

IR3535®

# NEWS



## ZIKA VIRAL EPIDEMIC – Repel the mosquito with IR3535® Insect Repellent

The **Aedes mosquito**, e.g. *Aedes aegypti*, is causing widespread fear in Brazil because it is spreading the Zika virus.

Infection with the Zika virus in pregnant women seems to be correlated to a developmental disorder called **microcephaly** in newborns. Other adverse effects like retina damage and autoimmune disease (guillain-barré syndrome) can possibly develop from viral infections with Zika or Chikungunya.

As no vaccine is yet available, it is the recommendation by the **WHO** to use different ways of prevention measures against mosquito bites like mosquito nets, wearing clothes that cover the extremities and using wire mesh screens on doors and windows. **There is also a strong recommendation to use repellents containing e.g. IR3535®.**

WHO Director General Margaret Chan called Zika an "extraordinary event" that needed a coordinated response.

As she said, the priorities were to protect pregnant women and their babies from harm and to control mosquitoes that are spreading the virus:

"I am now declaring that the recent cluster of microcephaly and other neurological abnormalities reported in Latin America following a similar cluster in French Polynesia in 2014 constitutes a public health emergency of international concern."

**In less than a year, the virus has spread to in 26 countries.**

## HOW CAN IR3535® SUPPORT THE PROTECTION OF PREGNANT WOMEN AND THEIR BABIES FROM ZIKA VIRUS INFECTION?

### Who is Aedes?

The *Aedes aegypti* mosquito is the main vector that is transmitting the virus. In the past, this species lived in a forest but it later adapted to rural, suburban human environments over the decades.

The virus is only passed by the female mosquito. The mosquito gets the virus while feeding on the blood of a person that is already infected. After a period between eight and twelve days, the virus can be transmitted to other humans by bites.

As the flight range of female *Aedes* studies show, they spend their lifetime around the houses where they emerge and do not go further than 400 metres. This fact shows that people, rather than the mosquitoes, spread the virus.

### What is Microcephaly?

Microcephaly is a condition where a baby is born with a small head (<33cm) or with a head which stops growing after birth.

Moreover, the condition is combined with a poor brain growth which can lead to developmental disabilities. Usually, it is a very rare condition. Indeed, only one baby in several thousand is born with it.

Today, there is no specific treatment for microcephaly. Early intervention with stimulation and play programmes may show positive impacts on development.

The current situation is that we already have 4000 confirmed cases of microcephaly reported.

### What is the efficacy of IR3535® against Aedes?

World Health Organization gives recommendations to both patients already infected and healthy people:

**Infected patients are recommended to stay under a bed net or stay in a place with intact window/door screens and should be protected with "IR3535® or Icaridin" from further bites.**

**The recommendations for nursing staff or all others are that they should rest under a mosquito net treated with or without insecticide, should wear clothes that cover the extremities, stay in places with air conditioning and should apply repellents to their exposed skin or clothes containing insect repellents like IR3535®.**

**IR3535® has been shown to be effective against various *Aedes* species (e. g. *Aedes aegypti* and *Aedes albopictus*), which are, amongst others, the main vectors for the Zika virus, Dengue virus, Yellow Fever virus, West Nile virus and Chikungunya virus.**

**In addition, various efficacy tests with *Culex* species that may also transmit West Nile virus have been performed.**

Tests have been conducted either with IR3535® in ethanol solution or with various



commercial formulations in cage tests and/or field trials.

Depending on the setup of the tests and the composition of the formulations, **protection times have been derived in the range of 4 to 12 hours.**

**For the registered/approved IR3535® EPA formulations, field tests were performed in the US and these show a high level of efficacy against *Aedes melanimon* (8 - 10 hours protection time). Based on the available data summarized in appendix<sup>1</sup>, it is concluded that IR3535®-based formulations can aid the population in the protection against the above-mentioned vector-borne diseases.**

**Numerous efficacy tests on adults against other active ingredients like DEET and Icaridin show a comparable efficacy between the compounds. In comparison IR3535® proved to be a mild solution but highly effective for prevent from Zika infection.**

**You can find an overview of these tests with the protection time in appendix<sup>1</sup>.**

## IR3535® - How it protects you

The high performance and long-term protective efficacy is given for all ages without any age restriction. If you are a new born, a child, a young mother or an elderly, who is potentially exposed to Zika, you can relax and rely on the protection from mosquito bites.



