Applied Cell Biology

ISSN : 2320-1991 Online
ISSN : 2320-1983 Print
Volume 10 Issue 4
DOI: https://dx.doi.org/10.53043/2320-1991.acb90035

Commentary
Appl Cell Biol, 10(4), 2022 [119-121]

Commentary: Labelling of Synthetic Endocrine Disrupting Chemicals (S-EDCs) as Substances of Very High Concern (SVHC)

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Synthetic endocrine disrupting chemicals (S-EDCs) and natural endocrine disrupting chemicals (N-EDCs) both have the potential to interact with receptors of the endocrine system. High exposures to N-EDCs may result from ingestion of various foods including soy-based diets, green tea, and sweet mustard. Human exposure to S-EDCs is by several orders of magnitude lower. Since both the N-EDCs and S-EDCs have about the same potencies and interact with the same receptors the assumption that the much lower exposures of S-EDCs induce effects is not plausible. It is not surprising that epidemiological studies searching for an association between S-EDC exposure and health effects have failed. Thus, labelling S-EDCs as SVHC is not justified.

Receptors are components of an organism, which bind molecules of diverse chemical structures. The specific binding of a ligand at its receptor is a prerequisite for its action and triggers a cascade of events. Classes of receptors are various hormone- and neurotransmitter-receptors. The receptor ligand interaction follows the law of mass action and its kinetic is similar to the Michaelis Menten equilibrium.

With this, replacement of a physiological ligand, *i.e.* an estrogen at a receptor by a xenoestrogen, depends on both the affinity of the receptor for that xenoestrogen and its concentration at the receptor site. For example, partial replacement of the physiological ligand from the receptor by a compound of 1000-fold lower affinity requires a 1000-fold higher concentration than the endogenous compound. This demonstrates the need for information on the relative binding affinities of the compounds in question and their concentration at the receptor.

Based on these biochemical principles [1] concluded that the manifestation of a detectable hormonal response depends on whether a sufficient number of specific cellular receptors are occupied by ligand molecules of sufficient specificity, potency, and concentration.

These fundamental biochemical principles are established knowledge about hormonal mechanisms with the obvious consequence that effects of hormonally active substances depend on potency and exposure. Thus, if chemicals were to interfere with natural endocrine signals, their doses/concentrations and potencies ought to be similar to or stronger than those of natural hormones [2-4]. However, whereas potencies of N-EDCs and S-EDCs are about the same their potency is orders of magnitude lower than that of endogenous hormones.

POTENCIES OF ENDOGENOUS HORMONES, DRUGS, N-EDCS AND S-EDCs

Already in 1995 Safe calculated the daily human intake of estrogen and anti-estrogenic equivalents, based on potencies relative to the endogenous hormone 17β−estradiol. It was shown that a woman taking a birth control pill ingests about 16,675 µg 17β−estradiol equivalents per day, postmenopausal estrogen therapy amounts to 3,350 µg, ingestion of estrogen flavonoids in food represents 102 µg, whereas daily ingestion of environmental organochlorine compounds of estrogenic activity was calculated to be 0.0000025 µg 17β−estradiol equivalents.

[5,6] demonstrated that N-EDCs or synthetic hormones such as ethinyl estradiol are 10,000 to 1,000,000-fold more potent than S-EDCs with an estrogenic activity. [7] reported, that the estrogenic potencies of ethinyl estradiol is 1,000,000), of the N-EDCs coumestrol 10,000, genistein 37, butylparaben 0.5, and benzylpareben 0.1.

As presented in the NTP-CERHR Expert Panel Report on bisphenol A (BPA) [8] concentrations in the blood of German, US and Japanese pregnant women average between 0.43 and 4.4 µg BPA/l with individual concentrations between 0.2 and

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18.9 µg/l. The relative estrogenic potencies of the average values for BPA for competition with 17β-estradiol binding to the estrogen receptor are approx. 570- to 5800-fold lower that of 17β-estradiol. The highest blood value of 18.9 µg BPA/l still had an approx. 125 times lower estrogenic potency than that of 17β-estradiol. From this an interaction of the compounds at the receptor with physiological consequences is unlikely.

[9] compared the relative potencies of the S-EDCs BPA and nonylphenol with those of the N-EDC daidzein and ethinyl-estradiol. Taking the N-EDC daidzein as reference (=1), relative uterotrophic activities in DA/Han rats followed the sequence: daidzein = 1; BPA = 1; p-tert- octylphenol = 2; o, p'-DDT= 4; ethinyl-estradiol = 40,000.

