AMIDD *Dies Academicus* Special: Ask David Anything

November 27, 2020

Agenda

1. Questions that you submitted so far - **thank you**
2. Any other questions that you may have spontaneously
3. Dismiss the class!

Questions

Type I: Doing a PhD or not

- Would it be possible to join a pharma company such as Roche or Novartis directly after completing a MSc?
- Would you suggest a PhD for people who would like to work as a data scientist/bioinformaticians in industry?
- Benefits and considerations for doing PhD? My feeling is that if you want to stay in the pharma industry you have to do one. What are your view about this? What do you think about the pro and cons of doing an industry PhD?

Type II: Career planning and development

- Where do you see the advantages/disadvantages of working in industry/academia?
- What kind of different positions are there e.g. at Roche for people with a background in Bioinformatics/Computational Biology?
- I would like to ask you about your experience pursuing a career away from your home country. What were some challenges that you faced as an international student and later a non-European working in Europe? Do you have any advice for students thinking of pursuing a research career abroad?
- Best advice for a successful career in industry

Type III: Questions about my work and me

- How do you experience the work-life balance in your job?
- how a day in your job looks like and what challenge you face or have faced?
- If there is another project besides the TG-GATEs example where you combined different statistical methods, machine learning models and biological knowledge to solve a problem?

Type IV: Questions about working in drug discovery

- I would be interested in hearing a little bit more about how and where machine learning is used in drug discovery.
- How is it to work in an interdisciplinary team and how important it is to have domain knowledge in different areas?
- The *gender problem* and taking responsibility for environment (see next slides)

The gender problem in drug discovery

Question: I recently heard about the "gender problem" in developing medicine (*more specifically, here, a sex problem at the first place, because while sex refers to biological characteristics and is determined by chrosomal composition, gender refers to socially constructed roles, norms, and identities, which can change and is not aligned with sex necessarily, edited by David*). The "gender problem" I am referring here is that women react differently to drugs than men do. But the drug research is done only on male cells (*not completely*). My question now here is, did this change? Does the industries start to do also tests on female cells? (*yes*, *but still much needs to be done*)

Table 1: Prescription Drugs Withdrawn From the United States Market, Jan. 1, 1997 Through Dec. 31, 2000

Drug	Type of Drug	Date Approved	Date Withdrawn	Primary Health Risk
Prescription Drugs With Evidence of Greater Health Risks in Women				
Pondimin (fenfluramine hydrochloride)	Appetite suppressant	6/14/1973	9/15/1997	Valvular heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant	4/29/1996	9/15/1997	Valvular heart disease
Seldane[a] (terfenadine)	Antihistamine	5/8/1985	2/27/1998	Torsades de Pointes (potentially fatal irregular heartbeat)
Posicor (mibefradil dihydrochloride)	Cardiovascular	6/20/1997	6/8/1998	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal (astemizole)	Antihistamine	12/19/1988	6/18/1999	Torsades de Pointes
Rezulin (troglitazone)	Diabetic	1/29/1997	3/21/2000	Liver failure
Propulsid[b] (cisapride monohydrate)	Gastrointestinal	7/29/1993	7/14/2000	Torsades de Pointes
Lotronex (alosetron hydrochloride)	Gastrointestinal	2/9/2000	11/28/2000	Ischemic colitis (intestinal inflammation due to lack of blood flow)
Prescription Drugs Without Evidence of Greater Health Risks in Women				
Raxar (grepafloxacin hydrochloride)	Antibiotic	11/6/1997	11/1/1999	Torsades de Pointes
Duract (bromfenac sodium)	Analgesic and anesthetic	7/15/1997	6/22/1998	Liver failure

Between 1997 and 2001, ten prescription drugs were withdrawn from the US market, and eight of those were more dangerous for women than for men. Source: U.S. General Accounting Office.