## IR3535® - Safety for everyone, at any time

### Safe for everyone

The excellent toxicological profile of our active IR3535® assures that it is the safest option in the market amongst synthetic repellents.

IR3535® is the only molecule classified as "U" by WHO-hazard classification which means "Unlikely to present acute hazard in normal use".

In addition to its favorable safety profile, IR3535® has an excellent ecotoxicological profile, i.e. it is not toxic to aquatic organism such as fish or algae and does not accumulate in the environment.

The toxicological profile is summarized in the appendix<sup>2</sup>. You may also find all the information about the non-age limitation in the appendix<sup>3</sup>.

### Safe for pregnant women / breastfeeding women

According to the attached statement of Dr. Thomas Broschard, it can be proven with a comprehensive data package on reproductive toxicity and the long history of safe use of IR3535® that there is no indication that the use of this active ingredient by pregnant and breastfeeding women might be of any risk neither to the expectant mothers nor the nursed babies.

You can find the confirmation of Dr. Thomas Broschard in appendix<sup>4</sup>.

# CONSUMERS CONCERN THEMSELVES WITH ZIKA IN THE MEDIA...

...We monitor: It can be proven from a research social media mining that consumers are looking for a safe and effective solution. Find a few examples out of our research:



## ...Guidelines for Pregnant Women During a Zika Virus...

centers for disease control and prevention

...all **pregnant** women about recent travel. **Pregnant** ... picaridin, and **IR3535** are safe for **pregnant** women...

published on 19 January 2016 at 04:52 | Magazine | Germany | [cdc.gov](http://cdc.gov)



## Before You Travel: What to Know About Protecting Yourself From Zika...

Marilyn Lewis

...recommends that **pregnant** women (in any trimester) or those considering becoming **pregnant** avoid ... younger than 3 or if you are **pregnant**. **IR3535**: This product, based on the amino acid alanine, is...

published 19 hours ago | Online News | United States | [moneytalksnews.com](http://moneytalksnews.com)



## Florida health officials urge precautions against Zika virus

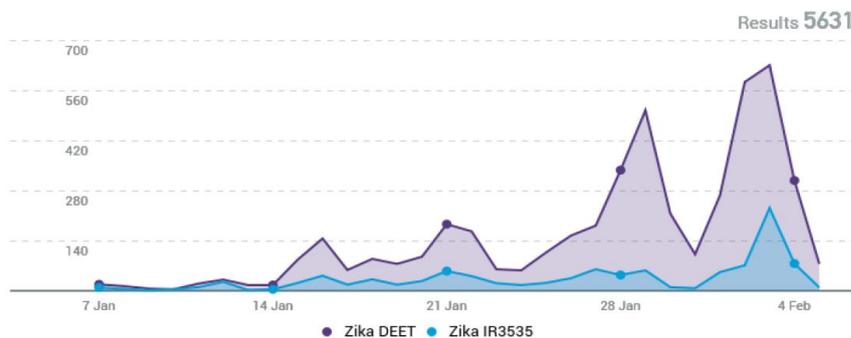
tallahassee democrat

A possible link between Zika virus infection in **pregnant** women and birth defects is being ... picaridin, oil of lemon eucalyptus, and **IR3535** are effective. Use mosquito netting to protect...

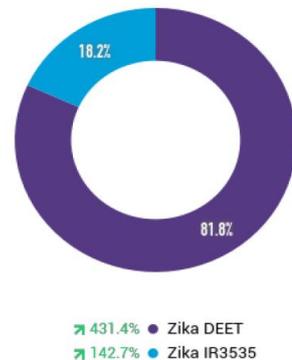
published on 21 January 2016 at 17:15 | Online News | United States | [tallahassee.com](http://tallahassee.com)

### RESULTS OVER TIME

by topics



### SHARE OF TOPICS



### DISTRIBUTION ON THE WORLD MAP

by topics





## IR3535®

### THE VARIOUS BENEFITS OF IR3535®

IR3535® has been created to help people protect themselves from mosquitoes. However, it also promotes comfort and ease for the individual on a number of levels. Other benefits include a nice skin feeling, a pleasant odour and a non-greasy feeling. In addition, it can be applied on you and your beloved and reapplied several times and even worn during the night without any concern.

