Consulta Interassociativa Italiana per la Prevenzione

Observations on the European Commission's proposal COM (2020) 571 final

Introduction

European strategies and commitments in the field of Safety and Health at Work, particularly of occupational carcinogens in the context of the Directives for workers' protection, are specified in numerous acts, including:

- **Communication from the Commission** on a Strategic Framework on Health and Safety at Work 2014-2020 (COM (2014) 332 final, - July 6, 2014, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014DC0332);

- **Communication from the Commission** on Safer and Healthier Work for All (COM (2017) 12 final (January 1, 2017, https://eur-lex.europa.eu/legal-content/IT/TXT/PDF/?uri=CELEX:52017DC0012&from=EN);

- **Communication from the European Commission** on the Implementation of the European Pillar of Social Rights (COM (2018) 130 final - March 13, 2018, https://ec.europa.eu/transparency/regdoc/rep/1/2018/IT/COM -2018-130-F1-IT-MAIN-PART-1.PDF

- **Council Conclusions** - December 10, 2019 (https://data.consilium.europa.eu/doc/document/ST-14630-2019-INIT/en/pdf): *"THE COUNCIL OF THE EUROPEAN UNION INVITES THE EUROPEAN COMMISSION: 31. To ADOPT a new EU Strategic Framework on Occupational Safety and Health for 2021 -2027, paying particular attention to the challenges identified in these conclusions. To eliminate hazards and prevent diseases, including cancer, resulting from dangerous substances in workplaces 38. To PROPOSE further binding limit values for priority carcinogens and other dangerous substances, based on the precautionary principle and up-to-date scientific evidence, and UPDATE existing limit values if required to protect workers. 39. To DEVELOP guidance on measurement of the binding limit values introduced at the European level, including, where relevant, biological limit values. 40. To CLARIFY the interface between OSH and REACH legislation and IMPROVE coordination by developing transparent procedures and criteria to be used when selecting the most appropriate substance-specific regulatory options ".*

- **EU Roadmap on Carcinogens -** European voluntary cooperation agreement between different Member States, social partners, companies, research organizations, and other organizations across Europe and beyond (https://roadmaponcarcinogens.eu/). First campaign for the period from 2016 - 2019 (Amsterdam in 2016, Vienna and Helsinki in 2019). In 2020 (Dortmund), new RoC 2.0 Campaign for the period from 2020 – 2024 (https://roadmaponcarcinogens.eu/wp-content/uploads/2020/11/200903_RoC2.0_Strategy.pdf).
- **European Parliament: Preventing occupational exposure to cytotoxic and other hazardous drugs. Policy recommendations** (2015, https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2016/05/Exposure-to-Cytotoxic-Drugs_Recommendation_DINA4_10-03-16.pdf).

- **European Biosafety Network "Amendments to the Carcinogens and Mutagens Directive"** (2019, https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2019/03/Amendments-and-Implications-of-CMD3-Italian.pdf).

All Member States must therefore draft the administrative acts at the national level to implement the contents of Directive 2004/37/EC, as subsequently amended by three revisions (EU Directives 2017/2398, EU 2019/130 and EU 2019/983), by January 17, 2020, February 20, 2021, and July 11, 2021, respectively. Overall, these Directives addressed seven other processes in addition to the five listed in Annex I of the first Directive; moreover, the three substances or groups of substances of Annex III of the first Directive have now become 22, with 20 new OELs.

As it is known, Treaties grant the possibility to adopt stricter limit values at a national level to guarantee better protection of workers' health from the risk of cancer.

As for all chemical agents and particularly for carcinogens, it is necessary to evaluate and check that workers' exposure is kept within the limit values and that the limit corresponds to the best protection possible, both at a technical and an organizational level. Several steps precede the instrumental assessment of compliance with the limit: a) Identification of carcinogens that enter the industrial production cycle and are currently not eliminable and therefore are subject to primary prevention actions such as closed-loop isolation, engineering controls. b) Management controls with information and specific training of workers concerning risks in all industrial production cycle, including storage and waste management. c) Evaluation of the reliability of the analytical methods with adequate certifications for monitoring compliance with the limits.

