Educational Administration: Theory and Practice
2024,30(4), 6806-6811
ISSN:2148-2403
https://kuey.net/

Research Article

Selection of Containment System for Handling Cytotoxic Drugs in Pharmaceutical Industry

S. Karthikeyan[1*], J. Ajay Inbaraj[2], P. Thangavel[3], D. Deepa[4], N. Saravanan[5], R. Karthikeyan[6]

[1*]Assistant Professor, Mechanical Engineering, Erode Sengunthar Engineering College, Perundurai, 638057, India., https://orcid.org/0000-0002-8955-6229,Email: karthiksamynathan@gmail.com

[2]PG Scholar Industrial Safety Engineering, Erode Sengunthar Engineering College, Perundurai, 638057, India.

[3]Professor, Mechanical Engineering, Erode Sengunthar Engineering College, Perundurai, 638057, India. , https://orcid.org/0000-0003-3844-8196, Email: ptvelmech@gmail.com

[4]Professor, Electronics and Communication Engineering, Bannari Amman Institute of Technology, Sathyamangalam, India. , https://orcid.org/0000-0002-6732-0055, Email: ddeepa@bitsathy.ac.in

[5]Professor, Mechanical Engineering, Erode Sengunthar Engineering College, Perundurai, 638057, India. , https://orcid.org/0000-0001-8314-4410, Email: saranvimal@gmail.com

[6]Assistant Professor, Mechanical Engineering, Kongu Engineering College, Perundurai, 638060, India. , https://orcid.org/0000-0001-8730-2498, Email: karthi.mech@kongu.ac.in

***Corresponding Author:** S. Karthikeyan
*Email: karthiksamynathan@gmail.com

Citation: S. Karthikeyan et Al. (2024), Selection of Containment System for Handling Cytotoxic Drugs in Pharmaceutical Industry, *Educational Administration: Theory And Practice*, *30*(4), 6806-6811
Doi: 10.53555/kuey.v30i4.2101

ARTICLE INFO

ABSTRACT

This article covers the topic of choosing the right containment system based on the occupational Exposure Limit (OEL) value to handle the cytotoxic drugs or waste generated in the pharmaceutical industry based on manufacturing steps/stages/activities associated with the pharma Industry. A safe and dedicated means of containment is essential for protecting both the person and their environment. The hazards in pharmaceutical industry workers or operators who handle, manufacture or dispose of cytotoxic drugs or waste are mainly caused by its toxicity and the extent and duration of exposure. Exposure to cytotoxic substances in pharma industry occurs during the production, testing & cleaning activity. It is occurring through inhalation of dust or aerosols, absorption through the skin, ingestion owing to unsafe practices, or from waste items.

Key Words: Cytotoxic, Occupational Exposure Limit (OEL), Toxicity, Pharmaceutical industry, Containment

Introduction

Cytotoxic drugs which are used to treat cancer and other medical conditions such as arthritis or autoimmune disorders. Cytotoxic wastes are generated from the pharma industry during manufacturing of cytotoxic drugs. This drug inhibits or prevents the function of cells &also these drugs can produce chromosome changes, cancer and reproductive abnormalities & it can create adverse effects in workers exposed to them. To manage workplace exposures effectively, efficiently the programs began in the 1980's with the advent of "high potency" drug products. OELs established too late in the drug development process. Initially Industry uncertainty about appropriate OELs, Analytical methods not sensitive enough & No engineering controls on the market. The 2006 guidelines were created to harmonize with the National Institute for Occupational Safety and Health (NIOSH) Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings issued in 2004.6.

In past, Varun Ahuja & Mohan Krishnappa has discussed in the article published on June 2021 "Approaches for setting occupational exposure limits in the pharmaceutical industry" about "OEL for Data Poor substances" In the case of data-poor substances, surrogate chemical data can be used to derive the OEL of the target chemical, based on the evaluation of data and expert judgment (ECETOC, 2006;ECHA, 2009). For data-poor substances, occupational exposure controls can be established using occupational exposure bands (OEBs), based on the intrinsic hazard properties, mechanism of action, and predicted potency (ABPI, 1995; ECETOC, 2006; Naumannet al., 1996).

At present, In pharma Industry, various reactions handled with several Mass transfer operations in production of cytotoxic Drugs with various production equipment to produce & test the cytotoxic drugs. The OEL values of intermediate stages of pharma products may not available & providing control measures are much complicated. In this study, the selection of control measure & technology shall be discussed

Methodology

Sources of Cytotoxic Waste in Pharma sector

In pharma industry cytotoxic materials generated in both upstream & downstream production activities & also in the testing labs.

