)} \tag{2}$$

The global non-health Hazard Index, GcHI(nH), is calculated as the sum of the non-health Hazard codes assigned to the compound (coded "200" and "400"), and concerns fire and explosion hazards and other specific properties, such as the ability to corrode materials and the potential for environmental hazard when improperly dumped (Equation (3)). The reference guidelines do not assign Gravity Index coefficients to the non-health Hazard Index, so that the Global Index for this class of hazards corresponds to the number of hazards highlighted in the SDS. The value of the sum is expressed as "Hazard Points".

$$\text{global GcHI(nH)} = \Sigma\ \mathrm{GcHI(H200; H400)} \tag{3}$$

For both classes of hazard, that for operators' health and that for safety, a global HI is calculated for each reaction, as the sum of the HIs of each material involved in the reaction.

The first example in the Results reports the data extraction and information retrieval for one individual chemical preparation, the text of which is reported. The second and third examples extend the exercise to a larger group of reactions.

## 3. Results

### *3.1. Data Extraction for the Chemical Preparations*

One randomly selected reaction among those described in the article [22] yields intermediate **40** from precursor **39**, *en-route* to the desired final product **14** which will be obtained according to the scheme reported in Figure 2.

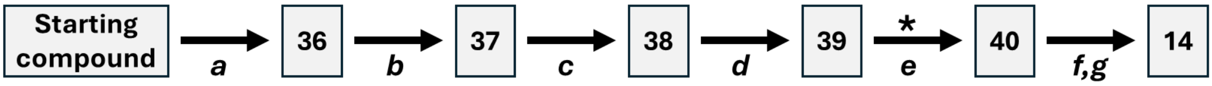

**Figure 2.** Scheme of the preparation of final compound 14 from the first starting material, as described in the article considered (Scheme 3 of ref. [21]). The asterisk identifies the reaction that prepares intermediate product **40** from intermediate product **39**.

This reaction exemplifies a task that can be assigned, in an academic laboratory, to an operator (student, staff technician, professional chemical researcher) in the frame of a wider project. The operator follows the instructions that are reported below, extracted from the Experimental section of the cited article [22].

> *"To a solution of* ***39*** *(280 mg, 0.94 mmol, 1.0 equiv) and methyl 5-(bromomethyl)thiophene-2-carboxylate (331 mg, 1.41 mmol, 1.5 equiv) in dry ACN (8 mL) was added* $Cs_2CO_3$ *(0.92 g, 2.82 mmol, 3 equiv), and the reaction mixture was stirred at 75 °C for 5 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), after being poured into water. The combined organic layers were washed with brine (3 × 10 mL), dried with anhydrous* $Na_2SO_4$*, and filtered, and the solvent was evaporated under vacuum. The crude mixture was then purified by silica gel column chromatography using DCM/MeOH (98:2, v/v) as an eluent to afford the pure* ***40*** *(80 mg, 20% yield) as an amorphous white solid"*

Table 2 reports, as the first example, the manually performed data extraction, from the experimental description above, as described in the Materials and methods (Sections 2.2. and 2.3). The global process employs three organic solvents, acetonitrile as the reaction solvent, methyl alcohol and dichloromethane for the chromatography, two inorganic salts classified as not hazardous and silica gel powder as stationary phase for chromatography. One employed reagent (R2, 3) is commercially available and has an SDS. The original intermediate product **39** and the desired product **40** are not further discussed, due to their original nature and, consequently, to the lack of any information on possible hazards. The same holds for all original products mentioned in the article.

For each compound ~~t~~that has an SDS, the H-codes have been extracted, and the global, Gravity-corrected Hazard Index (GcHIx) of the compound has been calculated, in "Hazard Points", as well.

Analogously, Table S2 reports the corresponding information for the 60 substances used in the reference article.

