

Science for Diplomats at EC-84

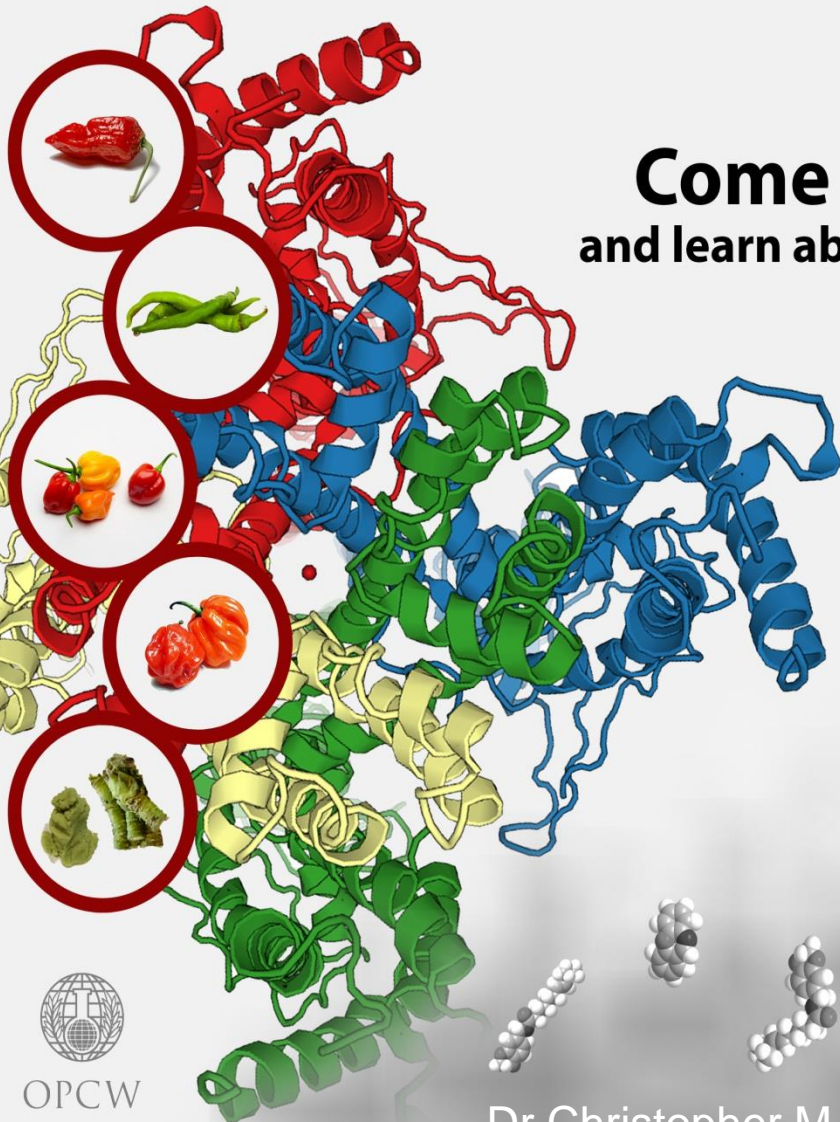
What Defines a Riot Control Agent?

Come activate your **TRP** receptors!
and learn about the biochemistry of **Riot Control Agents**

Wednesday, 8 March 2017
Ooms Room | 13.30-14.45

Light lunch available at 13.00

Dr Christopher M. Timperley (Chairperson of OPCW SAB)



OPCW

World War I



Riot control

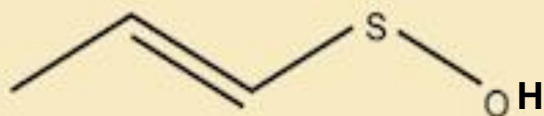


Nature produces sensory irritants

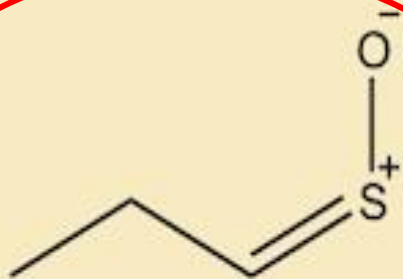


Irritant chemicals in onions

AMINO ACID SULFOXIDES



1-PROPENESULFENIC ACID

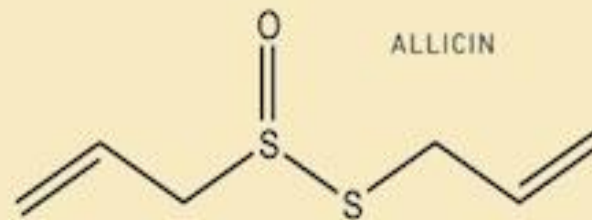
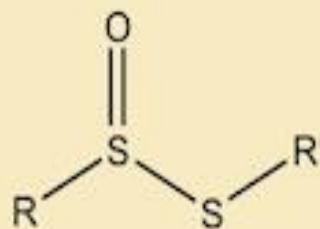


SYN-PROPANETHIAL-S-OXIDE

As onions are sliced, they release a class of enzymes, allinases, which break down amino acid sulfoxides. A specific compound produced during this process is 1-propenesulfenic acid, which is rearranged by another enzyme, called lachrymatory factor synthase, to produce syn-propanethial-S-oxide. Production of this gas peaks 30 seconds after mechanical damage to the onion, and it stimulates sensory neurons in the eye causing a stinging sensation; the eye therefore produces tears to flush it out.



ONION ODOUR & THIOSULFINATES



ALLICIN

Thiosulfinates are the primary flavour and odour producing molecules in an onion. These compounds are not present in intact bulbs, but are formed via enzymatic reaction from sulfur amino acids. Allicin is one of these compounds, which in turn quickly breaks down to form other sulfur-containing compounds.

Some irritant chemicals were discovered by accident

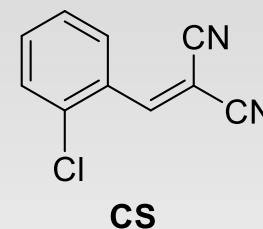
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MIDDLEBURY COLLEGE]

