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COMPREHENSIVE EVALUATION OF SPERM QUALITY AFTER EXPOSURE TO EPOXICONAZOLE IN MALE WISTAR HANNOVER RATS

ABSTRACT. *Epoxiconazole is a triazole that serves as a broad-spectrum fungicide, renowned for its enduring efficacy against cereal leaf spots, rust fungi, etc. There is increasing evidence from animal studies that exposure to epoxiconazole may affect reproductive function. Additionally, several studies in rats have confirmed the endocrine-disrupting properties of epoxiconazole. However, there are few studies examining its adverse effects on spermatogenesis.*
Aim. *This study aimed to assess sperm quality following exposure to two generic pesticides, epoxiconazole (Epox). The test substances epoxiconazole technical were sourced from different manufacturers, and the purity of the active ingredient was at 98. % (Epox-1) and 97.3 % (Epox-2).*
Material and Methods. *The test substances were administered intragastrically as an aqueous emulsion daily for 10 weeks to two groups of 10 male animals each. The doses administered were 0.5 and 2.0 mg/kg body weight. Control animals, comprising 10 males, were administered an equivalent amount of vehicle, consisting of distilled water with an emulsifier. Upon completion of the exposure period, an assessment of functional indicators of gonadal status was conducted. Specifically, the evaluation included counting motile sperm, total sperm concentration, and quantifying pathological forms of germ cells. Also, the absolute and relative weight of the testes and epididymis were evaluated. The sperm quality of males following exposure to Epox-2 was assessed using a computerised sperm analyser, specifically the CASA (Computer-aided Semen Analysis) SCA® Pack TOX Edition. In the case of Epox-1, the analysis of male sperm was conducted manually, utilising light microscopy.*
Results. *The findings indicated that exposure to Epox-1 at 2 mg/kg in males resulted in a significant reduction in the number of motile sperm and a decrease in the absolute and relative testicular weights. More severe outcomes were noted following exposure to the test substance Epox-2 at the identical dose of 2 mg/kg body weight. The observations included an elevated proportion of pathological sperm forms and immotile sperm, a decreased percentage of motile sperm, and a reduction in the absolute and relative testicular weights. At a dose of 0.5 mg/kg, neither test substance, Epox-1 nor Epox-2, exhibited a general toxic effect and did not adversely affect gonad function when exposed to male rats.*
Conclusions. *According to the results, the two test substances, Epox-1 and Epox-2, exhibit notable antiandrogenic activity when administered to male rats at 2 mg/kg body weight. This is evidenced by a deterioration in male sperm quality and a reduction in the weight of their gonads. Furthermore, the observed variation in toxicity following exposure to Epox-2 may be attributable to the lower purity of the test substance relative to Epox-1 in this instance. This underscores the significance of assessing generic pesticides with varying percentages of impurities.*
Keywords: *epoxiconazole, toxicity, gonads, sperm quality, spermatogenesis, male rat*

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КОМПЛЕКСНА ОЦІНКА ЯКОСТІ СПЕРМИ У САМЦІВ ЩУРІВ ЛІНІЇ WISTAR HANNOVER ПІСЛЯ ВПЛИВУ ЕПОКСИКОНАЗОЛУ

РЕЗЮМЕ. *Епоксиконазол — це триазол, що використовується як фунгіцид широкого спектра дії, відомий своєю тривалою ефективністю проти плямистостей листя злакових, іржастих грибів, тощо. З'являється все більше досліджень на тваринах, що вказують на негативний вплив епоксиконазолу на репродуктивну функцію ссавців. Крім того, низка досліджень на щурах підтвердила ендокринно-деструктивні властивості епоксиконазолу. Водночас існує обмежена кількість досліджень, присвячених його впливу на гонади та сперматогенез.*
Мета. *Метою цього дослідження було оцінити якість сперми після впливу двох генеричних пестицидів на основі епоксиконазолу (Epox). Досліджувані речовини технічного епоксиконазолу були синтезовані різними виробниками, а чистота діючої речовини становила 98 % для Epox-1 та 97,3 % для Epox-2.*
Матеріали та методи. *Досліджувані речовини вводили внутрішньошлунково у вигляді водної емульсії щоденно протягом 10 тижнів двом групам по 10 самців у кожній. Дози становили 0,5 та 2,0 мг/кг маси тіла. Контрольним тваринам (10 самців) вводили відповідну кількість розчинника (дистильовану воду з емульгатором). Після завершення періоду експозиції проводили*

