RESEARCH OF THE OCCUPATIONAL EXPOSURE OF HEALTH CARE PROFESSIONALS HANDLING WITH HAZARDOUS PHARMACEUTICALS

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Background:

Generally, any pharmaceutical agent is proposed to influence targeted biological systems but is well known that treatment with various drugs is very often accompanied by their adverse effects. Therefore any unnecessary release, exposure and uptake should be avoided. This especially applies to chemotherapeutic agents which besides their acute toxicity show serious long-term side effects such as carcinogenity, mutagenity, teratogenity. The quality and quantity of these effects depends on their physico-chemical properties as well on routes of exposition.

Occupational exposure to cytotoxic drugs (CDs) has been recognized as a potential health hazard since the 1970s, when Falck et al. showed an association between contact with antineoplastic drugs and increased urinary mutagenicity[1]. Since that time, several studies have brought some evidence that CDs can be expected in every places where are handled[2-4].

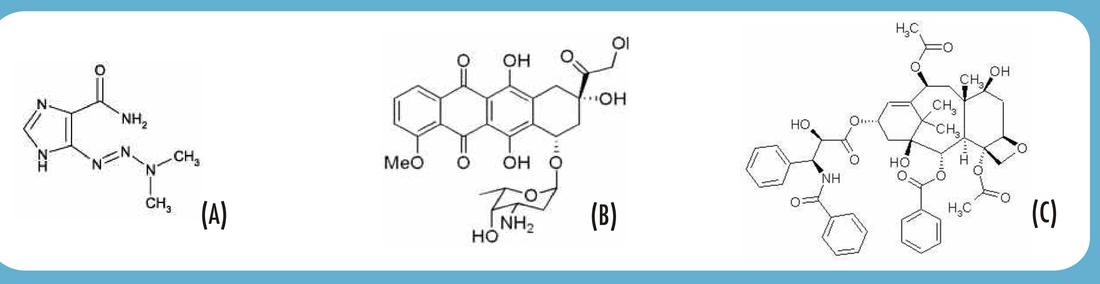
Masaryk Memorial Cancer Institute (MMCI) belongs to the international oncology centers network since 1935, however CDs are properly manage since 1991. Hospital pharmacy centralised preparation of CDs has been established during 1996 and managed on the highest international level with standardised procedures since 2000. All procedures were certified on ISO 9001 standard accordance in 2002. Preparation facility is equipped in accordance with Czech law with negative pressure isolators.

Beside the daily routine handling of CDs is the Hospital pharmacy of MMCI managing several colaborative investigational groups oriented to new scientific advances in several aspects of CDs manipulation. One of these scientific projects is the project 2B06171 supported by National Research Programme II that investigates the long-term occupational exposure of health care professionals handling with hazardous pharmaceuticals.

The scope of the project is focused on the ability of measurement the CDs contamination of workplaces and prediction of the expositions of employees and working environment in respect to individual pathways, working conditions, etc. In the group of CDs there are substances with various structures and physico-chemical properties. Some of these drugs has either carcino- or mutagenic effects.

In the beginning of our research we have focused on the evaluation of physical properties of the compounds. It is supposed CDs may evaporate under normal conditions. The rate of vaporization of chemicals can be determined as a vapour pressure (VP) of a compound, what is defined as the saturation pressure above its solid or liquid phase and depends on the temperature of environment. The equilibrium concentration can be calculated in the next step. In the past, the determination of vapour pressure of five frequently used CDs and the calculation of the equilibrium concentration were performed by IUTA, Germany. Nowadays we have required assessment of another three commonly used drugs: dacarbazine, doxorubicin and paclitaxel (Figure1).

