Do non-steroidal anti-inflammatory drugs effect the germination, development and growth of higher plants?

WITH PLYMOUTH UNIVERSITY

Wiebke Schmidt and **Clare Redshaw**

UNIVERSITY OF EXETER | MEDICAL SCHOOL

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THE PHARMA TRANSPORT TOWN

UNDERSTANDING THE ROUTES TO SUSTAINABLE PHARMACEUTICAL USE: AN EXERCISE IN INTERDISCIPLINARY STUDY

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European Centre for Environment & Human Health
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WINNER PEOPLE'S CHOICE POSTERS & GRAPHICS INTERNATIONAL SCIENCE AND ENGINEERING VISUALIZATION CHALLENGE 2012

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BACKGROUND

There are growing concerns about the ubiquitous presence of pharmaceuticals in the environment[1], especially when coupled with knowledge of the dramatic impacts individual drugs and mixtures can have upon biota[2,3] - such as antibiotic resistance[4,5] and endocrine disruption[6].

As future pharmaceutical usage is predicted to rise, due to a number of reasons including the aging demographic, availability of generics and global epidemics, such as obesity and bird-flu[7], it is essential that we begin to take steps towards limiting environmental contamination.

This information graphic poster shows the complex system of pharmaceutical transport around the areas in which we live (adapted from Petrović et al[8]). It also shows influence routes, suggesting possible points of intervention to begin to address the problems associated with environmental pharmaceutical pollution.

KEY

INFLUENCE
PHARMACEUTICAL TRANSPORT INTO ENVIRONMENT
ROUTES BACK TO PEOPLE

PROMOTIONAL INFLUENCES

The pharmaceutical industry spends billions of dollars annually promoting its products[9]. This plays an important role in raising medical professionals' awareness and potentially improving clinical outcomes. However, the pathways of promotional influences are not always recognised. Direct-to-consumer advertising and promotional gifts to physicians, neither of which should influence clinical decision making, have been shown to influence prescription rates and thus, indirectly, the amount of chemicals entering the environment[10].

REFERENCE LITERATURE

There are many different sources that health professionals use for reference when prescribing, including national formularies, published guidance, mobile phone apps, and others. However, the published scientific evidence on which such resources are based are sometimes funded by the pharmaceutical industry[11]. Those who receive such funding are more likely to report favorable results in the academic press than independent researchers[12,13].

TRAINING AND EDUCATION

Education can be an important way of encouraging responsible and effective prescibing practice. Health professionals' attitudes towards the pharmaceutical industry and their products are formed during training[14]. Restricting contact with pharmaceutical industry representatives during this time can attenuate positive attitudes towards the industry[15] and may subsequently reduce promotional influence on prescription rates[16].

AIR POLLUTION

The quantities of waste that can be incinerated are limited by the amount of air pollution that is considered safe - and depends on other sources of air pollution in the area.

FATE 2 – INCINERATION

High temperature incineration (above 1200°C) is viewed as the safest disposal route for unwanted pharmaceuticals (particularly those with high halogen content).
Unfortunately, high temperature incineration is expensive and in some situations only medium temperature incinerators (above 850°C) are available.

DRINKING WATER

Water treatment processes vary across the world; with water for processing sourced from groundwater, surface water or from waste water treatment plants. As pharmaceuticals are present in all these compartments, the presence of drugs in our drinking water is of little surprise[22,23].

FATE 3 – LOSSES

Degradation is the term used to describe the breakdown of a chemical into smaller component compounds or elements. Usually only partial degradation occurs (where specific chemical sub-structures are lost). Total degradation of a pharmaceutical to its elements, also termed complete mineralisation, is uncommon.

PHOTODEGRADATION

is a form of abiotic degradation, which can be important for the breakdown of pharmaceuticals, particularly in surface waters and during some waste water treatment processes. Absorption of radiant energy (photons), such as those in sunlight, by a compound results in photochemical transformation of the compound into smaller fragments.