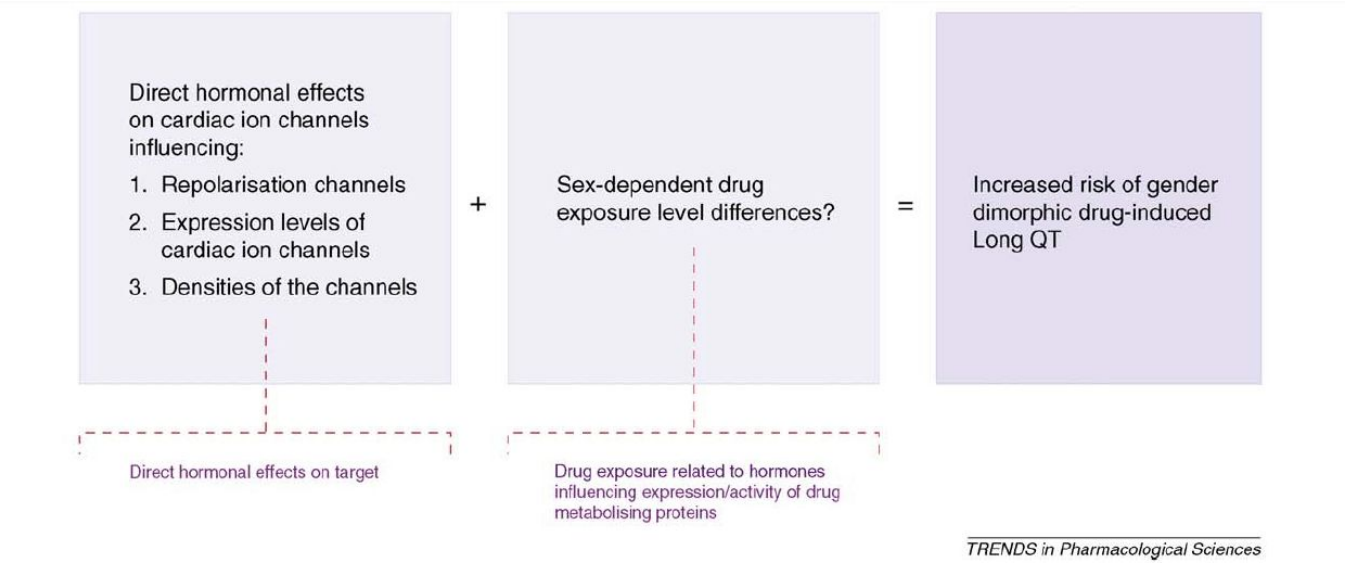
The gender program is being addressed by funding agencies, such as the EU Horizon program, academia, and independent organizations, and for the sake of translatability, by pharmaceutical companies as well. Source: https://doi.org/10.1038/d41586-020-03336-8

Possible biological reasons underlying the sex and gender difference

- Gene dosage and genetic risks factors associated with sex chromsomes, *e.g.* targets of X-linked autoimmune diseases, as well as unknown off-targets
- Body composition and physiology, *e.g.* hormonal influences during the menstrual cycle, menopause, and pregnancy
- Drug pharmacokinetics (ADME)
- Drug pharmacodynamics

