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Cadmium levels in human breast tissue and estradiol serum levels: Is there a connection?

Aleksandra Buha Djordjevic[1] , Milena Anđelković[1], Elena Kačavenda[2], Dragana Javorac[1], Evica Antonijević-Miljaković[1], Đurđica Marić[1*], Katarina Baralić[1], Danijela Đukić-Ćosić[1], Marijana Ćurčić[1], Biljana Antonijević[1], Zorica Bulat[1]

[1]University of Belgrade – Faculty of Pharmacy, Department of Toxicology "Akademik Danilo Soldatović", Vojvode Stepe 450, 11000 Belgrade, Serbia

[2]University of Belgrade – Faculty of Pharmacy, Center for scientific research work of the students, Vojvode Stepe 450, 11000 Belgrade, Serbia

*Corresponding author: Đurđica Marić, e-mail: dmaric@pharmacy.bg.ac.rs

Abstract

Cadmium (Cd), one of the most abundant environmental pollutants, is considered to have endocrine disrupting properties. However, data on the dose-response relationship between Cd dose and levels of hormones have been insufficiently studied, especially in human data sets. Thus, the aim of this study was to determine the possibility of analyzing data obtained from a case-control study in female patients with benign/malignant breast tumors, using the Benchmark dose (BMD) concept. The collected data on Cd levels in breast tissue and estrogen serum levels were processed in PROAST software using different variables. The dose-response relationship between the internal dose of Cd and estradiol levels in the serum was investigated and BMD intervals were calculated. The dose-response relationship between the Cd concentration in breast tissue and the estradiol serum level was shown, indicating lower estradiol serum levels as a consequence of higher Cd concentrations in breast tissue. As one of the few studies analyzing human data using the BMD approach, these findings could have a pivotal role in dose response analysis of data collected from human studies.

Keywords: endocrine disruption, cadmium, BMD concept, PROAST software, human studies

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Introduction

Cadmium is a widely spread toxic metal with no biological function in the body. Nowadays, it is considered to be one of the most common environmental pollutants (1). Its prevalence in the environment is a consequence of the use of fertilizers, as well as improper disposal and treatment of waste, which includes nickel-cadmium batteries and paints (2). For the general population, the primary sources of Cd exposure are tobacco, which is a Cd hyperaccumulator, and various food items (seafood, cereals, vegetables, etc.) (2,3). Great attention has been given to this metal because of its high toxicity and toxic effect on various organs through various mechanisms (4,5,6,7,8,9,10,11), as well as because of its possibility of bioaccumulation (12). Cd has been also linked to changes in sex hormone levels and reproduction. This metal has been shown to lead to histopathological changes at the ovaries and uterus, such as endometrial thickening, corpus luteum degeneration, and oocyte damage and reduction (3). Cd is also a metalloestrogen because it has the ability to bind to estrogen receptors located on cells, and thus mimics the action of natural estrogen (2,3). This estrogenic effect has been proven for low doses of Cd, while an anti-estrogenic effect is associated with higher doses of Cd. In a study using the same participants and data sets, Cd has already been linked to the development of breast cancer, since higher concentrations of this metal are found in tumor tissue than in surrounding healthy tissue, as well as due to binding to estrogen receptors (13). The fact that it accumulates in the reproductive organs, acting as a metalloestrogen, causing oxidative stress and thus interfering with normal reproduction, has brought Cd to the list of the most famous endocrine disrupting chemicals (EDCs). An endocrine-disrupting chemical is defined as ‘an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations’(14). Additionally, World Health Organization/The International Programme on Chemical Safety (WHO/IPCS) (14) emphasized the importance of the existence of a plausible causal relationship between endocrine activity and induced adverse effect(s) seen in an intact organism, or a (sub)population, which was later endorsed by the Scientific Committee of the European Food Safety Authority (EFSA) (15). It is evident that this field is still controversial and that many issues, such as improving testing strategies for EDC identification, managing low-dose effects of EDCs, non-monotonic dose-response phenomena, and appropriateness of the use of the threshold concept, need to be further addressed (16).