BIODEGRADATION

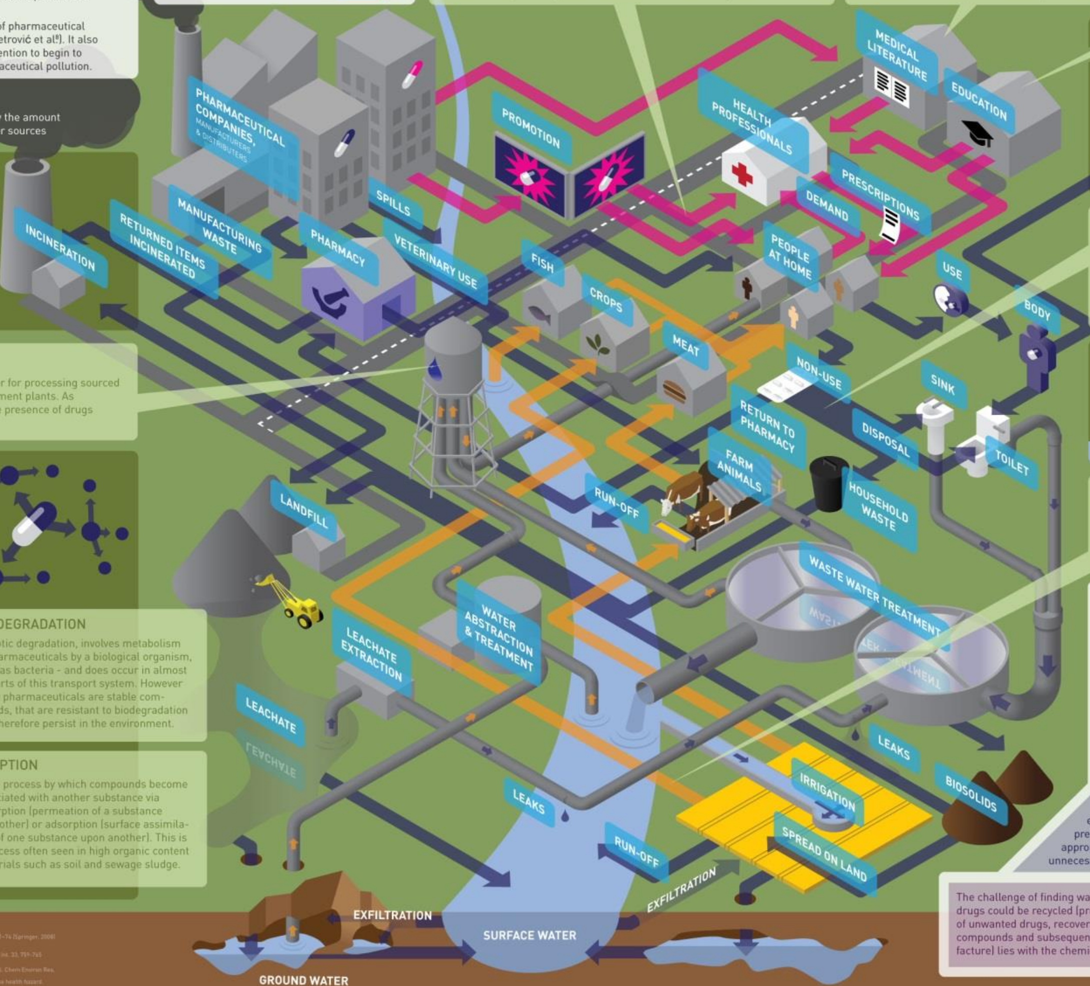
or biotic degradation, involves metabolism of pharmaceuticals by a biological organism, such as bacteria - and does occur in almost all parts of this transport system. However many pharmaceuticals are stable compounds, that are resistant to biodegradation and therefore persist in the environment.

BIOACCUMULATION

of pharmaceuticals can occur in organisms in the environment. Where a drug has a higher affinity for the chemical properties of particular tissues (e.g. fat) than it does the surrounding environment, it can become concentrated in an organism.

SORPTION

is the process by which compounds become associated with another substance via absorption (permeation of a substance by another) or adsorption (surface assimilation of one substance upon another). This is a process often seen in high organic content materials such as soil and sewage sludge.



FATE 1 – METABOLISM

When drugs are consumed, a proportion of the drug interacts or binds with a receptor in the body, which causes a biological response. The body transforms the remaining compound into a more water soluble form, allowing it to be excreted. Pharmaceuticals can be excreted as parent compounds (the drug consumed) or metabolites, in urine or faeces. In some cases an excreted metabolite can be as bioactive as the parent compound, such as Norfluoxetine, the metabolite of Fluoxetine HCl (Prozac®).

NON-USE

Many individuals do not take all, or even any, of their prescribed medication. Reasons include forgetting, reluctance, thinking them no longer necessary, side-effects and being 'out of date'[17,18]. Forgetting can be tackled using simple psychological techniques[19]. In the UK it is estimated that 63% of unused medication is disposed of via household waste, 12% via the sink or toilet and only 22% are returned to pharmacies for safe disposal[20]. Similarly low rates of safe disposal are reported in the US[21].

FATE 4 – DOWNSTREAM

Once pharmaceuticals have entered the environment they can continue to be transported via our waterways to other towns and eventually the sea. Some pharmaceuticals have even been found as far away as the arctic!

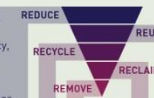
BIOAVAILABILITY?

We have an understanding of pharmaceutical transport around our environment, from our homes to waterways, aquatic organisms, fields and therefore potentially crops and/or animals. However, we lack knowledge about whether these compounds could be transferred to the consumer and if they have the same effect as taking medication.

ROUTES TO SUSTAINABILITY

This graphic illustrates the complex movement of pharmaceuticals around our social and physical environments, cycling endlessly.

Legislative pyramids[24] provide a hierarchy of management strategies for waste reduction (reducing in sustainability down the pyramid). This concept could be used to limit environmental contamination by pharmaceuticals.



Upstream interventions should be the highest priority. Green pharmacy, which seeks to develop specific targeted drugs and/or more effective delivery mechanisms, has the potential to reduce the dosages required[25]. Also, education of consumers and prescribers could result in more appropriate disposal and reduce unnecessary prescribing.

Widespread acceptance of medical donation programmes[26,27] would result in greater reuse of drugs and could be facilitated by use of smaller packaging.

Reclamation of pharmaceuticals (most likely at the waste water treatment works), followed by purification and reuse of drugs expensive to produce, could in theory be implemented alongside removal programmes.

The challenge of finding ways in which drugs could be recycled (processing of unwanted drugs, recovery of 'usable' compounds and subsequent product manufacture) lies with the chemical industry.

Removal programmes could incorporate capture and destroy approaches (e.g. granular activated carbon[28]), chemical transformation processes (e.g. ozone processing[29]), or could seek to maximise natural degradation processes by optimisation of treatment e.g. identifying, isolating and seeding with drug-degrading bacterial strains.

