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A sensitivity analysis of a human exposure model using the Sobol method

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Abstract
The Air Pollutants Exposure Model (APEX) is a stochastic population-based inhalation exposure model which (along with its earlier version called pNEM) has been used by the U.S. Environmental Protection Agency (EPA) for over 30 years for assessment of human exposure to airborne pollutants. This study describes the application of a variance decomposition-based sensitivity analysis using the Sobol method to elucidate the key APEX inputs and processes that affect variability in exposure and dose for the simulated population. Understanding APEX's sensitivities to these inputs helps not only the model user but also the EPA in prioritizing limited resources towards data-collection and analysis efforts for the most influential variables, in order to maintain the quality and defensibility of the simulation results. This analysis examines exposure to ozone of children ages 5–18 years. The results show that selection of activity diaries and microenvironmental parameters (including air-exchange rate and decay rate) are the most influential to estimated exposure and dose, their aggregate main-effect indices (MEIs) equaling 0.818 (out of a maximum of 1.0) for daily-average ozone exposure and 0.469 for daily-average inhaled ozone dose. The modeled person's home location, sampled from national Census data, has a modest influence on exposure (MEI = 0.079 for daily averages), while age, sex, and body mass, also sampled from Census and other survey data, have modest influences on inhaled dose (aggregate MEI = 0.307). The sensitivity analysis also plays a quality-assurance role by evaluating the sensitivities against our knowledge of the physical properties of the model.

Keywords Air pollutants exposure model · Exposure assessment · Sobol analysis · Sensitivity analysis · National ambient air quality standards

1 Introduction

The Air Pollutants Exposure Model (APEX; U.S. EPA 2019a, b), developed and maintained by the U.S. Environmental Protection Agency (EPA), is a stochastic population-based inhalation exposure model that can used to simulate behaviors, home environments, and exposures associated with ambient pollutant concentrations for a simulated population of thousands of individuals. The continued use of the model in regulatory applications necessitates regular efforts by EPA to update datasets and probability distributions associated with its inputs, including those describing human behaviors and the indoor environment, to ensure relevance to current conditions and ultimate defensibility of simulation results. However, EPA must prioritize these efforts to input variables that most greatly influence characterization of the variability of exposures across the population.

Such prioritization can be informed by sensitivity analysis (SA). An SA also can serve as a quality-assurance check to ensure that the relationships between the input and output variables make sense, which is critical for scientific and public confidence in the risk and exposure assessments that support the NAAQS and other efforts addressing public health (Saman et al., 2021). In recent years, several authors have provided helpful reviews of SA methods: Pianosi et al. (2016) reviewed the SA literature and

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provided practical guidelines for carrying out SA, while Douglas-Smith et al. (2020) carried out a literature review of SA methods and looked at trends in their use, and Razavi et al. (2021) also discussed different methods of SA and their uses. Methods for SA, regardless of the application, may be broadly grouped into local and global approaches. Local SA methods such as varying one input at a time by small amounts or methods based on partial derivatives commonly are used (Saltelli et al. 2000). These quantify the effects of perturbing inputs locally around nominal points. Global SA methods account for the sensitivity of variables over their entire range and can account for interactions between variables.

The Sobol method was proposed by Sobol' (1990 in Russian; 1993 reprinted in English). Here, we used the Glen and Isaacs (2012) implementation of the Sobol method to evaluate APEX; this implementation uses sampled Pearson correlation coefficients with the removal of spurious correlations. We conducted a simulation study using this Sobol implementation to investigate which APEX inputs most impact population variability in exposure and dose. We conducted this study, which assessed O_3 exposure in Chicago for children ages 5–18 years, with the goal of prioritizing key future data-collection and analysis efforts.

2 Background on APEX and Sobol implementation

2.1 General features of APEX

EPA has used APEX to estimate human exposure to sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and nitrogen dioxide (NO_2) (U.S. EPA 2020, 2018, 2014, 2010 and 2008), in support of reviews of the U.S. National Ambient Air Quality Standards (NAAQS). Other applications include modeling exposure to emissions from oil and gas operations (Holder et al. 2019).

APEX is both data-rich and highly flexible with many user-defined inputs. The model is provided with an extensive database of time-activity diaries (U.S. EPA 2019c; McCurdy et al. 2000), population databases (U.S. Census Bureau 2010, 2011), and well-parameterized distributions that capture variability in other model inputs. The APEX algorithms and current default input data and distributions have previously been described in detail (U.S. EPA 2019a, b), but a general description is provided here (see also Section A of the Online Resource). APEX models the exposure of individuals (termed "profiles") as they move through different microenvironments (MEs, which are described in more detail below), each of which has specific time-varying pollutant concentrations based on the user-supplied ambient data. The profiles have stochastically generated samples of demographic, physiological, and ME properties, intended as a representative sample of the target population, and they are modeled for the entire simulation period.

Apart from the air-quality and weather data (which are deterministic once a location is specified), all APEX variables are sampled from user-specified distributions. The variables to be assessed in this study are defined in Table 1 (we further discuss Table 1 in Sect. 3). The distributions are randomly sampled one or more times for each profile. The samples for each profile are independent of those for any other profile. There are no fixed or "frozen" variables in any APEX run. Some variables (e.g., age, sex) are sampled once per profile while others are sampled at regular time intervals. While each such sample is effectively an independent random variable, for analysis it is standard to assess the grouped impact of all the samples of a variable together. These account for hundreds or (for hourly) thousands of independent random samples per profile.

Each profile visits a sequence of MEs (locations of unique air quality, such as home or office, vehicle, outdoors, etc.) as determined by the selected time-activity diaries. For each indoor ME, ME parameter (MP) distributions are specified for indoor emission sources, pollutant decay rates (DEs), proximity factors (PRs) which modify nearby outdoor concentrations, and air-exchange rates (AERs) and penetration factors (PEs). Outdoor MEs also have PRs. MPs can be conditional on the values of other variables. For example, the AERs in the runs used in this study depend jointly on the outdoor temperature and the probability of having air conditioning. APEX has no stratification variables, so all differences between profiles are due to stochastic sampling differences in the inputs.