The Benchmark dose (BMD) concept is an approach that is used for determining a possible relationship between the dose of a test substance and the investigated effect. This concept is an alternative to the most commonly used approach of the No Observed Adverse Effect Level (NOAEL) (17). The result of the NOAEL approach is the identification of the highest tested dose that does not lead to any harmful effects in the experiment. This value depends not only on the selected dose range used in the experiment, but also on the ability to detect adverse effects in the experiment. The advantages of the BMD approach are that, in addition to threshold effects, it also includes non-threshold effects, gives better usability of experimental data, and the obtained results

do not depend on the dose range used in the experiment (17,18). The European Food Safety Authority (EFSA) considers this approach to be more advanced than the NOAEL approach (17). The BMD approach determines the dose that will lead to this change based on a previously determined statistically significant change in effect, i.e. the Benchmark response (BMR). Benchmark dose is the dose interval corresponding to a predetermined BMR, which in most cases is 5% or 10%, while BMDL represents the lower confidence limit for the selected BMD (17). As a final result of each BMD analysis, it is recommended to show the BMD interval, not individual values. A BMDL value is needed as a reference point in order to obtain a level of intake of the substance that is unlikely to lead to adverse effects on human health. BMDU (upper limit of BMD reliability) value is needed to establish a BMDU/BMDL relationship. The software that was created with the aim of enabling the analysis of the dose-response relationship and obtaining the Benchmark dose is the PROAST software (RIVM Institute, the Netherlands). A software that can also be used for such purposes is the Benchmark Dose Software (BMDS) developed by the U.S. Environmental Protection Agency (U.S. EPA).

This approach can theoretically be applied to data from human studies, animal studies and ecotoxicological studies (19). The advantage of using data from human studies in risk assessment is that there is no extrapolation of the obtained data in animals to humans. On the other hand, inaccuracy in the assessment of human exposure, as well as additional factors that must be taken into account, make the analysis of these data more complicated and sometimes less reliable than the analysis of data from experimental animal studies (19,20). The BMD concept has been used in a number of animal studies, but there is still little data on the use of this concept in the processing of data obtained in human studies (18). That is why the EFSA recommends examining the possibility of using this concept to process data obtained from epidemiological studies. One of the few studies in this field was based on the use of data obtained in a study on people occupationally exposed to lead, in order to obtain the dose responsible for lead-induced renal dysfunction using the BMD concept. Blood lead level was used as a biomarker of exposure, while total proteins, beta (2)- microglobulin and N-acetyl-beta-D-glucaminidase in urine were used as biomarkers of the effect. BMR was chosen to be 10%, while data were processed as dichotomized in BMDS (21). A similar study that also dealt with renal dysfunction aimed to define the concentration of Cd in urine that would lead to the renal dysfunction. Urinary Cd was chosen as the biomarker of exposure, while N-acetyl-beta-D-glucaminidase and its isoform B, beta (2)-microglobulin, retinol binding protein and albumin in urine were used as indicators of renal effects caused by Cd. BMR was chosen to be 5% and the BMDL value of Cd in urine was assessed for each of the effect markers (22). A study in children was also conducted to link serum concentrations of perfluorinated compounds to immunotoxicity using the BMD concept (20).

The aim of this study was to determine the possibility of analyzing data obtained in a case-control using the BMD concept and to determine whether there is a dose-response relationship between the internal dose of cadmium (Cd) in breast tissue and the level of estradiol in the blood which was tested.

Materials and methods

Study population

The study was conducted at the Clinic for Oncology of the Clinical Hospital Center Bežanijska kosa, Belgrade, Serbia. The study population included 55 women with a breast cancer diagnosis, and the control group consisted of 41 women with benign breast changes. The respondents were selected by a clinical specialist in the period between January and September 2019 and all participants gave informed consent to participate in the study. Ethical License No. 9740/3 was issued by the Scientific and Ethical Committee of the Clinical Hospital Center, Bežanijska kosa. The criteria for the inclusion in the study were a diagnosis of breast cancer and age over 18, while the exclusion criteria were age below 18, chemotherapy before surgery, oral contraceptive therapy and/or infertility treatment. Basic demographic and anthropometric data were collected by interview. Based on the data obtained, a total of 96 respondents were classified into one of three categories based on menopausal status: premenopausal, having regular cycles in the previous 12 months; perimenopausal, being in the transition period before menopause; and postmenopausal, not having a cycle for more than 12 months. The number of subjects in each group was 42, 3, and 51, respectively. Immediately before surgery, venous blood samples were obtained from the anterior cubital vein after a 12 h fasting period. Estradiol levels were determined in serum. After tumorous tissue removal, Cd levels were determined from the tumorous tissue and surrounding healthy tissue.

Sample preparation

After a 12-h fasting period, blood samples were collected by venipuncture of the anterior cubital vein prior the surgical procedure. For hormone analysis, blood was collected in additive-free vacutainers. After coagulation at room temperature (20 minutes), serum was separated by centrifugation at 3000× g for 30 min and stored at −20 °C until the measurement of estrogen level. Two samples of breast tissue (tumor and healthy surrounding sample) were sampled over the course of surgery from each subject. Prior to analyses, all samples were stored at− 20°C.

