Survey of the Use of (Quantitative) Structure Activity Relationship [(Q)SAR] Tools and Approaches at Health Canada and Partner Departments

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Survey of the Use of (Quantitative) Structure Activity Relationship [(Q)SAR] Tools and Approaches at Health Canada and Partner Departments

Report Prepared for the Task Force on Scientific Risk Assessment (TFSRA)

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EXECUTIVE SUMMARY

(Quantitative) Structure Activity Relationships [(Q)SARs] represent a continuum of different methods for predicting the activities and properties of untested chemicals based on their structural similarity to chemicals with known activities or properties. (Q)SAR tools and approaches have a long history of use in a range of academic and industrial settings, such as in pharmaceutical and pesticide design. More recently, regulatory agencies and international organizations have shown an increasing interest in (Q)SAR development and application to lessen the reliance on animal testing and increase the efficiency of the prioritization of chemicals for assessment and of risk assessments. Regulatory agencies have also begun to investigate combining empirical data, data from biochemical and cellular screening assays, (Q)SAR predictions and other data in Integrated Approaches to Testing and Assessment (IATA). IATA bring together data from a variety of tools in a weight of evidence approach that may make it possible to refine, reduce or replace selected in vivo tests and focus more rapidly on specific hypotheses while maintaining the scientific defensibility of human health and environmental risk assessments.

The current survey was designed to enable Health Canada to gain a better understanding of the current or planned use of (Q)SAR tools and approaches in risk assessment activities under various mandates across the department. The survey included 21 questions covering each respondent's program information, current and planned usage of (Q)SAR, tasks/projects for which (Q)SAR is applicable, present applications, predicted endpoints, types of approaches, specific tools, learning and collaboration, issues and concerns, and other groups to contact. The survey was sent to 23 individuals at 19 organizations within Health Canada and one key partner department, Environment Canada, with detailed responses received from 15 organizations.

Over half of the respondents indicated that they were currently using (Q)SAR tools and approaches in their work and the majority of those who do not currently use (Q)SAR are planning to use it in the future. Most of the current users of (Q)SAR apply it to identifying data requirements and to hazard assessments, along with grouping chemicals for assessment. Most specific applications relate to the prediction of toxicity, physical-chemical properties, and metabolism. For those not currently using (Q)SAR, potential applications included mammalian/human toxicity prediction and hazard assessment, prediction of physical/chemical properties, grouping of chemicals, identification of data requirements, and providing a basis for regulatory decisions.

Of the respondents currently using (Q)SAR tools and approaches, a similar number reported using specific (Q)SAR models, compared to those using chemical categories and analog approaches. For those respondents using (Q)SAR models the most frequently used model was TOPKAT followed by the Organization for Economic Cooperation and Development (OECD) (Q)SAR Toolbox. Models, chemical categories and analog approaches are most often used to predict human health-related toxicological endpoints with carcinogenicity, genotoxicity/mutagenicity as the most commonly predicted specific endpoints.
Of the eight groups who responded to the question about current difficulties and concerns related to the implementation of (Q)SAR tools and approaches, six reported encountering difficulties, while 6/11 groups who answered the question about potential future difficulties anticipated encountering difficulties accessing and implementing (Q)SAR. The most frequently cited current and potential difficulty with obtaining and implementing (Q)SAR tools and approaches relates to the need for training and a lack of knowledge/understanding of the various tools. Other sources of difficulties identified included the costs and associated lengthy and complicated contract/approvals processes for procuring software.

Respondents showed a widespread interest in learning about (Q)SAR tools and approaches with most respondents interested in a range of different learning activities (i.e., seminars, courses, workshops). A majority was also currently collaborating on (Q)SAR projects or was interested in future collaborations. Collaborative activities ranged from sharing software to involvement in joint projects to further the utility of (Q)SAR. These collaborative efforts are occurring across programs within the department, between departments (i.e., Health Canada and Environment Canada), and with other national/international agencies (i.e., Organization for Economic Cooperation and Development, European Chemicals Agency, United States Environmental Protection Agency, Canadian Centre for Environmental Modelling).

Based on an analysis of the results of the survey, the survey team developed a set of short, medium, and long-term recommendations for consideration by the TFSRA. The short-term recommendations are a set of projects that are estimated to take six months to a year to complete and include establishing a (Q)SAR working group, developing inventories of (Q)SAR tools, databases, training sessions, and (Q)SAR projects, as well as creating a BEE Workspace to organize/house the inventories and other information on (Q)SAR. Projects and activities in the medium-term recommendations include collaborative software purchases, software sharing agreements, joint training, and the identification of case studies for sharing on the BEE Workspace. These activities could be completed in one to two years. Recommendations for long-term projects which would require 2-3 years to complete include the development of (Q)SAR guidance documents, developing chemical databases and new predictive tools for (Q)SAR, and establishing a (Q)SAR expert advisory group to provide advice on challenging issues associated with the application of (Q)SAR in various programs across the department.
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1.0 INTRODUCTION

The inter-relationship between a chemical’s structure, physical-chemical properties and toxicity has been recognized since the 1860s, when Cros noted how the toxicity of primary aliphatic alcohols varied with solubility (Cros, 1863; Gramatica, 2008). At the beginning of the 1900s, Meyer (1899) and Overton (1901) subsequently related the narcotic effect of a certain class of organic compounds to lipophilicity (olive oil/water partition coefficient). This observation led to the development of the Meyer–Overton rule, which provided the foundation from which numerous researchers have since worked to develop the (Quantitative) Structure Activity Relationship [(Q)SAR] models used today that incorporate the systematic use of mathematical models and a multivariate approach (Hansch, 1991; Hansch et al., 1995; Gramatica, 2008; Lipnick, 1995). As (Q)SAR models have advanced, more mechanistic approaches have been adopted, linking (Q)SAR model descriptors to mechanism of action of the substance at the molecular target (Bradbury 1994, Russom et al., 1997).

