# Should monoclonal antibodies and their conjugates be considered occupational hazards

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**Monoclonal antibodies are a novel class of agents that often lack information concerning hazards for healthcare workers. Their large molecular weights would be expected to limit bioavailability and toxic potential. However, actual bioavailability in occupational settings remains uncertain.**

The toxicity of older-generation antineoplastic and other hazardous drugs has been well known since they were introduced in the 1940s. Because most of these antineoplastic drugs are non-selective in their mechanism of action, they affect non-cancerous as well as cancerous cells. In the 1970s, secondary malignancies were reported in patients who had previously received antineoplastic drugs for other malignancies [1]. Since that time, the International Agency for Research on Cancer has identified approximately 30 antineoplastic drugs as known or potential human carcinogens while many more are recognised as carcinogens based on laboratory research [2].

Although many safety provisions have been advanced to reduce exposure, recent studies have shown that workers continue to be exposed to these drugs despite safety policy improvements [3-5]. In 2004, the National Institute for Occupational Safety and Health (NIOSH) reviewed existing guidelines and published an alert reviewing the most recent information available and promoting a programme of safe handling during their use [1]. This alert included a listing of drugs that should be handled as hazardous. This list was updated in 2010 [6] and will be updated again in 2012 to keep abreast of new FDA drug approvals and warnings on existing drugs. The alert covers all workers in healthcare settings who are potentially exposed to hazardous drugs. Because of the expanding use of hazardous drugs into new areas and specialties, the number of workers who are not properly trained in their safe handling will continue to increase.

Reports have associated workplace exposures to conventional antineoplastic drugs with acute health effects such as hair loss, headaches, acute irritation, and/or hypersensitivity. In addition, adverse reproductive outcomes—including infertility, spontaneous abortions, and congenital malformations—and evidence of teratogenic outcomes in patients and healthcare workers have been reported [1, 7]. During the past 30 years, professional organisations and government agencies around the world have developed guidelines to protect healthcare workers from adverse effects associated with occupational exposure to antineoplastic drugs [1].

NIOSH [1] adopted a set of six criteria to identify the characteristics of a hazardous drug, see Table 1. Since each drug is unique and varies considerably in structure, biological activity, bioavailability, formulation, and other characteristics, NIOSH evaluates each drug on an individual basis and not as a member of a specific class. For example, the American Hospital Formulary Service [8] currently lists monoclonal antibodies, including conjugated forms, as one of eight categories of antineoplastic drugs, see Table 2. Because they are proteins in nature, monoclonal antibodies themselves are not required to be evaluated for carcinogenicity or genotoxicity, even if their therapeutic effects are directly mediated by antibody binding to a target antigen. However, monoclonal antibodies may be conjugated to other carcinogenic or genotoxic agents in order to target those toxic agents to specific cell types. For example, gemtuzumab ozogamicin was marketed in the US until 2010 [9]. The monoclonal antibody component of the drug targeted it to CD33, a cell surface antigen found on leukaemic blast cells. The toxic agent to which the anti-

**Table 1: NIOSH criteria for hazardous drugs [1]**

| |
|---|
| Carcinogenicity |
| Teratogenicity or developmental toxicity |
| Reproductive toxicity in humans |
| Organ toxicity at low doses in humans (> 10 mg/day) or animals (> 1 mg/kg/day) |
| Genotoxicity |
| New drugs that mimic existing hazardous drugs in structure or toxicity |

NIOSH: National Institute for Occupational Safety and Health.

