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HET-CAM TEST IN EVALUATION OF IRRITATING ACTION OF ADHESIVES USED IN SHOE MAKING INDUSTRY

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Key words: *shoe adhesives, irritating action, the hen's egg test on the chorioallantoie membrane assay,* in vitro *method*
Ключові слова: *взуттєві адгезиви, подразнювальний ефект, тест на хоріоалантоїсній оболонці курячого яйця, метод* in vitro

Abstract. HET-CAM test in evaluation of irritating action of adhesives used in shoe making industry. Lototska-Dudyk U.B., Kuzminov B.P., Chemodurova N.Ye., Turkina V.A. *The global tendency of the contemporary scientific studies is using alternative biologic models as substitutes of experimental animals. HET-CAM (The Hen's Egg Test on the Chorioallantoie Membrane Assay) is an alternative to in vivo tests involving experimental animals. This test is actively*

used in different biomedical studies. The aim of our work was to study the irritating potential of adhesives used in shoe making industry in experimental setting using the alternative HET-CAM method. Polyurethane, polychloroprene, rubber and styrene-butadiene adhesives that are widely used in shoe-making industry were studied . HET-CAM test was used for the evaluation of the irritating action of the aforementioned adhesives. All adhesives were applied directly onto the chorioallantoic membrane of chick embryos with reactions and changes (hemorrhages, vascular lysis and coagulation) observed and registered in 30, 120 and 300 seconds after the application of the adhesive. Irritating potential of the adhesives was evaluated according to a calculated irritating index. The most pronounced signs of irritating action were caused by polyurethane adhesives, namely hemorrhages and coagulation (30 sec) – two-component adhesive and hemorrhages (30 sec) and coagulation (120-300 sec) – one-component adhesive. Vascular reactions from application of styrene-butadiene adhesives manifested predominantly with lysis and hemorrhages (30 sec), in some samples these reactions were observed at a later time-point (120-300 sec). Irritating action of rubber adhesives manifested mostly with hemorrhages (30 sec), one observation showed lysis (120 sec). Polychloroprene adhesive caused hemorrhages (30-120 sec) and also lysis (30 sec) in one of the samples. According to the irritating index, polyurethane (one- and two-component) and styrene-butadiene adhesives were estimated to be strong irritants, while rubber and polychloroprene ones cause moderate irritating action. HET-CAM test can be used as a component in the evaluation of evidence of irritating action of shoe adhesives.

Реферат. Застосування HET-CAM-тесту для дослідження подразнювальної дії взуттєвих адгезивів. Лотоцька-Дудик У.Б., Кузьмінов Б.П., Чемодурова Н.Є., Туркіна В.А. *Глобальною тенденцією сучасних досліджень є використання альтернативних біологічних моделей на заміну чи обмеження експериментів на тваринах. HET-CAM (The Hen's Egg Test on the Chorioallantoie Membrane Assay) тест служить альтернативою тестів in vivo на експериментальних тваринах та активно використовується в різних галузях біомедичних досліджень. Метою роботи було дослідити в експериментальних умовах подразнювальний потенціал взуттєвих адгезивів з використанням альтернативного методу HET-CAM. Досліджували поліуретанові, поліхлоропренові, каучукові та стирол-бутадієнові адгезиви, які використовуються в технології виготовлення взуття. Для оцінки подразнювальної дії клейових сполук використано метод HET-CAM. Клей у нативному вигляді наносили безпосередньо на поверхню хоріоалантоїсної оболонки курячих ембріонів та спостерігали за змінами та реакціями: виникненнями геморагій, лізисом судин та коагуляцією. Ці ефекти відстежували через 30, 120 та 300 с від часу нанесення клею на хоріоалантоїсну оболонку. За розрахованим індексом подразнення оцінювали іритативну активність адгезивів. Найбільші прояви подразнювальної дії зафіксовані при нанесенні поліуретанових адгезивів, а саме: геморагії та коагуляція (30 с) – двокомпонентний адгезив; геморагії (30 с) і коагуляція (120-300 с) – однокомпонентний адгезив. Судинні реакції від нанесення стирол-бутадієнових клеїв проявилися переважно лізисом, геморагіями (30с), в окремих зразках ці зміни проявилися пізніше (120-300 с), коагуляцією в трьох пробах (30 с або 300 с). Подразнювальний потенціал каучукового клею проявляється переважно геморагіями (30 с), в одній пробі також і лізисом (120 с); поліхлоропренового клею – переважно геморагіями (30-120 с) та лізисом (30 с) одного зразка. За значенням індексу подразнення поліуретанові (одно- і двокомпонентні), стирол-бутадієнові адгезиви оцінено як сильні подразники, каучуковий та поліхлоропреновий – помірної подразнювальної дії. HET-CAM-тест може використовуватися як складова оцінки доказовості подразнювальної дії взуттєвих адгезивів.*