**Table 2.** Information extracted from ref. [22] for the preparation of product (40) from its precursor (39).

| | Role [a] | Substance | Amount [b] | Class [c] | CAS Number | MW | H [d] | Exp. Lim. Val. (TLV) [e] | HIx (T) [f] | HIx (A) [g] |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **S1** | Acetonitrile | 8 mL | **A** | 75-05-8 | 41.05 | H225<br>H302<br>H332<br>H312<br>H319 | TWA8h:35 mg/m$^3$;<br>STEL15: not ass.<br>TLV-C: Not ass;<br>Skin | **6** | **1** |
| **2** | **R1** | Original reagent (**39**) | 280 mg<br>0.94 mmol | **C** | Not ass. | 428.1 | Not ass. | | Not assigned | Not assigned |
| **3** | **R2** | methyl 5 (bromo-methyl)thiophene-2-carboxylate | 331 mg<br>1.41 mmol | **B** | 108499-32-7 | 235.1 | H302<br>H314 | Not ass. | **4** | **0** |
| **4** | **R3** | Cesium carbonate $Cs_2CO_3$ | 0.92 g<br>2.82 mmol | **B** | 534-17-8 | 325.8 | H318<br>H361f<br>H373 | Not ass. | **10** | **0** |
| **5** | **A1** | Sodium sulfate (anhydrous) | Not rep. | **A** | 7757-82-6 | 142.1 | Not ass. | Not ass.<br>Not haz. | **0** | **0** |
| **6** | **S2** | Ethyl Acetate | 30 mL | **A** | 141-78-6 | 88.1 | H225<br>H319<br>H336 | TWA8h:734 mg/m$^3$;<br>STEL15: 1468 mg/m$^3$<br>TLV-C: Not ass.<br>Skin | **3** | **1** |
| **7** | **A2** | Amorphous silica gel | Not rep. | **A** | 7631-86-9 | | Not ass. | Not ass.<br>Not haz. | **0** | **0** |

**Table 2.** *Cont.*

| | Role [a] | Substance | Amount [b] | Class [c] | CAS Number | MW | H [d] | Exp. Lim. Val. (TLV) [e] | HIx (T) [f] | HIx (A) [g] |
|---|---|---|---|---|---|---|---|---|---|---|
| **8** | **S3** | Methyl alcohol | Not rep. | **A** | 67-56-1 | 32.1 | H225<br>H301<br>H331<br>H311<br>H370 | TWA8h: 260 $mg/m^3$;<br>STEL15: Not ass.<br>TLV-C: Not ass.<br>Skin | **10** | **1** |
| **9** | **S4** | Dichloromethane | Not rep. | **A** | 75-09-2 | 50.1 | H315<br>H319<br>H351<br>H336 | TWA8h: 175 $mg/m^3$;<br>STEL15: 353 $mg/m^3$;<br>TLV-C: Not ass.;<br>Skin | **9** | **0** |
| **10** | **P1** | Original product (**40**) | 80 mg<br>20% yield | **C** | Not ass. | 451.1 | Not ass. | | Not ass. | Not ass. |

Notes. Chemical substances are listed and numbered in the likely order of use during the preparation, according to the reported experimental description. [a]: S (solvent, n); R (reagent, n); A (auxiliary, n); P (reaction product, n); [b]: preparation as described in the article; [c]: substance classification (A: substance with exposure limits); B (substance with SDS but no exposure limits; C (substance without SDS); [d]: H phrases in the SDS; [e]: Exposure limits (in Italy, from All. XXXVIII and XLIII of Decree 81/08); [f]: Hazard Index calculated for Health (toxic) effects according to the gravity factors of the MoVaRisCh tool [28,29]; [g]: Hazard Index for non-health effects (fire and explosion) expressed as the number of Hazard codes reported in the SDS. Substance codes from original ref. [23]: (**39**); 7-((1H-Indol-5-yl)methyl)-4-chloro-7H-pyrrolo[2,3-d]-pyrimidin-2-amine; (**40a**) Methyl 5-((5-((2-Amino-4-chloro-7H-pyrrolo[2,3-d]-pyrimidin-7-yl)methyl)-1H-indol-1-yl)methyl)thiophene-2-carboxylate**.**

### *3.2. General Safety and Health Characteristics of the Employed Chemical Substances*

Considering the Safety and Health related properties, collected in Table S2, of the 60 substances involved in the preparation of the 54 products described in ref [22], some initial considerations can be drawn.

First, 61/90 individual H-codes have been assigned to the 60 substances with a total of 227 occurrences, and the most frequent occurring code is H319 (ocular irritation) with 27 occurrences, i.e., in nearly 50% of the substances, for all three classes: Auxiliaries, Reagents and Solvents (Figure 3).