REACTIONS OF ALPHA, BETA-UNSATURATED DINITRILES

BY BEN B. CORSON AND ROGER W. STOUGHTON

RECEIVED AUGUST 7, 1928

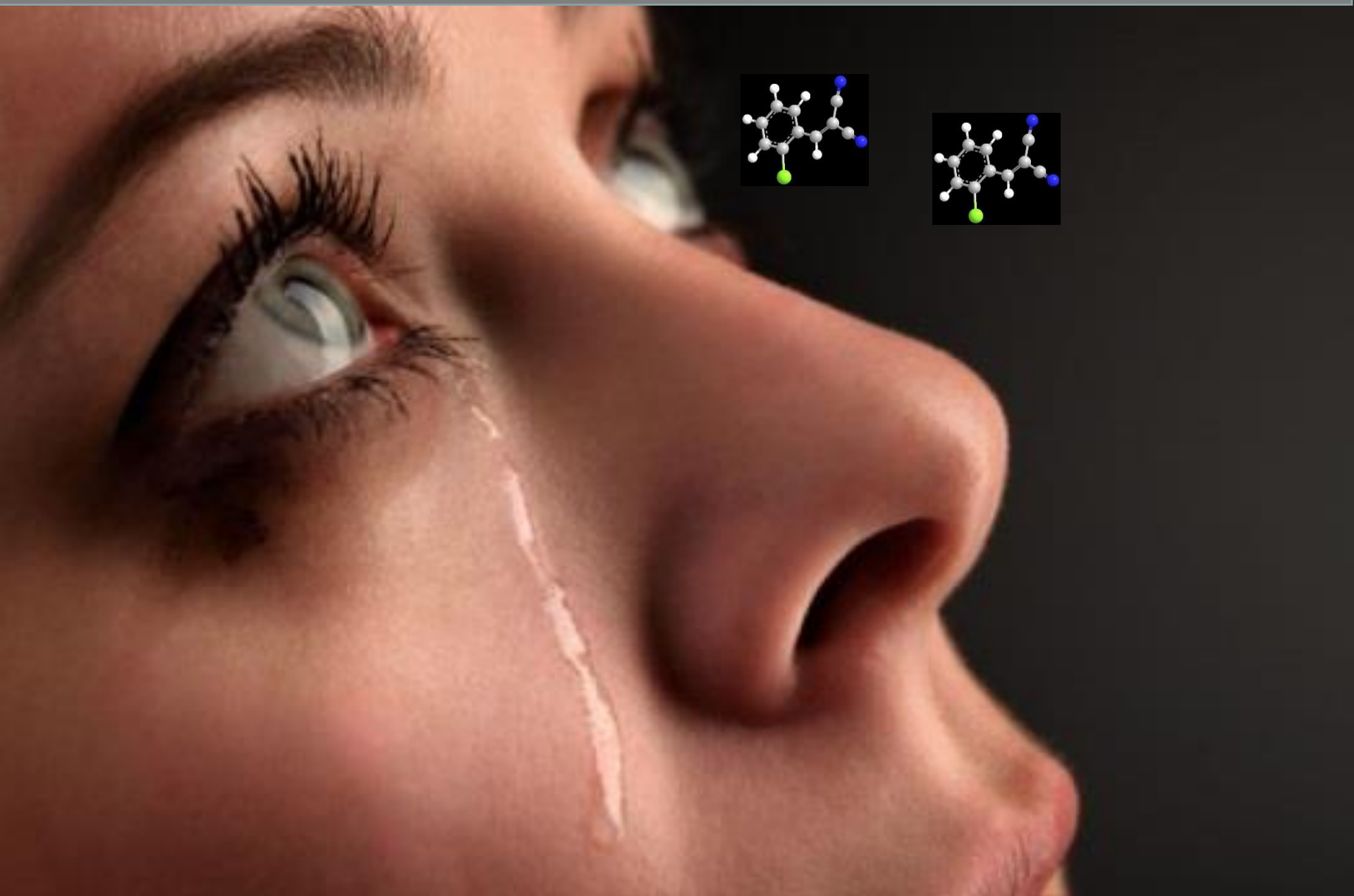
PUBLISHED OCTOBER 6, 1928



Physiological Properties.—Certain of these dinitriles have the effect of sneeze and tear gases. They are harmless when wet but to handle the dry powder is disastrous. When crystallizing *m*-nitrobenzalmalononitrile, for instance, the alcohol solution should not be boiled very much since the alcohol vapor has a peppery sting. In sneezing caused by *m*-nitrobenzalmalononitrile (XVIII) the mucous discharge from the nose becomes bright yellow on exposure to air. In sneezing caused by *o*-chlorobenzalmalononitrile (XX) the face smarts, especially if damp. The smarting is intensified by washing. Most of the discomfort can be avoided if a gas mask is worn whenever dry solid is to be handled. However, the majority of the dinitriles reported in this paper have no irritant effect, as furfuralmalononitrile (XXIII) and *p*-methoxybenzalmalononitrile (VI).



Lachrymators are chemicals that make you cry



Sternutators are chemicals that make you sneeze



Question to SAB from the Director-General in 2013

At SAB-20 the Technical Secretariat introduced a request from the DG to consider an indicative list of substances the Secretariat considered as riot control agents (RCAs)

The SAB was asked to provide advice on:

Whether the list reflects the current RCAs that could be declarable in accordance with Article III(1)(e) of the CWC; and in particular:

The soundness of the criteria used by the Secretariat in drawing up the initial list;

Which other considerations or criteria, if any, should be used in developing the list

Which chemicals, if any, should be deleted from the list; and

Which chemicals, if any, should be added to the list

Question

The SAB noted that this request was specific to RCAs and excluded Incapacitating Chemical Agents and that it would help to recall the SAB's previous advice on RCAs

Article III(1)(e) provides that, with respect to RCAs, States Parties shall “specify the chemical name, structural formula and Chemical Abstracts Service (CAS) registry number, if assigned, of each chemical it holds for riot control purposes. This declaration shall be updated not later than 30 days after any change becomes effective”

Definitions

The CWC defines two classes of chemical material distinguished by their toxic action, duration and severity of physiological effect. They are:

Article II(2) “Toxic Chemical”

“Any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or of their method of production, and regardless of whether they are produced in facilities, in munitions or elsewhere.”

Article II(7) “Riot Control Agent”

“Any chemical not listed in a Schedule, which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure.”

Findings

The definition of a prospective RCA hinges on whether it causes reversible irritation or disabling physical effects which disappear shortly after exposure. A chemical that does not do this, but is significantly harmful and deleterious to man, is excluded by Article II(7) from being categorised as a RCA.

In assessing the indicative list, the scientific literature describing the toxicology of each chemical was evaluated to decide whether the chemical fitted the RCA definition.

The term “can produce rapidly in humans sensory irritation or disabling physical effects within a short time following termination of exposure” in Article II(7) is not defined absolutely and implies a statistical probability of response.

Findings

Toxicities of chemicals vary in different animal species and under different conditions. It is not always possible in the absence of human data to predict accurately from animal data the effects on humans.

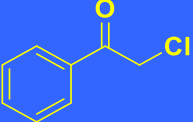
The Himsworth report (1971-1977) into toxicological aspects of CS and its use for civil purposes noted that the effects of any chemical intended for use in internal security operations should be studied in a manner “more akin to that in which we regard a new drug.”

Unfortunately toxicological studies on many of the chemicals on the initial list have not been performed to the level of scrutiny a new drug receives.

Assessment

In assessing the suitability of each chemical for consistency with the RCA definition of Article II(7) the scientific literature was reviewed.

Recommendations were made based on its analysis.

Chemical name and CAS number	Physical state	Notes	Physiological effect
<p>2-Chloroacetophenone (CN)</p> <p>Synonyms: Mace, CAP, KhAf</p> <p>CNB (10% CN, 45% benzene, 40% carbon tetrachloride), CNC (30% CN, 70% chloroform), and CNS (23% CN, 38.4% chloropicrin, 38.4% chloroform)</p> <p>CAS 532-27-4</p> 	<p>White solid with odour of apple blossom</p> <p>Mp 54-56 °C</p> <p>Bp 245 °C</p>	<p>Sparingly soluble in water, dissolves in chloroform and other organic solvents. Stable and does not decompose on heating or detonation; its lachrymatory effects are soon lost by condensation to the solid state soon after dispersion: non-persistent and not hydrolysed readily [7].</p>	<p>Immediately irritates eyes (at 0.3 mg/m³) and upper respiratory passages [8-28]. High concentrations cause tears, irritation, tingling and pain in the nose and throat; and burning and itching of tender skin, especially areas wet by perspiration. High concentrations cause blisters with effects similar to sunburn – blisters are harmless and disappear in a few hours. Some individuals experience nausea after exposure. IC₅₀ 80 mg/m³ [8]. LC₅₀ 7000 mg min/m³ from solvent and 14000 mg min/m³ from a thermal grenade. Rapid detoxification – effects disappear in minutes. Limit of supportability is 4.5 mg/m³ of air [9]. Animal studies show that toxic effects are more severe than those of CS [28]. CN has been superseded as an RCA by CS which is safer to use.</p>