APEX produces multiple outputs for each profile. In APEX, instantaneous exposure is the air concentration experienced by the profile (i.e., the pollutant concentration outside the body), and dose is the exposure multiplied by the breathing ventilation rate (i.e., the intake of the pollutant through inhalation, which depends on the profile's physiology and what activity they are doing). We make distinctions between exposure and dose throughout this study because some model inputs affect dose but not exposure (or have a stronger effect on dose relative to exposure). Exposure and dose are assumed to be constant until the activity or the ME changes, up to a maximum duration of one model timestep. Output metrics can include time averages, maxima, and counts of exposures and doses above user-specified thresholds.

Table 1 Grouping in each model run for each main type of stochastic model-input variable

Input random variable	Description	Input groups Run 1	Run 2	Run 3	Run 4
Sex	Male or female	1	0	0	1
Age	Age	2	0	0	2
HomeSec	Home tract	3	0	0	0
WorkSec	Work tract	4	0	0	0
Race	Race	0	0	0	0
Employ	Employment status	4	0	0	0
ProfFactor	Location-dependent profile factor	0	0	0	0
GasStove	Has gas stove	0	0	0	0
GasPilot	Has gas pilot on stove	0	0	0	0
AC_Home	Has air conditioning at home	5	0	0	0
AC_Car	Has air conditioning in car	5	0	0	0
ProfCond1-5	Profile conditional variables #1 to #5	0	0	0	0
RegCond1-5	Regional conditional variables #1 to #5	0	0	0	0
OtherD	AQ district other than home or work	5	0	0	0
NearHome	AQ district when in Near Home location	5	0	0	0
NearWork	AQ district when in Near Work location	5	0	0	0
WindowRes	Daily window status at residence (open, closed)	0	0	0	0
WindowCar	Daily window status in car	0	0	0	0
SpeedCat	Daily speed category for travel	0	0	0	0
DayCond1-3	Daily conditional variables #1 to #3	5	0	0	0
BodyMass	Body mass	8	0	0	3
Height	Height	8	0	0	4
BSA	Body surface area	8	0	0	5
RMR	Resting metabolic rate	8	0	0	6
VEAge	Regression terms for breathing versus age	8	0	0	7
Disease	Presence of disease	8	0	0	0
VO2max	Maximum O_2 consumption	8	0	0	8
ECF	Energy-conversion factor	8	0	0	9
RecoveryT	Recovery time for O_2 debt	8	0	0	10
Hemog	Hemoglobin density in blood	8	0	0	0
MaxOxD	Maximum possible O_2 debt	8	0	0	11
EndogCO	Endogenous CO production	8	0	0	0
BloodVol	Blood volume regression terms	8	0	0	12
SFast	Slope of fast O_2 debt recovery	8	0	0	13
FEVB1-9	dFEV terms #1 to #9	8	0	0	0
FEVreg	FEV regression parameters	8	0	0	0
FEVU	dFEV parameter U	8	0	0	0
FEVE1	dFEV parameter E1	8	0	0	0
FEVE2	dFEV variation parameter E2	8	0	0	0
VEBM	Regression terms for breathing ventilation	8	0	0	14
MET	Activity-specific MET values	8	0	0	15
AQData	AQ data drawn from distributions	0	0	0	0
DiarySel	Daily activity-diary selection	6	0	0	0
DAutoCor	Autocorrelation of diaries	6	0	0	0
Clus1	First diary-clustering parameter	0	0	0	0
Clus2	Second diary-clustering parameter	0	0	0	0
MP1	AER inside residence	7	1	1	16
MP2	AER inside office buildings or hospitals	7	2	1	16
MP3	AER inside schools	7	3	1	16
MP4	AER inside stores	7	4	1	16
MP5	AER inside restaurants	7	5	1	16
MP6	DE inside residence	7	1	2	16
MP7	DE inside office buildings or hospitals	7	2	2	16
MP8	DE inside schools	7	3	2	16
MP9	DE inside stores	7	4	2	16
MP10	DE inside restaurants	7	5	2	16
MP11	PR factor for residence	7	1	3	16
MP12	PR for office buildings or hospitals	7	2	3	16
MP13	PR for schools	7	3	3	16

Table 1 continued

Input random variable	Description	Input groups Run 1	Run 2	Run 3	Run 4
MP14	**PR for stores**	7	4	3	16
MP15	**PR for restaurants**	7	5	3	16
MP16	PR for outdoors - general	7	6	3	16
MP17	PR for outdoors - near major road	7	7	3	16
MP18	PR for vehicles	7	8	3	16
MP19	PE for vehicles	7	8	4	16

Group numbers are arbitrary, and within each "Run" column we use shading for easier distinguishing between group numbers. We further explain all variables in this table in U.S. EPA (2019a, b). For MPs not shown here, we held them constant and they did not contribute to output variance

AQ = air quality; O_2 = oxygen; CO = carbon monoxide; dFEV = lung-function loss; O_3 = ozone; MET = metabolic equivalent of task; MP = microenvironmental parameter; AER = indoor-outdoor air-exchange rate; DE = hourly decay rate; PR = proximity factor; PE = penetration factor

2.2 The Sobol implementation in APEX

The goal of a variance-based SA is to apportion the variance of model output among the set of stochastic inputs. This allows one to rank the inputs in terms of their influence on specified outputs and can provide an understanding of the relative influence of different factors in the model. Sobol analysis (Sobol' 1990, 1993) is based on variance decomposition. The specific implementation used here is that of Glen and Isaacs (2012) (see also Section B of the Online Resource). The method is well-suited for APEX as it is amenable for any number of independent samples per profile and allows for the straightforward collection of individual variables into meaningful groups (for assessment of collective influence). The main features of this method are that it:

(1) Allows any number of independent samples per profile (which is the stochastic unit).
(2) Is optimized for use with true random samples, not for quasi-randoms.
(3) Minimizes relative error, not mean absolute error.
(4) Has grouping that is completely flexible without any special considerations such as alterations to the random-number generation.

