LIFE Project Number

LIFE10 ENV/SK/086

Short Report

LIFE+ PROJECT NAME: "The impact of geological environment on health status of residents of the Slovak Republic", **Acronym "GEOHEALTH"**

Chemical composition of groundwater/drinking water and mortality for oncological diseases, Slovak Republic

(Action A5: „Environmental analysis")

30/10/2015

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Abstract

The study deals with the analysis of relationship between chemical composition of the groundwater / drinking water and the data on mortality for oncological diseases (MOD) in the Slovak Republic. Primary data consist of the Slovak national database of groundwater analyses (20,339 chemical analyses, 34 chemical elements/compounds) and data on MOD (17 health indicators) collected for the 10 years period (1994-2003). The chemical and health data were unified in the same form and expressed as the mean values for each of 2,883 municipalities within the Slovak Republic for further analysis. Pearson and Spearman correlation as well as artificial neural network (ANN) method were used for analysis of relationship between chemical composition of groundwater/drinking water and MOD. The most significant chemical elements having influence on MOD relative mortality were identified together with their limit values (limit and optimal contents). Based on the results of calculations, made through the neural networks, the following eight chemical elements/parameters in the groundwater were defined as the most significant for MOD: Ca+Mg (mmol l^{-1}), Ca, Mg, TDS, Cl, HCO_3, SO_4 and NO_3.

The obtained results document the highest relationship between MOD and groundwater contents of Ca+Mg (mmol l^{-1}), Ca and Mg. We observe increased MOD with low (deficit) contents of these three parameters of groundwater/drinking water. Following limit values were set for the most significant groundwater chemicals/parameters: Ca+Mg 1.73 – 5.85 mmol l^{-1}, Ca 60.5 – 196.8 mg l^{-1} and Mg 25.6 – 35.8 mg l^{-1}. At these concentration ranges the mortality for oncological diseases in the Slovak Republic reaches the lowest levels. These limit values are about twice higher in comparison with the current Slovak valid guideline values for the drinking water.

Key words
Groundwater, calcium, magnesium, oncological mortality, neural network, Slovak Republic

1. INTRODUCTION

Oncological diseases (OD) represent one of the most common causes of death in the Slovak Republic as well as worldwide. In Slovakia, they represent about 25% of all causes of death per year. The rate of OD on mortality for world as well as Slovak population has continuously increasing trend (NHIC 2012; OECD 2013).

The main risk factors for OD include stress, genetic predisposition, regular smoking, excessive alcohol intake, unhealthy eating habits, obesity as well as environmental factors. From environmental factors the most significant is contamination or chemical composition of waters, soil and air.

The most important risk elements – carcinogens in the environment are potential toxic elements (mainly As, Sb, Pb, Hg, Cd etc.) and wide scale of various organic pollutants (US EPA 2014; IARC 2015).

The present article discusses the issue of the impact of chemical composition of groundwater/drinking water on the mortality on OD in Slovakia. Groundwater is the most important source of drinking water for most of population in Slovakia; accordingly, our work covers the source of drinking water for approximately 90 % of inhabitants (Klinda and Lieskovská 2010). Approximately 10 % of the Slovak population uses water from individual wells for drinking and cooking purposes. About 50 % of the population is supplied with drinking water from local water companies using local water resources with a low discharge (less than 10 l s^{-1}) captured and distributed to water supply pipes in the vicinity of settlements. Only in southern Slovakia (especially in the Quaternary sediments) is the population supplied from large water resources that are distributed across distances of 50-100 km. In this work we consider groundwater and drinking water as one. However, we are aware of some inaccuracies, which may limit our results. But the size of the dataset (more than 20,000 chemical analyses, more than 30 set chemicals), reduces uncertainties to a large extent. We were not able to assess the proportion of different bottled water that people consume.

Mortality and increased incidence of OD are ofter associated with excess or deficit of various chemical elements/compounds in drinking water. The most commonly cited examples of health problems caused by naturally occurring trace elements are studies dealing with the excess exposure to arsenic (Smedley and Kinniburgh 2002; Duker et al. 2005). Many authors associate increased incidence of oncological diseases with other toxic trace elements, mainly Cd, Cr, Pb, Sb etc. (Landrigan et al. 2000; Arisawa et al., 2001; Fryzek et al. 2001; Rapant et al., 2009; ATSDR 2012). Among macrocomponents of chemical composition of groundwater/drinking water, increased MOD is associated mainly to contents of nitrates (Morales-Suarez-Varela et al. 1995; Weyer et al. 2001; Ward et al. 2005).

The association between OD and deficit contents in drinking water is rarely studied. The main objects of concern are mainly deificit contents of Ca and Mg. Studies from Taiwan documented increased mortaliy for breast cancer, prostate cancer, cancer of stomach, colon and other organs in case of deficit Ca and Mg contents in drinking water (Yang et al. 1997; 1998; 1999a; b; c; 2000a; b). The impact of deficit Ca and Mg contents in geological environment (including groundwater and soils) on increased MOD was documented also in Slovakia (Rapant et al., 2014a).

The main objective of this paper is determination of the most significant and influential chemical elements/compounds/parameters in groundwater/drinking water in the Slovak Republic for MOD in relation to geological structure of the country. Several mathematical, statistical methods (Artificial Neural Network – ANN, linear and Spearman correlation) are used to link data on chemical composition of groundwater (environmental indicators) and data on various diagnoses for mortality on oncological diseases (health indicators) in Slovakia. For derivation of limit values of chemical elements in groundwater linked with the lowest level of MOD method of ANN is used in this study. ANN represents highly innovative method of statistical data elaboration in the field of medical geology for analysis of relationship between geological environment and health status of population. Such approach of data analysis through ANN was used e.g. in the work of Rapant et al (2015).

2. MATERIAL AND METHODS

2.1 Chemical composition of the groundwater

The main data source for groundwater chemical composition comes from national environmental-geochemical mapping, mainly the *Geochemical Atlas of the Groundwater* and environmental-geochemical maps of Slovak regions (Rapant et al. 1999; Vrana et al. 1997). These were complemented in particular by data from national groundwater monitoring, hydrogeochemical maps and other regional and local geochemical works (SHMU www.shmu.sk/en; Kordík et al. 2000). The database thus includes virtually all sources of groundwater used for bulk supply of drinking water. The total number of chemical analyses of groundwater was 20,339. These include chemical analyses of the water since 1991, when the modern environmental-geochemical mapping of the Slovak Republic was started *under the IGCP 360 Geochemical Correlation Programme* (Darnley et al. 1995). The density of the groundwater samples was about one sample per 2.5 sqkm. The contents of chemical elements/compounds analysed and measured in the environment, in our case groundwater, represent so called environmental indicators - EI (Rapant et al. 2010).

