Statistical analysis of biogenic amines formation process under different levels of selected factors

M. Tláskal, P. Pleva, J. Michálek, L. Buňková, and F. Buňka

***Abstract*—**Some bacterial strains of enterococci are commonly used in food industry and therefore their ability of biogenic amine formation should be investigated. This enables to indicate decarboxylase-positive strains. Within the process of decarboxylation, these strains produce high amount of biogenic amine, which is a toxicologically important compound. Biogenic amines are present in certain foodstuffs (cheese, meat, wine ...) and at high concentrations they are considered risk factors for human health. The aim of this contribution was to explore production of eight chosen biogenic amines by *Enterococcus faecium* (DPE 002) from rabbit meat (*Oryctolagus cuniculus f. domesticus*) and to evaluate the effect of selected factors on the production.

To fit the data subsets involving different conditions of the experiment, appropriate regression models were used. Some of the growth curves such as Gompertz, logistic, and Richards are found to be very useful in many areas. The most suitable models for our data appeared to be Gompertz and logistic. Their three regression parameters, which are of biological interest, are an asymptotic value of concentration, a maximum production rate and a lag time. Model parameters were estimated and tested. The effect of different factor levels on the parameter values is studied.

***Keywords*—**Biogenic amines, Gompertz curve, Growth model, Logistic curve.

I. Introduction

BIOGENIC amines (BAs) are basic compounds (especially histamine, phenylethylamine, tyramine, tryptamine, putrescine, cadaverine, spermidine and spermine) formed in foodstuff mainly by microbial decarboxylation of relevant free amino acids (especially histidine, phenylalanine, tyrosine, tryptophan, lysine, ornithine and arginine). Many strains *Salmonella*, *Shigella*, *Escherichia*, *Serratia*, *Yersinia*, *Morganella*, *Pseudomonas* and lactic acid bacteria (e.g. *Lactobacillus* and/or *Enterococcus*) were identified as producers of BAs. The presence of biogenic amines is usually connected with food poisoning and can thereby threaten health of its consumers. Ordinary amounts of BA (practically <100 mg/l or mg/kg) in food are metabolized in intestinal tract of healthy individuals where they are detoxicated by proper enzymes (especially monoamine oxidase and diamine oxidase). Especially in sensitive consumers, excessive intake of histamine and tyramine can result in hyper- or hypotension, migraine, headache, vomiting, and respiration problems. Putrescine and cadaverine can potentiate the impact of tyramine and histamine occurrence, because they inhibit their detoxication enzymes. Polyamines (especially spermine and spermidine) can be converted to carcinogenic nitrosamines, which represent an issue to be studied [10], [17], [20].

Since some strains of enterococci are even used as starter cultures and/or probiotics, their decarboxylase activity should be studied to indicate decarboxylase-positive strains. The aim of the study was to explore production of eight biogenic amines (tryptamine, phenylethylamine, histamine, cadaverine, tyramine, putrescine, spermine and spermidine) by the selected *Enterococcus faecium* (DPE 002) from rabbit meat (*Oryctolagus cuniculus f. domesticus*) [15]. Different levels of factors influencing decarboxylase activity (pH, oxygen availability, concentration of NaCl and temperature) were set up in the experiment.

Mathematical models describing laws of growth and development phenomena are needed in many fields, like e.g. food microbiology (see [3], [6], [12], [23]), biomedicine [16], crop science, forestry [14], animal science, business and economics [19], and computer science [18]. We have considered Gompertz, logistic and Richards model (see [23]).

The aim of the work was to study production of biogenic amines by *Enterococcus faecium* (DPE 002) from rabbit meat (*Oryctolagus cuniculus f. domesticus*), to evaluate the effect of selected factors on the production and to fit the data by appropriate regression models.

II. Methods and Materials

Effects of additions of NaCl, values of pH and

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aerobic/anaerobic conditions, that could influence production of biogenic amines, were tested using *Enterococcus faecium* (isolated from rabbit meat (*Oryctolagus cuniculus f. domesticus*)). The tested *Enterococcus faecium* (DPE 002) strain was cultivated in MRS broth (Oxoid, Basingstoke, UK) enriched with the precursors of the monitored BAs (amino acids: arginine, histidine, lysine, ornithine and tyrosine, each with the concentration of 2 $g \cdot l^{-1}$; Sigma-Aldrich, St. Louis, USA). The cultivation medium of the volume 5 ml was inoculated with 25 µl overnight culture of the strain (~10^6 CFU/ml).

