It is shown, on the examples of concrete publications, that "person-years" category application in multi-factor health risks analysis can lead to false conclusions in the process of observation data grouping due to Simpson paradox influence when examinations are performed via demographic or epidemiological techniques. The paradox occurs when heterogeneous strata are being compared. "Person-years" category first appeared in the middle of the 17th century, long before first applications of mathematical tools in statistics and probability theory; it does not fully correspond to up-to-date requirements of epidemiological research. Risk theory should change 17–18 century paradigm as it focuses on conditional probability of unwanted events occurrence and not on a principle of comparing their intensities. It is particularly vital in case when we deal with determining possible damage to health caused by effects exerted by such factors and under such conditions when individual damage cannot be measured objectively but when it is possible to quantitatively determine regularities of changes in stochastic ability to survive for a large group of people or remote consequences occurrence for it.

We prove it is necessary to create specialized mathematical tools and hybrid software able to solve a risks assessment task as an inverse one. Mathematical tools of large contingency tables could serve as prototypes of such tools; we can also use multi-factor logistical and Poisson regressions which are usually applied in countable events analysis. We should note that it is also necessary to eliminate a number of methodological drawbacks which are attributable to the said tools.

Key words: lifelong risk, cohort, epidemiology, parameter, intensity, Simpson paradox, factor, remote consequences, software.

"Person-years" category [9] came to life when risks related to possible negative consequences for health were analyzed, first in population research, and later, in cohort one. An epidemiologic dictionary gives the following definition for the term: "Person-time is a dimension combining people and time in a denominator in calculating incidence and mortality ..., when individuals run risks of a disease or a lethal outcome during different time periods. It is a sum of all the time periods during which all the individuals ran risks". Obviously, John Graunt [3] was the first researcher who actually applied this concept in the middle of the 17th century. A number of observed person-years has been traditionally applied to assess mortality or morbidity intensity which are thought by most practicing epidemiologists to be directly related to such terms as "risk" or "risk parameter":

$$\lambda = \frac{\Delta M}{\Delta t},$$  \hspace{1cm} (1)

where \(\Delta M\) – is a number of "cases" over an
observation period; $\Delta A$ – is a number of observed person-years.

We should note that this value had first been applied before mathematics started to develop rapidly after differential and integral calculus were discovered as well as before probability theory and mathematical statistics were created. English reference books also determine the parameter as stratum-specific rate, or as "hazard". It was demographers who strove to apply it both in descriptive and mathematical statistics [3]. The word "statistic" itself is known to be first introduced by Gottfried Achenwal in 1746 as an equivalent for a "state study" subject in Marburg and Gottingen Universities, that is, in a descriptive meaning of the term.

Contemporary risk theory changes 17-18 centuries paradigm as it is based on probability category [1] and determines a risk as a probability of unwanted events occurrence (under a combination of certain conditions, that is as a conditional probability). It is especially vital for scientific demography and evidential epidemiology if we speak about determining possible health damage caused by such factors and under such conditions when it is impossible to objectively measure an individual damage but we can quantitatively determine regularities of changes in stochastic survival rate for a large group of people or long-term effects occurrence. Search for scientific approaches to measuring such biological effects has been intensified since 70ties last century in relation to all-around growth in chemical, pharmaceutical, radiation, ecological and other technogenic risks.

At first sight this change in scientific paradigm doesn't contradict to "person-years" category as a distribution of members in a homogenous examined cohort can be described with a function of distribution as per age $t$:

$$F(t)=1-\exp\left(-\int_0^t \lambda(t) \, dt\right), \quad (2)$$

where $\lambda(t)$ is an intensity of mortality caused by all reasons, for example; is a death risk and it is also a distribution function. Here $\lambda(t)=F'(t)/\{1-F(t)\}$ or $\lambda(t)=-S'(t)/S(t)$, where $S(t)$ – a survival function $S(t)=1-F(t)$.