Estrogen analyses

In vitro chemiluminescent immunoassay (CLIA) and electrochemiluminescence immunoassay (ECLIA) methodologies with commercial reagents and according to good laboratory practices were performed on the Liason (DiaSorin Inc, USA) and Cobas e411 analyzer families (Roche Ltd., Switzerland) for hormone assay analysis. All analyses were conducted in accordance with the manufacturers' recommendations.

Cadmium analysis in tumor tissues

Two samples of breast tissue (tumorous and healthy surrounding sample) were taken during the surgery. The verification of tissue type was performed by the Department of Pathological Anatomy University Hospital Medical Center Bežanijska kosa. Tissue samples (0.5 g of breast tissue) were digested using microwave digestion in Teflon

containers with 7 ml 65% HNO_3 and 1 ml 30% H_2O_2 (Milestone START D, SK-10T, Milestone Srl, Sorisole, Italy). A temperature of 180°C was reached in 15 min, then held for 15 min at the same temperature, and then cooling was performed during 15 min. The samples were quantitatively transferred into a 10 ml volumetric flask. Blank was prepared and analysed along with the samples and consisted of 7 ml 65% HNO_3 and 1 ml 30% H_2O_2. Cadmium was measured using graphite furnace atomic absorption spectrophotometry (AAS GTA 120 graphite tube atomizer, 200 series AA, Agilent technologies, Santa Clara, CA, USA). Calibration was carried out using an external standard method (multielement standard solution 1 g/L in diluted nitric acid (Merck, Darmstadt, Germany)). The accuracy of AAS was validated with standard reference material (SRM) SRM 1577c - Bovine liver (LGS Standard, UK), about 0.5 g of tissue liver sample were digested with 7 ml 65% HNO_3 and 1 ml 30% H_2O_2. The samples were quantitatively transferred into a 10 ml volumetric flask. All analyses were conducted in accordance with the manufacturers' recommendations.

Dose-response modelling

Dose-response modelling was performed using the PROAST software version 67.0 (**the Dutch National Institute for Public Health and the Environment, RIVM).** Data on estradiol and Cd levels were analyzed as continuous individual data, as well as data on variable factors, i.e. menopausal status and the presence of malignant/benign change collected by 94 subjects, while for one of the remaining two subjects no data on estradiol levels were available, and for the other subject no information on tissue Cd levels was available. Any value of estradiol lower than 10.0 pg/ml was characterized as not available (NA). The model averaging method was used to calculate the Benchmark dose, BMD, and interval, as an approach that takes into account the results obtained by applying all the available models. This approach is strongly recommended by the EFSA scientific committee over single model analysis, since it adjusts for model and data uncertainty (17). Akaike information criterion (AIC) was used to evaluate the model, i.e. to compare how well the data fit into certain models. It is considered that the model with the lowest AIC value should be chosen to obtain the BMD interval.

Results

The dependence of the concentration of estradiol (pg/ml) in the blood on the concentration of Cd (ng/g) in the surrounding healthy/tumor tissue was monitored, taking into account the status of menopause (pre, peri, post) or the presence of benign/malignant changes which are presented as variables. Table I presents the measured levels of Cd and estrogen, depending on the status of menopause and type of tissue. It should be noted that perimenopausal status was observed only in 3 subjects, hence, the data obtained in this group can not lead to any firm conclusions. BMR was chosen to be 10% in all four cases, having in mind that estradiol levels can greatly vary and still be considered as normal and inside the reference range. Taking into account the values obtained using the various

mathematical model (Full, Null, Expon,Hill...), model averaging method provided BMDU and BMDL values for each data set.

Table I Characteristics of the study population.
Tabela I Karakteristike učesnika u istraživanju.

Menopausal status	Type of tissue	Number of subjects	Cadmium concentration in tissue (µg/L)	Estradiol levels (pg/mL)
premenopausal	Tumorous	52	38.24	102.45
perimenopausal	Tumorous	3	65.45	94.65
postmenopausal	Tumorous	41	90.5	20.67
premenopausal	Healthy	52	24.53	102.45
perimenopausal	Healthy	3	39.34	94.65
postmenopausal	Healthy	41	34.78	20.67

When examining the dose-response relationship between the concentration of *Cd* (*ng/g)* in tumor tissue and the concentration of estradiol (*pg /ml*) in blood using the presence of malignant/benign change taken as a covariable, the following Benchmark confidence intervals (BMDL*:* lower level of BMD reliability – BMDU*:* upper level of BMD reliability) were obtained: 0.000037-414000 ng Cd/g tissue for subgroup with benign changes and 0.0137-136 ng Cd/g tissue for subgroup with malignant changes. Bootstrap curves obtained in the PROAST program based on model averaging are presented in Figure 1.