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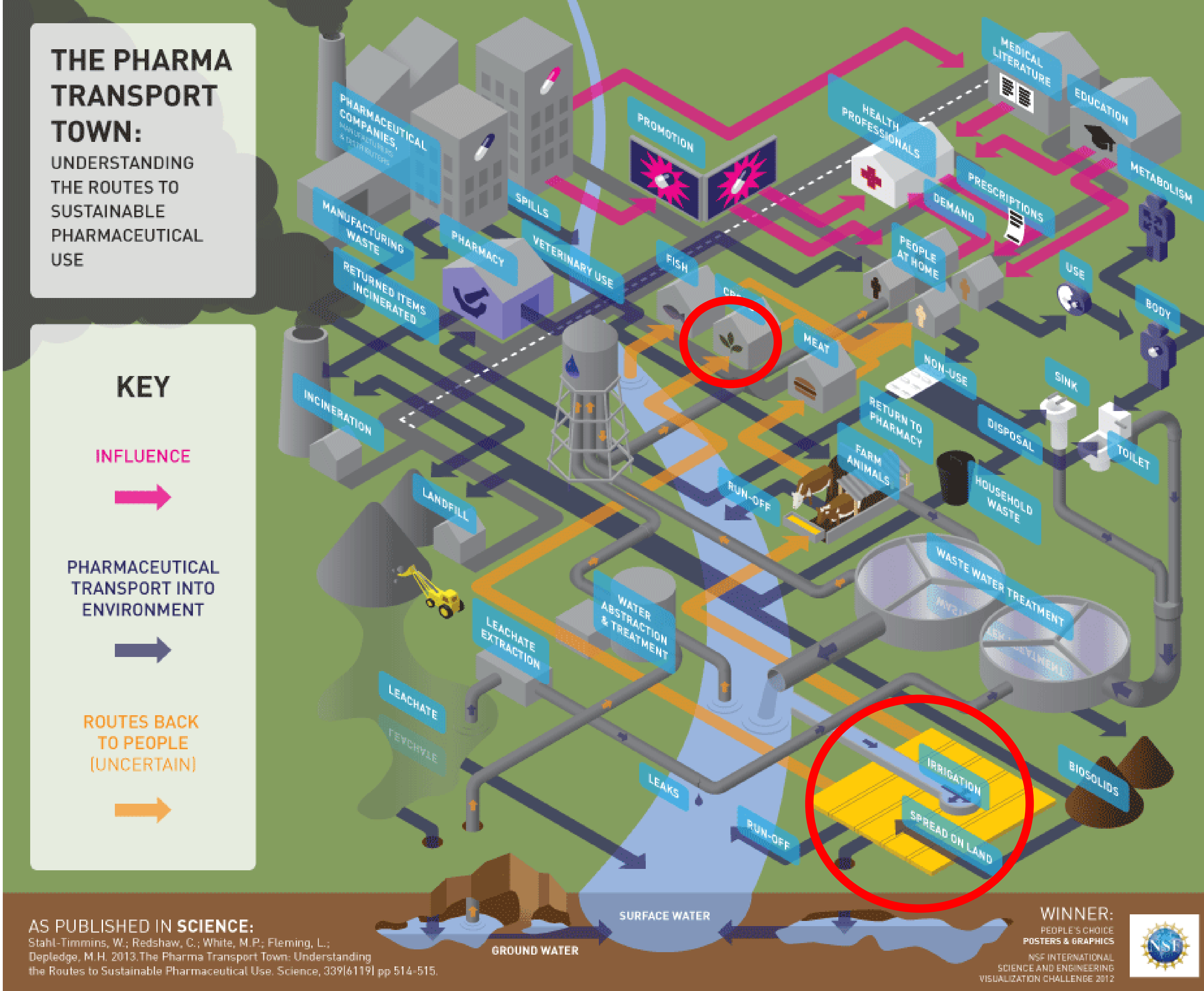
THE PHARMA TRANSPORT TOWN:
UNDERSTANDING THE ROUTES TO SUSTAINABLE PHARMACEUTICAL USE
KEY
INFLUENCE
PHARMACEUTICAL TRANSPORT INTO ENVIRONMENT
ROUTES BACK TO PEOPLE (UNCERTAIN)
PHARMACEUTICAL COMPANIES,
PROMOTION
MEDICAL LITERATURE
EDUCATION
HEALTH PROFESSIONALS
PRESCRIPTIONS
DEMAND
METABOLISM
SPILLS
MANUFACTURING WASTE
PHARMACY
VETERINARY USE
RETURNED ITEMS INCINERATED
FISH
PEOPLE AT HOME
USE
BODY
MEAT
NON-USE
SINK
RETURN TO PHARMACY
DISPOSAL
TOILET
INCINERATION
FARM ANIMALS
HOUSEHOLD WASTE
RUN-OFF
LANDFILL
WASTE WATER TREATMENT
WATER ABSTRACTION & TREATMENT
LEACHATE EXTRACTION
LEACHATE
IRRIGATION
SPREAD ON LAND
BIOSOLIDS
LEAKS
RUN-OFF
SURFACE WATER
GROUND WATER
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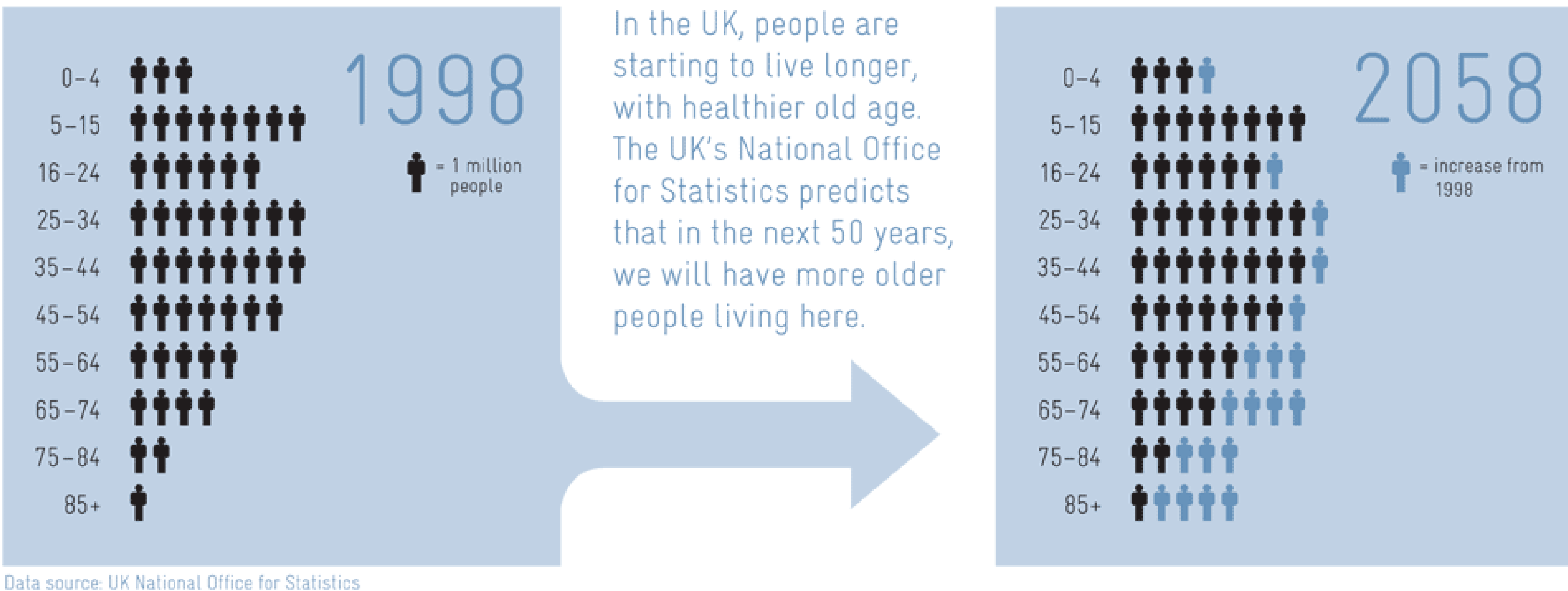
Wide ranging Environmental Impact