оцінку функціональних показників стану гонад. Зокрема, визначали кількість рухливих сперматозоїдів, загальну концентрацію сперматозоїдів та відсоток патологічних форм статевих клітин. Також оцінювали абсолютну та відносну масу сім'яників і придатків сім'янника. Якість сперми самців після впливу Epox-2 оцінювали за допомогою комп'ютеризованої системи аналізу сперми CASA (Computer-aided Semen Analysis), SCA® Pack TOX Edition. У випадку Epox-1 аналіз сперми проводили вручну з використанням світлової мікроскопії.

Результати. *Отримані дані показали, що вплив Epox-1 у дозі 2 мг/кг у самців призводив до значного зниження кількості рухливих сперматозоїдів та зменшення абсолютної та відносної маси сім'янників. Більш виражені ефекти спостерігалися після впливу Epox-2 в тій самій дозі 2 мг/кг маси тіла. Було відзначено підвищення відсотка патологічних форм сперматозоїдів і нерухливих сперматозоїдів, зниження відсотка рухливих сперматозоїдів, а також зменшення абсолютної та відносної маси сім'янників. Після впливу дози 0,5 мг/кг жодна з досліджуваних речовин (Epox-1 та Epox-2) не проявляла загальної токсичної дії та не впливала негативно на функцію гонад самців щурів.*

Висновки. *Згідно з отриманими результатами, обидві досліджувані речовини, Epox-1 і Epox-2, проявляють виражену антиандрогенну активність після впливу дози 2 мг/кг маси тіла на самців щурів. Це підтверджується погіршенням якості сперми та зменшенням маси гонад. Крім того, більш виражена токсичність, що спостерігалася після впливу Epox-2, може бути зумовлена нижчою чистотою діючої речовини порівняно з Epox-1. Це підкреслює важливість оцінки генеричних пестицидів із різним рівнем домішок.*

Ключові слова: *епоксиконазол, токсичність, гонади, якість сперми, сперматогенез, самці щурів*

Introduction. Epoxiconazole is a triazole fungicide that inhibits cytochrome P450–dependent enzymes involved in sterol biosynthesis. Beyond its antifungal activity, increasing evidence indicates that epoxiconazole can interfere with mammalian steroidogenesis, raising concerns about its potential endocrine-disrupting and reproductive effects. In the literature, several experimental studies across different laboratory animal species have shown that epoxiconazole induces adverse effects on reproduction and development. Reported effects include changes in anogenital distance, altered timing of vaginal opening and testes descent, modified fetal and maternal steroid hormone levels, and fetotoxicity. Similar endocrine-mediated effects have been described for other azole fungicides, supporting the hypothesis that disruption of key steroidogenic enzymes, such as CYP17, represents a central mechanism underlying their reproductive toxicity [1-5].

Notably, available data indicate that epoxiconazole can interfere with reproductive function across species, primarily through endocrine-mediated mechanisms [5]. However, few studies have examined its adverse effects on spermatogenesis. For instance, in a study of Japanese quail (Coturnix coturnix japonica), dietary exposure to epoxiconazole resulted in a significant reduction in spermatid numbers and histopathological alterations in the testes [6].

One of the epoxiconazole modes of action is its inhibition of aromatase, which is important and can impair the process of spermatogenesis. Moreover, it has been found that epoxiconazole can not only inhibit aromatase, which catalyses the conversion of androgens to estrogens, but also reduce 11- and 21-hydroxylase activity, resulting in higher androgen and lower corticosterone and aldosterone levels, as shown in rodent studies and in vitro [1, 2].

According to the European Food Safety Authority (EFSA) (2008) [7], the original molecule of epoxiconazole was evaluated in a two-generation reproductive toxicity study, which demonstrates adverse effects in parental and offspring animals. Specifically, reduced food consumption, dystocia, impaired fertility, prolonged gestation, vaginal haemorrhages, and liver effects were reported for parental animals, and offspring effects included reduced numbers of viable pups and increased perinatal mortality. The observed reproductive effects led to the classification of epoxiconazole as Xn; Repr. Cat. 3 (R62) "Harmful; Possible risk of harm to the unborn child", indicating possible risk of impaired fertility. However, assessment of sperm parameters was not included in that study, despite their critical importance in the evaluation of male fertility and reproductive capacity.