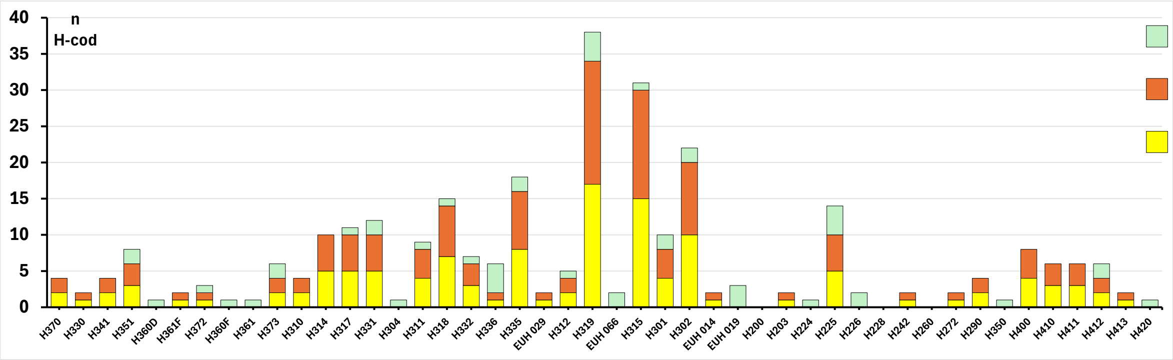

**Figure 3.** Number of occurrences of the H-codes (ordered from left by decreasing values of the respective Gravity Factor) in the SDS of the 60 chemical substances used in the work of ref. [22], including Solvents (yellow), Reagents (orange) and Auxiliaries (green).

Some auxiliary substances, such as Sodium chloride (brine used in liquid-liquid extraction), anhydrous Sodium sulphate (drying agent for organic solvents and extracts), silica gel (adsorbent for chromatography) are classified "non-hazardous". However, caustic strong alkali and acids present safety hazards in case of inadvertent contact or splashes. GCHIx values vary from 0, for "non-hazardous" substances, to 15 for hydrochloric acid.

Water, a "non-hazardous" substance, dissolves inorganic reagents and not irrelevant quantities of organic solvents and reagents. Laboratory wastewater is thus hazardous waste, for which specific directions for safe disposal apply.

A specific hazard consideration holds for amorphous silica used for the preparative purification of reaction products from crude synthetic mixtures by "direct-phase flash column chromatography" ([17], Ch. 2.31 Chromatography, pp. 197–234) This material is a highly purified, synthetic, coarse but size-controlled powder used in multi-gram amounts for each reaction. "Silica gel" is the adsorbent, or "stationary phase", through which a mixture of organic solvents, the "mobile phase", is flown and collected in fractions, until the desired compounds are recovered. The spent stationary phase is then discarded as laboratory waste but still contains adsorbed but not recovered components from the crude reaction mixture, all of which are of unknown toxicological characteristics.

Silica gel does not share any toxic property with crystalline silica. However, small amounts of spent silica dust settle on laboratory surfaces, diffuse in the workspace by re-suspension and re-deposition mechanism and airway or oral exposure can entail absorption of the organics embedded onto the particulate matter.

The 34 chemical reagents have very different properties for safety, health and environmental hazards, with corresponding GcHIx between 0 (the amino acid proline, used in one preparation) and 34.5 (hydroxylamine 50% in water, that is assigned 10 H codes, for some of which there are high correction factors for gravity). Furthermore, some chemical reagents escape the REACH regulation for the assignment of Hazard classification. As an example, four reagents of Table S2 are declared, in the respective SDSs, as exempted from the REACH registration while, according to the H codes and GcHIx assigned to each, all display serious hazardous properties. The substances are, in the decreasing order of their GCHIx, di-t-butylcarbonate (GcHix = 32.3), N-Bromosuccinimide (GcHix = 22.5), Azobis-isobutyronitrile (GcHix = 8.5) and Trimethylsilyl-hydroxylamine (GcHix = 7.3).

The 12 organic solvents used for reaction, extraction, crystallization or chromatography have GcHIx from the minimum of 4.0 assigned to ethyl alcohol to the maximum of 35.8 assigned to Carbon tetrachloride. Most organic solvents belong to category A, as substances regulated by the attribution of OELs, at least in one Country. To the uncommon solvent, 1,1,1-trifluoroethyl alcohol, only Latvia has assigned an OEL, a TWA-8h of 10 $mg/m^3$.