For more information on safety and effectiveness, you can visit our website: [www.ir3535.com](http://www.ir3535.com)

### REFERENCES

On the February, 2<sup>nd</sup> 2016 :

- World Health Organization : <http://www.who.int/denguecontrol/mosquito/en/>  
<http://www.who.int/emergencies/zika-virus/microcephaly/en/>  
Neurological syndrome, congenital malformations and Zika virus infection.
- BBC: <http://www.bbc.com/news/health-35459797>
- Ladepeche: <http://www.ladepeche.fr/article/2016/02/05/2270830-le-virus-zika-detecte-sur-une-femme-enceinte-en-espagne.html>
- Social Media Mining research

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# APPENDIX 1

## Efficacy Studies with Insect Repellent IR3535® for Human application

No	Author(s) / Institute(s)	Type	Target -Arthropod(s)	IR3535	Efficacy
1	Liebisch A. Institut für Parasitologie der Tierärztlichen Hochschule, Hannover	Lab test	Mosquito <i>Aedes aegypti</i>	10% 15% 20% 30%	252 min 351 min 447 min 456 min
2	Research Laboratory of Dainihon Ichugiku Co., Tokyo, Japan	Field test	Mosquito <i>Aedes albopictus</i>	0,5% 3% 5%	3h 5h 6h
3	Coosemans N. Prince Leopold Institute of Tropical Medicine, Antwerpen, Belgium	Lab test	Mosquito <i>Aedes aegypti</i>	30%	6h
4	Yap H.H. Vector Control Research Unit University Sains Malaysia	Field test	Mosquito <i>Aedes albopictus</i> <i>Culex quinquefasciatus</i>	25%	8h 8h
5	Mulitinovic et al. EKOSAN Co. Faculty of Pharmacy, MMA, Novos Co. Beograd, Yugoslavia	in-vivo lab test	Mosquito <i>Aedes aegypti</i>	10%	5h
6	Usavadee et al. National Institute of Health, Department of Medical Science Nonthaburi, Thailand	in-vivo lab- and field test	Mosquito <i>Aedes aegypti</i> <i>Culex quinquefasciatus</i> <i>Culex tritaeniorhynchus</i> <i>Anopheles dirus</i>	20%	9,8h 13,7h 14,8h 3,8h
7	Cilek J.E. Mulrennan Research Laboratory A&M University, Panama City, FL, IUSA	Cage test	Mosquito <i>Aedes aegypti</i>  <i>Culex quinquefasciatus</i>	10% 20% 10% 20%	116 min 179 min 344 min 393 min
8	Peters B.A. et al	Field test	Mosquito <i>Verrallinia funerus</i> <i>Ochlerotatus vigilix</i> <i>Aedes aegypti</i>  Biting midge <i>Culicoides ornatus</i>	20%	6h    6h
9	Naucke T.J. et al	Field Test	Mosquito <i>Aedes aegypti</i>	10% 15% 10%Spray 15%Spray 20%Spray	5,9h 5,4h 5,8h 6h 5,8h
10	Scott Caroll	Field test	Mosquito <i>Anopheles freeborni</i> <i>Aedes melanimon</i> <i>Aedes vexans</i> <i>Aedes nigromaculus</i> <i>Culex tarsalis</i> <i>Culex erythrothorax</i> <i>Culiseta incidens</i>	10% 20% Aerosol 20% Spray	8,5h 10,3h  8,4h

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To whom it may concern

Date 5 February 2016  
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## IR3535<sup>®</sup>: Toxicological Summary

