COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

on work involving exposure to cytostatic agents

This document summarises the work of the Expert Committee on "Health reference values" and the Working Group on "Carcinogenic processes".

Presentation of the issue

In its Article R4412-60, the French Labour Code defines chemical agents that are carcinogenic, mutagenic or toxic to reproduction (CMR) 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, mixtures and processes.

At present, the list in this Ministerial Order is essentially based on the transposition of Annex I of Directive 2004/37/EC (with the exception of formaldehyde, for which a decision was taken at national level) and includes the following processes:
- manufacture of auramine;
- work involving exposure to polycyclic aromatic hydrocarbons (PAHs) present in coal soot, coal tar, coal pitch, smoke or dusts from coal;
- work involving exposure to dust, fumes and sprays produced during the roasting and electro-refining of cupro-nickel mattes;
- strong acid process in the manufacture of isopropyl alcohol;
- work involving exposure to inhalable wood dusts;
- work involving exposure to formaldehyde;
- work involving exposure to respirable crystalline silica dust generated by a work process.

As part of revisions to Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work, currently under discussion at European level, ANSES received a formal request from the Directorate General for Labour (DGT) on 17 November 2017 to provide an opinion on new carcinogenic processes that could fall within the scope of the Ministerial Order.

ANSES was initially asked, through scientific and technical support, to determine 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 (without a clear existing regulatory framework to define it) combined with a high occurrence in the workplace, could fall within the scope of the Ministerial Order.
ANSES was asked to indicate, if appropriate, whether there were any available data that could help further clarify and/or restrict the scope of these four processes, for the first quarter of 2018. The work on these four processes was described in a Scientific and Technical Support Note published on 20 April 2018. Since no firm conclusions could be made in due time, it was recommended to further evaluate the following processes: work involving exposure to welding fumes, PAHs and cytostatic agents.

With regard to cytostatic agents, because of their action on the proliferation of target cells affected by cancer but also on that of healthy cells, they may have carcinogenic properties. The classifications of several cytostatic agents by the International Agency for Research on Cancer (IARC) and the US National Toxicology Program (NTP) support this hypothesis: among 47 substances assessed by IARC (non-exhaustive list) and identified as \textit{a priori} cytostatic agents, some\textsuperscript{1} are both classified in IARC's Group 1 (IARC, 2012) and considered as "known to be a human carcinogen" by the NTP (NTP, 2016). This would therefore be consistent with a Category 1A carcinogenic classification according to the CLP Regulation (see Annex 1). However, because the existence of various pharmacological modes of action and different classifications may suggest carcinogenic properties of varying severity, depending on the compound considered, a more detailed investigation was deemed necessary (ANSES, 2018).

ANSES was \textbf{subsequently} also asked to propose 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 present work aims to determine the relevance of recommending the inclusion of work involving exposure to cytostatic agents in the Ministerial Order establishing the list of carcinogenic substances, mixtures and processes.

\textbf{Organisation of the expert appraisal}

This expert appraisal was carried out in accordance with the French Standard NF X 50-110 "Quality in Expertise Activities". ANSES entrusted examination of this request to the Expert Committee on "Health reference values" (HRV Committee). The Agency also mandated the Working Group (WG) on "Carcinogenic processes" for this expert appraisal. The methodological and scientific aspects of this group's work were submitted to the Committee on 23 January 2020, 18 September 2020 and 22 October 2020. The report produced by the Working Group takes account of the observations and additional information provided by the CES members. The report as well as the summary and conclusions of the collective expert appraisal were adopted by the Expert Committee on Health Reference Values on 22 October 2020. This collective expert appraisal work and the summary report were submitted to public consultation from 04/11/2020 to 03/12/2020. The comments received were reviewed by the Working Group (WG) on "Carcinogenic processes". The Expert Committee on Health Reference Values adopted this final version on 11/12/2020.

\textbf{Prevention of risks of conflicts of interest}

ANSES analyses the interests declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal. The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

\footnotesize{\textsuperscript{1} azathioprine, busulfan, chlorambucil, cyclophosphamide, melphalan and thiotepe}
Description of the method

In order to improve understanding of the issue of exposure to active principle ingredients in cytotoxic/cytostatic anti-cancer drugs in the workplace, hearings were held to collect information on exposure to these active principle ingredients during drug manufacture, packaging, preparation, transport and handling, as well as exposure due to contamination of the working environment or via management of waste and excreta. ANSES therefore interviewed the following people and organisations: two people working at the National Veterinary School of Maisons-Alfort (ENVA), representatives of the European Biosafety Network, one person from the French National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS), and two people from the Paris public hospital system (AP-HP).

