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Are All Inhaled Drugs Climate Friendly?

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It is broadly known that human activity has a direct and/or indirect influence on the Environment and ultimately the Global Climate. Several industrial activities such as the manufacturing of refrigerants, aerosols, fire suppression agents or solvents, are being restructured in order to find the best "climate friendly" replacement for the most commonly and generically used agents. Inhaled drugs, on the other hand, still require greater commitment to develop more environmentally-compatible medications. This should be a priority.

However, the issue is, what are the environmental impacts that we expect from an inhaled drug? A response is not easy; however, some light may be shed when we consider the three main environmental hazards: the ozone layer depletion, the photochemical smog and the global warming.

The role of Cl and Br atoms in ozone layer depletion was discovered in 1974 [1]. The design of new non chorine-containing replacement species may be the feature to control and minimize this impact. The Montreal Protocol and its continuous updates on Substances that Deplete the Ozone Layer was established to phase-out the use of chlorinated compounds and their production. However there are still some volatile chlorinated species that are being readily used for some applications. For instance, and related to the inhaled drugs issue, chlorine-containing anesthetics such as halothane, isoflurane, and enflurane may be more destructive to the ozone layer than newer drugs, such as sevoflurane and desflurane, which are halogenated entirely with fluorine [2].

Concerning the photochemical smog, this originates due the ground level tropospheric oxidation of short-lived volatile organic compounds (VOCs) – lifetimes between hours or days and a month – that lead and contribute to a complex mixture of pollutants and particles (NO, NO_2, O_3, PAN, etc). Smog is a serious problem in many cities and continues to harm human health causing several respiratory diseases. It is worth noting that smog levels are continuously being monitored in cities as levels of O_3, NO, NO_2 and particles. Although smog is basically road traffic emissions issue, some other VOCs can contribute to smog episodes, when these are oxidized next to the source. Is it possible to minimize the smog risk from the origin, through an examination of the molecular structure? The answer is yes, however the methods to determine which species contribute less to smog formation are complex and usually require significant investment of time and money. Parameters such as the Maximum Incremental Reactivity (MIR) or the Photochemical Ozone Creation Potential (POCP) are being used as smog indicators and are based on the amount of O_3 formed during a certain period of time by the studied specie [3]. A combination of experimental systems such as smog chambers, along with theoretical modeling are needed to determine these parameters. What is clear from these measurements is that species with double or triple bonds strongly contribute to smog formation.

Inhaled drugs contribution to global warming of depends on: Firstly, the species ability and effectiveness at absorbing and emitting infrared radiation, which is directly related to the molecular structure of the molecule, and the infrared photons ability to reach the atmosphere from the Earth's surface and from the Sun – this can be characterized as a measurement called radiative efficiency that determines the contribution of the molecule to the greenhouse effect. Secondly, as not all molecules will stay in the atmosphere for the same time - different atmospheric lifetimes - and their climate effects might be different, the radiative efficiency parameters can be calculated through radiative transfer models whereby, the lifetimes are determined using complex experimental techniques [4]. In order to put together radiative efficiency and lifetime on a common scale and a same expression, the parameter Global Warming Potential (GWP) was chosen by the Intergovernmental Panel on Climate Change [5]. This parameter uses the gas CO_2 as a reference, and places the rest of gases on a CO_2-equivalent scale. The GWP is constructed by evaluating the time integral of the product of the radiative efficiency and the change of gas concentration with the time, over a given time (called "time horizon"), and dividing by the same integral due to 1 Kg emission of CO_2. A time horizon of 100 yrs is the preferred choice, unless the lifetime of the gas is short and then a time horizon of 20 yrs might also use [6]. Therefore, a gas A with a GWP_{100}=100 means that it contributes 100 times more than CO_2 to global warming. Picking up the previous question about the possibility of minimize the global warming contribution of gases by modifying the molecular structure, the answer is again yes. Several studies show that the presence of C-F bonds in the molecular structure enhances the infrared absorption within 700- 1500 cm^{-1}- spectral range called "atmospheric windows" - where the radiation is mainly absorbed by hydrofluorocarbons. An absorption in this wavenumber region leads to maximum radiative efficiency values and might drive large GWPs [7]. Nowadays, it is possible to predict GWPs for gases with useful accuracy by using computational techniques [8]. This methodology reduces the costs related to the direct measurement of parameters, turning the design of environmentally-benign gas into a reality.