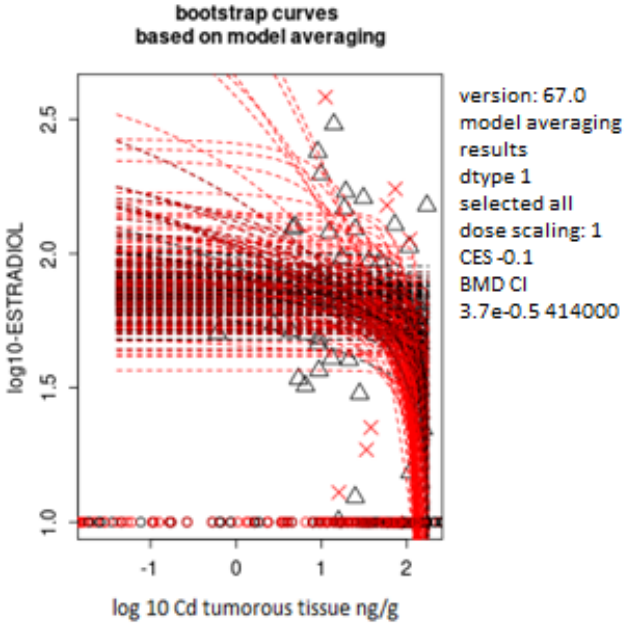

Figure 1. **The dependence of the estradiol blood level (pg*/ml)* on the concentration of *Cd* (*ng/g)* in the tumor breast tissue with malignant/benign change as variables based on *Model averaging.* The x axis represents log10 of Cd tissue levels, while the y axis represents log10 values of estrogen serum levels. The symbol △ represents subjects with malignant changes and x represents subjects with benign breast changes.**

Slika 1. **Zavisnost nivoa estradiola u krvi (pg/ml) od koncentracije Cd (ng/g) u tumorskom tkivu dojke sa prisustvom maligne/benigne promene kao promenljive na osnovu *Model averaging*. X-osa predstavlja logaritmovanu vrednost nivoa Cd u tkivu, dok su na y-osi predstavljeni logaritmovani nivoi estrogena u serumu. Simbol △ predstavlja ispitanice sa dijagnozom karcinoma dojke, dok x predstavlja ispitanice sa benignim promenama dojke.**

The dependence of the concentration of estradiol blood levels (*pg/ml*) on the concentration of Cd (*ng/g)* in the surrounding healthy tissue with malignant/benign changes as variables was also established with the following Benchmark confidence intervals: 4.91-164 ng Cd/g tissue for subgroup with benign changes and 3.47-54.8 ng Cd/g tissue for subgroup with malignant changes. The dependence of estradiol blood levels (*pg/ml*) on the concentration of Cd (*ng/g)* in the surrounding healthy tissue is presented in Figure 2.