Predictive toxicity tools based on (Q)SAR have been applied for many years in a range of academic and industrial fora, such as in pharmaceutical and pesticide design. Over the past 10 years there has been an increasing interest from regulatory agencies worldwide, including Health Canada, in the application of predictive methods such as (Q)SAR. This is a result of an interest in lessening the reliance on conventional animal testing and increasing the efficiency of assessments, especially in light of expanding mandates to address inventories of large numbers of data poor substances (Cronin et al., 2003; OECD, 2007). For example, (Q)SAR was a key component of the tools developed for categorization of the Domestic Substances List (DSL) by Health Canada and Environment Canada. (Q)SAR is also playing an important role in the follow-up to categorization, the Chemicals Management Plan (CMP), as phase II of the CMP will involve the assessment of the human health and environmental risks of prioritized DSL substances, many of which have little or no conventional data. International regulatory agencies face similar challenges and are working to expand their approaches to risk assessment into (Q)SAR and other alternative methods (Benigni et al., 2007; Richards, 2006). In particular, (Q)SAR will likely be employed extensively under the Registration, Evaluation, Authorization and Restriction of Chemicals overseen by the European Chemicals Agency (ECHA). At the same time, there have been on-going developments in predictive technology, particularly in terms of increased access to large electronic databases of test results on which to base predictions. Agencies, such as the Organization for Economic Cooperation and Development (OECD), have invested significant effort in furthering the development and dissemination of (Q)SAR tools and associated databases.

(Q)SAR exists at the intersection of chemistry, statistics, and biology and encompasses a variety of techniques for predicting the biological activities, physical-chemical properties or other characteristics of untested chemicals based on structural similarity to chemicals with known activities or properties. There are numerous different ways of defining structural similarity, such as the presence/absence of defined structural fragments, the arrangements of atoms and bonds in molecules (e.g., connectivity), structural descriptors (e.g., electronic, hydrophobic, steric, etc.), physical-chemical properties (e.g., log P, solubility, etc.) and other characteristics.
The parentheses around the word, “Quantitative”, signify that these techniques can involve either qualitative approaches to extrapolating from similar chemicals, also known as Structure-Activity Relationships (SAR), or estimates based on quantitative (statistical) methods which are referred to as QSAR. Examples of the types of properties that can be predicted using (Q)SAR include toxicity endpoints (e.g., mutagenicity, carcinogenicity, etc.), ecotoxicity endpoints (e.g., LC$_{50}$, NOAEC, etc.), other biological properties (e.g., metabolism/ transformation products, efficacy, etc.), environmental properties (e.g., fate/partitioning, etc.), and physical-chemical properties (e.g., log P, solubility, vapour pressure, boiling point, etc.).

(Q)SAR tools and approaches represent a continuum of methods for relating chemical structure to activity. These methods and tools range from simple extrapolations of the properties of a structural analog chemical to the chemical of interest; the identification of a group (category) of structurally similar chemicals and the interpolation/extrapolation of properties of the data rich group members to the data poor members (e.g., read-across, trend analysis); SAR models that predict activity based on libraries of structural alerts, decision trees and/or rules; and QSAR models that use databases of chemicals with known activities to develop statistical algorithms for predicting activities of untested chemicals.

Regulatory agencies, including Health Canada, are currently exploring processes for combining (Q)SAR predictions, empirical data, and data from other predictive methods in Integrated Approaches to Testing and Assessment (IATA). Unlike traditional chemical risk assessment approaches which rely largely on empirical data from conventional in vivo and in vitro studies, IATA bring together data from in vivo studies, high throughput screening assays (HTS), toxicogenomic studies, (Q)SAR predictions, toxicokinetic studies, mechanistic studies, exposure estimates and other sources in a weight of evidence approach to determine the potential need for additional in vivo/in vitro testing and/or develop conclusions regarding the potential human health and ecological risks of a chemical. IATA may make it possible to refine, reduce or replace selected in vivo/in vitro tests and focus more rapidly on specific hypotheses about a chemical while maintaining the scientific defensibility and human health and environmental protective ness of chemical risk assessments. The implementation of IATA could eventually bring about reductions in laboratory animal usage, as well as reductions in the time required for and costs of the testing and assessment of chemicals. The US National Academy of Sciences has recently presented a vision of IATA which is outlined in the report, *Toxicity Testing in the 21st Century a Vision and a Strategy* (NAS, 2007).

In light of the rapid expansion of the applications of (Q)SAR tools in government agencies, the Health Canada Task Force on Scientific Risk Assessment (TFSRA) perceived the need to gain a better understanding of the current or planned use of predictive methods in risk assessment activities under the various mandates across Health Canada. Consequently, a survey was conducted across departmental programs as well as in an important Health Canada partner department involved in the risk assessment of chemicals, Environment Canada.

The results of this survey are summarized in this report. It is anticipated that the observations included herein will serve to enhance communication and sharing of information across Health Canada on the application and development of (Q)SAR methodology. An increased understanding of how (Q)SAR tools may be used in human health risk assessment may foster development of common approaches for their incorporation in risk assessment products designed to meet the range of mandates delivered by the department and/or lead to potential sharing of (Q)SAR resources. The information presented in this report may also contribute to the development of recommendations for opportunities for learning for Health Canada scientists and enhanced collaboration across various programs.
2.0 METHODS

The survey contained 21 questions that ranged from simple yes/no check boxes to requests for more detailed responses. The questions were divided into groups covering: respondents’ program information; current and planned usage; tasks/projects for which (Q)SAR is considered to be applicable; present applications; predicted end points; approaches; specific tools; potential learning opportunities and collaborations; issues or concerns; and additional groups who could be contacted for input.

Relevant risk assessment programs were identified by the (Q)SAR project team and subsequently contacted regarding participation in the survey. Each group contacted that wished to participate in the survey identified contact individuals for their programs. The survey was e-mailed to the program contacts and returned to the survey coordinator once completed. In total 30 groups were initially identified including 27 from Health Canada and 3 from Environment Canada. The Health Canada branches or agencies contacted included the Healthy Environments and Consumer Safety Branch (HECSB), the Pest Management Regulatory Agency (PMRA), the Health Products and Food Branch (HPFB), and the Hazardous Materials Information Review Commission (HMIRC). The Environment Canada responses were consolidated from the Ecological Assessment Division, Science and Technology Branch and the New Chemicals Evaluation Section, Science and Technology Branch.

