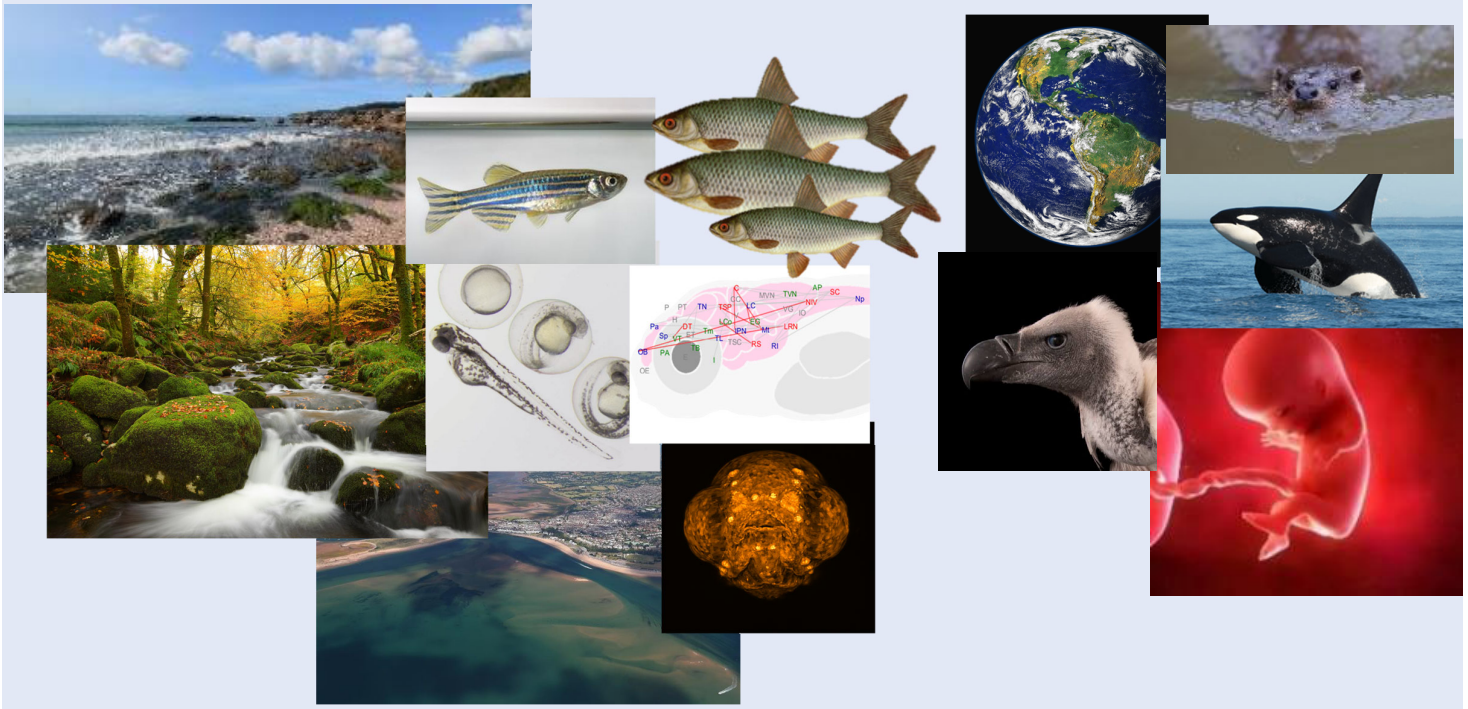
野生生物における内分泌かく乱：

35年以上にわたる研究の旅から得られた洞察

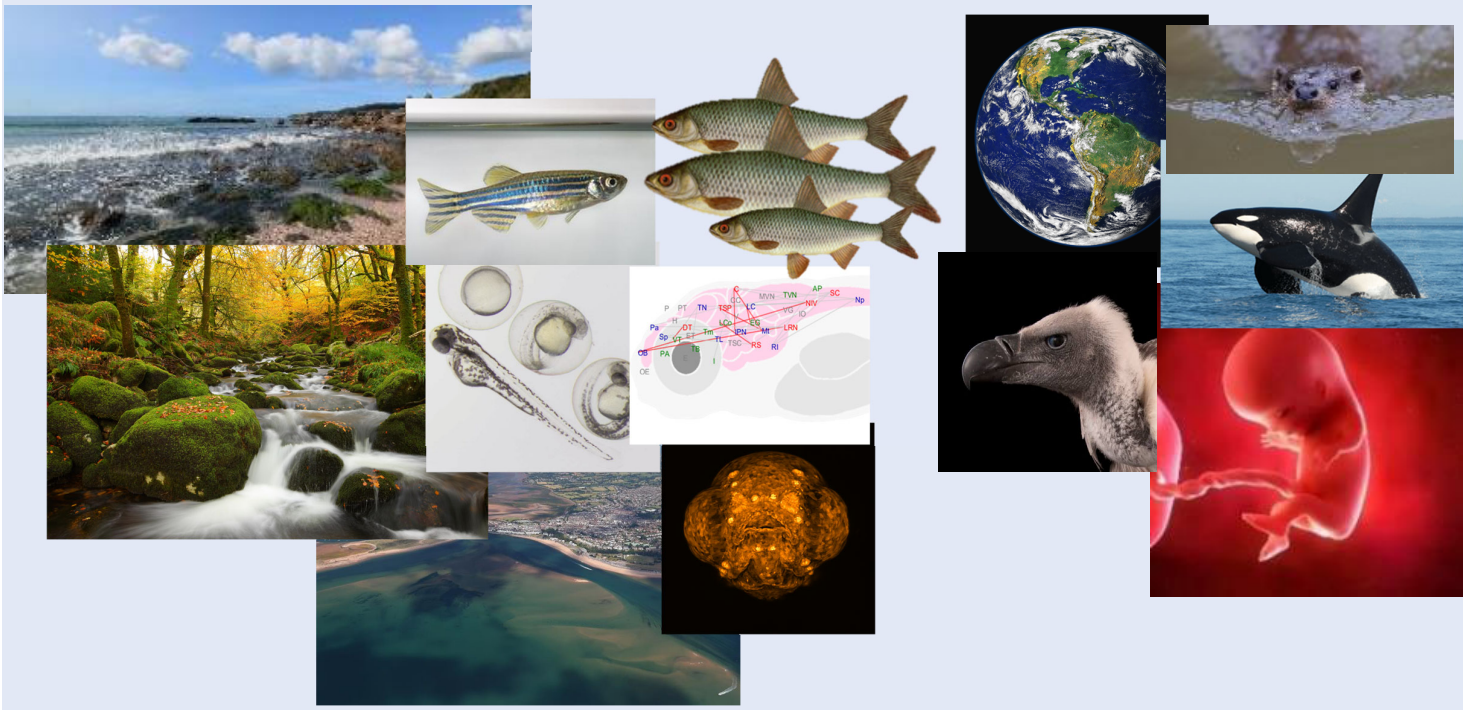
チャールズ・R・タイラー教授



Endocrine Disruption in Wildlife:

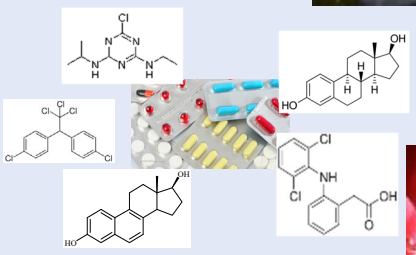
Insights from a Research Journey Over Three and a Half Decades

Professor Charles R. Tyler



プレゼンテーション概要

- 地球全体の健全性への目覚め、そして失われる生物多様性



- 化学的視点からみた環境、そして内分泌かく乱化学物質

- 野生生物における内分泌かく乱（魚類に焦点を当てて）

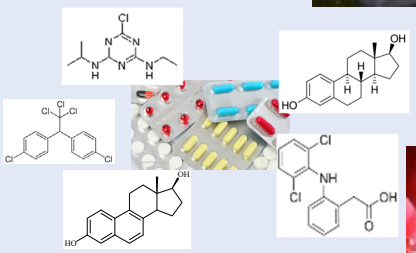
- 内分泌かく乱化学物質がどのように影響や害を及ぼすかについて理解を深める

- *考察、そして結論としての所感*

University of Exeter

Presentation Outline

- Waking up to Planetary Health and Biodiversity Loss



- The Chemical Environment and Endocrine Disrupting Chemicals

- Endocrine Disrupting in Wildlife (with a focus on Fish)

- Deepening our understanding on how Endocrine Disrupting Chemicals can cause effects – and harm

- *Reflections and a Few Concluding Thoughts*

画像 – チャールズ・R・タイラー

地球全体の健全性への目覚め

Image – Charles R. Tyler

Waking up to Planetary Health

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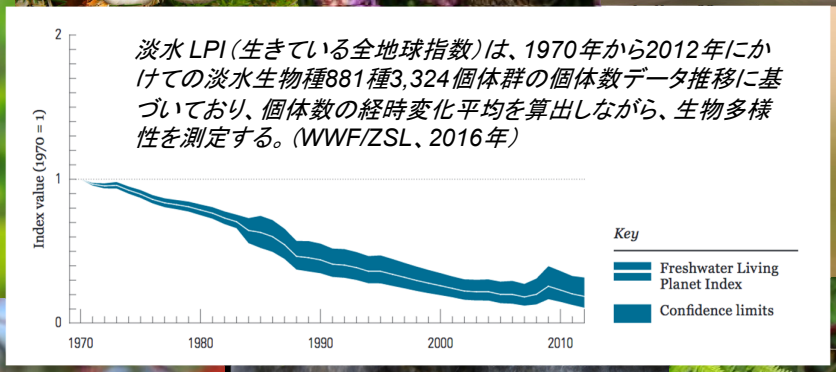
地球全体の健全性への目覚め

生物多様性の危機



淡水 LPI（生きている全地球指数）は、1970年から2012年にかけての淡水生物種881種3,324個体群の個体数データ推移に基づいており、個体数の経時変化平均を算出しながら、生物多様性を測定する。（WWF/ZSL、2016年）

化学物質汚染が重大な要因となっている

画像 – チャールズ・R・タイラー

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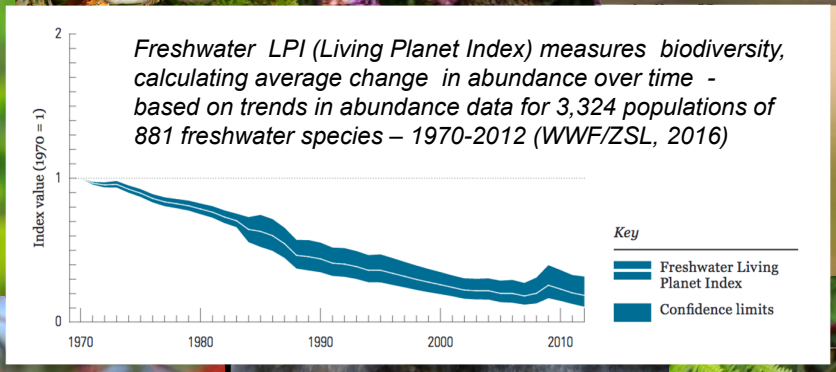
Waking up to Planetary Health

The Biodiversity Crisis



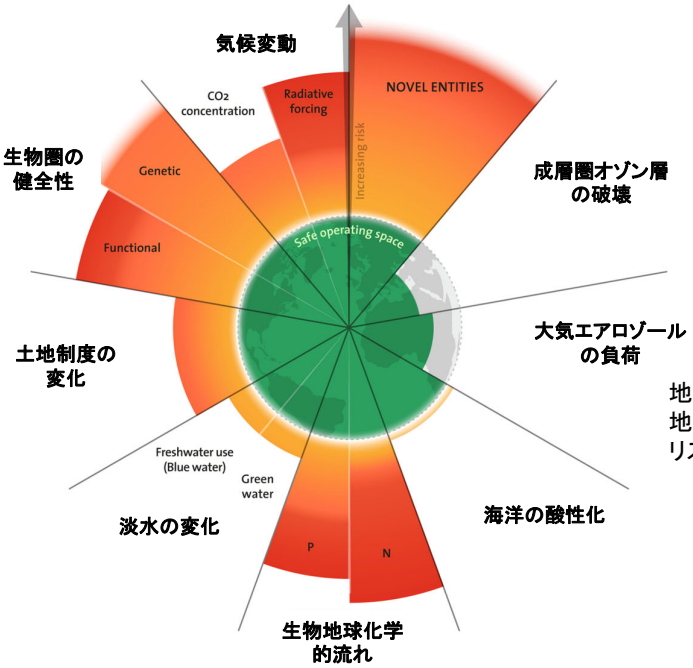
Freshwater LPI (Living Planet Index) measures biodiversity, calculating average change in abundance over time - based on trends in abundance data for 3,324 populations of 881 freshwater species – 1970-2012 (WWF/ZSL, 2016)

Chemical Pollution is a Considerable Contributing Factor

Images – Charles R. Tyler

地球全体の健全性への目覚め

9の深刻な地球規模的プロセスでの人為的活動によって、高まりつつあるリスク

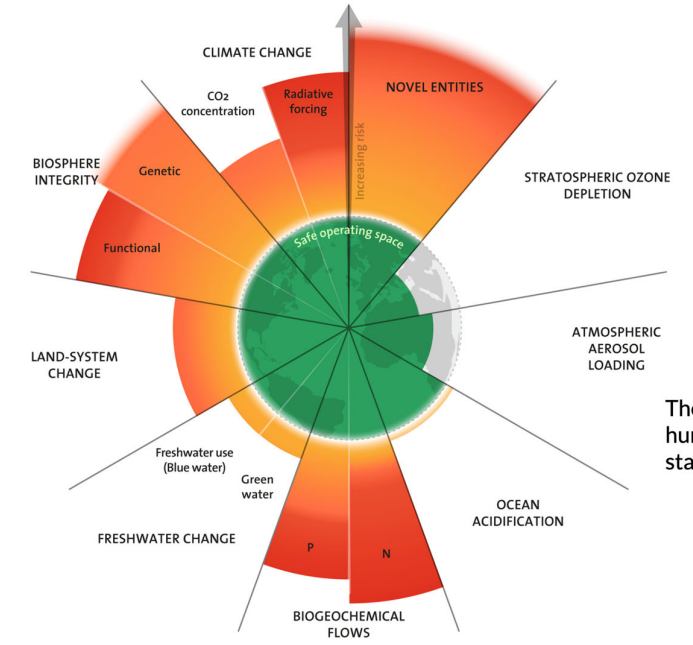


地球境界枠組みは、地球の安定性と回復力を制御する深刻な地球規模的プロセスでの人為的活動によって高まるつつあるリスクを浮き彫りにしている

The 2025 update to the Planetary boundaries. Licensed under CC BY-NC-ND 3.0. Credit: "Azote for Stockholm Resilience Centre, based on analysis in Sakschewski and Caesar et al. 2025".

Waking up to Planetary Health

Rising Risks from Human Pressures on Nine Critical Global Processes

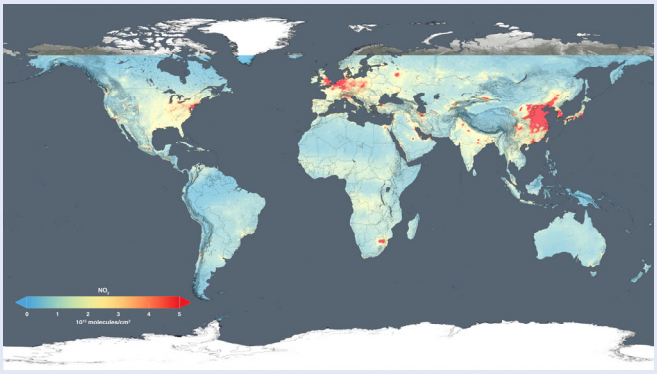


The planetary boundaries framework highlights the rising risks from human pressure on nine critical global processes that regulate the stability and resilience of the Earth

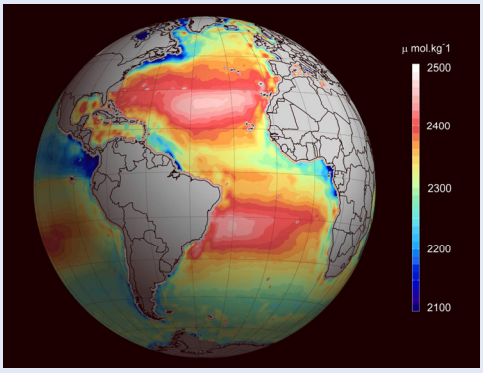
The 2025 update to the Planetary boundaries. Licensed under CC BY-NC-ND 3.0. Credit: "Azote for Stockholm Resilience Centre, based on analysis in Sakschewski and Caesar et al. 2025".