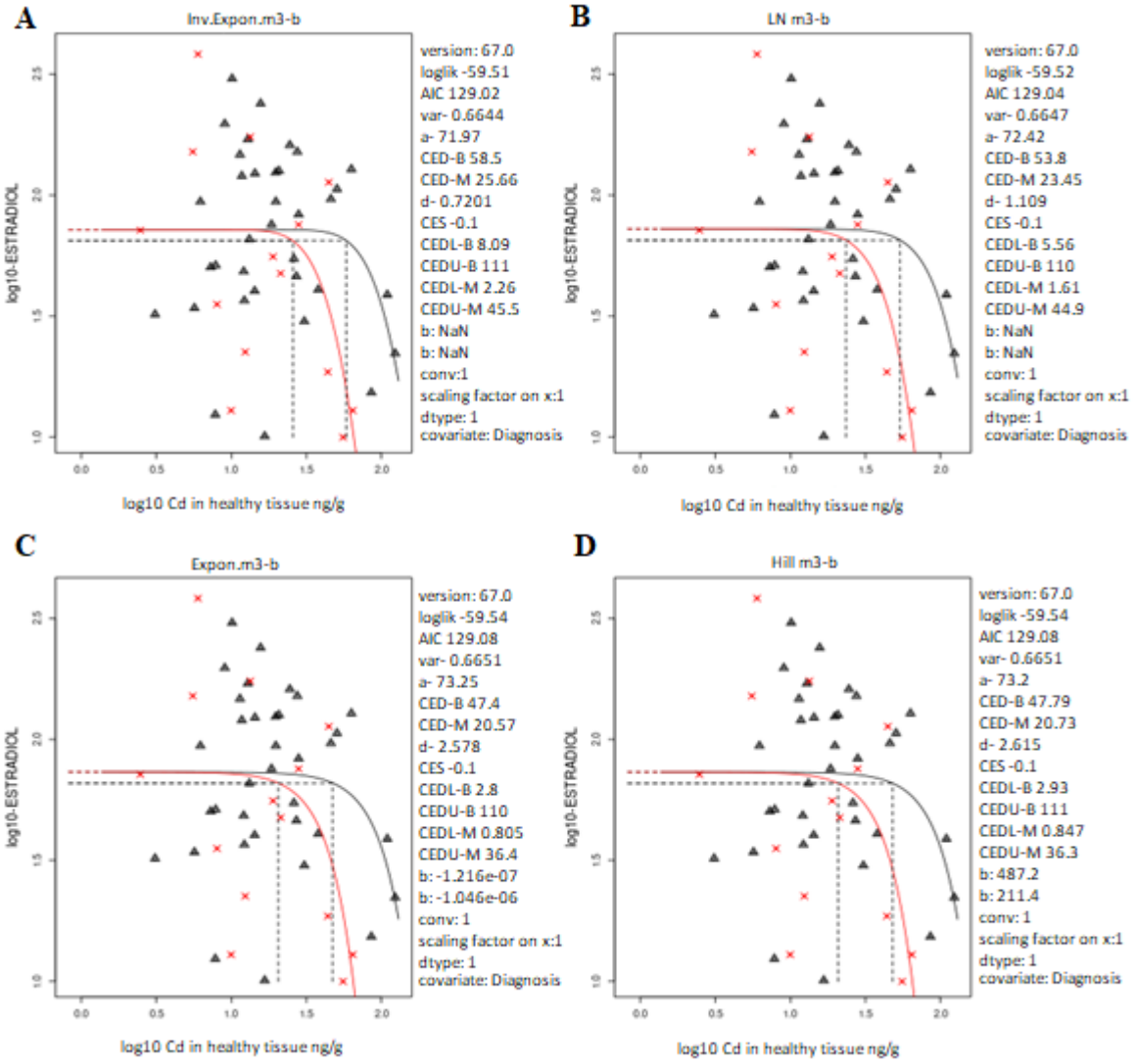

Figure 2. **The dependence of the of estradiol blood levels (*pg/ml*) on the concentration of *Cd* (*ng/g)* in the surrounding healthy breast tissue with the presence of malignant/benign changes as variables. The x axis represents log10 of Cd levels in healthy tissue while the y axis represents log10 values of estrogen serum levels. Panels A, B, C, and D represents different models of the dose-response dependence calculated in the PROAST software. The symbol △ represents subjects with malignant changes and x represents subjects with benign breast changes.**

Slika 2. **Zavisnost nivoa estradiola u krvi (pg/ml) od koncentracije Cd (ng/g) u okolnom zdravom tkivu dojke sa prisustvom maligne/benigne promene kao promenljive. X-osa predstavlja logaritmovanu vrednost nivoa Cd u zdravom tkivu, dok su na y-osi predstavljeni logaritmovani nivoi estrogena u serumu. Delovi slike A, B, C i D predstavljaju jednačine različitih modela doza-odgovor zavisnosti izračunati u softveru PROAST. Simbol △ predstavlja ispitanice sa dijagnozom karcinoma dojke, dok x predstavlja ispitanice sa benignim promenama dojke.**

The dependence of estradiol blood level (*pg/ml*) on Cd concentration (*ng/g)* in tumor tissue using menopausal status (pre, peri, post) as a variable revealed the following BMD confidence intervals: 1.47-67.4 ng Cd/g tumor tissue, 12.3-13500 ng Cd/g tumor tissue, and 49.4-245000 ng Cd/g tumor tissue in premenopause, perimenopause, and postmenopause subgroups, respectively (Figure 3).