The survey questionnaire was pilot tested with volunteers from the New Substances Assessment and Control Bureau (HC) and the Ecological Assessment Division of Environment Canada. Feedback and suggestions were collected from the pilot and the questionnaire modified accordingly. The final survey was e-mailed to all identified contact individuals and the responses collected. Generally, program contacts submitted one collated response for each program to the survey coordinator. The survey responses were examined individually and then rolled up into an overall response table for each question. From an analysis of the responses, general conclusions were made and recommendations developed. The survey questionnaire is attached in Appendix I, the groups surveyed are listed in Appendix II, and contact information for the groups who responded to the survey is listed in Appendix III.
3.0 RESULTS

3.1 Survey Response Rate

The (Q)SAR survey was sent to 23 individuals at 19 organizations, some of which contained multiple directorates or units (Appendix II). Detailed survey responses were received from 15 organizations, three recipients did not respond, and one group indicated that they did not deal with (Q)SARs. This was judged to be an acceptable response rate based on experience with similar intradepartmental surveys. Also, the number and variety of organizations that responded were considered to provide a representative picture of the use of (Q)SAR in Health Canada and a key partner department, Environment Canada. Responses to the survey from organizations that responded and indicated that they use (Q)SARs or will potentially use them in the future are discussed in Sections 3.2 to 3.5 of this survey report.

3.2 Current & planned use of (Q)SAR

(Survey Questions 3, 4, and 5)

Survey questions 3, 4, and 5 were designed to identify whether groups are currently using (Q)SAR, whether they are planning on using them in the future, and what is each group’s time frame for the implementation of (Q)SAR tools and approaches. Seven out of the 15 respondents stated that they were currently using (Q)SAR-like tools and applications in their work. Six of the eight respondents who currently do not use (Q)SARs have given strong indications that they plan to include (Q)SARs in their work in the future, whereas the remaining two indicated only a possible interest. Of the six that indicated an interest in using (Q)SARs, most did not mention a specific time frame to start using these tools, whereas two groups mentioned one to two year time frames. Several groups talked about using specific tools when they become available and the need for support and training in conjunction with the use of (Q)SARs.

3.3 Applications of (Q)SAR Tools and Approaches

(Survey Questions 6, 7, and 8)

The purpose of questions 6, 7, and 8 was to obtain information on current and potential applications of (Q)SAR tools and approaches at Health Canada. Based on the responses to question 3, seven groups at Health Canada and the Science and Technology Branch of Environment Canada are currently using (Q)SAR tools and approaches. Respondents who are currently using (Q)SAR tools and approaches were asked to provide details on the types of applications and the biological activities and/or properties predicted. This information is summarized in Table 3.1.
Out of the seven groups who are currently using (Q)SAR, most indicated they are using it for hazard assessment and identifying data requirements (i.e., for assessments), with grouping of chemicals and regulatory decisions, as other more frequent applications. This likely relates to the fact that the mandates of many of these groups involve the human health hazard and/or risk assessment of chemicals. Similarly, most current users of (Q)SAR are predicting toxicity (human health related) with physical-chemical properties and metabolism as other frequently predicted properties and activities. Two groups, the New Substances Assessment and Control Bureau, HECSB and the Ecological Assessment Division, Environment Canada use (Q)SAR for ecotoxicity and environmental fate/exposure parameters which is probably reflective of their respective mandates compared to those of other groups. These same two groups also use (Q)SAR in the most varied range of applications and for predicting the most varied range of activities and properties.

Respondents who are not currently using (Q)SAR and even some of those who do use these tools and approaches also provided information on tasks or projects where (Q)SAR could potentially be applicable. The key tasks/projects are outlined in Table 3.2. Although respondents identified a range of tasks/projects for (Q)SAR, some of the most common potential applications included mammalian/human toxicity prediction and hazard assessment, prediction of physical/chemical properties, grouping of compounds, identification of data requirements, and regulatory decisions. Some fairly unique potential applications included the use of (Q)SAR to assess biological activity/efficacy of drugs, to assess nanotechnological substances, to elucidate the mutagenic potential of impurities in new drug products, to qualify leachables and extractables in parenteral and ophthalmic drug products, to guide the application of the threshold of toxicological concern (TTC) for cosmetics and consumer products, and to estimate toxicity for mixtures.

Table 3.1 Current Applications and Activities/Properties Predicted by Respondents Using (Q)SAR

<table>
<thead>
<tr>
<th>GROUP</th>
<th>IDENTIFICATION OF DATA REQUIREMENTS</th>
<th>HAZARD ASSESSMENT</th>
<th>EXPOSURE ASSESSMENT</th>
<th>REGULATORY DECISIONS</th>
<th>GROUPING CHEMICALS</th>
<th>DIRECTING RESEARCH</th>
<th>PHYS-CHEM PROPERTIES</th>
<th>TOXICITY</th>
<th>ECOTOXICITY</th>
<th>ENV FATE / EXPOSURE</th>
<th>METABOLISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computational Toxicology Laboratory / HECSB</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecological Assessment Division / Environment Canada</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food Contaminant Toxicology Assessment Section/Chemical Health Hazard Assessment Division / Bureau of Chemical Safety / Food Directorate / HPFB</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Existing Substances Risk Assessment Bureau/ HECSB</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Evaluation Directorate / PMRA</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>New Substances Assessment and Control Bureau / HECSB</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic Products Directorate / HPFB</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

a Data from responses to questions 7 and 8 of the Survey on the use of (Quantitative) Structure Activity Tools within Health Canada and Partner Departments/Agencies
Table 3.2 Potential Applications of (Q)SAR Tools and Approaches