Given that azole fungicides are potent aromatase inhibitors and have been shown to impair reproductive function, including fertility, through endocrine-disrupting mechanisms, there remains limited information regarding their effects on spermatogenesis in mammals. Notably, sperm quality parameters were not comprehensively evaluated in previous studies of the original epoxiconazole molecule. Therefore, the present study aimed to provide a detailed assessment of sperm quality in male rats following exposure to epoxiconazole.

Materials and Methods. The studies were conducted in a Good Laboratory Practice (GLP)-certified Laboratory of Experimental Toxicology and Mutagenesis at the L.I. Medved's Research Centre of Preventive Toxicology, Food and Chemical Safety, Ministry of Health of Ukraine.

Identification of test substance

The two pesticides epoxiconazole (generic formulation) were obtained from different manufacturers. The purity of the active ingredient was 98.7 % for the first technical-grade epoxiconazole (Epox-1) and 97.3 % for the second technical-grade epoxiconazole (Epox-2).

Animals

Male Wistar Hannover rats were sourced from the SPF Animal Nursery of the L.I. Medved's Research Centre of Preventive Toxicology, Food and Chemical Safety, Ministry of Health of Ukraine. All animal procedures were conducted in compliance with the requirements and provisions of the Commission for the Ethics of Medical and Biological Research of the same institution, in accordance with the Law of Ukraine No. 3447-IV of February 21, 2006, "On the Protection of Animals from Cruelty," and the European Communities Council Directive 86/609/EEC of November 24, 1986.

Animal husbandry and condition

To evaluate the morpho-functional state of the male gonads, specifically spermatogenesis, 30 males aged 9-12 weeks were included in each study. Animals were housed in a clean area of a conventional barrier-type vivarium with controlled environmental conditions: forced ventilation (12 air changes per hour), temperature of 19–25 °C, humidity of 30–70 %, and a 12-hour light/dark cycle. They had ad libitum access to deionized, UV-disinfected, reverse osmosis–filtered water and a balanced, low-phytoestrogen pelleted diet (Altromin 1326 R, Germany). The animals were randomly assigned to groups. During a five-day acclimation period, animals were monitored and excluded if they showed signs of pathology or significant deviations in body weight. Each animal was individually identified and housed in polysulfone M4 cages with sterilized paper bedding, which was changed weekly; cages were washed and disinfected weekly.

Preparation of solutions, doses and route of administration

The test substances were administered by oral gavage daily for 10 weeks to two groups of 10 male animals each. The doses administered were 0.5 and 2.0 mg/kg body weight. For both test substances, suspensions were prepared daily using water as the solvent with OP-10. The concentrations of test substances were 0.01 % and 0.04 %, at a dose volume of 0.5 mL per 100 g body weight. Control animals (10 males) received an equivalent volume of water with OP-10 as a vehicle. Animals were weighed weekly to adjust dosing according to body weight.

Morpho-functional evaluation of the male gonads' state (sperm analysis Male fertility depends on the continuous daily production of millions of spermatozoa. Spermatogenesis is an exceptionally complex process that involves a coordinated series of mitotic and meiotic divisions, highly specialised stages of cytodifferentiation, and dynamic intercellular interactions regulated by autocrine, paracrine, and endocrine signalling pathways [8, 9, 10]. All stages of spermatogenesis in male rats take approximately 70 days to complete, which determined the duration of exposure to the test substances. At the end of the 10-week exposure period, functional indicators of gonadal status were evaluated. Animals were euthanised by C02 asphyxiation. After the epididymis was removed and weighed, qualitative and quantitative evaluations of sperm were performed. In the Epox-1 study, sperm parameters in males were assessed manually using light microscopy, as previously described in recent work [11]. The analysis included the determination of total sperm concentration, the enumeration of motile sperm, and the quantification of pathological germ cell forms. In the Epox-2 study, sperm quality was assessed using a computerized sperm analyzer (CASA; SCA® Pack TOX Edition). In addition to the parameters evaluated in the Epox-1 study, this system enabled detailed assessment of sperm motility, including classification of progressive motility into fast- and medium-progressive categories. In both studies, the absolute and relative weights of the testes and epididymides were also measured.