We transformed the data on water chemical composition (EI) into a form compatible with the data on OD to give one value for each administrative-territorial unit of the Slovak Republic (2,883 municipalities) as follows. A 1 km^2 pixel map of spatial distribution of elements and components was compiled from all the input data for the entire Slovak Republic using MapInfo Professional 9.0 software. For each pixel an average value of elemental concentration was computed based on inverse distance from the pixel centre to the nearest ten samples. The average value for chemicals for specific administration units (villages, districts and Slovak Republic) was then calculated as the arithmetic mean value of each pixel falling under the administration units. Pixels only partly within an administration unit were proportionally included in the calculation.

The set of evaluated chemicals in the groundwater (EI) with respective mean values for the Slovak Republic is reviewed in Table 1 (Rapant et al. 2014a).

Table 1 Characteristics of chemical composition of the groundwater in the Slovak Republic (mean values)

GROUNDWATER (n=20,339)												
pH	**TDS**	**COD_{Mn}**	**Ca+Mg**	**Li**	**Na**	**K**	**Ca**	**Mg**	**Sr**	**Fe**	**Mn**	**NH_4**
7.33	629.75	2.18	3.5	0.019	20.34	11.10	93.56	28.29	0.36	0.17	0.12	0.10
F	**Cl**	**SO_4**	**NO_2**	**NO_3**	**PO_4**	**HCO_3**	**SiO_2**	**Cr**	**Cu**	**Zn**	**As**	**Cd**
0.13	32.96	79.32	0.11	38.76	0.20	303.85	18.21	0.0013	0.0026	0.2673	0.0019	0.0010
Se	**Pb**	**Hg**	**Ba**	**Al**	**Sb**	**^{222}Rn**	**^{226}Ra**					
0.0010	0.0014	0.0001	0.0747	0.0297	0.0009	14.46	0.053					

Note: Data except of pH in mg l^{-1}, Ca+Mg in mmol l^{-1}, ^{222}Rn and ^{226}Ra in Bq.l^{-1}

The example of map interpretation of chemical composition of the groundwater for Slovak Republic is shown in Fig. 1 for Ca+Mg (mmol l^{-1}). Other chemicals are available online at www.geology.sk/geohealth.

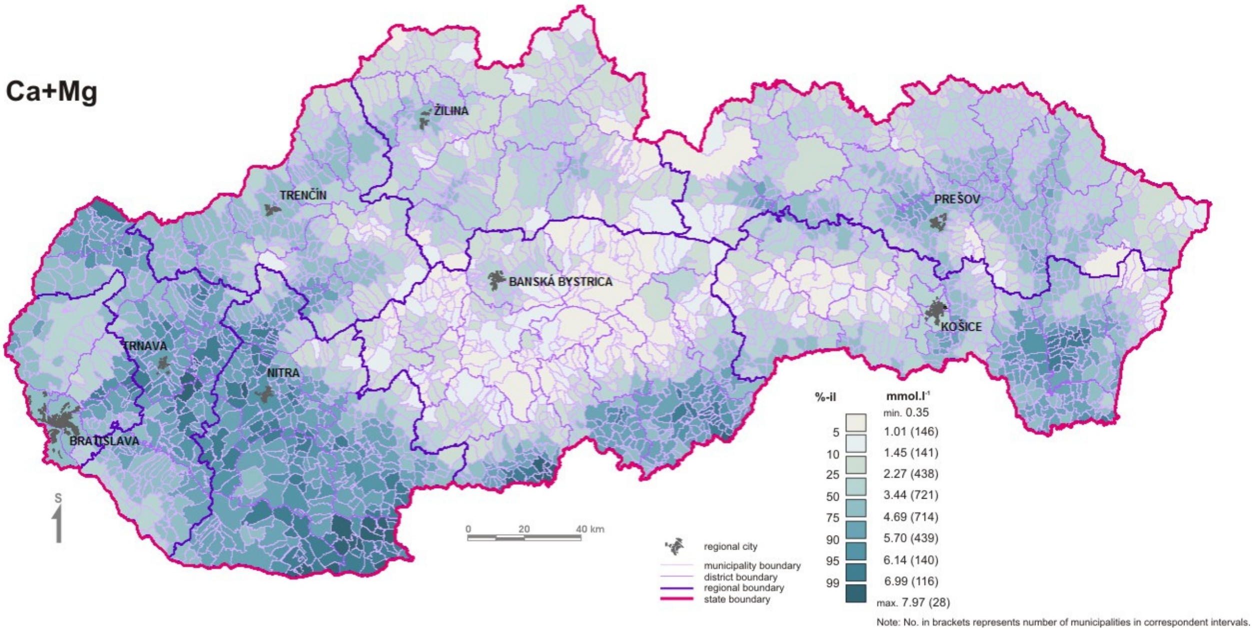

Fig. 1 Ca+Mg (mmol l^{-1}) distribution in the groundwater of the Slovak Republic at municipality level

2.2 Mortality of oncological diseases

In accordance with the international classification of diseases (ICD, 10th revision, www.who.int/classifications/icd/en/) OD include all malignant neoplasms (tumors and melanoma) – diagnoses C00-C97. These are oncological diseases of gastrointestinal, respiratory, urogenital system, blood, skin, musculoskeletal system etc. Total number of 536 specific diagnoses is included.

In our work, we use only data on mortality for oncological diseases. Certainly data on incidence of oncological diseases would be also appropriate, but unfortunately these data are not available.

The OD data used in this paper are characterized in the form of health indicators (HI) for selected oncological diagnoses. They represent average values for the period 1994–2003, and are thus the average values for each municipality of the Slovak Republic (2,883 municipalities). They were derived from the database of the Statistical Office of the Slovak Republic (www.statistics.sk).

For characteristic of MOD we have elaborated data for following group diagnoses: C00-97 (all malignant neoplasms), C15-26 (malignant neoplasms of gastrointestinal system), C16 (malignant neoplasms of stomach), C18-20 (malignant neoplasms of colon and rectum), C30-39 (malignant neoplasms of respiratory system), C50 (malignant neoplasms of breast), C64-68 (malignant neoplasms of urinary tract), C81-96 (malignant neoplasms of organs of hematopoiesis), C91-95 (all leukemia) and C00-D48 (neoplasms (malignant, benign together). Mortality for other diagnoses was for evaluated period in Slovak municipalities relatively rare, documented in less than about 70% of municipalities and therefore we did not include them into health data evaluation. Mortality for individual diagnoses were calculated in the form of health indicators, expressed as relative mortality, standardized mortaliy and potential years of lost life.

All health indicators were calculated as a cumulative function for the years 1994 to 2003, i.e. for a ten-year period, when all cases were summed up and all numbers of inhabitants were taken as persons-per-years (number of inhabitants as of December 31 in a pertinent year) for each territorial unit assessed. Calculation methodology and standardization of health indicators was carried out according to recommendations of WHO, Beaglehole et al. (1993); Jeníček (1995); Last (2001), Bencko et al (2003a; b).

The evaluated health indicators (HI) evaluated in our work are reviewed in tab. 2 with characteristics of methods of their calculation. We present map visualization of relative mortality for all OD (ReC00-C97) in the Slovak Republic in Fig. 2. Other evaluated health indicators are available online at www.geology.sk/geohealth.