Contraceptive Pill
17α-ethinylestradiol (EE2)

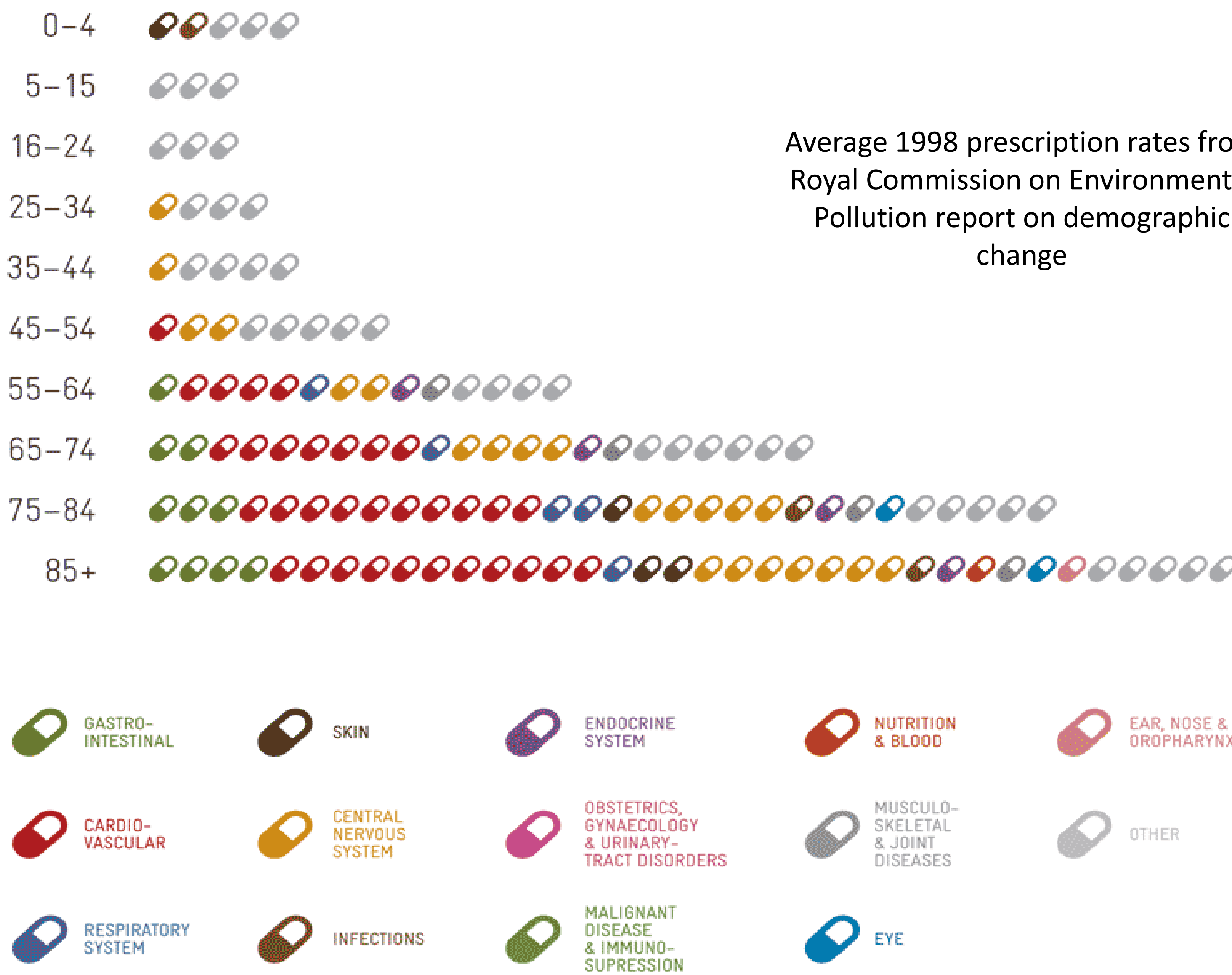
Diclofenac (NSAID)