Statistical analysis

The obtained results from the studies were statistically assessed. Statistical analyses were performed using GraphPad Prism (version 10,

GraphPad). Group mean values and standard error of the mean (SEM) were calculated as appropriate. For all statistical analyses, the significance level was set at $p \leq 0.05$. The statistical comparison between treated and control groups was assessed using a one-way analysis of variance (ANOVA) followed by Fisher's LSD test.

Results and discussion

Clinical observations and body weight

During the 10-week exposure period, Epox-1 and Epox-2 did not cause premature mortality in treated rats. Throughout the study, no clinical observations were noted at the daily examinations of all males. Across the exposure period by Epox-1 and Epox-2, no meaningful differences in body weight gain were observed between the other dosed male groups and the control group. Additionally, there were no significant differences in terminal body weight compared with the control group value (see Tab.).

Males reproductive organs weight

Assessment of male reproductive organ weights in both the Epox-1 and Epox-2 studies demonstrated a statistically significant reduction in absolute and relative testicular weights in the high-dose group (2.0 mg/kg bw/day). In the Epox-1 study, exposure resulted in decreases of 9.5 % in absolute testicular weight and 10.1 % in relative testicular weight compared with the concurrent control group (Tab; $p < 0.01$). Similarly, in the Epox-2 study, males in the high-dose group exhibited reductions of 10.7 % in absolute testicular weight and 10.4 % in relative testicular weight relative to controls, as shown in Table 1 ($p < 0.002$). No significant differences were observed in the absolute or relative weights of the epididymides in males exposed to either Epox-1 or Epox-2 compared with the respective control groups.

Sperm parameters

Male sperm analysis after exposure to Epox-1

As noted previously, in the Epox-1 study, sperm quality was assessed manually using light microscopy. Sperm concentration, motility, and morphology were evaluated using a Goryaev chamber. As shown in Fig. 1A, exposure to Epox-1 at a high dose of 2.0 mg/kg bw/day resulted in impaired sperm motility in males. The number of motile and immotile spermatozoids were lower on 15 % ($p < 0.05$) in comparison to the control value. Sperm motility was not affected in a group of males after exposure to a low dose of 0.5 mg/kg bw/day. Assessment of sperm morphology revealed a small proportion of abnormal forms, with a dose-dependent increase that did not reach statistical significance (Fig. 1B). No significant differences in total sperm count were observed in either treatment group compared with the corresponding control group (Fig. 1C).

Table

Reproductive organ weights of Epoxiconazole-treated male Wistar Hannover rats

Parameters	Epox-1			Epox-1		
	Control	Dose		Control	Dose	
		0.5 mg/kg	2.0 mg/kg		0.5 mg/kg	2.0 mg/kg
Terminal body weight (g)	396.90 ± 2.04	391.70 ± 2.65	399.80 ± 3.88	412.10 ± 4.99	408.50 ± 3.70	411.40 ± 5.50
Testes (g)						
Absolute	3.78 ± 0.08	3.64 ± 0.06	3.42 ± 0.07*	3.94 ± 0.10	3.72 ± 0.04	3.52 ± 0.11**
Relative	9.53 ± 0.21	9.29 ± 0.15	8.57 ± 0.21*	9.56 ± 0.22	9.11 ± 0.09	8.57 ± 0.32**
Epididymis (g)						
Absolute	1.18 ± 0.03	1.13 ± 0.03	1.13 ± 0.04	1.19 ± 0.04	1.17±0.03	1.16±0.05
Relative	2.97 ± 0.08	2.89 ± 0.09	2.82 ± 0.09	2.88 ± 0.08	2.88 ± 0.08	2.82 ± 0.10

Note: g = grams. Results presented as mean per group ± SEM (n = 10 per group).
Statistics were compared with the control group; * $p \leq 0.01$; ** $p \leq 0.002$.

Male sperm analysis after exposure to Epox-2

In the Epox-2 study, sperm quality in male rats was assessed using a computerized Computer-Assisted Sperm Analysis (CASA) system, which enables objective evaluation of sperm motility, including progressive motility, as well as more detailed morphological assessment while minimizing observer-related bias.