Riot control agents act on the peripheral nervous system

spinal cord

brain

CNS-ACTIVE COMPOUNDS

Do not fit description of riot control agents

CS

C#N/C=C/c1ccccc1

CR

C1=CN=C2C=CC=CC2O1

eyes

nose

mouth

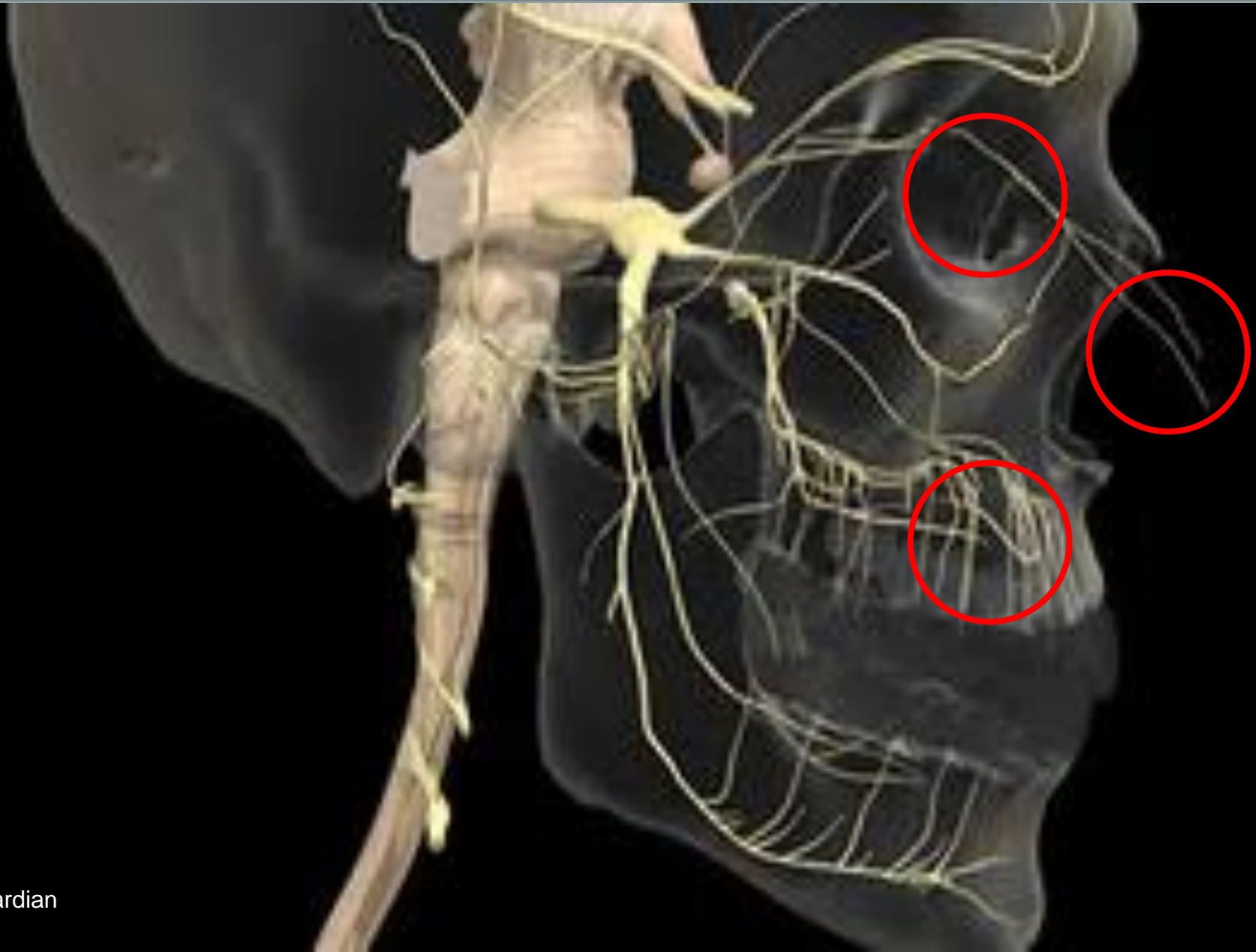
skin

CN

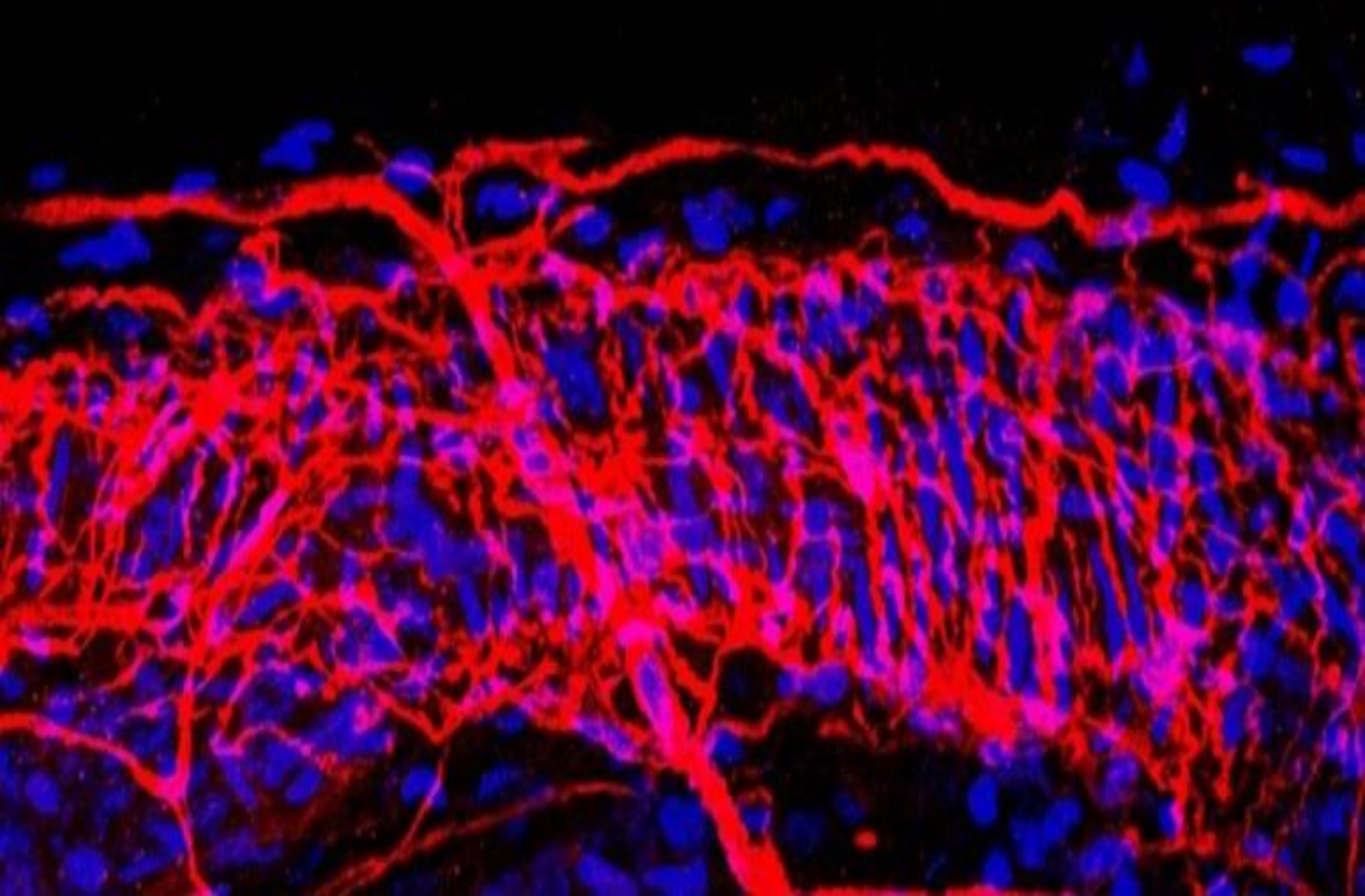
ClCC(=O)c1ccccc1

RCA's PNS-ACTIVE - cause short-lived pain

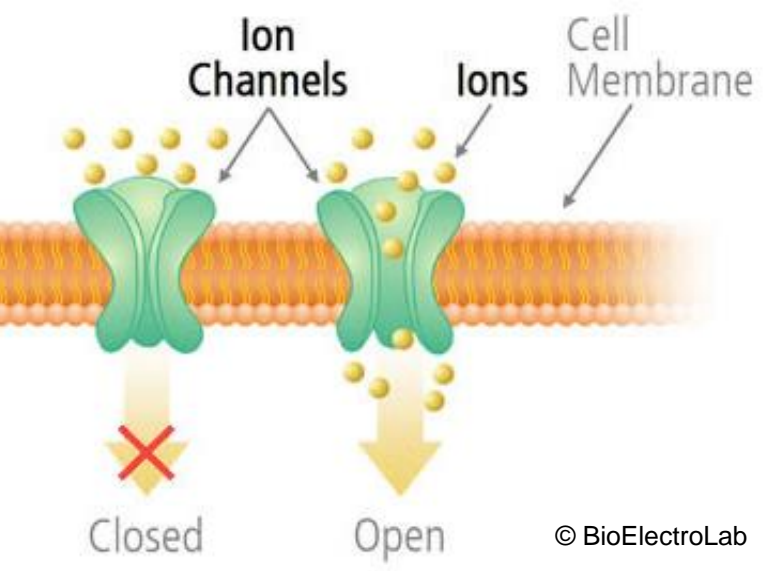
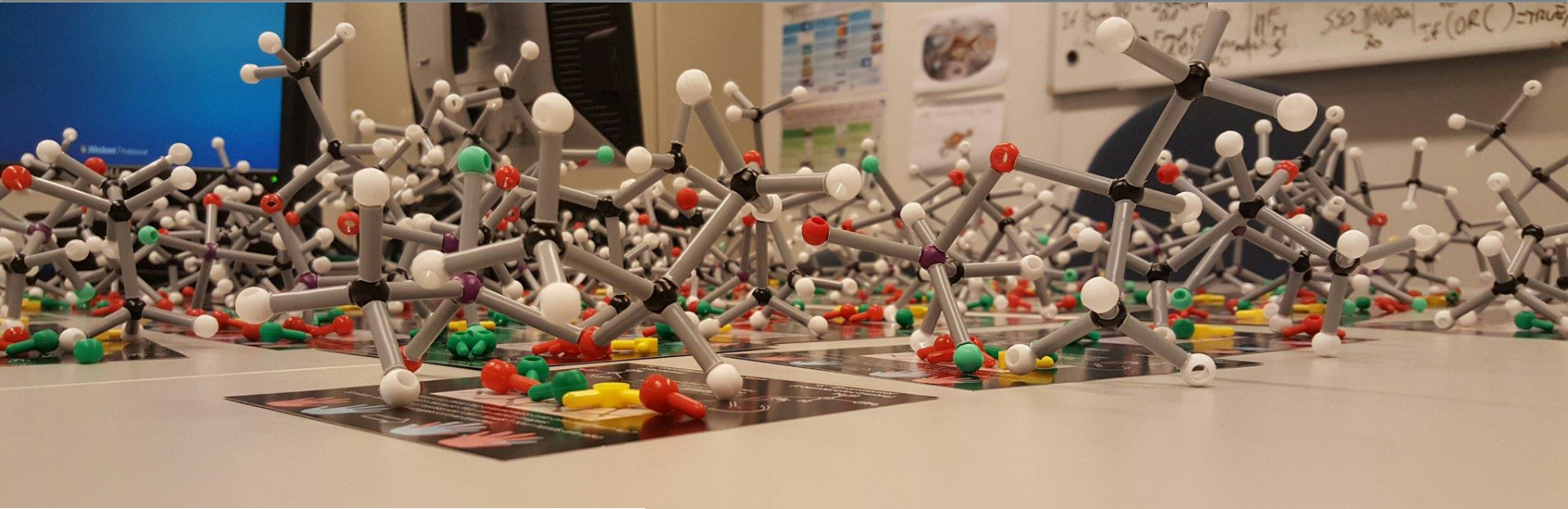
The trigeminal nerve