**Table 2: American Hospital Formulary Service Classification 10:00 Antineoplastic Agents [8]**

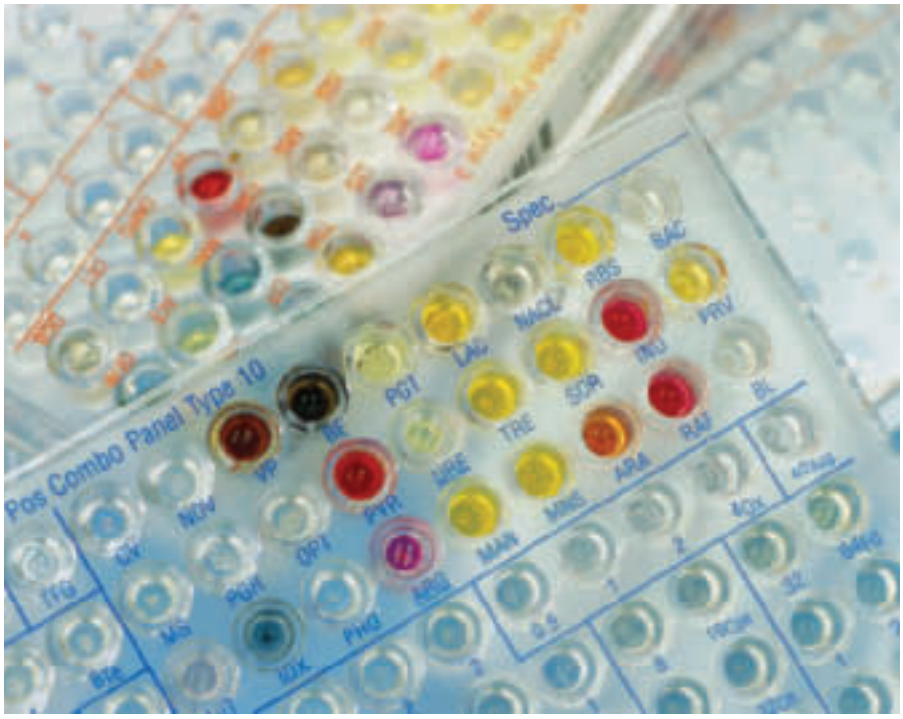
| |
|---|
| Alkylating agents |
| Antibiotics |
| Antimetabolites |
| Topoisomerase II inhibitors |
| Hormonal agents |
| Monoclonal antibodies |
| Interferons |
| Vaccines |

body was conjugated, a calicheamicin cytotoxic agent, worked by binding to DNA [10].

Although they may be applicable to bioactive agents conjugated to monoclonal antibodies, three of the six NIOSH criteria—carcinogenicity, genotoxicity, and new drugs that mimic existing hazardous drugs in structure or toxicity—are not applicable to the monoclonal antibodies themselves because of their unique characteristics. An additional three criteria might apply to either unconjugated or conjugated monoclonal antibodies: teratogenicity or developmental toxicity, reproductive toxicity in humans, and organ toxicity at low doses in humans (> 10 mg/day) or animals (> 1 mg/kg/day). For many of the therapeutic monoclonal antibodies and conjugates, little information is available on these criteria. The majority of the monoclonal antibodies, according to the manufacturers' drug package inserts, fall in FDA Pregnancy Category C*.

Currently, only one monoclonal antibody has a safe handling warning recommended by the manufacturer. Brentuximab vedotin, a conjugated monoclonal antibody that contains the microtubule disrupting agent *monomethyl auristatin E*, has safe handling guidelines and is also listed as Pregnancy Category D [11].

In the 1970s, a study from Finland indicated that healthcare workers may be at risk of harmful effects from antineoplastic drugs as a result of possible drug uptake from occupational exposure [12]. Since then, reports from several countries have documented drug contamination of the workplace, identified drugs in the urine of healthcare workers, and measured genotoxic responses in workers [1, 3-5]. Exposure of healthcare providers to antineoplastic drugs is varied based on unique settings, but the routes of exposure are typically inhalation or dermal. Workers may be exposed by inhalation via droplets, particulates, and vapours when they create aerosols, generate dust by crushing tablets, and clean up spills and bodily wastes. Dermal exposure may occur when workers touch surfaces that are contaminated with hazardous drugs during their preparation, administration, or disposal. Exposure can also result from contact with surfaces contaminated with the waste products of patients treated with these drugs that may contain the parent drugs and/or metabolites of the drugs. Additionally, oral exposure from hand-to-mouth contact and accidental injection with an antineoplastic drug, although rare, has been documented [1]. These studies have dealt with conventional lower molecular weight compounds and not with high molecular weight monoclonal antibodies and conjugates that target specific antigens on cell surfaces.




## Dermal exposure to monoclonal antibodies

Given their large molecular weight (> 140 kDa) the potential for dermal uptake of unconjugated monoclonal antibodies or intact conjugates in the occupational setting is very low. Research has postulated the upper limit for dermal absorption of compounds at 500 Daltons [13]. However, local irritation or allergic reactions in damaged skin might facilitate dermal uptake [10]. Healthcare workers in general, and especially nursing personnel, have an unusually high incidence of dermatitis [14, 15], which could possibly contribute to dermal uptake of the monoclonal antibodies. Approximately one in three nurses has some form of dermatitis. Routine use of gloves when handling monoclonal antibodies is recommended and would prevent possible dermal uptake by normal or damaged skin.