Experimental setup to the following scheme: (i) effect of NaCl additions at concentrations 0; 10; 20; 30 and 60 g/L; (ii) effect of pH-value: 5.0; 6.0 and 7.0; (iii) cultivation temperature: 6; 12 and 30 °C; and (iv) aerobic and anaerobic environment. The development of biogenic amines was observed during cultivation: 0; 2; 4; 6; 8; 10; 12; 24; 30; 34 and 48 hours (30 °C), 0; 24; 48; 72; 96; 144; 168; 216; 240; 312 and 360 hours (12 and 6 °C).

The production of eight biogenic amines (tryptamine, TRY; histamine, HIS; tyramine, TYR; phenylethylamine, PHE; putrescine, PUT; cadaverine, CAD; spermidine, SPD; spermine, SPN) was monitored by an high performance liquid chromatography system equipped with a binary pump; an autosampler (LabAlliance, State College, USA); a column thermostat; a UV/VIS DAD detector (λ = 254 nm); and a degasser (1260 Infinity, Agilent Technologies, Santa Clara, USA).

After cultivation of the tested bacteria, the broth was centrifuged (4000 x *g*; 22±1 °C; 20 minutes) and the acquired supernatant was diluted (1:1; v/v) with perchloric acid (c = 0.6 $mol.l^{-1}$). The mixture was filtered (porosity 0.22 µm) and the acquired filtrate was subjected to derivatisation with dansylchloride according to [5]; 1,7-heptanediamine was used as an internal standard. The derivatised samples were filtered (porosity 0.22 µm) and applied on a column (Agilent Zorbax Eclipse C18, 50 × 3.0 mm, 1.8 µm; Agilent Technologies; Agilent, Paolo Alto, CA, USA). The conditions for separation of the monitored BA are described by [13]. Each of the three cultivated broths was derivatised once and applied on the column.

To sum up, totally 33 measurements were made (11 time points, 3 samples) for every combination of individual factor levels and the total number of combinations was 90.

III. Statistical analysis

The three nonlinear regression models that we have considered as suitable for description of temporal progress of biogenic amine concentration were Gompertz, logistic and Richards model. Equations of the sigmoidal growth curves, which correspond to these models, are as follows:

Gompertz model:

$$y(t)= A \exp\left\{- \exp\left[\frac{\mu \cdot e}{A}(\lambda - t)+1 \right]\right\}$$

logistic model:

$$y(t)= A \left\{1+ \exp\left[\frac{4\mu}{A}(\lambda - t)+2 \right]\right\}^{-1}$$

Richards model:

$$y(t)= A \left\{1+ \nu \exp\left[1+\nu + \frac{\mu}{A}(1+\nu)^{1+1/\nu}(\lambda - t) \right]\right\}^{-1/\nu}$$

Here y(t) stands for production of biogenic amines and *t* is time. Parameterization of the curves according to [23], where their parameters have a clear biological meaning, was used. The parameter A is the asymptotic concentration (for *t* approaching ∞, in $mg \cdot l^{-1}$), µ is the maximal production rate (in $mg \cdot l^{-1} \cdot h^{-1}$) and λ is the lag time (in hours, defined as the *t*-axis intercept of the tangent through the inflection point).

All the three curves under consideration are S-shaped and have some similar properties [22]. On the other hand, a substantial difference among them is the ordinate of the point of inflection. In the case of Gompertz curve it is A/e, in the case of logistic curve it is A/2, and in the case of Richards curve, the additional parameter ν affects the ordinate of the inflection point [23].

First of all, data values which are obviously outliers were removed from data sets (approximately 0.4 % of measured values). Every data set representing different conditions of the experiment was processed by tools of nonlinear regression analysis. As appropriate nonlinear models we have considered Gompertz, logistic and Richards model. By means of Akaike information criterion [2] it was decided which model fits the data best. Where possible, the datasets were tried to be fitted by the three above mentioned models. Nevertheless, none of the models was considered as suitable for some datasets and therefore model-free spline fit was used for description of the data. In these cases, standard deviations of parameter estimates were not calculated and the combination of experimental conditions was not encompassed in the subsequent Bonferroni procedure. Regression analysis was performed with the use of the R 3.0.1 software, the package *grofit* was exploited for fitting data sets by growth curves. To obtain initial values of regression parameters (A, µ, and λ), the given time series was fitted by local weighted regression method (implemented in the function *lowess*). For more information about *grofit* package and corresponding R-functions that are used in connection with the problem of growth curve fitting see [11]. The package is available from http://cran.r-project.org/package=grofit. Values of the cubic interpolation spline parameters were used as initial parameter estimates for the subsequent iterative procedure, which calculates parameter estimates by the nonlinear least squares method. Final estimates of parameters were obtained by applying Gauss-Newton algorithm.