The instrumental quantification of exposure (environmental and biological monitoring) is essential for carcinogens, leaving for predictive models an ancillary role of first classification. Compliance with the limit is a necessary but not sufficient element to protect the worker from cancer risk.

Workplace exposure also involves more general considerations concerning the substances used, considering the provisions of the REACH and CLP regulations. The life cycle of a carcinogenic substance can involve exposure from manufacture to use in production processes to management as waste.

1. Proposal for a fourth Directive amending Directive 2004/37/EC

With the Proposal for a fourth Directive amending Directive (**COM (2020) 571 final**) published on September 22, 2020 (2020/0262 (COD), the Commission is now proposing the European Parliament to adopt new

limit values. This would mean the addition of 2 additional priority substances or groups of substances to Annex III: Acrylonitrile (1 mg m^{-3}), and Nickel compounds (from 01/25/18: 0.01 mg m^{-3} (breathable), 0.05 mg m^{-3} (inhalable), until then 0.1 mg m^{-3}) and the reduction of the limit values for Benzene (0.66 mg $m^{-3}$from the fourth year after entry into force, from 2 years up to 4 years after entry into force, 1.65 mg m^{-3}). Member States will have to implement the new Directive within two years of its entry into force (20 days from publication in the GUE).
The preparatory document of the European Commission published on September 20, 2020 (**SWD (2020) 183 final**, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020SC0183&from=EN) considered the limit values for these three carcinogens, examined the comments of the social partners (see **Annex 2: Stakeholder consultation**).
The values proposed and examined, somewhat discordant with each other, should have led to choosing the most protective values, particularly for Benzene, by reviewing the previous limit in consideration of the high number of possible exposed workers.

Current national limits varied in reasonably wide ranges:

- Acrylonitrile between 0.5 and 7 mg m^{-3}
- Nickel compounds (as inhalable fraction) between 0.03 and 0.25 mg m^{-3}
- Benzene between 0.7 and 3.35 mg m^{-3}

The options arising from the statements contained in the Commission document narrowed these fields:

- Acrylonitrile: 0.5-1-2 mg m^{-3}
- Nickel compounds: 0.03- 0.05–0.1 mg m^{-3}
- Benzene: 0.16-0.66-1.32 mg m^{-3}

As already pointed out in a previous note (see CIIP Annex 1), we believe that based on the general precautionary principle declined as “as low as reasonably achievable” (ALARA), the most protective values should always be chosen.

2. Reprotoxic substances and hazardous drugs containing carcinogens or mutagens

In line with ETUI considerations (“More than a million workers affected by the revision of the directive on cancers”, https://www.etui.org/news/more-million-workers-affected-revision-directive-cancers), it is observed that:

- Specific commitments had been made in the 2019 Revision Directives for the regulation of reprotoxic substances and hazardous drugs:

    - **DIRECTIVE (EU) 2019/130: (6)** *No later than in the first quarter of 2019, the Commission, taking into account the latest developments in scientific knowledge, should assess the option of amending the scope of Directive 2004/37/EC to include reprotoxic substances. On that basis, the Commission should present a legislative proposal, if appropriate, after consulting management and labour.*

- **DIRECTIVE (EU) 2019/983, (6)**[1] and **Article 1, second subparagraph**: *"No later than June 30 2020, the Commission shall, taking into account the latest developments in scientific knowledge, and after appropriate consultation with relevant stakeholders, in particular health practitioners and health professionals, assess the option of amending this Directive in order to include hazardous drugs, including cytotoxic drugs, or to propose a more appropriate instrument for the purpose of ensuring the occupational safety of workers exposed to such drugs. On that basis, the Commission shall present, if appropriate, and after consulting management and labour, a legislative proposal".*

- The need to introduce reprotoxic substances and drugs of well-known toxicity appears well justified by the large number of people exposed at work, by the results of numerous scientific publications, and the description of actual cases.