Sensory nerve endings are present in skin



How does the human body sense irritant chemicals?



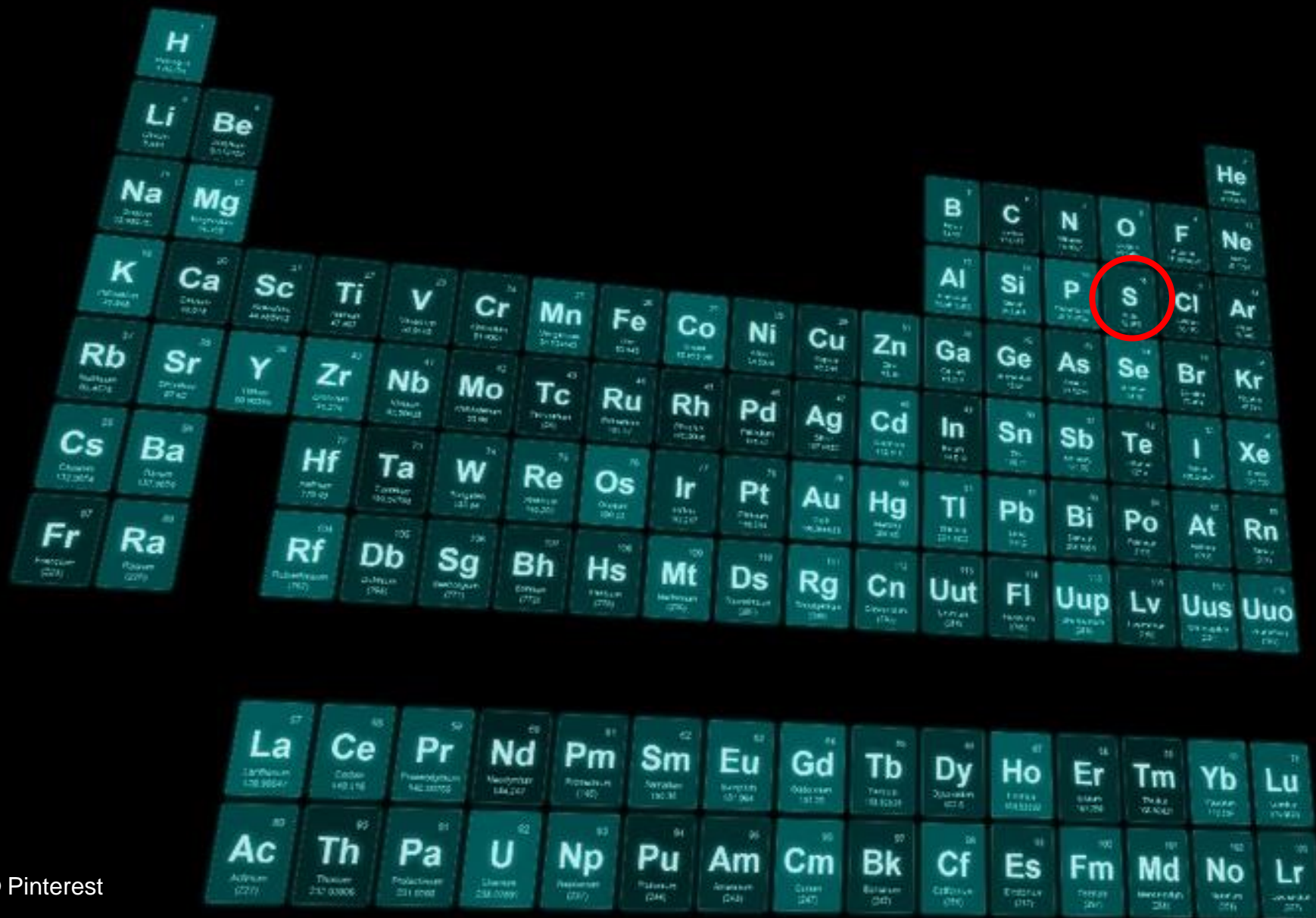
Ion channel TRPA1

Transient Receptor Potential Ankyrin 1
senses CN, CS, CR, many other irritants

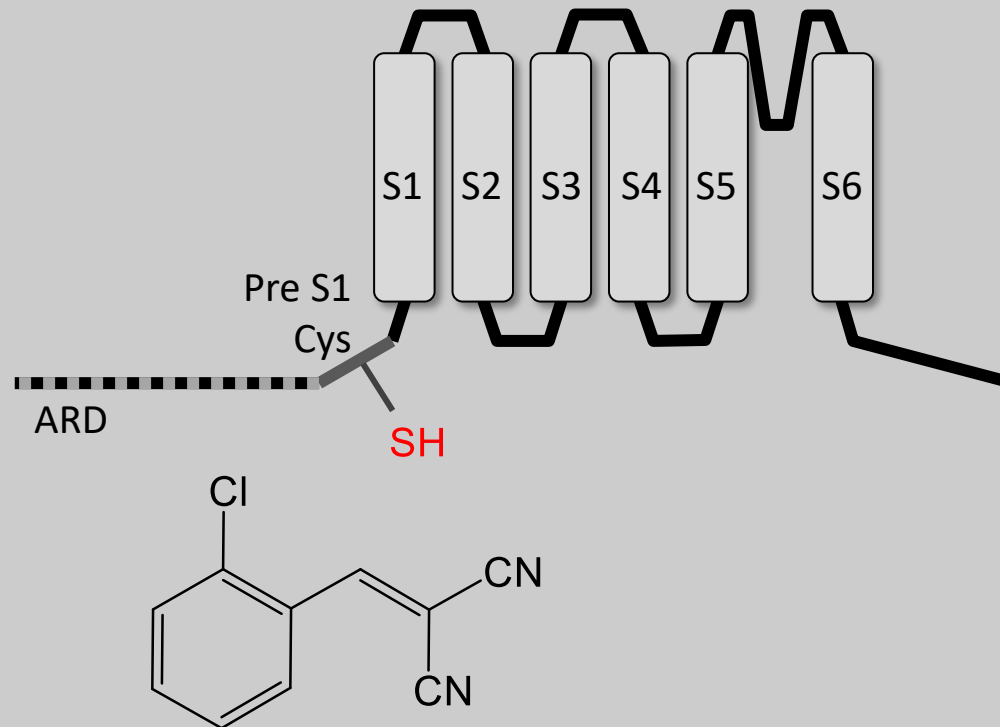
Ion channel TRPV1

Transient Receptor Potential Vanilloid 1
senses capsaicin and some close relatives