An example of "making the switch" to more environmentally-compatible alternatives is the change of chlorofluorocarbon (CFC) to novel propellants – hydrofluoroalkane (HFA) – asthma inhalers. Asthma is a problem worldwide, with an estimated 300 million affected individuals [9]. Inhalers based on CFC propellants were used until 2008 when the Food and Drug Administration announced that these inhalers could no longer be manufactured or sold as of 2012, in agreement with the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer [10]. There is no presence of chlorine atoms in the HFA molecular structure and therefore, the contribution to ozone layer depletion is negligible. However HFAs are greenhouse gases with high GWP values. For instance the GWP_{100} for the mostly common propeller-used HFA, HFA-

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134a (CH_2FCF_3) and HFA-227ea (CF_3CHFCF_3), are 1430 and 3220, respectively, whereas the GWP for the CFC that replace, CFC-11 (CCl_3F), is just a little bit lower (4750) [5]. Therefore, the propellants that are being used are not completely environmentally- benign.

The inhaled anesthetic overview is similar to the asthma propellants. Only in 2006 in the United States, general anesthetics were administered to at least 50 million patients. Besides, anesthetic gases are widely used in dentist offices, veterinary clinics and research laboratories. N_2O is the most popular anesthetic gas, and according to some estimates, the emissions of N_2O during 2006 were approximately $3.5x10^4$ tons used for anesthetic purposes for 70 million patients, that is 3% of total N_2O emissions in the United States during 2006 [11]. It is worth noting that N_2O contributes to both global warming (GWP_{100} = 298) and ozone layer depletion [5,12]. Aside from N_2O, all volatile anesthetic currently used are halogenated gases. Efforts were carried out to replace anesthetic containing Cl and/or Br atoms with some novel ones – mainly hydrofluoroethers (HFE) – that do not contribute to the ozone layer. For example, desflurane ($CHF_2OCHFCF_3$) and seroflurane ($(CF_3)_2CHOCH_2F$) are currently two of the most common volatile anesthetic agents, and have replaced others such as isoflurane ($CF_3CHClOCHCF_2$), halothane ($CF_3CHClBr$) or enflurane (CHF_2OCF_2CHFCl) [4]. Nevertheless, as happened with the HFA propellants, they all have again relatively large GWPs – for instance desflurane and sevoflurane show GWP_{100} values of 1620 and 210, respectively [13]. This suggests that both HFAs and HFEs are useful alternatives to combat the ozone layer depletion but still contribute to the global warming issue.

In conclusion, some inhaled drugs contribute to the global warming and ozone depletion. Nowadays, it is possible to predict by computational and/or experimental methods the environmental compatibility of gases before their manufacturing and marketing. Some novel alternatives are being introducing in several pharmacy and medicine applications, such as anesthetic or asthma inhaler propellants. Since these inhaled drugs are greenhouse gases, it is necessary to characterize their climate effect and find ways to monitor their emissions. When more than one inhaled gas can be chosen for the same use and there is no compelling clinical reason to prioritize one, the less harmful one to the environment should be chosen. Finally, we may think that by using HFEs and HFAs and monitoring their emissions everything is done, however the issue is much trickier. As the emissions of non-ozone depleting inhaled drugs decreases, the emissions of novel drugs with a high contribution to global warming increases so, what more can be done? This time, the answer is easier said than done: Invest more resources into the investigation of novel environmentally-harmless inhaled drugs.

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