<table>
<thead>
<tr>
<th>GROUP</th>
<th>POTENTIAL APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Quality Assessment Section / Air Health Sciences Division / Safe Environments Directorate / HECSB</td>
<td>(Q)SAR is one of the approaches that will be investigated for estimating toxicity for mixtures and substances with no existing Reference Concentrations</td>
</tr>
<tr>
<td>Chemical Assessment Section / Water Quality Science Division / Water, Air and Climate Change Bureau / Safe Environments Directorate / HECSB</td>
<td>Assessment of chemical/physical properties to help predict the behaviour of chemicals in the environment</td>
</tr>
<tr>
<td>Consumer Product Safety Directorate / HECSB</td>
<td>Anticipate conducting more chemical risk assessments following passage of CCPSA. Investigating application of threshold of toxicological concern (TTC) for cosmetics and consumer products. (Q)SAR data may help to guide these approaches.</td>
</tr>
<tr>
<td>Environmental Assessment Directorate / PMRA</td>
<td>Identification of data requirements for environmental transformation products from pesticide active ingredients where no data have been provided</td>
</tr>
<tr>
<td>Hazardous Materials Information Review Commission</td>
<td>Prediction of physical/chemical properties and mammalian/human toxicity related to hazard assessments and regulatory decisions</td>
</tr>
<tr>
<td>Marketed Health Products Directorate / HPFB</td>
<td>Application to assessments of natural health product active substances for which very little information exists</td>
</tr>
<tr>
<td>New Substances Assessment and Control Bureau / HECSB</td>
<td>Assessment of nanotechnological substances, when appropriate (Q)SAR tools become available</td>
</tr>
<tr>
<td>Office of Research and Surveillance / HECSB</td>
<td>Grouping and screening compounds (e.g., drugs) that have the potential to be abused in order to assess their biological activity/efficacy (including activity/efficacy for receptors) and their potential hazards/toxicity for use in the preparation of risk assessments and to make regulatory decisions</td>
</tr>
<tr>
<td>Therapeutic Products Directorate / HPFB</td>
<td>The potential role of (Q)SAR in the risk assessment process for pharmaceuticals is being evaluated including the development of guidance on characterizing the mutagenicity of impurities using (Q)SAR and TPD is participating in an ICH working group on this topic. Currently, TPD does not have specific guidance on the use of (Q)SAR tools or access to (Q)SAR predictions from drug sponsors/manufacturers on mutagenic potential of new drug impurities (i.e., usually Derek predictions) (Q)SAR could be used as a regulatory screening tool to determine types of studies necessary to further characterize hazard/risk TPD is working on a project to develop a qualification strategy for leachables and extractables in parenteral and ophthalmic drug products that would utilize Derek, Toxtree, and the Cramer classification scheme</td>
</tr>
<tr>
<td>Toxicology Research Division / HPFB</td>
<td>Prioritization/screening, identification of data requirements, hazard assessment, regulatory decisions, grouping chemicals, and directing research</td>
</tr>
</tbody>
</table>

*Data from responses to question 6 of the Survey on the use of (Quantitative) Structure Activity Tools within Health Canada and Partner Departments/Agencies*
3.4 **Types of (Q)SAR Tools and Approaches Used**

*(Survey Questions 9, 10, and 11)*

The survey gathered information on the (Q)SAR tools and approaches used by respondents in questions 9 to 11. From the responses to question 9 it was observed that six out of the 15 organizations that responded reported using analog extrapolation. Five reported using chemical categories and six use specific (Q)SAR models to assess hazard and exposure. To clarify their use of specific (Q)SAR models, the Therapeutic Products Directorate noted that they have evaluated specific (Q)SAR model predictions submitted to them rather than generated predictions themselves. Also, an additional respondent, the Computational Toxicology Laboratory/HECSB, identified specific (Q)SAR models they use in their response to question 10.

3.4.1 **(Q)SAR Tools and Predicted Biological Activities/Properties**

The survey queried respondents as to the types of tools they used and what endpoints or properties were predicted. Seven groups submitted information regarding the (Q)SAR models that they used (Table 3.3). The most frequently used model was TOPKAT with four groups (Food Contaminant Toxicology Assessment Section/HPFB, Existing Substances Risk Assessment Bureau Division/HECSB, Health Evaluation Directorate/PMRA, and New Substances Assessment and Control Bureau/HECSB) reporting its use for human hazard related endpoints. The New Substances Assessment and Control Bureau and the Ecological Assessment Division also use TOPKAT to estimate environmental endpoints such as ecotoxicity and biodegradation potential. TOPKAT has been widely used to predict carcinogenicity, as well as a variety of other toxicities such as acute and chronic toxicity and mutagenicity. The next most widely used tool was the OECD (Q)SAR Toolbox with four groups reporting use. This tool is used to predict a variety of toxicological endpoints, group chemicals, form categories, find analogues, retrieve experimental data, identify structural alerts, and predict a number of environmental endpoints. The Existing Substances Risk Assessment Bureau/HECSB and the Health Assessment Directorate/PMRA reported having used Derek for Windows, Multicase Caseotox, and Leadscope Model Applier to predict carcinogenicity, mutagenicity, sensitization/irritation and a variety of other toxicological endpoints. In addition the Therapeutic Products Directorate indicated that they have received submitted reports based on Derek for mutagenicity potential and Cramer toxicity classifications from Toxtree and have used these reports in support of their health risk assessments. The Existing Substances Risk Assessment Bureau/HECSB has used Caesar for predicting carcinogenicity and genetic toxicity, as well as to predict developmental toxicity. This group also reported using Oncologic to predict carcinogenicity and Multicase Meta-PC was used to predict mammalian metabolism pathways. The New Substances Assessment and Control Bureau and the Ecological Assessment Division/Environment Canada have used a wide range of mass balance models developed by the Canadian Centre for Environmental Modelling and Chemistry (CEMC) and some OASIS models such as POPs and Catalogic to predict environmental fate, sewage treatment plant removal and bioaccumulation. The New Substances Assessment and Control Bureau and the Ecological Assessment Division/Environment Canada have also used models to predict physical-chemical properties in support of exposure estimation. Some of the models reported by these groups include EPISUITE, Pallas, Accord, Sparc and ACD Labs. The Computational Toxicology Laboratory/HECSB has utilized the software models GastroPlus and ADMET Predictor to estimate metabolic properties, gastric intake and metabolism.
### Table 3.3 (Q)SAR Models in use by survey respondents from Health Canada and Environment Canada

<table>
<thead>
<tr>
<th>Model</th>
<th>Food Contaminant Toxicology Assessment Section / HPFB</th>
<th>Existing Substances Risk Assessment Bureau / HECSB</th>
<th>Health Evaluation Directorate / PMRA</th>
<th>New Substances Assessment and Control Bureau / HECSB</th>
<th>Therapeutic Products Directorate / HPFB</th>
<th>Ecological Assessment Division / Environment Canada</th>
<th>Computational Toxicology Laboratory / HECSB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-commercial</td>
<td></td>
<td></td>
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<tr>
<td>OECD (Q)SAR Toolbox</td>
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<td>x</td>
<td>x</td>
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<td>EPISUITE</td>
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</table>

* Data from responses to question 10 of the Survey on the use of (Quantitative) Structure Activity Tools within Health Canada and Partner Departments/Agencies
3.4.2 Details on (Q)SAR Approaches and Applications

A number of groups involved in risk assessment use (Q)SAR tools to support hazard assessment. Most often the tools are used to predict toxicological endpoints for human health concerns. The most commonly predicted endpoints are carcinogenicity along with genotoxicity/mutagenicity. Other hazard endpoints that have been predicted include acute and chronic toxicity, developmental, reproductive, neurotoxicity, sensitization/irritation, and even localized effects. The New Substances Assessment and Control Bureau have used tools to predict aquatic toxicity, biodegradation, environmental fate, partitioning and sewage treatment plant removal. The Ecological Assessment Division of Environment Canada has additionally predicted food chain magnification, long range transport and androgen/estrogen receptor binding. Output from these tools has aided in the prediction of stable metabolites and has also helped to refine data requirements. While the output from these tools is not usually used to make risk based decisions the predictions are often used to flag potential concerns and can be used to justify the generation of additional information for a substance. Predictive tools are used when there is a lack of experimental data or suitable surrogates are not available. In addition, predictions can be useful for hazard estimation for metabolites/degradates and impurities. Information from a variety of sources is often used in a weight of evidence scheme sometimes even using multiple tools for the same endpoint estimation.