With thousands of random variables, the average index for any one is very small. Minimization of relative error ensures these small values are still accurate. This method gives estimates of exactly zero with no stochastic error for variables that have no contribution at all. Saltelli et al. (2004, 2008) discussed using SA methods for assessing scientific models and global SAs in general, respectively, and Mokhtari and Frey (2006) also reviewed Sobol and other SA methods for applications simulating human exposure and dose. Other recent applications of the Sobol method include: Kumar et al. (2020) who implemented the Sobol method for a risk assessment of groundwater, Wei et al. (2020) who conducted a Sobol analysis of distributed energy systems, Gatel et al. (2020) who conducted a Sobol analysis of a surface-water model, and Zhang et al. (2015) who described the use of the Sobol method for evaluation of pharmacology models.

The Sobol implementation in APEX is discussed at length in Chapter 11 of the APEX Technical Support Document (U.S. EPA 2019b). An output variable with one value per profile is selected for analysis, and each such output will have a different set of sensitivity indices. Two random values (called the "sample" and "resample" values) are generated for each combination of profile and random input variable. A series of model runs are performed in which selected inputs are assigned their sample values while the remainder of inputs are assigned their resample values. The random values are the same on each pass but are not stored and must be regenerated using seed control. Every random number in APEX is seed controlled.[1] By systematically varying the inputs assigned to each set and comparing the outputs across pairs of runs, the contribution of each input variable to the variance of the output may be quantified.

Grouping of input variables allows faster evaluation because the full set of thousands of profiles must be

[1] Every combination of profile and random variable is assigned two "seeds" (32-bit integers) which are derived from an overall run seed using a special random generator with a period of (2^32) − 2. When one or more random values are required for a modeling variable, the standard Fortran uniform random generator is used. This generator uses two 32-bit seeds, so if the sample value is desired the two 32-bit seeds allotted to this profile-variable combination are used in the order AB, but if the resample value is desired the BA order is used. Exhaustive testing has confirmed that the values A and B are always different until the entire period of length (2^32) − 2 has been sampled.

generated (2 N + 2) times, where N is the number of groups, creating many millions of independent random samples. Every pass through the code, regardless of grouping, is an equally valid representative sampling of the model space and could be used as a standalone variability run. The downside to input grouping is that the contributions of each member of a group cannot be separated out. Therefore, multiple runs with different groupings may be used to obtain such details. While the modeling variables may be grouped arbitrarily in APEX, the code assumes that samples pertaining to the same modeling variable (such as the samples that are applied at different simulation times) are automatically grouped. Variable groups may contain continuous or categorical variables, or both, without restriction.

APEX has a built-in mode to conduct all the necessary runs in a single submission, and it reports both the main-effect index (MEI) and total-effect index (TEI) for each input grouping, for a series of output variables. Both MEI and TEI are unitless. The Sobol indices are not affected by the units used for the inputs and do not depend on an imposed ordering for categorical variables. Each MEI reflects the impact (as a decimal fraction) one input variable has by itself on the variance of the output, so each MEI must be between zero and one, and their sum cannot exceed one. Each TEI measures the influence one input has either by itself (the MEI) or in interactions with other inputs, so TEI $\geq$ MEI. The sum of all TEIs exceeds one because interaction terms are counted once for each contributing variable. Stochastic error may occasionally result in estimates that violate these limits if the number of profiles is too small. Since such results cannot be correct, the number of profiles should be increased to resolve this issue.

3 Methods

We applied APEX (version 5.2) to the Chicago area for the O_3 season (April–October) in 2011, modeling children ages 5–18 years. The APEX input data fall into the following general categories: human-activity data; population, employment, and commuting data; air-quality data; temperature data; physiological distributions; and ME distributions. The human-activity data are from the Consolidated Human Activity Database (CHAD) (McCurdy 2000; U.S. EPA 2019c), which contains over 179,000 daily activity diaries. We used tract-level population data from the 2010 census (U.S. Census Bureau 2010) in conjunction with employment and home-to-work commuting flows. We used hourly O_3 air-quality data from 16 fixed-site monitors within and around Cook County, each covering the entire April–October period; therefore, the model timestep was one hour. We obtained hourly temperature measurements from the National Weather Service data files (Integrated Surface Database). In Section C of the Online Resource, we provide a map of the monitors (i.e., air quality districts), meteorological stations, and an illustration of the local population density. We used the default APEX physiological data, which are based on Isaacs and Smith (2005). We used eight MEs: inside residence, inside office/hospital, inside school, inside store, inside restaurant, outdoor general, outdoor near road, and in vehicle. We also briefly examined the Los Angeles air basin as a comparative example.

APEX converts the population data to probabilities and randomly samples age, sex, race, and home tract for each profile. Other profile variables are conditional on these. One activity diary is selected on each modeled day for each profile. Each tract is assigned hourly outdoor concentrations from the air-quality-monitoring site closest to each tract center. Similarly, each tract uses data from the closest weather station. Temperatures affect the selection of activity diaries and the estimation of AERs for indoor MEs. We used a mass-balance AER model for the indoor MEs and a regression-based PE model for in-vehicle MEs (these models are described in the APEX User's Guide and Technical Support Document: U.S. EPA 2019a, b). To capture the variability relating to spatial interpolation between air-quality-monitoring sites, the PR MPs were fitted to the empirical distribution of concentration ratios between adjacent monitors. The details of the MP distributions are listed in Section D of the Online Resource. The data underlying the ME variables are described in U.S. EPA (2014).

This study presents results from one modeling exercise, divided into four "runs" each with identical inputs apart from Sobol grouping. All four runs had identical sample (and resample) values for every random variable; the only difference was when the sample or resample value was chosen to represent the variable. All variables within a group always make this choice the same way. See Table 1 for the assignments of input variables to groups in each run (see Section E of the Online Resource for fuller descriptions of these variables). The numbering of the groups was arbitrary, though Group 0 in each run contained the input variables of lesser interest in that run. The Sobol indices are unaffected by the choice of group numbers, provided the group membership remains unchanged. Variables grouped together are still sampled independently. The groupings determine whether each variable uses its "sample" values or its "resample" values in a particular APEX iteration, but all random values are independent of each other. The number of groups "N" ranged from 5 to 17, and each run comprised (2 N + 2) sets of 25,000 profiles. Preliminary SA runs of APEX (not shown) have

demonstrated that the stochastic error in the Sobol indices was about 1% of their value when 25,000 APEX profiles were used; we considered this error to be acceptable for the current analysis. The modeling error is harder to assess and is beyond the scope of this study.

