

## Containment

### Introduction

When talking today about solid dosage form production, in 9 out of 10 cases containment immediately becomes one of the issues. Why? The first reason is that APIs are becoming more and more potent. According to an estimation by ISPE (Winter Conference Berlin 2002), by 2010 more than 85 % of all NCE will be classified potent (OEL < 10 µg/m<sup>3</sup>). The second reason is that health and safety authorities all around the world are putting more focus on the protection of operators dealing with these substances. The third reason is that suppliers of various hardware components have developed a huge variety of containment solutions, making it difficult to decide on the optimal solution, even for experienced people.

Before we look at the factors defining the required containment levels, and discussing the possible hardware solutions, some fundamental thoughts about containment need to be covered first.

### Regulatory situation

“It is the first duty of the employer to protect (the health) of his employees.” Even though the regulatory situation differs from country to country, the above statement (taken from the UK COOSH rules) should be seen as general guidance when handling potent substances.

As a matter of fact, approximately 30% of all people in western societies will develop some form of cancer during their lifetime. If one of these had been exposed to a carcinogenic substance, whilst working for a pharmaceutical company, there is the potential for a legal claim against the company. This could result in high cost compensation and also in very bad publicity, unless the company can prove that the employee had been protected according to the state of the art.

*Where as the UK COSSH rules show a clear hierarchy of control measures:*

- 1. Elimination at the source**
- 2. Substitution with a less hazardous material or form**
- 3. Reduction of the quantity below critical limits**
- 4. Engineering controls to prevent intolerable operating staff exposure (contained handling)**
- 5. Administrative Controls**
- 6. Use of Personal Protection Equipment (PPE)**

In many other countries no legislation enforces this hierarchy. On the other hand there are good reasons for this order of preference. Especially that PPE should only be used as a last resort (for maintenance; for necessary, but unforeseen interactions; or if any other method further up in the hierarchy has been considered without success). Why is this? Firstly, PPE only protects the operator. The hazardous substance is not contained, which means that the associated problems are increased. Changing of filters, cleaning of rooms and equipment, inside and outside, become major containment issues. Additionally, depending on the PPE system used, the levels of protection are limited. For systems taking the air from the room via a filter system, the best filters (P3 according EN 149) offer NPFs (Nominal Protection Factors) of 30. This means that if the

dust concentration in a room is 3 mg/m<sup>3</sup> (typical for open production), at best the concentration inside the system will be 100 µg/m<sup>3</sup>. Additionally, the lifetime of the filter element is limited because of the high dust loading.

The situation is different if air-fed systems are used. These systems can provide better protection levels, but there are still some areas of concern. The performance of these systems is very operator-dependant, and in most countries it is not acceptable to put the responsibility for his health (or even life) into his own hands. The working conditions inside an air-suit are unpleasant. Frequently, problems with temperature, humidity, poor visibility and restrictions in movement occur. This results in low levels of operator efficiency, and the need to take frequent breaks, reducing efficiency even further.

*It is also important to notice the hidden costs associated with those systems such as:*

- **large number of systems required**
- **lifetime of suits and filters is limited**
- **cost for clean air supply**
- **requirement for extra changing and storage areas**

These areas are most critical for the performance of the systems. After working in the contaminated area, the outside of the suit is contaminated with API. This needs to be removed, which can be done either by air or wet showers. Whichever method is chosen, the remaining residuals, especially for very potent substances, can still be critical.

The effectiveness of air suits needs to be understood. It is a common misconception they provide total protection, but in reality typical NPF and APF (Applied Protection Factors) are:

Equipment Item	NPF	APF
Air Fed Suit	10.000	200
Air Fed Half Suit	2.000	100
Air Fed Hood	2.000	40
Filter Air Hod	500	40

APFs represent the reality of daily operation. Using the same example as above, this means that if the dust concentration in a room is 3 mg/m<sup>3</sup>, at best the exposure level for an operator wearing a full air-fed suit will be 15 µg/m<sup>3</sup>.