私たちは地球の化学的なバランスを根本的に変えつつある……

衛星画像は、私たちによる化学的な影響が地球に及ぼす範囲について強い洞察を与えている：以下に二つの例を示す。



二酸化窒素

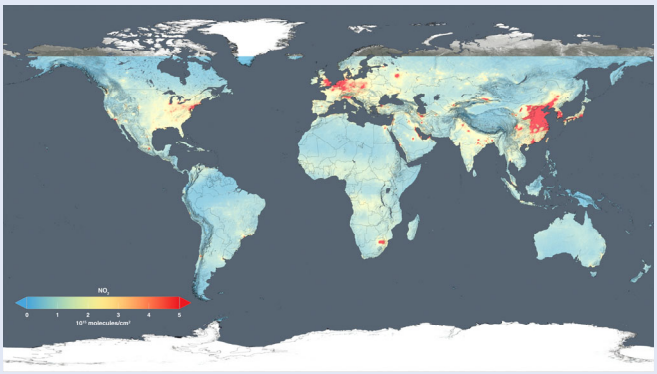


海洋酸性化

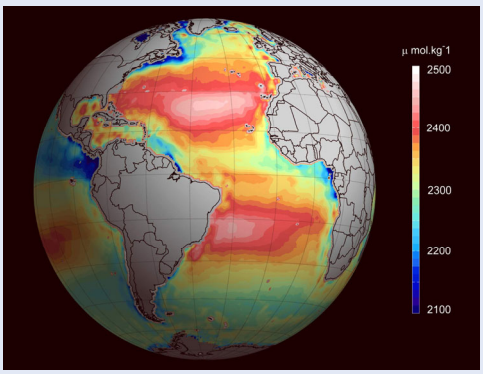
信じがたい事実：世界では毎年450km³ を超える家庭・産業・農業排水が水環境に流入し、その処理には6,000km³ の淡水が必要となり、これは世界の利用可能地表水の3分の2に相当する

We are fundamentally changing the chemical balance of our planet…..

Satellite images provide powerful insights into the extent of our chemical influence on the planet: here are two examples,



Nitrogen dioxide



Ocean acidification

An incredible fact: Globally, over 450 km³ of domestic, industrial and agricultural wastewater enters our aquatic environments each year, and requires 6000 km³ of freshwater for treatment –two thirds of the world's usable surface freshwater

ヒト健康への影響 – 事実

- 汚染は、ヒトの疾患及び若死にの最大の環境要因である。2017年には900万人が汚染による若死にを遂げ、これは全世界の死亡者数の16%を占める（エイズ、結核、マラリアの合計を上回る）
- 汚染関連死の約92%は低中所得国で発生している
- 最も高い総合的リスク下にあるのは小児である
- 汚染はコストとなる:
  - 汚染関連疾患による生産性の損失は、低中所得国ではGDPの2%に相当する
  - 医療費：高所得国で1.7%、汚染が進み経済成長が急な低中所得国では7%までに相当
- 福祉的な損失は年間4.6兆米ドル（経済生産高の6.2%）
- 健康影響への負担はおそらく過小評価されている！

Landrigan et al., : The Lancet Commission 2017

Human Health Effects – The FACTS

- Pollution is the largest environmental cause of disease and premature deaths in humans; 9 million premature deaths in 2017 – 16% of all deaths worldwide (> AIDS, TB and Malaria combined)
- Nearly 92% of pollution –related deaths occur in low-income and middle-income countries (LMICs)
- Children are at the greatest overall risk
- Pollution is costs:
  - Productivity loses due to pollution related diseases are at 2%GDP in LMICs
  - Health spending: 1.7% in HIC and up to 7%in polluted, rapid developing MIC
- Welfare losses US$4.6 trillion per year (6.2% economic output)
- Health impact burdens are probably underestimated!

Landrigan et al., : The Lancet Commission 2017

化学物質と健康


私たちの化学物質への依存

私たちは、製品中の数万種類の化学物質を使用している（世界規模で3兆ドルの産業）
.....可塑剤、肥料、農薬、医薬品など

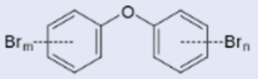
そのほとんどは、環境中や野生生物の体内、特に水生環境で生きる動物体内へと流れ込む。

特に懸念される化学物質

優先化学物質が、有害健康影響を示す確かな科学的根拠があるとして懸念されるものとして見出されれてる。

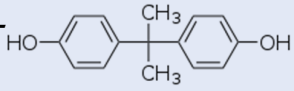
健康への懸念が高まっているその他の化学物質には以下のようなものがある：

ペルオロオクタン酸（PFOA）
（コレステロール異常及び慢性腎臓病）



ポリ臭化ジフェニルエーテル類
（甲状腺機能障害）

ポリカーボネート*系ポリマー*
（肥満、生殖機能）



医薬品：17*α*-エチニルエストラジオール（EE2）、17*β*-エストラジオール（E2）、ジクロフェナク、SSRI（抗うつ剤）

Chemicals and Health


Our Dependence on Chemicals

We use tens of thousands of chemicals in products (a $3 trillion global enterprise)
..... plasticizers, fertilisers, pesticides, pharmaceuticals, etc.

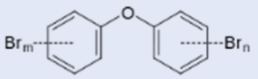
Most end up in the environment and in the bodies in of wildlife - notably animals living in aquatic environments.

Chemicals of Particular Concern

Priority Substances have been identified for which we have concern because there is good evidence for adverse health effects.

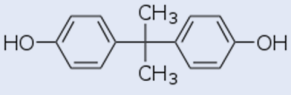
Other Chemicals for which there is increasing health concern include:

Perfluoro octanoic acid (PFOAs)
(cholesterol and chronic kidney disease)



Polybrominated diphenyl ethers
(thyroid dysfunction)

Polycarbonate *polymers*
(obesity, reproduction)



Pharmaceuticals: 17 alpha-ethinyloestradiol (EE2), 17 beta-oestradiol (E2), Diclofenac, SSRIs (antidepressants)

化学物質と健康

内分泌かく乱化学物質

世界保健機関（WHO）は内分泌かく乱化学物質（EDC）を次のように定義している：

「内分泌系の機能を変化させ、その結果として健全な生物個体やその子孫、または(準)個体群に有害な健康影響をもたらす外因性の物質または混合物」。

EDCは、人工又は天然の化学物質であり、受容体、ホルモン合成又は分解酵素、ホルモン分泌などを介して、あるいはその他の方法で体内のホルモンに干渉する。

Chemicals and Health

Endocrine Disrupting Chemicals

The **World Health Organization (WHO)** defines an endocrine-disrupting chemical (EDC) as:

“an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations”.

EDCs can be a man-made or natural chemical and they interfere with the body's hormones via receptors, enzymes synthesising or degrading hormones, hormone excretion, and in other ways.

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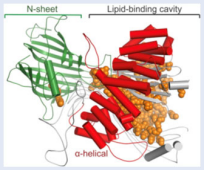
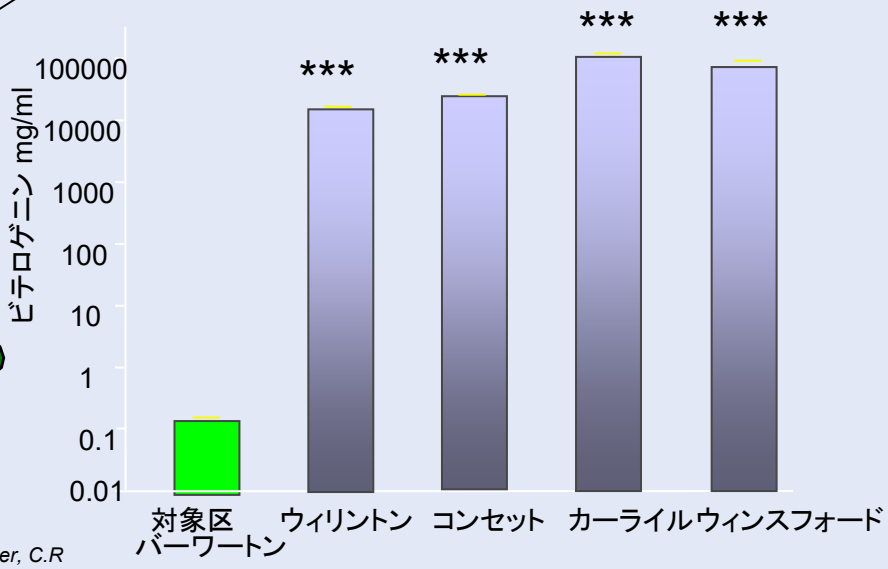
野生生物（魚類）における内分泌かく乱

私たちの初期の観察事項

廃水処理施設からの排水はエストロゲン作用を有する



ビテロゲニン（卵黄）



Purdom, C.E., Hardiman, P.A., Bye, V., Eno, N.C., Tyler, C.R and Sumpter, J.P. (1994). Chemistry and Ecology. 8:275-285.

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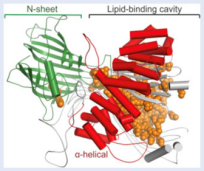
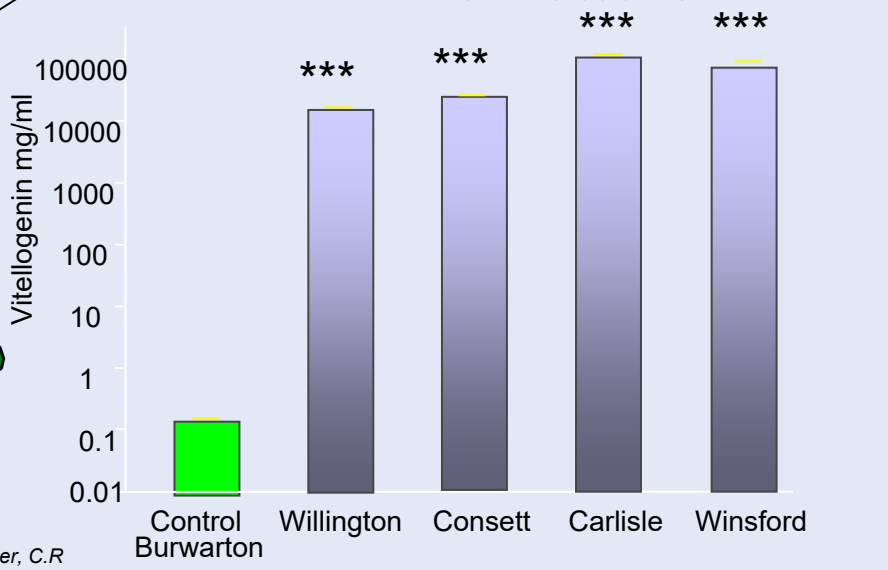
Endocrine Disruption in Wildlife (Fish)

Our Initial Observations

Wastewater Treatment Works Effluents are Oestrogenic



Vitellogenin (egg yolk)



Purdom, C.E., Hardiman, P.A., Bye, V., Eno, N.C., Tyler, C.R and Sumpter, J.P. (1994). Chemistry and Ecology. 8:275-285.

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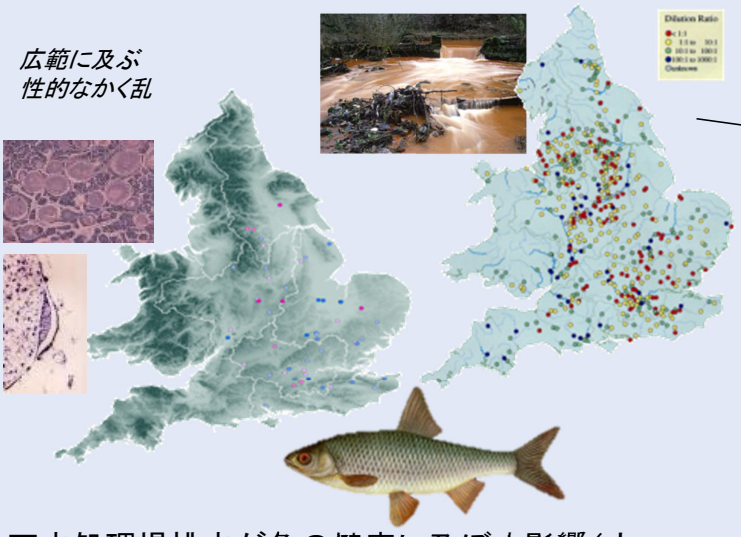
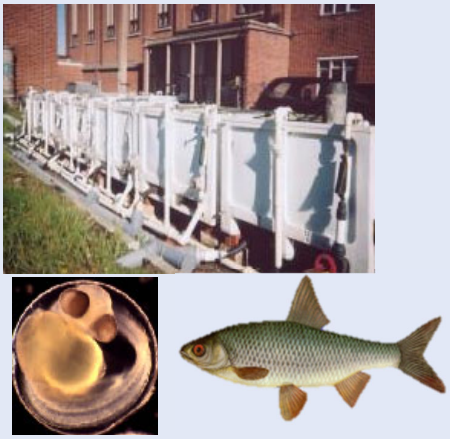
野生生物（魚類）における内分泌かく乱

英国河川における魚類（ローチ - Rutilus rutilus）の雌性化





下水処理場排水が魚の健康に及ぼす影響（内分泌活性化学物質）

•51地点中44地点（86%）で間性の出現
•「雄」での間性発現率が全体の23%

Jobling, S., Nolan, M., Tyler, C.R., Brighty, G., and Sumpter, J.P. (1998).. Environmental Science and Technology 32: 2498-2506.
Jobling,S., Williams, R., Johnson, A., Taylor, A., Gross-Sorokin, M., Nolan, M., Tyler, C.R,van Aerle, R., Santos, E.M.,and Brighty, G. (2006).Environmental Health Perspectives 114: 32-29

すべての雌性化作用は下水処理場排水へのばく露によって引き起こされる

Liney, K.E., Jobling, S. Shears, J., Simpson.P.,Tyler, C.R. (2005)* .Environmental Health Perspectives 113 (10): 1299-1307.

Rodgers-Gray, T. P., Jobling, S., Kelly,C., Morris, S., Brighty, G., Waldock, M, Sumpter, J.P and Tyler C.R. (2001).* Environmental Science and Technology 35:(3) 462- 470

この研究は20年以上前に実施された！

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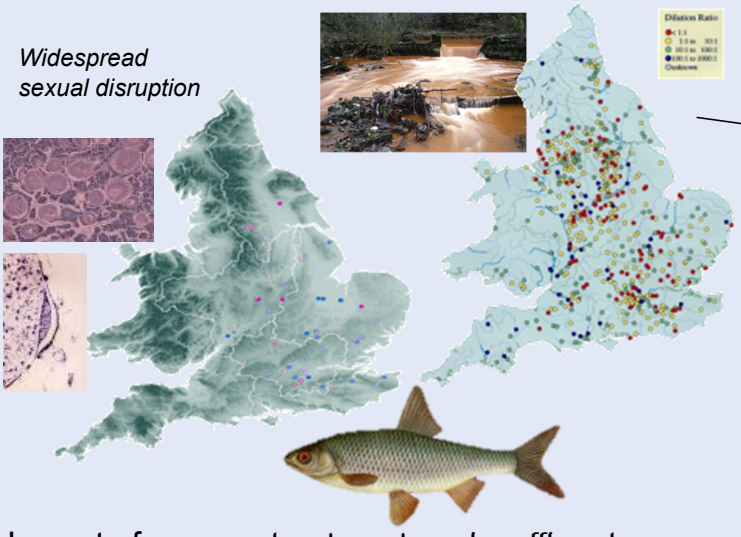
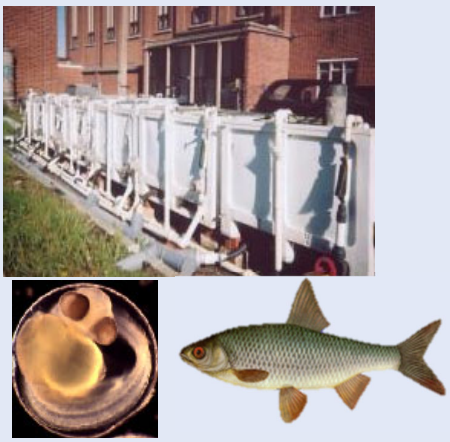
Endocrine Disruption in Wildlife (Fish)

Feminisation of Fish (Roach -Rutilus rutilus) in English Rivers





Impact of sewage treatment works effluents on fish health (endocrine active chemicals)

• Intersex present at 44 (86%) of 51 sites
• Overall incidence of intersex in ‘males’ of 23%

Jobling, S., Nolan, M., Tyler, C.R., Brighty, G., and Sumpter, J.P. (1998).. Environmental Science and Technology 32: 2498-2506.
Jobling,S., Williams, R., Johnson, A., Taylor, A., Gross-Sorokin, M., Nolan, M., Tyler, C.R,van Aerle, R., Santos, E.M.,and Brighty, G. (2006).Environmental Health Perspectives 114: 32-29

All feminised effects are induced by exposure to WWTW effluents

Liney, K.E., Jobling, S. Shears, J., Simpson.P.,Tyler, C.R. (2005)* .Environmental Health Perspectives 113 (10): 1299-1307.

Rodgers-Gray, T. P., Jobling, S., Kelly,C., Morris, S., Brighty, G., Waldock, M, Sumpter, J.P and Tyler C.R. (2001).* Environmental Science and Technology 35:(3) 462- 470

This work was done more than two decades ago!

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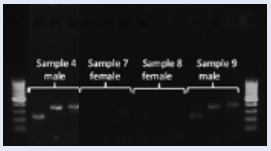
野生生物（魚類）における内分泌かく乱

英国河川における魚類（ローチ - Rutilus rutilus）の雌性化 より新しい情報：

小規模調査：8河川・9地点（各地点30～50尾）

- 血漿中ビテロゲニン（VTG）は全ての雄魚に検出されたが、過去の調査と比較して低濃度であった。
- 調査地点の60%で雌性化（卵巣様）精巣を持つ遺伝的雄が認められ、その頻度及び重篤度は調査地点の80%において過去に認められた程度とは差異が認められなかった。
- 雌性化した生殖腺を持つ遺伝的雄魚が調査地点の60%で認められ、野生ローチにおける完全な性転換（雄から雌への）の発生も確認されるた。

Alice Baynes, Anke Lange, Nicola Beresford, Euan Bryden, Katie Whitelock, Charles R. Tyler and Susan Jobling. (2023) Environmental Science and Technology https://doi.org/10.1021/acs.est.3c02854



ローチにおける
遺伝的性決定プローブ

Lange, A., Paris, J.R., Gharbi, K., Cézard, T., Miyagawa, S., Iguchi, T., Studholme, D.J., Tyler, C.R., 2020. Mol. Ecol. Resour. 20, 1007–1022.