In these runs, more than 15,000 samples and 15,000 resamples (i.e., more than 30,000 random samples) are needed per profile. With 25,000 profiles, each run requires over 750,000,000 independent random samples per pass. Our "Run 4" in this study, for example, has 16 input groups and therefore requires 34 such passes. The model runtime of each set was about 20 min, so the longest run (Run 4) was about 12 h.

Run 1 examined the main demographic variables in detail. Age and sex are physiological in nature but were included here grouped separately (i.e., Group 1 and Group 2, respectively) because they determine activity-diary selection and hence influence the set of MEs visited, thus affecting exposure and dose. Group 3 was the home-tract assignment of the profile, while Group 4 was the employment status and work-tract assigned to the profile, and so on. Run 1 otherwise grouped together all the MPs (MP1–MP19; Group 7) and grouped together all the physiological variables (Group 8). Group 0 held variables that cannot affect the results, so MEI and TEI for Group 0 should both be zero for all output statistics. Note that APEX still assigns sample and resample values to these variables, although they logically should not affect the output. Demonstrating that the indices are zero serves as a quality check.

Runs 2 and 3 focused on the MPs, with Run 2 grouping them by ME (e.g., all "inside residence" MPs in Group 1, all "office buildings or hospitals" MPs in Group 2, etc.) and Run 3 grouping them by variable type (e.g., all AER MPs in Group 1, all DE MPs in Group 2, etc.). All other input variables were in Group 0.

Run 4 examined the physiological variables in detail, with body mass in Group 3, height in Group 4, etc. Age and sex are grouped separately (Groups 1 and 2) because they determine activity-diary selection and hence influence the set of MEs visited, thus affecting exposure and dose; all the other physiology variables can affect dose (i.e., intake of pollutant directly outside the body) but have no effect on exposure (i.e., concentration outside the body). Metabolic equivalent of task (MET) is one such variable: it is the activity-specific ratio of energy expenditure to the resting rate for that individual (e.g., the energy expenditure of running, cleaning the house, watching television, etc., relative to the person's resting baseline), which directly affect the profile's breathing ventilation rate and, thus, intake of pollutant.

The daily output statistics subject to Sobol analysis in these runs are presented in Table 2. For each daily statistic there were two "day types" of summaries over the simulation period: the maximum day and the average day (midnight to midnight). The maximum day was profile-specific, so it did not have to be the same day for different profiles. Each of the four APEX runs produced MEI and TEI estimates for all the output statistics in Table 2.

4 Results

The results for each of the four runs are presented in Tables 3, 4, 5, 6 and 7. These tables cover multiple daily statistics and day types, although due to space limitations not all combinations are shown. Within each (daily statistic, day-type) combination, the groups are ranked by decreasing TEI. Values are rounded to three decimal places. Refer to Table 1 for the specific variables in each group.

4.1 Run 1: influence of demographic variables

Table 3 presents the results for Run 1, which focused on the influence of demographic variables plus age and sex because they impact exposure through influencing selections of activity diaries. We placed the remaining variables in broad groups, and these included the other physiological variables which have no effect on exposure but impact dose.

The first section (AvgExp) of Table 3 reports the variables affecting the variation of average exposure over the simulation (the overall average of the individual daily averages). The MP values (MEI = 0.426, TEI = 0.441) and diary selection (MEI = 0.392, TEI = 0.410) together accounted for over 80% of the variation. The home tract (where the profile lives) was next in importance (MEI = 0.079, TEI = 0.108). Age and sex had some minor influence (about 3% cumulative MEI) through their impact on diary selection. The work tract and employment would be expected to have more influence for adults, but for the modeled age group (ages 5–18 years) only a small percentage (all age 16 or more) were employed, leading to little influence. The results confirm that the other physiological variables have no effect on exposure.

The influence of activity diaries manifests itself in two ways. Each diary is labeled by the age and sex of the person who supplied it. The diary sex must match that of the profile, and age has a ± 15% tolerance for matching. These effects of restricting the pool of available diaries are attributed to "age" and "sex" in the Sobol indices. The stochastic selection of specific diaries within those diary pools is attributed to "diary selection", whose effect (MEI = 0.392, TEI = 0.410) was much larger than the age and sex terms, indicating that the variability in behavior

Table 2 Daily output statistics used

Daily Statistic	Description
AvgExp	Average exposure for the day
Max1Exp	Maximum 1 h exposure for the day
Max8Exp	Maximum 8 h running-average exposure ending on the day
AvgDose	Average inhaled dose for the day
Max1Dose	Maximum 1 h inhaled dose for the day

Table 3 Sensitivity of selected exposure metrics to the groups of input variables in Run 1

Daily statistic	Day type	Main-effect index (MEI)	Total-effect index (TEI)	TEI rank	Group # and label
24-hour-average exposure (AvgExp)	Average	0.426	0.441	1	7 MP1–MP19
		0.392	0.410	2	6 Diary selection
		0.079	0.108	3	3 Home tract
		0.017	0.049	4	2 Age
		0.028	0.030	5	5 Other location variables
		0.011	0.025	6	1 Sex
		0.000	0.002	7	4 Work tract and employment
		0.000	0.000	8	8 Other physiological variables
		0.000	0.000	9	0 All variables not in other groups
Maximum 8-hour exposure (Max8Exp)	Average	0.614	0.646	1	6 Diary selection
		0.231	0.252	2	7 MP1–MP19
		0.041	0.061	3	3 Home tract
		0.030	0.059	4	2 Age
		0.018	0.038	5	1 Sex
		0.015	0.016	6	5 Other location variables
		0.000	0.003	7	4 Work tract and employment
		0.000	0.000	8	8 Other physiological variables
		0.000	0.000	9	0 All variables not in other groups
Maximum 1-hour exposure (Max1Exp)	Maximum	0.325	0.763	1	6 Diary selection
		0.073	0.460	2	7 MP1–MP19
		0.043	0.367	3	3 Home tract
		0.042	0.343	4	1 Sex
		0.017	0.209	5	2 Age
		0.000	0.028	6	4 Work tract and employment
		0.000	0.001	7	5 Other location variables
		0.000	0.000	8	8 Other physiological variables
		0.000	0.000	9	0 All variables not in other groups