Aging Demographic (UK)



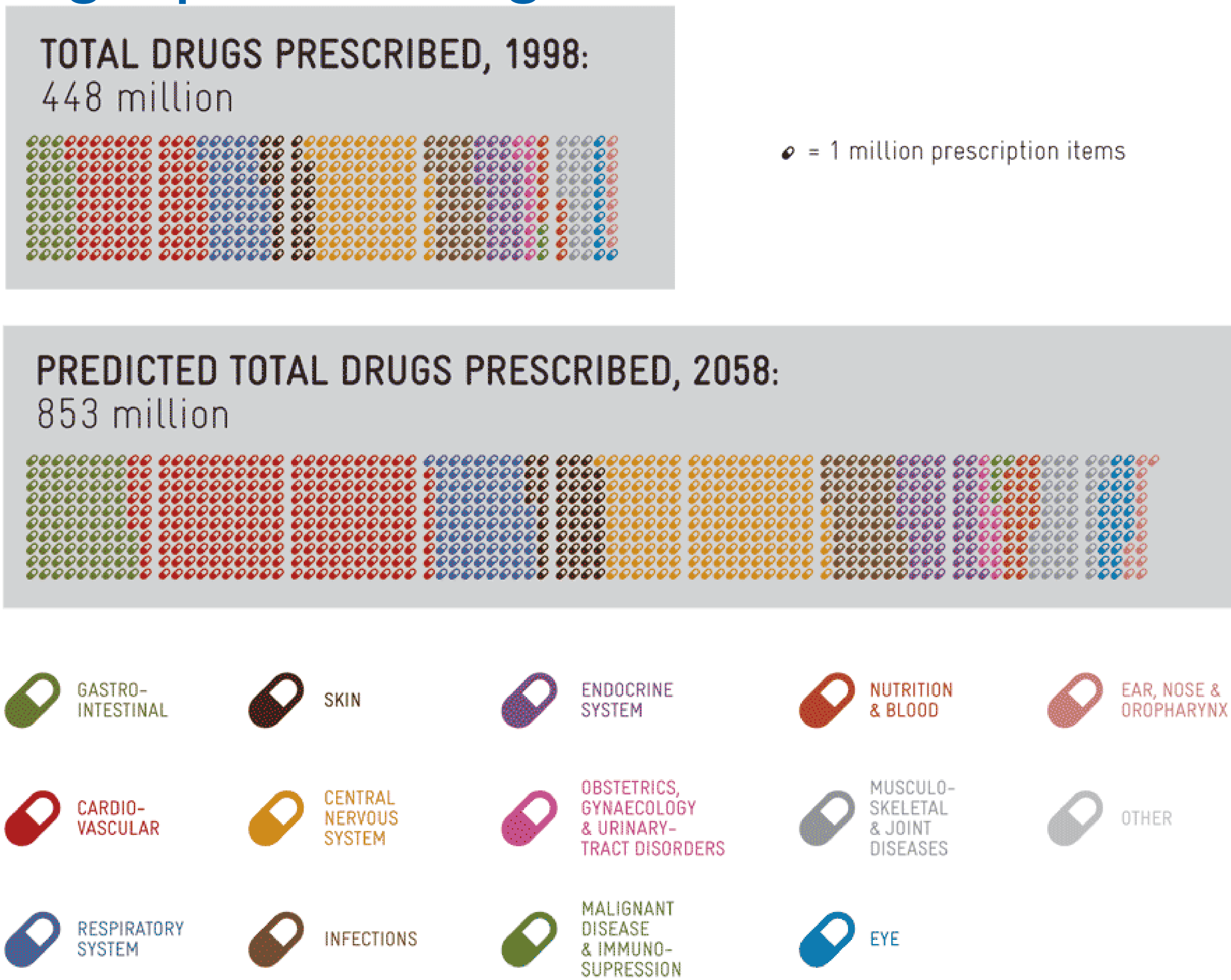
Demographic change predictions from the UK National Office of Statistics.
Graphic prepared by Dr. Will Stahl-Timmins.