Distribution function and survival function are assessed empirically. Due to it we can come to the formula (3) at any finite interval of observation $\Delta t$ at a sufficient examined sampling value $N_0$ together with the condition $N(t) \approx N_0 S(t)$:

$$\lambda(t)=-S'(t)/S(t) \approx \frac{N_0(S(t+\Delta t)-S(t))}{N_0 S(t) \Delta t} = \frac{\Delta N}{\Delta A} = \frac{\Delta M}{\Delta A}. \quad (3)$$

Therefore, such concepts as risk and risk intensity are equal in a descriptive sense. So it seems, all we have to do is to select a reference group and come to some conclusions. But application practices tell us it would be wrong. And it is not only because risks intensities ratios and ratios of risks themselves in a focus group and a reference one differ in their meaning and value, but also because each of these parameters is determined for a homogenous group, and the parameters themselves should differ only as per 1 examined factor. However, it is this circumstance that is not always strictly controlled by researchers.

**Our research goal** was to highlight typical observation examples for Simpson paradox when heterogeneous groups were compared when heterogeneity was observed as per more than 1 factor controlled by a researcher. This paradox has been
known since Karl Pearson's time (1900) but it has been repeatedly rediscovered. Uncontrolled factors are also known as "disturbing" variables. A technique involving comparison between a focus group and a reference one actually leads to contingency tables estimate. They are built both on direct risk comparison principle (classic contingency tables) and on a principle when events observation intensities are compared. And 'person-years' category is exactly applied in the latter case. To illustrate mathematic artifacts Simpson's paradox belongs to we suggest to look at Table 1.

Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Miami</th>
<th></th>
<th>Alaska</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔA, people/year</td>
<td>ΔM (died)</td>
<td>Parameter, (%) per year</td>
<td>ΔA, people/year</td>
</tr>
<tr>
<td>&lt;15</td>
<td>114 350</td>
<td>136</td>
<td>1.19</td>
<td>37 164</td>
</tr>
<tr>
<td>15–24</td>
<td>80 259</td>
<td>57</td>
<td>0.71</td>
<td>20 036</td>
</tr>
<tr>
<td>25–44</td>
<td>133 440</td>
<td>208</td>
<td>1.56</td>
<td>32 693</td>
</tr>
<tr>
<td>45–64</td>
<td>142 670</td>
<td>1 016</td>
<td>7.12</td>
<td>14 947</td>
</tr>
<tr>
<td>65+</td>
<td>92 168</td>
<td>3 605</td>
<td>39.11</td>
<td>2 077</td>
</tr>
<tr>
<td>All ages*</td>
<td>562 887</td>
<td>5 022</td>
<td>8.92</td>
<td>106 917</td>
</tr>
</tbody>
</table>

Note: *– crude rate.

As we can see, parameters are statistically significantly different between all the age groups in each region (p < 0.02). However, if we compare each age group in different regions we can see there are no statistically significant discrepancies (p ≥ 0.05). At the same time combined (crude) mortality parameters in the same regions can paradoxically differ, and this difference can reach 3 times (8.92 against 2.67 people per 1,000 a year; p < 0.001). Demographists understand the reason for the artifact quite well. It is that when strata were combined, such a hidden factor as regional difference in people distribution as per age played its role. A combined regional stratum turned out to be heterogeneous. And a way to correct the mistake here is also well known. Indeed, we can introduce any "standard" distribution as per age categories in our consideration, for example, simply combining two administrative units in one. Then the parameters assessment will be reduced to simple calculation of a weighted average as per age group. For example, let us fix shares distribution structure in a unified standard with the following ratios: 0.23 : 0.15 : 0.25 : 0.23 : 0.14. The parameter will be equal to 7.88‰•year⁻¹ for "Miami" sub-group, and for Alaska sub-group, to 7.63‰•year⁻¹. Obviously, given the observed discrepancy, now we can't state there are statistically significant differences in health of population living in these two regions. And a paradox would seem to be overcome.

However, standardization procedure itself doesn't remove heterogeneity. No wonder, that standardized annual risk parameter is being criticized [15] as it is impossible to make any judgments on population being healthy/unhealthy only on its value. You can come to this conclusion yourselves if, for example, you compare three age dependences for intensity of mor-
tality caused by lung cancer for three different population groups where standardized risk was arithmetically identical (Figure 1), but lifelong risk was 1.25 times different and its values were higher not in a cohort where specific mortality was maximum intense.