### *3.3. Safety and Health of Performed Chemical Reactions*

The sum of the GcHIx of the substances involved in one chemical preparation is a global estimation of the hazards involved in the activity. However, as anticipated, this estimation does not consider hazards from substances without Hazard classification, nor that from original ones (Precursor 39 and Product 40). Explicitly, this assessment does not consider the quantities used of substances.

Taking as example the single reaction of Table 2, a total value of 53.25 “Hazard Points” is obtained. The most prominent contribution to the global GcHIx is from three hazardous solvents, acetonitrile (GcHI = 17.5), dichloromethane (GcHI = 21) and methyl alcohol (GcHI = 27.3). The inorganic Cesium carbonate is assigned a GcHI of 19 (codes H318, H361f, H373, to which particularly high Gravity Index values are assigned: 4.5, 7.5 and 7, respectively).

The same calculation applied to all seven reactions for the preparation of target compound 14 affords the results of Figure 4. Reactions ***a***, ***b*** and ***g*** are associated with higher GcRIx, due to the use of solvents and reagents with higher health hazards. Step ***a*** employs two of the reagents with the highest individual GcHIx among those of this sequence of reactions. Step ***b*** employs as solvent Carbon tetrachloride, which is classified as human carcinogen. The lowest-hazard step ***f*** uses alkali in a dioxane-water mixture, where the former solvent is labelled as a carcinogen. This amount of laboratory work envisages, *inter alia*, a possible task that a supervised operator, such as a chemistry student at the B.Sc. or M.Sc. level, may be requested to perform as part of a project, during chemistry studies.

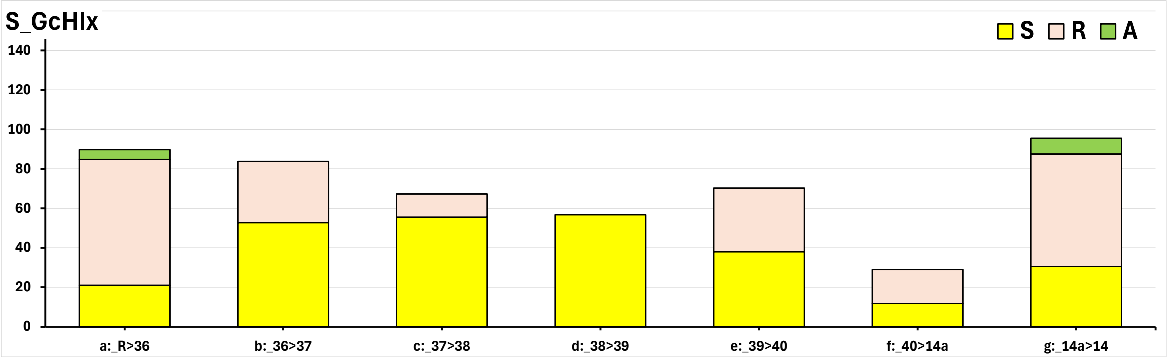

**Figure 4.** Gravity-corrected Risk Index calculated for each of the reactions a-g of Figure 1, as sum of the GCRIx of all Solvents, Reagents and Auxiliaries.

This reaction sequence has been particularly interesting in the data extraction phase, because only manual inspection of the text could highlight the two-step reaction within the same paragraph, while the adopted ChatCPG tool could not be instructed to look for this important information.

The same process is applied to all 54 reactions described in the article and the corresponding calculation is reported in Figure 5, where the contribution of the different classes of chemicals is highlighted.