Sperm motility decreased in a dose-dependent manner following Epox-2 exposure and reached statistical significance at 2.0 mg/kg bw/day, with a 27 % reduction compared to the concurrent control group ($p < 0.0001$). As shown in Fig. 2A, the overall decline in motility was primarily attributable to a marked reduction in progressively motile sperm, which decreased by 47.3 % relative to the control level ($p < 0.01$).

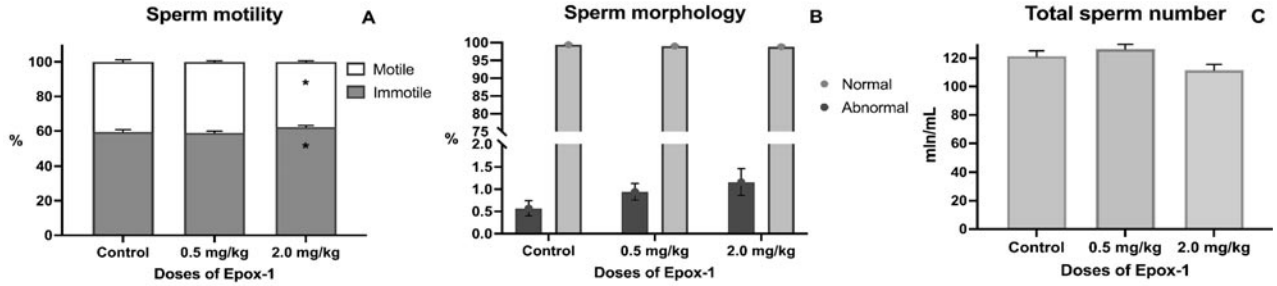

Fig. 1. Sperm parameters of male Wistar Hannover rats exposed to the Epox-1 via manual analysis. Data presented as Mean ± SEM (n = 10 per group). A – a percentage of motile and non-motile sperm, B – a percentage of normal and abnormal forms of spermatozoids, and C – the total amount of spermatozoids (mln/mL). Statistics were compared with the control group – * $p \leq 0.05$.