- The 11 Recommendations stated in **Preventing occupational exposure to cytotoxic and other hazardous drugs. Policy recommendations (European Parliament, 2015) need to be considered, particularly No. 4**: *"The prevention of occupational diseases due to exposure to cytotoxic drugs should be specifically addressed in the European legislation. European recommendations for the promotion of successful prevention should be issued by the European Commission".*

- Moreover, the introduction of **"Amendments to the Directive on carcinogens and mutagens"** (**European Biosafety Network, 2019**) points out the proposed amendment to Article 16 concerning limit values: *"As mentioned in relation to Article 5, threshold levels of exposure to hazardous drugs cannot be predicted, and it is, therefore, difficult to establish limit values. Therefore, contact with genotoxic carcinogens should be avoided at all levels, in accordance with the "As Low As Reasonably Achievable" (ALARA) principle, and also that is why hazardous drugs should be included as a work category in Annex I of the CMD, not Annex III. Most of the studies performed on surface monitoring of hazardous drugs in Europe (e.g., in Germany and Spain) suggest 0.1 ng/cm^2 as the threshold level. In one Dutch study, urine samples from healthcare professionals who worked in facilities with contamination levels < 0.1 ng/cm^2 were negative for one of the most widely used carcinogenic hazardous drugs cyclophosphamide".*

- In this regard, it is worth remembering some attempts to assign experimental limits that could be taken into consideration: (**CIIP, "Your work matters, protect yourself. E-book Chemical Risk"**, https://www.ciip-consulta.it/index.php?option=com_phocadownload&view=category&id=17:ebook-rischi-chimici&Itemid=609[2].

[1] **DIRECTIVE (EU) 2019/983, (6):** *Hazardous drugs, including cytotoxic drugs primarily used for cancer treatment, could have genotoxic, carcinogenic or mutagenic properties. It is therefore important to protect workers who are exposed to such drugs through work involving: the preparation, administration or disposal of hazardous drugs, including cytotoxic drugs; services related to cleaning, transport, laundry or waste disposal of hazardous drugs or of materials contaminated by such drugs; or personal care for patients treated with hazardous drugs. Hazardous drugs, including cytotoxic drugs, are subject to Union measures providing for minimum requirements for the protection of health and safety of workers, in particular those provided for in Council Directive 98/24/EC (6). Hazardous drugs that contain substances that are also carcinogens or mutagens are subject to Directive 2004/37/EC. The Commission should assess the most appropriate instrument for ensuring the occupational safety of workers exposed to hazardous drugs, including cytotoxic drugs. In doing so, access to the best available treatments for patients should not be jeopardized.*

[2] **CIIP, E-book Chemical Risk**: *"It is interesting to point out some considerations from the recent work by Grignani et al. 'Carcinogenic risk assessment in hospital: antiblastic drugs' Ital. J. Occup. Environ. Hyg., 2017, 8 (4) | 125. In Italy and Germany [Sottani et al.,*

3. Limit values

It should be highlighted that:

- The number of carcinogens for which a "health-based or risk-based" limit is established is still minimal (far from the Trade Unions request for limits for 50 substances), and the numerical value of some of them is higher than that proposed by other agencies. For example, with regard to free crystalline silica (α quartz) and formaldehyde, the ACGIH proposes 0.025 mg m^{-3} starting from 2009 and 0.12 mg m^{-3} starting from 2016 - values that are much more protective than to European ones.

- It should be remembered that, for some time, Guidelines for the acceptability of oncogenic risk for "non-threshold based genotoxic carcinogens" have also been proposed. This can be seen in the EPA proposal as early as 1998, which for occupational exposure allowed as "tolerable" an incremental risk level in the interval 10^{-5}- and 10^{-4} calculated for the entire lifespan.