We use conditional shading on the index values to better distinguish larger index values (darker shade) from smaller ones (lighter shade). We shade the MEI and TEI columns independently

MP microenvironmental parameter

Table 4 Sensitivity of selected dose metrics to the groups of input variables in Run 1

Daily statistic	Day type	Main-effect index (MEI)	Total-effect index (TEI)	TEI rank	Group # and label
24-hour-average dose (AvgDose)	Average	0.400	0.456	1	6 Diary selection
		0.185	0.215	2	8 Physiological variables
		0.120	0.190	3	2 Age
		0.093	0.156	4	1 Sex
		0.069	0.077	5	7 MP1–MP19
		0.018	0.034	6	3 Home tract
		0.004	0.005	7	5 Other location variables
		0.000	0.004	8	4 Work tract and employment
		0.000	0.000	9	0 All variables not in other groups
Maximum 1-hour dose (Max1Dose)	Maximum	0.243	0.485	1	2 Age
		0.230	0.360	2	8 Physiological variables
		0.106	0.328	3	6 Diary selection
		0.111	0.249	4	1 Sex
		0.010	0.146	5	7 MP1–MP19
		0.010	0.141	6	3 Home tract
		0.000	0.025	7	4 Work tract and employment
		0.000	0.000	8	5 Other location variables
		0.000	0.000	9	0 All variables not in other groups

We use conditional shading on the index values to better distinguish larger index values (darker shade) from smaller ones (lighter shade). We shade the MEI and TEI columns independently

MP microenvironmental parameter

within age-sex groups greatly exceeds the differences between those groups. The Sobol indices for any variable conditional on others do not include the effects of selections made earlier.

The second section of Table 3 (Max8Exp) presents results for the largest 8 h running-average exposure on each day, averaged over all simulation days for each profile. The main contrast with the AvgExp results, which were daily, was the increased importance of diary variables (MEI = 0.614, TEI = 0.646) with the 8-h results. This is reasonable since the diaries determine when the profiles are outdoors (where exposures are usually higher), and there is more variability in the fraction of outdoor time over shorter time windows. Home tract is a constant over time for each profile and its effect (MEI = 0.041, TEI = 0.061) here was smaller than it was for AvgExp, which indicates that the other factors were producing greater variability.

The third section of Table 3 (Max1Exp) presents results for the largest hourly exposure for each profile. The MEI was large (0.763) only for diary selection. The peak O_3 concentrations are at fixed times, so the variation in maximum hourly exposure depends largely on where the diary places the profile during those times. The top five groups (by TEI ranking) all exhibited much larger total indices than their corresponding main indices, indicating the dominance of interaction terms. Age, sex, and home tract had similar MEIs to those in AvgExp and Max8Exp, but they all had much larger TEIs in Max1Exp. This indicates that these variables matter only if that profile is assigned other stochastic variables with certain values at the same point in time. The determination of which interactions (combinations of variables) drive the exposure variability of short-term exposures is outside the scope of this work.

Table 4 shows the Run 1 results for average inhaled dose. Dose is the product of air concentration (that is, exposure) and breathing ventilation rate, both of which change with time, so dose is also a time-series at the diary-event level for each profile. This definition of dose is not normalized by body weight, so heavier persons tend to have larger intake doses. The variable groupings are the

Table 5 Sensitivity of daily-average exposure to the groups of input variables in Run 2

Day type	Main-effect index (MEI)	Total-effect index (TEI)	TEI rank	Group # and label
Aver-age	0.559	0.574	1	0 All variables not in other groups
	0.398	0.408	2	1 AER, DE, PR indoor-residences
	0.018	0.020	3	3 AER, DE, PR indoor-school
	0.008	0.009	4	8 PR, PE in-vehicle
	0.002	0.002	5	4 AER, DE, PR indoor-stores/other
	0.001	0.002	6	2 AER, DE, PR indoor-office buildings/hospitals
	0.001	0.002	7	6 PR outdoor-general
	0.000	0.000	8	7 PR outdoor-near road
	0.000	0.000	9	5 AER, DE, PR indoor-restaurants
Max-imum	0.311	0.680	1	0 All variables not in other groups
	0.306	0.613	2	1 AER, DE, PR indoor-residences
	0.004	0.120	3	6 PR outdoor-general
	0.001	0.018	4	3 AER, DE, PR indoor-school
	0.000	0.010	5	2 AER, DE, PR indoor-office buildings/hospitals
	0.000	0.009	6	4 AER, DE, PR indoor-stores/other
	0.001	0.002	7	8 PR, PE in-vehicle
	0.000	0.001	8	5 AER, DE, PR indoor-restaurants
	0.000	0.001	9	7 PR outdoor-near road

We use conditional shading on the index values to better distinguish larger index values (darker shade) from smaller ones (lighter shade). We shade the MEI and TEI columns independently

AER air-exchange rate, *DE* hourly decay rate, *PR* proximity factor, *PE* penetration factor

Table 6 Sensitivity of daily-average exposure to the groups of input variables in Run 3

Day type	Main-effect index (MEI)	Total-effect index (TEI)	TEI rank	Group # and label
Average	0.559	0.574	1	0 All variables not in other groups
	0.380	0.391	2	2 DE in indoor MEs
	0.033	0.037	3	1 AER in indoor MEs
	0.006	0.009	4	3 PR in all MEs
	0.006	0.007	5	4 PE in vehicles
Maximum	0.311	0.680	1	0 All variables not in other groups
	0.061	0.385	2	1 AER in indoor MEs
	0.018	0.354	3	3 PR in all MEs
	0.178	0.220	4	2 DE in indoor MEs
	0.001	0.002	5	4 PE in vehicles

We use conditional shading on the index values to better distinguish larger index values (darker shade) from smaller ones (lighter shade). We shade the MEI and TEI columns independently

DE hourly decay rate, *ME* microenvironment, *AER* air-exchange rate, *PR* proximity factor, *PE* penetration factor

same as in Table 3. The two cases shown are for the longest and shortest averaging times: the overall simulation average, and the highest single-hour inhaled dose for each profile.