Further gender factors

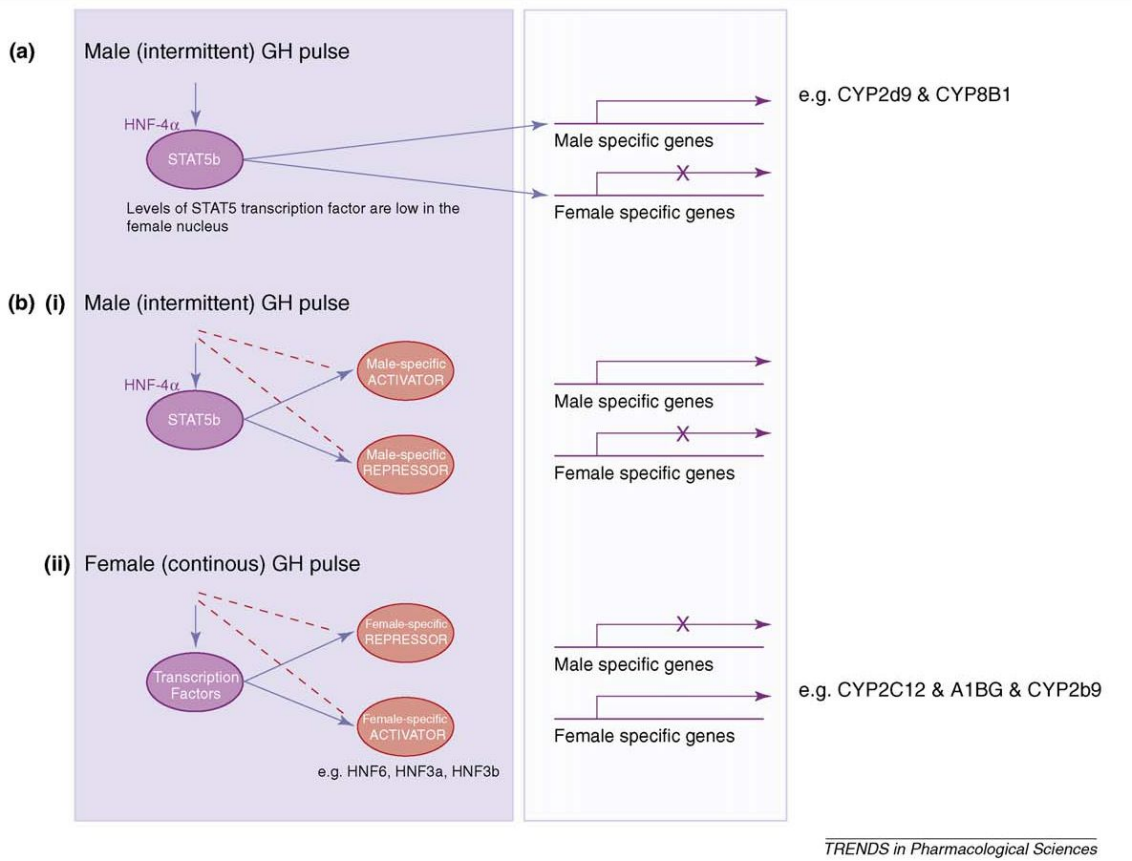
- Epidemiological factors including risk factors of diseases, prevalence, management, and outcome;
- Clinical trials often recruit young and middle-aged me, and women are under-represented.



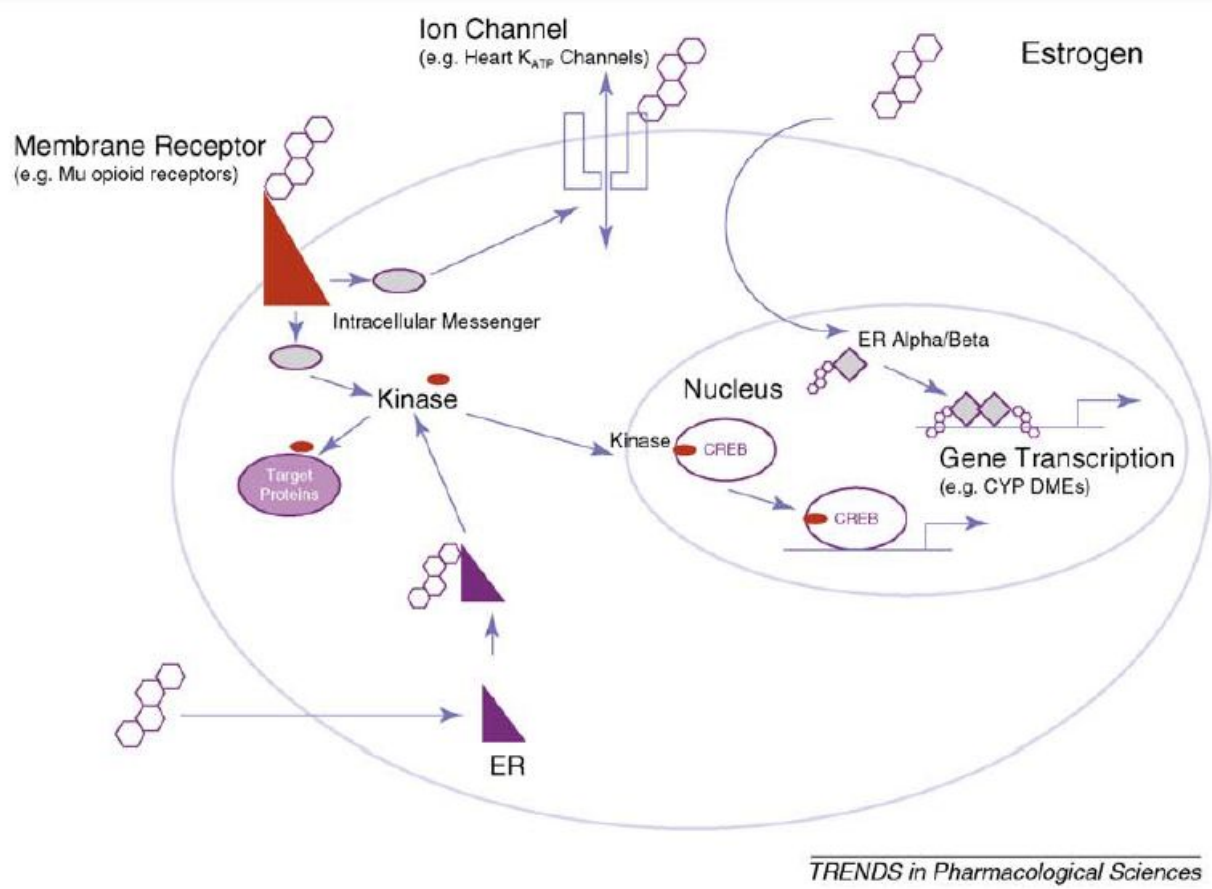
Drug-induced long QT hypothesis: gender-associated risk is thought to be the result of various factors involving direct hormonal effects on heart ion channels, as well as other factors, most probably drug exposure differences (related to expression/action of drug metabolising proteins) between the sexes.