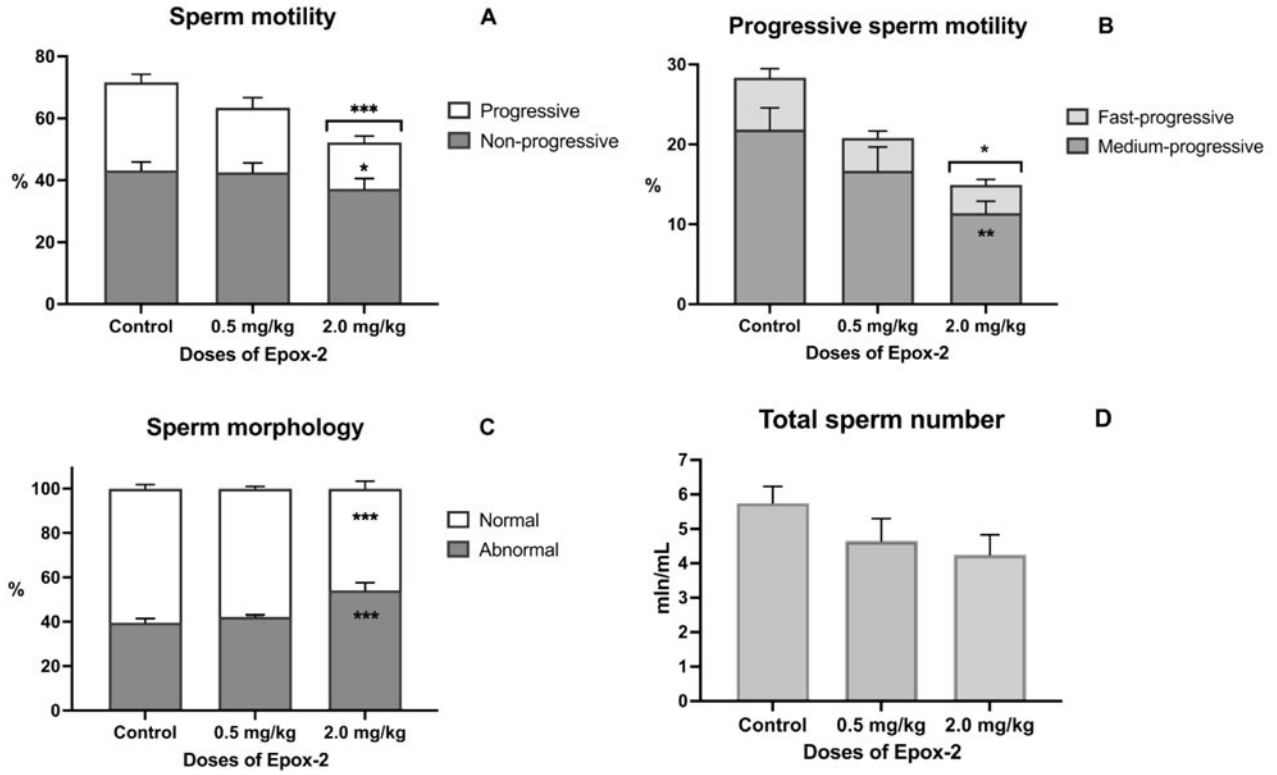

Fig. 2. Sperm parameters of male Wistar Hannover rats exposed to the Epox-2 using CASA. Data presented as Mean ± SEM (n = 10 per group). A – a percentage of motile sperm (progressive and non-progressive motile sperm), B – progressive motile sperm (fast-progressive and medium-progressive motile sperm), C – a percentage of normal and abnormal forms of spermatozoids, and D – the total amount of spermatozoids (mln/mL).
Statistics were compared with the control group - * $p \leq 0.01$; ** $p \leq 0.001$; *** $p \leq 0.0001$.

Consequently, further analysis of progressive motility (Fig. 2B) demonstrated dose-dependent decreases in both fast- and medium-progressive spermatozoa. A statistically significant reduction ($p < 0.001$) was observed in medium-progressive sperm in males receiving the high dose (2.0 mg/kg bw/day), with a 47.8 % decrease compared with the control group.

Assessment of sperm morphology revealed a significant increase in abnormal sperm forms in males exposed to Epox-2 at 2.0 mg/kg bw/day (36.8 %; $p < 0.0001$), accompanied by a 24.3 % decrease in the proportion of normal sperm ($p < 0.0001$) compared with the concurrent control group. In contrast, no significant differences in sperm morphology were observed between males receiving the low dose (0.5 mg/kg bw/day) and the corresponding control group (see Fig. 2C).

Evaluation of total sperm count showed a dose-dependent decrease Fig. 2D). However, the reduction did not reach statistical significance.

Taking into account the results of the two studies evaluating morphofunctional gonadal parameters in males exposed to generic epoxiconazole formulations of differing purity, the test substances were associated with adverse effects on male reproductive function, including impaired sperm quality and reduced gonadal weight, when administered at 2 mg / kg body weight. These alterations suggest antiandrogenic-like effects, consistent with endocrine-mediated mechanisms affecting male reproductive function, and are supported by the existing literature demonstrating that azole fungicides interfere with steroidogenic pathways [12, 13].

Assessment of sperm parameters using the CASA system provided a more detailed and objective analysis, minimizing the risk of overlooking subtle effects and reducing observer-related error. Nevertheless, manual evaluation also revealed impaired sperm parameters, confirming the adverse effect. The greater toxicity observed following exposure to Epox-2 may be attributable either to its lower purity compared with Epox-1 or to the increased sensitivity of the computerized sperm analysis.

Overall, these findings underscore the importance of thoroughly evaluating generic pesticide formulations with varying impurity profiles, as differences in composition may substantially influence their toxicological properties.

Conclusion. In conclusion, both studies demonstrate that exposure to generic epoxiconazole formulations at 2 mg / kg body weight suggest antiandrogenic-like effects in male rats, as reflected by impaired sperm quality and reduced gonadal weight. The use of the CASA system allowed for a more sensitive and objective detection of alterations in sperm parameters, although manual assessment also confirmed adverse effects. The differences in toxicity observed between Epox-1 and Epox-2 likely relate to variations in formulation purity and impurity profiles. Overall, these findings emphasize the need for comprehensive toxicological evaluation of generic pesticide formulations, as differences in composition may significantly impact their biological and reproductive effects.

Conflict of Interest. The author note that there is no conflict of interest

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A – concept and design; B – research; C – analysis, preliminary preparation;
D – software, statistical analysis; E – writing of the article; F – editing; G – final approval of the article.

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