Average Pharmaceutical Usage by Age



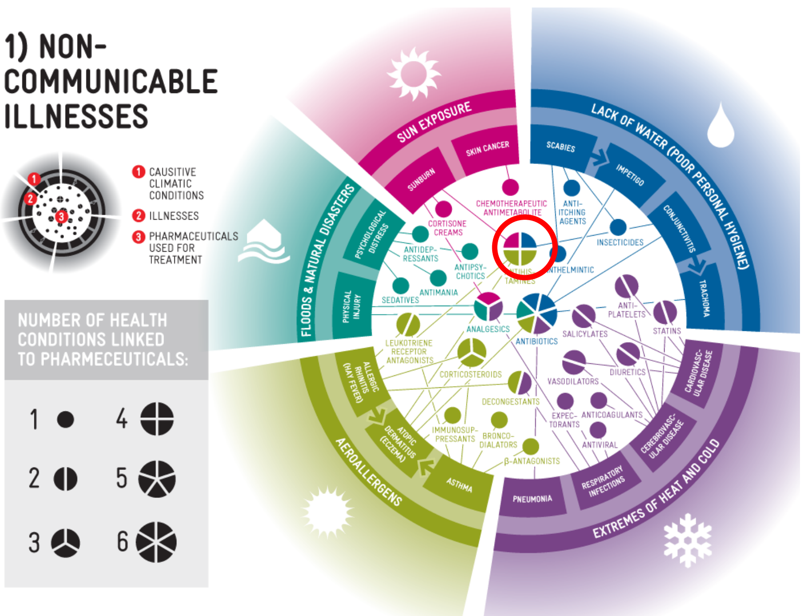
Average 1998 prescription rates from Royal Commission on Environmental Pollution report on demographic change

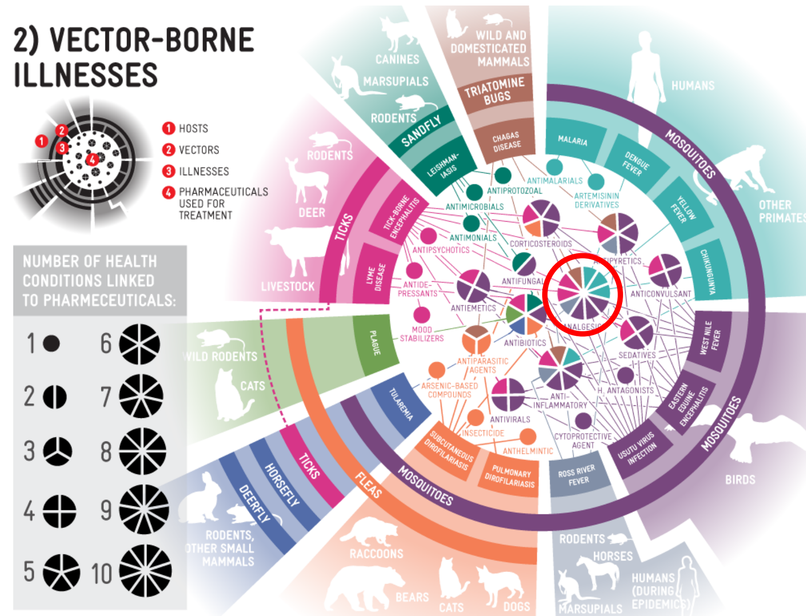
Demographic change and increases in usage

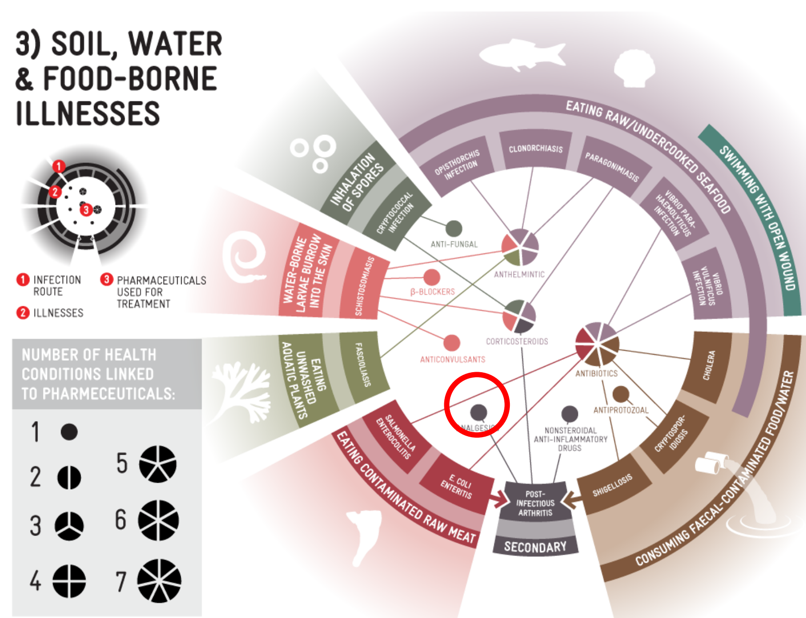


Demographic change predictions from the UK National Office of Statistics. Pharmaceutical usage data for this figure was generously provided by Ruth Willis (Royal Commission on Environmental Pollution report on demographic change). Data analysis and figure preparation was kindly performed by Dr Will Stahl-Timmins.

Climate change & Pharmaceutical Use







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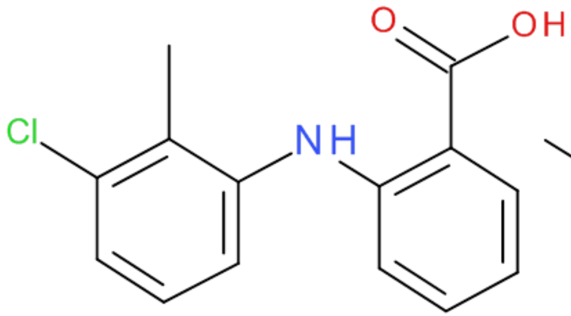
Target Compounds: NSAIDs