Table 2 Characteristics of evaluated health indicators for oncological diseases

Health Indicator	Description of indicator	Method of calculation	Mean SR*
	Relative mortality for selected cause of death		
ReC00-C97	malignant neoplasms	100 000 x [No. of deaths for selected cause / number of inhabitants]	212.79
ReC15-C26	malignant neoplasms of gastrointestinal system		76.14
ReC16	malignant neoplasms of stomach		15.2
ReC18-C20	malignant neoplasms of colon and rectum		24.24
ReC30-C39	malignant neoplasms of respiratory system		45.19
ReC50	malignant neoplasms of breast		24.8
ReC64-C68	malignant neoplasms of urinary tract		11.25
ReC81-C96	malignant neoplasms of organs of hematopoiesis		13.28
ReC91-C95	all leukemia		6.20
ReC00-D48	neoplasms (malignant, benign together)		
	Standardized mortality for selected cause of death		
SMRC00-C97	malignant neoplasms	indirect age-standardized mortality rate of inhabitants to the Slovak standard (19 age groups)	100
SMRC15-C26	malignant neoplasms of gastrointestinal system		100
SMRC30-C39	malignant neoplasms of respiratory system		100
SMRC81-C96	malignant neoplasms of organs of hematopoiesis		100
	Potential years of lost life for selected cause of death		
PYLLC00-C97	malignant neoplasms	100, 000 x [the sum of the years of people up to the age of nearly 65 years (deaths at age between 1 to 64 years) / number of inhabitants]	1,005.20
PYLLC15-C26	malignant neoplasms of gastrointestinal system		242.26
PYLLC30-C39	malignant neoplasms of respiratory system		186.2

Note: Health indicators are classified according to International classification of diseases (ICD), 10th revision (http://www.who.int/classifications/icd/en/), * mean for the Slovak Republic for the period 1994 – 2003

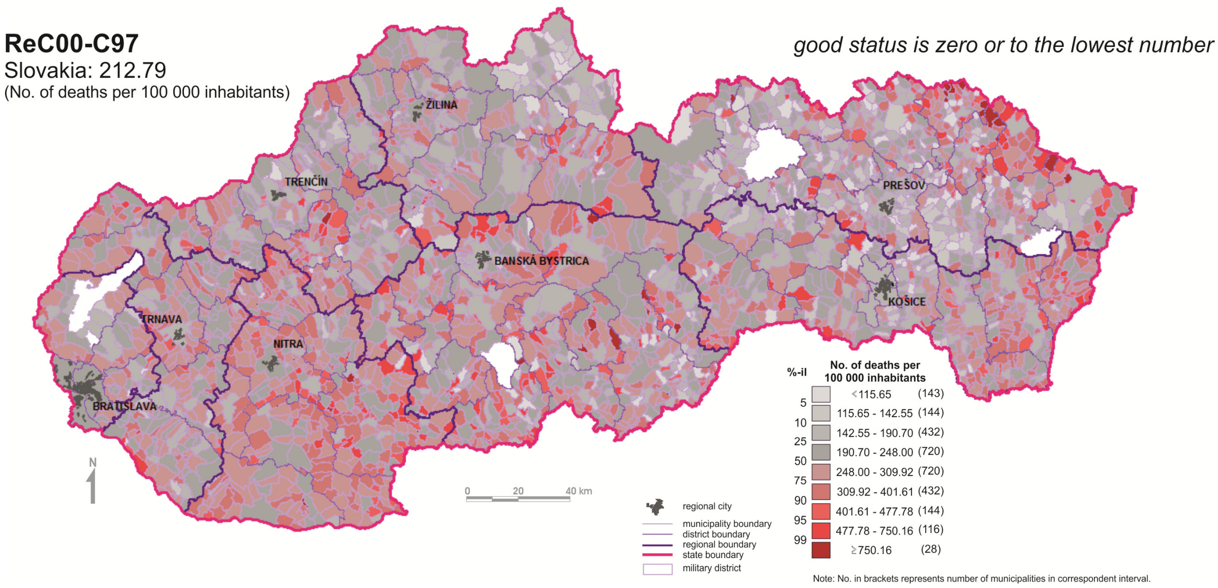

Fig 2 Relative mortality for oncological diseases (all malignant neoplasms) in the Slovak Republic

2.3 Division of environmental and health indicators according to geological structure

Geological structure of the Slovak Republic is rather complicated. It is characterized with alteration of rocks with various geneses, age and therefore various mineralogical and petrographic character and variable geochemical backgrounds (Kohút et al. 1999). It is reflected in variable chemical composition of groundwater/drinking water that we suppose can have different influence on OD occurrence.

The territory of the Slovak Republic has been categorized into eight units Rapant et al. (2014a) as follows:

1. Paleozoic: mostly metasediments, metavolcanics,
2. Crystalline: mostly granites, gneisses and migmatites,
3. Carbonatic Mesozoic and basal Paleogene: mainly limestones, dolomites, carboniferous conglomerates,
4. Carbonatic-silicate Mesozoic and Paleogene: mainly marl, marly limestones, dolomites, sandstones and shales,
5. Paleogene Flysch: mainly sandstones, shales, claystones,
6. Neovolcanic rocks: mainly andesites, basalts and their volcanoclastics,
7. Neogene: mainly clays, claystones, conglomerates, sands, gravels,
8. Quaternary: mainly gravel, sand, clay, rock fragments.

Geological units were from the point of view of health indicators ordered (from the most favourable to the most unfavourable) as follows: Paleogene Flysch, Carbonatic-silicate Mesozoic and Carbonatic Mesozoic and basal Paleogene, Neogene, Quaternary, Crystalline, Paleozoic, Neovolcanic rocks. Generally, the most favourable rock environments for human health were defined carbonatic rocks and the most unfavourable silicate rocks.

Subsequently, we have divided our data on chemical composition of groundwater – environmental indicators (EI) and indicators of mortality for oncological diseases – health indicators (HI) into partial datasets according to defined geological units.

2.4 Statistical analysis

Statistical analysis of relationship between EI and HI was based on standard methods of data correlation, including linear (Pearson) and non parametric (Spearman) correlation. Statistical significance of calculated correlation coefficients were evaluated and characterized as follows: level of significance P = 0.05 – verified dependence (+), P = 0.01 – high dependence (++), P = 0.001 – very high dependence (+++).

2.5 Neural network analysis

Investigation of relationships between two different variables is the domain of statistics. However, the selection of appropriate statistical methods to link two databases requires a correct choice to measure relevant interdependency and relationships. Correlation coefficients express the intensity of stochastic dependence between two variables, demonstrating dependant relationships between measured attributes. Classical Pearson correlation coefficients express the degree of simple linear dependence of two variables. Spearman correlation coefficients are a measure of monotonic dependence. Our data were not normally distributed, but unevenly distributed, and often spoiled by errors, being incomplete with exhibit high variability. The uncertainties of the health indicators data that could modify our results are mainly associated with the complication of statistical reports when in the cases of more diagnoses as the cause of death, the diagnoses ranker in the first place is usually selected and recorded by responsible registrar. However, the selected diagnosis may not always be the main cause of death. In case of oncological patient who was treated with chemotherapeutic agents, is not usually ranked in the first place the diagnosis mortality for oncological disease but e.g. mortality for renal failure. The uncertainties described above could affect our results.