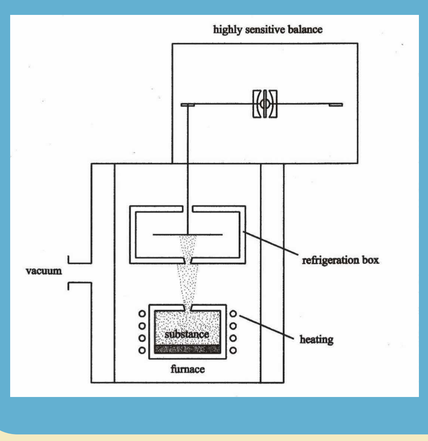
Figure 1: Molecular structures of dacarbazine (A), doxorubicin (B) and paclitaxel (C)



Materials and Methods:

The test substances (dacarbazine, doxorubicin and paclitaxel) were tested in pure state (production of Pliva-Lachema, Brno, Czech Republic). The purity of the substances was 99 % or higher.

The vapour pressure of dacarbazin, doxorubicin and paclitaxel were determined according to an OECD test method using a vapour pressure balance[5]. This method is suitable for vapour pressure assessment in the range 10^{-3} to 1 Pa.



Every substance was heated in a small furnace, placed in an evacuated bell jar. The furnace is covered by a lid, which carries small holes of defined diameters. The vapour of the substance, escaping through one of the holes, is directed up to a balance pan of a highly sensitive balance which is also enclosed in the evacuated bell jar. The balance pan is surrounded by a refrigeration box, providing heat dissipation to the outside by thermal conduction, and is cooled by radiation so that the escaping vapour condenses on it. The momentum of the vapour jet acts as a force on the balance. The vapour pressure can be derived directly from the force on the balance pan.

Table 1: Temperature dependance of vapour pressure of tested cytostatic drugs

Temperature [°C] (experimental)	Vapour pressure [*10^{-5} hPa]		
	Dacarbazine	Doxorubicin	Paclitaxel
20	n.d.	n.d.	22.5
30	n.d.	n.d.	27.9
40	n.d.	2.8	30.1*
50	n.d.	4.5	33.6*
60	6.9	4.9	36.6
70	8.5	6.1	44.4
80	10.9	6.9	46.9
90	11.0	7.4	46.1
100	12.5	3.9	42.4
110	14.0	4.5	48.0

n.d. = not defined; *extrapolated

Figure 2: Vapourization of Paclitaxel, Dacarbazine and Doxorubicin

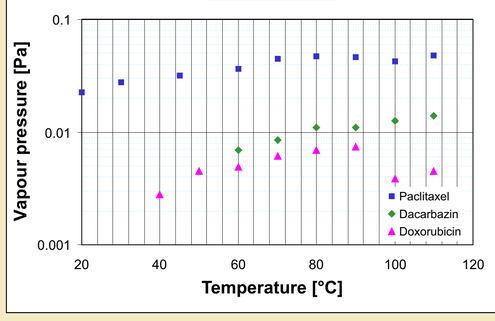


Table 2: Vapour pressures and equilibrium concentrations for CDs (measured by Institute of Energy and Environmental Technology, Duisburg, Germany)

Substance	Vapour pressure (Pa)		Calculated equilibrium concentration (mg/m^3)	
	T=20C	T=40C	T=20C	T=40C
Carmustine	0.019	0.53	1.7	44
Cisplatin	0.0018	0.0031	0.22	0.36
Dacarbazine	<0.001	<0.001	<0.07	<0.07
Doxorubicin	<0.001	0.0028	<0.22	0.58
Cyclophosphamide	0.0033	0.0090*	0.36	0.9
Etoposide	0.0026	0.0038	0.63	0.86
Fluorouracil	0.0014	0.0039	0.08	0.2
Paclitaxel	0.0225	0.0301*	7.89	9.87

*extrapolated

Results and Discussion:

The temperature dependence on the vapour (saturation) pressure of tested compounds is shown in Table 1 and on Figure 2. Generally, found values of vapour pressure of tested CDs measured at 20°C were in the range of <1-22.5 mPa ($9,9*10^{-9}$ - $2,2*10^{-7}$ atm). These findings correspond with previous results obtained for other CDs[6].