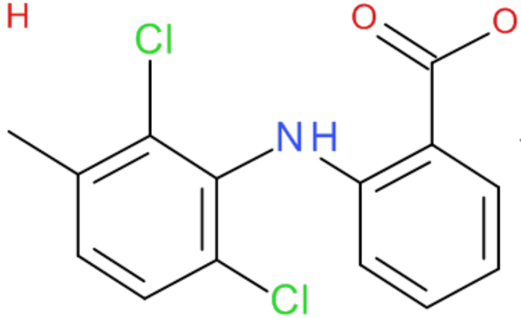
- Non-steroidal anti-inflammatory drugs
- Mode of action: COX-1 & COX-2 inhibition
- Heavily used (prescription & OTC):
  - Daily > 30 million people worldwide use prescribed NSAIDs (Singh, 2000)
  - England, 15.6 M prescriptions in 2011 (McGettigan & Henry, 2013)
  - > 90% of prescriptions for people aged 65+ (Lanas & Ferrandez, 2007)
- Ibuprofen + diclofenac + naproxen = 45% world sales (Conaghan, 2012)
- Prescribing / usage practices vary by region (McGettigan & Henry, 2013)
  - E.g. Mefenamic acid
    - 2.6% in England 2011
    - 34.7% in Philippines in 2011
- Water framework directive (2013/39/EU)
  - Diclofenac (100 ng/L)
  - 17-α-ethinylestradiol (EE2; 0.035 ng/L)
  - 17-β-estradiol (E2; 0.4 ng/L)

Q1: Do NSAIDs effect the germination of lettuce and radish seeds?

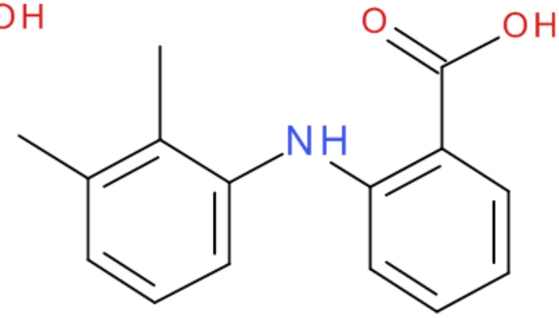
FENAMIC ACID CLASS



Tolfenamic acid
(TOL)

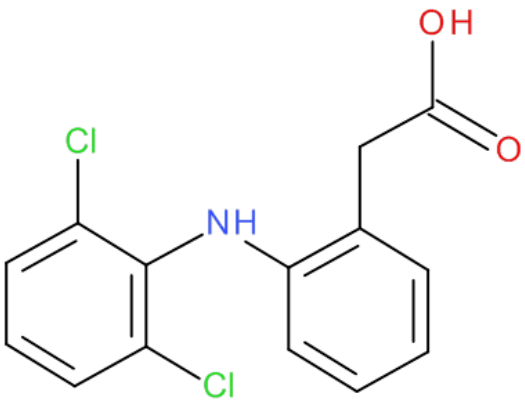


Meclofenamic acid
(MCF)



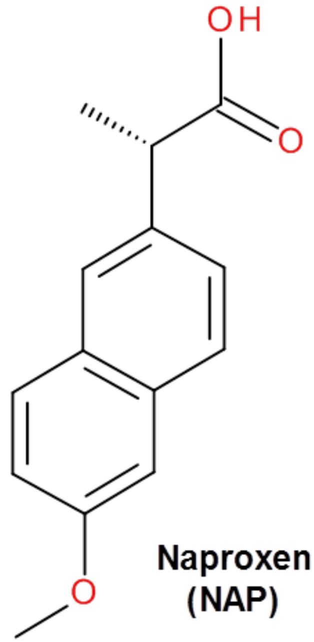
Mefenamic acid
(MF)

ACETIC ACID CLASS

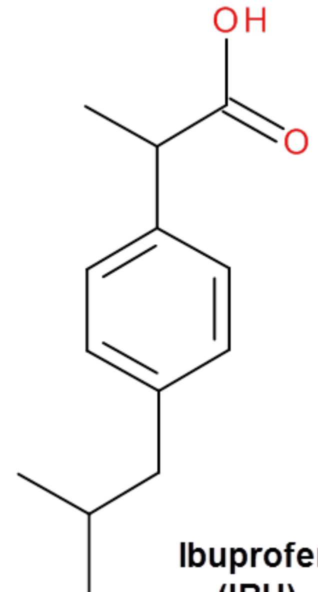


Diclofenac
(DCF)

PROPANOIC ACID CLASS



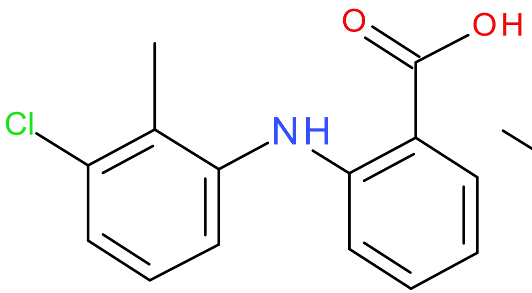
Naproxen
(NAP)



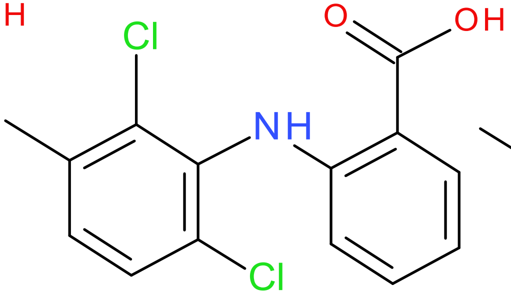
Ibuprofen
(IBU)

Q2: Do NSAIDs effect the growth of the radish plants?