### **Containment risks**

During most of the manufacturing process, the APIs are inside machines or vessels which are more or less tight. The main risk of material escaping into the environment exists whenever a connection between those pieces of equipment needs to be made or broken, when a sample needs to be taken, and last, but not least, when the machines need to be cleaned after the end of a manufacturing campaign.

### **How much containment is required?**

In an ideal world operators would not be exposed to a single molecule of a harmful substance, but as we live in a real world, this is simply not possible. Three main factors dictate how much containment is required or, in other terms, which type of containment solution can be applied. The nature, especially the potency, of the API handled is of paramount importance, the type of process to be executed, and lastly the working regime of the operators.

### The product

The potency of a substance is, in most cases, characterized either by the OEL (Occupational Exposure Limit) or by the ADI (Acceptable Daily Intake). The ADI describes the absolute amount of a specific drug substance that an operator can daily take into his body, without any negative effect for his health. The OEL describes the maximum concentration of a drug substance which can be tolerated in the air of the production room, without any negative effect to the health of the operators. For established substances, these values are listed in textbooks such as ISBN 07176 2083 2 EH40/2002 OEL 2002 & ISBN 07176 2172 3 EH 40/2002 Supplements 2003. According to those, the OEL for Paracetamol is 10 mg/m<sup>3</sup>, while the OEL for Ethinyl estradiol is 35ng/m<sup>3</sup>. It is important to understand that those values are based on certain assumptions. Also, those values might change during the lifecycle of a substance, especially after more toxicological data is generated. If an OEL for a substance cannot be obtained from the literature, the value can be determined as follows:

$$\text{OEL} = \text{NOEL} [\text{mg}/(\text{kg} \times \text{day})] \times \text{BW} [\text{kg}] /$$

$$V [\text{m}^3/\text{time}] \times \text{SF}_1 \times \text{SF}_2 \times \dots\dots$$

with:

- **OEL** = Occupational Exposure Limit
- **NOEL** = No Observable Effect Level
- **BW** = Body Weight
- **V** = Breathing Volume
- **SF** = Safety Factor

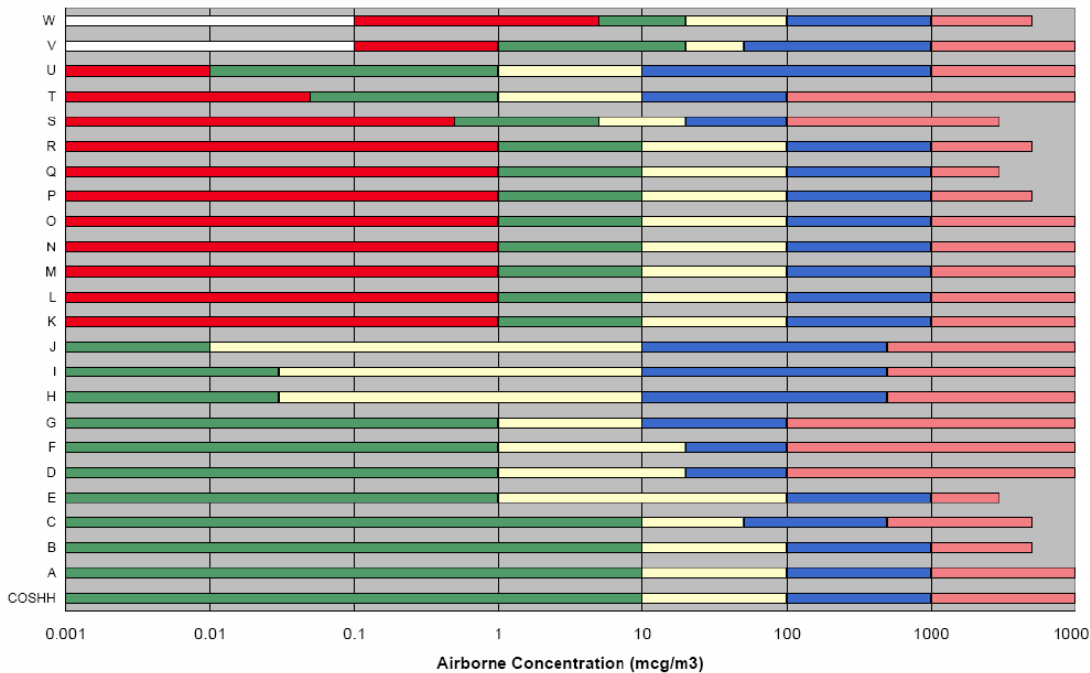
ADI and OEL are interconnected by the typical breathing volume of an operator (normally estimated as 10 m<sup>3</sup>/shift). Therefore;-