The parameter estimates and their standard deviations were

calculated and under different experimental conditions, differences in their values became obvious. To test whether the observed differences are statistically significant, method of multiple comparisons was applied. We have assumed an asymptotic normality of estimated parameters. Multiple comparisons of parameters were performed by the Bonferroni method ($\alpha = 0.05$). This procedure was carried out for all datasets excepting the sets that were modelled by spline. For testing hypotheses about parameters, the asymptotic normality of parameter estimators was used and *u*-tests were applied.

IV. Results of Analysis

Production of high concentrations was detected in the cases of phenylethylamine (PHE) and tyramine (TYR). None of the datasets was fitted by Richards model. It seems that the three-parameter Gompertz and logistic curves are models, which are sufficient for the description of kinetics of biogenic amines formation. To be honest, we must note that in 1 out of 125 cases (where parametric models were used) the four-parameter Richards model was chosen as the best. Nevertheless, as the difference between Richards model and the second best model – logistic is visually negligible in this case and for the reasons of unification and simplification we have decided to choose logistic model for this dataset.

A few other exceptions of model selection were made. For phenylethylamine; temperature of 30 °C; pH-value of 7; NaCl concentration of 3 %; aerobic conditions, the data show only the exponential phase of production, more precisely, the time series is well modelled by exponential phase of Gompertz curve. Therefore A parameter estimate is not reliable. Taking into consideration values of parameter estimates for the same level of temperature and pH-value (two most influential factors, this can be seen from Fig. 3), spline model was used instead. It should be mentioned that A parameter estimates from spline fit mean (approximately) the maximal mean concentration, not the asymptotic concentration. For both biogenic amines and temperature of 6 °C, the time series do not follow an S-shaped curve. In spite of this fact, in some cases (TYR, pH of 5 and partly of 6) the time series is well approximated by a sigmoidal curve. Data and regression curve display revealed that only upper part (linear production phase and asymptotic phase) of a sigmoidal curve was observed. For this reason, these estimates of parameter λ (16 in all) are negative and unreliable. Moreover, they cannot be biologically interpreted. A similar case is combination TYR; temperature of 12 °C; pH of 5; NaCl concentration of 6 %; anaerobic environment. They were excluded from the Bonferroni procedure and thus only two levels (12 and 30 °C) of temperature were tested. In the graphs on Fig. 3 and 4 these estimates are not drawn as well as other negative λ estimates from spline fit.

All the factors (temperature, pH, NaCl concentration, and anaerobic/aerobic conditions) proved to be statistically significant at a level of significance of 5 % as in [21]. In comparison with [21], slightly different algorithm for Bonferroni procedure was applied and more precise results were obtained. After data revision for temperature level of 12 °C, some numerical results can slightly differ from [21].

Detailed results follow.

A. Results for phenylethylamine formation

Growing pattern was observed for temperatures of 12 and 30 °C. In these cases, coefficient of determination R^2 realised in the range from 0.721 to 0.999. For temperature of 6 °C the maximal mean concentration (obtained from spline fit) is less than 10 $mg \cdot l^{-1}$ and decreases with increasing pH-value. (And for pH-value of 7, values of PHE concentration were very low and mainly not detected by the measurement device and thus no datasets could have been processed.) The maximum asymptotic concentration determined by the parameter A was observed for temperature of 30 °C; pH-value of 6; concentration of NaCl of 2 %; anaerobic environment.

For pH-value of 5 and 6 it holds that temperature level of 30 °C provides better conditions for PHE formation (substantially higher values of estimated parameters A and μ, lower values of parameter λ) than environment with temperature of 12 °C. With only very few exceptions (parametric) estimates of A and μ are higher for temperature of 12 °C than (spline) estimates for temperature of 6 °C. For environment with pH-value of 7 we have an ambiguous result: the values of parameter λ are lower for temperature of 30 °C than for temperature of 12 °C, however, with the exception of NaCl concentration of 6 %, values of parameter A are lower as well. The level of pH-value of 7 has an obvious decreasing influence on parameters A and μ in the case of temperature of 30 °C. For temperature levels of 12 and 30 °C, and with the exception of the combination temperature of 30 °C; pH value of 7, it is apparent, that the level of NaCl concentration of 6 % provides the worst conditions for PHE production (lower values of parameters A and μ, higher values of parameter λ). Mostly, anaerobic environment gives higher values of parameters A and μ (and lower values of parameter λ).