Table 7 Sensitivity of selected dose metrics to the groups of input variables in Run 4

Daily statistic	Day type	Main-effect index (MEI)	Total-effect index (TEI)	TEI rank	Group # and label
24-hour-average dose (AvgDose)	Average	0.423	0.492	1	0 All variables not in other groups
		0.120	0.190	2	1 Sex
		0.093	0.156	3	2 Age
		0.094	0.112	4	3 Body mass
		0.068	0.078	5	7 Breathing vs. age coefficients
		0.069	0.077	6	16 MP1–MP19
		0.018	0.021	7	6 Resting metabolic rate
		0.002	0.004	8	8 Maximum O_2 consumption
		0.000	0.001	9	11 Maximum possible O_2 debt
		0.001	0.001	10	9 Energy-conversion factor
		0.000	0.001	11	13 Slope of fast O_2 debt recovery
		0.000	0.000	12	15 Activity-specific MET values
		0.000	0.000	13	10 Recovery time for O_2 debt
		0.000	0.000	14	14 Breathing vs. body mass coefficients
Maximum 1-hour dose (Max1Dose)	Maximum	0.243	0.485	1	2 Age
		0.120	0.354	2	0 All variables not in other groups
		0.111	0.249	3	1 Sex
		0.136	0.173	4	3 Body mass
		0.010	0.146	5	16 MP1–MP19
		0.000	0.070	6	15 Activity-specific MET values
		0.055	0.064	7	7 Breathing vs. age coefficients
		0.019	0.041	8	8 Maximum O_2 consumption
		0.000	0.031	9	14 Breathing vs. body mass coefficients
		0.008	0.019	10	13 Slope of fast O_2 debt recovery
		0.006	0.013	11	11 Maximum possible O_2 debt
		0.003	0.012	12	6 Resting metabolic rate
		0.000	0.001	13	10 Recovery time for O_2 debt
		0.000	0.001	14	9 Energy-conversion factor

We use conditional shading on the index values to better distinguish larger index values (darker shade) from smaller ones (lighter shade). We shade the MEI and TEI columns independently

MP microenvironmental parameter, *O_2* oxygen, *MET* metabolic equivalents of task

The physiological variables matter for dose, as they directly affect the breathing rate. Age (MEI = 0.120, TEI = 0.190) was more important than sex (MEI = 0.093, TEI = 0.156) in accounting for variability in AvgDose. For the Max1Dose, age (MEI = 0.243, TEI = 0.485) and sex (MEI = 0.111, TEI = 0.249) both were elevated in

importance compared to their AvgDose effects. For both dose metrics (AvgDose and Max1Dose), the same four groups (age, sex, diary selection, and physiological variables) were the most important in both MEI and TEI.

The other large change for dose variability relative to exposure variability was the reduced importance of the MPs. This indicates that indoor time is of less importance in variability of dose than it is for variability of exposure. Breathing rates are generally higher when outdoors, giving increased relative importance to outdoor events. Diaries are important in determining whether a profile spends a lot of time outdoors (hence their high importance).

4.2 Run 2: influence of microenvironmental parameters stratified by microenvironment

Run 2 uses the same model settings as Run 1, including random-number seed, but with different variable groupings (see Table 1) to focus on the collective effect of MPs for each ME. The exposure results for the daily (24 h) average from Run 2 are presented in Table 5. See Section D of the Online Resource for the distributions assigned to these MPs. Values for each profile and each ME are sampled independently. AER was resampled daily, while DE was sampled once. PR was sampled daily, except in vehicles and outdoors near roads were sampled once. PE was used only in vehicles and sampled once. The distribution for DE was the same in all indoor MEs.

Group 0 included diary selection and, while influential, that group is not of interest for examining the effects of MPs by ME. The indoor-residence ME (MEI = 0.398, TEI = 0.408) dominated the others in its influence on average exposure (the top section of Table 5). Much more time is spent in the home (an average of nearly 18 h/day according to the diaries) compared to any other ME. The second section of Table 5 reports effects on the maximum daily exposure per profile. Here, the MEIs tended to be smaller, but TEIs larger, than for the average day. Group 6 (outdoor-general) had a substantial effect (TEI = 0.12) on maximum daily exposure (unlike average exposure), but still considerably less effect than Group 1 (indoor-residence; TEI = 0.613), again due to relatively large amounts of time spent indoors at home.

Since this run is for (primarily) school-age children, the presence of MP for schools is expected, but those had relatively little effect (TEI = 0.018) on exposure. The coefficient of variation for AER was much lower for schools (0.42) than for homes (0.60–1.5, depending on outdoor temperature and air conditioning). Children's exposures also exhibit little variation when they are in school. Overall, while exposures at school are important considerations for children, schools were not the driver of exposure differences between children (indoor-residences and to a certain extent outdoor-general were the drivers). Vehicles and other MEs each account for 1% or less toward the overall variability in exposure.

4.3 Run 3: influence of microenvironmental parameters stratified by variable type

The results of Run 3 are shown in Table 6. Run 3 splits MPs by variable type. Since Group 0 contained the same variables as in Run 2, the indices were the same as before. The top section of Table 6 shows that DE was the dominant type of MP for the overall average exposure (MEI = 0.380, TEI = 0.391). The bottom section of Table 6 presents the results for the maximum day of exposure, and while DE still had the largest main effect (MEI = 0.178) among MPs, the total effects for AER (TEI = 0.385) and PR (TEI = 0.354) were larger than that of DE (TEI = 0.220).

The large TEIs for AER and PR for maximum daily exposures (relative to their MEI) indicate strong interactions with other variables. For example, the interaction terms that include AER accounted for 32.4% (that is, TEI-MEI = 0.385–0.061, expressed as a percentage) of total variation in the maximum day's exposure, and the PR interaction terms were even greater at 33.6%. Since interaction terms contribute equally to all the variables in the interaction, AER and PR are either interacting with each other or with diary selection, or both. The evaluation of specific interaction effects has not been coded into APEX.