The Food Contaminant Toxicology Assessment Section of HPFB uses (Q)SAR tools for the identification of data requirements, hazard assessment, and regulatory decisions. According to Health Canada’s Food Packaging Materials guidelines, structure activity data for chemicals with a potential daily intake of 0.025–0.1 µg/kg bw are required. These data are rarely provided in support of submissions and are often not available in the open literature. Therefore, (Q)SAR estimates have been generated when needed.

The Existing Substances Risk Assessment Bureau (HECSB) routinely faces a scarcity of experimental data that has necessitated the use of (Q)SAR tools to assess the possible risk posed by existing substances to human health in Canada. Predictions have been used by the bureau for categorization (prioritization) of the Domestic Substances List (DSL) as well as in support of hazard assessments of batch chemicals in the Phase I of the CMP. Predictions have been generated for toxicological endpoints of human health concern (e.g., carcinogenicity, genetic toxicity, developmental and reproductive toxicity, metabolites etc.). (Q)SAR-based methods have also been utilized for read across from data rich analogues and chemical class specific approaches to fill data gaps in some assessments.

The Health Evaluation Directorate at PMRA is responsible for the assessment of the possible risks of pesticides to human health in Canada. At the current time (Q)SAR software is not regularly used for pesticide assessments, but it is being investigated for potential application to pesticide assessments through a North American Free Trade Agreement (NAFTA) joint project with the United States Environmental Protection Agency (US EPA). The Directorate has reviewed (Q)SAR toxicity predictions when such information has been submitted as supplementary data on metabolites/degradates. It has also used (Q)SAR/bridging techniques to define and refine data requirements.
3.5 **Difficulties, Concerns and Other Issues:**
*(Survey questions 16, 17, 18, 19, 20)*

Of those survey respondents who provided information on whether they encountered difficulties in obtaining or implementing (Q)SAR tools and approaches (i.e., question 16), the majority (6/8) indicated that they did encounter difficulties. Also, just over half of the respondents (6/11) anticipated potential difficulties with accessing and implementing (Q)SAR (i.e., question 17).

Table 3.4 provides a breakdown of the current and potential difficulties encountered by respondent.

The most frequently cited current and potential difficulties associated with obtaining and implementing (Q)SAR tools and approaches was a lack of training on (Q)SAR tools and knowledge of various aspects of the tools (i.e., 6/13 groups). This indicates that many groups see the importance of their staff having an adequate understanding of various aspects of (Q)SAR tools (e.g., strengths/limitations, domain of applicability, interpretation, etc.) before accessing and implementing (Q)SAR tools and approaches into their programs. Costs of the (Q)SAR software and the associated contract/approvals processes are other sources of difficulties identified by several groups. This may relate to the relatively high cost of commercial (Q)SAR software, the infrequent purchasing of this type of software, the specialized IT requirements for (Q)SAR software, and the lengthy and very complicated contracting processes associated with commercial (Q)SAR software.

A less frequently cited problem is the limitations with certain (Q)SAR tools. These limitations relate to concerns about validation and poor predictive performance, confidentiality, non-transparency, domains of applicability, lack of high quality program specific experimental data for modelling, and reliability and acceptability of predictions. Other difficulties mentioned by individual groups include problems with using (Q)SAR predictions for complex mixtures, problems associated with obtaining external expert advice, strategies for the use of (Q)SAR (e.g., giving access to all staff or instituting dedicated “modeling officers”), ensuring the application of a range of (Q)SAR tools, not overstating the predictability of the tools, not using (Q)SAR to create hazard based assessment approaches, trying to decide on which tools to use, and a lack of exposure to other groups in Health Canada who are using (Q)SAR.

In addition to discussing difficulties with obtaining and implementing (Q)SAR, survey respondents were also provided with an opportunity to raise other (Q)SAR related issues (Question 20). It was suggested that more opportunities should be available to discuss (Q)SAR related issues with global regulatory agencies and international bodies to develop common understandings and acceptability of these methods. In addition, there were recommendations that (Q)SAR should be used in weight of evidence type approaches, combined with other sources of data (e.g., conventional studies, high throughput assays, etc.) and that similar to empirical studies, (Q)SAR predictions should be evaluated for their adequacy before being applied in regulatory risk assessments (e.g., consideration of validity, applicability, reliability, relevance). Finally, it was noted that (Q)SAR tools are a continuum of different methodologies, so that extrapolation of test results from structural analog to an untested chemical is based on similar principles as the use of a statistical (Q)SAR model.
### Table 3.4 Current and Potential Difficulties with Obtaining and Implementing (Q)SAR Tools and Approaches