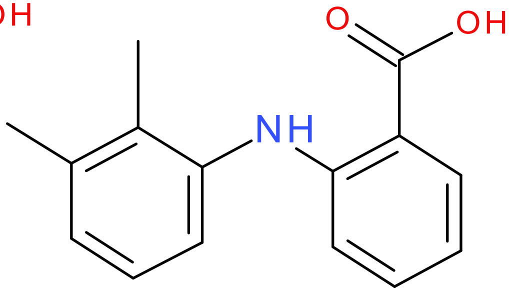
FENAMIC ACID CLASS



Tolfenamic acid (TOL)

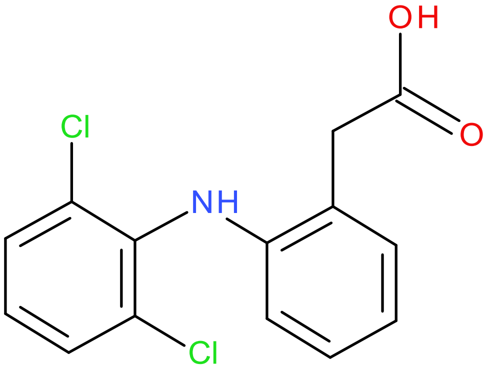


Meclofenamic acid (MCF)

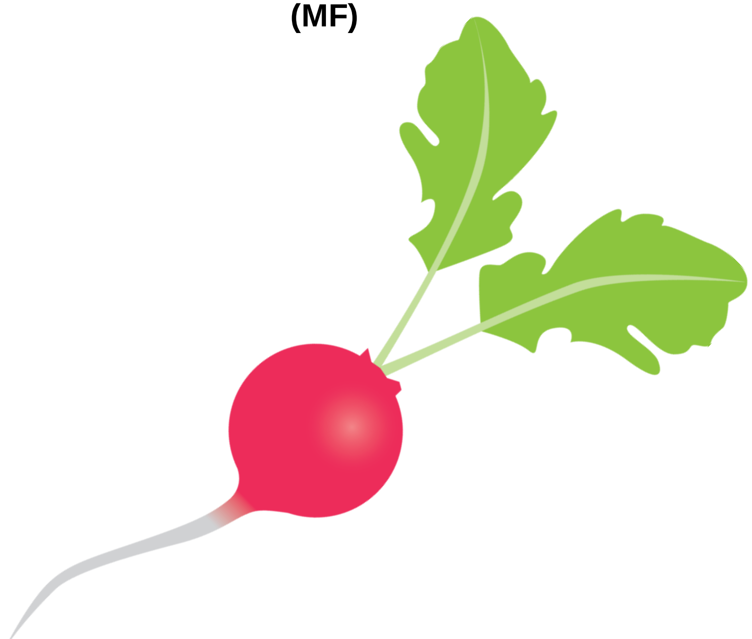


Mefenamic acid (MF)

ACETIC ACID CLASS

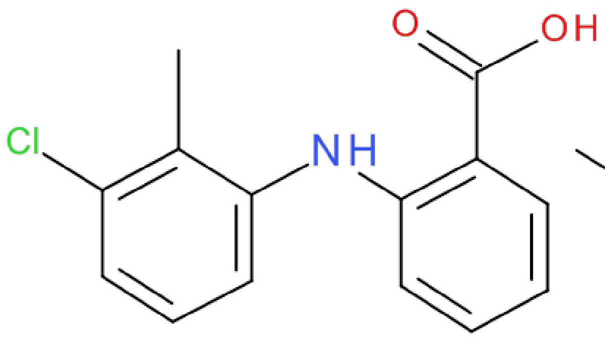


Diclofenac (DCF)

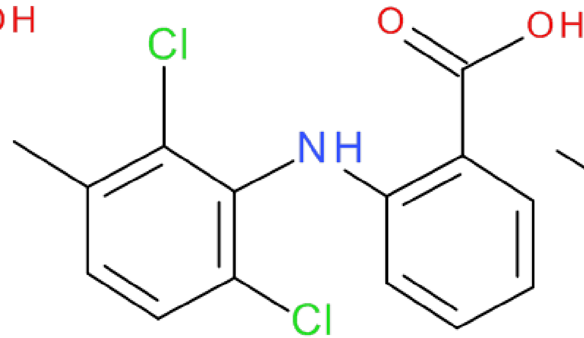


Structures Summary

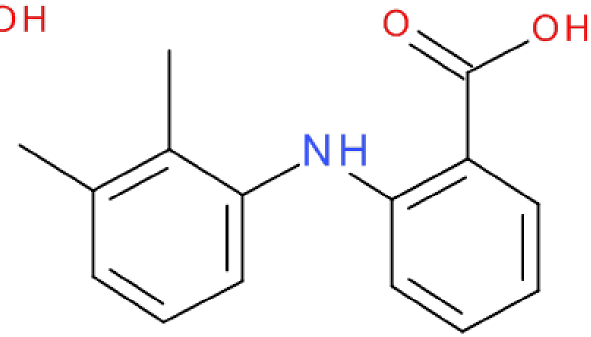
Fenamic Acid Class



Tolfenamic acid
(TOL)



Meclofenamic acid
(MCF)



Mefenamic acid
(MF)

Key features:

- Benzoic acid group
- Methyl phenyl (CH_3 at C2 or C3)
- + further C2 or C3 substitution (CH_3 or Cl)

Conclusions

- Impacts of pharmaceuticals upon higher plants are specific:
  - **Plant species**
  - **Compound specific**

Q: Should we re-evaluate the use of 'model' compounds in such studies?

- Need to develop suitable standardised tests assessing **chronic effects** of pharmaceuticals upon plants.

- Tests should combine both **phytotoxicity and uptake measurements**.

- Implications for **sustainability** and **food security** need to be considered

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