Source: Pollitzer, E. Cell sex matters. *Nature* **500,** 23–24 (2013). https://doi.org/10.1038/500023a, and Nicolson, Tamara J., Howard R. Mellor, and Ruth R. A. Roberts. 2010. "Gender Differences in Drug Toxicity." Trends in Pharmacological Sciences 31 (3): 108–14. https://doi.org/10.1016/j.tips.2009.12.001

Sex differences in hormone secretion and response on the molecular and cellular level



GH=Growth hormone



ER=estrogen receptor

Sex differences on the organ and system level

Table 1 Gender differences in absorption, distribution, metabolism, and excretion

Parameter	Sex differences
Drug bioavailability	
Absorption	M > W
Gastric acid secretion	M > W > P. Decreases absorption of weak acids but increases absorption of weak bases in M
Gastric emptying	M > W > P. E inhibit gastric empting
Gastrointestinal transit times	
Gut metabolism	M = W
Body composition	
Body surface area	M > P > W. Absorption increases when body surface is larger
Organ (heart) size	M > W
Organ blood flow	Greater blood flow to skeletal muscle and liver in M; greater to adipose tissue in W. Blood flow increases during P
Total body water	M > P > W

Table 2 Sex-related differences in drug pharmacokinetic parameters

Drug class	Outcomes in females
Anaesthetics: propofol	Plasma propofol levels decline more rapidly in W at the end of infusion
Alcohol	Lower gastric alcohol dehydrogenase activity in W. Higher plasma concentrations in W as compared with M following an equivalent drink
Antidepressants	Higher AUC and C_{max} in W
H1-antihistamines	Slower metabolism and elimination in W
Antipsychotic drugs[a]	Higher plasma levels and Vd and lower Cl in W. Reduce the dosage in W or increase dosage in M. Olanzapine is more rapidly eliminated in M than in W
Aspirin	Bioavailability and plasma levels of aspirin and salicylate are higher in W possibly due to lower activity of aspirin esterase, larger Vd and lower Cl in W than in M. Differences disappear with OCP
Benzodiazepines	Lower initial plasma levels due to larger Vd, and possibly higher Cl, in W. OC reduce their Cl. Higher plasma levels of free diazepam in W
Beta-receptor agonists	W are less sensitive
Beta blockers: metoprolol, propranolol	W have higher plasma levels due to a smaller Vd and slower Cl. Drug exposure to metoprolol increases by OC
	Renal Cl of atenolol and metoprolol increases during P due to enhanced hepatic metabolism
Calcium channel blockers	Faster Cl of verapamil, and nifedipine in W. Increased bioavailability and decreased clearance of oral vera-