The effect of experimental conditions on value of parameter A

At a significance level of 5 % all the factors proved to be statistically significant. More precisely, the hypothesis of A parameters equality was rejected in 100, 71, 53, and 64 % of all cases, respectively for the factor temperature, pH of the environment, NaCl concentration, and aerobic/anaerobic conditions, respectively. The impact of oxygen availability (64 % significant tests) differs substantially for the temperature levels of 12 and 30 °C, respectively. The ratios of significant *u*-tests are 91 % and 43 %, respectively. For all these statistically significant differences, the anaerobic environment provides higher asymptotic concentrations. This can be seen in the top graph in Fig. 3.

The effect of experimental conditions on value of parameter μ

The impact of pH of the environment is apparent for temperature of 30 °C: the maximum growth rate was highest in the case of pH-value equal to 6 and lowest in the case of pH-value equal to 7. The difference between levels of pH-value of 5 and 6 is statistically significant in 40 % of cases. At a significance level of 5 % all the factors proved to be statistically significant. The hypothesis of μ parameters equality was rejected in 88, 71, 45, and 56 % of all cases, respectively for the factor temperature, pH, NaCl concentration, and aerobic/anaerobic environment, respectively. Similarly as for A parameter, we should evaluate the impact of oxygen availability with regard to temperature level. The ratios of significant *u*-tests are 21 % (for temperature of 30 °C) and 100 % (for temperature of 12 °C). In the latter case, the anaerobic environment provides higher maximum production rates with the exception of the highest 6 % NaCl concentration level.

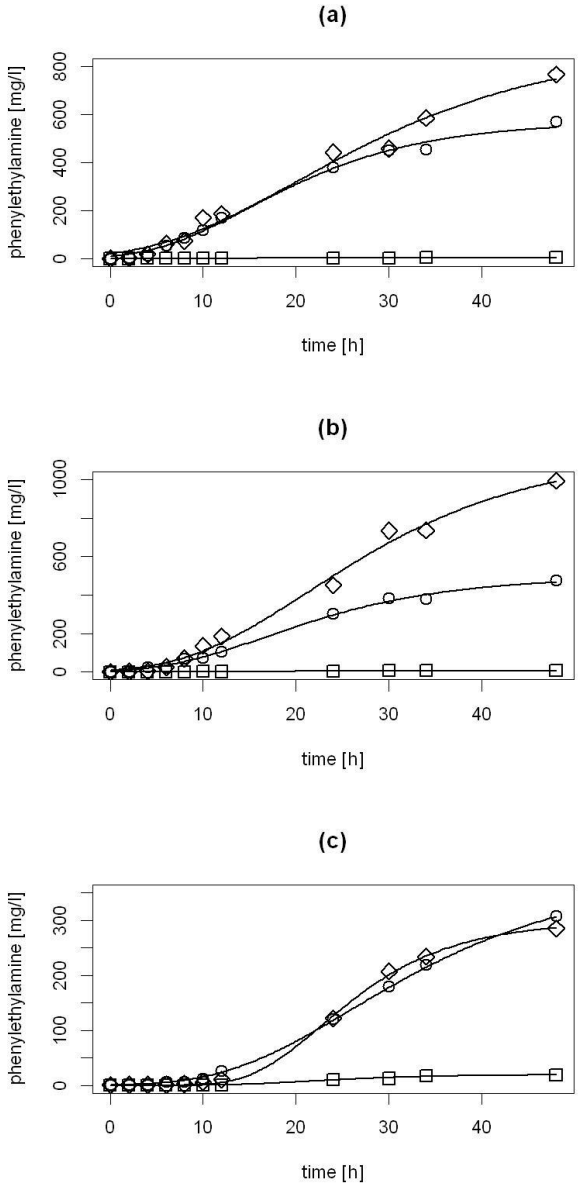

Fig. 1 Impact of pH of the environment on the asymptotic concentration and the maximum production rate of phenylethylamine. Graphical illustration is for temperature of 30 °C, anaerobic environment. Levels of NaCl concentration are gradually (a) 0 %; (b) 2 %; (c) 6 %. Markers at 11 time points denote average values of measurements (pH 5 circle, pH 6 diamond, pH 7 square). Corresponding Gompertz (or logistic) curves are drawn as well.