The active principle ingredients of cytotoxic/cytostatic anti-cancer drugs currently available for human and veterinary use were identified with the help of a person from the French Health Products Safety Agency (ANSM) for medicinal products for human use and a person from the French Agency for Veterinary Medicinal Products (ANMV) for medicinal products for veterinary use.

An initial analysis and summary of the scientific literature on the PubMed database was carried out on 17 February 2020, in order to describe adverse effects reported in workers exposed to anti-cancer drugs. A second literature search was conducted on the risk of secondary cancers in patients treated with chemotherapy, in order to assess the carcinogenic properties of active principle ingredients of cytotoxic/cytostatic anti-cancer drugs to which certain occupational categories may be exposed. Several searches were performed with the help of an expert from the working group and from the National Cancer Institute (INCA) on two search engines (PubMed and Web of Science) in May and June 2020.

The Expert Committee on "Health reference values" adopted the collective expert appraisal work and its conclusions and recommendations, which are covered in the report, at its meeting of 22/10/2020, with a view to submitting them for public consultation.

Conclusions and recommendations of the collective expert appraisal

Scope of the appraisal and definition of substances of interest

The request from the DGT concerned the justification for including work involving exposure to cytostatic agents in the Ministerial Order establishing the list of carcinogenic substances, mixtures and processes, enabling the transposition of Annex I of Directive 2004/37/EU into French law. In order to be included in the Ministerial Order, a substance, mixture or process must meet the criteria for classification as a Category 1A or 1B carcinogen as set out in the CLP Regulation, or criteria that can be considered equivalent to them. It should be emphasised that the aim of this expert appraisal was not to assess in detail the carcinogenicity data with respect to the classification criteria under the CLP Regulation, but to draw on existing carcinogenicity assessments.

Early discussions within the working group led to this expert appraisal being focused on "active principle ingredients of cytotoxic/cytostatic anti-cancer drugs" whose mechanisms of action are through direct cytotoxicity on cells via effects on DNA or on cell replication processes. These active principle ingredients are capable of inducing adverse effects regardless of the level of exposure (non-threshold effect). Conversely, for active principle ingredients that act by
another mechanism, a significant level of exposure is needed to cause adverse effects (threshold effect).

The active principle ingredients used in hormonotherapy and immunotherapy were not retained any further in this expert appraisal, as they are considered to act by another mechanism of action. Unconjugated monoclonal antibodies were also excluded from the expert appraisal because of their high molecular weight, which limits their absorption and therefore the risk of developing cancer following occupational exposure.

**Potential exposures**

Many workers are potentially exposed to these types of active principle ingredients: from manufacturing to handling, and including transport, waste management, cleaning, etc. They are used in human and veterinary medicine in healthcare institutions such as hospitals, specialised oncology units, home medical care, hospices, nursing homes and veterinary clinics. The active principle ingredients of cytotoxic/cytostatic anti-cancer drugs can also be used in departments other than oncology, such as rheumatology, immunology, nephrology, dermatology, gynaecology, etc. (Lepage, 2016; ENVA, 2019; NDaw, 2019; European biosafety network, 2019; AP-HP, 2020; Matinet, Rosankis et Leonard, 2020)

**Description of the methodology implemented**

The literature review did not identify any epidemiological studies of sufficient quality to reach an overall conclusion for workers as to the carcinogenic properties of active principle ingredients of cytotoxic/cytostatic anti-cancer drugs (Skov et al., 1990 &1992; Gabriele et al., 1993; Szmyd & Haus, 2011; Villarini et al., 2016; Mahmoodi et al., 2017; Ursini et al., 2019). It was therefore decided to list all the active principle ingredients of interest for this expert appraisal and to document their classification as established by various recognised bodies assessing the carcinogenicity of chemical agents. The working group then decided to draw up a list of cytotoxic/cytostatic active principle substances used in human and veterinary medicine that might meet the necessary criteria for inclusion in the Ministerial Order.

The working group therefore primarily selected agents classified as Category 1A and 1B carcinogens according to the CLP Regulation, and agents classified by IARC in Groups 1 and 2A, whose classification criteria are deemed equivalent to those of the CLP (see Annex 1 of this document). When IARC and EU classifications do not agree (i.e. a CLP Category 1A or 1B classification versus an IARC Group 2B classification, or an IARC Group 1 or 2A classification versus a CLP Category 2 classification), a case-by-case assessment of CLP and IARC assessments has to be carried out in order to decide whether or not to include the substances in the Ministerial Order.