Nature chose sulfur to sense irritant chemicals



CS acts on the TRPA1 ion channel

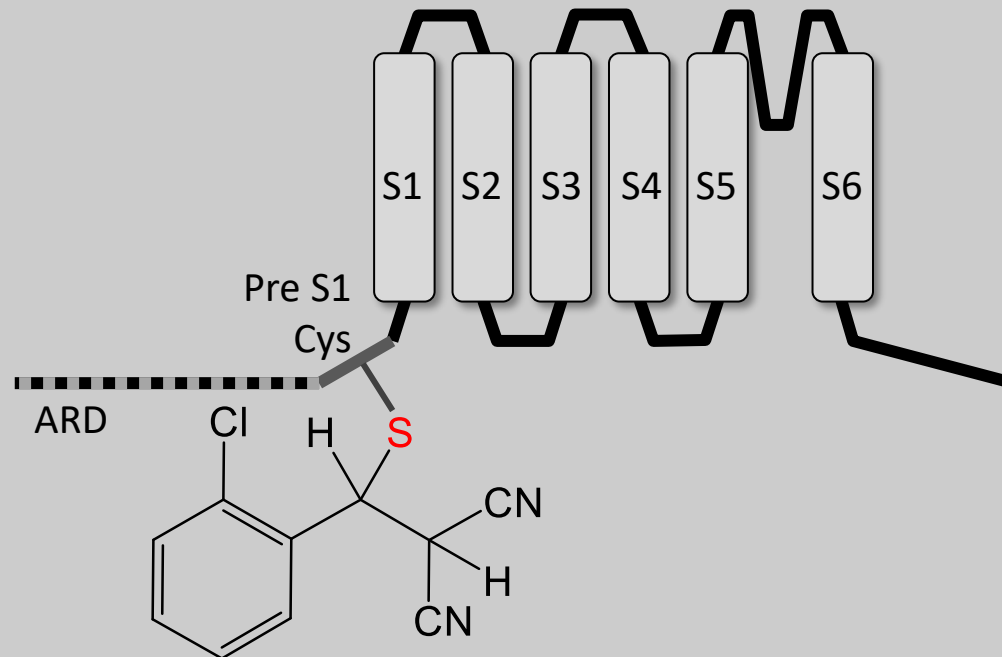


Macpherson *et al.*, *Nature* 445 (2007) 541-545

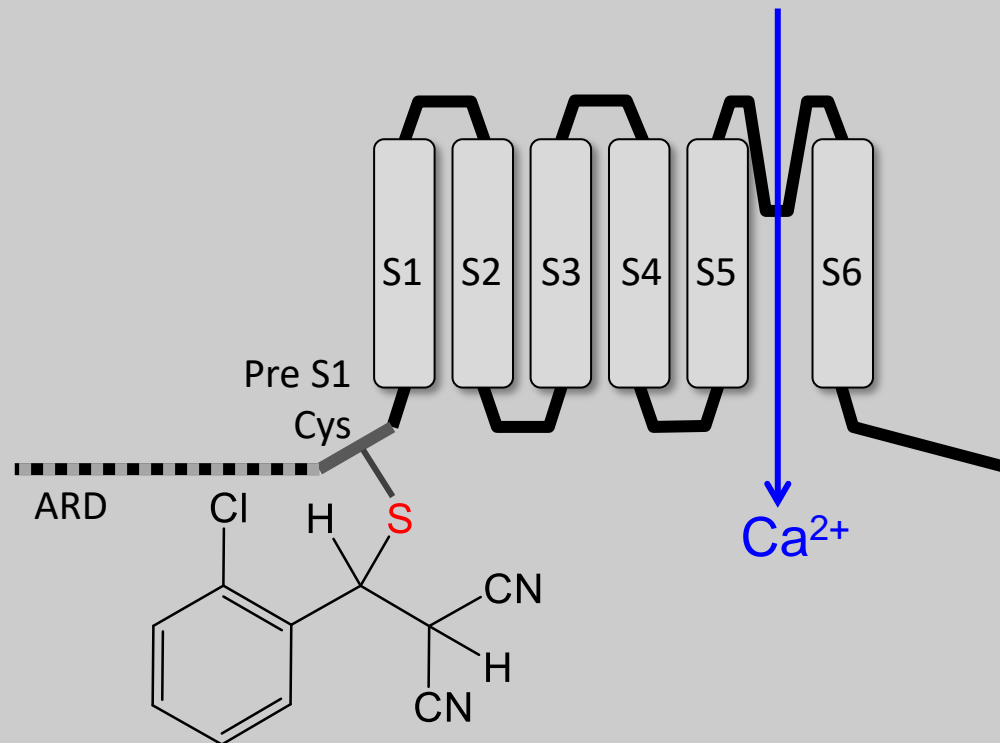
Brône *et al.*, *Tox. Appl. Pharmacol.* 231 (2008) 150-156