Our data have all attributes of daily life. It would be incorrect to assume the existence of a functional relationship. Classical methods of regression analysis may not explore the situation fully in its complexity and may lead to wrong conclusions. Complex situations merit complex analytical approaches. Therefore, for the analysis of relationships between chemical composition of the groundwater and mortality on OD we used artificial intelligence - artificial neural networks (ANN).

ANN one of the most widely used modeling techniques in many areas of research. A detailed overview of the history of origin and development of neural networks is given in Kriesel (2007).The most significant feature of neural networks is that they are universal function approximator. This universality of neural networks for estimation has been demonstrated mathematically (Hornik et al. 1989). The advantage of artificial neural networks consists of the depiction of complex nonlinear relations. Their disadvantage is that we do not necessarily know the mechanism of inter-action between various factors included in the output parameter. The equivalent of regression equation known from regression analysis is absenting.

Each of practiced networks represents a unique result, which is uniquely defined only by the network topology and vector of synaptic weights. The global sensitivity analysis of neural networks, however, provides knowledge about the importance of particular input variables in practiced network. Kovalishyn et al. (1998) and Zurada et al. (1995) submitted several methods of measuring of the sensitivity of artificial neural network input variables. Gevrey et al. (2003) presented and compared seven methods of measuring the importance of input variables. When the sensitivity coefficient s_r for a given input variable is less than one, we can assume that its exclusion will not lower, but rather, it will increase the network efficiency (StatSoft 1999) and vice versa.

The quality of the neural network can be evaluated using several metrics. The correlation coefficient R is the most widely used, determining the relationship between outputs and objectives, i.e. estimated values and the values of output variable. A value of 1 means close dependence while 0 means no dependence.

By applying artificial neural networks, the size of effects of elements in the water on OD mortality were determined, together with the limit values (maximum allowable or minimal required) and optimum ranges for their groundwater concentrations. The order of effects of chemicals in groundwater on OD was determined from the value of the sensitivity coefficient s_r. Mortality on OD is influenced by those chemical elements in the water for which the average sensitivity coefficient is greater than one.

In order to identify the important parameters of the chemical composition of the groundwater, 200 networks were created. Selected number 200 networks has proven to be fully satisfactory, because for next networks the value of correlation coefficient do not increase, but stagnated or declined.

Despite satisfactory performance (reliability) of the network, the impact of various environmental indicators was relatively low and was different for each created network. Therefore, the most influential chemicals were ordered based on median values of s_r of 50 the best networks with the highest correlation coefficient. This approach is well recognised, e.g. by Opitz&Shavlik (1996); Han et al. (2011); Kourentzes et al. (2014) and Rapant et al (2015). Based on median value (from 50 the best networks) of sensitivity rate (s_r) calculated for each chemical element we assess the influence of the chemical element on MOD. The influence increases with the increase of s_r value. Chemical elements with s_r<1 are defined as not influential on MOD. Statistical significance of calculated coefficients s_r is characterized by coefficient of determination R^2. Statistical significance of s_r increases with the increase of R^2. The results of calculations of ANN necessary for determination of shape of dependence between EI and HI were verified through method of decils. The approach was as follows. The range of concentrations of each element evaluated in groundwater was divided into deciles. We found centroid of points of which x-coordinate belonged in individual deciles. Subsequently we found the second degree polynomial that ran a straight line through the centre of deciles 2 to 9. The conformity for the very influential elements was excellent. In the decline elements influence the consensus exists, but the similarity decreases.

ANN method is very usefull also for derivation of limit values for chemical elements in groundwater in relation to level of MOD, it means to derive content levels for evaluated chemicals at which the mortality for OD is the lowest. We define two types of limit values, including limit (critical) values and optimal limit values. Limit (critical) contents represent intersection of model curve of chemical content with average value for health indicator for MOD. Optimal limit contents represent in case of straight line shape of statistical dependence between EI and HI intersection with 40% value of health indicator and in case of curve shape they represent intersection with average value for HI ± standard deviation of HI. In case that model curve of chemical content does not intersect average value of HI we were not able to determine the limit values. The average value for HI for evaluated oncological diseases we use empirical Bayesian balanced average. In spatial analysis of attributes measured for spatial units it is often necessary to transform extensive variable (e.g. No. of cases of diseases, No. of deaths) into intensive variable that take into consideration size of population. Number of cases (disease incidence, deaths) is usually divided by number of inhabitants to “normalize” evaluated data. In this way unequal reliability caused by different number of inhabitants in spatial units (this case municipalities) are eliminated. This problem is serious mainly for municipalities with low number of inhabitants. Calculated rates (but also age standardized rates) for municipalities with low number of inhabitants can be in case of some municipalities too high but also with high standard error. Because variability of local rates depends on number of inhabitants, some rates are estimated better compared to other. Rates in municipalities with low number of inhabitants fluctuate and vary to a higher extent in comparison with rates in municipalities with higher number of inhabitants. One of method that reduces “noise” in rates associated to geographic regions is spatial smoothing. Smoothing of rates is approach used to statistically improve risk estimates within single spatial unit, based on information included in other spatial units. Therefore in our subsequent calculations we use empirical Bayesian balanced values instead of real values of health indicators (Chaikaew et al., 2009; Chen et al., 2008).

3. RESULTS

Mean values of health indicators for MOD in two the most favourable geological units (Paleogene Flysch, Carbonatic-silicate Mesozoic and Paleogene) and two the most unfavourable geological units (Neovolcanic rocks and Paleozoic) in relation to health indicators are rewieved in tab. 3 together with mean values for the Slovak republic as well as two selected districts of SR. Krupina district is entirely built up by rock environment of Neovolcanics (in terms of HI, it is the least favourable geological environment) and resident population is supplied only by drinking water from local groundwater sources of this district. Bardejov district is entirely built up by rock environment of Flysch Paleogene (in terms of HI it is the most favourable geological environment) and resident population is supplied from local groundwater sources of this district. Mean contents of 10 the most influential chemical elements/parameters on mortality for oncological diseases according to ANN together with two typical potentially toxic elements (PTE) – arsenic and lead are shown for above mentioned units in tab. 4.

Selected results of linear and Spearman correlations between Ei and HI for oncological diseases for geological environment as a whole are summarized in tab. 5.

In tab. 6 and 7 we summarize the results of calculations of ANN. Tab. 6 provide a review of the results of sensitivity coefficients for the most influential chemical elements/parameters in groundwater and evaluated health indicators for MOD, together with order of influence for single elements. In tab. 7 the results of calculations of ANN for relative mortality on oncological diseases (expressed as ReC00-C97) are shown including derived limit values for the most influential chemical elements/parameters in groundwater. The approach of definition of limit values for the influential elements in relation to ReC00-C97 is documented in graphic form on Fig. 3.