Indeed, let us assume that cohorts 1 and 2 were exposed to different impacts exerted by a certain pollutant. The background cohort with zero exposure is used as a reference group. Obviously, if we don't apply standardized risk parameter but choose a probable damage done to a cohort health, we will obtain higher parameter for cohort 2. It is explained by the following: deaths caused by cancer in cohort 2 in the same volumes will be registered earlier and this, as we can calculate, will lead to a greater cumulative effect and a lifelong risk of death due to cancer can serve as an example of this effects. So, if changes in distribution form is a response to impacts exerted by a pollutant then we should choose a correct biologic effect measure. It can't be equal to just "average temperature in a hospital".

Works by a well-known group of researchers [2,4,6–8] also contain an incorrect application of annual risk parameters and Poisson regression. According to their observations, there is a statistically significant decrease in morbidity with arterial hypertension together with growth in an internal irradiation dose on the liver which is higher than 0.05 Gy among men contacting Pu compounds (Table 2). Meanwhile, 0.05 Gy Pu dose is equal to an external irradiation dose of 1.0 Sv which corresponds to 50 years of work with fixed dose limits of tolerable irradiation being equal to 20 mSv/year for professionals. So, this "favorable" impact exerted by Pu on male bodies doesn't correspond to the existing Radiation Safety Standards. This phenomenon can be explained almost in the same way as in case with table 1, but here we can see more sources of strata heterogeneity as the samplings are made up of workers employed at various technological sectors with two completely different radiation types. Even risk parameters standardization the authors were quite able to apply didn't help them much [4]!

The same researchers "found" even greater paradoxes due to their heterogeneous groups examination. Thus, when studying consequences of chronic influence exerted by ionizing radiation on intensity of mortality caused by cerebrovascular diseases, they "revealed" that if male workers received alpha-radiation within a dose range equal to 0.1-0.5 Gy, then mor-

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tality grew together with a dose, but as for
the overall male part of a cohort, they "ob-
served" statistically significant decrease
with the following trend:
$$\text{ERR}_{gy} = -0.056 \text{ Gy}^{-1}$$ (95% CI: from −0.094 to
−0.018) [8]. They managed not to come to
conclusions that internal irradiation caused
by radionuclides which penetrated a body
was actually "useful", but Simpson para-
doxx was well there. There is another simi-
lar work where performed research results
are applied by its authors to state that regu-
lar alcohol intake by male workers from
the same cohort causes an increase in mor-
bidity with cerebrovascular diseases with
high confidence probability level [6]. On
the contrary, the same parameter for wom-
en is lower among those drinking alcohol.
And here we also see that absurdity and
Simpson paradox go hand in hand.

Dose trend assessment inconformity
which occurs in examinations of senile
cataract is also obvious there where these
assessments are based on intensity of the
disease evolvement risk [2]. For example,
we can see in Table 3 that if observation
grouping was one-factor, as per radiation
dose in the basic workers' group with Rad-
iation Safety Standards being undoubted-
ly met, morbidity parameter was
$$\lambda_0 = 1631/255036 = 0.0639 \% \cdot \text{year}^{-1}.$$ However,
the same parameter was $$\lambda_4 = 12.31 \% \cdot \text{year}^{-1}$$ in a group who received more than
1 Gy. Then excess relative risk per a dose
unit within a hypothesis on a linear trend
would be equal to (4):
$$\hat{E} \hat{D}_D \approx \frac{\lambda_4 - \lambda_0}{\lambda_0 (D_4 - D_0)} = 0.89 \text{ Gy}^{-1} \quad (4)$$

### Table 2

Morbidity with arterial hypertension among workers employed at PA "MAYAK", ex-
posed to different internal irradiation doses [4]

<table>
<thead>
<tr>
<th>Sex</th>
<th>$D &lt; 0.025 \text{ Gy}$</th>
<th>$0.025–0.05 \text{ Gy}$</th>
<th>$D &gt; 0.05 \text{ Gy}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>Parameter (%) per year</td>
<td>Number of cases</td>
</tr>
<tr>
<td>Men</td>
<td>1416</td>
<td>21.11 ± 0.5</td>
<td>481</td>
</tr>
<tr>
<td>Women</td>
<td>694</td>
<td>18.59 ± 0.71</td>
<td>253</td>
</tr>
</tbody>
</table>

Note: * – Statistically significant observation.