Although the various structures found inside of group of CDs their VPs are in the similar orders. VP obviously doesn´t depend on the substance structure. We have checked a relation between VP and molecular weight of CDs, but there was found no correlation too.

In the Table 2 there is the summary of VP together with calculated saturation concentrations for all tested CDs at 20°C and 40°C.

Although these values were measured under model conditions (one-component system in vacuum), it is possible to apply them to real conditions in the cytotoxic preparation room (operating under atmospheric pressure and in the presence of air).

In case of occurrence of a depot of CDs big enough in the cytotoxic preparation room, the CDs concentration in the room would correspond (in regard to temperature) to calculated equilibrium concentration. Under real conditions this situation can´t be expected because of air conditioning. In cytotoxic preparation room there is guaranteed at least the thirty-fold exchange of air volume every hour. Further, according to the fact that the process of vaporization runs till the equilibrium between both phases is reached, we can expect that every undesirably released amount of CDs evaporates to the air.

Figure 3 compares VPs of antineoplastics with VPs of other well-known groups of chemical substances. The lower limit of the scale is 10^{-12} (substances with lower value of VP are believed nonvolatile).

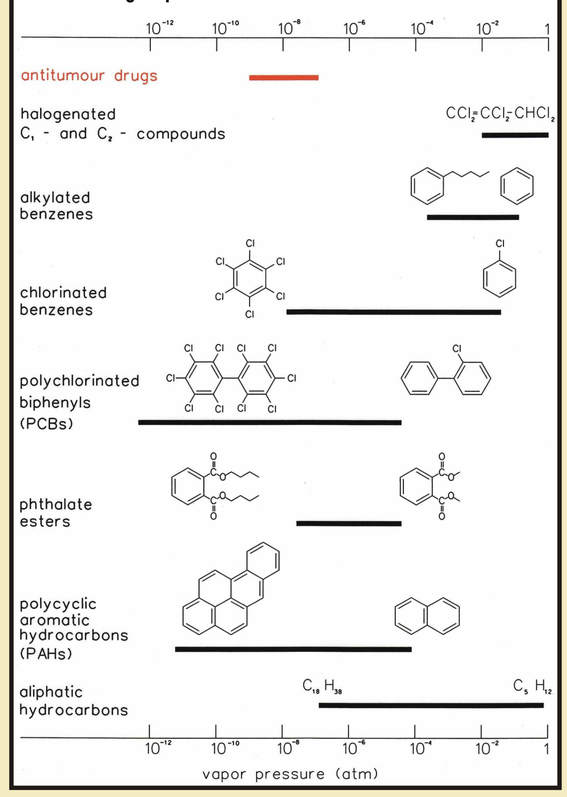
Conclusions:

As it was shown, when handling CDs it should be expected these compounds evaporate to ambient air and may enter bodies of pharmacists and nurses through inhalation pathway. Neither currently used of special technical equipment of cytotoxic preparation room nor personnel protective clothing don´t avoid the aerosolisation and vaporization of CDs during the routine handling. From this point of view it is better to use the negative pressure isolators with own exhaust ducting than recirculating models of safety cabinets.

It´s not possible to analyse all used substances in the monitoring study. It is necessary to choose reliable model substance. Together with information about the usage and consumption of CDs, knowledge of the VPs is useful. In the respect of measured value of VP of paclitaxel, this substance certainly will be included in the monitoring program.

Knowledge of physico-chemical properties is only first step to establishment of long term monitoring of exposition of working personnel. Therefore analytical methods for sampling, enrichment, extraction and determination of trace levels of selected pharmaceuticals in all relevant matrices (air, surfaces, textiles, excreta, blood) are going to be optimised, validated and applied.

Figure 3: Vapour pressure of CDs in comparison with other well-known groups of chemical substances



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