Facts described above clearly indicate that S-EDCs and N-EDCs have a much lower potency than drugs designed to pharmacologically interfere with the endocrine system and that the potencies of S-EDCs (e.g. BPA) are similar to that of N-EDCs. Remarkably, the intake of the highly potent ethinylestradiol (EE) for contraception of young and middle-aged females is not questioned as a potential issue regarding EDCs although the potency of EE is about 100,000fold higher than that of S-EDCs or N-EDCs.

EXPOSURE OF SYNTHETIC EDCs VERSUs NATURAL EDCs

An array of information adds to the evidence that the daily intake of natural EDCs greatly exceeds that of S-EDCs [9-13].

The intake of phytoestrogens from food varies widely among different populations (British < 1 mg/d, in Asian countries up to 100 mg/d), depending on their dietary habits [14].

[15] evaluated the intake of flavons and other phytoestrogens in human diets. Soy being abundant in traditional Asian diets results in isoflavonoid consumption as high as 50 mg/kg body weight per day. In the US consumption ranges from 1 to 3 mg/kg eating "Western" diet, whereas a vegetarian life-style or use of supplements can reach intake levels at or above Asian levels. The level of daily intake of most S-EDCs is significantly lower, that of approximately 35 ng/kg BPA per day a factor 3000 lower than that of isoflavonoids.

Regarding the health benefits or adverse effects, it can be concluded that like alcohol or caffeine there are pros and cons associated with moderate intake of isoflavonoids, suggesting that current data neither warrant an alarm of consumers regarding soy nor that a soy rich diet offers clear health benefits.

According to [9] who compiled the exposure data from the existing literature, the daily exposures to N-EDCs (phytoestrogens) are 4.5-8 mg/kg for infants on soy based formula, 1-3 mg/kg for adults (western population), 50-100 mg (East Asian population). By contrast, dietary exposures to individual S-EDCs are about 1000-fold lower: polychlorinated biphenyls 0.1 µg/kg, nonylphenol 2.3-5.31 µg/kg, BPA 1 µg/kg.

[16] investigated the concentrations, daily intake, and possible biological effects of phytoestrogens via soy-based infant food. Soy products, which contain the phytoestrogens genistein and daidzein, are becoming increasingly popular as infant foods. When fed according to the manufacturer's instruction, soy formulas provide the infant with a daily dose of total isoflavones (i.e., genistein + daidzein) of approximately 3 mg/kg body weight, which is maintained at a fairly constant level between 0 and 4 months of age. Since the available evidence suggests that infants can digest and absorb dietary phytoestrogens in active forms and since neonates are generally more susceptible than adults to perturbations of the sex steroid milieu, [16] suggest that it would be highly desirable to study the effects of soy isoflavones on steroid-dependent developmental processes in human babies.

According to [17] the major groups of phytoestrogens present in the diet and food supplements are isoflavons, phenylflavonoids, coumestans and lignans. In Asian countries, where fermented soy products are part of the traditional diet, isoflavone intake may amount to 15-50 mg per day, whereas in Western diets less than 2 mg per day are reported. It may be higher for menopausal women who take soy-based preparations as an alternative to hormones. The doses recommended by the distributers vary between 20 and 80 mg isoflavons per day.

These and an array of other studies show that human exposures to N-EDCs is several orders of magnitude higher than to S-EDCs. Even for these much higher exposures a definite conclusion on possible beneficial or adverse health effects cannot be made. This further adds to the evidence that the much lower exposure of S-EDCs is unlikely to lead to adverse effects in humans.

ADVERSE OR POSITIVE HEALTH EFFECTS OF EXPOSURE TO S-EDCs AND N-EDCs?

During the past decades, particular focus has been given to the potential harmful effects of S-EDCs to the reproductive system of humans [13].

The serious drawback of all these studies is that while the mere presence of EDCs (in food or in the organism based on biomonitoring) is considered to be a risk, whereas the actual extent of EDC exposure is not discussed in context

with the confounding exposure to natural EDCs. Based on the low exposures and low potencies of S-EDCs the only biologically plausible and reasonable conclusion is that there is no association. Accordingly, [18] have evaluated the causes for the changing trends in possibly endocrine related diseases in the Western world, which are thought to originate from exposure to endocrine disruptors. The authors concluded that factors such as paternal age and maternal age at first pregnancy and parity explain a substantial proportion of the reported increases. Other factors such as BMI may play a similar role in the observed trend.