Lindsay *et al.*, *Royal Soc. Open Sci.* (2015) DOI: 10.1098/rsos.140160

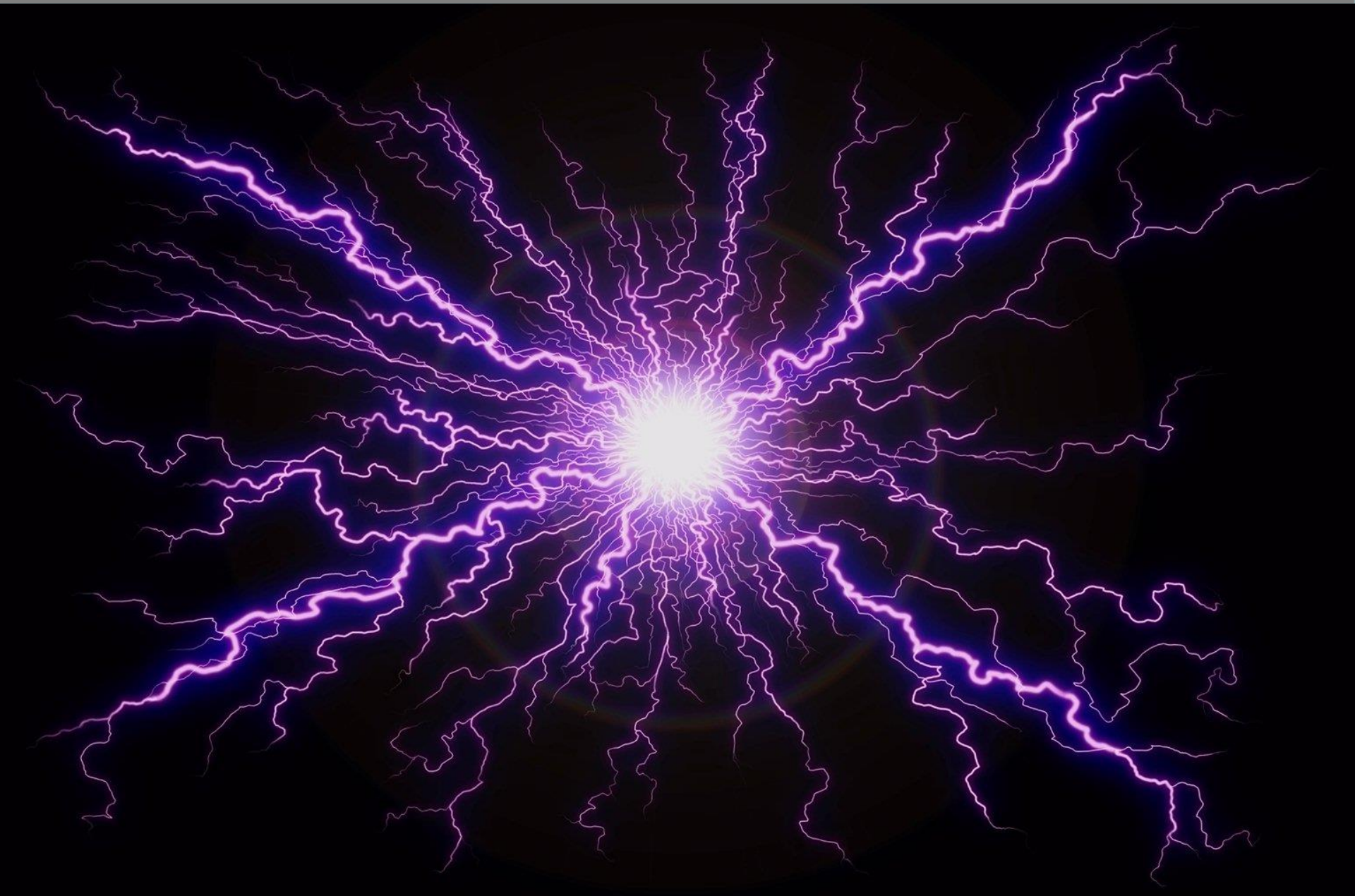
CS acts on the TRPA1 ion channel



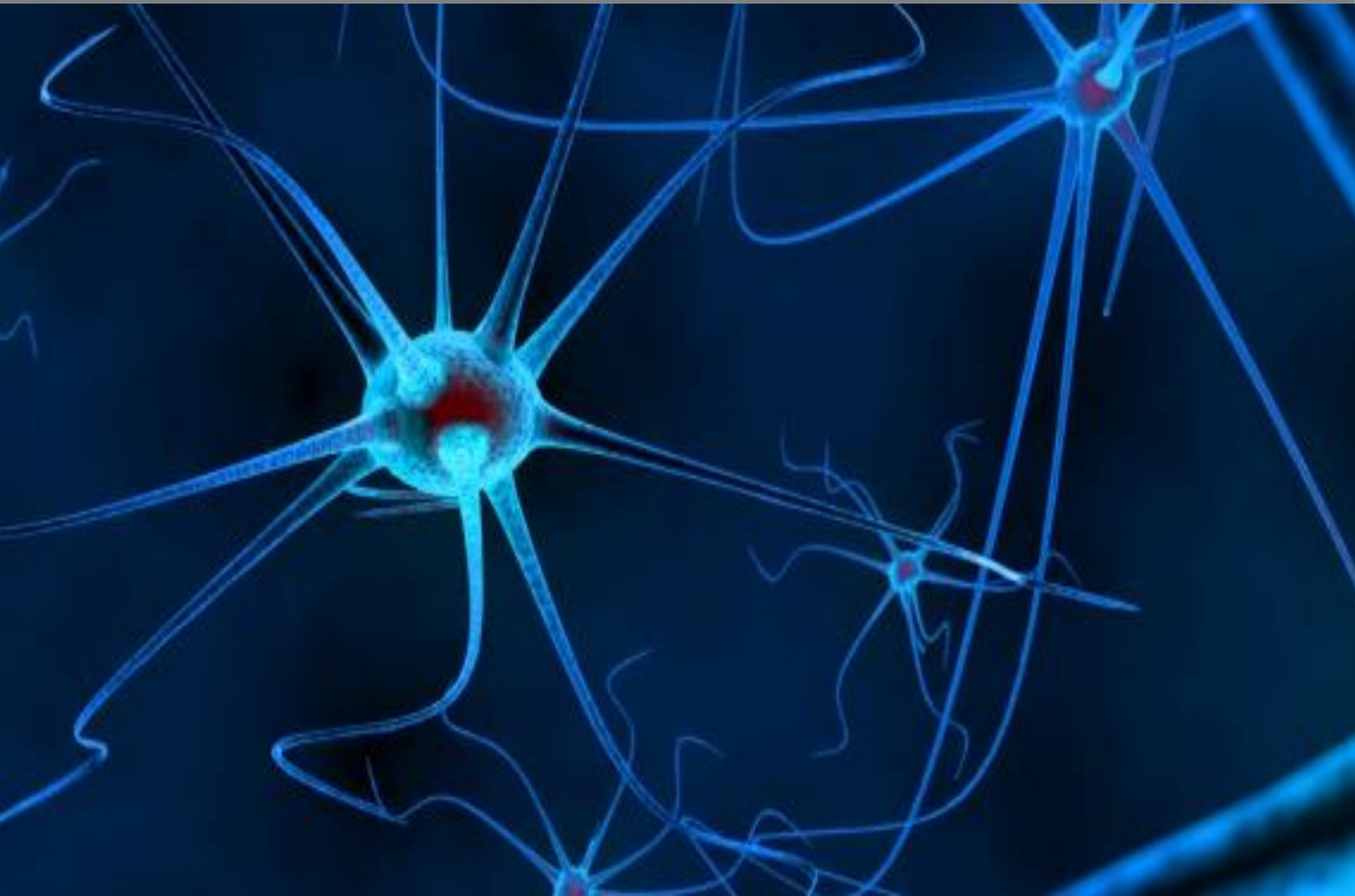
CS acts on the TRPA1 ion channel



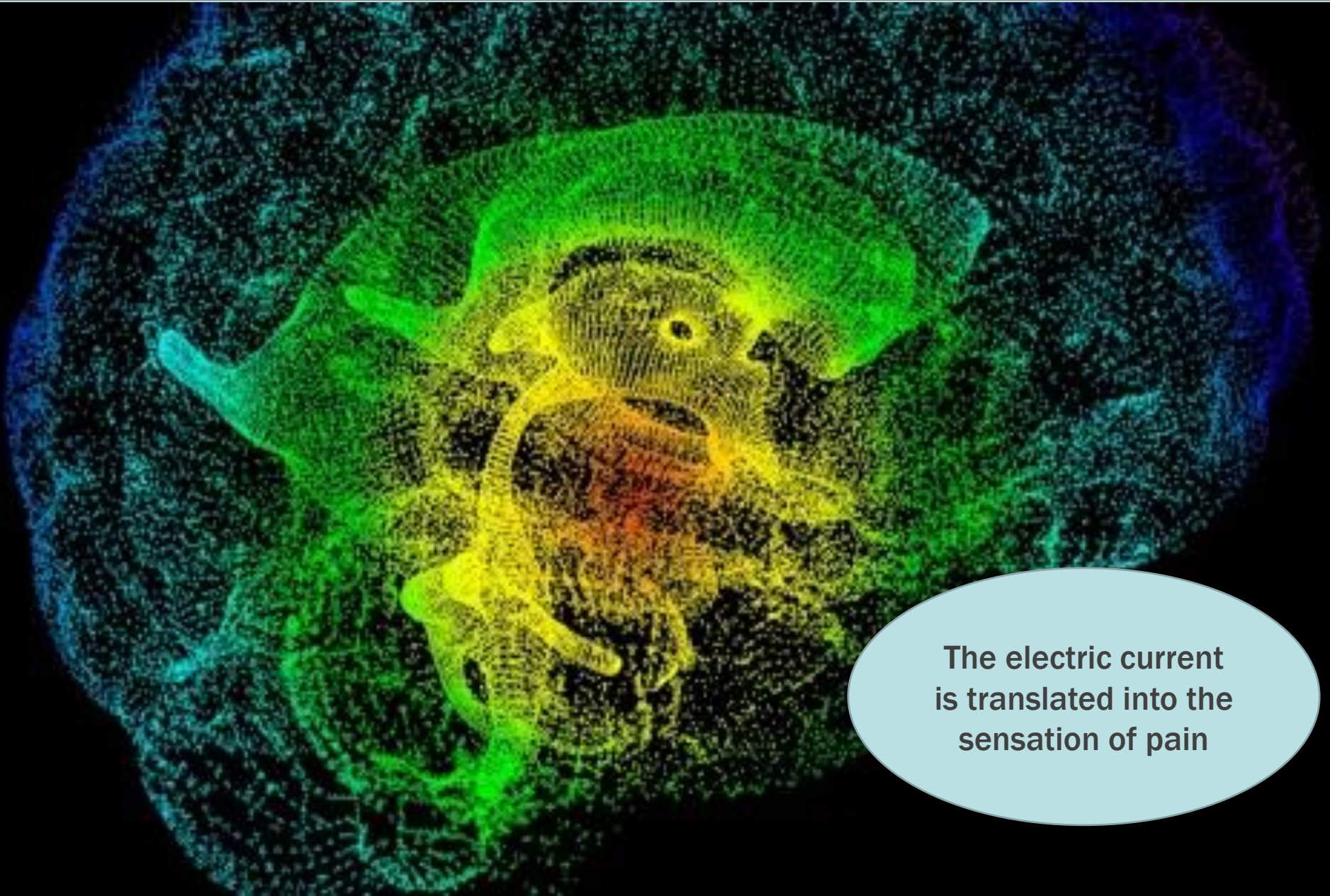
Inward flow of calcium ions generates an electric current



The electric current passes along the nerve cells



The electric current is interpreted by the brain



The electric current is translated into the sensation of pain

Personal taster kit



OPCW

Science for Diplomats at EC-84 What Defines a Riot Control Agent?

Come activate your TRP receptors
and learn about the biochemistry of Riot Control Agents

Wednesday, 8 March
Ooms Room | 13.30-15.00

Light lunch available



Sensory irritant competition

• TASTER SAMPLES

- Horseradish (contains 10% wasabi)
- Another horseradish (“wasabi-like”)
- Mont Blanc mustard
- Siracha chilli sauce
- Red hot pepper sauce
- Red rocket chilli pepper hot sauce
- Phet-so red hot pepper sauce
- Two hot pepper sauces from China *
- Chil jalapeno hot sauce
- Madagascan bourbon vanilla extract

* Courtesy of SAB Vice-Chair : Mr Cheng Tang

- Participants to provide a 1-10 scale rating of potency and persistence of the taster samples and to record the data on the scorecards provided

COUNTERMEASURES

Water

Vanilla ice cream



Allyl isothiocyanate

responsible for wasabi's spicy attitude

Chilli peppers



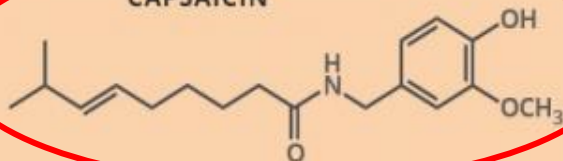
Pepper spray



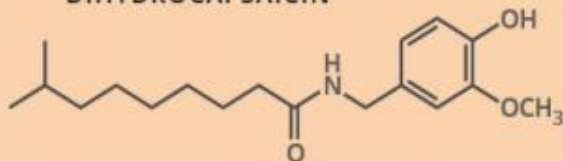
Chemical ingredients of chilli peppers

CAPSAICINOIDS

CAPSAICIN



DIHYDROCAPSAICIN



The spiciness of chillis is due to the presence of compounds called capsaicinoids. The two compounds above are the main capsaicinoids in chilli peppers. They cause a burning sensation when they come into contact with mucous membranes, due to their interaction with pain and heat sensing neurons.