$$\text{ADI} = \text{OEL} \left[ \frac{\text{mcg}}{\text{m}^3} \right] \times V \left[ \frac{\text{m}^3}{\text{day}} \right]$$

$$\text{ADI} = 10 \times \text{OEL} [\text{mcg}/\text{day}]$$

$\text{ADI} = \frac{\text{NOEL} [\text{mg}/(\text{kg} \times \text{day})] \times \text{BW} [\text{kg}]}{\text{SF}_1 \times \text{SF}_2 \times \dots\dots}$
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Additionally, it is common practice to describe the potency of a drug substance by an easy categorization system classifying all potent substances from 1 (less potent) to 5 (most potent). This allows production equipment to be classified as suitable for the production of a class X compound, plus it easily shows to operators the potency of the substance. However, when talking about this simple classification system, two important remarks need to be made. It is not totally universal, as the attached diagram shows - nearly each company has its own classification system.



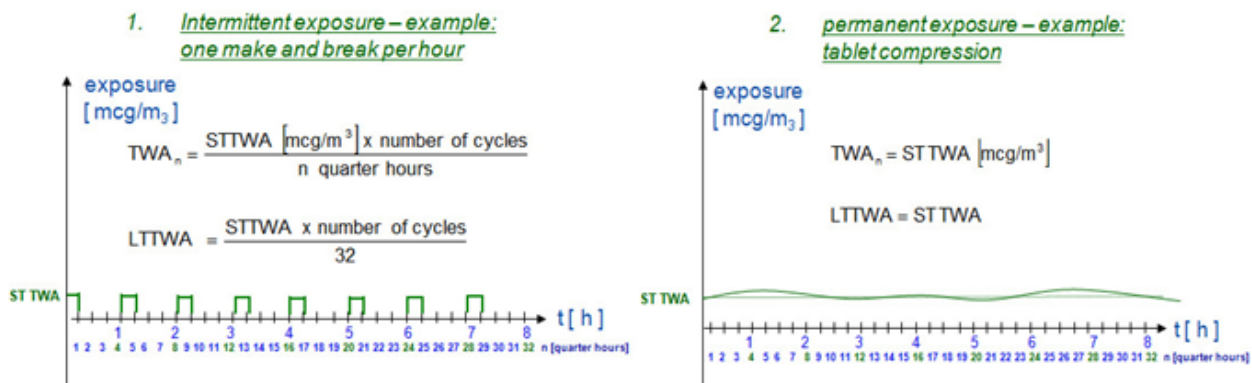
As we will see in the following chapters, the concept of production lines suitable for the manufacturing of all class x compounds can be questioned. It oversimplifies the situation, not taking into consideration dilution (not all substance handled is pure API, especially when dealing with very potent substances often a large percentage of the mixture is excipient), the real number of operations, or also the fact that operators might not be present all time.

### The equipment

Less than 10 years ago nearly all suppliers of “containment equipment” promoted these items with claims such as “3 µg/m<sup>3</sup>”, “better than 1µg” or even worse “OEL 2 µg/m<sup>3</sup>”. All of these claims were meant to describe the containment performance of equipment such as extraction booths or containment valves. While the last claim obviously is wrong (OEL is a product related number, it only has the same unit as the containment performance of a piece of equipment), the problem of the other claims was that the test conditions were not defined. This made it extremely difficult to compare figures obtained by using different test materials, different samplers, different sampler positions or different analytical procedures.