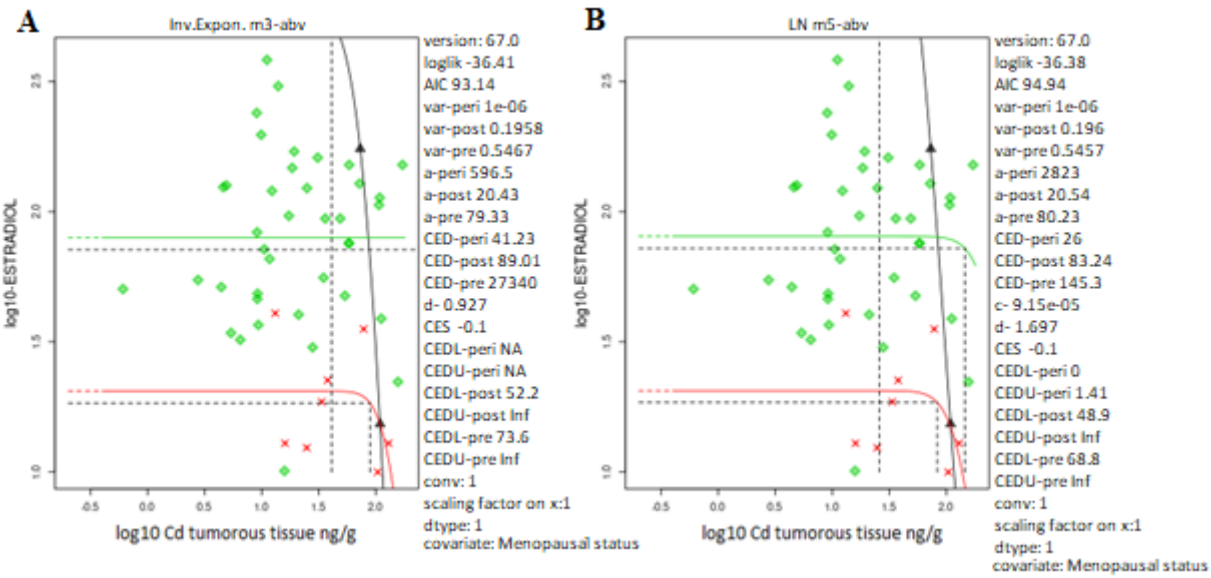

Figure 3. Demonstration of the dependence of the concentration of estradiol (*pg/ml*) in the blood on the concentration of *Cd* (*ng/g)* in tumorous breast tissue with the status of menopause as a variable. The x axis represents log10 of Cd levels in tumorous tissue while y axis represents log10 values of estrogen serum levels. Panels A and B represent different models of the dose-response dependence calculated in the PROAST software. The symbol Γ represents subjects with premenopausal status and x represents subjects with postmenopausal status.

Slika 3. Zavisnosti koncentracije estradiola (pg/ml) u krvi od koncentracije Cd (ng/g) u tumorskom tkivu dojke sa statusom menopauze kao promenljive. X-osa predstavlja logaritmovanu vrednost nivoa Cd u tumorskom tkivu, dok su na y-osi predstavljeni logaritmovani nivoi estrogena u serumu. Delovi slike A i B predstavljaju jednačine različitih modela doza-odgovor zavisnosti izračunati u softveru PROAST. Simbol Γ predstavlja ispitanice u predmenopauzalnom statusu, dok x predstavlja ispitanice u postmenopauzalnom statusu.

When Cd was measured in the surrounding healthy tissue, the obtained intervals were 0.000283-64.1, 0.151-2220, and 0.5-108 ng Cd/g tumor tissue in premenopause, perimenopause, and postmenopause subgroups, respectively. The obtained curves in PROAST software are presented in Figure 4.