Stage-01 Upstream- Reaction Process

- Charging of cytotoxic Raw Material in the reactor- Fugutive emissions (dust or aersol contains cytotoxic properties)

Stage-02 Downstream- Extraction Process

- Filtration & separation of products- Generation of Mother Liquor (ML)contains cytotoxic properties.
- Loading & unloading activity of cytotoxic drugs in to the drier for drying- Fugutive emissions (dust or aersol contains cyto-toxic properties)

Stage-03 Testing

- Generation cyto-toxic waste during s In-process & finished Good sampling & analysis.

In pharma industry, Upstream, Downstream activities further listed as below:

- Raw Material Dispensing
- Reactor Charging
- In-Process Sampling
- Centrifugation
- Pressure Nutsche Filtration
- Vacuum Drying
- Milling and Sieving
- Final Sampling
- Quality control Testing

Raw materials

The qualities of the basic materials being processed are critical in determining the appropriate containment system. The occupational exposure level (OEL), as well as the materials' physical and chemical qualities, must all be carefully evaluated.
Some materials require specific handling and processing, such as APIs utilised in new products, which are growing increasingly potent. Thus, containment systems should be capable of securing the production space while also preserving a specified atmosphere when working with these substances.

Process Flow:

Containment assessment for each step involved in the process, including the amount of material being handled.
• Material input • Material output
• Manipulation. • Decontamination

Material transfer from one process step to the next must be contained and suited to the OEL level. Decontamination methods and procedures must be properly established for process equipment and containment systems.

Activities where there is a risk of exposure for operators & chemist.

Sources of exposure

The following are the major sources of exposure of cytotoxic waste:

- Worker exposure occurs by inhalation of drug dust or aerosol, absorption through the skin.
- Injection via way of means of unintentional pores and skin puncture and ingestion thru touch with infected food & drink.

Exposure may occur when:

- Cleaning spills or leakages of cytotoxic drugs and related waste in the manufacturing area
- Handling cytotoxic drugs in liquid, solid or semi solid form during manufacturing activities
- Detoxification of cytotoxic Mother liquor & PPE's used while handling cytotoxic drugs.
- Cytotoxic Sample weighing, testing & discarding unused samples.

Exposure routes

Exposure to cytotoxic waste may occur through:

- by inhalation
- by ingestion
- by dermal absorption
- by mucosal absorption

Effects to Cytotoxic Waste in the human body

When control measures are insufficient & inadequate, occupational exposure to cytotoxic waste may have negative health impacts.

- Direct contact with the skin or mucous membranes may result in contact dermatitis, a local toxic reaction, or an allergic response.
- alterations in normal blood cell counts, as well as cytogenic abnormalities and mutagenic activity linked to exposed personnel.
- stomach aches, hair loss, nasal sores, vomiting, liver damage, and changes in fertility.
- fetal loss and birth defects in exposed pregnant mothers' progeny.

Risk Control:

The manufacturing of cytotoxic drugs poses the greatest risk of workplace exposure due to the concentrations and volumes required. Reducing or eliminating health risks is the top goal when it comes to protecting workers' health.

Risk control measures include:

- Organizing and arranging the workspace to reduce exposure to cytotoxic substances.
- Adopting engineering controls, utilizing specialised equipment and control procedures, such as containment facility, glove boxes, fume hoods, isolator ..etc
- Creating written guidelines and procedures to guarantee the secure management of cytotoxic drugs & wastes
- Educating and training employees, putting in place of strict protocols for handling waste materials and drugs
- Impart training to them to wear personal protective equipment.
- Incorporating a health monitoring program that: - comprises screening and counselling potential employees before they start working with cytotoxic drugs and related waste and periodic medical health check-up & monitoring

OEL value

OEL: Airborne concentrations which will not result in adverse effects in most healthy workers (8 hr/day, 40 hours/week)

$$\text{OEL (8 hr-TWA)} = \frac{\text{NOEL or LOEL (mg/kg/day)} \times \text{BW(kg)}}{\text{V(m3/day)} \times \text{S(days)} \times \text{UF} \times \alpha}$$

NOEL : No-Observed-Effect-Level
LOEL : Lowest-Observed-Effect-Level
BW : Average human body weight (50 - 70 kg)
V : Volume of air breathed in an 8-hour workday (10 m3)
S : Pharmacokinetics (half-life and accumulation)
UF : Uncertainty Factors
A : Used to adjust the absorption of a compound via inhalation

Finding OEL Band & value of Cytotoxic drugs/wastes handled in the pharma industry by getting the data from the occupational toxicology professionals.