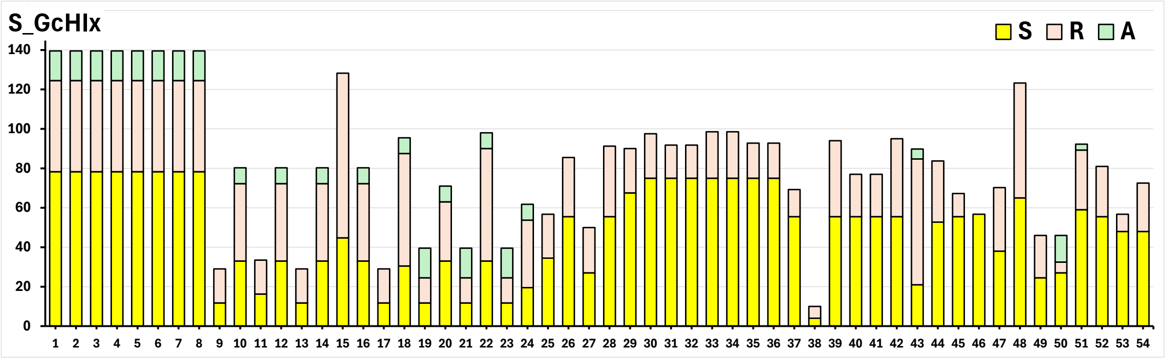

**Figure 5.** Gravity-corrected Risk Index calculated for each of the reactions 1–47 of ref. [22], calculated as sum of the GcRIx of all Solvents (yellow), Reagents (orange) and Auxiliaries (green).

The overall activity entails the use of 60 substances: 13 classified as Auxiliaries; 34 as Reagents and 12 as Solvents (when a substance is used in multiple times in a single preparation, each time counts as one).

As can be appreciated, the contribution of the solvents to the GcHIx of the reaction is mostly similar, and accounts for approx. 50% of the total (median 56%; from 23% to 100%, in the single case where the reaction only entailed heating the precursor in solvent). On the contrary, a high contribution from solvent use to the hazard of the procedure derives from the column chromatography separation step, employed in 26/54 procedures, that most often employs a mixture of *n*-hexane and ethyl acetate as the mobile phase. In few cases (reactions 15, 43, 18, 22) the calculated contribution of the reagents to the global hazard is higher than that of the solvents, with a very limited contribution from the Auxiliaries. The lowest-hazard reaction, (38) employs ethyl alcohol as the solvent and iron / ammonium chloride for the reduction of an amino group. The maximum value of GcHIx = 139.50 is assigned to a group of 8 reactions (Figure 5, reactions 1–8) that that use reagents with high GcHIx, on a group of similar original precursors, for which the GCHIx is not available. In this specific case, the employed reagents and solvents are hydroxylamine (GcHIx = 34.50), the solvents tetrahydrofuran (GcHIx = 21.75), methyl alcohol, (GcHIx = 23.25), diethyl-ether (GcHIx = 10.0), and the auxiliaries Sodium hydroxide (GcHIx = 11.75) and hydrochloric acid (GcHIx = 15.0).

As an example of the possible use of GcHIx for planning Safety & Health-oriented laboratory research, in 25 preparations, *n*-hexane (GcHIx = 21.0) was used for preparative chromatography. Substitution with *cyclo*-hexane (GcHIx = 13.0) is possible without changes [31], lowering the GCHIx of the procedure by 12 Hazard Points.

The considered work simulates the laboratory activity performed by one individual chemical researcher within a few months of activity. Under optimal workflow, one compound can be prepared, purified and characterized in two days and used for the next reaction step the third day. Therefore, 53 reactions can be performed in about 15–16 work weeks, or around four months of committed laboratory work. Of course, different work schedules, such as parallel work by more than one operator, or similar reactions being run in parallel by the same operator, are also possible, under a different organization, such as on a tighter time constraint of the project.

## 4. Discussion

The reaction example used for this data analysis describes the typical activity of an academic laboratory that prepares small, micromole amounts of new organic substances for further research. The aim is to determine whether the available or retrievable information is adequate for preliminary evaluation of the operating conditions for the workers involved. Information in the article allows identifying all chemical substances employed in the work, the reaction conditions and the procedures employed to separate and purify the obtained products. Regulatory information in public sources on the commercial reagents, solvents and auxiliary products is sufficient to identify the respective safety and health hazards. Regulatory agencies have established occupational exposure limits for the protection of workers' health for some chemical substances, mainly organic solvents, the values of which somewhat change among countries. The GcHIx-based risk assessment calculation is not universally valid: those reported in this article refer to the current Italian law.