The effect of experimental conditions on value of parameter λ

The influence of all the factors was evaluated as statistically significant again (at a significance level of 5 %). The hypothesis of λ parameters equality was rejected in 79, 8, 24, and 4 % of all cases, respectively for the temperature, pH, NaCl concentration, and aerobic/anaerobic environment factor, respectively.

The impact of pH of the environment can be seen in Fig. 1. The effect of all factors on PHE production parameters can be seen in Fig. 3.

B. Results for tyramine formation

Growing pattern was observed for all temperature levels of 6, 12 and 30 °C. Coefficient of determination R^2 realised in the range from 0.814 to 0.995. It should be noted that tyramine always gives substantially higher asymptotic concentration (parameter A) than phenylethylamine. For instance, the maximal values of A parameter are 1,875 $mg \cdot l^{-1}$ (TYR) and 1,134 $mg \cdot l^{-1}$ (PHE), respectively. The maximum asymptotic concentration was observed for temperature of 30 °C; pH-value of 6; concentration of NaCl of 1 %; and anaerobic environment.

The impact of temperature on A parameter values is not as transparent as in the case of PHE. It is obvious, that the worst conditions for TYR production are given in the environment with temperature of 6 °C (substantially lower values of parameters A and μ, with few exceptions for NaCl concentration level of 6 %). The impact of levels of 12 and 30 °C is comparable, with the exception of the environment with pH-value of 6, where higher level gives higher values. In the two remaining cases it holds that the values of parameter A are similar (except NaCl concentration of 6 %). The difference is that nearly asymptotic concentrations are reached sooner in the case of temperature of 30 °C (this is implied by lower values of parameter λ and substantially higher values of parameter μ). For the temperature of 6 °C, values of parameter A decrease with increasing pH-value, however, the impact of pH value of the environment is not generally clear. Anaerobic conditions provide higher values of parameter A in the environment with temperature of 12 °C (with the exception of NaCl concentration of 6 %). Decreasing effect of 6 % level of NaCl concentration on parameter A values is apparent mainly

in the case of temperature of 12 °C.

The effect of experimental conditions on value of parameter A

At a significance level of 5 % all the factors proved to be statistically significant. To be more precise, the hypothesis of A parameters equality was rejected in 81, 64, 35, and 29 % of all cases, respectively for the factor temperature, pH, NaCl concentration, and aerobic/anaerobic environment, respectively. It shoud be noted, that the impact of oxygen availability clearly depends on temperature level. For levels of 6 and 30 °C oxygen availability factor is statistically insignificant. On the other hand, for temperature of 12 °C it proved to be statistically significant in 10 out of 12 cases. (With the exception of NaCl concentration level of 6 % it holds that anaerobic environment gives higher asymptotic concentrations.)

The effect of experimental conditions on value of parameter μ

At a significance level of 5 % all the factors proved to be statistically significant. The hypothesis of μ parameters equality was rejected in 96, 36, 25, and 9 % of all cases, respectively for the temperature, pH, NaCl concentration, and aerobic/anaerobic environment factor, respectively. Similarly as in the case of parameter A, for levels of 6 and 30 °C oxygen availability factor is statistically insignificant. Furthermore, it is insignificant also for temperature of 12 °C and pH-values of 6 and 7.

The effect of experimental conditions on value of parameter λ

The influence of all the factors tested was evaluated as statistically significant (at a significance level of 5 %). The hypothesis of λ parameters equality was rejected in 79, 46, 33, and 12 % of all cases, respectively for the factor temperature, pH, NaCl concentration, and aerobic/anaerobic environment, respectively. The impact of pH of the environment (46 % significant results) is different for the temperature levels of 12 and 30 °C, respectively. The ratios of significant *u*-tests are 18 % and 67 %, respectively. In the latter case, this is due to the highest level of pH of 7, which gives higher values of λ parameter. Anaerobic/aerobic environment is statistically insignificant factor for temperature of 30 °C; temperature of 12 °C with pH values of 6 and 7.

The impact of pH of the environment and aerobic/anaerobic environment is illustrated in Fig. 2. The effect of all factors on TYR production parameters can be seen in Fig. 4.