Capsaicin is also used in some brands of pepper spray, and studies have shown it may be capable of killing prostate and lung cancer cells. It is toxic in large quantities.

THE SCOVILLE HEAT INDEX



The Scoville scale is a taste detection based method for rating the heat of chilli peppers. A measured amount of pepper extract has sugar added to it incrementally until the heat is undetectable through taste. Though it is an imprecise method, it has been estimated that 1 unit corresponds to 18µM.



The Scoville scale



The Scoville scale

SCOVILLE HEAT SCALE

THE SCOVILLE SCALE IS A MEASURE OF A PEPPER'S HOTNESS OR MORE CORRECTLY PIQUANCY OF A CHILI PEPPER. THESE FRUITS CONTAIN CAPSAICIN WHICH STIMULATES NERVE ENDINGS IN THE SKIN. THE # OF SCOVILLE UNITS INDICATES THE AMOUNT OF CAPSAICIN PRESENT. THE GREATER THE # THE HOTTER THE PEPPER.

NO, TO SOME, HEAT.



What heat?

100-500
500-1,000

BELL PEPPER

CUBANELLE

ANANEIM

HEAT, BUT COMFORTABLE



Oh, that heat.

1,000-1,500
1,500-2,500

POBLANO ANCHO PASILLA

CASCABEL

STARTING TO SWEAT



Uh ohh...

2,500-5,000
5,000-15,000

JALAPEÑO (MILD) RED FRESNO

JALAPEÑO (HOT) HUNGARIAN HOT WAX

THAT'S QUITE HOT ENOUGH NOW



Ha ha... ha...

15,000-30,000
30,000-50,000

SERRANO DE ARBOL

CAYENNE TABASCO

ABSURD



Uh ohh...

50,000-100,000
100,000-500,000

THAI

HABANERO

ANANEIM PEPPER \$2.99

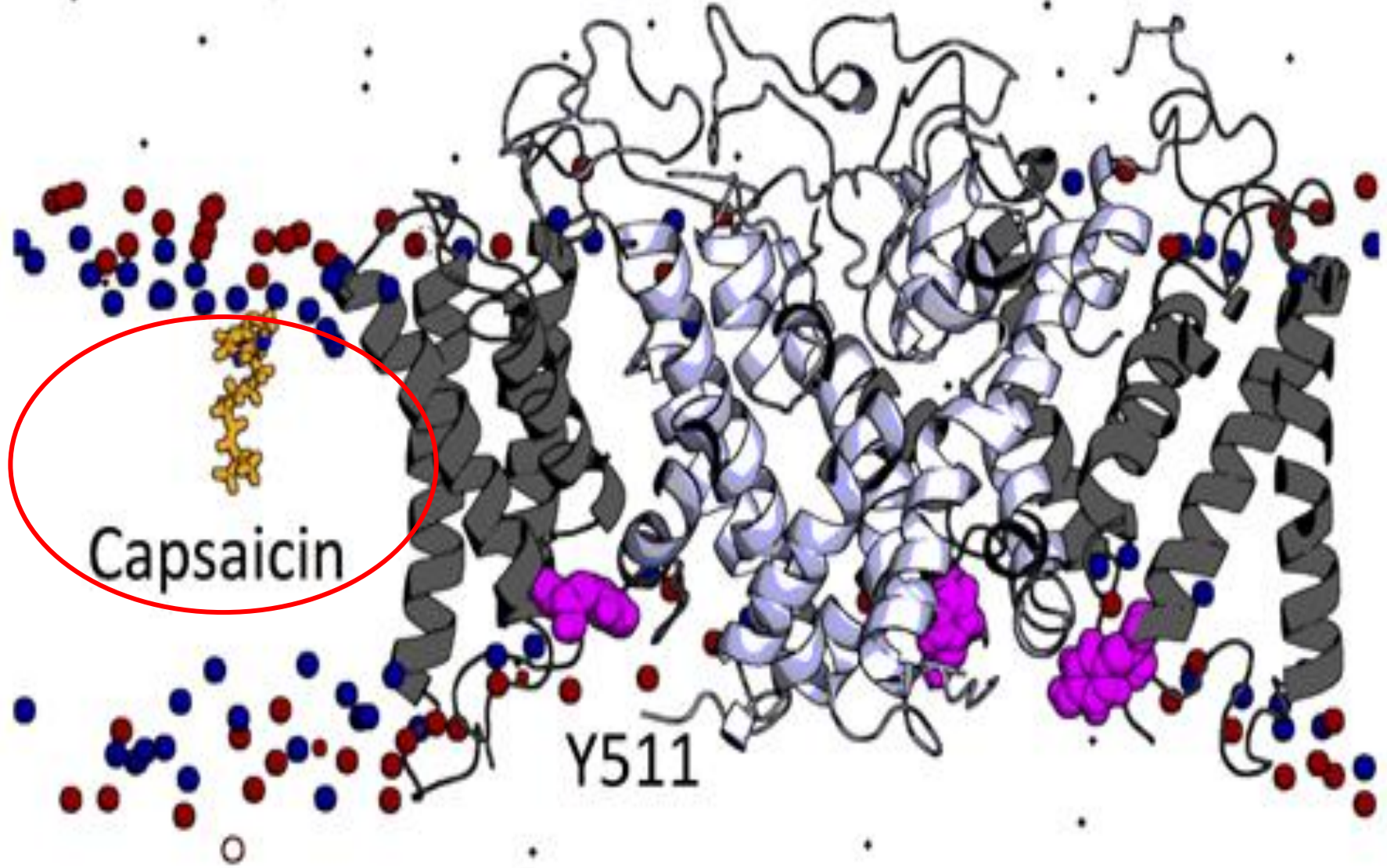
POBLANO PEPPER \$5.99

POBLANO PEPPER \$2.19

LOCAL FLAVOR \$6.99

PEPPER \$3.99

Capsaicin acts on the TRPV1 ion channel



SAB responses to specific questions from the DG, in 2013

The list reflected the current RCAs that could be declarable in accordance with Article III(1)(e)

Criteria used by the Technical Secretariat to draw up the list were judged sound

The main point in considering the list was whether the toxicity profile of each chemical matched the definition of a RCA in Article II(7)

No chemicals were deleted from the list and those whose toxicity profiles did not match the definition of a RCA in Article II(7) were identified

Chemicals that were added to the list were those linked in the scientific literature to riot control, and therein their physiological action compared to RCAs, or those having physiological properties that could favour their research or potential use.

Conclusions in 2013

Three of the 14 chemicals declared as RCAs since the CWC entered into force had properties that excluded their definition as a RCA under Article II(7). They were 10-chloro-5,10-dihydrophenarsazine (Adamsite), 2-bromoethyl acetate, and 4'-chloroacetophenone. Through their chemical action on life processes they can cause death or permanent harm.

The conclusion that Adamsite is too toxic for classification as a RCA was consistent with the conclusion reached by the SAB many years ago, in that “it should no longer be used as a RCA, as it fails to meet today’s concerns for safety”.

Conclusions in 2013

Cis-4-acetylamino-dicyclohexylmethane, *N,N'*-bis(isopropyl) ethylenediamine, and *N,N'*-bis(*tert*-butyl)ethylenediamine were considered in addition to the initial list. They met the criteria used by the Secretariat and the definition of an RCA under Article II(7).

42 other chemicals, comprising those on the initial list supplemented by 12 additions, did not fit the definition of an RCA.

Trichloronitromethane (chloropicrin) appears on Schedule 3A(4) under the descriptor Toxic Chemical, and is thus excluded as an RCA under the Article II(7) definition.