雄ローチにおける雌性化は依然として広く認められる現象である

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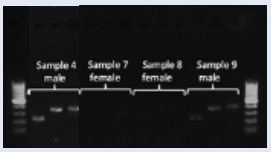
Endocrine Disruption in Wildlife (Fish)

Feminisation of Fish (Roach -Rutilus rutilus) in English Rivers- A more recent update:

Smaller Scale Survey : 8 rivers, 9 sites (30-50 fish for each site)

- Plasma vitellogenin (VTG) was present in all male fish but at lower levels compared with the historic surveys.
- Genetic males with feminised (ovo) testes were found at 60% of the survey sites and the frequency and severity of this condition was not different from historic levels at 80% of sites sampled
- Genetic male fish with a female-like gonad were present at 60% of the sites, confirming the occurrence of full sex reversal (from male to female) in wild roach.

Alice Baynes, Anke Lange, Nicola Beresford, Euan Bryden, Katie Whitelock, Charles R. Tyler and Susan Jobling. (2023) Environmental Science and Technology https://doi.org/10.1021/acs.est.3c02854



Genetic Sex Probe
for the Roach

Lange, A., Paris, J.R., Gharbi, K., Cézard, T., Miyagawa, S., Iguchi, T., Studholme, D.J., Tyler, C.R., 2020.). Mol. Ecol. Resour. 20, 1007–1022.

Feminisation in male roach is still a widespread phenomenon

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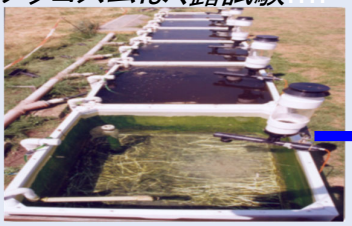
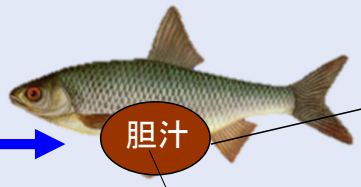
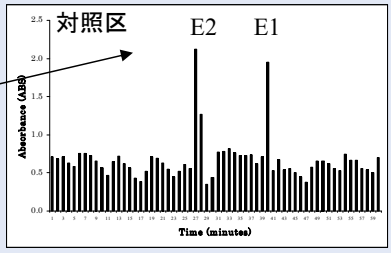
野生生物（魚類）における内分泌かく乱

下水処理場排水から魚類へ移行する環境エストロゲン

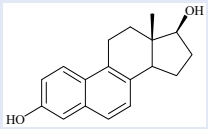
メソコスムばく露試験



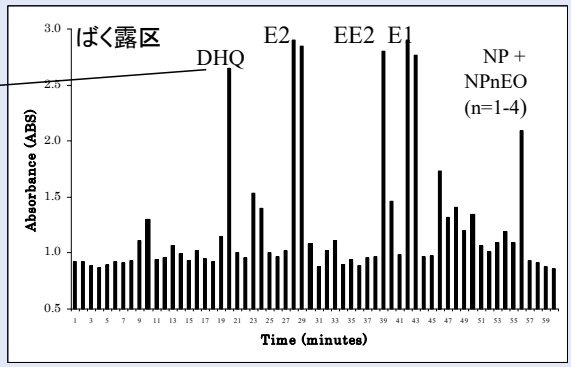




測定された試験排水中の
エストロゲン活性



17β-ジヒドロエキレニン
+ (エキレニン)



魚類は下水処理場排水から非常に広範な種類のエストロゲン作用を持つ化学物質を体内に取り込む

胆汁を分析し（抗）エストロゲン性化合物及びその代謝物を同定
……酵素加水分解 – RP-HPLC + 酵母スクリーニング LC-NMR-MS/GC-MSMS

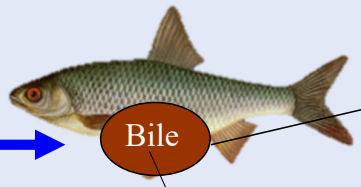
Gibson, R., Smith, M.D., Spary, C., Tyler, C.R., Hill, E.M. (2005). ES&T 39(8) 2461-2471
Tyler C.R., Spary, C, Gibson, R., Shears, J., Santos, E., Sumpter, J.P., Hill, E.M. (2005). ES&T 39 (8) 2599-2607
Tyler, C.R, Filby, A.L., Hill, E.M., Liney, K.E., Katsu, Y., Bickley, L.K., Lange, A., Winter, M., Gibson, R., Shears, J.A., Iguchi, T.(2009). ES&T. 43:3897-3904

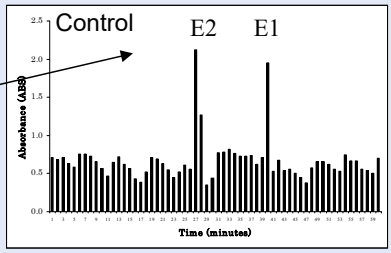
University of Exeter

Endocrine Disruption in Wildlife (Fish)

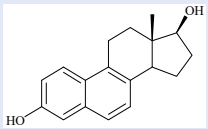
Environmental oestrogens entering fish from WwTW effluents

Mesocosm exposures

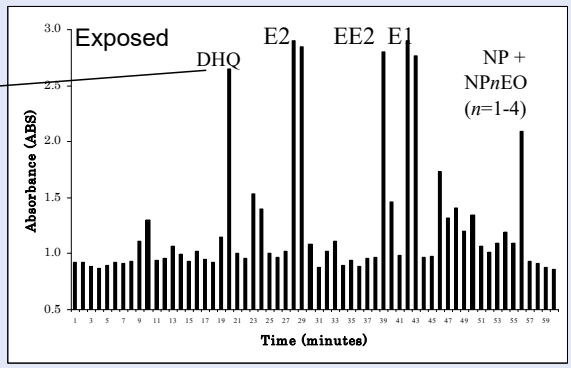




The oestrogenic activity of the test effluents measured



17β-dihydroequilenin
+ (Equilenin)



Fish take up a very wide range of oestrogenic chemicals into their bodies from the WWTW effluent

Bile analysed to identify (anti-)oestrogenic compounds and their metabolites ……Enzymic hydrolysis –RP-HPLC + yeast screens LC-NMR-MS/GC-MSMS

Gibson, R., Smith, M.D., Spary, C., Tyler, C.R., Hill, E.M. (2005). ES&T 39(8) 2461-2471
Tyler C.R., Spary, C, Gibson, R., Shears, J., Santos, E., Sumpter, J.P., Hill, E.M. (2005). ES&T 39 (8) 2599-2607
Tyler, C.R, Filby, A.L., Hill, E.M., Liney, K.E., Katsu, Y., Bickley, L.K., Lange, A., Winter, M., Gibson, R., Shears, J.A., Iguchi, T.(2009). ES&T. 43:3897-3904

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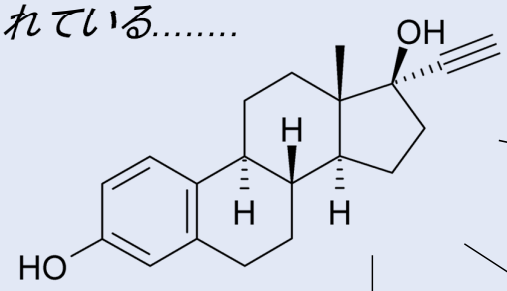
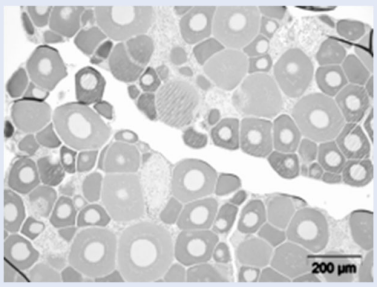
野生生物（魚類）における内分泌かく乱

実験室研究によって環境中のステロイド構造を持つ複数ののエストロゲン作用物質が野生のローチに認められるあらゆる雌性化作用を引き起こすことが示されている.....

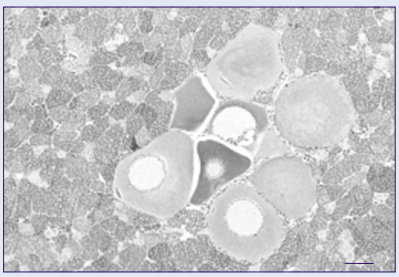


エチニルエストラジオール

EE2（0.3ng/L）へのばく露はビテロゲニン合成を誘導する



EE2への生涯ばく露は完全な性転換を誘導する（4ng/L）



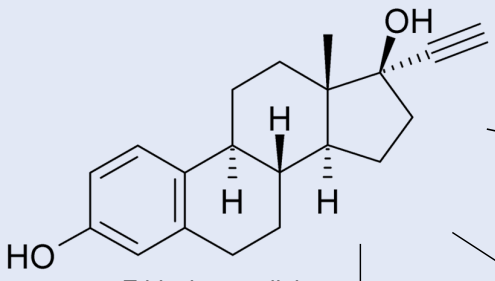
EE2（0.3ng/L）へのばく露は卵巣腔の形成及び間性を誘導する

Lange, A. Katsu ,Y. R. Ichikawa , Greg Paull, Laura L. Chidgey , Tobias S. Coe Iguchi, T, and. Tyler, C.R. (2009).. Toxicological Sciences 106(1), 113–123
Lange, A., Katsu, Y., R. Ichikawa, Chidgey, L. Iguchi, T.and. Tyler, C.R. (2009). Environmental Science and Technology 43 (4), 1219-1225.

University of Exeter

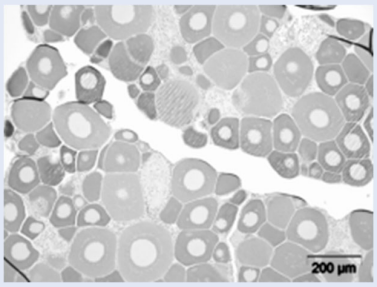
Endocrine Disruption in Wildlife (Fish)

Laboratory studies show that environmental steroidal oestrogens can induce all the feminised effects seen in wild roach.....

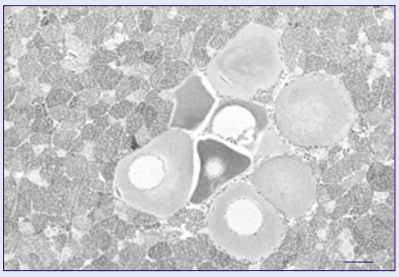


Ethinyloestradiol

Exposure to EE2 (0.3ng/L) can induce vitellogenin synthesis



Life-long exposures to EE2 can complete sex reversal (4ng/L)

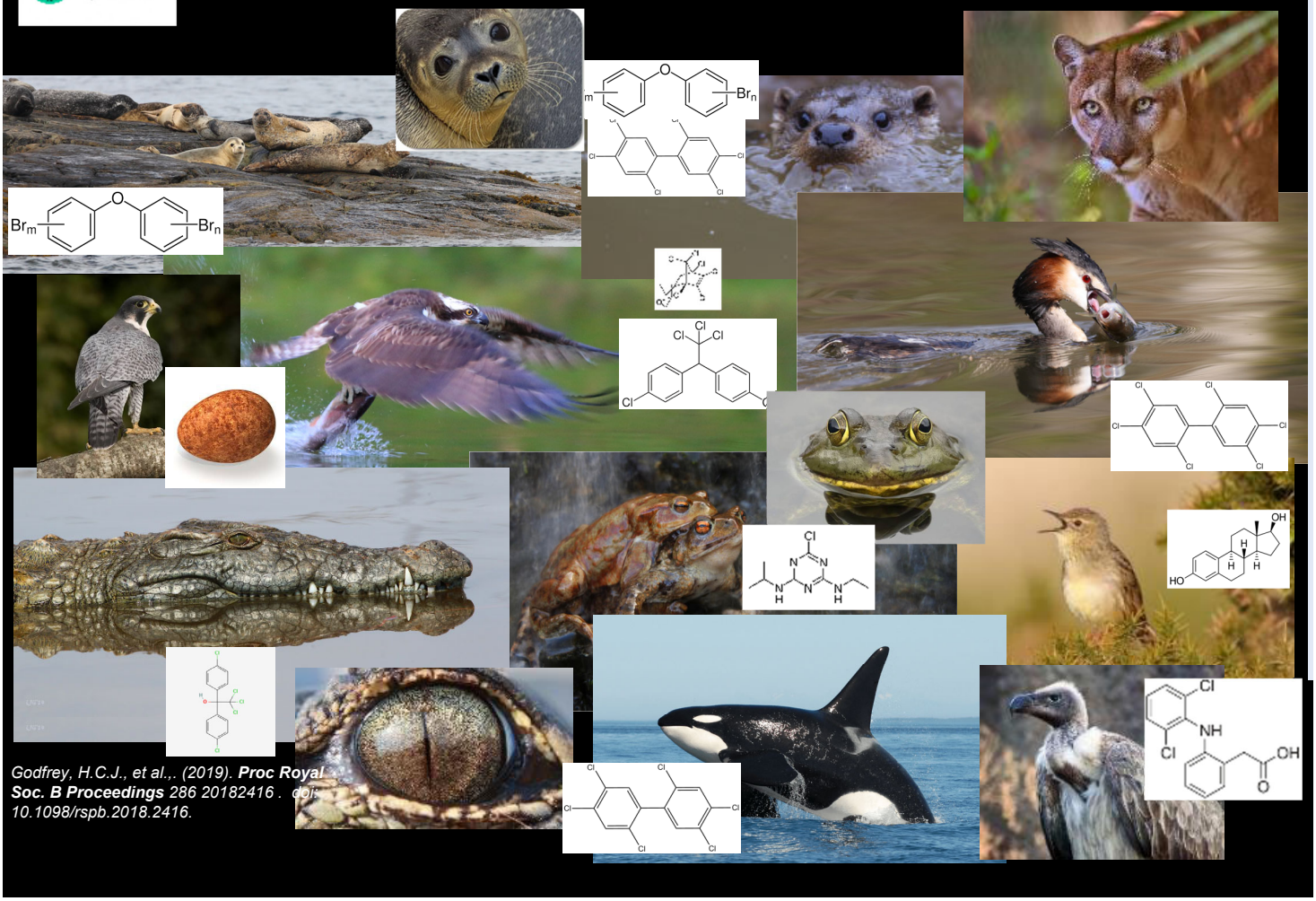


Exposure to EE2 (0.3ng/L) can induce ovarian cavity formation and intersex

Lange, A. Katsu ,Y. R. Ichikawa , Greg Paull, Laura L. Chidgey , Tobias S. Coe Iguchi, T, and Tyler, C.R. (2009).. Toxicological Sciences 106(1), 113–123
Lange, A., Katsu, Y., R. Ichikawa, Chidgey, L. Iguchi, T.and. Tyler, C.R. (2009). Environmental Science and Technology 43 (4), 1219-1225.

