CARCINOGENIC ACTIVITIES AND PROCESSES - THE FRENCH APPROACH OF CLASSIFICATION FOR CYTOSTATIC AGENTS

Symposium of the International Section of the ISSA on Prevention in the Chemistry Industry
"Carcinogenic substances: Risks and Prevention"

Lauranne VERINES-JOUIN

Unit of Chemicals Assessment – Risk Assessment Department
French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

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Regulatory context

Regulatory Context

- The French Labour Code lays down carcinogenic, mutagenic or toxic to reproduction (CMR) chemical agents as:

  - any substance or mixture meeting the criteria for classification as a CMR in Category 1A or 1B set out in Annex I to Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (the CLP Regulation);
  - any substance, mixture or process listed in the Ministerial Order establishing the list of carcinogenic substances, preparations and processes.

- At present, the list of this Ministerial Order is essentially based on the transposition of Annex I of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work, (with the exception of formaldehyde, for which a decision was taken at national level)

The request of the French Ministry of Labour

- As part of revisions to Directive 2004/37/EC currently under discussion at European level, ANSES received a formal request from the Directorate General for Labour (DGT) to provide an opinion on new carcinogenic processes that could fall within the scope of the Ministerial Order.

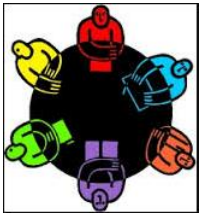
- ANSES was asked:
  - to determine initially whether four processes identified by the DGT (i.e. work involving exposure to welding fumes, work involving exposure to crystalline silica, work involving exposure to polycyclic aromatic hydrocarbons (PAHs) and **work involving exposure to cytostatic agents**), with strongly suspected carcinogenic properties could fall within the scope of the Ministerial Order;
  - to propose in a second way a method for concluding whether or not a process can be classified as carcinogenic and to define classification criteria for justifying a process's inclusion in the Ministerial Order. This work will be covered in a collective expert appraisal report by ANSES at a later date.

The overall methodology

Organisation of the work

- The Agency mandated an ad hoc Working Group (WG) on "Carcinogenic processes" for this expert appraisal composed of physicians, toxicologists, epidemiologists, occupational hygienists

Launch of an international consultation to gather information on existing methodologies to classify occupational processes as carcinogens, criteria used to classify them and any on-going work of others institutions



Litterature review and stakeholder hearings were held to collect information on topics needed (health effects; occupational exposure to cytotoxic/cytostatic agents; existing procedures for using these agents….)

Working approach applied on “work involving exposure to cytostatic agents”

Scope of the study and definition : « The active ingredients of cytotoxic/cytostatic anti-cancer drugs

- this expert appraisal focuses on "active ingredients of cytotoxic/cytostatic anti-cancer drugs" **whose mechanisms of action involves direct cytotoxicity on cells** via effects on DNA or on cell replication processes

these active ingredients may also be used for **other indications** than cancer treatments :

☛ Uses in departments other than oncology, such as rheumatology, immunology, nephrology, dermatology, gynaecology, etc.

Scientific approach

- **No availability of epidemiological studies of sufficient quality** enabling to reach an overall conclusion for workers concerning the carcinogenic properties of active ingredients of cytotoxic/cytostatic anti-cancer drugs

- → **Establishment of a list of 127 active ingredients of cytotoxic/cytostatic drugs with a marketing authorisation in France for cancer treatment**

  → **Select only agents classified in Category 1A and 1B carcinogens according to the CLP Regulation or in "equivalent" classifications established by recognised bodies assessing the carcinogenicity of chemical agents**

  - First intention : CLP 1A, 1B or IARC 1 « Carcinogenic to humans », 2A « Probably carcinogenic to humans »
  - Second intention (with a case-by-case analysis): US EPA: « carcinogenic to Humans » ; NTP: « known to be a human carcinogen » ; ACGIH®: « A1 » ; SGH 1A, 1B (Japon)

Results

- **18 substances are currently proposed for inclusion in the Ministerial Order on the basis of their CLP (Car 1A or 1B) or IARC, (Group 1 or 2A) classifications**

  - only 1 substance classified by the CLP : arsenic trioxide (Carc. Cat. 1A according to CLP ; also IARC group 1)
  - 8 substances classified IARC Group 1 : azathioprine, busulfan, chlorambucil, cyclophosphamide, etoposide, melphalan, thiotepa, treosulfan
  - 8 susbtances classified IARC Group 2A : adriamycin, azacitidine, carmustine, chlormethine, cisplatin, lomustine, procarbazine, teniposide
  - 1 substance : prednimustine because of its hydrolysis to chlorambucil which is classified IARC Group 1

- **2 protocoles classified in IARC Group 1 :**

  - etoposide in combination with cisplatin and bleomycin
  - The MOPP (mechlorethamine (or chlormethine), oncovin, procarbazine, prednisone)

☛ These two protocols should be added to the Ministerial Order but, as among the protocols, at least one substance is already belonging to the 18 substances proposed for inclusion, **there is no need to add these two specific protocols in the Ministerial Order**

Additional points investigated

1) Assessment of the risk of secondary cancers in patients treated by chemotherapy : ☛ No impact on the list of substances for inclusion in the Ministerial Order because :

- treatments involving several anticancer drugs and often combined with radiotherapy (know as human carcinogen);
- latency between treatment and occurrence of secondary cancer and evolution of therapeutic strategies over time;
- evidence currently limited for certain substances.

2) In addition to the assessment of individual substances considered to be carcinogens, the experts questioned the possibility of including therapeutic classes as a whole (alkylating agents, antimetabolite, etc.):

☛ this approach was found inadequate because :

- no or too few studies were available according to therapeutic classes;
- inadequate studies for an extrapolation to occupational exposure;
- there was no consistent pattern of carcinogenicity by therapeutic class when some data were available.

Conclusions

In order to update the Ministerial Order establishing the list of carcinogenic substances, mixtures and processes, the recommendation is to add **«work involving exposure to cytotoxic/cytostatic active ingredients used specifically in the context of anti-cancer treatments for human and veterinary uses and considered equivalent to Category 1A or 1B carcinogens according to the CLP Regulation.»**

➢ **The exposure circumstances to be taken into account should include in particular:**

- exposure during the manufacture, packaging, preparation, transport and handling of medicinal products;
- exposure when implementing protocols involving one or more of the substances proposed for inclusion;
- exposure through contamination of the working environment or via management of waste and excreta.

➢ **The list of the 18 substances identified should be taken into account**

Other key recommendations

- implement occupational exposures monitoring, in particular by carrying out biological monitoring of exposures and developing the associated tools; when biomonitoring is not possible, environmental monitoring of exposure via surface contamination measures and/or atmospheric measurements shall be considered;
- to produce a national or European guide of good practices for all professionals potentially exposed to the anti-cancer active ingredients, from reception to cleaning, waste and *excreta* management, in order to define standardised procedures to be applied in the different exposure situations;
- organize the update of the list of active substances by conducting a literature review on cancer therapies, including in particular new molecules;
- extend consideration to all active ingredients with genotoxic potential and/or suspected carcinogenic potential;
- propose active ingredients of drugs as potential candidates for CLP classification;
- improve and harmonise the conclusions of section 5.3 of the summaries of product characteristics (SPC) on genotoxicity and carcinogenicity

➢This work focused on the carcinogenic nature of these substances. However, these active ingredients may in addition have **effects on reproduction and development**, which should also be taken into account for the prevention of occupational risks.

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