The safety profile of IR3535<sup>®</sup> has been thoroughly investigated in many *in vitro*, *in vivo* and clinical tests. Based on the results of acute toxicity studies in several species (rat, mouse, dog), IR3535<sup>®</sup> is not acute toxic or harmful after oral, dermal or inhalative exposure. From studies in animals and humans it can be concluded, that IR3535<sup>®</sup> is not a skin irritant and not a skin sensitizer. The undiluted substance is moderately irritating to the eyes. No potential for phototoxicity or photoallergenicity was observed in *in vivo* studies in guinea pigs. The systemic toxicity following repeated application of IR3535<sup>®</sup> is very low: Repeat dose toxicity studies have been performed in several species (rat, dog, rabbit) with different routes of exposure (oral, dermal) and different exposure times (28 days, 90 days). From all these studies, a No Observed Adverse Effect Level (NOAEL) of 500 mg/kg bw/day was selected as the point of departure (PoD) for risk assessment. This NOAEL was derived from a 4-week oral toxicity study in rabbits, which is the most sensitive species after oral administration due to local irritation of the gastrointestinal tract. However, this effect is not considered relevant for humans.



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From a battery of *in vitro* and *in vivo* studies, it is concluded that IR3535<sup>®</sup> poses no mutagenic or genotoxic risk to humans. In developmental toxicity studies (rats and rabbits) and a 2-generation study in rats IR3535<sup>®</sup> was not teratogenic and did not show any toxicity to reproduction. From *in vivo* studies there is no indication for any neurotoxic potential of IR3535<sup>®</sup>. Likewise, no adverse findings suggestive of potential immunotoxicity have been observed in 90-day toxicity studies in rats and dogs or in any of the repeated dosing tests in animals. From a study in volunteers under use conditions, a dermal penetration rate of 14% was obtained for IR3535<sup>®</sup>. Metabolism studies have shown that the carboxylic acid derivative is formed immediately from IR3535<sup>®</sup> as the only metabolite which is rapidly excreted from the body via urine with no evidence of bioaccumulation.

IR3535<sup>®</sup> has been tested for toxicity to aquatic organisms in algae (*S. subspicatus*), daphnia (*D. magna*) and zebrafish (*D. rerio*). The EC<sub>50</sub>- and LC<sub>50</sub>-values from all studies exceeded the limit dose of 100 mg/L. The substance is not toxic to bacteria (EC<sub>20</sub>>1000 mg/L). IR3535<sup>®</sup> is not readily biodegradable, however, total degradation (99%) was observed in a sewage treatment simulation test. In aquatic sediment test, a high transformation rate of IR3535<sup>®</sup> was observed. IR3535<sup>®</sup> did not accumulate in the sediment.

Darmstadt, 5 February 2016



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## **Insect Repellent IR3535<sup>®</sup>:**

### **Use in Infants and Children**

The insect repellent IR3535<sup>®</sup> (Ethyl butylacetylaminopropionate) is a derivative of  $\beta$ -alanine, a naturally occurring amino acid. IR3535<sup>®</sup> is a clear, colorless and practically odorless liquid compound and fulfills all the requirements for the outstanding properties of an excellent repellent.

The safety of IR3535<sup>®</sup> for consumers has been demonstrated in a comprehensive number of in vitro and in vivo studies on acute toxicity, local tolerance, phototoxicity, repeated dose toxicity, mutagenicity, reproductive toxicity and toxicokinetics. Risk assessments based on all these data show that IR3535<sup>®</sup> does not pose a risk to human health. It is especially noteworthy that IR3535<sup>®</sup> possesses a very low degree of systemic toxicity following single or repeat doses in animals. IR3535<sup>®</sup> is not a developmental or reproductive toxicant and there was no indication of a potential for immunological or neurological toxicity. Therefore, it is reasonable to conclude that there is no harm from exposure to the general population including children. This assessment is supported by a history of safe use as an insect repellent in several European Countries for more than 40 years. No evidence of adverse health effects to adults or children has come up so far.