化学物質の内分泌かく乱作用に関する公開セミナー - 環境省 2025

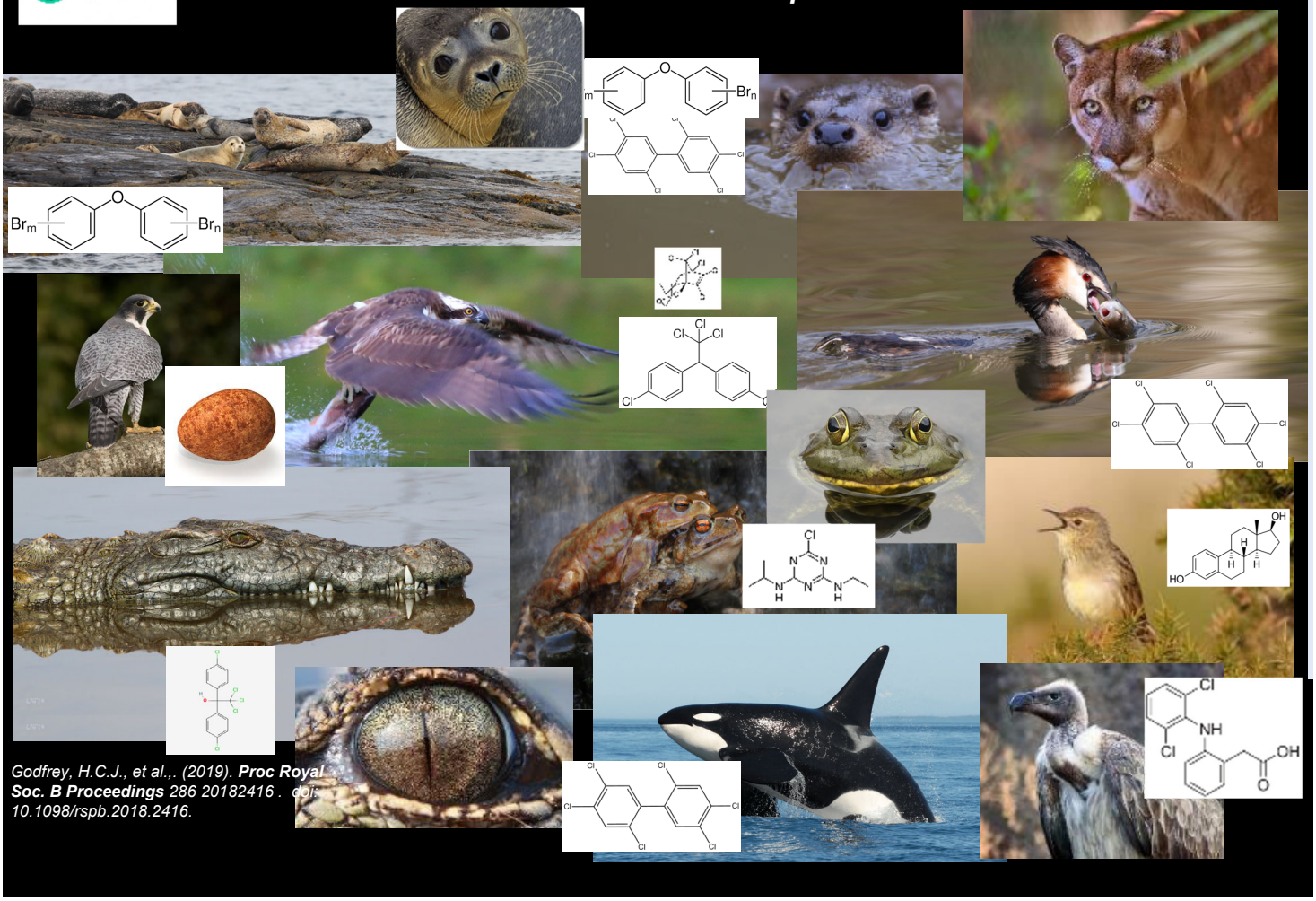
野生生物における内分泌かく乱の科学的根拠



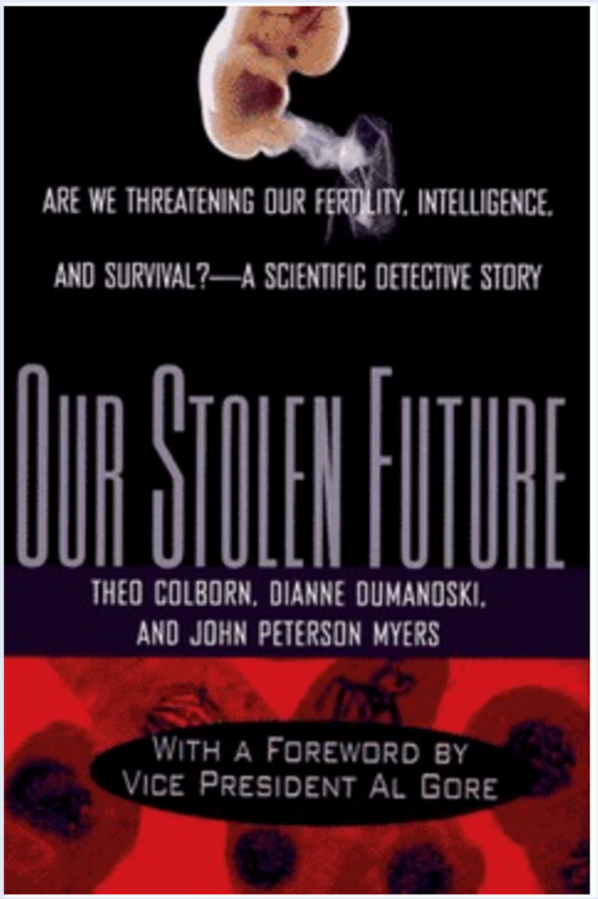
Godfrey, H.C.J., et al.,. (2019). **Proc Royal Soc. B Proceedings** 286 20182416 . doi: 10.1098/rspb.2018.2416.

Public Seminar on Endocrine Disrupting Effects -MoE, Japan 2025

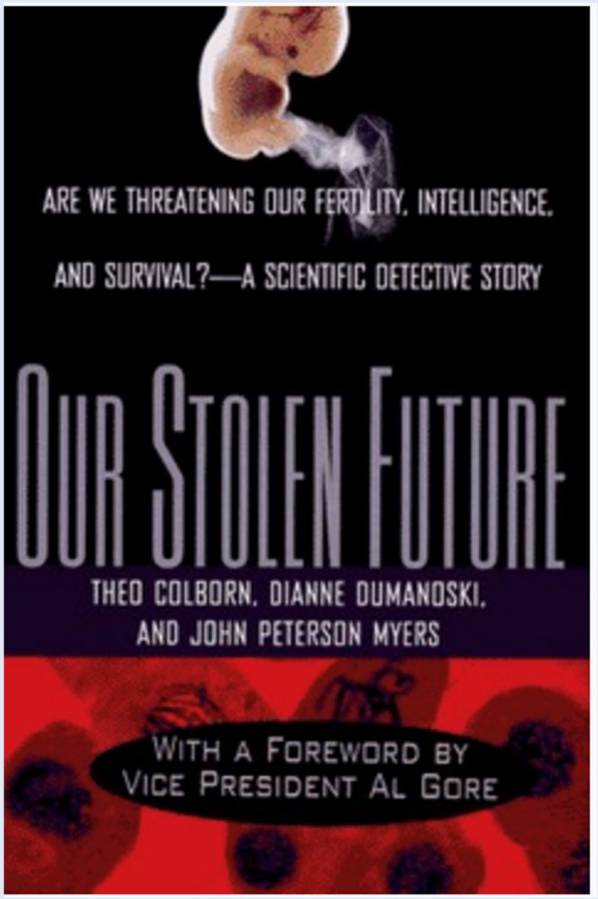
Evidence for Endocrine Disruption in other Wildlife



Godfrey, H.C.J., et al.,. (2019). **Proc Royal Soc. B Proceedings** 286 20182416 . doi: 10.1098/rspb.2018.2416.



Public Seminar on Endocrine Disrupting Effects -MoE, Japan 2025



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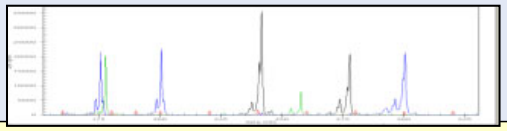
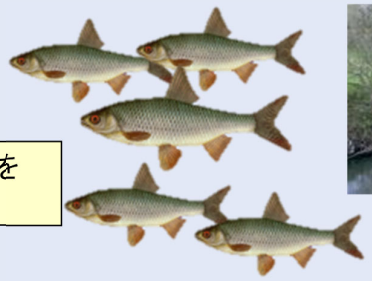
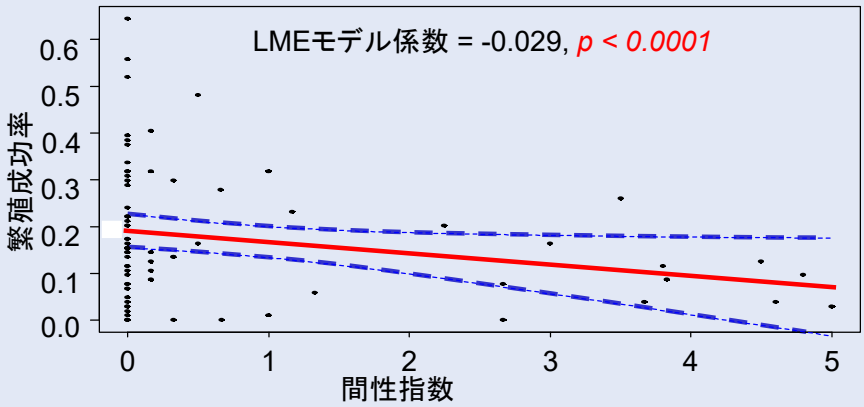
野生生物（魚類）における内分泌かく乱

重要か？.....雄ローチの雌性化が繁殖に及ぼす影響



DNAマイクロサテライト - 高変異性プライマーを開発し、親子関係解析に応用（*成功率100%*）





中程度から重度の間性（指数 2 以上）のローチでは、間性指数の 1 増加毎に 15% の低下が予測された（本試験中最も雌性化した個体では 75% の減少）。

野生ローチを用いた繁殖試験

すべての親魚及び仔魚（各水槽から50～104尾の稚魚）の遺伝子型決定。成魚の生殖腺病理組織学的解析を実施。

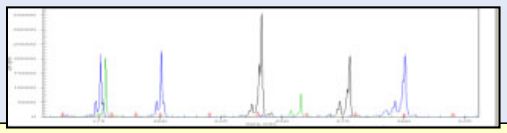
雌性化は、雄の繁殖能力に影響を与える

Harris, Hamilton, Runnalls, Jobling, Vinciotti, Henshaw, Hodgson. Coe, Tyler,. Sumpter (2010). EHP. 119:306–311

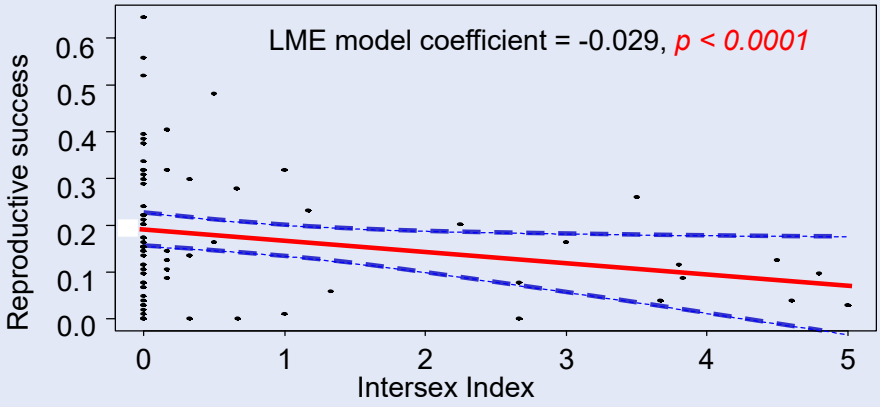
University of Exeter

Endocrine Disruption in Wildlife (Fish)

Does it matter?.....Breeding Consequences of Feminisation of Male Roach



DNA microsatellites - highly variable primers were developed and applied for parentage analysis (*100% success*)



Breeding trials with wild roach

Genotyped all parents and offspring (50-104 fry from each tank). Histopathology analysis of adult gonads.

*For roach that are moderately to severely intersex (index >2) there was an estimated 15% reduction for each incremental increase in the intersex index (*75% reduction for the most feminised individuals included in this study).

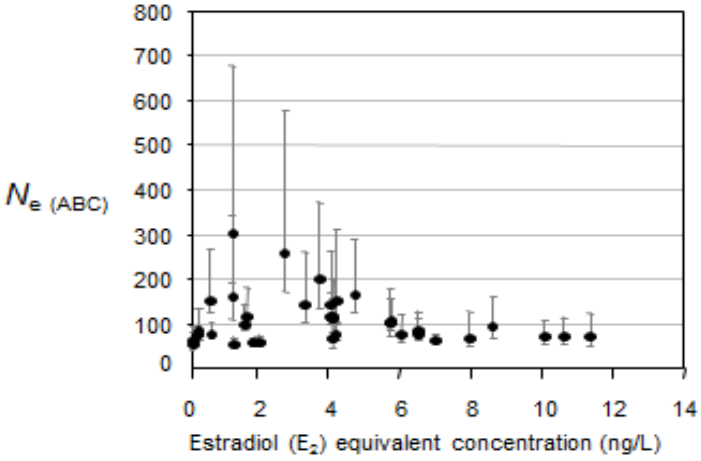
Feminisation affects the ability of males to breed

Harris, Hamilton, Runnalls, Jobling, Vinciotti, Henshaw, Hodgson. Coe, Tyler,. Sumpter (2010). EHP. 119:306–311

野生生物（魚類）における内分泌かく乱

野生ローチ個体群は有害影響を受けているのか？

英国河川中のエストロゲン量（予測エストロゲン含有量）と親個体群の繁殖サイズの指標との関係を調査した遺伝学的研究（$N_{e\ (ABC)}$）



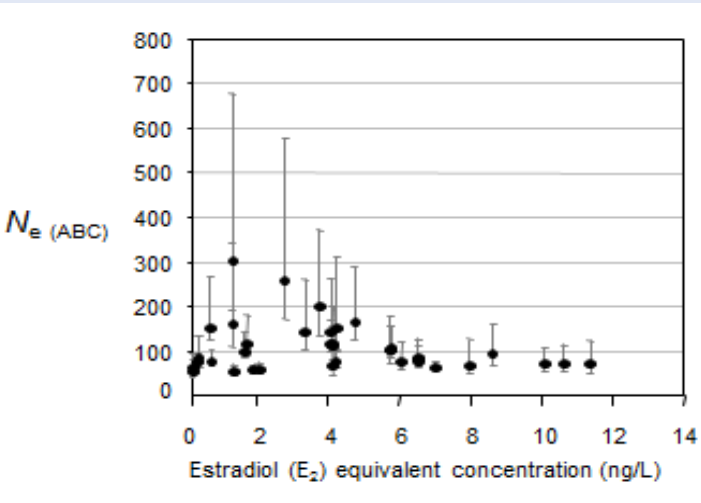
Patrick B. Hamilton、Elizabeth Nicol、Eliane S. R. De-Bastos、Richard J. Williams、John P. Sumpter、Susan Jobling、Jamie、R. Stevens、Tyler、C.R (2014)。BMC Biology 12:1*

回答：私たちは、この点について明確な見解を得ていない

Endocrine Disruption in Wildlife (Fish)

Are Wild Populations of Roach Adversely Impacted?

Genetic studies undertaken investigating the relationship between the amount of oestrogen in English rivers (predicted oestrogen content) and an indicator of the breeding size in the parental population ($N_{e\ (ABC)}$)



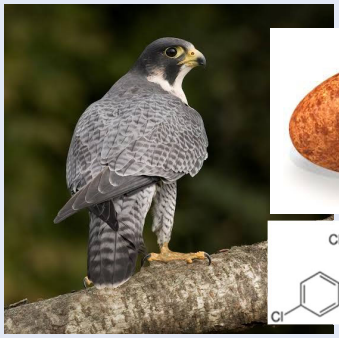
Patrick B. Hamilton, Elizabeth Nicol, Eliane S. R. De-Bastos, Richard J. Williams, John P. Sumpter Susan Jobling , Jamie, R. Stevens, Tyler, C.R (2014). BMC Biology 12:1*

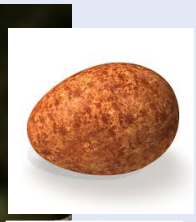
Answer : We do not have a clear picture on this

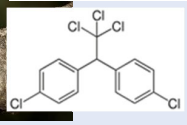
野生生物における内分泌かく乱

化学物質(内分泌かく乱化学物質等)が野生脊椎動物に及ぼす個体群レベルでの影響

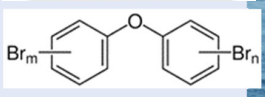
確立された因果関係





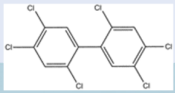


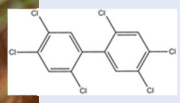
ハヤブサ



アザラシ

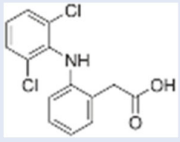
シャチ





フロリダパンサー

シロハゲワシ



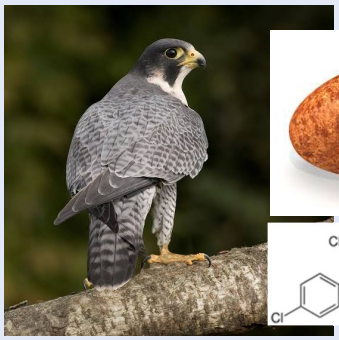
決定的な事例が、個体群レベルの崩壊後に初めて見出された！

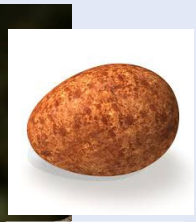
Reviewed in: Godfrey, H.C.J., Stephens, A.E.A., Jepson, P.D., Jobling, S., Johnson, A.C., Matthiessen, P., Sumpter, J.P., Tyler, C.R., *McLean, A.R. (2019).* ***Proc Royal Soc. B Proceedings*** *286 20182416 . doi: 10.1098/rspb.2018.2416.*

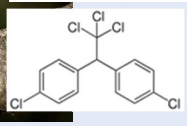
Endocrine Disruption in Wildlife

Population level Consequences of Chemicals (incl. EDCs) in Vertebrate Wildlife

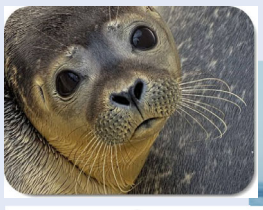
Established Cause –Effect Relationships

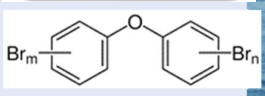






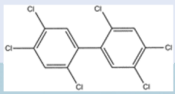
Peregrine Falcon

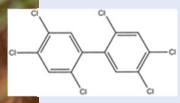




Seals

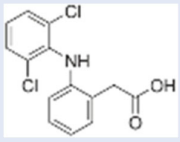
Orca

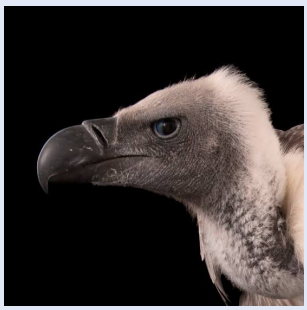




Florida Panther

White backed vulture





Key examples have been identified only after population level collapses!