After inventing the split valve technology, GEA Buck Valve again took the lead to form (under the umbrella of ISPE) an expert working group, consisting of experts from pharma companies, engineering companies and containment equipment suppliers. This group developed a guideline <http://www2.ispe.org/eseries/scriptcontent/orders/ProductDetail.cfm?pc=IGPGAPCUS> in which all of the variants discussed above are defined. The accepted test procedure uses Lactose of a defined grade (other substances are possible), uses the equipment in a defined environment (humidity, temperature, number of air changes), and places the defined samplers in specific positions. The test includes performing the intended task, and collecting air (via the filters of the samplers) for 15 minutes. Analyzing the filters gives the quantity of lactose in a measured amount of air, which is the containment performance of the equipment. As the average of 15 minutes is taken, this performance is called STTWA (Short Term Time Weighted Average). It is important to note that the total amount of powder escaping is measured. If dealing with potent APIs, often only a small percentage of a powder mixture is active, while the rest is excipient. The LTTWA is defined as the containment performance over a longer period of time, for example one shift of 8h.

The diagram shows two different scenarios



It is important to distinguish if there is an intermittent exposure as shown on the left side, or a permanent exposure as shown on the right side.

### The Operator

The most important numbers to describe the exposure of the operator are ROI (Real Operator Intake) and RDI (Real Daily Intake). These numbers describe the amount of API which gets into the body of the operator, while being for a certain period of time in an area with a certain airborne drug concentration. If we know the breathing rate of the operator, and the dust concentration in the room, then the drug uptake can be calculated. For example, this is shown in

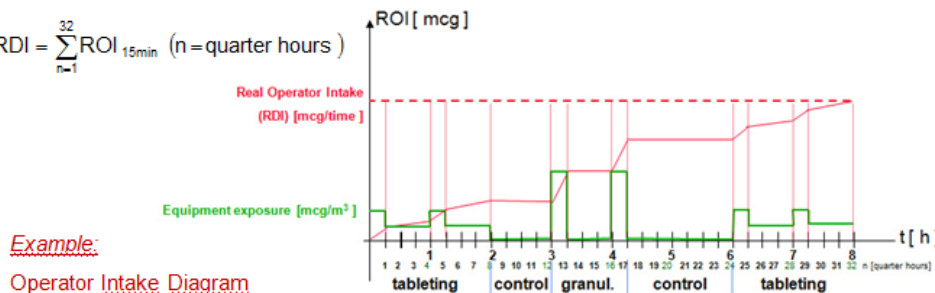
#### How to calculate the Real Operator Intake (ROI)

$$ROI_{15min} = ST\ TWA \times V_{15min} \times dilution\ factor \quad \left( V_{15min} = \frac{10m^3/day}{32\ quarter\ hours/day} \right)$$

$$ROI_{15min} = ST\ TWA \ [mcg/m^3] \times 0,3125 \frac{m^3}{15min} \times dilution\ factor$$

#### How to calculate the Real Daily Intake (RDI)

$$RDI = \sum_{n=1}^{32} ROI_{15min} \quad (n = \text{quarter hours})$$



If the actual RDI is less than the drug specific ADI, the situation is fine. If the RDI exceeds the ADI, measures must be taken to improve the situation. In our example the most effective way would be to upgrade the granulator by a loading/unloading system with a better containment performance.

### Conclusion

This visualization helps the concept to be easily understood. For real situations of course, a detailed risk analysis needs to be done in order to judge the containment performance of an existing installation, or to select the appropriate equipment for an upgrade of an existing facility, or the design of a new facility.



GEA Pharma Systems not only offers the largest variety of hardware solutions for contained materials transfers, but also unrivalled experience in identifying the most appropriate solution, based on a containment risk analysis.