Table 3 Mean values for health indicators of oncological diseases in selected areas of the Slovak Republic

Geological unit/district	**1**	**6**	**4**	**5**	**Krupina**	**Bardejov**	**SR**
Health indicator	n = 100	n = 309	n = 154	n = 727	n = 36	n = 86	
ReC00-C97	209.46	236.28	195.96	177.99	243.23	175.32	212.79
ReC15-C26	72.77	85.30	71.04	62.64	95.32	61.70	76.14
ReC16	13.93	17.57	15.83	15.30	15.23	13.52	15.2
ReC18-C20	25.25	29.33	22.05	17.89	34.51	17.56	24.24
ReC30-C39	43.61	49.60	40.16	38.51	49.19	33.47	45.19
ReC50	25.75	25.67	24.80	18.62	30.58	14.27	24.8
ReC64-C68	11.31	11.62	10.73	9.60	11.53	10.79	11.25
ReC81-C96	13.34	15.46	12.60	11.71	14.66	13.70	13.28
ReC91-C95	6.20	7.69	5.87	5.23	9.11	4.69	6.2
ReC00-D48	210.48	238.21	195.68	179.24	243.23	176.63	213.62
SMRC00-C97	101.78	102.91	95.18	95.03	99.73	91.20	100
SMRC15-C26	98.90	102.20	97.86	94.11	108.40	91.56	100
SMRC30-C39	101.43	102.36	92.00	97.37	95.20	82.51	100
SMRC81-C96	103.39	107.42	97.29	98.12	91.69	111.13	100
PYLLC00-C97	1,053.42	1,097.32	921.47	909.88	1,121.60	808.81	1,005.2
PYLLC15-C26	260.15	268.13	261.11	231.28	324.48	191.11	242.26
PYLLC30-C39	191.13	217.41	169.69	170.91	268.28	143.46	186.2

Note: 1 – Paleozoic, 4 – Carbonatic-silicate Mesozoic and Paleogene, 5 – Paleogene Flysch, 6 – Neovolcanic rocks, SR – mean for the Slovak Republic, n = number of municipalities in evaluated geological unit/district

4. DISCUSSION

Based on comparison of mortality for oncological diseases (tab. 3) in single geological units and two selected districts there are no significant differences documented. We can state that carbonatic geological units (Paleogene and Mesozoic sediments) are characterized with significantly lower levels of practically all health indicators for oncological diseases. For example summary health indicator ReC00-C97 for all malignant neoplasms is in the most favourable geological unit (unit 5, Flysch Paleogene=177.94) about 33% lower compared to the most unfavourable geological unit (unit 6, Neovolcanic rocks=236.8). Similar trend is evident although not such marked also in case of other evaluated health indicators of OD. Even more significant difference between health indicators of mortality for oncological diseases is in case of two selected districts supplied by drinking water from local groundwater sources within the districts. The difference between level of ReC00-C97 in both districts is nearly 39% and in case of some other specific health indicators (ReC18-C20, Rec50) more than 100%. Both districts can be characterized as rural areas with similar socioeconomic character (Rapant et al., 2014a). More significant difference in levels of health indicators of mortality for oncological diseases between them compared to differences documented between single geological units we attribute to fact, that silicate rocks (Crystalline, Paleozoic, Neovolcanics) are aquiferous to a lesser extent and resident population is often supplied by drinking water from distant dominantly carbonatic units which are in conditions of the Slovak Republic much more aquiferous. Discussed differences between health indicators of OD between carbonatic and silicate geological units are attributed mainly to different levels of Ca, Mg contents and water “hardness” (Ca+Mg). These chemical elements/parameters are significantly higher in carbonatic geological units (tab. 4). We did not observe significant differences between contents of other chemicals/compunds/parameters within evaluated geological units.

Table 4 Mean values for selected chemical elements/parameters in groundwater in selected areas of the Slovak Republic

Geological unit/district	**1**	**6**	**4**	**5**	**Krupina**	**Bardejov**	**SR**
element	n = 100	n = 309	n = 154	n = 727	n = 36	n = 86	
TDS [$mg.l^{-1}$]	302.27	439.73	586.79	524.64	362.34	484.79	629.75
Ca+Mg [$mmol.l^{-1}$]	1.68	2.11	3.45	3.02	1.58	2.75	3.50
Na [$mg.l^{-1}$]	8.53	16.09	12.79	12.74	13.12	10.34	20.34
Ca [$mg.l^{-1}$]	43.15	56.13	99.86	88.53	42.01	80.75	93.56
Mg [$mg.l^{-1}$]	14.70	17.14	23.27	19.67	12.96	17.98	28.29
Cl [$mg.l^{-1}$]	13.18	21.66	21.24	17.14	13.81	13.77	32.96
SO_4 [$mg.l^{-1}$]	45.65	49.70	65.38	62.72	22.42	44.96	79.32
NO_3 [$mg.l^{-1}$]	18.02	26.44	21.72	16.19	16.49	14.84	38.76
HCO_3 [$mg.l^{-1}$]	138.29	191.51	323.63	287.65	174.23	282.12	303.85
As [$mg.l^{-1}$]	0.00863	0.00241	0.00135	0.00079	0.0018	0.00114	0.00192
Se [$mg.l^{-1}$]	0.00063	0.00086	0.00074	0.00068	0.0006	0.00068	0.00097
Pb [$mg.l^{-1}$]	0.00142	0.00134	0.00121	0.00125	0.0018	0.00094	0.00136

Note:
1 – Paleozoic, 4 – Carbonatic-silicate Mesozoic and Paleogene, 5 – Paleogene Flysch, 6 – Neovolcanic rocks, SR – mean for the Slovak Republic, n = number of municipalities in evaluated geological unit/district

From the results of linear and Spearman correlations (tab. 5) cannot be made practically any significant conclusions. Our variables (EI and HI) do not have normal distribution and analysed dependences are generally not linear, often even monotonous. That is why we do not find achieved results probatory. Correlation coefficients are in both correlations very low and they range in more than 90% between levels $\pm < 0.1$. However, very important fact is that correlation coefficients for Ca, Mg a water hardness and evaluated health indicators of mortality for oncological diseases show in all cases (also in case of other HI than reviewed in tab. 5) negative values and dominantly at levels with statistical high significance. This fact indicates relationship between increased mortality for OD at low (deficit) Ca and Mg contents and water hardness of groundwater/drinking water in the Slovak Republic.