Reviewed in: Godfrey, H.C.J., Stephens, A.E.A., Jepson, P.D., Jobling, S., Johnson, A.C., Matthiessen, P., Sumpter, J.P., Tyler, C.R., *McLean, A.R. (2019).* ***Proc Royal Soc. B Proceedings*** *286 20182416 . doi: 10.1098/rspb.2018.2416.*

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野生生物における化学物質によるかく乱

アジアにおいてジクロフェナクがハゲワシに及ぼす影響の生態系レベルでの結果

Rabies lyssavirus

- 4,500万羽以上のハゲワシの死
- 3,500億ドルの国内経済上の損失（2000-2005年）
- ヒトの死亡率が4%以上増加

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ドキュメンタリー動画：

https://www.youtube.com/watch?v=5DO6kkOmZCQ
https://www.youtube.com/watch?v=ZCA24OGENNo
https://www.youtube.com/watch?v=y8f7HftHtT4

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Chemical Disruption in Wildlife

Ecosystem level consequences of diclofenac impacts on vultures in Asia

Rabies lyssavirus

- Death of over 45 million vultures
- $350 billion loss to the country’s economy (2000-2005)
- Human mortality rate increased by more than 4 %

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Documentary videos:

https://www.youtube.com/watch?v=5DO6kkOmZCQ
https://www.youtube.com/watch?v=ZCA24OGENNo
https://www.youtube.com/watch?v=y8f7HftHtT4

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環境エストロゲンが魚類にどのように影響を及ぼすかを理解する

体内のエストロゲンの役割

エストロゲンが介在するのは:

- 女性（及び男性）の生殖機能
- 成長
- 骨の発達
- カルシウム恒常性
- 防御（免疫機能）

エストロゲンシグナル伝達:

- 特定の受容体を介して
  （魚類には3つのサブタイプ：ESR1、
  ESR2α、ESR2β）
  （＋膜受容体、エストロゲン関連受容体）
- クロストーク

体内のあらゆる細胞にエストロゲン受容体が存在する可能性が高い！

エストロゲンに類似した化学物質へのばく露は、生殖影響よりもはるかに広範な潜在的健康影響をもたらす可能性がある。

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Understanding how environmental oestrogens affect fish

Roles of Oestrogens in the Body

Oestrogens mediate:

- Female (and male) reproduction
- Growth
- Bone development
- Calcium Homeostasis
- Defence (Immune function)

Oestrogens signalling:

- Via specific receptors
  (3 subtypes in fish- ESR1,
  ESR2α, ESR2β)
  (+ membrane receptors, oestrogen
  related receptors)
- Cross talk

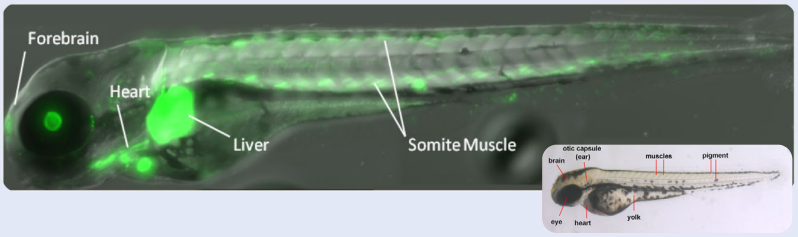
Every cell in the body probably has an oestrogen receptor!

For exposures to chemical that mimic oestrogens there are much wider potential health effects that those on reproduction.

環境エストロゲンが魚類にどのように影響を及ぼすかを理解する

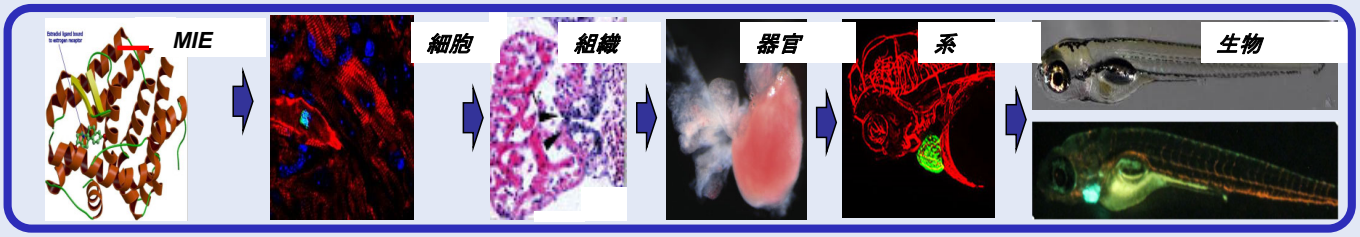
遺伝子組み換え魚類 – 化学物質の活性とAOPs（有害性発現経路）の相互関係を伝えてくれる

高度に統合された健康影響解析において化学物質の作用をリアルタイムで評価する強力な全身系ツール。



化学物質の組織特異的な応答性及び相対効力を見い出す

AOP（有害性発現経路）

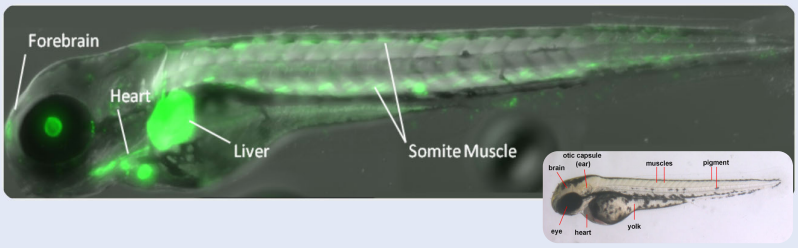


事務局注） MIE：molecular initiating event（分子開始事象）

Understanding how environmental oestrogens affect fish

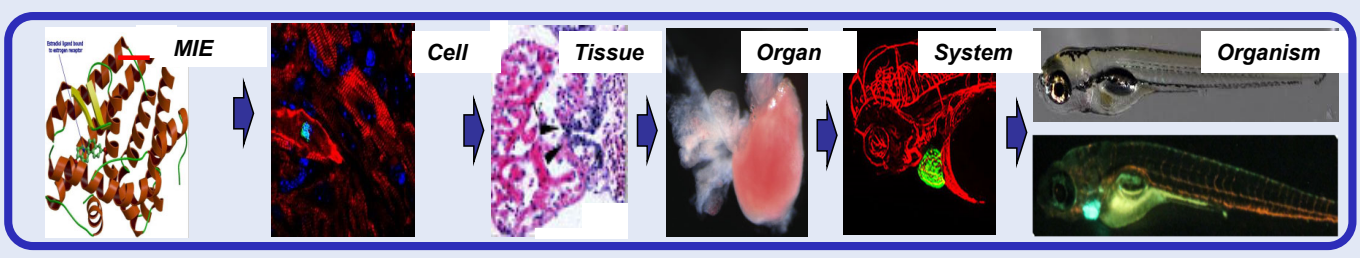
Transgenic Fish – informing interrelationships between chemical activity and AOPs

Powerful, whole body systems tool for assessing interaction of chemicals in real time for highly integrated health effects analysis.



Identify tissue response specificities and relative potencies of chemicals

Adverse Outcome Pathways



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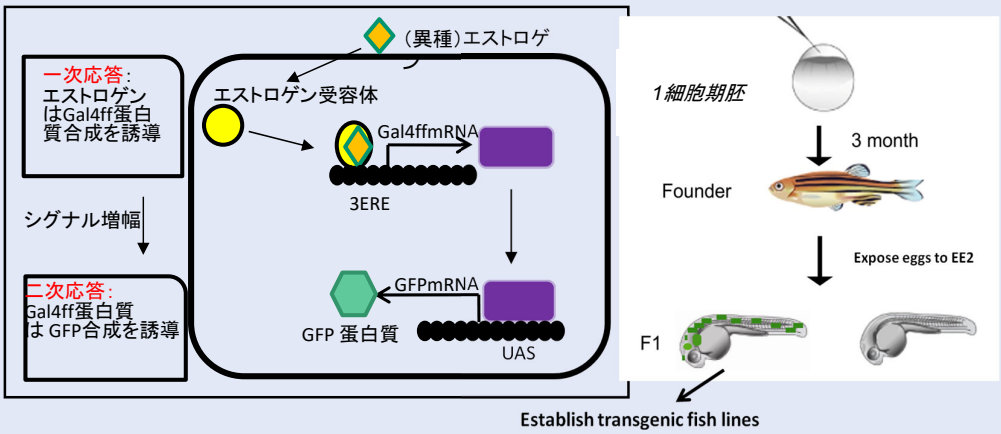
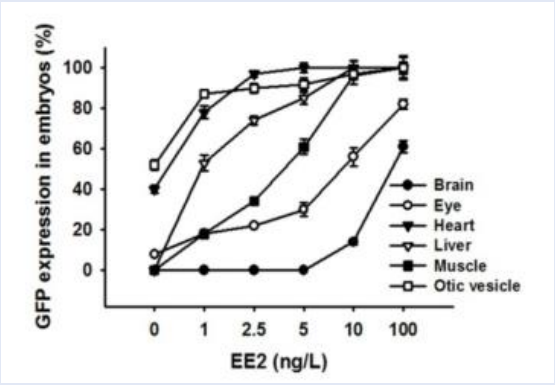
環境エストロゲンが魚類にどのように影響を及ぼすかを理解する

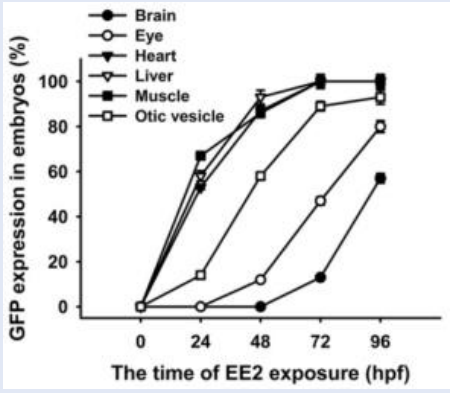


Establish transgenic fish lines

私たちは、環境エストロゲンが体内でどこに作用するかを研究するために、エストロゲン応答性遺伝子組み換えゼブラフィッシュを作成した。



反応を示す体内組織の感受性(96時間)



反応を示す体内組織における時間的動態

Okhyun Lee, Aya Takensano, Masa Tada, Charles R. Tyler and Tetsuhiro Kudoh (2012) *Environ Health Perspect.* ***120****, 990-996*

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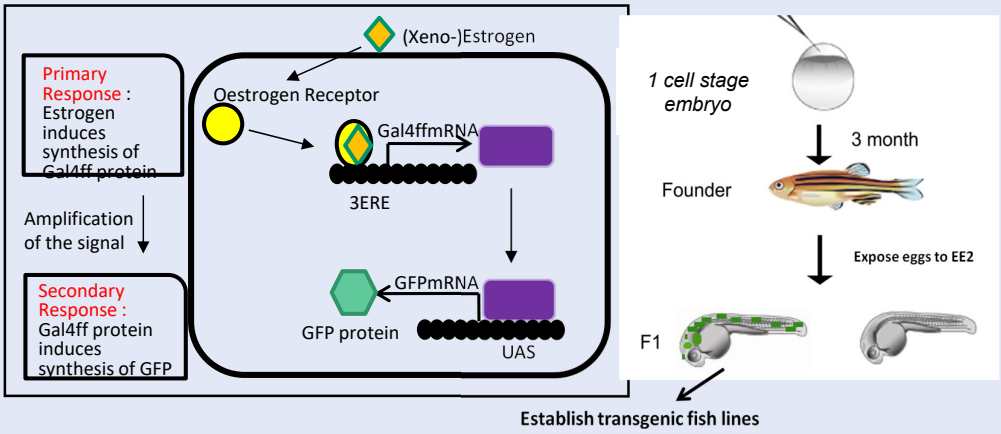
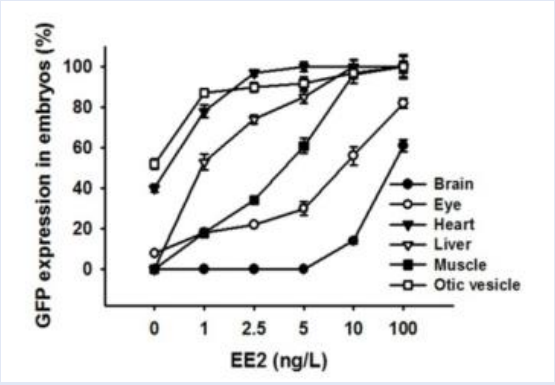
Understanding how environmental oestrogens affect fish

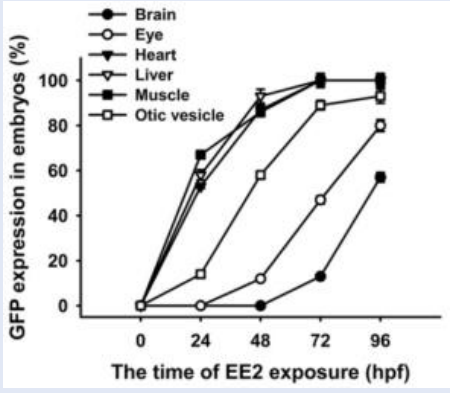


Establish transgenic fish lines

We created an oestrogen responsive transgenic zebrafish for studying where environmental oestrogens interact in the body



Sensitivities in responding body tissues (96h)



Temporal dynamics in responding body tissues

Okhyun Lee, Aya Takensano, Masa Tada, Charles R. Tyler and Tetsuhiro Kudoh (2012) *Environ Health Perspect.* ***120****, 990-996*

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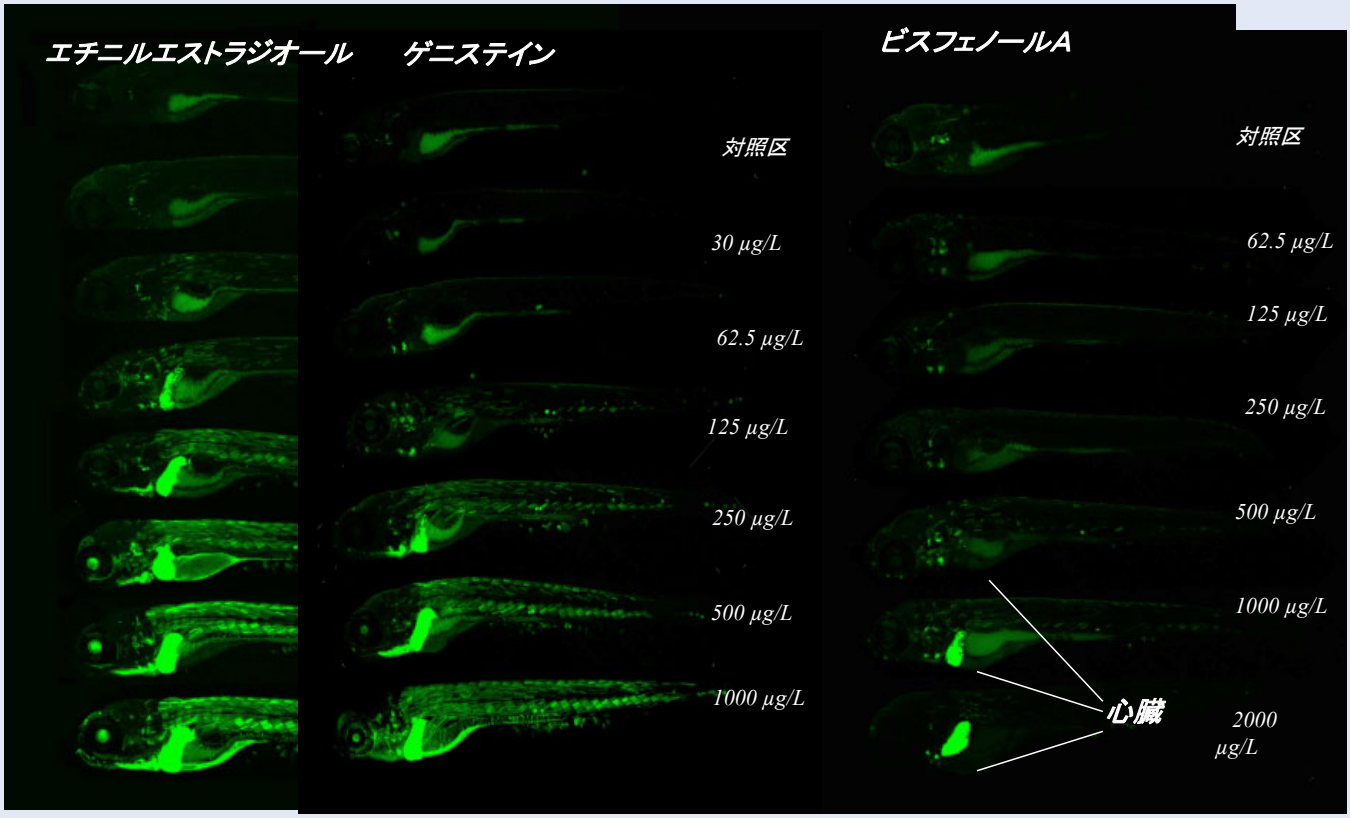
環境エストロゲンが魚類にどのように影響を及ぼすかを理解する

環境エストロゲンの反応パターン（異なる標的組織）



Green, Metz, Lee,Trznadel, Takesono,, Brown, Owen, Kudoh, Tyler (2016). Environ Sci & Technol 50 (12) 6536–6545