In a second step, the agents classified in the highest categories by the US EPA, NTP, ACGIH® and the GHS in Japan, i.e. in the categories: "carcinogenic to humans" for the US EPA, "known to be a human carcinogen" for the NTP, "A1" for the ACGIH®, and "1A" and "1B" for the GHS in Japan, were considered.

Furthermore, according to previous work on the equivalence of classification systems for carcinogenic agents carried out at ANSES, some agents classified by IARC in Group 2B may equate to a classification in Category 1B of the CLP (see Annex 1 of this document). This approach, considering agents classified by IARC in Group 2B as equivalent to agents classified in Category 1B by the CLP Regulation, is mainly used in the context of prioritisation or prevention work on carcinogenic risks. The experts' work consisted in identifying cytotoxic/cytostatic anti-cancer drugs with known or suspected carcinogenic properties under the terms of the CLP Regulation. For this reason, the experts did not consider the proposed equivalence between IARC's Group 2B and the CLP Regulation's Category 1B to be relevant to this expert appraisal. It should also be noted that the Group 2B classifications assigned by IARC for certain cytotoxic/cytostatic anti-cancer drugs are generally based on non-standard carcinogenicity studies conducted via the parenteral route. According to the classification criteria
as specified in the CLP Regulation, such studies can not be used to classify substances as Category 1A or 1B carcinogens.

The experts did not consider the classification categories "likely" (US EPA), "reasonably anticipated to be a human carcinogen" (NTP) and "A2" (ACGIH®) to be equivalent to categories 1A or 1B of the CLP Regulation. They were therefore not considered for drawing up the list of carcinogens to be included in the Ministerial Order.

Analysis and results

A total of 18 substances are currently proposed for inclusion in the Ministerial Order on the basis of their CLP or IARC classifications. They include 11 belonging to the class of alkylating agents (busulfan, carmustine, chlorambucil, chloromethine [in hydrochloride form], cisplatin, cyclophosphamide, lomustine, melphalan, procarbazine [in hydrochloride form], thiopeta, treosulfan), three from the anti-topoisomerase II class (adriamycin or doxorubicin [in hydrochloride form], etoposide, teniposide), one that is a DNA methyltransferase inhibitor (azacitidine), another that is an antimetabolite (azathioprine) and the last one, arsenic trioxide, which does not belong to any specific therapeutic class. In addition to these substances, the experts decided to add one more substance, prednimustine (belonging to the alkylating agents) because of its hydrolysis to chlorambucil which is classified IARC Group 1.

At the time of the expert appraisal, no substances had been classified as carcinogens in the highest categories of the US EPA, NTP, ACGIH® and the GHS in Japan without having been previously identified as a Category 1A or 1B carcinogen by the CLP or Group 1 or 2A by IARC. In most cases, the substances listed are cytotoxic/cytostatic anti-cancer substances that have been known for many years. However, new treatments and drugs are regularly appearing on the market. As the list of substances to be considered was drawn up at the time this expert appraisal was carried out, it will need to be updated in line with developments in knowledge. It is therefore particularly important to monitor substances recently placed on the market that have not, to date, undergone an expert appraisal of their carcinogenic properties by a recognised body or for which very few toxicological data are currently available. The experts also wish to stress the importance of producing carcinogenicity data for these new substances.

In addition to this list of individual substances considered to be carcinogens, the experts discussed the possibility of including therapeutic classes as a whole. However, in many cases, it was found that the level of details in the results of the carcinogenicity assessments carried out by the drug agencies, which are outlined in the Summaries of Product Characteristics (SPCs), precluded any critical analysis. Therefore it was not possible to identify potentially carcinogenic therapeutic classes and it would be useful to homogenise presentation of the data included in the SPC, in order to be able to systematically exploit these conclusions when assessing the carcinogenicity of the compounds.

In the absence of relevant data investigating an association between occupational exposure to cytotoxic/cytostatic anti-cancer drugs and the risk of developing cancer, the experts decided to focus on the risk of secondary cancers in patients treated by chemotherapy, in order to assess the carcinogenic properties of these drugs to which certain occupational categories may be exposed and identify therapeutic classes, protocols or active principle ingredients that are potentially carcinogenic.