Table 3 Sex differences in drug pharmacodynamics

Drug class	Outcomes
Alcohol	Higher vulnerability of W to acute and chronic complications of alcoholism
Anaesthetics: propofol	W are less sensitive to propofol. W wake up faster and require higher doses than M for the same effect
ACEIs	No mortality benefit in W with asymptomatic LV systolic dysfunction
Antidepressants	W respond better to selective serotonin/noradrenaline uptake inhibitors. M respond better to TCA and MAO inhibitors than W
Antipsychotic drugs	More effective in W. They require lower doses to control symptoms
Aspirin	Higher protective effect against stroke in W and against MI in M. Aspirin is more active in male pla-

Table 4 Examples of sex differences in adverse drug reactions

Drug class	Outcomes in females
Analgesic drugs	W report more adverse effects to perioperative analgesic drugs
Anaphylactic shock	Anaphylactic shock induced by neuromuscular blocking agents, hypnotics, opioids and benzodiazepines is more frequent in W
Anaesthetic drugs	W are more prone to ADR postoperatively
Angiotensin converting enzyme inhibitors	Dry cough is 2 to 3 times more frequent in W. No gender preference for angioedema/urticaria
Anorectics	Cardiac valvulopathy is more frequent in W exposed to phentermine, dexfenfluramine, or fenfluramine
Antiarrhythmic drugs	Higher risk of QT prolongation and TdP in W
Anticoagulants	More frequent and severe bleedings in W
H1-Antihistamines	W are more vulnerable to sedation and drowsiness
Antiplatelets	More frequent and severe bleedings in W
Antipsychotics	W present more extrapyramidal and anticholinergic effects and QTc prolongation. M reported more sexual problems
Aspirin	Increased risk of bleeding in W. More ulcer complications in M
Beta blockers	Enhanced BP lowering and heart rate reduction with metoprolol in W
Benzodiazepines	Diazepam impaired the psychomotor skills more in W than in M. Dependency is more frequent in W
Calcium channel blockers	Higher risk of oedema in W. Women taking OCP and diazepam during menstruation become relatively intoxicated
Digoxin	Higher mortality in W with HF. Digoxin plasma levels < 0.8 ng/mL are recommended in W
Diuretics	Higher rates of hospitalizations due to hypo-osmolarity, hypokalaemia and hyponatraemia and higher risk of arrhythmias in W
Drug-induced TdP	W have a longer QTc intervals and development of TdP more frequently than M
GPIIb/IIIa inhibitors	W experience more bleeding than M
Heparin	W present higher bleeding risk
Opioid receptor agonists	W experience more ADRs (nausea and vomiting, respiratory depression) despite smaller dose requirements for pain control
NSAIDs	M display a higher prevalence of ADRs than W
Paracetamol	Acute liver failure due to paracetamol overdose is more common in W
Procainamide	Systemic lupus erythematosus more common in W
Skin diseases	W > M (systemic lupus erythematosus and photosensitivity)
Statins	Myopathy is more frequent in older W with low body weight
Thiazides	More hyponatraemia and hypokalaemia in W
Thiazolidinediones	Double the risk of fractures among diabetic W, but not among M
Thrombolytics	Higher risk of bleeding and intracranial haemorrhagic in W
Unfractioned heparin	W develop higher plasma levels and higher bleeding risk
Zolpidem	To reduce the risk of morning-after activity impairment decrease the dose of zolpidem by 50% in W

References are presented in Supplementary material online, *Table S4*.
ACEIs, angiotensin-converting enzyme inhibitors; ADR, adverse drug reactions; BP, blood pressure; CV, cardiovascular; E: oestrogens; GP, glycoprotein; HF, heart failure; M, men; NSAIDs, non-steroidal anti-inflammatory drugs; OCP, oral contraceptives; QTc, corrected QT interval; TdP, torsades de pointes; W, women.

Source: Tamargo, J., G. Rosano, T. Walther, J. Duarte, A. Niessner, J. C. Kaski, C. Ceconi, et al. 2017. "Gender Differences in the Effects of Cardiovascular Drugs." European Heart Journal - Cardiovascular Pharmacotherapy 3 (3): 163–82.

