

НАУЧНЫЕ ПОДХОДЫ К ТОКСИКОЛОГИЧЕСКОЙ
ОЦЕНКЕ ПЕСТИЦИДОВ-ГЕНЕРИКОВ
С ЦЕЛЬЮ ИХ ГОСУДАРСТВЕННОЙ
РЕГИСТРАЦИИ В УКРАИНЕ

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С точки зрения регуляторной токсикологии проблема токсикологической оценки пестицидов-генериков заключается в необходимости доказательства их биологической эквивалентности оригинальной молекуле.

Большинство генериков относятся к пестицидам первого-третьего поколений, токсикологическая оценка которых проводилась более пятнадцати, а то и двадцати лет назад. В связи с этим, объем наработанных в то время токсикологических данных не всегда соответствует современным требованиям, а уровни недействующих доз, особенно по отдаленным эффектам действия, являются недостаточно обоснованными с точки зрения последних достижений науки. Технология производства генерика может существенно отличаться от оригинальной, что приводит к различию в составе примесей, определить токсикологическую значимость которых не всегда представляется возможным.

Поэтому, с нашей точки зрения, применяемый в некоторых странах мира подход, при котором для регистрации генерика достаточно химико-аналитического подтверждения соответствия содержания в действующем веществе значимых примесей, не является достаточно надежным. Требования к пестицидам-генерикам не должны отличаться от существующих требований к оригинальным препаратам: необходимо наличие полного досье, содержащего все разделы – от характеристики физико-химических параметров до исчерпывающей токсиколого-гигиенической оценки. При этом токсикологический раздел досье может содержать отдельные части, составленные с использованием данных открытых публикаций. Однако, с целью подтверждения биологической эквивалентности, считаем обязательным проведение следующих исследований: для действующего вещества и препаративной формы – изучение острой токсичности при различных путях поступления в организм, раздражающего

действия на кожу и слизистые оболочки глаз, сенсибилизирующих свойств; для действующего вещества – изучение субхронической токсичности и мутагенной активности. В случае если лимитирующим показателем при оценке опасности пестицида являются данные по отдаленным эффектам действия (канцерогенность, тератогенность, репродуктивная токсичность, нейротоксичность) – экспериментальные исследования по такому эффекту также обязательны.

Ключевые слова: пестициды-генерики, регуляторная токсикология, биологическая эквивалентность

TRANSPLACENTAL EXPOSURE TO TOBACCO
SMOKE AND ITS GENOTOXIC EFFECT

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Exposure to pollutants continues to be a hot topic as the introduction and use of chemicals is continuously increasing with society modernization. Although this affects the entire human population, increased vulnerability towards *in utero* carcinogenic exposures has been proposed due to a high rate of cell proliferation, relatively high numbers of target cells at risk, altered ability to repair DNA damage, immaturity of metabolism, endocrine immunological systems and longer life span ahead in which to develop chronic disease as compared with adults.

In this context, the analysis of transplacental exposure to different chemicals using either cord blood or placenta has captured the attention of researchers in the last decade culminating in the study of the possible effects of environmental pollutants on infants and mothers' health using DNA adducts micronuclei, DNA damage and epigenetic alterations.

The main goal of this study was to analyze the effect of exposure to tobacco smoke during pregnancy in the levels of DNA damage evaluated in cord blood samples using the alkaline comet assay. The influence of other environmental pollutants, namely, mercury was also considered as the population enrolled in the study was resident in

Aveiro district (previously studied for its mercury levels). A total of 53 women were enrolled in the study at the time of hospital admission for delivery. Smoking status was established on the basis of cotinine concentrations analyzed in maternal plasma by ELISA. Exposure to Hg was assessed by analysis of umbilical cord samples using atomic absorption after thermal decomposition (direct combustion).

Results obtained showed that there was no statistically significant association between observed DNA damage and tobacco smoke exposure or Hg levels. However, the median cotinine value was below 1 ng/mL indicating low exposure to this environmental pollutant. After data discretization, an increase in DNA damage levels was associated to cotinine increases but as the number of individuals included in each class is very low, further studies on this matter are needed.

To the public health sector, these data constitutes a significant contribution to improve knowledge on the effects of tobacco smoke exposure and to support the implementation of measures that may reduce the negative health impact of tobacco smoke, particularly during pregnancy.

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THE ASSESSMENT OF GONADOTOXIC ACTIVITY OF THIAMETHOXAM PESTICIDE IN FORM OF THREE GENERICS

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The purpose of the study was to assess the influence of Thiamethoxam TG (technical grade) pesticide (insecticide-neonicotinoid) produced by three different manufactures (test substances T1, T2 and T3 each of them contains 95.5%, 95.4% and 97% of active ingredient respectively) on fertility parameters of Wistar Han male rats. The studies were performed exposing 40 Wistar Han male rats for each test substance in two different doses (low dose of 1.5 mg/kg and high dose of 15 mg/kg). The detection of functional state of the gonads and evaluation of the reproductive ability for males were performed in the end of exposure period. The reproductive parameters for intact females mated with exposed males were assessed on the 20th day of pregnancy. The test substances T1 and T3 in the maximum dose of 15 mg/kg reveal signs of reproductive toxicity only for exposed males. The test substance T2 in the maximum dose in its turn reveal signs of reproductive toxicity for exposed males and intact females. Based on the results we can conclude that obtained effects are dose-dependent and no effect levels are the same for all test substances (1.5 mg/kg). The observed additional embryotoxic effect at the maximum dose for the test substance T2 presumably is the result of the origin of the test substance.

GENOTOXICITY TESTING OF GENERIC PESTICIDES GLYPHOSATE IN FLUCTUATION AMES ASSAY

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Determination of potential genotoxic effects within generic pesticide studies is an obligatory requirement for justifying their safety usage and evaluation of potential risks. In our research center, we successfully conduct the recommended standard mutagenicity test battery in compliance with GLP, which includes gene mutation tests in bacteria *in vitro* (fluctuation Ames assay OECD 471) and gene mutation tests in mammalian cells *in vivo* and *in vitro* (micronucleus assay OECD 475, 487 and metaphase chromosomal aberration assay OECD 474). The aim