WORKING SAFELY WITH HAZARDOUS CHEMICALS IN A PHARMACEUTICAL COMPANY

1 General information

Country: Croatia.

Available language: English.

The **sector covered** in this case study is manufacture of basic pharmaceutical products and pharmaceutical preparations.

Tasks covered: handling chemicals, manufacturing.

Worker groups covered (vulnerable groups): all workers (no specific groups), breastfeeding mothers, pregnant workers.

The **purpose of this example of good practice** was to improve risk assessments and training, and to raise awareness.

The **target groups** are workers and workers' representatives.

2 Initiator/organisations involved

Genera Inc., Rakov Potok, Croatia.

Occupational Health Practice, Samobor, Croatia.

Institute for Medical Research and Occupational Health, Zagreb, Croatia.

3 Description of the case

3.1 Introduction/background

Hazard — physical state: not applicable.

Hazard — health effect: carcinogens, mutagens, reprotoxic substances, toxic substances.

Biological agents: none.

Exposure route: inhalation.

Substance description (CAS/EC) (only if possible): ethidium bromide, levothyroxine.

Genera is a company with more than 100 years of tradition and its origin dates back to the foundation of the Royal Croatian–Slavonian Bacteriological Institute in 1901. In the second half of 2015, Genera became part of Dechra Pharmaceuticals PLC Group. Genera is engaged in research and development (R&D), production, and the sales and marketing of veterinary medicines, feed additives and a range of care products for animals. Genera employs approximately 220 workers, of whom 75% are women working in production, quality control and R&D laboratories. The company uses large amounts of chemicals in everyday production. In 2017, active substances or co-formulants amounted to around 87,000 kg.

Coordinated actions are continuously being undertaken with the aim of ensuring the effective management of chemicals and a safe and healthy working environment, in line with EU and Croatian safety and health rules. These actions are as follows:

- the identification and registration of chemicals used in the workplace;

- risk identification (using safety data sheets);
- risk notification in the workplace (using pictograms and simple guidelines for safety management, i.e. short instructions on how to ensure safe and healthy working);
- technical/infrastructural measures (i.e. operating mostly in closed systems);
- the monitoring of chemicals (measuring the concentrations of chemicals in the working environment by an externally certified company periodically (every 3 years), and when new technology is introduced);
- the provision of personal protective equipment;
- the education of workers (at company and national levels);
- accident management (theoretical and practical education in first aid, safety showers for eyes/body, antidotes/adsorbents);
- pre-employment and periodical medical examinations of exposed workers (by an occupational medicine specialist).

3.2 Aims

At the beginning of 2017, the company implemented a new hazard reducing system whose main objective was to further reduce risks in the workplace and reduce (or assess) the impacts of exposure to harmful substances in production, quality control and R&D laboratories.

3.3 What was done and how?

A meeting with all staff (from managers to workers) was held to explain the different stages of the hazard reducing system and the importance of their engagement and feedback. Before implementing the risk reduction action, the owner's (Dechra Pharmaceuticals PLC Group) lead safety manager held training sessions on 'management safety'.

Workers have been engaged throughout the whole process as partners. The health and safety system is reviewed periodically (every year) by the environmental health and safety department to identify areas in which the system could be improved.

3.3.1 Identification of risks

The basic health and safety measures were supplemented as follows:

- Risk assessments were performed for each process involving chemicals.
- Toxicology assessments were conducted for new and/or the most hazardous chemicals by gathering and analysing data on toxicological characteristics/endpoints.

- **Examples**

Ethidium bromide is a highly hazardous compound. It is a common marker molecule in electrophoresis, used for the identification and visualisation of nucleic acid bands. Because it can bind to DNA, it is classified as a Category 2 mutagen, according to the EU's CLP Regulation. Ethidium bromide may have carcinogenic or teratogenic effects, although this has not been confirmed with scientific evidence. Exposure to ethidium bromide is possible by inhalation, ingestion or absorption through the skin. Acute ethidium bromide exposure may cause irritation of the exposed surfaces: the upper respiratory tract, skin, eyes or mouth. Technical prevention measures involve the use of fume hoods. Furthermore, full protective clothing (including appropriate gloves, goggles and closed-toe shoes) is recommended when handling pure ethidium bromide.

Occupational exposure to levothyroxine (which is the thyroid hormone) may occur through inhalation or dermal contact. Levothyroxine is not classified as a hazardous chemical, according to EU legislation, and no specific workplace exposure limits have been determined, although the manufacturer's recommend that the air concentration is limited to 0.1 µg/m^3. It is not known if long-term occupational exposure can cause hyperthyroidism, as described with clinical use, or foetal toxicity, as found in animal studies, so every effort should be made to limit contact with levothyroxine during the manufacturing process or use. It should also be noted that, although exposure to pharmaceuticals during production falls under occupational safety and health legislation, pharmaceutical products (medicinal and veterinary drugs) are outside the scope of EU chemicals legislation (REACH and CLP).

3.3.2 Prevention measures

The work procedures were reviewed according to the outcome of risk assessments, which estimate the risk due to exposure after applying control measures to reduce risk.