## Inhalation exposure to monoclonal antibodies

The bioavailability of high molecular weight substances (> 100 kDa) has been estimated at a maximum of 5% by inhalation. Given the much higher molecular weights of monoclonal antibodies, the absorption rate of unconjugated monoclonal antibodies or intact conjugates will probably be even lower [16]. If monoclonal antibodies were to be administered to patients by aerosolisation, the potential for exposure of the healthcare worker would be increased. The feasibility of delivery by aerosolisation of one unconjugated monoclonal antibody drug, cetuximab, has been explored and suggests a potential method of drug delivery [17]. However, since monoclonal

antibodies are not usually administered by aerolisation, their routine administration should not expose healthcare workers to conditions that could result in substantial exposure by inhalation.

## Oral exposure to monoclonal antibodies

While it is possible that hand-to-mouth transmission of drugs can take place, any exposure to monoclonal antibodies by the oral route would result in denaturation and digestion in the gastrointestinal tract [10], severely limiting exposure to the monoclonal antibody itself by this route. However, this might, in theory, release lower molecular weight agents from conjugates which could then act directly on the gastrointestinal tract or be absorbed systemically.

In some cases, a monoclonal antibody may be conjugated with a radioactive moiety as in the case of ibritumomab tiuxetan and tositumomab. As radiopharmaceuticals, these monoclonal antibodies fall into a separate class of hazards that are under the control of nuclear regulatory agencies and require special handling due to their radioactivity.

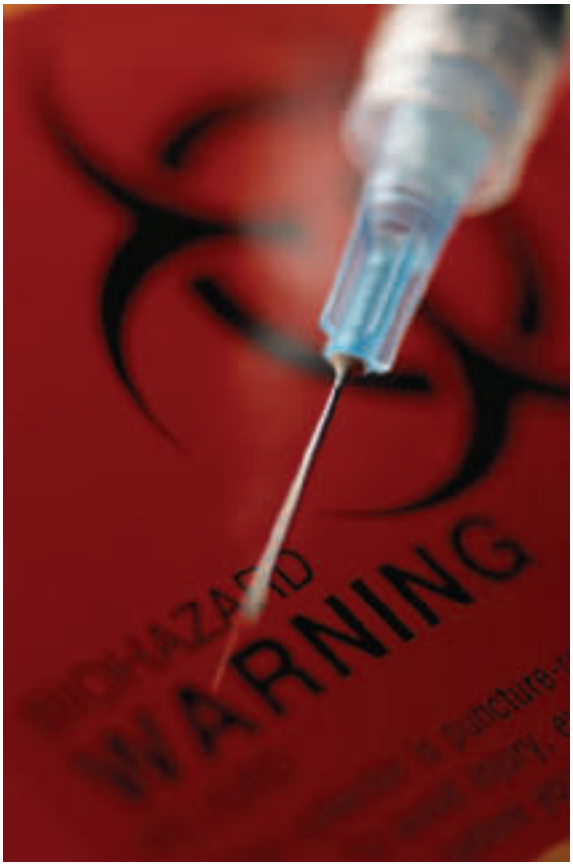
Two approaches have been published that have attempted to characterise the occupational risk of handling monoclonal antibody-containing therapeutic agents. Langford et al. [18] developed a risk assessment tool based on the antigenic properties and the toxic potential of monoclonal antibodies and conjugates. These authors recommended that the majority of monoclonal antibodies available in the UK at that time should be considered high to moderate risk and should only be prepared in the pharmacy. A smaller group of monoclonal antibodies was considered low/moderate risk and could be prepared in the clinic if need be. However, given the complex nature of preparation for some monoclonal antibodies and the need for aseptic preparation conditions, preparation outside the pharmacy is not recommended [19].

Halsen and Krämer evaluated a number of monoclonal antibody-containing agents based on reproductive and developmental toxicity and effects on fertility [10]. For the majority of these agents, the authors reported that significant data were lacking for these endpoints. However, they concluded that all of the monoclonal antibodies they evaluated had the potential for some level of reproductive toxicity. They also concluded that oral and dermal exposure to these agents would be very minimal. They postulated a possible exposure scenario by inhalation of aerosols but speculated that this route would also result in minimal exposure.

A recent publication describing a three-tiered approach to the safe handling of hazardous drugs [20] considered drug molecular weight as an important consideration in formulating recommendations to exclude all interferons and monoclonal antibodies from their three proposed risk categories: high-, low-, or reproductive-risk.