The global tendency of the contemporary scientific studies is using alternative biologic models as substitutes of experimental animals. European directive 2010/63/EU has declared the 3R principle: replace, reduce and refine, when it comes to experimental studies, encouraging innovations in experimental models, such as in vitro and in silico ones [1, 2]. The model of chorioallantoic membrane of a chick embryo (CAM) can be an excellent platform that corresponds to the 3R principle.

CAM is a useful model for studying irritating potential of chemicals because of its ability to react to them with full-scale inflammation due to high vascularization. This process is similar to the one developing in rabbit conjunctiva following exposure to chemical substances and thus can be used as a substitute of the Draize's test [3].

HET-CAM test (The Hen's Egg Test on the Chorioallantoie Membrane Assay) is actively used in different areas of biomedical studies, including to predict toxity of industrial toxins, pesticides, medical agents, cosmetics, antiseptics and dental materials [4, 5, 6, 7].

HET-CAM test is a relatively simple, fast and cheap model that allows screening of large quantities of samples in a short time span [8, 9]. This test does not require formal procedures of an ethics committee approval because chick embryos are not considered living organisms in many countries until the 14th day of its development. CAM is not innervated and the experiments are terminated before the development of pain centers in the brain, which makes the system free of the need to seek formal approval required for animal experiments [10].

Universality, possibility of different substances use, speed and simplicity of the method make HET-CAM test a promising alternative for the evaluation of irritating potential of adhesives. Therefore, the purpose of the work was experimental evaluation of irritating potential of shoe adhesives with the use of HET-CAM test.

MATERIALS AND METHODS OF RESEARCH

Polyurethane, polychloroprene, rubber and styrene-butadiene adhesives used in shoe-making industry were studied.

HET-CAM test was used for the evaluation of irritating action of adhesive substances [11]. The procedures followed the recommendations of the Law of Ukraine "On approval of the procedure for carrying out experiments on animals No. 249 of 03.01.2012, "Directive 2010/63/EU of the European parliament and of the Council of 22.09.2010 on the protection of animals used for scientific purposes as amended by regulation". The study was approved by the Board of Bioethics at Danylo Halytsky LNMU, protocol No. 6, dated June 22, 2019.

The object of the study was chorioallantoic membrane (CAM) of 9-10 days old chick embryos. Fresh (up to 7 days old) chicken eggs weighting 50-60 g were used (n=24). The eggs were checked using an ovoscope; the eggs that were deformed, not viable, had thin or cracked shells or other defects were excluded from the study. The selected eggs were incubated at 38.3±0.2°C and relative humidity of 58±2%. Ovoscopy and control of the embryos development were conducted daily during incubation.

0.9% solution of sodium chloride (NaCl) was used as a negative control. 1% solution of sodium dodecyl sulfate (SDS) known for its irritating effect in vivo experiments was used as a positive control.

To test each adhesive, three eggs were used. Positive and negative controls were tested on three eggs as well. 0.3 ml of each adhesive was applied directly onto the surface of CAM using a disposable glass pipette. Reactions of CAM were observed for the duration of 300 sec using a microcamera-endoscope. The following reactions were observed:

- hemorrhages (hemorrhage from a vessel);
- vascular lysis (lysis of blood vessels);
- coagulation (intravascular and extravascular denaturation of proteins).

Appearance of the aforementioned effects was registered in 30, 120 and 300 sec after the application of the adhesive onto CAM. The results were evaluated according to Table 1.

Table 1

Criteria of the study results evaluation (in points) [11]

Effect / Exposition	Points		
	30 sec	120 sec	300 sec
Lysis	5	3	1
Hemorrhage	7	5	3
Coagulation	9	7	5

The irritating index (total score) was calculated as a sum of all points for all tested effects. The irritating index was used as the criterion for classification of irritating action of the adhesives tested (Table 2).