### Table 3

Relative risk (RR) of morbidity with cataract depending on a cumulative external gamma-irradiation [2]

<table>
<thead>
<tr>
<th>Cumulative dose of external $\gamma$-irradiation (Gy)</th>
<th>Average dose of external $\gamma$-irradiation (Gy)</th>
<th>Person-years of observation</th>
<th>Cataract cases</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0–0.25)</td>
<td>0.08</td>
<td>255036,0</td>
<td>1631</td>
<td>1</td>
</tr>
<tr>
<td>[0.25–0.50)</td>
<td>0.36</td>
<td>69097,1</td>
<td>702</td>
<td>1.23 (1.11–1.35)</td>
</tr>
<tr>
<td>[0.50–0.75)</td>
<td>0.62</td>
<td>35678.2</td>
<td>365</td>
<td>1.13 (1.00–1.28)</td>
</tr>
<tr>
<td>[0.75–1.00)</td>
<td>0.87</td>
<td>25915.0</td>
<td>321</td>
<td>1.38 (1.21–1.57)</td>
</tr>
<tr>
<td>[1.00–1.25)</td>
<td>1.12</td>
<td>18191.8</td>
<td>224</td>
<td>1.43 (1.23–1.66)</td>
</tr>
<tr>
<td>[1.25–1.50)</td>
<td>1.37</td>
<td>15147.2</td>
<td>217</td>
<td>1.57 (1.34–1.83)</td>
</tr>
<tr>
<td>[1.50–2.00)</td>
<td>1.73</td>
<td>20066,3</td>
<td>296</td>
<td>1.59 (1.39–1.83)</td>
</tr>
<tr>
<td>&gt;=2,00</td>
<td>2.67</td>
<td>25498,0</td>
<td>387</td>
<td>1.61 (1.41–1.83)</td>
</tr>
</tbody>
</table>
And it is even higher in small doses range. However, E.V. Bragin et al. give another estimation in their work performing it partially allowing for observations stratification, but for the overall cohort, namely $ERR_{0} = 0.28 \text{Gy}^{-1}$ (95% CI: 0.20 – 0.37) [2]. That is, one estimation doesn't match within a confidence interval of the another and they are approximately three times different from each other. Again, Simpson paradox. And what estimations are we to trust here? Probably, not one of them.

T.V. Azizova et al. made an attempt to separately examine influence exerted by two ionizing radiation types on circulatory system diseases (CSD) within a separate one-factor analysis framework, but it again led to a paradox [7]. Excess relative risk per a dose unit under exposure to external gamma-irradiation was $RR = 0.11$ (95% CI: 0.0–0.11). They also detected a statistically significant rising trend for CSD-caused mortality as an absorbed dose of internal alpha-radiation in liver was growing: $RR = 0.48$ (95% CI: 0.12–0.48). Given relative biological efficiency of alpha-radiation in comparison with gamma-radiation, we obtain the following: (95% CI: 2.4–9.6), which is substantially higher than among victims of Hiroshima and Nagasaki bombing and is extremely strange by itself. But it didn't prevent the authors from stating that "... Research results ... are well in line with risk assessments obtained in a Japanese cohort of people who survived in atomic bombing ...". We should note that the authors saw how "... decreased and became statistically insignificant when an adjustment as per an external gamma-irradiation was introduced" [2].