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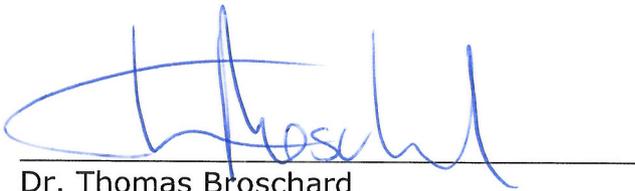
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Based on an exposure and risk assessment, the application of IR3535® to infants below 1 year of age is acceptable. This is essential as there might be a need for repellents that can be used on infants in regions where vector diseases are present. Nevertheless, caution must still be taken when using these products on infants. It is recommended to use physical protection such as mosquito nets and to use products very responsibly.

Darmstadt, 26 Jan. 2016



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## **Insect Repellent IR3535®:**

### **Use in Pregnant and Breast-Feeding Women**

The insect repellent IR3535® (Ethyl butylacetylaminopropionate) is a derivative of  $\beta$ -alanine, a naturally occurring amino acid. IR3535® is a clear, colorless and practically odorless liquid compound and fulfills all the requirements for the outstanding properties of an excellent repellent.

The safety of IR3535® for consumers, workers and the environment has been demonstrated in a comprehensive number of *in vitro* and *in vivo* studies on acute toxicity, local tolerance, phototoxicity, repeated dose toxicity, genotoxicity/mutagenicity, reproductive toxicity, toxicokinetics and ecotoxicity. Risk assessments based on all these data show that IR3535® does not pose a risk to human health and the environment.

It is especially noteworthy that IR3535® has been investigated comprehensively for a possible reproductive and developmental toxicity:

IR3535® was neither teratogenic nor embryotoxic when investigated in rats [1] and rabbits [2] according to OECD test guideline No. 414. No malformations or developmental variants up to and including maternal toxic doses were observed. IR3535® is not considered toxic to development.



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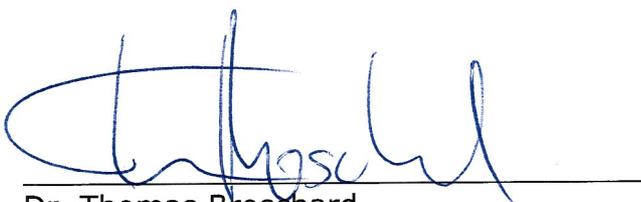
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In addition, the reproductive toxicity of IR3535<sup>®</sup> was investigated in a 2-generation study in rats according to OECD test guideline No. 416 [3]. There were no findings on reproductive or on developmental parameters. The number and development of the pups was normal and comparable to the concurrent control. IR3535<sup>®</sup> was not toxic with regard to reproduction or development.

No data are available in humans regarding the application of IR3535<sup>®</sup> during pregnancy and lactation. However, IR3535<sup>®</sup> is used in repellents since more than 40 years. During this time we have not received any indication on possible effects on the progeny due to the application of IR3535<sup>®</sup> by pregnant or breast-feeding women.

Taking the comprehensive data package on reproductive toxicity and the long history of safe use into account, there are no indications that the use of IR3535<sup>®</sup> by pregnant and breast-feeding women might be of any risk for children. This is essential as there might be a need for repellents that can be used by pregnant and breast-feeding women in regions where vector diseases are present. Nevertheless, caution must still be taken when using insect repellents. It is recommended to use physical protection such as mosquito nets and long-sleeved clothing and to use insect repellent products in a responsible manner.

Darmstadt, 4 February 2016



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## References

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- 1 Leuschner F (1975) The effect of BE 3535 on the pregnant rat and the fetus after administration by gavage (pilot study with 1 dose level), Institute of Pharmacology and Toxicology, Report of September 30, 1975, Hamburg, Germany
- 2 Schardein J (1997) A developmental toxicity study of IR3535 in rabbits. WIL Research Laboratories Inc., Study No. WIL-149020, Ashland, USA on behalf of Merck KGaA
- 3 Gleich J (1997) Insect Repellent 3535 (Art. No. 111887): 2-Generation reproduction study with oral administration to rats, Merck KGaA, Institute of Toxicology, Study No. T 9381, Darmstadt, Germany



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