The data obtained were analyzed using variative statistics methods using Google Sheets and MedStat v.5.2. (Copyright© 2003-2019). Taking into consideration small size of samples, non-parametric statistical methods were applied: the data were presented as the median and quartiles while describing quantitative results (Me [Q1; Q3]) [12].

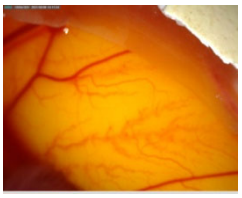
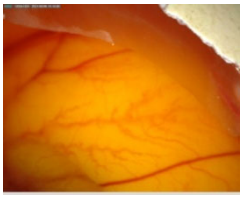
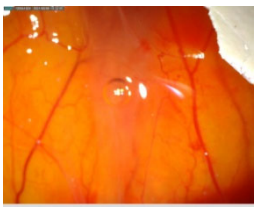
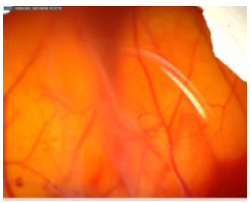
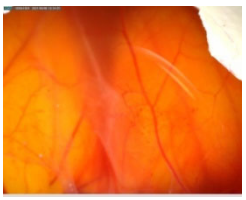
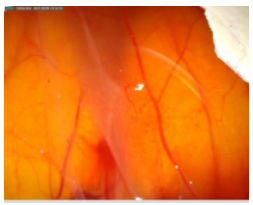
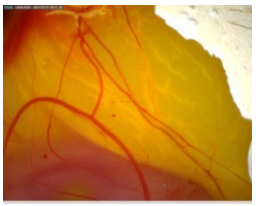
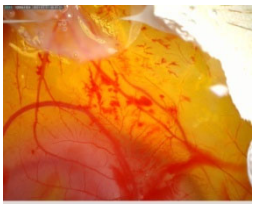
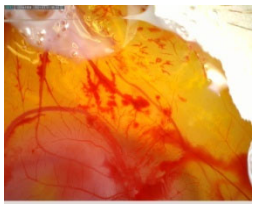
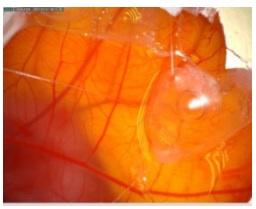
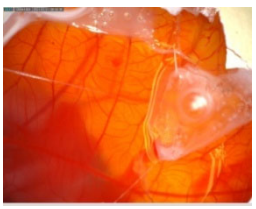
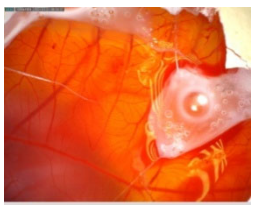
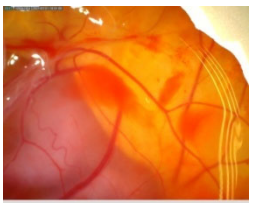
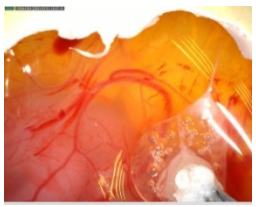
RESULTS AND DISCUSSION