Importance of OEL:

OELs are significant because they set a goal for the containment tactics and capabilities of the unit operation. Effective containment is essential for preventing cross-product contamination in addition to preventing occupational illnesses. In the case of substances with extremely low OELs (less than 1 ug/m3), more complex controls must be used. Unlike regulatory restrictions like permissible exposure limits, which are based primarily on health considerations, OELs do not consider the technical or economic difficulties of holding a substance below that airborne concentration. Additionally, it's critical to keep in mind the following details regarding OELs.

OELs are typically not regarded as legal limitations in the sense that they are specified by the Occupational Safety and Health Administration (OSHA) or other regulatory bodies that oversee occupational safety

- OELs are not boundaries between situations that are safe and unsafe.
- The OEL for a given substance may vary

Examples of OEL's for API's

OEL Band	OEL range (µg/m³)	Substance	OEL (µg/m³)
A	>1000	Trifluridine	15000
B	1000 – 100	Ketoconazole	200
C	100 – 10	Nicotine	70
D	10 – 1	Cisplatin	2
E	<1	Fentanyl	0.1

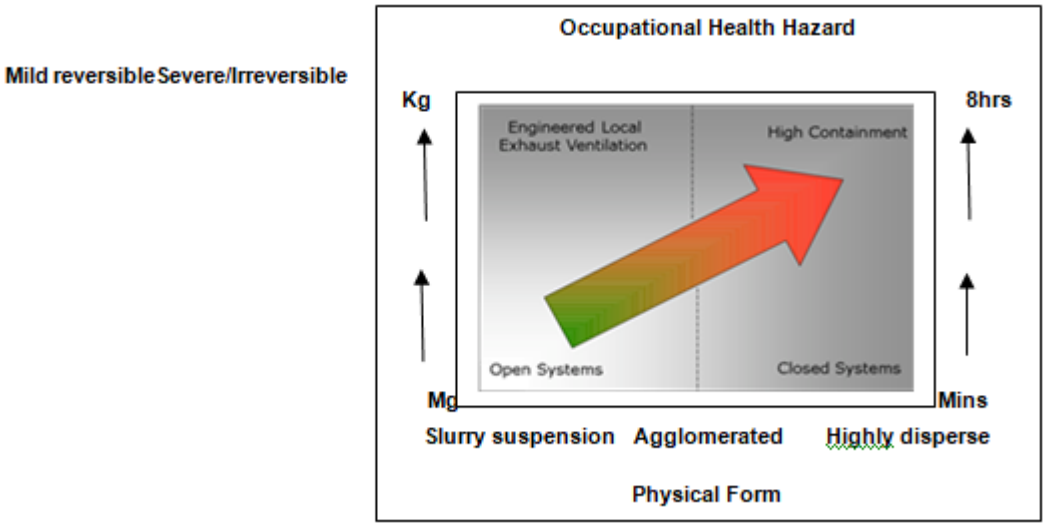
Assess Exposure Risks

• **Dustiness** – Categorize the substance as typical powder, granular/agglomerated, solid, suspension, or extremely dispersed.
• **Process** – Assess the risk of particle release caused by the machinery, the degree of confinement, the energy used in the operation, and the amount of manual handling.
• **Quantity-** Assess the handling Quantity
• **Task Frequency and Duration**– Consider task duration and frequency as well as potential for acute toxicity

Explore the Control Technology available for Handling Cytotoxic Drugs:

The main method of limiting exposure to levels below the OEL shouldn't be the use of personal protective equipment (PPE), such as respirators, cartridge mask..etc. PPE should only be used as a backup plan or as a temporary measure to protect yourself while engineering controls are being put in place.

Factors Inducing Control Selection



The following table provides the control system required for cytotoxic drug handling:

OEL Band	OEL range (µg/m3)	Control Technology
A	>1000	Fume hood withengineered Localexhaust ventilation (LEV)
B	1000 – 100	Directional laminarflow with LEV
C	100 – 10	
D	10 – 1	Closed systems(Cytotoxic safety Cabinet)
E	<1	High containment Isolator

Results and Discussion

There are different types of reactions handled in reactor & different Mass transfer operations are involved while manufacturing cytotoxic products. But the OEL values are derived based on the final drug substances. The OEL values of intermediate stages may not scientifically proven & not calculated. Also, while producing cytotoxic drugs in the manufacturing area, the product form or nature of the product may vary based on reaction conditions such as in slurry, semi solid, solid, agglomerated, Powder & fine powder form. Also, task duration in production activity will be more than an hour & batch size i.e quantity handled in kilograms. So, to eliminate the risk involved in the manufacturing of cytotoxic products, we select the best available control technology called as Isolators. Isolators will provide us high containment facility.