- The incremental risk levels for workplaces still vary in the same range with a tendency to assume the value of 10^{-5} (see European Chemical Agency, which proposed in 2012, in the context of REACH, 10^{-5} and Committee of Hazardous Substances of the German Federal Ministry of Labor and Social Affairs (AGS), which proposed 4 x10^{-5} starting from 2018, admitting 10^{-4} for the previous five-year period. We are far from what is inferred from the current legislation, in particular as regards Chromium VI.

- The CMR notation *(May cause cancer, May cause genetic defects, May damage fertility or the unborn child)* for carcinogenic substances that cause significant and long-term health damage appears in ECHA documents when considering carcinogens *(CMR categories 1A or 1B of CLP)* and the need to include them in an Annex, as can be seen from the document: "**CMR substances from Annex VI of the CLP Regulation registered under REACH and notified under CLP - a first screening Reference**" (ECHA -12-R-01-EN, May 2012).

- In the same European context, the application of REACH has already taken into consideration a much higher number of carcinogenic, mutagenic, and reprotoxic substances, introducing them into the table of substances of very high concern (SVHC). One of the selection criteria for SVHC substances is the identification according to the criteria defining carcinogenic, mutagenic, and toxic substances for reproduc-

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2017; Kiffmeyer et al., 2013], occupational exposure to the most common antiblastic chemotherapy drugs was assessed according to the MEWIP project procedure, based on monitoring by wipe testing. A reference standard has been proposed which is based on the 90th percentile of the distribution: as regards the Italian data recorded from 2009 to 2011, it was 3.6 ng /cm^2 for the phosphamide cycle, 1.0 ng / cm^2 for the - fluorouracil, 0.9 ng / cm^2 for gentamicin and 0.5 ng /cm^2 for platinum compounds. Based on the experimental results of the last decade and the considerations of Sessink (2011) and other authors, technical limits to be used for exposure control have been proposed: as far as cyclophosphamide is concerned, a range between 0.1 and 1 ng /cm^2 has been proposed as a still safe range while a range between 1 and 10 ng /cm^2 indicates the need for interventions. The laboratory activity has made it possible to create two databases that allow defining hospital contamination maps, one relating to the period 2009-2011 for the five active ingredients chosen as exposure markers, and one relating to the period 2014-2017, which includes almost 5,000 results divided by year, active ingredient, sampling positions relating to the two main sectors: preparation and administration".

tion *(CMR categories 1A or 1B of CLP).* Identified SVHC substances are included in the Candidate List for Authorization and subsequently, in case of approval of the need for authorization, in Annex XIV.

- The recent **Candidate List** includes **209** substances characterized by the following properties:
  - Carcinogenic, mutagenic, and toxic for reproduction (CMR): **137**
  - CMR with persistent, bioaccumulative and toxic (PBT) properties or very persistent and very bioaccumulative (vPvB) properties: **14**
  - CMR with endocrine-disrupting properties (ED): **6**
  - CMR with specific target organ toxicity after repeated exposure (STOT RE): **9**
  - Persistent, bioaccumulative and toxic (PBT) o very persistent and very bioaccumulative (vPvB): **25**
  - Endocrine disruptors (ED): **11**
  - Respiratory sensitizers (RS): **5**
  - Others: **2**

- 3 out of the 4 substances added to the Candidate List on June 25, 2020 are toxic for reproduction. This demonstrates a focus on reprotoxic substances that is not yet reflected in the limits established by SCOEL.

- For substances of very high concern (SVHC), the availability of a safer substance or alternative is sufficient reason to refuse the Authorization or grant it for a limited time to plan and carry out the substitution of the substance.