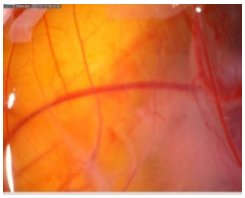
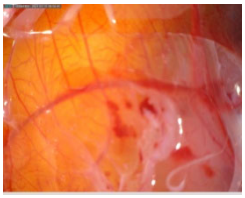
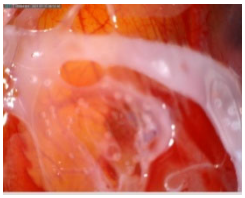
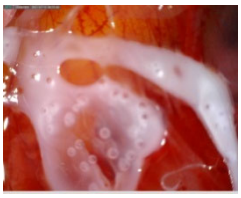
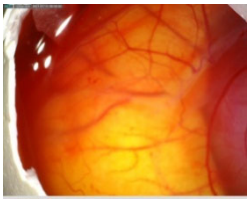
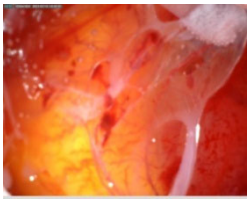
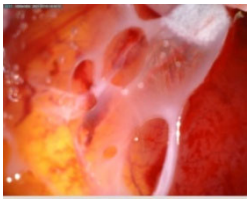
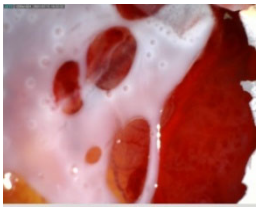
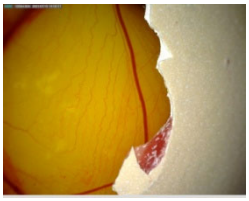
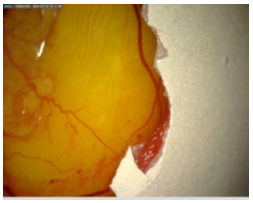
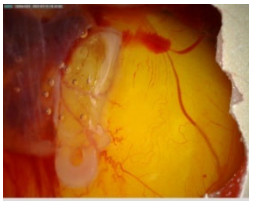
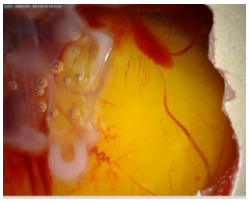
Changes of CAM induced by 1% SDS, 0.9% NaCl and adhesives samples are presented on Figure.

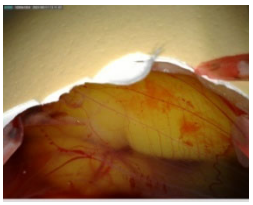
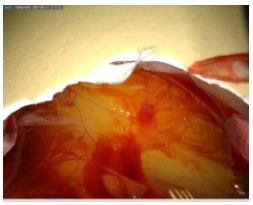
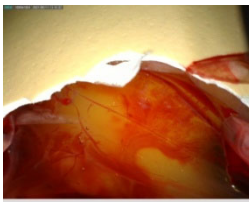
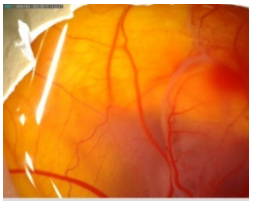
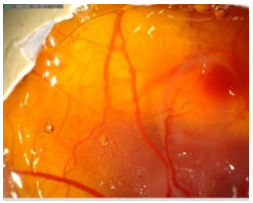
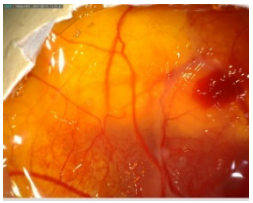
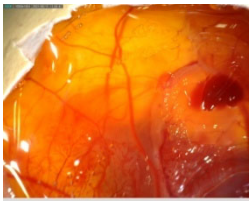
Table 2

Classification of irritating action according to the irritating index [11]

Irritating Index (points)	Risk Category for Irritating Action
0-0.9	No irritating action
1-4.9	Weak irritating action
5-8.9	Moderate irritating action
9-21	Severe irritating action

Sample	Before the exposition	Exposition		
		30 sec	120 sec	300 sec
Negative Control				
Egg № 1				
Egg № 2				
Egg № 3				
Polyurethane adhesive Bonicol Pur				
Egg № 1				
Egg № 2				
Egg № 3				

	Polyurethane *adhesive Bonicol Ter*			
Egg № 1				
Egg № 2				
Egg № 3				

	Styrene-butadiene-styrene (SBS) adhesive			
Egg № 1				
Egg № 2				
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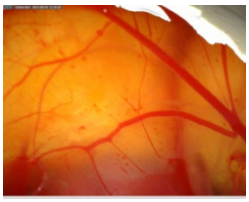
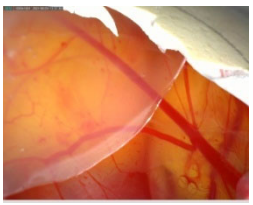
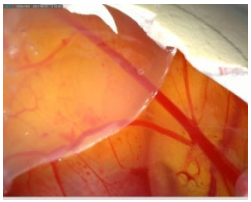
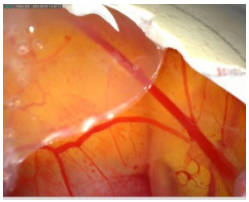
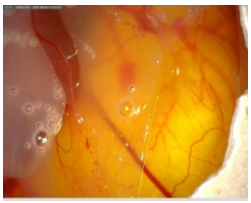
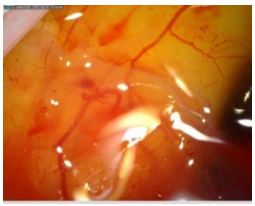
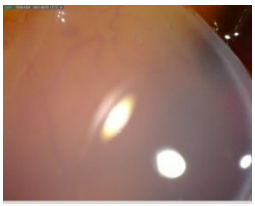
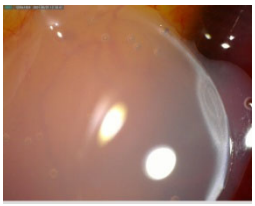
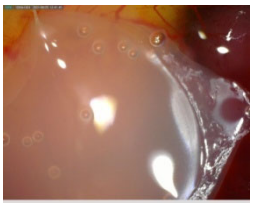
Egg № 1				
Egg № 2				
Egg № 3				