<table>
<thead>
<tr>
<th>GROUP</th>
<th>DIFFICULTY</th>
<th>DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Quality Assessment Section / HECSB</td>
<td>Trying to decide which tools to use</td>
<td>Difficulties with deciding which tools to use</td>
</tr>
<tr>
<td>Computational Toxicology Laboratory / HECSB</td>
<td>Need for training on (Q)SAR tools</td>
<td>Lack of training or exposure to other groups in Health Canada</td>
</tr>
<tr>
<td>Consumer Product Safety Directorate / HECSB</td>
<td>Overstating predictability of (Q)SAR</td>
<td>Concerns about overstating predictability from (Q)SAR</td>
</tr>
<tr>
<td></td>
<td>(Q)SAR should only be used as supporting evidence and not result in a hazard based system</td>
<td>Concern that (Q)SAR results should only be used as supportive evidence and not result in a hazard based system</td>
</tr>
<tr>
<td>Ecological Assessment Division / Environment Canada</td>
<td>Implementation strategy for (Q)SAR</td>
<td>Need for an implementation strategy for (Q)SAR – i.e., every evaluator obtains and implements (Q)SAR tools or form a working group to provide (Q)SAR resources to evaluators to enable consistent application and training</td>
</tr>
<tr>
<td></td>
<td>Need to budget for software on an annual basis</td>
<td>Need to budget for (Q)SAR models on an annual basis as some are very expensive and others are free</td>
</tr>
<tr>
<td></td>
<td>Need proper use or “codes of good model practice”</td>
<td>Need proper use or “codes of good model practice” (e.g., domain of applicability guidance) for all evaluators and basic familiarization with models via seminars</td>
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<td></td>
<td>Need to understand domain of applicability, when to not accept model results, and how to interpret model results</td>
<td>Users should have a sufficient understanding of domain of applicability, when to not accept model results, and how to interpret model results</td>
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<tr>
<td></td>
<td>Need for prediction and model reporting formats</td>
<td>Although existing (Q)SAR reporting formats (e.g., OECD) can be laborious, there is a need for prediction and model reporting formats</td>
</tr>
<tr>
<td>Environmental Assessment Directorate / PMRA</td>
<td>No compelling reason to use (Q)SAR tools</td>
<td>No compelling reason to replace or substitute registrant submitted ecotoxicological and environmental fate data on pesticides with data generated by (Q)SAR tools</td>
</tr>
<tr>
<td>Food Contaminant Toxicology Assessment Section / HPFB</td>
<td>Cost of (Q)SAR software</td>
<td>Difficult to justify costs of (Q)SAR software due to low number of predictions required (e.g., 5/year on average)</td>
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<td>Lack of access to up-to-date tools</td>
<td>Lack of access to most up-to-date (Q)SAR tools</td>
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<tr>
<td></td>
<td>Need for training on (Q)SAR tools</td>
<td>Need for training in the application of (Q)SAR tools</td>
</tr>
<tr>
<td>Existing Substances Risk Assessment Bureau / HECSB</td>
<td>Contracts/approval processes for (Q)SAR software</td>
<td>Problems encountered with contract/approvals for acquisition of (Q)SAR software</td>
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<tr>
<td></td>
<td>Lack of a common understanding of strengths and limitations of (Q)SAR tools/approaches</td>
<td>Potential problems due to lack of understanding of strengths and limitations of tools/approaches</td>
</tr>
<tr>
<td></td>
<td>Improperly validated models, confidentiality, non-transparent algorithms, reliability/acceptability of predictions</td>
<td>Potential problems due to improperly validated models, confidentiality issues, non-transparent model algorithms, reliability/acceptability of modeled information, etc.</td>
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<td></td>
<td>Lack of high quality experimental data for model training sets</td>
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<td>Only partial adherence of some models to OECD (Q)SAR validation principles</td>
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<tr>
<td>Hazardous Materials Information Review Commission</td>
<td>Cost of (Q)SAR software</td>
<td>Costs of purchasing (Q)SAR software likely to be prohibitive so that a collaboration or group effort is needed</td>
</tr>
<tr>
<td>Health Evaluation Directorate / PMRA</td>
<td>Cost of (Q)SAR software</td>
<td>Agreement with HECSB to share access to (Q)SAR software because of high costs</td>
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<td></td>
<td>Poor predictive performance of models</td>
<td>Poor predictive performance of several commercial software packages for pesticide compounds based on validation testing results</td>
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<tr>
<td></td>
<td>Lack of program/mandate (pesticide) specific data in model training sets</td>
<td>Many commercial (Q)SAR models have a lack of pesticide compounds in their databases</td>
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<td></td>
<td>Data confidentiality issues</td>
<td>Potential difficulties in using applicant submitted toxicity data to build model databases because of data confidentiality issues</td>
</tr>
<tr>
<td>Marketed Health Products Directorate / HPFB</td>
<td>Use of (Q)SAR for complex mixtures</td>
<td>Potential concerns with the use of (Q)SAR for predictions on complex mixtures (e.g., extrapolation of predictions for single phytochemicals to whole natural health products)</td>
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</table>
### Survey of the Use of (Quantitative) Structure Activity Relationship [(Q)SAR] Tools and Approaches at Health Canada and Partner Departments

#### Group Details

<table>
<thead>
<tr>
<th>Group</th>
<th>Difficulty</th>
<th>Details</th>
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<tbody>
<tr>
<td>New Substances Assessment and Control Bureau / HECSB</td>
<td>Contract/approval processes for (Q)SAR software</td>
<td>Problems with CIO and Public Works approval processes for software purchases</td>
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<td>Approval processes for LAN-based (Q)SAR applications</td>
<td>Lack of clear documentation about rules, policies and procedures for purchasing specialized software or SOPs for putting together contracts for software</td>
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<td></td>
<td>Access and cost issues associated with single licence copies of software</td>
<td>Lack of clear understanding of funding and procedures can lead to uncertainties, delays, and potential cancellations of software orders</td>
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<td></td>
<td>Lack of domain of applicability guidance for many tools</td>
<td>Difficulties in getting approval for LAN-based (Q)SAR applications</td>
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<td></td>
<td>Need for training on (Q)SAR tools</td>
<td>Purchase of single licence software can make it difficult to access software simultaneously resulting in delays, make access difficult to impossible for teleworking staff, and result in added expense for separate licences</td>
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<td>Need for adequate knowledge of models, proper use, and new developments</td>
<td>Concern that many tools don’t provide clear guidance on their domain of applicability</td>
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<td></td>
<td>Need for dedicated “modeling officers”</td>
<td>Users need to be sufficiently trained in (Q)SAR methodology and have adequate current knowledge of models and their proper use as well as new models under development</td>
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<td>Need for dedicated scientific “modeling officers” responsible for modeling service, knowledge maintenance/training, keeping up with new (Q)SAR developments, and acting as resource persons</td>
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<td>Problems with CIO and Public Works approval processes for software purchases</td>
<td>Concerns about how good (trustworthy) (Q)SAR tools and approaches are for predicting pharmacological/toxicological activities or health risks when there is an absence of sufficient in silico, in vitro or in vivo data available for certain compounds</td>
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<tr>
<td>Office of Research and Surveillance / HECSB</td>
<td>Trustworthiness of (Q)SAR tools/approaches when there is a lack of program/mandate specific data for modeling</td>
<td>No (Q)SAR training provided to employees</td>
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<td>In the absence of in-house training, it may be difficult to access external expertise due to costs and the requirement for security clearance to access certain data</td>
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<td>Need to ensure a flexible approach to (Q)SAR to allow the application of tools other than DEREK, MCASE, etc.</td>
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<td>Need for evaluation of validation, standardization, and how tools are used within regulatory frameworks</td>
<td>Need for evaluation of validation, standardization, and how tools are used within regulatory framework taking into account international work and existing regulatory frameworks</td>
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</table>

#### 3.6 Learning and Collaboration

**Survey questions 12, 13, 14, 15**

The theme of questions 12, 13, 14, and 15 was learning and collaboration with the aim of identifying whether groups in Health Canada are interested in or are currently pursuing learning opportunities and collaborative efforts on (Q)SAR projects and the types of learning activities and collaborations in which they are interested.