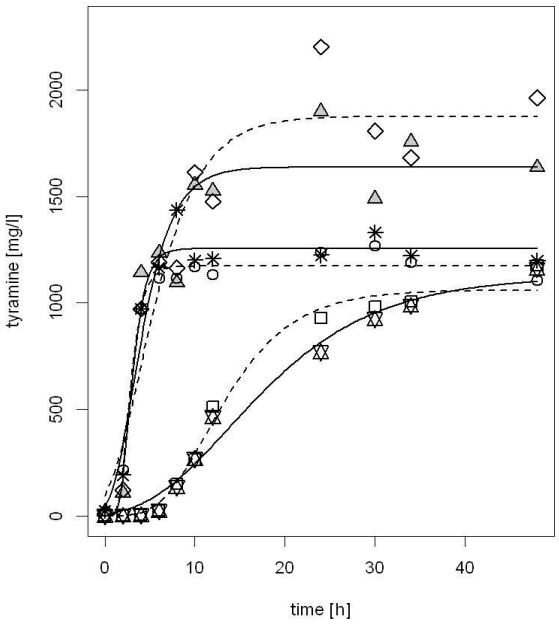

Fig. 2 Impact of pH of the environment and aerobic/anaerobic conditions on the asymptotic concentration of tyramine. Graphical illustration is for temperature of 30 °C, NaCl concentration of 1 %. Markers at 11 time points denote average values of measurements (aerobic environment: pH 5 asterisk, pH 6 full triangle, pH 7 hexagram star; anaerobic environment: pH 5 circle, pH 6 diamond, pH 7 square). Corresponding Gompertz (or logistic) curves are drawn as well (aerobic environment: solid curve; anaerobic environment: dashed curve).

V. Discussion

Presence of oxygen influenced synthesis of biogenic amines ([1]). It was a factor which does not influence decarboxylase activity of microorganisms in clear way. Different cultures and strains could react on oxygen presence in different manners. According to [1], facultative anaerobic microorganisms produced lower amount of biogenic amines in anaerobic environment in comparison with aerobic environment. Presence of oxygen has lesser impact on biogenic amines production compared to other factors, such as NaCl and lactose concentration and pH of environment ([3]).

Similarly as in our study, [3], [4], [7], [9] and [8] observed maximum amine productions in the presence of low amounts (up to 2.5 %) of NaCl in the media while culturing *Lactococcus lactis*, *Enterococcus durans*, *Enterobacter* spp. and *Enterococcus. faecalis*, respectively. Higher NaCl concentrations (up to 6 %) minimised the content of BAs in the media ([7], [8], [9]). The decarboxylase activity is generally stronger in an acid environment, with the optimum pH ranging between 4.0 and 5.5 ([8], [10]).

VI. Conclusion

It was observed that *Enterococcus faecium* (DPE 002) produces high concentration only of two biogenic amines, namely phenylethylamine and tyramine. In the cases of other biogenic amines no concentration growing pattern is obvious (and the maximal mean concentration is less than 50 $mg \cdot l^{-1}$). In most cases, Gompertz or logistic model visually gave reasonably good fits of the data. In 87 % of the cases, the preferable model was the Gompertz than the logistic.