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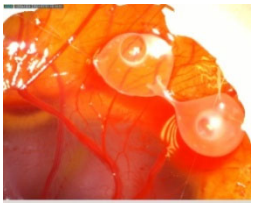
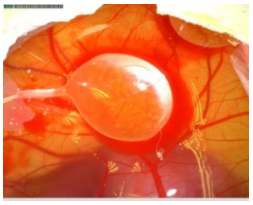
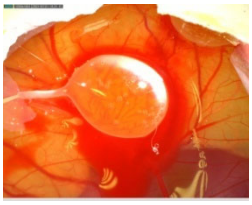
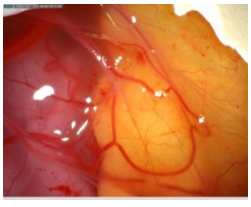
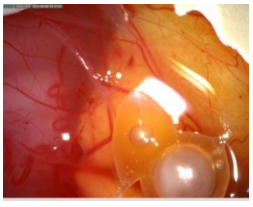
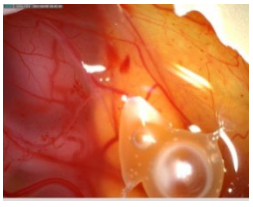
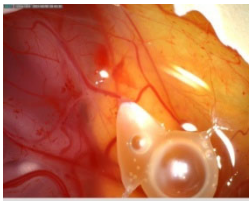
Egg № 1				
Egg № 2				
Egg № 3				

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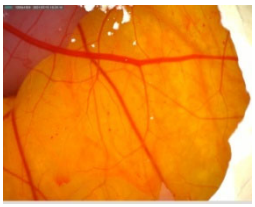
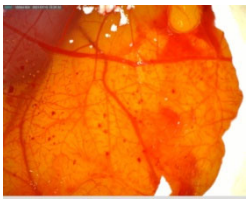
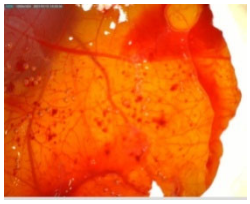
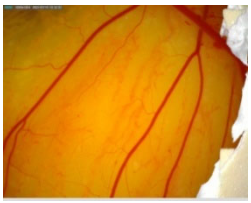
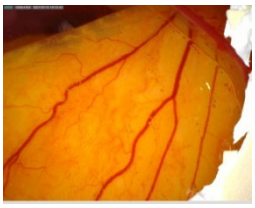
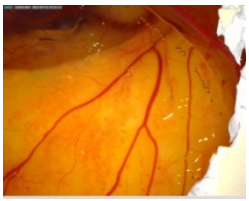
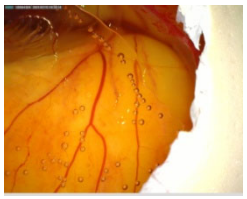
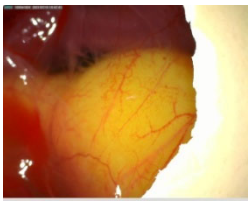
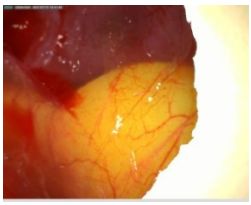
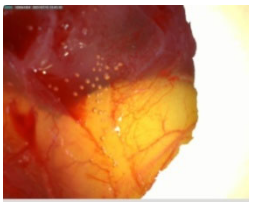
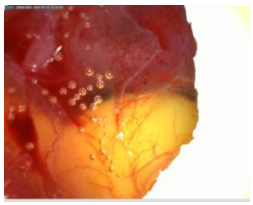
Egg № 1				
Egg № 2				
Egg № 3				