Result of the SAB study in 2013



OPCW

Technical Secretariat

Office of Strategy and Policy
S/1177/2014
1 May 2014
ENGLISH only

NOTE BY THE TECHNICAL SECRETARIAT

DECLARATION OF RIOT CONTROL AGENTS: ADVICE FROM THE SCIENTIFIC ADVISORY BOARD

1. In accordance with subparagraph 1(e) of Article III of the Chemical Weapons Convention (hereinafter “the Convention”), States Parties are required to declare riot control agents (RCAs), which are defined in paragraph 7 of Article II of the Convention.
2. At its Twentieth Session, the Scientific Advisory Board (SAB) was requested by the Director-General (Annex 4 of SAB-20/1, dated 14 June 2013) to provide technical advice on an initial list of RCAs that had been declared by States Parties, researched, or were commercially available.

17 chemicals conform to RCA definition

The SAB has advised the Director-General that the following 17 chemicals correspond to an RCA as defined by paragraph 7 of Article II of the Convention:

- (a) 2-Chloroacetophenone (CN) [CAS¹ 532-27-4];
- (b) 2-Chlorobenzylidenemalonitrile (CS) [CAS 2698-41-1];
- (c) Dibenzo[*b,f*][1,4]oxazepine (CR) [CAS 257-07-8];
- (d) Oleoresin capsicum (OC) [CAS 8023-77-6];
- (e) 8-Methyl-*N*-vanillyl-*trans*-6-nonenamide (capsaicin) [CAS 404-86-4];
- (f) 8-Methyl-*N*-vanillylnonamide (dihydrocapsaicin) [CAS 19408-84-5];
- (g) *N*-Vanillylnonamide (pseudocapsaicin, PAVA) [CAS 2444-46-4];
- (h) *N*-Vanillyl-9-methyldec-7-(*E*)-enamide (homocapsaicin) [CAS 58493-48-4];
- (i) *N*-Vanillyl-9-methyldecanamide (homodihydrocapsaicin) [CAS 20279-06-5];
- (j) *N*-Vanillyl-7-methyloctanamide (nordihydrocapsaicin) [CAS 28789-35-7];
- (k) 4-Nonanolylmorpholine (MPA) [CAS 5299-64-9];
- (l) 2'-Chloroacetophenone [CAS 2142-68-9];
- (m) 3'-Chloroacetophenone [CAS 99-02-5];
- (n) α -Chlorobenzylidenemalononitrile [CAS 18270-61-6];
- (o) *Cis*-4-acetylamino-dicyclohexylmethane [CAS 37794-87-9];
- (p) *N,N*-Bis(isopropyl)ethylenediimine [CAS *E,E* 28227-41-0; *Z,Z* 185245-09-4] and
- (q) *N,N*-Bis(*tert*-butyl)ethylenediimine [CAS 30834-74-3; *E,E* 28227-42-1].

These act on the TRPA1 ion channel

These act on the TRPV1 ion channel

Sensory irritant taster summary

SAMPLES	TRP CHANNEL
• Horseradish (contains 10% wasabi)	A1
• Another horseradish (“wasabi-like”)	A1
• Mont Blanc mustard	A1
• Siracha chilli sauce	V1
• Red hot pepper sauce	V1
• Red rocket chilli pepper hot sauce	V1
• Phet-so red hot pepper sauce	V1
• Two hot pepper sauces from China *	V1
• Chil jalapeno hot sauce	V1
• Madagascan bourbon vanilla extract	No irritant action
COUNTERMEASURES	
• Water	No irritant action
• Vanilla ice cream	No irritant action
• Fat content of ice cream helps reduce the irritant action of the sauces	

If you wish to discover more about how CS causes irritation . . .

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Cite this article: Lindsay CD, Green C, Bird M, Jones JTA, Riches JR, McKee KK, Sandford MS, Wakefield DA, Timperley CM. 2015 Potency of irritation by benzylidenemalonitriles in humans correlates with TRPA1 ion channel activation. *R. Soc. open sci.* **2**: 140160. <http://dx.doi.org/10.1098/rsos.140160>

Potency of irritation by benzylidenemalonitriles in humans correlates with TRPA1 ion channel activation

Christopher D. Lindsay, Christopher Green, Mike Bird, James T. A. Jones, James R. Riches, Katherine K. McKee, Mark S. Sandford, Debra A. Wakefield and Christopher M. Timperley



OPCW

Riot Control Agents

What is the definition of a Riot Control Agent (RCA)?

From paragraph 7, Article II of the Chemical Weapon Convention:

"Any chemical not listed in a Schedule, which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure."

What are Riot Control Agents?

Chemicals that meet the criteria of an RCA include the following:

 2-Chloroacetophenone (CA) Synonym: CA Physical status: White solid with odour of applesauce Melting Point 63-64 °C Boiling Point 205 °C	 2-Chlorobenzyl isocyanide (CI) Synonym: CI Physical status: White solid with pungent pepper odour Melting Point 60-61 °C Boiling Point 170-171 °C	 Dichloro(1,1,1-trifluoroethyl)phosphine (DC) Synonym: DC Physical status: Yellow to red liquid Melting Point 12 °C Boiling Point 107 °C	 2-Chloroacetophenone (CA) Synonym: CA Physical status: White solid with odour of applesauce Melting Point 63-64 °C Boiling Point 205 °C	 2-Chlorobenzyl isocyanide (CI) Synonym: CI Physical status: White solid with pungent pepper odour Melting Point 60-61 °C Boiling Point 170-171 °C
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How do Riot Control Agents work?

RCA's produce irritation through binding to TRP (Transient Receptor Potential) receptors. This activates some of the same biochemical pathways that are triggered by eating horseradish or hot peppers.

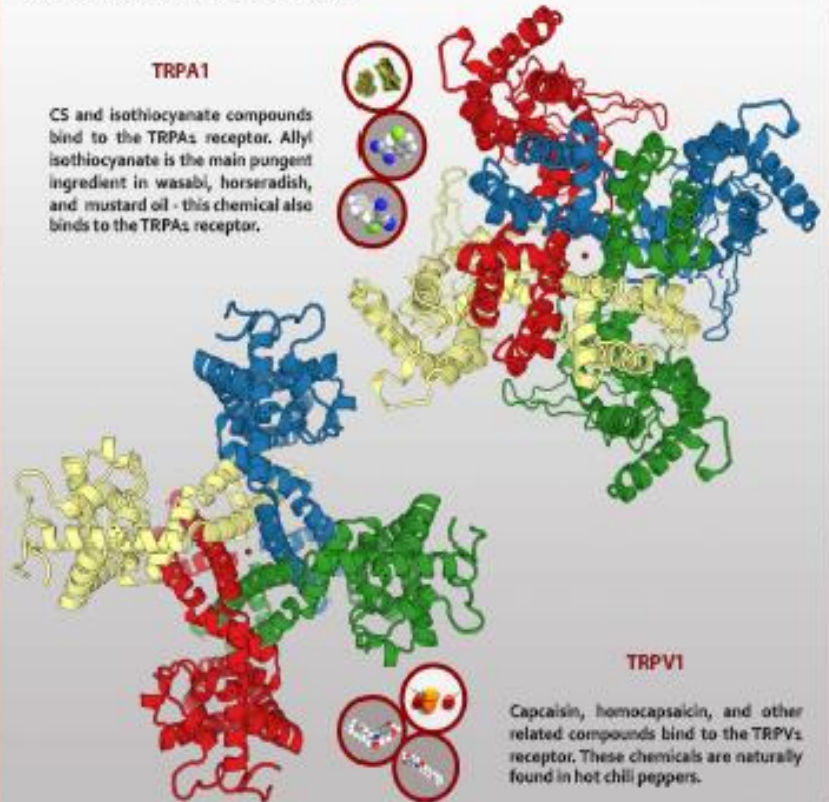
What are TRP Receptors?

TRP receptors are a family of ion channel receptors mainly located on plasma membranes of multicellular organisms. TRP receptors are classified into seven subfamilies: TRPC (canonical or classical), TRPV (vanilloid), TRPM (melastatin), TRPA (ANKTM1 homologues), TRPP (polycystin), TRPML (mucopolin), and TRPN (NOMP-C homologues).

TRP receptor functions are diverse, serving as versatile sensors that allow individual cells and entire organisms to detect changes in their environment. This includes experiencing changes in temperature, touch, taste and other stimuli (including pain).

TRPA1

CS and isothiocyanate compounds bind to the TRPA1 receptor. Allyl isothiocyanate is the main pungent ingredient in wasabi, horseradish, and mustard oil - this chemical also binds to the TRPA1 receptor.



TRPV1

CapSAin, homocapsaicin, and other related compounds bind to the TRPV1 receptor. These chemicals are naturally found in hot chili peppers.