This "person-years" category is widely used in epidemiologic research on radiation effects. And it is this category that makes risk researchers come to unjustified conclusions and generalizations which ignore initial probabilistic meaning of parameters introduction. There is a serious methodological defect when we measure "hazard" parameters when assessing death risk in radiation-epidemiologic research and not "risk" itself. Logical contradiction is especially typical when stochastic events in a cohort are examined. They usually depend on an impact dose which is cumulative in its sense while a risk parameter is a "momentary" property of a cohort which can be attributed to a certain age. One-value correlation between and a dose seems logical for acute impacts exerted by a hazardous substance but it is totally non-relevant for long-term ones. For example, chronic low intense irradiation involves a correlation between age and dose. If stratification which is usual for epidemiology is made as per both these values than it will be natural in case of low irradiation doses that an observed dose will be higher for people with comparatively older ages of death. Maximum likelihood techniques application according to Epicure Users Guide [23] will lead to false interpretation of this fact: registered life span will be higher for cohort members with greater doses, but "momentary" specific mortality parameters will be lower for them. So, application of mortality/morbidity intensity parameter can cause epidemiologic "observation" of false hormesis which actually could be not more than just a mathematical artifact. In spite of the subjunctive mood applied in the previous sentence, the author is sure that the above-mentioned artifact was repeatedly observed in small doses area where it should obviously be most apparent. And this phenomenon was thought by many researchers to be a true radiation-epidemiologic hormesis or even anti-tumor effect [10–16, 18–22, 24, 25].
Risk assessment issues: discussion and analysis. Basic risk factors awareness and standardization underlies state sanitary-epidemiologic control and surveillance. But each science based on experience requires its own unique toolset. It is not enough to simply give a theoretical definition of risk. It is also necessary to be able to measure it practically. Risk is always caused by several internal and external reasons, that is, it is a multi-factor value. We can provide strict one-factor risk dependence in an experiment only, which, due to ethical reasons, cannot always be performed on people. Multi-factor epidemiologic or clinical-epidemiologic research is an alternative. Risk management practice is not possible without this information as it requires an ability to predict risks in preset sanitary-epidemiologic conditions.

Analysis of existing risk assessment practices reveals that it is hard to adapt traditional contingency tables or one-factor statistic tools to multi-factor randomized observations. As we have already stated, Poisson regression built on wrong application of "person-years" observation category can lead to false conclusions. A solution to a problem can be a transition to assessment of strictly stochastic specific risk parameters, for example conditional lifelong risk. There is a positive example in radiation epidemiology sphere acknowledged by International Commission on Radiological Protection (ICRP) [5].

Statistic research algorithm based on cumulative effects assessment can be applied in non-radiation effects analysis but only if their value can be characterized with certain cumulative "doses". Risk can be only conditional, so it will depend on sex, exposure occurrence moment, a moment of individual effects observation in a group, on concomitant physiological processes which can influence an observed effect marker, on smoking status, on damage localization, and on exposure nature. Even a biological effect observation technique (diagnostic technique) can a factor which causes a sampling heterogeneity. "Detectability" category is applied by epidemiologists not for nothing. And finally, examined long-term effects risk depends on how possible realization of other lethal risks is. All these factors are conditions for conditional probability realization and so they are also to be conditions for its assessment.

Conclusions. Assessment of lifelong risk and its dose trend in any heterogeneous cohort is a complicated statistical multi-factor analysis problem which cannot be solved without specialized computing facilities. As a rule, universal software which is available at present is not suitable for the purpose. It is necessary to work out specialized software able to solve risk assessment task as a inverse one. A logistic regression could be a prototype if we don't overemphasize a logistic function role here; it would be better to replace it with a more flexible approximation tool. For example, it is possible to apply artificial neuron networks as a generator of models describing correlations between risks and examined factors. In particular, it would allow to give up stratification of randomized observations results and, consequently, to exclude well-known influence exerted by strata limits setting on assessment results. There are a lot of spheres in medicine and healthcare where all the above-mentioned can be applied, for example, predictions made on screening results (oncology, cardiology, gastroenterology etc.), medical statistics, cohort and clinical epidemiology, clinical toxicology, as well as development of software for processing other statistic data which are of probabilistic nature.
References


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