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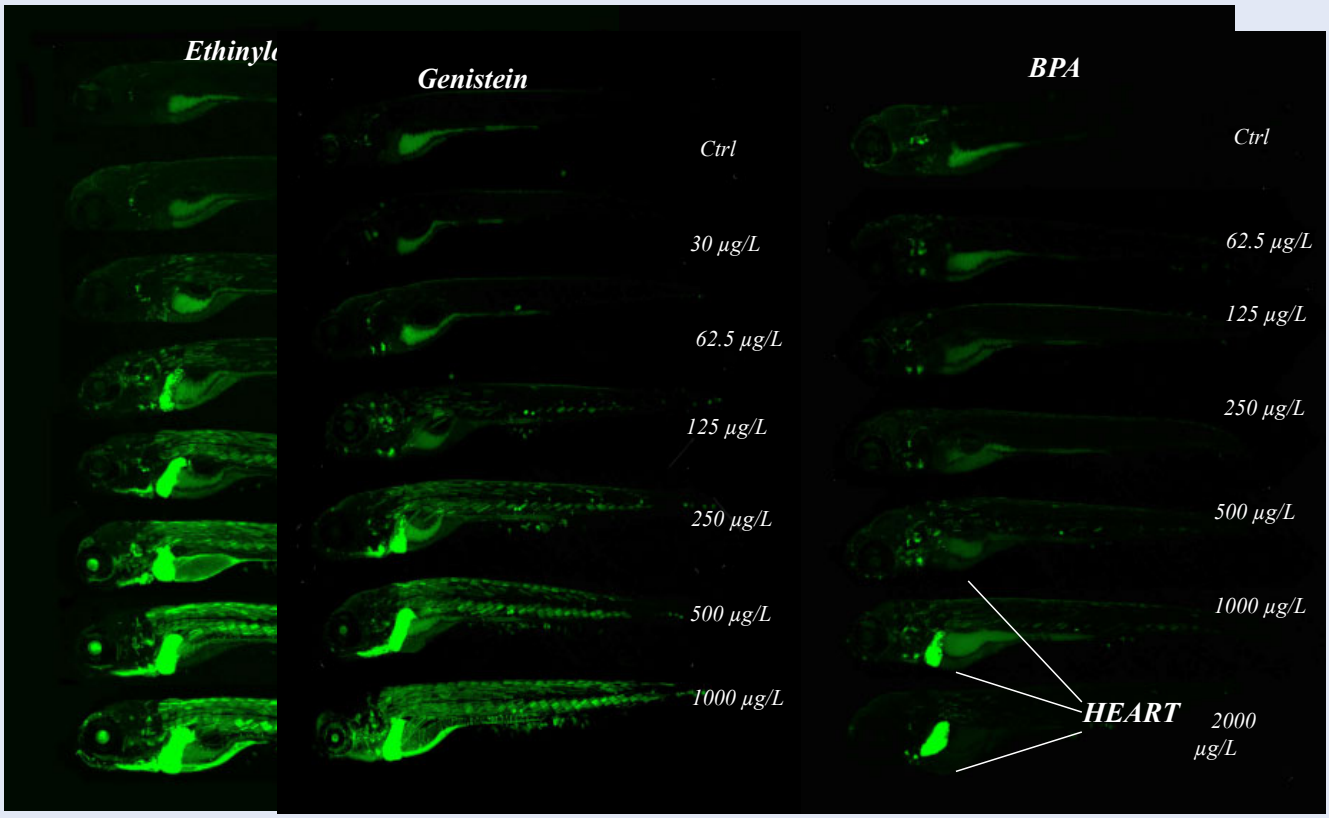
Understanding how environmental oestrogens affect fish

Response patterns (different target tissues) of environmental oestrogens



Green, Metz, Lee,Trznadel, Takesono,, Brown, Owen, Kudoh, Tyler (2016). Environ Sci & Technol 50 (12) 6536–6545

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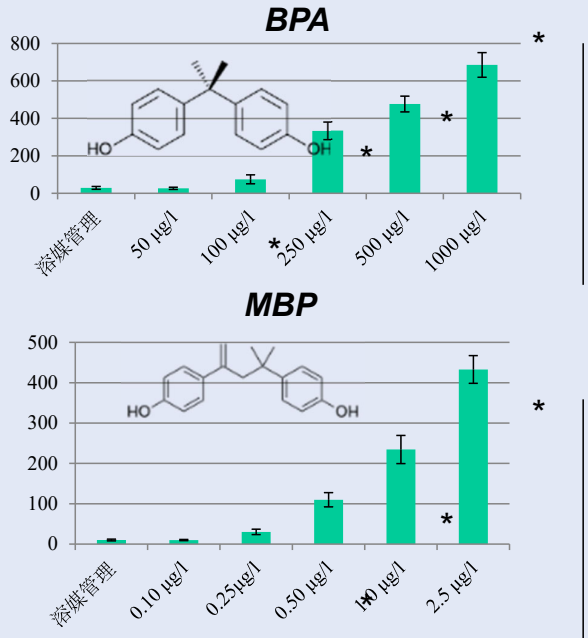
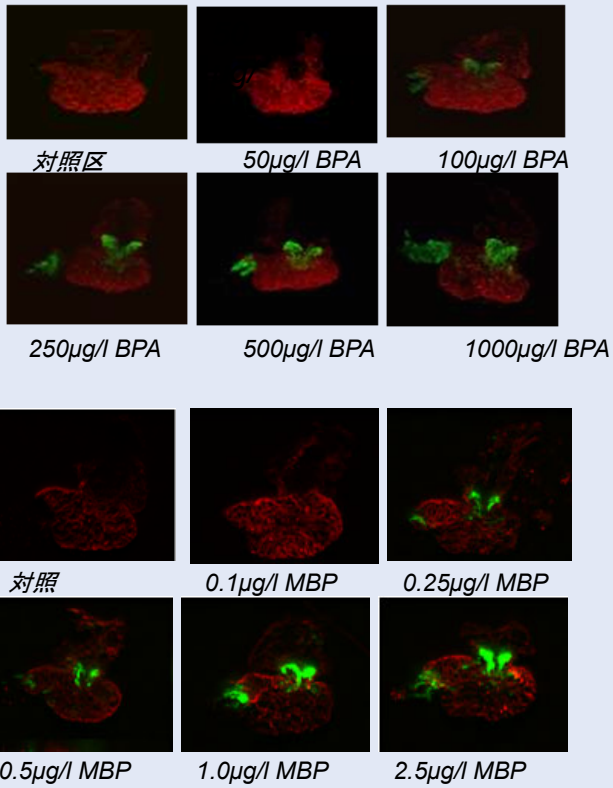
環境エストロゲンが魚類にどのように影響を及ぼすかを理解する

ビスフェノールA及びその代謝産物4-メチル-2,4-ビス(4-ヒドロキシフェニル)ペンタ-1-エン[MBP]にばく露したERE遺伝子組み換えゼブラフィッシュにおける心臓でのGFP発現



ERE-TG ゼブラフィッシュ(5dpf)心臓について測定した蛍光強度値はp<0.05 対照区との比較



GFP, MF-20

Brown, Green, Moreman, Gunnarsson, Mourabit, BallWinter, MTrznadel, Correia, Hacker, Perry, WoodHetheridge, Currie, Tyler (2019) Environ Sci Technol DOI: 10.1021/acs.est.8b04281

Moreman, et al. (2018) Environ Sci Technol 52(11):6656-6665. doi: 10.1021/acs.est.8b01095

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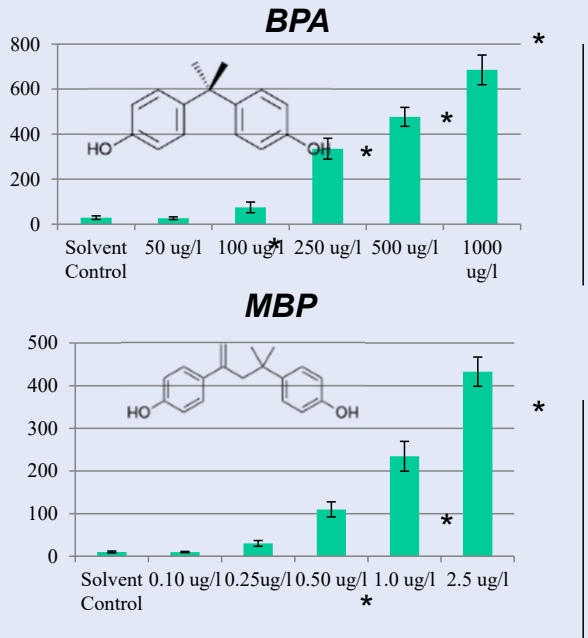
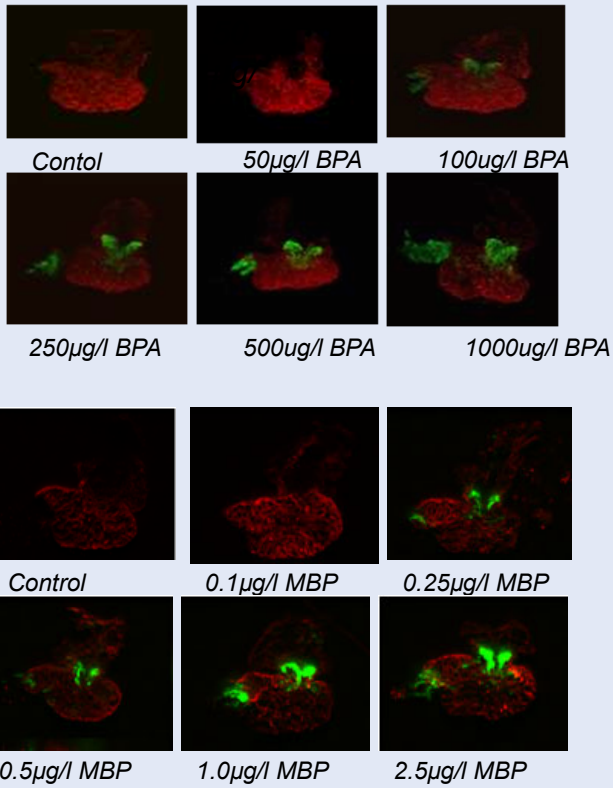
Understanding how environmental oestrogens affect fish

GFP Expression in the Heart in ERE-Transgenic Zebrafish exposed to Bisphenol A and its metabolic product 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene [MBP]



Fluorescence intensity values measured from hearts of ERE-TG zebrafish (5dpf) p<0.05 compared to control



GFP, MF-20

Brown, Green, Moreman, Gunnarsson, Mourabit, Ball Winter, M Trznadel, Correia, Hacker, Perry, Wood Hetheridge, Currie, Tyler (2019) Environ Sci Technol DOI: 10.1021/acs.est.8b04281

Moreman, et al. (2018) Environ Sci Technol 52(11):6656-6665. doi: 10.1021/acs.est.8b01095

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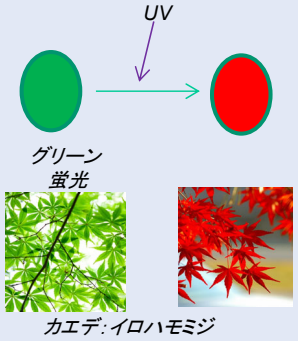
環境エストロゲンが魚類にどのように影響を及ぼすかを理解する

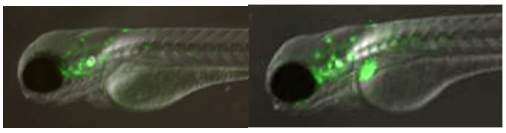
エストロゲンへの反復ばく露による影響

ERE-Kaede Casper Model

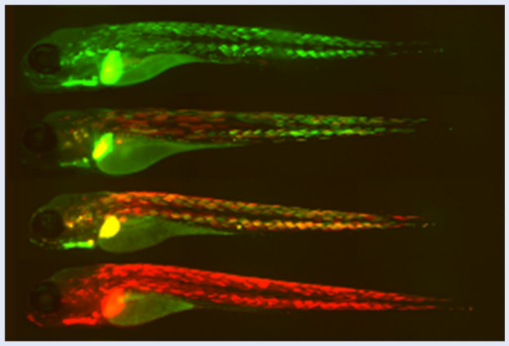


A 5 dpf Controls

対照区（非ばく露）の幼生及び10 ng EE2/Lに48時間（0-2 dpf）初期ばく露した幼生を3 dpfで撮影（A）。その後、紫外線照射によってカエデ応答は緑色蛍光から赤色蛍光に完全変換した

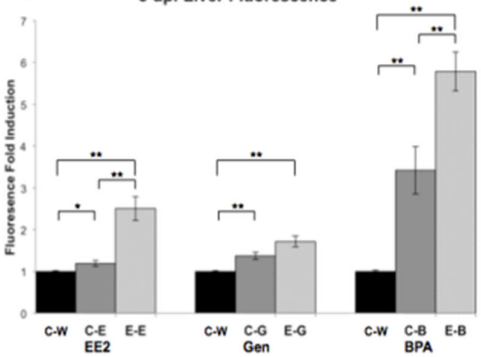


C- EE2 **EE2 –EE2**



エストロゲンへの感受性は反復ばく露によって強化される。

B 5 dpf Liver Fluorescence



D 5 dpf Somite Muscle Fluorescence

エストロゲンにばく露したERE-Kaede-Casper遺伝子組み換えゼブラフィッシュにおける標的組織応答の蛍光誘導法による定量化。*5dpfでの肝臓及び心臓の蛍光強度を定量化した。EE2、ゲニステイン、BPAばく露後の応答を3-5 dpfにて定量した。データは平均誘導倍率±SEM（n=18）として（EE2-10ng/L、ゲニステイン-500mg/L、BPA-2000mg/L）報告された。*

Green, Lange, Scott, Trznadel, Wai, Takesono, Brown, Owen, Kudoh, Tyler (2018). Scientific Reports 8 Article number 2699

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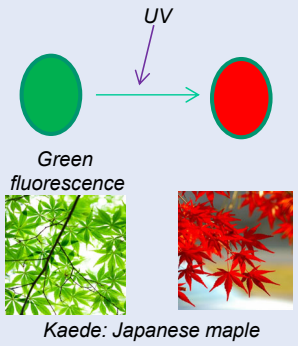
Understanding how environmental oestrogens affect fish

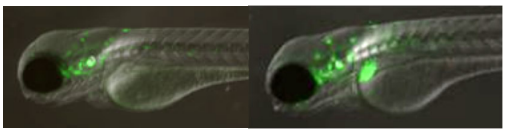
Effect of Repeat Exposures to Oestrogens

ERE-Kaede Casper Model

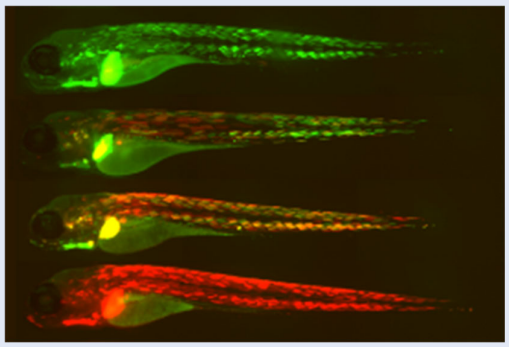


A 5 dpf Controls

Control (non exposed) larvae and larvae exposed initially to 10 ng EE2/L over the period of 48h (0-2 dpf) were imaged at 3 dpf (A) and the Kaede response was then converted fully from green to red fluorescence via UV exposure

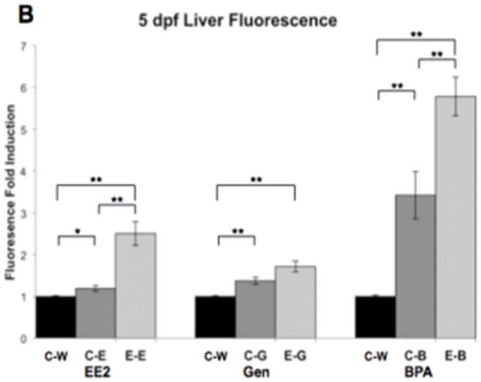


C- EE2 **EE2 –EE2**



Sensitivity to oestrogen is enhanced for repeated exposures.