Table 5 Pearson and Spearman correlation between EI and MOD for geological environment in the Slovak Republic

	Linear correlation			Spearman correlation		
Parameter	**r**	**P**	**significance**	**R**	**P**	**significance**
Ca & ReC00-C97	-0.082	0.001	++	-0.132	0.000	+++
Mg & ReC00-C97	-0.079	0.001	++	-0.128	0.000	+++
Ca+Mg & ReC00-C97	-0.085	0.000	+++	-0.134	0.000	+++
NO_3- & ReC00-C97	-0.050	0.043	+	-0.112	0.000	+++
As & ReC00-C97	-0.001	0.960	-	0.080	0.001	++
Pb & ReC00-C97	-0.045	0.063	-	-0.040	0.101	-
Ca & SMRC00-C97	-0.041	0.094	-	-0.043	0.082	-
Mg & SMRC00-C97	-0.013	0.603	-	-0.022	0.370	-
Ca+Mg & SMRC00-C97	-0.033	0.175	-	-0.038	0.119	-
NO_3^- & SMRC00-C97	0.012	0.618	-	-0.004	0.861	-
As & SMRC00-C97	0.006	0.798	-	0.086	0.000	+++
Pb & SMRC00-C97	-0.037	0.132	-	-0.035	0.151	-
Ca & PYLLC00-C97	-0.086	0.000	+++	-0.097	0.000	+++
Mg & PYLLC00-C97	-0.054	0.028	+	-0.081	0.001	+++
Ca+Mg & PYLLC00-C97	-0.079	0.001	++	-0.095	0.000	+++
NO_3 & PYLLC00-C97	-0.028	0.258	-	-0.042	0.086	-
As & PYLLC00-C97	-0.001	0.971	-	0.106	0.000	+++
Pb & PYLLC00-C97	-0.019	0.429	-	0.003	0.892	-

Note: r – Pearson correlation coefficient, R – Spearman correlation coefficient, P – value; level of significance = 0.05 – verified dependence (+), P = 0.01 – high dependence (++), P = 0.001 – very high dependence (+++)

The calculations of ANN (tab. 6) result in identification of the most influential elements/compunds/parameters of the chemical composition of groundwater/drinking water and health indicators of OD as follows: Ca+Mg, Ca, TDS, HCO_3, Mg, SO_4, Cl, NO_3. These 8 elements are found in the group of the first 10 most influential EI in case of all evaluated health indicators of MOD. Other EI - Na, SiO_2, Mn and Se were ranked between 10 the most influential parameters only in case of some evaluated health indicators of MOD. Their averaged influence (xP) on health indicators of MOD is relatively low, more than 10 and their s_r values are the lowest. There can be clearly identified three groups of chemical elements/compounds/parameters among the most influential EI on MOD. The first group are Ca, Mg and Ca+Mg. We attribute to these three EI the highest influence on MOD. They show the highest levels of s_r. The second group of EI (TDS and HCO_3) is considered to have only stochastic relationship (influence) to MOD. It is given by the fact that chemical composition of groundwater in the Slovak Republic is mainly of Ca-Mg-HCO_3 character. TDS and HCO_3 can be generally seen as indicators of Ca and Mg groundwater content. HCO_3 is the commonest anion in groundwater in the Slovak Republic and its concentrations is associated mainly with Ca and Mg cations (mineralization due to dissolution of carbonates). Similarly TDS values depend mainy on the Ca and Mg contents (the most represented cations) and HCO_3 (the most represented anion) content in groundwater of the Slovak Republic (Rapant et al., 1996). The third group of the influential elements represent SO_4, Cl and NO_3. These three parameters are typical example of anthropogenic groundwater contamination in the Slovak Republic. Their influence is, based on levels of sensitivity coefficients s_r, markedly lower (mainly about one order) compared to the influence of Ca, Mg and Ca+Mg.

Table 6 Coefficients of sensitivity and order of influence for 10 the most influential elements/parameters in groundwater in relation to health indicators of oncological diseases according to calculations through ANN

element	ReC00-C97		ReC15-C26		ReC18-C20		ReC30-C39		ReC91-C95		SMRC00-C97		SMRC15-C26		PYLLC00-C97		*xP*
	s_r	P	s_r	P	s_r	P	s_r	P	s_r	P	s_r	P	s_r	P	s_r	P	
Ca+Mg	1.0269	3	1.0560	1	1.0060	3	1.1321	1	1.0863	1	1.0025	3	1.0329	1	1.0443	1	*1.8*
Ca	1.0132	4	1.0318	4	1.0079	2	1.0626	2	1.0552	2	1.0029	2	1.0248	3	1.0084	3	*2.8*
TDS	1.0740	1	1.0354	2	1.0258	1	1.0088	5	1.0133	4	1.0008	8	1.0259	2	1.0155	2	*3.1*
HCO_3	1.0338	2	1.0167	5	1.0050	4	1.0100	4	1.0037	5	1.0018	4	1.0212	4	1.0023	5	*4.1*
Mg	1.0047	8	1.0322	3	1.0011	8	1.0390	3	1.0327	3	1.0044	1	1.0205	5	1.0041	4	*4.4*
SO_4	1.0092	5	1.0065	6	1.0037	5	1.0022	7	1.0003	11	1.0006	10	1.0091	6	1.0008	10	*7.5*
Cl	1.0067	6	1.0035	7	1.0007	10	1.0027	6	1.0002	16	1.0014	5	1.0017	8	1.0016	6	*8*
NO_3	1.0064	7	1.0034	8	1.0007	11	1.0011	8	1.0003	13	1.0005	11	1.0023	7	1.0010	8	*9.1*
Na	1.0032	9	1.0016	11	1.0002	14	1.0005	10	1.0002	18	1.0004	12	1.0015	9	1.0012	7	*11.3*
SiO_2	1.0010	12	1.0019	10	1.0004	12	1.0001	20	1.0006	7	1.0009	6	1.0003	12	1.0004	13	*11.5*
Mn	1.0000	20	1.0023	9	0.9999	32	1.0000	25	1.0004	10	1.0008	7	1.0001	15	1.0010	9	*15.9*
Se	1.0014	10	1.0005	16	1.0000	22	1.0001	21	1.0002	19	1.0003	13	1.0000	28	1.0000	27	*19.5*

Note : s_r – coefficient of sensitivity, P – order of influence, xP – arithmetic mean of order of influence for all evaluated health indicators

Table 7 Results of calculations of ANN and derived limit values for 10 the most influential chemical elements/parameters in groundwater of the Slovak Republic in relation to ReC00-C97

Order	Parameter	s_r	R^2	Limit content		Optimal content		Evaluated function of dependence	Contents*	
				LL	UL	LL	UL		min	max
1	**MIN**	1.074	0.851	570.46	836.73	not defined	not defined	convex parabola	87.30	1412.30
2	**HCO_3**	1.034	0.850	not defined	not defined	not defined	not defined	convex parabola	16.57	592.05
3	**Ca+Mg**	1.027	0.895	1.73	5.85	2.23	5.34	convex parabola	0.35	7.97
4	**Ca**	1.013	0.987	60.56	196.84	91.18	166.21	convex parabola	9.83	201.01
5	**SO_4**	1.009	0.903	not defined	not defined	not defined	not defined	convex parabola	9.38	319.50
6	**Cl**	1.007	0.783	not defined	125.90	17.00	70.12	convex parabola	1.23	143.74
7	**NO_3**	1.006	0.582	not defined	146.58	5.50	80.24	convex parabola	1.33	227.09
8	**Mg**	1.005	0.856	25.66	35.83	not defined	not defined	convex parabola	2.45	97.75
9	**Na**	1.003	0.549	not defined	not defined	not defined	not defined	convex parabola	0.71	119.69
10	**Se**	1.001	0.978	not defined	0.0009	not defined	not defined	straight line	0.00	0.01