4.4 Run 4: influence of physiological variables on dose

Run 4 split the group of physiological variables, as they can affect dose. Here, each relevant physiological variable was a separate group (totaling 15), with one combined group for all MPs and one group for all other variables, making 17 groups in all. The role of these specialized physiological variables is discussed in Chapters 7 and 10 of U.S. EPA (2019b). Group 0 included variables not applicable to O_3 and certain physiological-response variables such as lung-function loss that cannot alter the inhaled dose. Height, body surface area, and blood volume (Groups 4, 5, and 12) also have no effect on inhaled dose (in APEX) but we included them as test cases of performance; however, given that their effect indices were 0 for all output variables, they are excluded from the results in Table 7.

Table 7 compares directly with Table 4. The age and sex results are the same in both tables. Here, Group 0 contains all the variables from Groups 0, 3, 4, 5, and 6 from Table 4. Among the physiological variables (apart from age and sex), body mass (MEI = 0.094, TEI = 0.112) and the regression coefficients for breathing ventilation as a function of age (MEI = 0.068, TEI = 0.078) were the most

important for the AvgExp output. The resting metabolic rate (MEI = 0.018, TEI = 0.021) was of minor importance, and the rest of the physiological variables contributed very little.

The second section of Table 7 (Max1Exp) also shows body mass (MEI = 0.136, TEI = 0.173) to be the most important physiological variable. Next in total effect was the activity-specific MET values (MEI = 0.000, TEI = 0.070). Note that MET is conditional on the type of activity, so variations in activity are attributed to the diary selection, and the Sobol indices for MET reflect only the variation in dose within given activities. The MEI was negligible for MET because in isolation most of the variation in MET occurs during passive activities or away from the worst air-quality. For MET to matter it must be paired with high-ventilation activities and poor air quality. Therefore, the interaction terms for MET were far greater than the main effect.

For children, age and sex matter more than MET in determining extreme intake dose because a young child aged 5 or 6 years cannot match the breathing ventilation volume of a teenager. The MET index was smaller than might be expected for another reason: a child exercising outdoors is likely to do that on multiple days. The Max1-Dose output selects the highest intake dose over these events, which (if the activity is the same) is likely to be the one with the highest MET. Thus, the MET variability between children on these selected events is less than the overall variation in MET.

4.5 Los Angeles example

We repeated the same four APEX runs but in a five-county area centered on Los Angeles, California and for June–August 2010. This study area includes multiple air basins separated by mountains, so the O_3 levels show much greater geographical variation than in Chicago. The results (not shown) indicate that the home tract had substantially more importance in Los Angeles than in Chicago, but all other variables were close to their rankings in the Chicago runs. The rankings of the variables in Tables 5 through 7 also aligned closely in both study areas, indicating that the same ME and physiological variables were influential in both study areas.

5 Discussion

Exposure models such as APEX quantify the intersection of people and pollutants. APEX has supported regulatory action at EPA for nearly twenty years (e.g., U.S. EPA, 2007, 2008, 2010, 2014, 2018 and 2020) The APEX Sobol methodology has been validated using known functions (see Glen and Isaacs 2012). In the present runs, certain results can be anticipated due to the model structure. For example, the physiological variables have indices of zero for exposure but not for dose. Another check is that the same variables have the same MEI and TEI regardless of the grouping of other variables; for example, the indices for age and sex in Table 7 are the same as in Table 4. Because we chose the four runs to highlight different groupings, there are just a few such examples. Other tests have confirmed that the indices for a group are completely unaffected by any change in other groupings, provided the same overall random seed is used for reproducibility (otherwise, the indices will show stochastic differences).

While the model accepts many inputs and can produce myriad outputs of exposure metrics, Sobol SA can illuminate which inputs are most influential over the desired output metrics. Utilizing simulations of the ozone season in Chicago and Los Angeles, we have demonstrated that diary selection and the MP variables (namely, AER, DE, and PR) for indoor residences are the main drivers of variability of daily-average exposures for children, which is not surprising as those parameters largely determine exposure location and the air quality there, and children in the diary database spend on average 74.4% of their time at home. Diary selection has similar importance for dose, but the MPs are reduced in influence and are replaced by physiological variables which impact pollutant intake. Age, sex, and body mass also have a degree of importance in dose estimates. Age and sex are assigned first and have relatively high indices; they influence both the time spent in each ME (through the diaries) and the breathing ventilation rate. The body mass reflects variation only within given age-sex combinations, yet it still accounts for 10–20% of the variation in dose (depending on the dose metric). In observing similar rankings of the importance of model variables utilizing two different modeling scenarios, this suggests that the rankings are features of the model structure and pollutant rather than being driven by idiosyncrasies of one scenario's data. Improvements in the characterization of these variables of exposure factors, through refined input data and/or model algorithms, would have substantial benefit in estimating the variability in exposure and the frequency of high-end exposures, the latter being particularly important in regulatory contexts for human health. It remains to be seen how important employment status and work location would be for a population of workers.

For the inhaled dose, we additionally expected breathing ventilation-age regression terms and resting metabolic rate to be influential. However, these had relatively low influence, each accounting for less than 8% of the variation in dose, although breathing rates depend on several variables and the Sobol indices give an indication of the (low)

importance of each. A somewhat surprising result is the minimal effect of MET on daily-average dose. The influence of MET as shown here reflects only the variation in breathing ventilation rate for a fixed activity; any variation in activities is attributed to the diaries. The MET index reflects the variability in energy consumption for a fixed activity type, given age, sex, body mass, and resting metabolic rate. This accounted for 7% of the dose variability for the maximum hour, but for longer averaging times many random samples of MET are being averaged, which reduces their influence.

For the physiological variables, our testing quantified the importance of the variables as a group as well as the importance of the individual variables, and a comparison of the breakdown of those indices reveals the importance of interaction terms. For daily exposures, the sums of the individual indices of physiological variables (MEI = 0.183, TEI = 0.218) were very close to the indices of the group of physiological variables (MEI = 0.185, TEI = 0.215) this is consistent with the expectation that splitting the variables may decrease (but never increase) the total MEI and increase (but never decrease) the TEI, due to the way the interactions are tallied. The interaction terms for average dose are likewise quite small. For maximum hourly dose, on the other hand, while the sum of the individual MEIs of physiological variables was close to the MEI of the group (0.227 and 0.230, respectively), the TEIs were quite different (0.425 and 0.360, respectively), indicating substantial higher-order interactions. For example, a third-order interaction between two group members with a third variable outside the group is counted once if the group is merged, but it is counted twice if the group is split. Splitting the physiological variable group added 0.065 (about 20%) to the total effects of that group, reflecting the importance of higher-order interactions.