Tools for preliminary risk assessments of chemical exposure have been developed in Italy for workplace scenarios in which direct measurements are not sufficient, feasible, or practical [28,29], such as in Small Size Enterprises. However, the relevance that these models assign to the quantity of manipulated products in the envisioned scenarios downplays the risk assessment in research laboratories where preparation of new compounds is performed at the millimole scale but using unusual chemical reagents and "building blocks" and unavoidably performing manual operations. Recent Italian documents recommend general safe laboratory practices and adherence to labelling precautions [32–36]. At the same time, aligning the peculiar needs of contemporary research academia with existing regulations [37,38] and tools [33–36] is a topic of current multi-disciplinary debate.

This experience shows that data collection is the key and limiting step of the whole process. In our simulation, information was manually extracted from the experimental section of the employed scientific article. The manual procedure entailed several days of a two-person team, an effort, an effort not compatible with available professional resources. The use of General-purpose AI tools may still be too unreliable, due to the difficulty of instructing the AI program on the style variants adopted in describing the synthesis recipe. The growing adoption of electronic laboratory logbooks, which present information in a uniform and structured format [39], can substantially simplify the process and enhance its reliability. This approach aligns with the objectives of the emerging FAIR (Findable, Accessible, Interoperable, Reusable) principles for the long-term preservation of research data and results, including the reuse of scientific information for purposes not anticipated at the time of data generation [40,41].

Another aspect that risk assessment in chemical research laboratories should consider is that of management of waste, including water, deriving from the small-scale chemical reactions and for which the forecast of possible biological properties, including systemic toxicity, is not reliable, or even feasible. Reported mishandling organic waste in academic laboratories led to infringement of local bylaws and to purported clusters of cancer cases [13].

The creation of large databases on a greater number of workers, operating in different laboratories over extended periods, would enable the efficient development of activity maps that identify both the frequency of use of substances with specific hazards and the workers potentially exposed to them. Such information can guide targeted protection and prevention strategies, including the use of more sensitive and specific health-monitoring tests—an approach already well established for industrial and healthcare professionals exposed to ionizing radiation, biological agents, carcinogens, mutagens, and reprotoxic chemicals.

Of course, one key ingredient of chemical risk management in occupational health is estimation of exposure, which is very difficult to estimate in the specific work condition of research laboratories. At this preliminary stage, the described hazard assessment does not consider the amount of the manipulated materials, which are mostly in the millimole, or even smaller. The scale of the chemical reactions determines the employed quantities of all necessary materials and generated organic waste. Several similar operations can go along simultaneously in each chemical laboratory, by operators who share bench space, equipment and collective protection facilities, such as chemical hoods and safety chemical cabinets. Each operation, such as a different chemical preparation, uses its own reagents and “building blocks”, in order that, in a single day, up to a few tens of different chemical substances can be in use in the several laboratories of a department building. All operations entail potential exposure of the operator, of bystander colleagues and even of auxiliary personnel tasked with cleaning and laboratory waste disposal. For this reason, the working pattern can be reconstructed, for OSH purposes, only using actual documents, such as the day-by-day logbooks of all research workers at the facility.

Example for quantitative exposure assessment may derive from similar scenarios, such as the preparation and administration of antineoplastic drugs in hospital facilities, where hundreds of grams are manipulated per day. In past situations without specialized equipment and thorough hygienic procedures, with insufficient training of healthcare personnel, measurable doses of drugs, in the microgram range, were measured in pharmacy technicians’ and nurses’ urines. Monitoring of surfaces in preparation cabinets and rooms revealed dispersion factors in the 0.1–10 parts-per-million of the prepared drugs [42,43]. Although this working scenario is very different from the activity in research chemical laboratories, this represents the closest available analogue for envisaging monitoring strategies and establishing dispersion models based on use data derived from accessible information sources [44].

## 5. Conclusions

This proof-of-principle test shows that even the information published in a scientific article, which is of public availability, is sufficient to identify the chemical substances used and the reaction products of an academic synthesis project and to preliminarily assess the main occupational hazards and potential exposure. The global Gravity-corrected Health Hazard Indexes that rank the substances and indicate priorities in organizing prevention in the laboratory during use, including waste disposal can be calculated from the information retrieved from public sources, such as the SDS from the suppliers, to indicate priorities in organizing prevention in the laboratory during use, including waste disposal and to rationalize prevention in academic laboratories where multiple activities are run in shared facilities. Of course, the laboratory notebook contains much more information relevant to OSH, such as a timed record of all activities, such as chemical reactions analogous to those exemplified, performed over time, in different conditions, using different quantities of described materials [45,46]. Therefore, sharing the information from the logbook between the academic workers, who are the stakeholders of occupational safety and health prevention, and the technical specialists in charge of occupational prevention can improve chemical risk assessment for large groups of workers under an extended time frame, indicate priorities for intervention and allow retrospective evaluations [47–49].