- The Authorization procedure for SVHC substances may contain limitations of use for specific initiation cycles or processes and constitutes an important preventive measure for minimizing the carcinogenic risk as well as an incentive to substitute the substance. In fact, technological, organizational, and specific protection measures can be as effective or even more effective than a limit value.

- The reasoned collection of reliable exposure data can be a vital element for the continuous revision of limit values in the workplace as well as for epidemiologists' work.

- The impact on environmental matrices must also be taken into account while In setting the limits.

- The differences in approach in establishing limits are highlighted in the document of the **Joint Task Force ECHA/RAC - SCOEL, "Scientific aspects and methodologies related to the exposure of chemicals at the workplace"** (Final Version – February 28 2017, https://echa.europa.eu/documents/10162/13579/rac_joint_scoel_opinion_en.pdf/58265b74-7177-caf7-2937-c7c520768216

- Since 2009, SCOEL has identified four groups of carcinogenic and mutagenic substances[3].

[3] **SCOEL**: *"- Group A: Non-threshold genotoxic carcinogens - Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported - Group C: Genotoxic carcinogens for which a practical threshold is supported - Group D: Non-genotoxic carcinogens and non-DNA-reactive carcinogens, for which a true threshold is associated with a funded NOAEL"* and rec-

- The model for deriving limits according to these criteria and relative results have been recently examined by Johanson G., Tinnerberg H. in the editorial **"Binding occupational exposure limits for carcinogens in the EU – good or bad?"** (Scand J Work Environ Health 2019;45(3):213-214). In the conclusions, on which we agree, the authors claim: "*So, are the new EU BOELV good or bad? Well, certainly they are a start, and maybe even a good one at that. However, in our opinion, some of the limits are outrageously high and breach the fundamental rights of safe and healthy working conditions. Moreover, there are still very few binding values; many more are needed to protect workers more thoroughly against occupational cancer*".

4. Conclusions

- Occupational cancers currently account for 52% of occupational diseases, and it is reasonable to think that the fraction of cancers attributable to the work environment may be underestimated. This is due to both work fragmentation, which could make it difficult to detect the epidemiological correlation of certain exposures and the fact that obtaining clinical evidence of cancer takes a long time.

- The **IARC** document **"World Cancer Report 2020"** highlights that the "industrial hygiene" measures aimed at reducing or eliminating workers' exposure to carcinogens (i.e., elimination, replacement, engineering controls, education of workers, organizational controls, adoption of means of protection) include compliance with the exposure limit to carcinogens at the workplace.

- Greater efforts are needed to address the causes of carcinogens, starting from dermal and inhalation exposure.

- It is necessary to specify the criteria and methodologies for setting limit values, differentiating between Health-Based and Risk-Based values.

- Setting limits for the most recurrent carcinogens is the first step to limit exposure to the lowest possible levels to ensure the best protection for workers.

- The number of carcinogens for which a limit has been set is still far too limited. The proposed limit value for several carcinogens is too high.

- The fourth stage of the revision of the Carcinogens Directive may provide an opportunity to set more binding limit values for the three substances under review, undertake a comprehensive review of the limits adopted to date, and include reprotoxic substances and certain hazardous drugs in the Directive.

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ommends two types of limits: *"1). Health-based OELs, which are based on a clear threshold. This OEL is derived from a No Observed Adverse Effect Level (NOAEL) or a Lowest Observed Adverse Effect Level (LOAEL) and applied to carcinogens classified in group C or D. The recommend OEL is presented. 2). Risk-based OELs, which are based on effects without a threshold (i.e., genotoxicity) and which carry some finite risk*".

- The revision of the limit values of carcinogens must be periodic based on scientific findings and experimental data on environmental and/or biological monitoring that are reliable as they are set with validated criteria and methodologies.

- Alignment with the provisions of the European REACH and CLP regulations.

- Assessment of cumulative exposure due to the simultaneous presence of several carcinogens and other hazardous substances for which it is reasonable to carry out a cumulative risk assessment.

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