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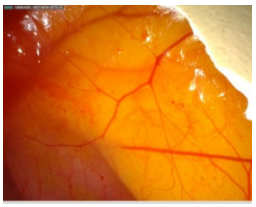
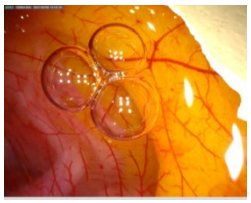
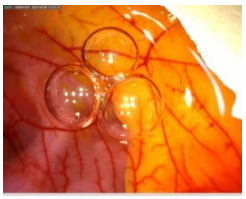
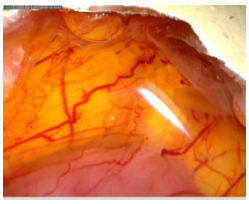
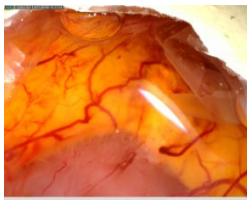
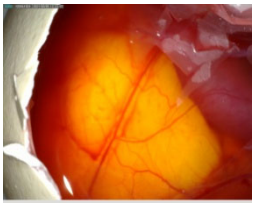
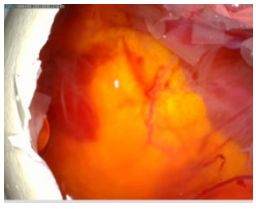
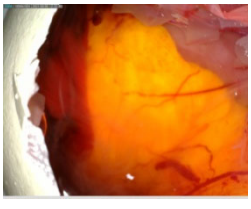
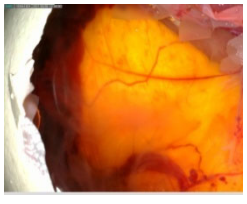
Egg № 1				
Egg № 2				
Egg № 3				

Analysis of irritating action of shoe adhesives. Images of CAM inoculated with negative control, positive control and samples of the adhesives

Dynamics of vascular impairment (lysis, hemorrhages, coagulation) of CAM at certain time-points is shown in Table 3.

Application of 0.9% NaCl onto CAM did not cause any visible changes for the duration of the experiment with the exception of 2 samples that showed minor vascular lysis at 300 sec. On the contrary, application of 1% SDS onto CAM resulted in full inflammatory reaction.

Table 3

Irritation action signs (points)

Observation / Effect	Lysis			Hemorrhage			Coagulation			Total score
	30 sec	120 sec	300 sec	30 sec	120 sec	300 sec	30 sec	120 sec	300 sec	
Negative control										
Observation 1	-	-	-	-	-	-	-	-	-	0
Observation 2	-	-	1	-	-	-	-	-	-	1
Observation 3	-	-	-	-	-	-	-	-	-	0
Polyurethane adhesive Bonicol Pur										
Observation 1	-	-	-	7	-	-	-	7	-	14
Observation 2	-	-	-	-	5	-	-	7	-	12
Observation 3	-	-	-	7	-	-	-	-	5	12
Polyurethane adhesive Bonicol Ter										
Observation 1	-	-	-	7	-	-	9	-	-	16
Observation 2	-	-	-	7	-	-	9	-	-	16
Observation 3	-	-	-	7	-	-	-	7	-	14
Styrene-butadiene-styrene (SBS) adhesive										
Observation 1	-	3	-	7	-	-	-	-	-	10
Observation 2	5	-	-	7	-	-	-	-	-	12
Observation 3	5	-	-	-	-	-	9	-	-	14
Rubber adhesive Bonicol MG										
Observation 1	-	-	-	7	-	-	-	-	-	7
Observation 2	-	-	-	7	-	-	-	-	-	7
Observation 3	-	3	-	7	-	-	-	-	-	10
Polychloroprene adhesive Naryt GTA-1										
Observation 1	-	-	-	7	-	-	-	-	-	7
Observation 2	5	-	-	-	5	-	-	-	-	10
Observation 3	-	-	-	7	-	-	-	-	-	7
Styrene-butadiene rubber latex (SBR)										
Observation 1	-	-	-	7	-	-	-	-	5	12
Observation 2	-	-	1	7	-	-	-	-	-	8
Observation 3	-	-	-	7	-	-	-	-	5	12
Positive control										
Observation 1	5	-	-	-	5	-	-	-	5	15
Observation 2	5	-	-	7	-	-	-	-	5	17
Observation 3	5	-	-	7	-	-	-	-	-	12

The most pronounced signs of irritating action on CAM were caused by polyurethane adhesives, namely hemorrhages and coagulation (30 sec) – two-component adhesive and hemorrhages (30 sec) and coagulation (120-300 sec) – one-component adhesive.