Operation	Recommended Isolator Type	Picture
RawMaterial Dispensing Reactor Charging In-Process Sampling	Dispensing, RM Charging & sampling Isolator	
Centrifugation	Centrifuge Isolator	
Pressure Nutsche Filtration (PNF)	PNF Isolator	
Vacuum Tray Drying (VTD)	VTD Isolator	
Milling and Sieving	Milling and Sieving Isolator	
Final Sampling for Quality control Testing	Sampling & Pack off Isolator	

The above isolators given in the table are specially designed to accommodate the process equipment & to

provide superior control to the operator while handling cytotoxic drugs in various forms.
The isolator is a key control measure in preventing employee exposure to waste cytotoxic drugs, many of which are classified as hazardous to health and may also be carcinogens.
Isolators are classified into two types: positive and negative pressure isolators. The isolator has differential pressure, which can be negative or positive depending on how it is used. Isolators are designed to eliminate or control the operator's exposure to cytotoxic hazardous waste.

Negative pressure isolators are intended to provide the best possible protection to the operator. Positive pressure isolators, which are widely used in aseptic manufacturing, are intended to improve product protection. Air entering and leaving the isolator, whether positive or negative, goes through HEPA filters.

A leak in the isolator, such as a hole in an isolator glove or a faulty seal, allows air to escape or enter the isolator and bypass the HEPA filters. In a negative pressure system, bacteria-containing air may enter the isolator and contaminate the aseptic product. If the breach is obvious, the isolator should be removed from service until it has been repaired. The control system for the isolator must provide containment while also monitoring, controlling, and alarming pressure inside the isolator. The Isolator is intended to operate in laminar flow under negative pressure within the primary working chamber. The Isolator controls will generate an alarm on two times. First, in the event of a containment breach, and until corrected, gloves will give 'in rush' protection. Second, when the outlet filter becomes obstructed, the isolator will sound an alarm.

Conclusion

In this study, we are concluding that negative pressure isolator system which has designed & validated for products that having a OEL level of 1µg/$m^3$for 8 hours operation which provides superior protection to the worker & it is the best superlative control technology during handling of Cytotoxic drugs or waste in the pharmaceutical industry. On considering operator & environment safety during the manufacturing of cytotoxic products in different stages with OEL Band B, C, D & E, the negative pressure isolator system shall keep the operator exposures within acceptable limits and to protect the environment to handle high-containment compounds.

References

1. History - ACGIH. (2023, June 9). Retrieved from https://www.acgih.org/about-us/history.
2. Guidelines on setting in-house occupational exposure limits for airborne therapeutic substances. (1995, January 1). Retrieved from https://www.abpi.org.uk/publications/guidelines-on-setting-in-house-occupational-exposure-limits-for-airborne-therapeutic-substances/
3. Ahmad, A. (2003). managing-cytotoxic-drugs. Malaysian Journal of Pharmacy, 1(3), 63–68. https://doi.org/10.52494/bwlz9208
4. Ahuja, V., & Krishnappa, M. (2021). Approaches for setting occupational exposure limits in the pharmaceutical industry. Journal of Applied Toxicology, 42(1), 154–167. https://doi.org/10.1002/jat.4218
5. Natrajan S. Iyer, Dr. Aditya P. Sharma, Arun Kumar, Ratnesh Verma, Vivek Kumar Sharma and Rekha Mehta (2017)" Performance Qualification And Occupational Exposure Limit (Oel) For Isolator" wjpmr,3(7), 157-162.
6. Capoor, M. R., & Bhowmik, K. (2017, September 14). Cytotoxic Drug Dispersal, Cytotoxic Safety, and Cytotoxic Waste Management: Practices and Proposed India-specific Guidelines. https://doi.org/10.4103/ijmpo.ijmpo_174_16
7. Khalid, N., Masih, S., & Afzal, M. (2022). Practices On Safe-Handling of Cytotoxic Drugs Among Oncology Nurses in Two Public Sector Hospitals. Pakistan Journal of Health Sciences, 131–136. https://doi.org/10.54393/pjhs.v3i07.449
8. Asscher, W. (1986). Handling cytotoxic drugs. BMJ, 292(6512), 59–60. https://doi.org/10.1136/bmj.292.6512.59-b
9. Developing guidelines for the safe handling of cytotoxic drugs in academic research laboratories. (2017). Pharmaceutical Journal. https://doi.org/10.1211/pj.2017.20202343
10. Kaijser, G. P., Underberg, W. J. M., & Beijnen, J. H. (1990). The risks of handling cytotoxic drugs. Pharmaceutisch Weekblad Scientific Edition, 12(6), 228–235. https://doi.org/10.1007/bf01967822