#### 3.6.1 Learning Opportunities

Based on the responses to questions 12 and 13 there is widespread interest across the department in learning more about (Q)SAR tools and approaches. Responses were almost entirely in favour (14/15) with only one “maybe” from one program currently not using (Q)SAR and unsure about potential for future applications. No preference was given regarding the form of learning opportunities, as all respondents (with the one exception) indicated interest in participating in seminars, training courses and workshops. In addition, respondents indicated interest in discussions or information sessions with individuals/programs already using the tools, as well as shadowing to obtain hands on experience. The respondent(s) from Environment Canada expressed interest in the development of guidance documents for applications common across federal government departments.

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*a Data from responses to questions 18 and 19 of the Survey on the use of (Quantitative) Structure Activity Tools within Health Canada and Partner Departments/Agencies*
3.6.2 Collaboration

Most respondents indicated that they already are collaborating with or would be interested in collaborating with other groups in Health Canada on the development and/or application of (Q)SAR tools and approaches. Only 2/15 respondents indicated that collaboration was less likely; neither of these programs currently use (Q)SAR tools and both are uncertain at this point in time regarding potential future applications.

The nature of current internal collaborative activities ranges from sharing software to involvement in joint projects to further the utility of (Q)SAR. Several programs reported sharing software, either through informal occasional provision of access to models or through more formal mechanisms (such as a letter of agreement). A number of programs (3/15) reported frequent or occasional consultations or discussions on technical aspects of running and interpreting the results of commercial (Q)SAR models or issues related to model development. Three respondents indicated that they were collaborating on specific projects to further the breadth of application of (Q)SAR in their risk assessment programs. The respondent(s) from Environment Canada noted that Health Canada staff have been informally included in Environment Canada (Q)SAR training courses, and expressed an interest in co-development of (Q)SAR applications with Health Canada as well as the exchange of training materials.

Four respondents indicated that they or their programs were involved in collaboration with other national or international organizations. Two programs (Existing Substances Risk Assessment Bureau, HC and Ecological Assessment Division, EC) are directly involved with the Organization for Economic Cooperation and Development (OECD) (Q)SAR Working Group. The Existing Substances Risk Assessment Bureau is also cooperating with the European Chemicals Agency (ECHA) on a number of (Q)SAR related projects. The Pest Management Regulatory Agency is currently working with the Office of Pesticide Programs (OPP) at the US EPA on a NAFTA Technical Working Group project on 21st Century Toxicology: Integrated Approaches to Testing and Assessment. This project includes a number of (Q)SAR related activities and the Existing Substances Risk Assessment Bureau has also contributed to these activities. Finally, the New Substances Assessment and Control Bureau noted that they are collaborating with the Canadian Centre for Environmental Modelling and Chemistry (CEMC) at Trent University on the development of environmental fate models.

Of the four groups that provided information on future collaborations in which they may be interested, one indicated that any collaboration they have will likely be exploratory at first, and three have an interest in getting access to (Q)SAR experts and training, obtaining (Q)SAR data, and being involved in the development of (Q)SAR tools and approaches with groups who already have (Q)SAR expertise, particularly those with expertise in specific areas such as drug development.
4.0 CONCLUSIONS

The purpose of this survey of the use of (Q)SAR tools and approaches was to gain a better understanding of the current and planned use of these predictive methods in the various programs in Health Canada and one major partner department, Environment Canada. The survey was designed to solicit information on five main topics or themes: current and planned use of (Q)SAR, applications of (Q)SAR tools and approaches, types of (Q)SAR tools and approaches used, difficulties and concerns, and learning and collaboration.

In terms of the extent of current and planned use of (Q)SAR, there appears to be significant interest in (Q)SAR as nearly half of the survey respondents indicated that they currently use it in their assessment or research work and the majority of the remaining respondents are planning to incorporate the use of (Q)SAR in the future, some within two years, and others with no specified date.

Hazard assessment and the identification of data requirements are the most frequent applications of (Q)SAR cited by current users. Most specific applications relate to the prediction of toxicity, physical-chemical properties, and metabolic pathways and products. Those who are not currently using (Q)SAR appear to be interested in applying it to mammalian/human toxicity prediction and hazard assessment, the prediction of physical/chemical properties, grouping of chemicals, identification of data requirements, and support for regulatory decisions. Some unique program specific potential applications were also identified such as assessing nanotechnology substances and guiding the application of the threshold of toxicological concern approach for consumer products and cosmetics.

Of the respondents currently using (Q)SAR tools and approaches, most indicated they were using analog approaches, chemical categories, and specific (Q)SAR models. In terms of specific (Q)SAR models, the most popular was TOPKAT followed by the OECD (Q)SAR Toolbox. Analog approaches, chemical categories, and models are most often used to predict human health related toxicological endpoints with carcinogenicity, genotoxicity/mutagenicity as the most commonly predicted specific endpoints.

When asked about difficulties and concerns related to the implementation of (Q)SAR tools and approaches, eight groups responded and the majority of them reported encountering difficulties, while six groups anticipated encountering difficulties. The most frequently cited current and potential difficulty with obtaining and implementing (Q)SAR tools and approaches appears to be the need for training and a lack of knowledge/understanding of the various tools. Other sources of difficulties identified included the costs of commercial (Q)SAR software and the associated contract/approvals processes.