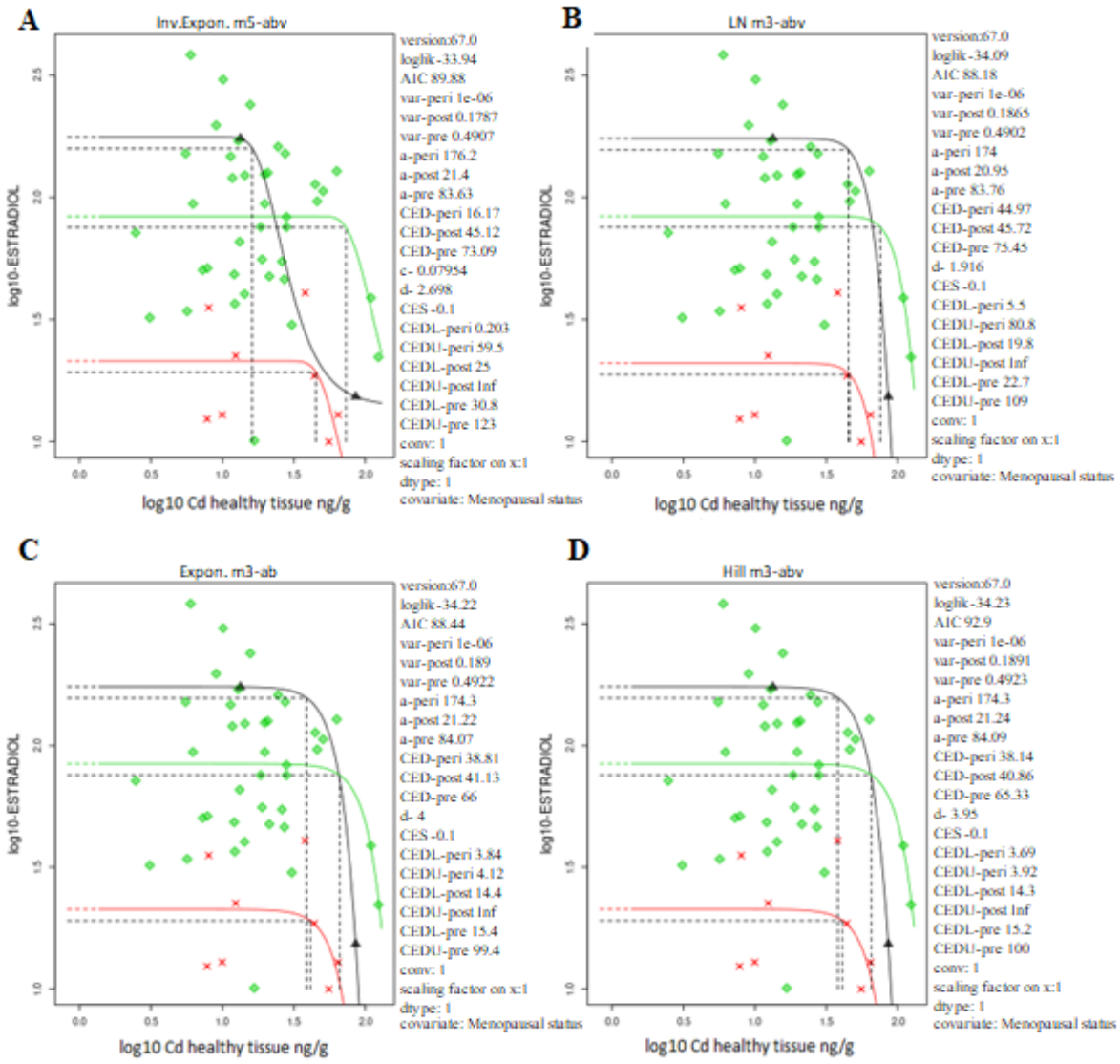

Figure 4 **The dependence of the blood estradiol level (*pg/ml*) on the concentration of *Cd* (*ng/g)* in the surrounding healthy breast tissue with the status of menopause as a variable. The x axis represents log10 of Cd levels in healthy tissue while y axis represents log10 values of estrogen serum levels. Panels A and B represents different models of the dose-response dependence calculated in the PROAST software. The symbol Γ represents subjects with premenopausal status and x represents subjects with postmenopausal status.**

Slika 4. **Zavisnost nivoa estradiola u krvi (pg/ml) od koncentracije Cd (ng/g) u okolnom zdravom tkivu dojke sa statusom menopauze kao promenljive. X-osa predstavlja logaritmovanu vrednost nivoa Cd u zdravom tkivu, dok su na y-osi predstavljeni logaritmovani nivoi estrogena u serumu. Delovi slike A i B predstavljaju jednačine različitih modela doza-odgovor zavisnosti izračunati u softveru PROAST. Simbol Γ predstavlja ispitanice u predmenopauzalnom statusu, dok x predstavlja ispitanice u postmenopauzalnom statusu.**

Discussion

In this paper, applying the BMD concept to data obtained from a human study, by processing continuous-type data, it was possible to calculate BMD, i.e. to obtain the relationship between the internal agent dose, Cd and continuous-type response or estradiol levels in the blood. The obtained results indicate a decrease in blood estradiol concentration with increasing Cd concentration in tumor/surrounding healthy breast tissue. In rare similar human studies involving premenopausal and postmenopausal women, a decrease in blood estradiol levels has been demonstrated, along with an increase in blood/urine Cd concentrations (23,24). The relationship between Cd and estradiol in these studies was assessed by multivariable linear regression, which differs from the approach examined in this study. Moreover, the mentioned studies took into account additional covariates: smoking status, age, body mass index, as well as alcohol consumption. Taking these factors into account could lead to a different BMDL/BMDU ratio calculated for the data considered in this study. The established relationship between the internal dose of the toxic agent and the observed response of the continuous type indicates the possibility of using PROAST software in the processing of data obtained from epidemiological studies in order to obtain adequate results. An important factor which significantly influenced the obtained values for BMD intervals was taking into account the presence of malignant/benign changes and the status of menopause as variable parameters.

Endocrine disruptors, such as Cd, pose a major threat to human health, especially if we consider the fact that people in real life are exposed to mixtures of different chemicals, rather than individual chemicals (16), on a daily basis via different routes of intake. What makes it very difficult to assess the risk of endocrine disruptors is that animal toxicological studies and consequent risk assessments generally study a single, isolated chemical, through a single route of administration, in a narrow, limited dosing regimen and in a very short period of time (16,25). Such a strictly controlled method of testing cannot adequately reflect real, everyday exposure to endocrine disruptors. Therefore, based on the results from such tests, adequate conclusions cannot always be drawn on the safety levels of exposure to certain chemicals. The solution may be in the design of tests that would be conducted over a long period of time using low doses of chemicals. This approach is of special importance in the investigations of endocrine disruptors, since it has been proven that very low doses of these substances can have a strong impact on the endocrine function of the organism, as well as that these chemicals can sometimes be characterized by a non-monotonic dose-response (4). Nonmonotonic dose-response curves (NMDRCs) are mathematically defined as a change in the sign of the slope of a dose-response relationship (i.e., from positive to negative or vice versa), over the range of doses (26); i.e. maximum responses may occur at very low and very high doses, or maximal response may occur at medium doses. This shows that the data obtained from experiments using high doses cannot be always used to predict what type of biological effect will be produced by low doses. In this paper, it has been shown that very low