Predicting toxicity of original synthetic molecules to highlight possible, unforeseen health hazards for chemical researchers is, however, a harder task. While AI-directed drug design has already demonstrated capacity to design molecules endowed without (or with [50]) specific toxic activity, not only the reverse problem seems currently harder to tackle [51,52], but, furthermore, the needed tools may not be convenient for preventive toxicity assessment at the scale chemical researchers devise and prepare new molecules in their laboratories.

Long-term health protection of academic research workers can accelerate the transformation of occupational safety and health in academia from a legally enforced duty to a culturally embraced, shared opportunity for ethical scientific progress [53,54].

## Supplementary Materials

The additional data and information can be downloaded at: https://media.sciltp.com/articles/others/2512301440395099/WAH-25110050-Supplementary-Materials.pdf. Table S1: P-scores assigned to the H-codes according to the most recent release of the MoVaRisCh document [28]. Table S2: List and main toxicological and regulatory properties of the 60 substances involved in the preparation of the 54 products described in ref [23], for which documentation is available.

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## Institutional Review Board Statement

Not applicable.

## Informed Consent Statement

Not applicable. The starting data are in the public domain and there was no contact of the author with the chemists who performed the work re-examined in this article.

## Data Availability Statement

Data sharing is not applicable to this article as no new data was created in this study.

## Conflicts of Interest

The author declares no conflict of interest.

## Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

## Appendix A

This appendix reports, in an English translation checked by the original Author, the text of an alert note he published in Italian in the national professional magazine *La Chimica e l'Industria* [Chemistry & Industry] in 2005 [15], to warn colleagues on the respiratory hazard presented by a class of original chemical compounds he was working at. Since this information is unavailable to a wider community of occupational health practitioners and describes first-hand an unusual occupational hazard and the ensuing health concern of the stricken professional worker, we deem it useful that the original text is reported here. Lunelli B. Hazard of $C_4O_2XY$ compounds. *La Chimica e l'Industria* **2005**, *86*, 99 (English translation by FMR, checked by the original author) [15].

Health hazard from $C_4O_2XY$ compounds. By means of this communication, I wish alert on the effects of even short and limited exposure to the vapors of some derivatives of cyclobutenedione $C_4O_2XY$ (X and Y being halogens and perhaps other groups). Effects are particularly insidious because consequences are not immediate, however heavy for the health. Even if these compounds generally have a very low vapor pressure, less than one Torr at ambient temperature, they have pungent odours, but not to the point of raising alert. It is possible that these compounds enter the organism by inhalation or through the skin, since most are lipid soluble. However, in the living tissue, they probably hydrolyze to squaric acid, $C_4O_2(OH)_2$, a poorly soluble strong acid, and to other substances, that can be more or less irritating and toxic.

I have been using these compounds over many years -among those I handled, they are the sole for which there are no safety specifications- in quantities generally lower than 100 mg, and I performed all chemical and physical manipulations within vacuum lines or inside efficient chemical safety cabinets. Inhalation or absorption of vapors may have taken place within the approx. 30 s necessary to load the sample in a vacuum infrared spectrophotometric cell or disk.

Recently, more than 24 h after recording the spectrum of one compound (likely a chloro-fluoro derivative, as anticipated), I felt breathing difficulty and the necessity of hospital care. My stay lasted for two weeks, and the diagnosis was acute pulmonary oedema. In addition, a chest CT scan highlighted not only the acute inflammation, but also an underlying fibrosis of a substantial proportion of my lungs. This condition had not been highlighted in the previous obligatory physical examinations that myself, and all staff of our department, undergo at least yearly, if we are classified as users of chemical products.

What I highlight leads, in my opinion, to two conclusions. First, we should strive to tolerance-zero for exposure to the vapours of $C_4O_2XY$ compounds. Second, the obligatory periodic health check for all chemists who use non-commercial compounds, for which there are no safety indications, should include a chest CT scan, if even not on a yearly basis.

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