- **Substitution of dangerous substances with less dangerous substances**

Recently, ethidium bromide was substituted with GelRed nucleic acid gel stain. GelRed is a commercial DNA stain, marketed as being the most safe, sensitive and robust nucleic acid gel stain and less hazardous than ethidium bromide. It is a non-mutagenic and non-cytotoxic chemical at concentrations well above the working concentrations used for gel staining. It does not penetrate standard latex gloves and there is no need to dispose of it as hazardous waste. It is not classified as a hazardous chemical according to the EU's CLP Regulation.

Ethidium bromide had been used previously because it is less expensive and easier to use, the procedures involving ethidium bromide are well characterised, and robust results could be expected. Some researchers experienced sensitivity/visualisation problems even with well-known gel extraction protocols. However, by switching from ethidium bromide to GelRed, hazardous waste disposal costs have decreased significantly, and the time-consuming procedures of decontaminating electrophoresis buffers are now unnecessary.

- **Improved technical safety measures that aim to minimise exposure**

The company decided to change processes that use harmful substances. This resulted in a new central weighing room equipped with a state-of-the-art ventilation system, and laminar flow cabinets with high-efficiency particulate air (HEPA) filters for weighing solid chemicals in low and intermediate toxicity categories (Picture 1). Chemicals are transported in sealed packages from this room to their place of use and sucked into a closed system for product formulation.

Picture 1: Laminar flow cabinet with HEPA filters. Source: Genera.

The company decided to acquire a glove box for working with high-potency active pharmaceutical ingredients (HPAPIs). HPAPIs (specifically levothyroxine) were removed from the weighing room and moved to the production area to make it possible to limit potential exposures to one controlled workspace. The production area is equipped with a heating, ventilation and air conditioning (HVAC) system, with high efficiency particulate air) filters (HEPA) on the air inlets and outlets. This also protects the environment. A personnel air-lock (PAL) system with mist showers is planned for the production area. Anyone working with HPAPIs will wear personal protective equipment in the form of a special suit with a protective hood and self-contained breathing apparatus. After workers finish their work, they will pass

through the PAL system and the mist showers will remove any particles of HPAPIs. The suits will be disposed of in special containers.

3.3.3 Care for pregnant and breastfeeding workers

As a precaution, pregnant employees are not allowed to work in workplaces in which there is a risk of exposure to hazardous chemicals. Such employees are moved to a more suitable workplace immediately after announcing pregnancy. This is followed by an updated risk assessment for the pregnant/breastfeeding employee, carried out together with an occupational medicine specialist. After the evaluation, in most cases, the worker remains in a job without any risk of hazardous exposure.

3.3.4 Education and raising of awareness of harmful substances

The enterprise organises courses for employees who work with hazardous substances. Workers are trained about the chemicals they handle, including hazard identification, information on health risks, procedures in cases of emergency, responsible behaviour when working with chemicals and labelling of chemicals.

3.4 What was achieved?

The measures resulted in:

- intensified communication among workers and managers about safety at work;
- improved control of hazardous substances in the working environment;
- greater awareness and engagement of workers about their safety and health at work;
- a reduction in the number of hazards while handling hazardous substances;
- improved prevention of health impairments related to chemicals.

3.5 Problems faced

It was difficult to find relevant data about chemicals. Some material safety data sheets were missing, some were out of date and the overall quality of available data sheets was not sufficient for making sound decisions on specific occupational safety and health measures. Specifically, the problem was the poor quality of toxicological and health and safety information available from free internet sources, and the poor quality of the safety data sheets provided by suppliers. Safety data sheets are usually not in REACH format, the classification and labelling are often not in accordance with the (latest) CLP Regulation and basic toxicity data are often missing ('data not available'). An issue that companies face on a daily basis is that data on occupational exposure limit values are not given in safety data sheets. However, there many companies now sell such data, and the price per substance/chemical product is about EUR 600.

Initially, the degree of awareness of workers of the risks related to the management of chemicals was low. Workers were reluctant to engage in training on safe working with chemicals. For example, they argued that they did not need training because they had worked with the same chemicals for years. Managers are involved in the practical aspects of all manufacturing processes that pose potential risks to the safety of workers, especially in relation to chemicals. They are present in the workplace and try to set good practice examples.

3.6 Success factors and challenges

Several success factors can be identified:

- the strong safety and health policy of the Dechra group;
- the commitment of the leadership team to drive the full implementation of the system;
- the positive financial status of the company;
- training sessions for workers (including Napo animations);

- a participatory approach: putting workers in the position of partner in the process of exposure assessments and the everyday management of chemicals, and including workers' suggestions for improving prevention measures;
- plans for the implementation of new software to store relevant information about chemicals.

3.7 Transferability

The approach taken is applicable to companies across the pharmaceutical and chemical sectors.

The following elements can be transferred to any initiative: inviting specialist experts for special risks, awareness raising and workers' participation in the entire process, high-level management commitment, and solutions based on the hierarchy of prevention measures: substitution and technical prevention should be used before personal protection.

3.8 Costs and/or economic impacts

A cost–benefit analysis was not performed, because these actions were based on the company's principle that 'safety and health have no price'.

3.9 Evaluation

The case study:

- is transferable to other companies/sectors/countries;
- focuses where possible on preventing risk at source;
- includes all relevant parties, especially those who will be affected by the actions;
- comes from a credible source;
- does not include/contain advertisements;
- involves a realistic work situation;
- provides contacts for further information.

3.10 Further information

Contacts

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