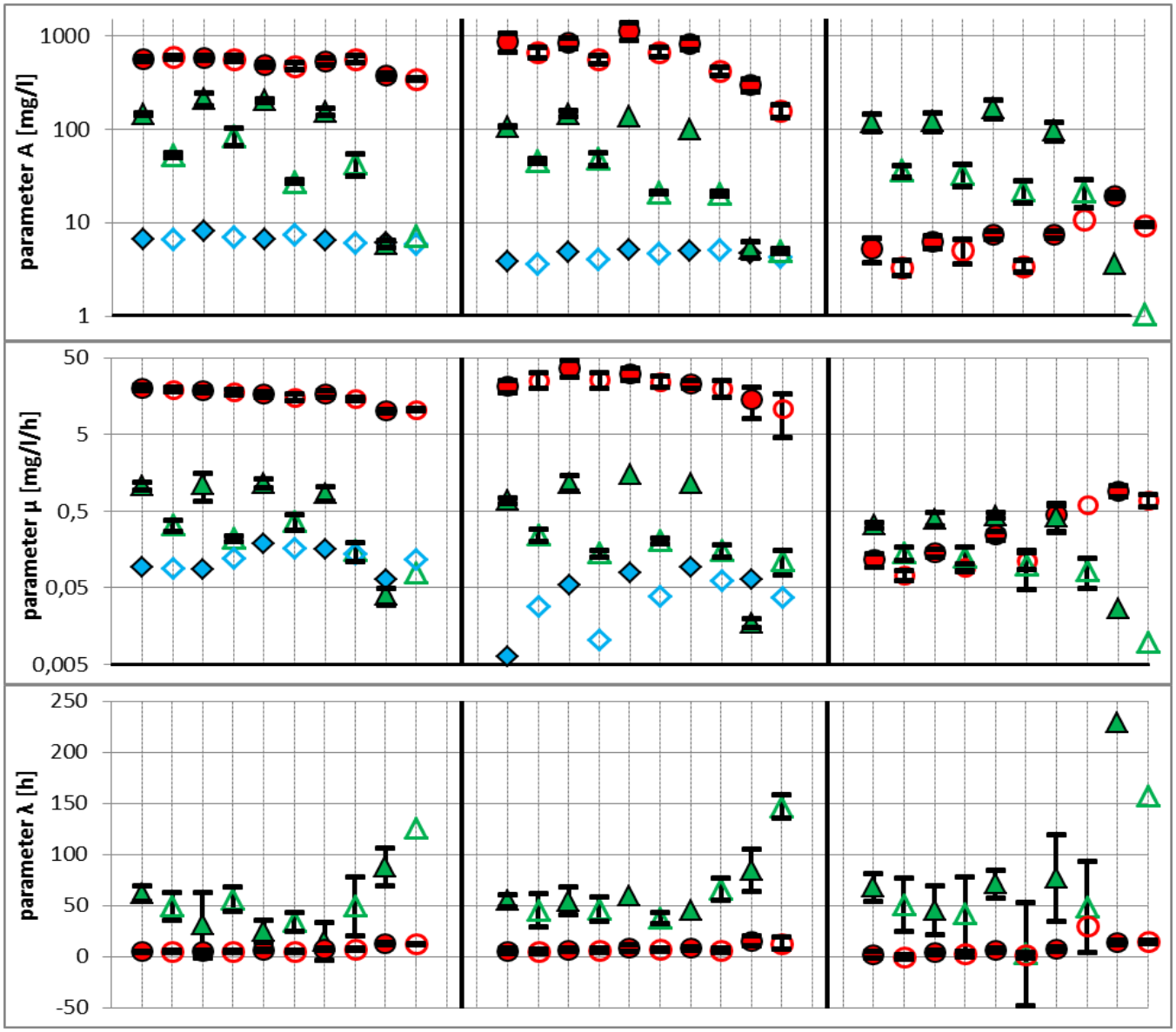

Fig. 3 Impact of selected factors on phenylethylamine formation parameters. F1 denotes environment factor (anaerobic (A) or aerobic (E)), F2 denotes level of NaCl concentration (in %), F3 denotes pH value of the environment. Values of parameter estimates for different levels of temperature are drawn by different colours and markers as follows: 30 °C by red circle, 12 °C by green triangle, and 6 °C by blue diamond. Anaerobic environment is denoted by full markers, aerobic environment by empty markers. The left column (ten symbols on the left side of the graph), the middle column (ten symbols in the middle of the graph), and the right column (ten symbols on the right side of the graph) are related to different levels of pH value of the environment (gradually 5, 6, and 7). For every column, levels of NaCl concentration gradually increase (from left to the right), more precisely they are gradually 0, 0, 1, 1, 2, 2, 3, 3, 6, 6 (couples of zeros relate to the anaerobic/aerobic couples). 95 % asymptotic confidence intervals for parameters are drawn as well with exception of some factor levels combinations, which datasets were modelled by spline and therefore only markers are drawn. Note that for A and μ parameters representation log-scale was used.