Note: s_r – coefficient of sensitivity, R^2 – coefficient of determination, LL – lower limit, UL – upper limit, *minimum – maximum contents of chemical elements/parameters in groundwater of the Slovak Republic (units in mg l^{-1}, Ca+Mg in mmol l^{-1})

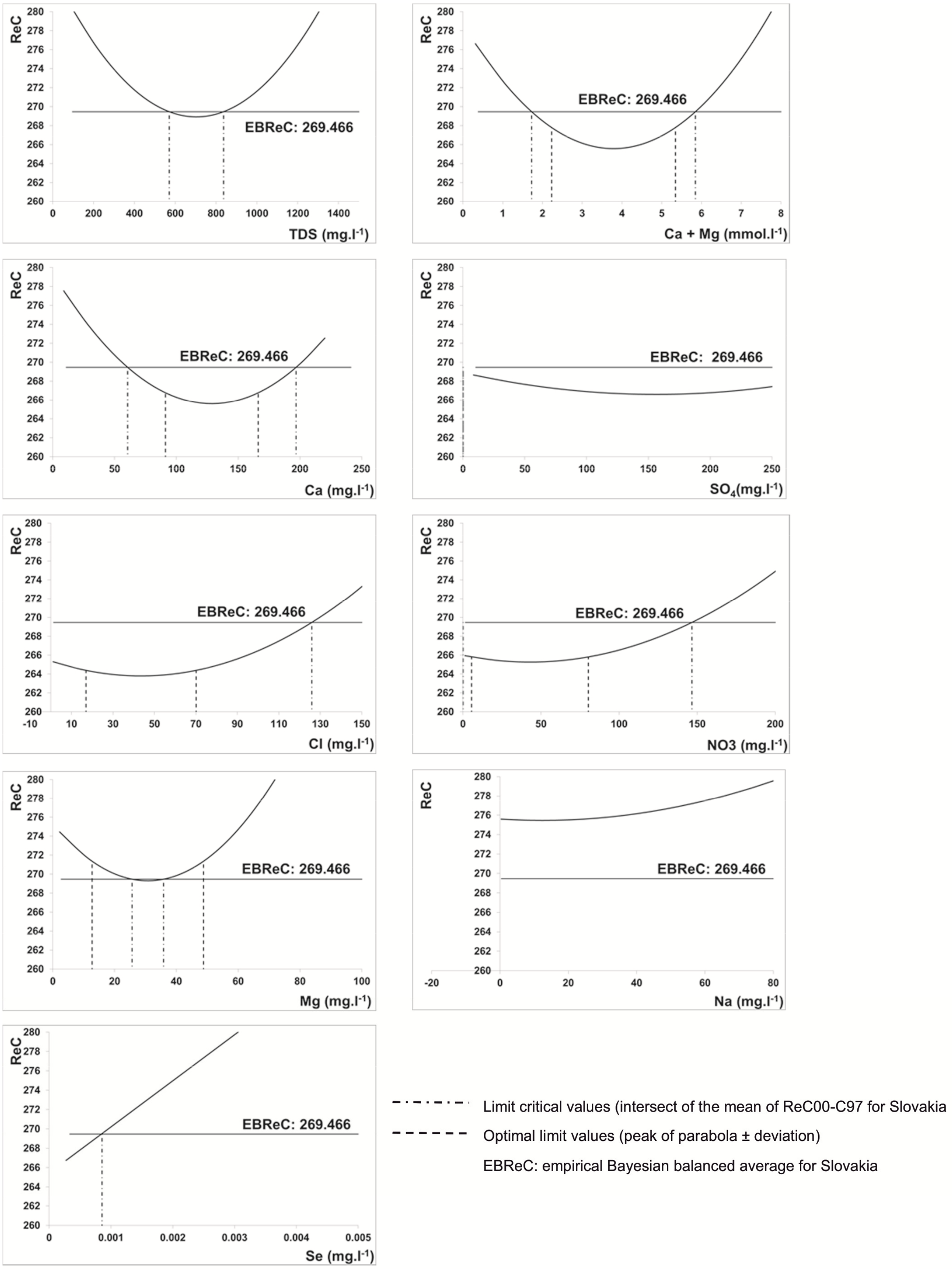

Fig. 3 Definition of limit values for the influential elements on ReC00-C97

In case of these three parameters the important fact is that their increased contents in groundwater of the Slovak Republic due to anthropogenic contamination are accompanied mainly by increased contents of Ca and Mg, which were documented in this study as the most influential parameters in relation to mortality on OD.

The results of ANN calculations for ReC00-C97 are reviewed in tab. 7 together with calculated limit values. As influential elements ($s_r > 1$) were documented also following parameters: PO_4, SiO_2, F, Ba, ^{222}Rn, COD_{Mn}, K, NO_2, NH_4, Mn, As, Al. As non influential ($s_r < 1$) were characterized following elements/parameters: Pb, Zn, Cr, Sb, Hg, ^{226}Ra, Cd, Cu, Fe and pH. The results of ANN calculations for other evaluated health indicators of MOD are available on the website www.geology.sk/geohealth. Very interesting our finding that practically all potentially toxic elements were found as non influential, in case of arsenic with negligible influence ($s_r < 1.0001$). This fact is in accordance with current knowledge on low impact of potentially toxic elements on human health of resident population living in the contaminated historical mining areas in the Slovak Republic (Rapant et al., 2014b).

Quality of ANN networks calculated to determine influential elements/parameters based on correlation coefficients (R) between measured values and balanced values through ANN is average (R=0.13803), but their statistical dependence is significant, at level of significance 0.0001. It results from the wide range of values of health indicator ReC00-C97. A half of 200 networks is characterized by the correlation coefficient higher than 0.08344, it means median of correlation coefficients of created networks is 0.08344. For completeness we add that 133 networks showed correlation coefficients between measured and balanced values through ANN at level of statistical significance 0.05. The significance of correlation coefficients, although relatively low values, is caused by a big number of measurements (2,883). Quality of networks describing dependence of health indicator ReC00-C97 on environmental indicators is also statistically highly significant (tab. 8).

Idea of data buffering through ANN consists in fact that ANN maintain average of values but decrease the range even about an order. This led to succesfull use of regression analysis to describe analysed dependence (relationship). Coefficients of determination (R^2) measuring relevance of shape of regression curve ranged between 0.5189 - 0.9869. Eight from ten coefficients of determination were higher than 0.78. We can conclude that coefficients of determination are high and all of them are statistically significant. The results of testing of model relevance generally confirmed relevance of selected regression curve. These facts warranted us to use achieved regression curves to define limit values for evaluated environmental indicators.