The sex difference in toxicity is addressed explicitly in preclinical drug discovery

- In preclinical development, a necessary step is to perform the General Toxicity study.
- For rodent studies, in general group sizes used in one-month studies are 10 animals/sex/group, and in six-month studies are typically 15 animals/sex/group.
- For non-rodents, the study design requested by health agencies, for instance EMA, requires four animals per dose per sex (+ 2 -3 recovery animals, onlyin pivotal studies). Both sexes need to be tested, only in case of sexual hormones is the use of one gender acceptable (adjustable exceptions can be made).
- **Question to the class: what other approaches, especially mathematical and informatics tools can we use to predict and reveal sex differences?**

Table 1
Example of a study design for a six month rat study with assessment of recovery and satellite animals.

Dose Group	Low	Medium	High	Control
No. of animals	15M + 15F	15M + 15F	15M + 15F	15M + 15F
No. of TK satellites[b]	9M + 9F	9M + 9F	9M + 9F	3M + 3F
No. of recovery[b]			5M + 5F	5M + 5F
Maximum total for one study				200[a]

[a] There is variation in approach between companies; not all companies carry out the studies exactly as described in this table.
[b] Recovery animals are not usually included on all studies.

Table 5
Example of a study design for one month general toxicity study in non-rodents with assessment of recovery.

Dose group	Low	Medium	High	Control
No. of animals	3M + 3F	3M + 3F	3M + 3F	3M + 3F
No. of recovery[b]			2M + 2F	2M + 2F
Maximum total for one study				32[a]

[a] There is variation in approach between companies; not all companies carry out the studies exactly as described in this table.
[b] Recovery animals are not usually included on all studies.

Table 6
Example of a minimised study design for non-rodents without recovery controls.[b]

Dose group	Low	Medium	High	Control
No. of animals	3M + 3F	3M + 3F	3M + 3F	3M + 3F
No. of recovery			2M + 2F	
Maximum total for one study				28[a]

Source: Sparrow, Susan S., Sally Robinson, Sue Bolam, Christopher Bruce, Andy Danks, David Everett, Stephen Fulcher, et al. 2011. “Opportunities to Minimise Animal Use in Pharmaceutical Regulatory General Toxicology: A Cross-Company Review.” Regulatory Toxicology and Pharmacology 61 (2): 222–29. https://doi.org/10.1016/j.yrtph.2011.08.001.

Suggestions to improve our understanding of gender differences, exemplified by effects of cardiovascular drugs

Table 5 Suggestions to improve our understanding of gender differences in the effects of cardiovascular drugs

1. Increase the number of women recruited in all phases of clinical trials
   - Include an adequate number of women unless adequately justified or enrol only woman when indicated
   - Limit the exclusion criteria to facilitate the extrapolation of the results to the general population
   - Gender-specific power calculations should be conducted and published
2. When designing and analysing the results of clinical trials gender-related cardiovascular endpoints should include outcomes important for women
3. Gender-specific PD/PK differences have not been investigated for many CV drugs and the clinical relevance of many gender-related differences remains unproven.
   a. Preclinical studies should consider sex differences in expression and function of target receptors, both for efficacy and safety
   b. Prospective clinical studies should be designed to better understand:
      - Sex differences in the pathophysiology and prevalence risk factors of CVD
      - Sex-related differences in the efficacy and safety of cardiovascular therapy and the mechanisms involved
      - The role of sex–gender on the PD/PK variations induced by pathological conditions
      - The potential interactions of CV drugs with endogenous or therapeutically supplied sex hormones
      - All this information should be correlated with the incidence of ADRs
   c. Gender-specific analyses should be conducted and cost-effectiveness analysis should be conducted and published for both efficacy and safety.
   d. Quality-of-life measures should be part of outcomes evaluated by gender
   e. Reasons for nonadherence to therapy and/or interventions should be documented according to gender
4. Disseminate the results regarding significant gender differences in CV drug efficacy/safety
   - Gender differences in PK/PD of CV drugs should be part of medical education and should be presented as an intrinsic characteristic of many drugs
   - Develop educational programmes to increase awareness of sex-specific differences in PD/PK of CV drugs
   - Sex-specific dosage recommendations for CV drugs should be included on their labels
   - Provide sex-specific data on drug efficacy and safety in all guidelines on CVD
5. Gender differences in dosing, efficacy, and safety of CV drugs are the first step to design safer and more effective personalized treatments

ADR, adverse drug responses; CV, cardiovascular; CVD, cardiovascular diseases; PD, pharmacodynamics; PK, pharmacokinetics.