Given the uncertainties surrounding the handling of monoclonal antibodies, the following issues have been observed and will require careful consideration in classifying monoclonal antibodies as occupational hazards:

- In most cases, the amount of information available on the toxicity of monoclonal antibody-containing therapeutic agents, whether conjugated or unconjugated, is limited.
- Testing monoclonal antibodies for carcinogenicity or genotoxicity is typically not required by regulatory agencies and therefore these important criteria are not usually available.
- Though the potential for uptake of monoclonal antibodies by healthcare workers appears to be low (due to large molecular weight > 140 kDa), long-term, low-dose exposure to monoclonal antibodies may result in sensitisation of healthcare workers, particularly if the monoclonal antibodies are xenogeneic. However, if small toxic agents were released from conjugates, they could potentially pose a greater problem.
- If healthcare workers become sensitised through occupational exposure it could limit treatment of those sensitised workers if they require treatment for cancer and other illnesses in the future.
- Dermatitis and other damage to the skin may facilitate the dermal uptake of monoclonal antibodies.




- The normal preparation and administration by healthcare workers of monoclonal antibodies should not result in the formation of aerosols sufficient to be an inhalation hazard. However, when the monoclonal antibodies are administered as aerosols, the potential for exposure of healthcare workers is increased.
- Many monoclonal antibodies are under development or are being approved, requiring continual attention.

Overall, the potential for occupational exposure of healthcare workers to unconjugated monoclonal antibodies and intact conjugates is generally minimal. Exposure scenarios that apply to lower molecular weight antineoplastic drugs do not apply to intact protein-based molecules with the molecular weights of the monoclonal antibodies. Thus, potential for disassociation of conjugates may be an important consideration in the assessment of healthcare worker risk. The approach by NIOSH in evaluating drugs as potential occupational hazards is to evaluate each drug on an individual basis and not as a member of a group. Monoclonal antibodies that have been evaluated by NIOSH to date have not met the current criteria for a hazardous drug. However, if new information becomes available on a specific monoclonal antibody, NIOSH will review that information and re-evaluate the hazard potential. Thus, monoclonal antibodies currently in use or new approvals may be listed as hazardous drugs as more information becomes available.

Given the complex procedures for the preparation of some of the monoclonal antibodies and the requirement for aseptic preparation, many of the same procedures used in the preparation of the drugs identified as hazardous should apply to the preparation of monoclonal antibodies. Preparation should be performed in a biological safety cabinet or an aseptic compounding isolator using proper procedures and personal protective equipment. Following these procedures will protect both the integrity of the monoclonal antibody and the health of the worker [1, 19].

**Pregnancy Category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Available from: depts.washington.edu/druginfo/Formulary/Pregnancy.pdf*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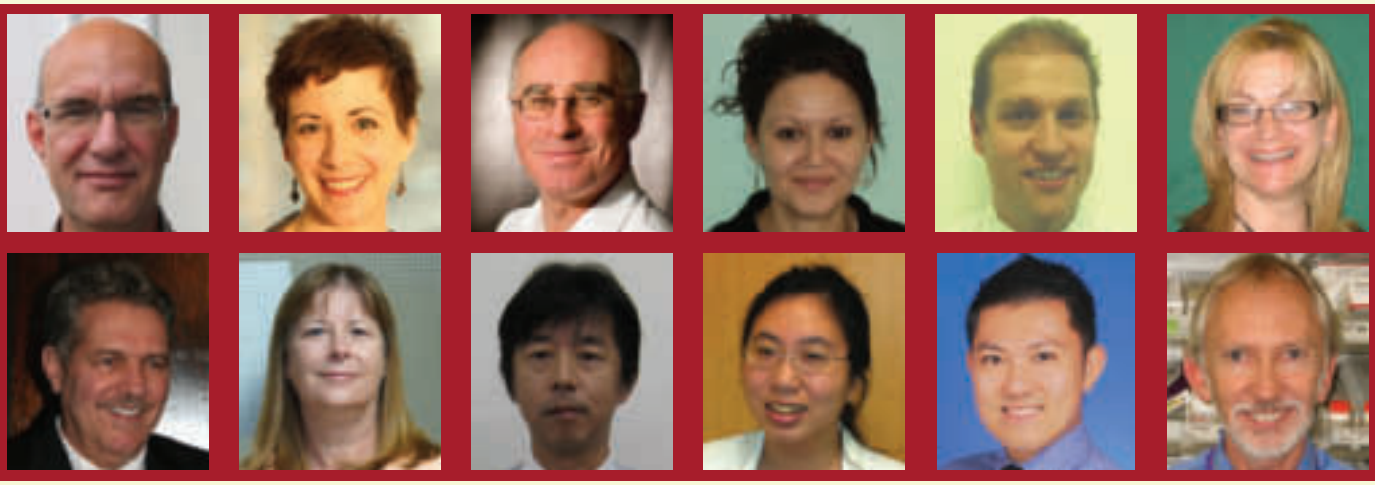

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