Vascular reactions of CAM resulting from application of styrene-butadiene adhesives manifested predominantly with lysis and hemorrhages (30 sec), in some samples these reactions were observed at a later time-point (120-300 sec).

Irritating action of rubber adhesives is manifested mostly with hemorrhages (30 sec), one CAM showed lysis (120 sec).

Polychloroprene adhesive caused hemorrhages (30-120 sec) and also lysis (30 sec) in one of the samples.

Median values of irritating indices of the adhesives studied and the degree of their irritating action are shown in Table 4.

The value of the irritating index for the positive control is 15(13.5÷16) for 1% SDS. In the negative control, i.e. 0.9% NaCl (sodium chloride), irritating index was 0(0÷0.5).

According to the irritating indices (Table 4), polyurethane (one- and two-component) and styrene-butadiene adhesives are classified as agents of severe irritating action, while rubber and polychloroprene adhesives – of moderate irritating action. The results obtained by us coincide with the data given in the scientific literature [13, 14, 15]. This action of the shoe adhesives is cased mostly by their functional components, with solvents playing the main role.

Table 4

Risk category according to irritating potential of shoe adhesives

Type of adhesive	Irritating index Me (Q1÷Q3)	Risk category according to irritating potential
Polyurethane adhesive Bonicol Pur	**12 (12÷13)**	**Severe irritating action**
Polyurethane adhesive Bonicol Ter	**16 (15÷16)**	**Severe irritating action**
Styrene-butadiene-styrene (SBS) adhesive	**12 (11÷13)**	**Severe irritating action**
Rubber adhesive Bonicol MG	**7 (7÷8.5)**	**Moderate irritating action**
Polychloroprene adhesive Naryt GTA-1	**7 (7÷8.5)**	**Moderate irritating action**
Styrene-butadiene rubber latex (SBR)	**12 (10÷12)**	**Severe irritating action**

The authors [16, 17] confirmed the irritating effect of organic solvents and proved that even in low concentrations (up to 10%) they exhibit the properties of serious irritants. This explains the severe irritating effect of polyurethane adhesives, where the solvent makes up 75-80%, and moderate, which is due to reduction of part of solvent in polychloroprene and rubber adhesives.

The increase in the irritating effect of adhesive Bonycol Ter is due to the addition of an isocyanate solution to its composition, which is confirmed by researchers [18, 19], SBS and SBR adhesives – styrene and methacrylic acid [20]. Irritating action of the components of shoe adhesives is confirmed by their inclusion into the ChemSkin DB [19].

The study of the irritating effect of shoe adhesives by the HET-CAM method expands the spectrum of research of industrial compounds in *in vitro* toxicology. Researchers [20, 21] noted the excellent sensitivity of HET-CAM test for insoluble and slightly soluble compounds, shoe adhesives among them.

CONCLUSIONS

1. Hemorrhages were the main effect of shoe adhesives application onto CAM observed in 30 sec in the majority of samples and in 120 sec in three samples. Coagulation was observed in case of application of polyurethane and styrene-butadiene adhesives (30-120-300 sec of the experiment). Lysis was seen (30 sec) in case of styrene-butadiene and polychloroprene adhesives application. Four types of adhesives were estimated as strong irritants and two others as moderate irritants respectively.
2. HET-CAM test can be used as a part of proven estimation of irritating action of shoe adhesives.

Contributors:

Lototska-Dudyk U.B. – project administration, conceptualization, visualization, writing – original draft, writing – review&editing;

Kuzminov B.P. – project administration, conceptualization, methodology, validation, writing – review & editing;

Chemodurova N.Ye. – research design, visualization, data curation;

Turkina V.A. – methodology, software, formal analysis.

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Conflict of interests. The authors declare no conflict of interest.

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