How drug discovery may be improved to be responsible for environment

Question: Plastic in our environment is a problem in our world. But not only there. We have also a lot of softening agents in our food and drinks which are leached out of their plastic container. But the same problem we have also in medicine, when someone gets for example an intravenous infusion.Do you know if there are people researching on alternative products or can you find that out?

Excipients Used In the Formulation of Liquid Dosage Forms (no plastic particles)

1. Vehicle/solvents (water, alcohol, glycerol/glycerin, etc.)
2. Co-solvents
3. Surfactants
4. Preservatives
5. Viscosity modifiers, also known as suspending agents (minimize interparticle attraction and aggregation)
6. pH buffers
7. Antioxidants
8. Chelating agents, also known as sequestrants (binding to metal ions, protecting drugs from catalysts that accelerate oxidative reaction)
9. Sweeteners
10. Flavouring agents
11. Colourants
12. Antifoaming agents
13. Humectants (retard the evaporation of aqueous vehicle from dosage forms during storage and use)
14. Emulsifying agents (reducing the interfacial tension and preventing droplet coalescence
15. Flocculating agents neutral electrolytes capable of preventing caking of suspended solids)

› Pediatr Surg Int. 2002 Sep;18(5-6):310-4. doi: 10.1007/s00383-002-0810-7. Epub 2002 May 14.

Plastic particle migration during intravenous infusion assisted by a peristaltic finger pump in an animal model