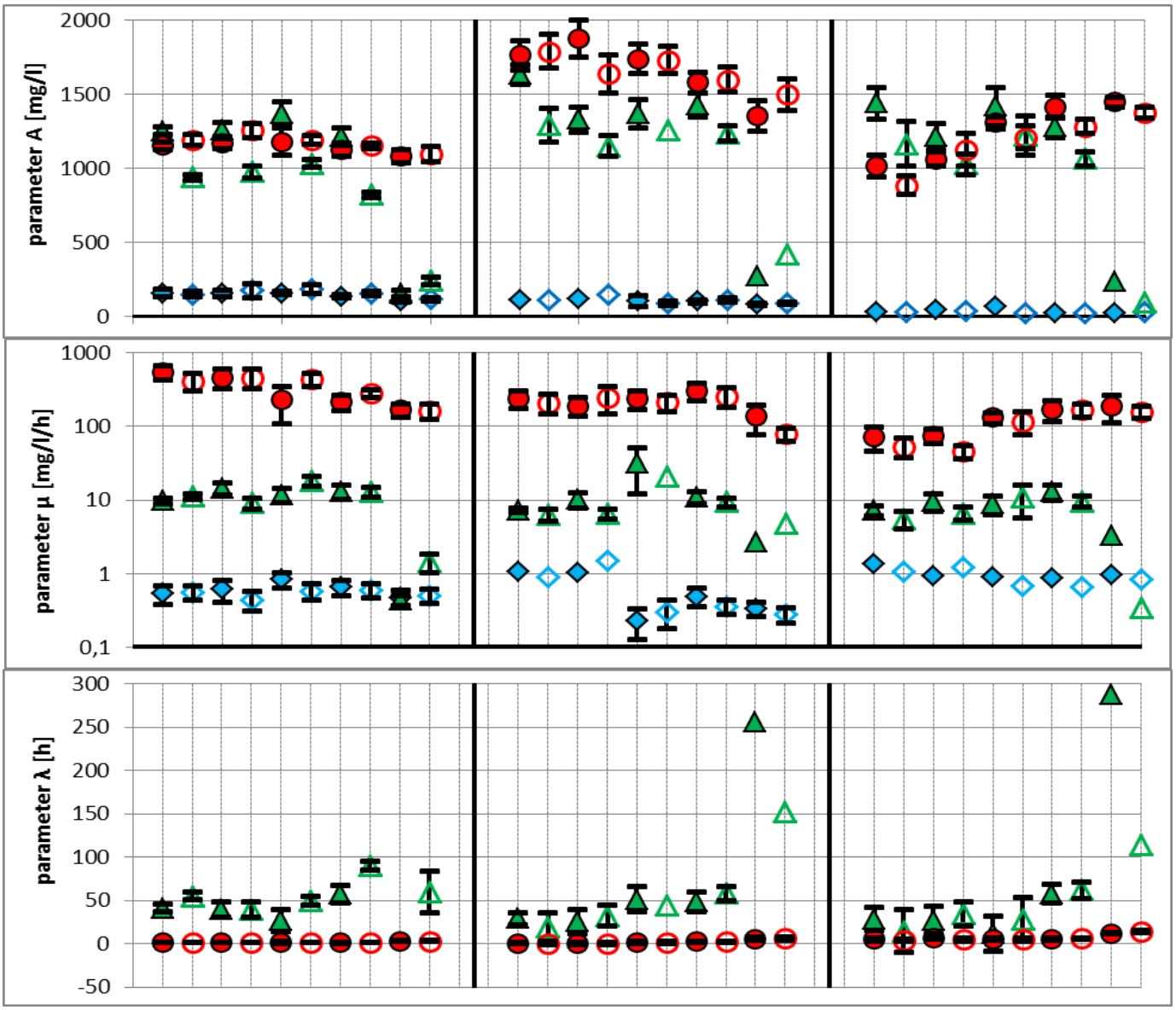

Fig. 4 Impact of selected factors on tyramine formation parameters. F1 denotes environment factor (anaerobic (A) or aerobic (E)), F2 denotes level of NaCl concentration (in %), F3 denotes pH value of the environment. Values of parameter estimates for different levels of temperature are drawn by different colours and markers as follows: 30 °C by red circle, 12 °C by green triangle, and 6 °C by blue diamond. Anaerobic environment is denoted by full markers, aerobic environment by empty markers. The left column (ten symbols on the left side of the graph), the middle column (ten symbols in the middle of the graph), and the right column (ten symbols on the right side of the graph) are related to different levels of pH value of the environment (gradually 5, 6, and 7). For every column, levels of NaCl concentration gradually increase (from left to the right), more precisely they are gradually 0, 0, 1, 1, 2, 2, 3, 3, 6, 6 (couples of zeros relate to the anaerobic/aerobic couples). 95 % asymptotic confidence intervals for parameters are drawn as well with exception of some factor levels combinations, which datasets were modelled by spline and therefore only markers are drawn. Note that for μ parameter representation log-scale was used.

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