B 5 dpf Liver Fluorescence



D 5 dpf Somite Muscle Fluorescence

Quantification of target tissue responses in ERE-Kaede-Casper transgenic zebrafish exposed to estrogen treatment, as determined by fluorescence induction. *Fluorescence intensity was quantified in liver and heart at 5 dpf. Responses were quantified after EE2, genistein and BPA exposures for 3-5 dpf. Data are reported as mean fold induction ± SEM (n=18). EE2-10ng/L, Genistein- 500μg/L, BPA- 2000μg/L)*

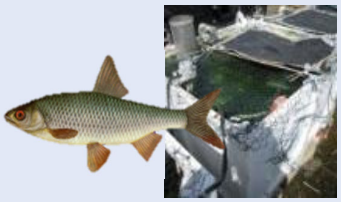
Green, Lange, Scott, Trznadel, Wai, Takesono, Brown, Owen, Kudoh, Tyler (2018). Scientific Reports 8 Article number 2699

混合作用

*ヒト及び野生生物は**複雑な化学物質混合物**にさらされている*

- 胎児は出生前から数百種類の工業用化学物質にばく露されている。臍帯血（北米一般集団）;

ポリ臭化ジフェニルエーテル類（PBDEs）、ポリ塩化ビフェニル類（PCBs）、有機塩素系農薬類、多環芳香族炭化水素類（PAHs）、ポリ塩化ダイオキシン類及びフラン類（PCDD/PCDFs）、フタル酸エステル類



- 魚類の体内は化学的な周辺環境の青写真である:

下水処理場排水にばく露した魚（ローチ）の精巣から検出された化学物質

NSAIDs（ジクロフェナク、イブプロフェン、ナプロキセン、メフェナム酸）、SSRI（フルオキセチン、ノルフルオキセチン、パロキセチン、セルトラリン、ノルセルトラリン、シタロプラム、ベンラファキシン）、内分泌かく乱化学物質（ビスフェノールA、トリクロサン、クロロフェン、プロピコナゾール）、その他の異物（ノルジアゼパム、クロザピン、ノルクロザピン、クエチアピン、ノルクエチアピン、ワルファリン、カルバマゼピン、プロプラノロール、ゲムフィブロジル、クロピドグレル）

これらの化学物質は総じて、ステロイドホルモン、セロトニン（「幸福感」ホルモン）、プロスタグランジン生合成に影響を与える可能性がある

David, A., Abdul-Sada , A; Al-Salhi ,R.,Lange, A., Tyler, C.R., Hill E.M. (2014).. J. Chromatography A 1365, 72-85.
David, Arthur, Lange, Anke, Abdul-Sada, Alaa, Tyler, C.R and Hill, Elizabeth M (2016) . Env Science & Technol. 51 (1). 616-624.
Arthur David, Anke Lange, Charles R. Tyler, Elizabeth M. Hill (2018). Sci. Tott Env, 621, 782-790

Mixture Effects

*Humans and Wildlife are exposed to **complex mixtures of chemicals***

- Babies are exposed to hundreds of industrial chemicals even before birth. Cord blood (North American general population);

Polybrominated biphenyl ethers (PBDEs), Polychlorinated biphenyls (PCBs), Organochlorine pesticides, Polyaromatic hydrocarbons (PAHs), Polychlorinated dioxins and furans (PCDD/PCDFs), Phthalates

- Fish bodies are blueprints of their chemical surroundings:

Testes content in fish exposure to WwTW effluents

NSAIDs (diclofenac, ibuprofen, naproxen, mefenamic acid), SSRIs (fluoxetine, norfluoxetine, paroxetine, sertraline, norsertraline, citalopram, venlafaxine), EDCs (bisphenol A, triclosan, chlorophene, propiconazole), Other xenobiotics (nordiazepam, clozapine, norclozapine, quetiapine, norquetiapine, warfarin, carbamazepine, propranolol, gemfibrozil, clopidogrel)

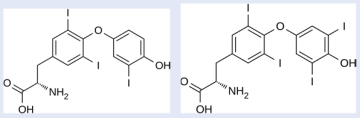
Collectively these chemical can affect steroid hormone, serotonin ('well being' hormone) and prostaglandin biosynthesis

David, A., Abdul-Sada , A; Al-Salhi ,R.,Lange, A., Tyler, C.R., Hill E.M. (2014).. J. Chromatography A 1365, 72-85.
David, Arthur, Lange, Anke, Abdul-Sada, Alaa, Tyler, C.R and Hill, Elizabeth M (2016) . Env Science & Technol. 51 (1). 616-624.
Arthur David, Anke Lange, Charles R. Tyler, Elizabeth M. Hill (2018). Sci. Tott Env, 621, 782-790

内分泌かく乱に対する視野を広げる

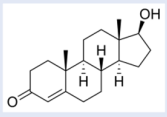
内分泌かく乱化学物質（EDCs）の多様化とその作用経路

例



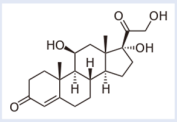
甲状腺ホルモン模倣物質／かく乱物質

ポリ塩化ビフェニル類（PCB）、ポリ臭化ジフェニルエーテ類ル（PBDE）、過塩素酸塩、ビスフェノールA、フタル酸エステル類



アンドロゲン模倣物質/かく乱物質
抗アンドロゲン類

ビンクロゾリン、リヌロン、イプロジオン、クロゾリネート、プロシミドン、フルタミド、*p,p'*-DDE（*p,p'*-DDT代謝物）、ケトコナゾール



グルココルチコイド模倣物質／かく乱物質

λ-シハロトリン、サイパーメトリン、レスメトリン、*o,p'*-DDT、*p,p'*-DDT、メトキシクロル、エチオフェンカルブ

ヒトにおけるEDC影響に対するより広い視野

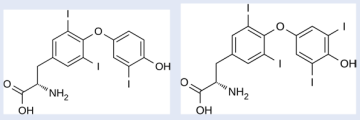
胎児期や思春期におけるEDCばく露は以下に関与する：

- *男性・女性の生殖系疾患の増加、*
- *内分泌関連がん*
- *感染症、*
- *ぜん息*
- *肥満、*
- *糖尿病、*
- *行動及び学習障害*

The Widening Landscape of Endocrine Disruption

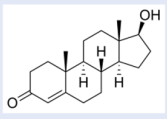
The increasing diversity of EDCs and their effects pathways

E.g.



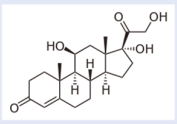
Thyroid hormone mimics/disruptors

Polychlorinated Biphenyls (PCBs), Polybrominated Diphenyl Ethers (PBDEs), Perchlorate, Bisphenol-A and phthalates



Androgen mimics/disruptors
Anti-androgens

vinclozolin, linuron, iprodione, chlozolinate, procymidone, flutamide, p,p'-DDE, a metabolite of p,p'-DDT, and ketoconazole



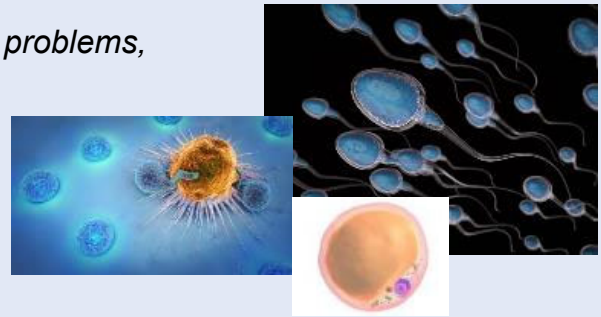
Glucocorticoid mimics/disruptors

λ-cyhalothrin, cypermethrin, resmethrin, o,p'-DDT, p,p'-DDT, methoxychlor, ethiofencarb,

The wider landscape of EDC effects- in humans

Exposure to EDCs during foetal life and/or puberty plays a role in:

- *Proliferation of male and female reproductive problems,*
- *Endocrine-related cancers*
- *Infections,*
- *Asthma*
- *Obesity,*
- *Diabetes,*
- *Behavioural and learning disorders*



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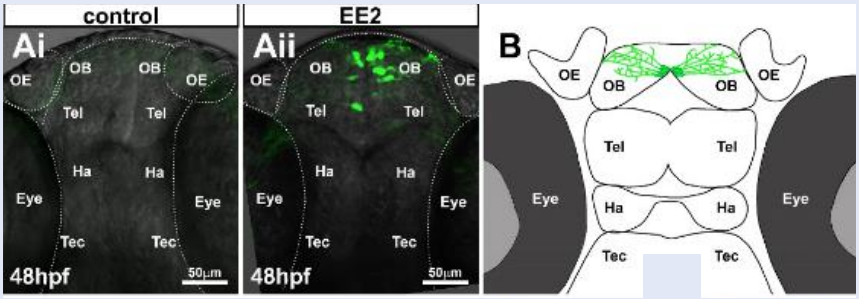
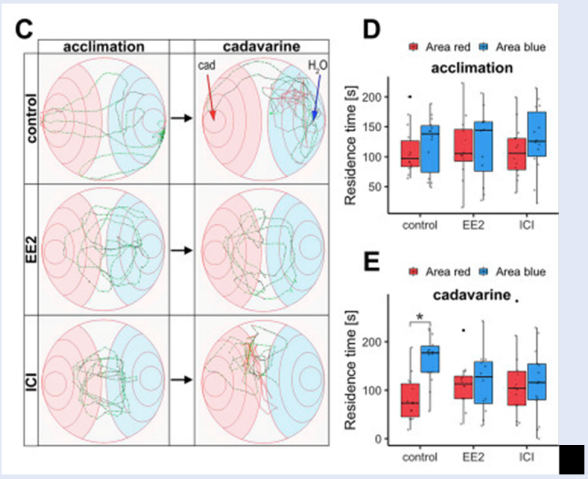
内分泌かく乱に対する視野（複雑性）を広げる

ゼブラフィッシュにおける神経内分泌作用

嗅覚／感知……及び行動に関連する影響



*エストロゲンはエストロゲン応答性グリア細胞を介して嗅覚系の初期胚発生を調節する - **エストロゲン応答性嗅球応答（EROB）細胞***



EROBsの初期発生におけるエストロゲンシグナル伝達の変化は、後期の嗅覚能力の障害を引き起こす

Aya Takesono, Paula Schirrmacher, Aaron Scott, Jon M. Green, Okhyun Lee, Matthew J. Winter, Tetsuhiro Kudoh and Charles R. Tyler (2022). Development 149, dev199860. doi:10.1242/dev.199860

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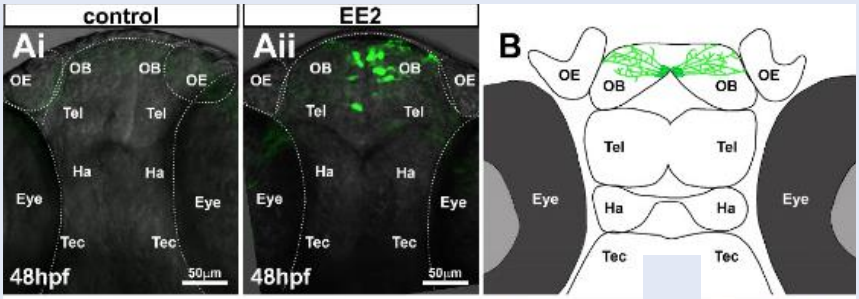
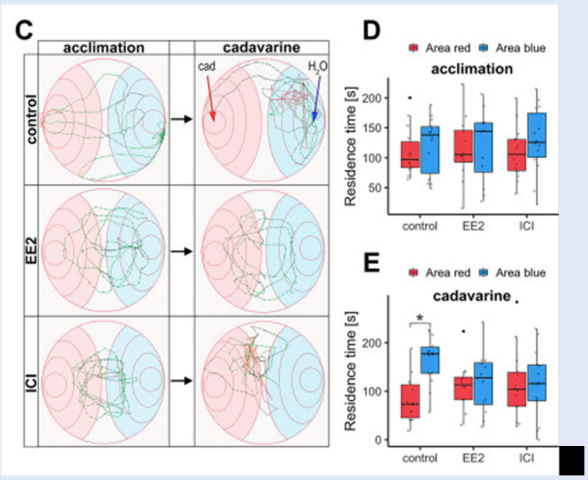
The Widening Landscape (Complexity) of Endocrine Disruption

Neuro-Endocrine Interactions in Zebrafish

Effects relating to olfaction/sensing…….and behaviour



*Estrogen regulates early embryonic development of the olfactory sensory system via estrogen-responsive glia- **Estrogen Responsive Olfactory bulb Response (EROB)** cells*



Altered oestrogen signalling during early development of the EROBs causes disruption in olfactory capabilities in later life

*Aya Takesono, Paula Schirrmacher, Aaron Scott, Jon M. Green, Okhyun Lee, Matthew J. Winter, Tetsuhiro Kudoh and Charles R. Tyler (2022). **Development** 149, dev199860. doi:10.1242/dev.199860*

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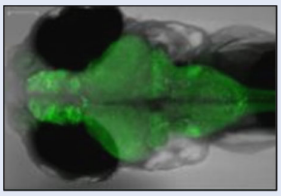
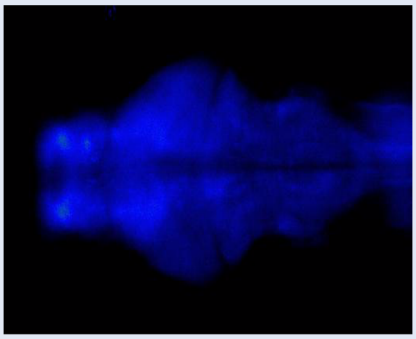
内分泌かく乱の広がりゆく景観（複雑性）

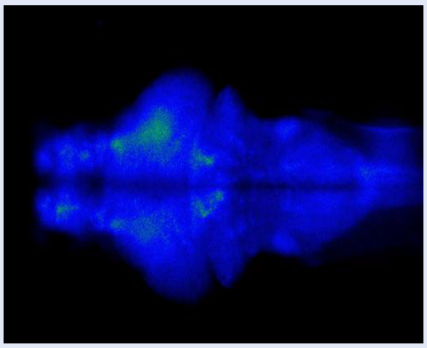
魚類の脳と行動に対する内分泌かく乱化学物質の影響



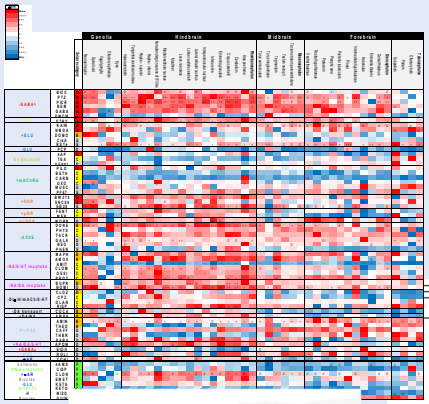
elavl3:GCaMP6s 幼生

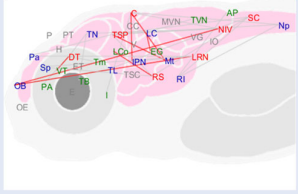


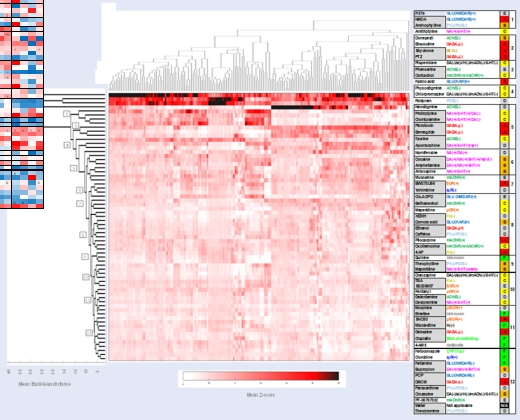
未処理対照区



4-AP処理区







Winter; MJ, Windell, D., Metz, J., Matthews, P., Pinion, J., Brown, J., Hetheridge, M., Ball, J., Owen, S, Redfern, W., Moger, J., Randall, A., Tyler, C.R (2017)..Scientific Reports. DOI:10.1038/s41598-017-06646-6

Winter, MJ., Pinion, J., Tochwin, A., Takesono, A., Ball, J., Grabowski, P., Metz· M., Trznadel, M., Tse, K., Redfern, WS, Hetheridge, MJ, Goodfellow, M, Randall, AD, Tyler, CR (2020).British Journal of Pharmacology 178:2671–2689.

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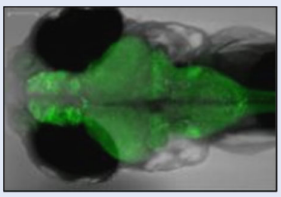
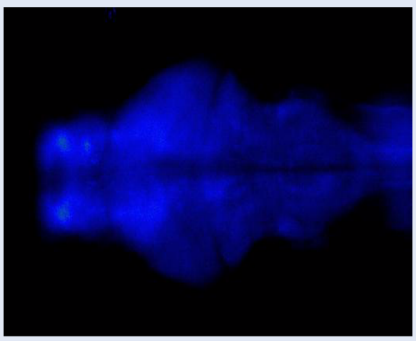
The Widening Landscape (Complexity) of Endocrine Disruption

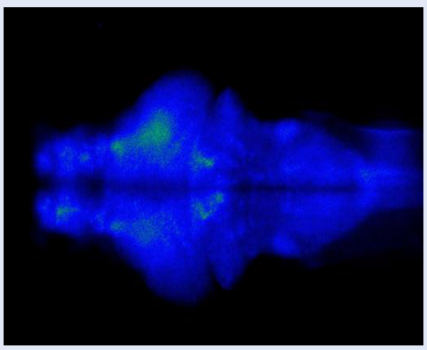
EDC effects on the Brain- and Behaviour in Fish



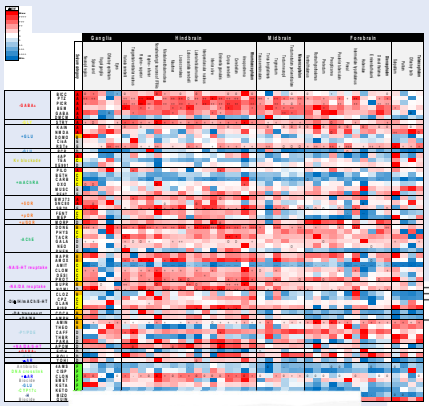
elavl3:GCaMP6s larvae

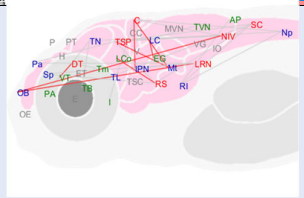


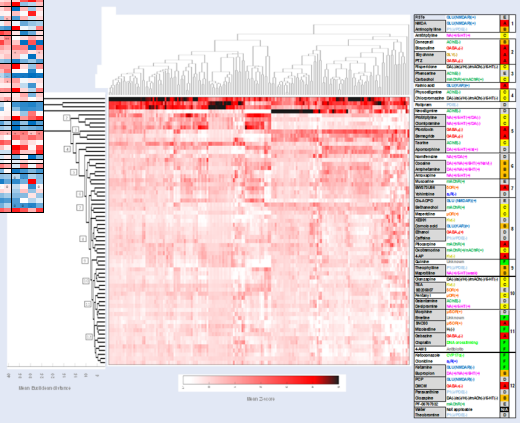
Untreated control



4-AP treated







*Winter; MJ, Windell, D., Metz, J., Matthews, P., Pinion, J., Brown, J., Hetheridge, M., Ball, J., Owen, S, Redfern, W., Moger, J., Randall, A., Tyler, C.R (2017).. **Scientific Reports**. DOI:10.1038/s41598-017-06646-6*