P A Dewan [1], H Ehall, G A Edwards, D J Middleton, J Terlet

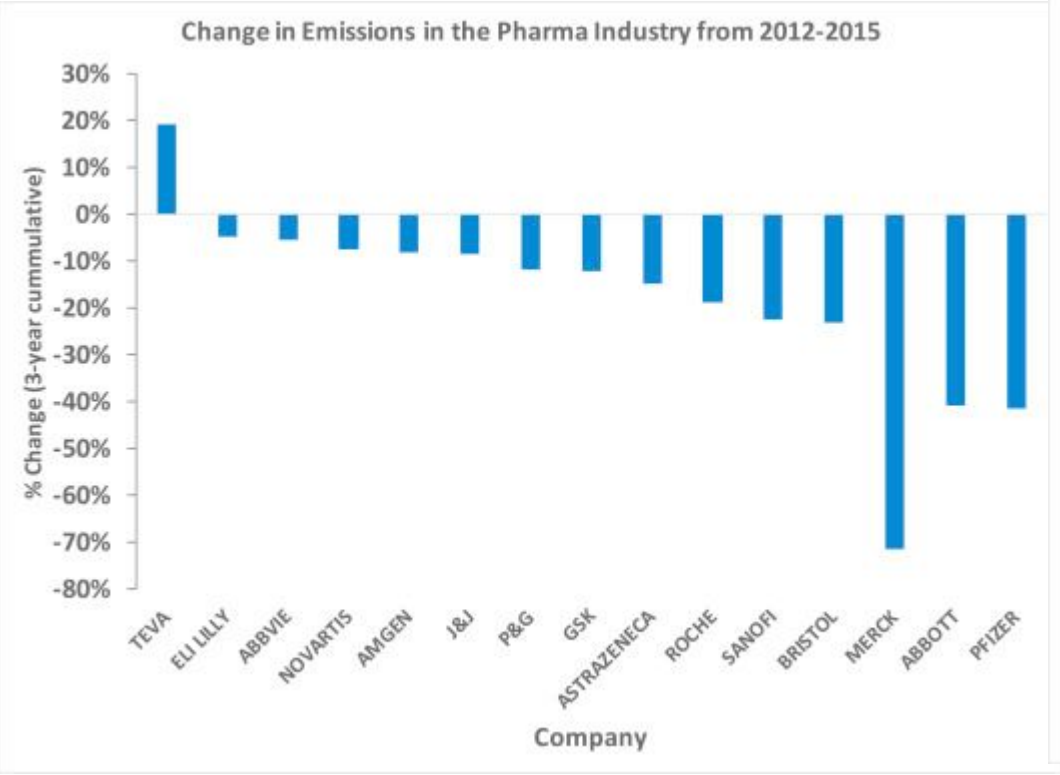
Affiliations + expand

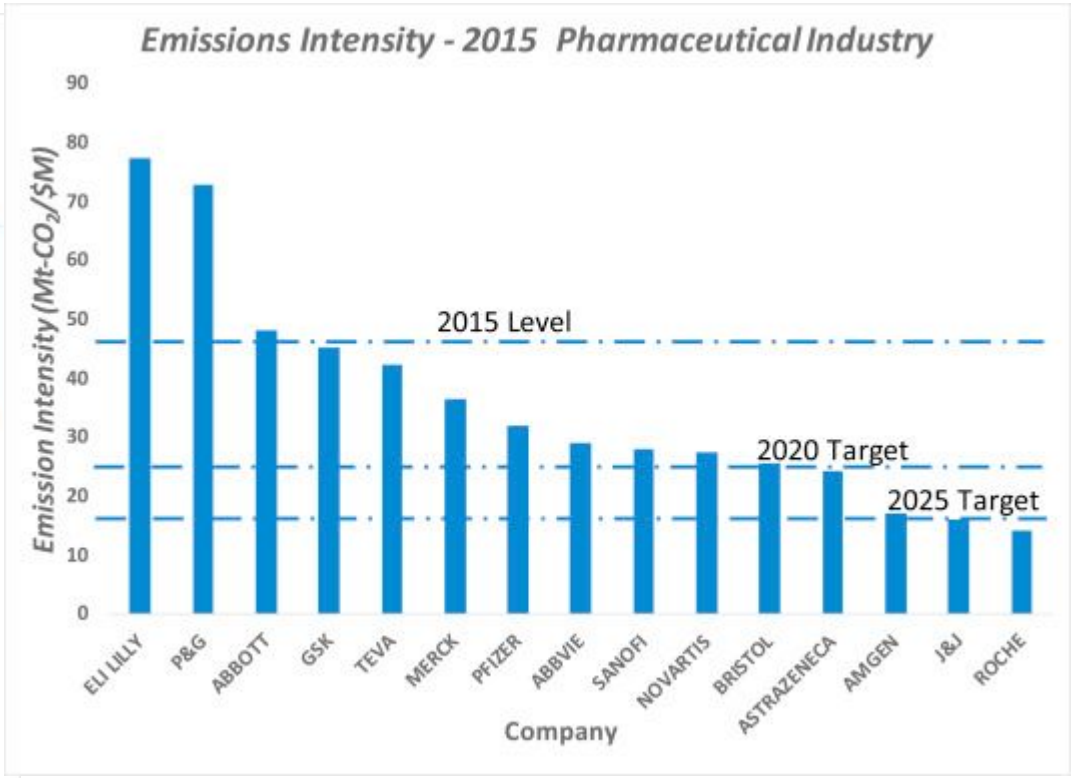
PMID: 12415345 DOI: 10.1007/s00383-002-0810-7

Silicone particles were found in 8 of 10 animals in the experimental group and in 2 of 9 control animals, indicating that silicone particles are dislodged during pump-assisted IV infusions. The difference between the control and infused animals was statistically significant using Fisher's exact test (P = 0.023). However, silicone plastic particles in control animals suggest that there is also environmental exposure to silicone in addition to those particles that come from a therapeutic source, … The clinical significance of each of these two findings is yet to be determined.

Source: https://www.pharmapproach.com/excipients-used-in-the-formulation-of-liquid-dosage-forms/2/, and references therein

Emissions by the pharma industry are reducing, though potentials remain





Source: “Carbon Footprint of the Global Pharmaceutical Industry and Relative Impact of Its Major Players.” 2019. Journal of Cleaner Production 214 (March): 185–94. https://doi.org/10.1016/j.jclepro.2018.11.204.

Spontaneous questions

Class dismissed

https://xkcd.com/2385/