Thus, leukaemia is the most commonly encountered chemo-induced cancer, for which evidence is accumulating on the involvement of alkylating agents and anti-topoisomerases (INCA, 2013; Swerdlow et al., 2011; IARC, 2012). Estimating the carcinogenic risk of chemotherapy treatments using data obtained from patients is nevertheless complicated by the fact that these patients are exposed to multiple agents (combinations of several drugs, radiotherapy or other). In particular, the management of many cancers involves chemotherapy treatments coupled with radiotherapy treatments that have a clearly demonstrated carcinogenic potential (IARC, 2012; Franklin et al., 2005; Wong et al., 2014; Swerdlow et al., 2011). Moreover, due to the latency between taking a treatment and the onset of a secondary cancer, some of the risks described in
the literature are associated with the use of therapeutic strategies that have evolved over time and do not concern more recently treated patients (Al-Juhaishi et al., 2019; INCA 2013; IARC 2012). Conversely, there is insufficient hindsight for assessing the carcinogenicity of medicinal products recently placed on the market. Concerns raised during the analysis of the SPCs and assessments carried out by the Food and Drug Administration (FDA) led the experts to conduct a specific literature review for eight anti-cancer drugs. The few studies identified to date do not provide adequate evidence of an increase in secondary cancers during treatment with cladribine, methotrexate, mitoxantrone or pipobroman. Taken together, the data for dabrafenib, ibrutinib, sorafenib and vemurafenib suggest an increased risk of skin cancer with these tyrosine kinase inhibitors (Hauschild et al., 2020; Coutre et al., 2019; Bond et al., 2020; Brose et al., 2014; Boussemart et al., 2016). However, the limited evidence currently available does not make it possible to come to a conclusion regarding the intrinsic carcinogenic properties of these substances in light of the criteria defined in this expert appraisal. These substances are therefore not currently being proposed for inclusion in the Ministerial Order.

In addition, the completion of this appraisal through the various hearings (AP-HP, National Veterinary School of Maisons-Alfort, European Biosafety Network, INRS) and the contributions received during public consultation revealed the existence of regulations, procedures, guides or protocols for handling these cytotoxic/cytostatic anti-cancer drugs in the context of occupational risk prevention. These documents (i.e. procedures implemented at AP-HP on the handling of cytotoxic agents during hospitalisation and home medical care or in the event of accidental spillage; INRS’s brochures, regulatory guide of good practices for the use of anticancer drugs in veterinary medicine developed by the national council of the order of veterinaries, etc.) should be pooled with a view to developing a national and/or European good practice guide enabling to summarize the preventive measures to be implemented for the different types of professionals potentially exposed to anti-cancer active ingredients. The need to raise awareness and train staff in contact with these active principle ingredients was also mentioned during the hearings. This is all the more important as frequent staff turnover is observed, particularly in the hospital departments exposed to these drugs (AP-HP, 2020; NDaw, 2019; ENVA, 2019; European biosafety network, 2019; Labrèche et al.; 2020).

Lastly, it should be stressed that this expert appraisal only examined the carcinogenic properties of cytotoxic/cytostatic anti-cancer active principle ingredients. However, other types of active principle ingredients not considered in this expert appraisal may also have carcinogenic and/or genotoxic properties that warrant investigation. Furthermore, due to their direct cytotoxicity on cells via effects on DNA or on cell replication processes, certain active principle ingredients of anti-cancer drugs may pose a risk of infertility and/or teratogenic effects, which should be taken into account for the prevention of occupational risks.

**Recommendations**

Based on the elements presented in the report, the WG issues recommendations for:

- the update of the Ministerial Order establishing the list of carcinogenic, mixtures and processes (or even of Annex I of Directive 2004/37/EC);
- the protection and awareness of workers potentially exposed to the carcinogenic cytotoxic/cytostatic active principle ingredients;
- knowledge improvement on the carcinogenic risk associated with exposure to cytotoxic/cytostatic anti-cancer drugs.

In order to update the amended Ministerial Order establishing the list of carcinogenic substances, mixtures and processes, the WG recommends:

adding to the Ministerial Order : work involving exposure to cytotoxic/cytostatic active principle substances used specifically in the context of anti-cancer treatments for human and veterinary
use and considered equivalent to Category 1A or 1B carcinogens according to the CLP Regulation.