CONCLUSION

Labelling of S-EDCs without considering potency and exposure is not justified, scientifically. Since S-EDCs and N-EDC compounds have similar potencies and act via the same mechanisms it is proposed to investigate the potential and relative potency of S-EDCs in an appropriate in vitro test system as compared to the potency of standard N-EDCs. If the potency of the S-EDC is similar or smaller than that of the N-EDC, further studies and regulations are not warranted unless human exposure predictions suggest similar or higher exposure than the reference N-EDCs.

REFERENCES

1. Borgert CJ, Baker SP, Matthews JC (2013). Potency matters: thresholds govern endocrine activity. Regul Toxicol Pharmacol 67, 83-88
2. Dietrich DR (2010) Courage for simplification and imperfection in the 21st century assessment of ‘‘Endocrine disruption’’. ALTEX 27, 264–278
3. Golden RJ, Noller KL, Titus-Ernstoff L, et al (1998) Environmental endocrine modulators and human health: an assessment of the biological evidence. Crit Rev Toxicol 28, 109–227
4. Marty MS, Rowlands JC (2011) Endocrine disruption: historical perspectives and its impact on the future of toxicology testing. Toxicol Sci 120, 93-108
5. Witorsch RJ (2002) Endocrine disruptors: can biological effects and environmental risks be predicted? Regul. Toxicol. Pharmacol. 36, 118–130
6. Witorsch RJ, Thomas JA (2010) Personal care products and endocrine disruption: a critical review of the literature. Crit Rev Toxicol 40, 1–30
7. Nohynek GJ, Borgert CJ, Dietrich D, Rozman KK (2013) Endocrine disruption: Fact or urban legend? Toxicol Letters 223, 295-305
8. NTP-CER Expert Panel Report on Bisphenol A (2007)
9. Bolt HM, Janning P, Michna H, Degen GH (2001) Comparative assessment of endocrine modulators with oestrogenic activity: I. Definition of a hygiene-based margin of safety (HBMOS) for xeno-oestrogens against the background of European developments. Arch Toxicol 74, 649-662
10. Safe SH (1995) Environmental and dietary estrogen and human health: is there a problem? Environ Health Perspect 103, 346-351
11. Safe SH (2000) Endocrine disruptors and human health – is there a problem? An update. Environ Health Perspect 108, 487-493
12. Dekant W, Colnot T (2013). Endocrine effects of chemicals: aspects of hazard identification and human health risk assessment. Toxicol Lett 223, 280-286
13. Autrup H, Barile FA, Berry Sir C, Blaauboer BJ, Boobis A, et al. (2020) Human exposure to synthetic endocrine disrupting chemicals (S-EDCs) is generally negligible as compared to natural compounds with higher or comparable endocrine activity. How to evaluate the risk of the S-EDCs? Computational Toxicology 14: 100124.
14. Cassidy A (1998) Risks and benefits of phytoestrogen-rich diets. In: Eisenbrand G, Daniel H, Dayan AD, Elias PS, Grunow W, Kemper FH, Löser E, Metzler M, Schlatter J (ed) Symposium: Hormonally active agents in food, organized by the DFG Senate Commission of Food Safety. Kaiserslautern, October 6-9th, pp 91-117
15. Patisaul HB and Jefferson W (2010) The pros and cons of phytoestrogens. Front Neuroendocrinol 31, 400-419
16. Irvine CH, Fitzpatrick MG, Alexander SL (2019) Phytoestrogens in soy-based infant foods: concentrations, daily intake, and possible biological effects. Proc Soc Exp Biol Med 217, 247-253
17. Rietjens IMCM, Louisse J, Beekmann K (2017) The potential health effects of dietary phytoestrogens. Brit J Pharmacol 174, 1263-1280
18. Swaen GMH, Boffetta P, Zeegers M (2018) Impact of changes in human reproduction on the incidence of endocrine diseases. Crit Rev Toxicol 48, 789-795
19. Dekant W, Dietrich D, Domingo JL, Gori GB, Greim H, et al. (2020) Human exposure to synthetic endocrine disrupting chemicals (S-EDCs) is generally negligible as compared to natural compounds with higher or comparable endocrine activity: how to evaluate the risk of the S-EDCs? Arch Toxicol 94, 2549–2557

Citation: Greim H (2022) Commentary: Labelling of Synthetic Endocrine Disrupting Chemicals (S-EDCs) as Substances of Very High Concern (SVHC). Appl Cell Biol, 10(4), 2022 [119-121]