internal doses of Cd can lead to hormonal changes, such as reduced estradiol concentration, which can further cause a wide range of changes in the body.

The ability of cadmium to act as a metalloestrogen can be an explanation for its role in breast cancer development as well. Epidemiological data indicate that risk factors for the development of breast cancer are numerous - gender, age, late first pregnancy, obesity, smoking. Risk factors also include the exposure to various environmental agents, including Cd (13). Studies have shown that this metal leads to hormonal imbalance, has a high affinity for the estrogen receptor, and can replace zinc from the part on the estrogen receptor (27). The results of our study support the evidence of hormonal imbalance, more specifically the effect of Cd on estradiol levels.

Rather low calculated BMD values indicate that even levels lower than 1 ng Cd/g breast tissue can lead to a 10% change in measured estrogen serum levels. However, it is important to highlight that some of the obtained intervals are rather wide, indicating a great level of uncertainty when interpreting calculated values. Furthermore, it is unclear whether the investigated 10% change in estradiol levels is of biological importance, especially when taking into account that estradiol levels in blood depend on many factors. However, the study implies the presence of dose-response behavior of EDCs and proposes the Benchmark method for processing data from epidemiological studies. Further research on this topic is necessary so that the extrapolation of data from animals to humans can be at least partly replaced by the BMD approach, thus facilitating risk assessment, especially for EDCs.

Conclusion

In this paper, cadmium has been linked to a decrease in estradiol levels in the blood and this link was shown to be dose-dependent, indicating the need for further investigation of the relationship between this endocrine disruptor and its effects on the hormonal balance in the body. Moreover, the results of this and rare similar studies are only the very beginning of discovering the possibilities of human data analysis using the proposed BMD approach.

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Nivoi kadmijuma u humanom tkivu dojke i nivoi estradiola u serumu: Postoji li veza?

Aleksandra Buha Djordjevic[1], Milena Anđelković[1], Elena Kačavenda[2], Dragana Javorac[1], Evica Antonijević-Miljaković[1], Đurđica Marić[1*], Katarina Baralić[1], Danijela Đukić-Ćosić[1] , Marijana Ćurčić[1], Biljana Antonijević[1], Zorica Bulat[1]

[1]Univerzitet u Beogradu – Farmaceutski fakultet, Katedra za toksikologiju „Akademik Danilo Soldatović", Vojvode Stepe 450, 11000 Beograd, Srbija

[2]Univerzitet u Beogradu– Farmaceutski fakultet, Centar za naučnoistraživački rad studenata, Vojvode Stepe 450, 11000 Beograd, Srbija

*Autor za korespondenciju: Đurđica Marić, e-mail: dmaric@pharmacy.bg.ac.rs

Kratak sadržaj

Kadmijum (Cd), jedan od najzastupljenijih zagađivača životne sredine, dokazan je endokrini ometač. Međutim, podaci o postojanju odnosa između doze Cd i odgovora-nivoa hormona nisu dovoljno istraženi, posebno podaci sakupljeni iz studija na ljudima. Stoga je cilj ove studije bio da se utvrdi mogućnost analize podataka dobijenih iz studije slučaja-kontrole kod pacijentkinja sa benignim/malignim tumorom dojke, primenom koncepta Benčmark doze (BMD). Prikupljeni podaci o nivoima Cd u tkivu dojke i serumskim nivoima estrogena obrađeni su u PROAST softveru uz korišćenje različitih varijabli. Ispitivan je odnos doza-odgovor između unutrašnje doze Cd (koncentracije u tkivu dojke) i estradiola u serumu i izračunati BMD intervali. Utvrđeno je postojanje odnosa između koncentracije Cd u tkivu dojke i nivoa estradiola u serumu koje ukazuje na niže nivoe estradiola u serumu kao posledica veće koncentracije Cd u tkivu dojke. Kao jedno od retkih istraživanja ovog tipa, dobijeni rezultati mogli bi predstavljati početak otkrivanja mogućnosti analize podataka prikupljenih u studijama na ljudima primenom BMD pristupa.

Ključne reči: endokrini ometači, kadmijum, BMD koncept, PROAST softver, humane studije