Table 8 Values of correlation coefficients between balanced values through ANN and values of regress parabola (in case of Se straight line)

Parameter	TDS	HCO_3	Ca+Mg	Ca	SO_4	Cl	NO_3	Mg	Na	Se
R of median of networks	0.0825	0.0799	0.0772	0.0507	0.0579	0.0458	0.0926	0.1176	0.0231	0.0315

As we have already mentioned, from the point of view of mortality for OD we found contents of Ca and Mg and levels of water hardness (Ca+Mg) as the most influential. In all three cases we were able to derive limit values including low and upper levels. It means that for these parameters favourable content levels exist, not too low either too high, at which mortality for OD is the lowest possible. In tab. 9 we provide a review of our derived limit values for the most influential elemenst on MOD compared to current valid limit values set by

Slovak legislative for drinking water. In case of the most influential elements (Ca, Mg, Ca+Mg) are our derived limit values significantly higher (about 2 times compared to Slovak guideline for drinking water. We were not able to define limit values for HCO_3 (curve did not intersect average value EBReC). In case of TDS we can conclude that limit values are fundamentally in accordance with Slovak guideline for drinking water. For NO_3 we have derived only upper limit (critical) level (146.58 $mg.l^{-1}$) and optimal limit contents in range 5.5 - 80.24 $mg.l^{-1}$.

Table 9 Comparison of limit values of Slovak guideline for drinking water (Anon 2010) with our derived limit values

parameter	unit	limit value according to Anon 2010	limit contents*		Optimal contents*	
			LL	UL	LL	UL
TDS	$mg.l^{-1}$	1 000[a]	570.46	836.73	-	-
HCO_3	$mg.l^{-1}$		-	-	-	-
Ca+Mg	$mmol.l^{-1}$	1.1 - 5.0[b]	1.73	5.85	2.23	5.34
Ca	$mg.l^{-1}$	> 30 [b]	60.56	196.84	91.18	166.21
SO_4	$mg.l^{-1}$	250 [a]	-	-	-	-
Cl	$mg.l^{-1}$	250 [a]	-	125.90	17.00	70.12
NO_3	$mg.l^{-1}$	50 [a]	-	146.58	5.50	80.24
Mg	$mg.l^{-1}$	10 - 30 [b]	25.66	35.83	-	-
Na	$mg.l^{-1}$	200 [a]	-	-	-	-
Se	$mg.l^{-1}$	0.01[c]	-	0.0009	-	-

Note: *our derived limit and optimal contents, [a]upper value, [b]recommended value, [c]the highest upper value, LL – lower level, HH – upper level

Upper limit levels are significantly higher compared to Slovak guideline value for drinking water (50 mg l^{-1}). The relationship between MOD and NO_3 groundwater contents are significantly influenced by the fact that anthropogenically increased NO_3 contents are almost always accompanied by increased contents of Ca and Mg that have positive influence on MOD. Therefore we characterize achieved dependence as stochastic. Similar situation is in case of Cl. Mean Cl groundwater contents in the Slovak Republic without any anthropogenic influence is mainly lower than 10 mg l^{-1} (Rapant et al., 1996). In case of SO_4 we were not able to define limit values as well. Therefore we can conclude that following three anions Cl, SO_4, NO_3 have negligible influence on MOD. These conclusions do not definitely exclude possibility of negative health effects of these parameters on humans that can be of relevance in areas with their locally increased contents from single point sources of groundwater/drinking water contamination. We only state that at national level, for the whole territory of the Slovak Republic they do not have significant influence on MOD.

Among identified eight the most influential elements/parameters related to MOD calculated through ANN we finally characterize as influential only Ca, Mg and Ca+Mg. Other elements/parameters are found as stochastic or with negligible influence on MOD.

Our achieved results are fully in accordance with findings of prof. Yang, obtained in Taiwan, who associate increased occurrence of MOD with deficit contents of Ca and Mg (Yang et al. 1997; 1998; 1999a; b; c; 2000a; b). Ca and Mg are important intracellular cations, which are significantly involved in many enzymatic systems. They are essential for hematopoiesis, heart activty as well as in the prevention of oncological disease (Bencko et al. 2011). Several epidemiological studies link increased Ca and Mg contents in human tissues and liquids with decrease incidence of cancer of breast, prostate, stomach and digestive tract (Rodriguez et al. 2003; Larsson et al. 2006; Ahn et al. 2007; Lin et al. 2007; Butler et al. 2010).

Based on results from ANN calculations we propose as limit values for drinking water in relation to MOD following groundwater contents for Ca > 60 mg l^{-1}, Mg > 25 mg l^{-1} and Ca+Mg > 1.7 mmol l^{-1}. Upper limit values for Ca, Mg or water hardness are not found as relevant. Occurrence of groundwater/drinking water exceeding such levels of these parameters (limited by Slovak guideline or our derived limit contents) in the Slovak Republic is very rare and this water is not used for public water supply.

4. CONCLUSION

Based on achieved results we can conclude that mortality on oncological diseases in the Slovak Republic is influenced by chemical composition of groundwater/drinking water, mainly Ca, Mg contents and Ca+Mg levels. Mortality on OD is significantly lower compared to Slovak average when groundwater content of these parameters are following: for Ca > 60 mg l^{-1}, for Mg within range of 25-35 mg l^{-1} and for Ca+Mg within range of 1.7-5.8 mmol l^{-1}. Our derived limit values are about 2 times higher compared to limits defined within the Slovak guideline for drinking water and therefore we recommend increasing them. We are aware of certain uncertainties that limit our results. The most important fact is that people do not consume exactly the same water as it is defined by our average groundwater analysis for single municipalities. On the other hand, our model includes whole territory of the Slovak Republic (about 50,000 sqkm), whole Slovak population (about 5.5 millions of people) divided to all 2,883 municipalities. We have evaluated more than 20,000 chemical analyses for groundwater including 34 chemical elements/compounds/parameters and we have analysed except of summarizing health indicators for OD – ReC00-C97 (all malignant neoplasms) also other 16 health indicators of mortality for oncological diseases.

The significance of Ca and Mg groundwater contents was in the Slovak Republic determined also for mortality on cardiovascular diseases (Rapant et al. 2015). There are a number of works dealing with the Ca and Mg relevance to cardiovascular disease mortality (e.g. Dawson et al. 1978; Shaper et al. 1980; Rylander et al. 1991; Rosborg 2015). For oncological diseases only already mentioned studies of prof. Yang from Taiwan were published so far.

Oncological and cardiovascular diseases represent in developed countries key causes of deaths for majority of population (about 65-75%). However, Ca and Mg groundwater contents (or water hardness) are not revised by World Health Organization (WHO) as parameters influencing human health. Based on achieved results for oncological as well as cardiovascular diseases we propose to WHO to give consideration to determine international drinking water standards for Ca and Mg content levels.

Acknowledgements

This research has been performed within the projects Geohealth (LIFE10 ENV/SK/000086) and Life for Krupina (LIFE12 ENV/SK/000094) which are financially supported by the EU’s funding instrument for the environment: Life+ programme and Ministry of the Environment of the Slovak Republic.

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