The circumstances of exposure to be taken into account include specifically the following:

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

The list of active principle substances to be taken into account is as follows:

- adriamycin or doxorubicin [CAS No. 23214-92-8] (in hydrochloride form in the proprietary pharmaceutical product [CAS No. 25316-40-9])
- azacitidine [CAS No. 320-67-2]
- azathioprine [CAS No. 446-86-6]
- busulfan [CAS No. 55-98-1]
- carmustine [CAS No. 154-93-8]
- chlorambucil [CAS No. 305-03-3]
- chloromethine (tri) [CAS No. 51-75-2] (in hydrochloride form in the proprietary pharmaceutical product [CAS No. 55-86-7])
- cisplatin [CAS No. 15663-27-1]
- cyclophosphamide [CAS No. 50-18-1]
- etoposide [CAS No. 33419-42-0]
- lomustine [CAS No. 13010-47-4]
- melphalan [CAS No. 29069-24-7]
- prednimustine [CAS No. 29069-24-7]
- procarbazine [CAS No. 671-16-9] (in hydrochloride form in the proprietary pharmaceutical product [CAS No. 366-70-1])
- teniposide [CAS No. 29767-20-2]
- thiopeta [CAS No. 52-24-4]
- treosulfan [CAS No. 299-75-2]
- arsenic trioxide [CAS No. 1327-53-3]

In order to protect and raise awareness among workers potentially exposed to the active principle ingredients of cytotoxic/cytostatic cancer drugs for human and veterinary use, the WG recommends:

- in accordance with the provisions of the French Labour Code,
  - carrying out an assessment at least annually of the carcinogenic risk for the various personnel involved, in order to implement adequate preventive and protective measures;
  - raising awareness of the carcinogenic risk of these substances among personnel in contact with them, starting from when they first take up their positions and continuing on a regular basis. This should cover all areas, from manufacturing in the pharmaceutical industry through to management of waste and excreta, and including handling (healthcare establishments or research laboratories) and cleaning, in both human medicine (oncology and other departments) and veterinary medicine;
- establishing the monitoring of occupational exposure, in particular by carrying out biological monitoring of exposure, and developing the associated tools; when biomonitoring of exposure is not possible, environmental monitoring of exposure via surface contamination measurements and/or via atmospheric measurements must be considered
- including a training module on the carcinogenic risk associated with these drugs in the training curriculum for healthcare personnel;
- producing a national or even European good practice guide for all professionals potentially exposed to anti-cancer active ingredients, from receipt through to cleaning
and management of waste and *excreta*, in order to define standard procedures to be applied in the various exposure situations.

**In order to improve knowledge on the carcinogenic risk of exposure to these drugs, the WG recommends:**

- planning and organising the updating of the list of active principle substances by monitoring the literature on cancer therapies, especially for new compounds;
- broadening the debate to include all active principle ingredients with genotoxic potential and/or suspected carcinogenic properties;
- proposing medicinal active principle substances as potential candidates for classification according to the CLP Regulation;
- improving and harmonising the conclusions of Section 5.3 of the SPCs regarding genotoxicity and carcinogenicity for human drugs.

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


Annex 1: Summary table of equivalences between CLP and other classification systems taken into account by the experts (extract from an unpublished training report)

<table>
<thead>
<tr>
<th>Combination of scientific evidence</th>
<th>CLP</th>
<th>IARC</th>
<th>US EPA (2005)</th>
<th>ACGIH®</th>
<th>NTP</th>
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<td><strong>Human data</strong></td>
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<td>Sufficient</td>
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<td><strong>Animal data</strong></td>
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<td><strong>Additionnal considerations/ mechanistic data</strong></td>
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<td>- relevant tumor type in humans</td>
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<td>Carcinogenic to Humans</td>
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<td>Known</td>
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<td>- low background incidence in animals</td>
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<td>- multi-site responses/effects</td>
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<td>- progression towards malignancy</td>
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<td>- effects appearing in several species (a single species may be sufficient)</td>
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<td>- effects appearing in both sexes (a single sex study may be sufficient)</td>
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<td>- mechanism of action relevant in humans</td>
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<td>1B (case-by-case)</td>
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<td>2A</td>
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<td>A2</td>
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<td>2B (exceptionally 2A)</td>
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<td>A2</td>
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<td>- no progression towards malignancy</td>
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<td>- spontaneous tumors at high doses, or in susceptible animal strains</td>
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<td>- mechanism of action reflecting the existence of a toxicity threshold</td>
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<td>2 (or no classification)</td>
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<td>Mechanism of action non extrapolable to humans</td>
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<td>3 (if animal data are sufficient)</td>
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<td>Not Likely</td>
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