*Winter, MJ., Pinion, J., Tochwin, A., Takesono, A.,. Ball, J., Grabowski, P., Metz· M., Trznadel, M., Tse, K., Redfern, WS, Hetheridge, MJ, Goodfellow, M, . Randall, , AD, Tyler , CR (2020). **British Journal of Pharmacology**178:2671–2689.*

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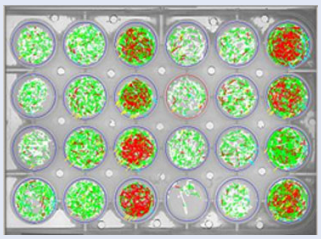
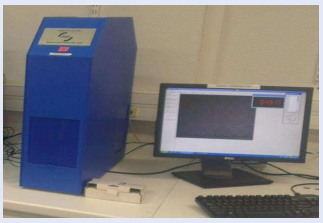
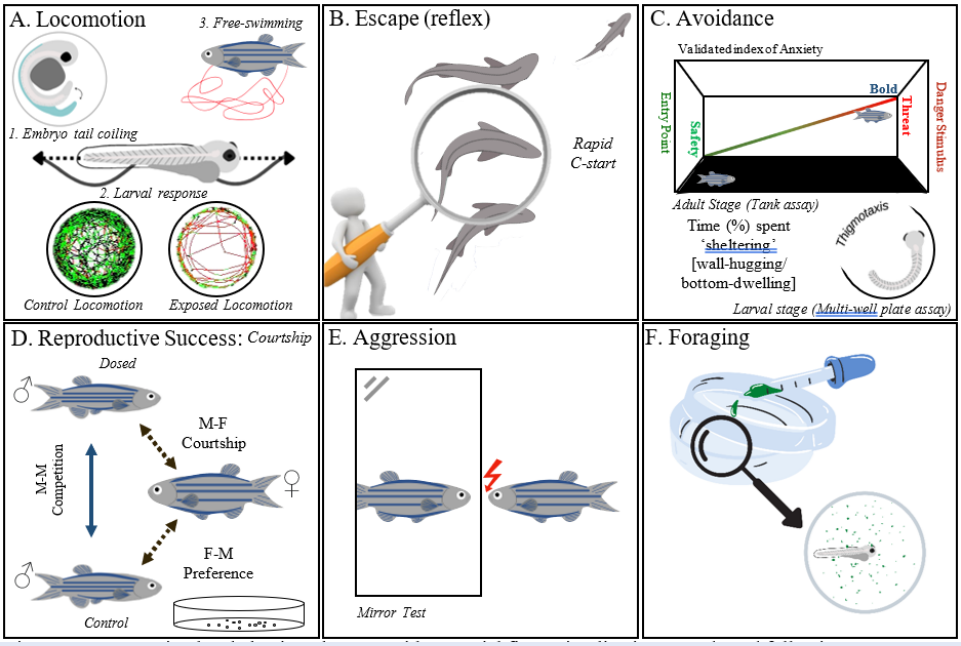
内分泌かく乱に対する視野（複雑性）を広げる

内分泌かく乱化学物質応答における脳の活動変化と行動との関連性

A) 半自動化、
中程度スループット







Gaby Wasser, A Ross Brown, Sam Maynartd, Stewart F. Owen, Charles. R. Tyler (2024). Critical insights into the Potential Risks of Antipsychotic Drugs to Fish, including through behavioural mechanisms. Biological Reviews https://doi.org/10.1111/brv.70031

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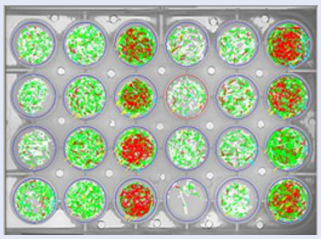
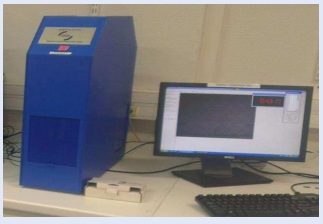
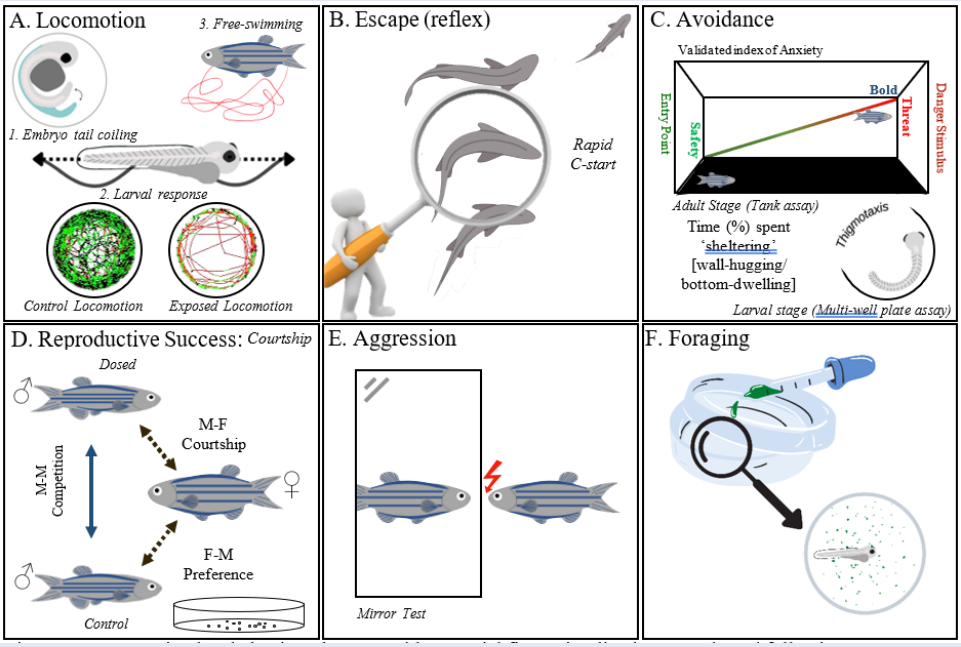
The Widening Landscape (Complexity) of Endocrine Disruption

Linking Changes in Brain Activity in Responses to EDCs with Behaviour

A) Semi-automated,
medium through-put





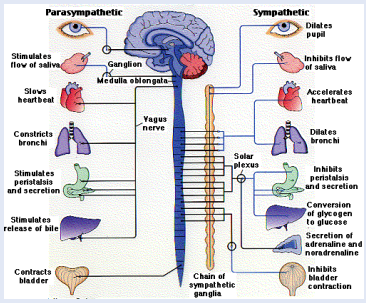


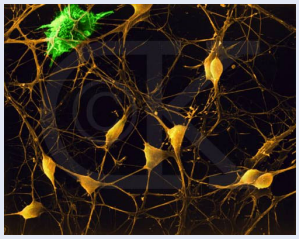
Gaby Wasser, A Ross Brown, Sam Maynartd, Stewart F. Owen, Charles. R. Tyler (2024). Critical insights into the Potential Risks of Antipsychotic Drugs to Fish, including through behavioural mechanisms. Biological Reviews https://doi.org/10.1111/brv.70031

内分泌かく乱化学物質が体内の通信システムに及ぼすより広範な意味合い

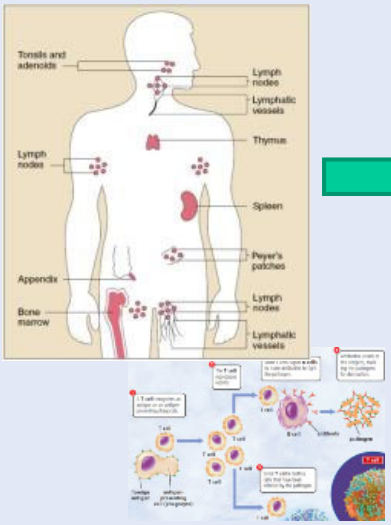
内分泌かく乱化学物質は、当初認識されていたよりもはるかに複雑な方法で、伝達経路をかく乱し、更には発生経路や機能経路をかく乱する可能性がある

神経系、内分泌系、免疫系は、高度に相互に連結されている

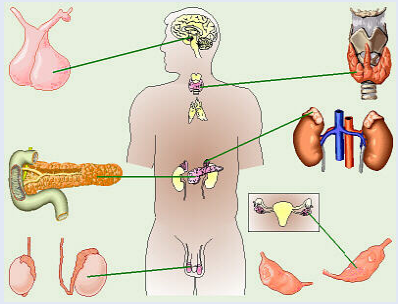


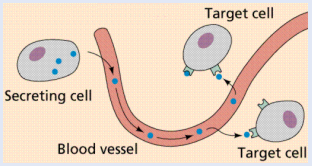


神経系 - *電話ネットワーク*



免疫系





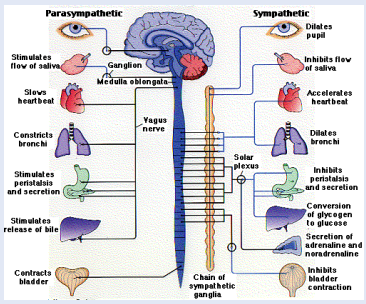
内分泌-*配送システム*

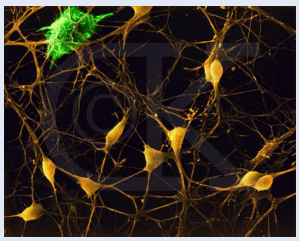
ホルモンとは、特定の反応を指令する化学的メッセージである

Wider implications EDCs on the body's communication systems

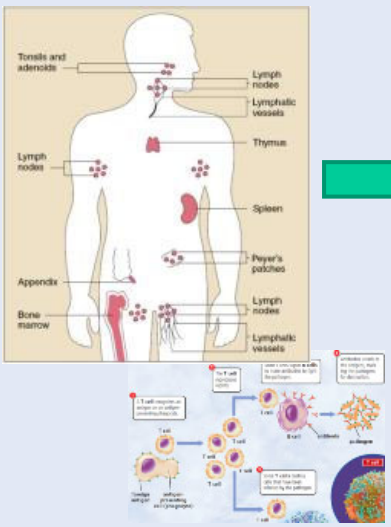
EDCs can disrupt comunication pathways and in turn development and functional pathways in a far more complex manner than we ever first realised

The nervous, endocrine and immune systems are highly interconnected

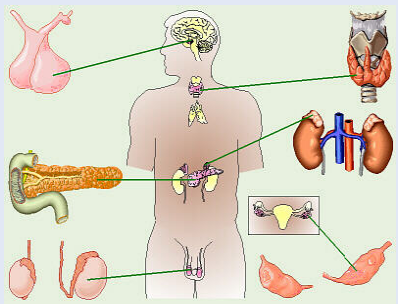


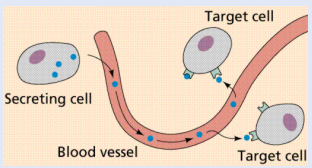


Nervous- *telephone network*



Immune system

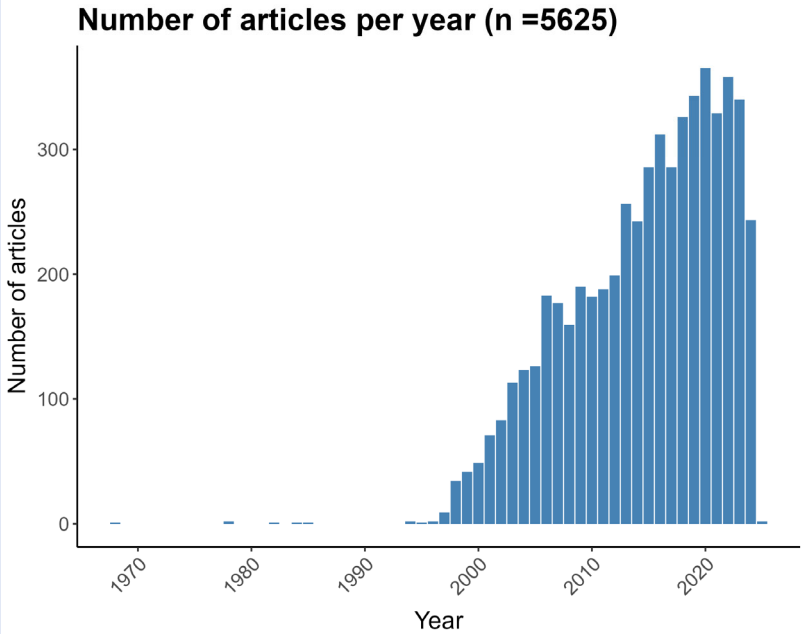




Endocrine- *postal system*

A hormone is a chemical message that instructs a specific response

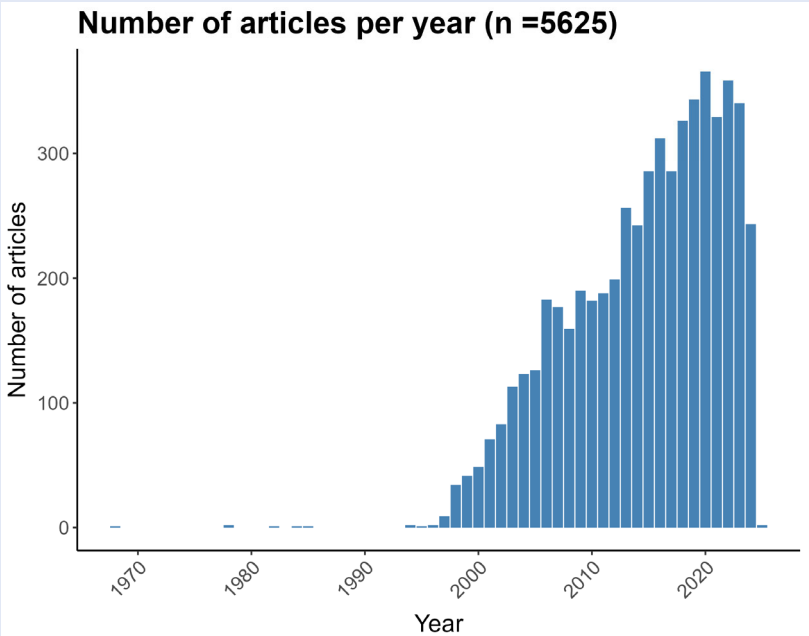
内分泌かく乱研究活動 – 科学論文



Web of Science における検索クエリ: TS = “内分泌かく乱” (n = 6929) TS = “内分泌かく乱化学物質” (n = 40) TS = (“内分泌活性” AND (“化学物質” OR “物質”)) (n = 395) TS = “内分泌調節物質”(n = 6) 選定された全論文を単一データセットに統合 (n = 7,370) 後、重複を除去 (n = 7,238; 重複132件)。その後、論文種別で分類し、一次研究論文を特定して分析対象とした (n = 5,625)。

依然として関心は高い!!

Endocrine Disruption Research Activity – Scientific Publications



Web of Science using the following search queries: TS = “Endocrine Disruption” (n = 6929) TS = “Endocrine Disruption Chemicals” (n = 40) TS = (“Endocrine Active” AND (“Chemicals” OR “Substances”)) (n = 395) TS = “Endocrine Modulating Substances” (n = 6) All selected papers were then compiled into a single dataset (n = 7,370), and duplicates were removed (n = 7,238; 132 duplicates). The papers were subsequently categorised by document type, identifying primary research articles for further analysis (n = 5,625).

There is still much Interest!!

結論としての所感

- 内分泌かく乱化学物質は、野生生物とヒト健康の両方に潜在的な脅威をもたらす。
- いくつかの内分泌かく乱化学物質とその生物学的影響については多くの知見が得られているが、慢性ばく露がどのように発現し、世代を超えて影響を及ぼすかについては十分に解明されていない。
- 環境に関連したばく露（タイミング、混合物、他のストレス要因との相互作用等）について、より深く理解する必要がある。
- 野生生物個体群に関する研究は依然として非常に限定的である。
- 分子生物学的技法（例：遺伝子組み換え魚）は、毒性物質が体内でどのように作用するかを理解するのに役立ち、より統合的な健康影響評価に向けて情報を提供している。
- 内分泌かく乱は、化学物質へのばく露が健康に及ぼす潜在的な影響に対する考え方をより一般的な観点からに変えた。
- 私たち（ヒト）は、魚類その他の野生生物とそれほど大きな違いはない。野生生物は、化学物質が私たちの健康に及ぼす潜在的影響を前もって知らせる役目を担っている!!

A few concluding thoughts

- EDCs potentially threaten both wildlife and human health.
- We have learnt a lot about a few EDCs and their biological effects but how chronic exposures manifest and over generations are poorly established
- We need to better understand environmental relevant exposures (incl. timing, mixtures, interactions with other stressors etc.)
-
- Studies on wildlife populations are still very limited.
- Molecular technologies (e.g transgenic fish) are helping us to understand how toxicants work in the body for informing more integrative health effects assessments.
- Endocrine Disruption has changed the way we consider the potential health consequences for exposure to chemicals more generally
- We (humans) are not that much different from fish and other wildlife – that provide us with sentinels for potential impact of chemicals on our own health!!

素晴らしい日本の友人たちとの協働は、内分泌かく乱化学物質研究における私の歩みの重要な部分です

英国・日本パートナーシップにおける内分泌かく乱化学物質及び懸念化学物質研究の国際アドバイザー

ありがとうございました！

An important part of my journey in Endocrine Disruption has been working with some great friends in Japan

International Advisor for our UK-Japan Partnership for studies into Endocrine Disrupting Chemicals and Chemicals of Concern

Thank you!

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ご清聴ありがとうございました

画像：チャールズ・R・タイラー

ご質問は？

Thank you for listening

Image: Charles R. Tyler

Questions?