The Sobol indices measure the importance of population variability but not uncertainty (unless incorporated into the input distributions). For example, a few activities have MET distributions set to a point value with no variability, so those contributions to the MET Sobol indices are zero. This does not mean that the MET value is correct, or that it has no effect on dose. Any shift in the input point value would create a corresponding shift in the dose distribution that cannot be estimated from the current runs. Instead of using a point input, one could supply a distribution that captured the uncertainty. The Sobol indices would then quantify the importance of that uncertainty.

There are several ways to characterize the importance of uncertainty in input variables. One option, which is compatible with Sobol analysis, would be to combine variability and uncertainty into one distribution. Some variables such as age and sex effectively have no uncertainty. Most variables are not as well characterized. For example, the average MET value for certain activities could be off by 20% or more, but most such activities occur rarely, so the influence of one activity is small. A 20% error in the average AER or DE (if such an error existed) would matter much more due to their larger Sobol indices and because those variables operate throughout the simulation.

Refinements to the APEX inputs could reduce uncertainty but not variability as that is a characteristic of the population. This work can help prioritize the places where refinements would be most productive. Currently, AER in APEX is dependent on outdoor temperature and the use of air conditioning, but it could be characterized by house age, type, or size, or by creating autocorrelation across days in AER. The DE distributions could be treated similarly. The PR could be geographically localized with suitable information on spatial variability within the study area. Models such as APEX can use far more data than it is practical to collect, so the prioritization of data needs through SA may lead to more efficient allocation of limited resources.

While the Sobol indices measure variability and could in principle be indicators of very low extremes (not just high extremes), in practice exposures and doses tend to be lognormal and are skewed to the right, so the main drivers of variance are in the upper tail. Thus, variables (or groups) that create high-end exposures or doses will have relatively high Sobol indices. The output could be log-transformed before applying the Sobol analysis, but this is not desirable because then the lower-tail exposures would drive the indices as much as the upper-tail exposures, making the prioritization of inputs more difficult.

The SA methodology used here potentially is applicable to a wide variety of complex stochastic models. It is not necessary (or possible) in APEX to sample all parts of the model input hyperspace to determine the influential variables. Nearly all the variation in APEX comes from a relatively small number of random choices, with the vast majority contributing very little to variability. This has some similarity to principal components analysis, in which a many-dimensional system can be reduced to a much smaller number of influential dimensions by an appropriate rotation in hyperspace. The number of profiles needed for stable indices depends on the effective (rather than nominal) dimensionality. If more variables were sampled more frequently in APEX, it could require over one million random samples to define one profile, but the same SA method would work without any alteration. Furthermore, without a fundamental change to the model structure it is unlikely that more profiles would be needed to obtain stable estimates of the sensitivity indices.

There are no applications of Sobol's method to probabilistic inhalation exposure models with which to compare our results. In another application to a complex model, Mokhtari et al. (2006) applied seven sensitivity analysis

techniques to a multipathway, probabilistic human exposure model for pesticides, a simplified version of the model SHEDS (Zartarian et al. 2000). The output variable of interest was the total exposure, from inhalation and dermal exposures and ingestion pathways. They singled out the Fourier amplitude sensitivity test (FAST) (Helton and Davis 2002) and Sobol's method as more advanced methods, and they focused their paper on Sobol's method since the FAST method has limitations with respect to applicability to models with large numbers of inputs. They listed 26 probabilistic input variables, two of which stood out as being the most important: the fraction of pesticide available for transfer from surface to body or hands and the fraction of pesticide residue that dissipates daily. Interaction effects also contributed to a large part of the variance of the estimated exposure. It is fairly typical of applications of Sobol's method to complex models that only a few input variables contribute to the majority of the output variance (for example, Karunanidhi et al. 2021; Kumar et al. 2020; Nossent et al. 2011). In our application, we also found that a small number of the stochastically sampled inputs contribute most of the variability in the output.

6 Conclusions

Sobol analysis of APEX exposure and dose output variables demonstrates that a small number of the stochastically sampled inputs contribute most of the variability in the output. The selection of activity diaries is important for both exposure and dose, with even more effect when looking at the maximum day rather than the average day. For this reason, APEX would benefit from the collection of additional activity diaries, allowing for more precise targeting of diaries to each profile. The MP values which characterize the O_3 concentrations in MEs are also important for the exposure metrics. Some MPs such as AER are dependent on the type of housing and climate in the study area, so the collection of site-specific data for these variables would improve the model. The home-tract location, which in a default APEX run is created by sampling from Census data, has a modest effect in Chicago, but it could be larger is a less homogeneous area. Age and sex, assigned based on Census sampling, and body mass, sampled from national survey data, also have modest effects on dose. With the division of MET into about 300 activity-specific distributions, the variability in MET within activities is no longer a major factor in the dose calculations, especially over longer averaging times. By contrast, the variability across activities is ascribed to diary selection, and is much larger. Finally, the physiological variables that most affect dose are age, sex, body mass, and (on short time scales) MET, with all other randomly sampled variables contributing relatively little to the overall variability in exposure or dose.

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Data availability The APEX model, documentation, and default input files are in the "APEX52 installer", at https://www.epa.gov/fera/download-trimexpo-inhalation-apex. The additional files needed to run the Sobol simulations discussed in the paper can be found in "APEX5.2 input files for Sobol sensitivity analysis" at the same location.

Code availability The APEX model is written in Fortran and freely available for download and use as an executable (.exe) file from EPA: https://www.epa.gov/fera/download-trimexpo-inhalation-apex. Model inputs are text files, and default inputs as well as an example case study are available at the same website. These files, along with the source code, are packaged up in a simple installer approximately 100 MB in size. APEX has been tested on Windows and Linux operating systems, and modern computers typically easily satisfy the RAM and processor requirements of the model. Detailed documentation of APEX also is available at the same site.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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