Respondents showed a widespread interest in learning about (Q)SAR tools and approaches with most respondents interested in a range of different learning activities (i.e., seminars, courses, workshops). A majority was also currently collaborating on (Q)SAR projects or was interested in future collaborations. Collaborative activities ranged from sharing software to involvement in joint projects to further the utility of (Q)SAR.
These collaborative efforts are occurring across programs within the department, between departments (i.e., Health Canada and Environment Canada), and with other national/international agencies (i.e., OECD, ECHA, US EPA, CEMC).

In summary, several of the programs responding to this survey are currently employing (Q)SAR tools and approaches, while others expressed interest in potentially applying (Q)SAR tools and approaches in the future. There was also significant interest in collaborating and sharing expertise in (Q)SAR and the enhancement of learning opportunities across Health Canada and with similar programs in Environment Canada.
5.0 RECOMMENDATIONS

As discussed in the survey document and in the introduction and conclusion to this report, the survey was designed to solicit input on particular (Q)SAR issues that could lead to enhanced communication and sharing of information on (Q)SAR tools and approaches across Health Canada and with partner departments and agencies. It is also believed that the results could lead to collaborative (Q)SAR projects, the development of common approaches to the use of (Q)SAR, the identification of learning opportunities, and the sharing of (Q)SAR resources.

The survey team analyzed the results of the survey in the context of their potential impacts on communication and collaboration and developed a set of short-, medium-, and long-term recommendations as a path forward. These recommendations represent a set of goals/projects that are estimated to take approximately six months to one year to complete for the short-term recommendations, one to two years for the medium-term recommendations, and two to three years for the long-term recommendations.

The individual recommendations have not been prioritized at this time, but in terms of ease of implementation and highest chance of success, the order of priority would likely be from short-term, to medium-term, to long-term recommendations.
5.1 **Short-term Recommendations (6 months – 1 year)**

The short-term recommendations developed by the survey team are summarized in Table 5.1 below.

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>DESCRIPTION</th>
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</thead>
</table>
| (Q)SAR Working Group                   | • Regular face to face meetings between groups within Health Canada and partner departments with an interest in (Q)SAR  
• Forum for exchange of information on questions, problems, solutions, success stories  
• Forum for seminar series on (Q)SAR  
• Lead, contribute to or facilitate other activities under short-, medium- and long-term recommendations |
| Inventory of (Q)SAR Tools              | • Table/database of available freeware (Q)SAR tools, links for accessing and background information, and identification of groups in Health Canada using these tools  
• Table/database of commercial (Q)SAR tools licensed to various groups in Health Canada  
• Include information/links on source(s) of tools, descriptions of methods, endpoints/properties predicted, sources of training set data, etc. |
| Inventory of Databases for (Q)SAR Approaches | • Table/database of links and other information on publicly accessible databases of structural information, toxicity, properties, and other data on chemicals related to the mandates of various groups in Health Canada.  
• These databases could be used for the development and testing of (Q)SAR tools |
| Inventory of Upcoming (Q)SAR Training Sessions | • Table/database of upcoming (Q)SAR Training sessions  
• Include information on topics to be discussed, provider(s) of training, Health Canada contacts, and whether attendance is restricted or open to various groups in Health Canada |
| Inventory of (Q)SAR Projects           | • Table/database of on-going and upcoming (Q)SAR projects from various groups in Health Canada |
| BEE Workspace on (Q)SAR                | • Health Canada wide BEE Workspace with access for all interested groups\(^a\)  
• Workspace could be used to organize/house inventories of (Q)SAR tools, databases of information on chemicals, upcoming (Q)SAR training sessions, and (Q)SAR projects (above)  
• Include links to websites of national/international organizations involved in (Q)SAR  
• Include announcements of upcoming (Q)SAR conferences/workshops  
• Include any available documents on (Q)SAR approaches, SOPs, case studies, etc. from various groups in Health Canada |

\(^a\) Feasibility of potential access to BEE Workspace for groups outside of Health Canada (i.e., Environment Canada) would have to be discussed with IT staff in Health Canada

The establishment of a (Q)SAR working group would help to ensure regular face to face communication among the various groups at Health Canada and partner departments with an interest in (Q)SAR projects. Such a group could be modeled after other similar working groups at Health Canada (e.g., Genomics Working Group) and would bring together practitioners to promote the exchange of questions, problems, success stories, etc. related to the use of (Q)SAR tools in the assessment of substances. It could also serve as a forum for exchanging information on new developments in the field or initiatives from other regulatory bodies. Part of this exchange of information could be through a regular seminar series of presentations by external and internal experts. A working group could help to address the fact that many of the groups who were surveyed expressed an interest in the application of (Q)SAR tools but cited a lack of knowledge as a hindrance to their usage. Finally, a working group could take the lead or facilitate many of the other activities included in the short-, medium- and long-term recommendations.
The bulk of the short-term recommendations involve establishing various inventories of information and data that would be readily accessible within Health Canada and by key partner agencies. An inventory of (Q)SAR tools would enable groups that are relatively inexperienced with a particular tool to learn about it and gain insights from the experience of groups who have used the tool, and explore potential options for sharing access to tools (i.e., commercial software). The inventory of databases of chemical information could be very useful to groups that are interested in identifying analogs, building chemical categories or even developing (Q)SAR models. Information on (Q)SAR training sessions in Health Canada may provide opportunities for groups with limited (Q)SAR resources to piggy-back on training sessions organized by others when spaces are available. Alternatively, knowledge of training sessions could lead to proposals to share training resources or to the organization of joint future joint training sessions. Finally, an inventory of on-going (Q)SAR projects would encourage various groups to have a dialogue on projects of potential mutual interest and suggest areas for current or future collaboration.

As suggested in the final short-term recommendation, all of the inventories described above could be rolled up into a (Q)SAR BEE workspace for Health Canada to facilitate access by various groups in Health Canada and partner agencies. Such a BEE workspace could also be used as a “one stop shop” for links to information on (Q)SAR from various national/international agencies, information on upcoming (Q)SAR conferences and workshops, and a site for housing documentation approaches to (Q)SAR, standard operating procedures, case studies and other documents that could be valuable information resources for groups that only have limited experience with (Q)SAR. A workspace could also serve as notice board and inventory of the activities of the (Q)SAR working group. This type of shared workspace would be consistent with current initiatives related to enhancing knowledge transfer mechanisms across Health Canada. Similar to the inventories described above, a BEE workspace could be established in a relatively short period of time, but would require dedicated resources in order to ensure the accuracy and currency of the content on an on-going basis.

5.2 Medium-term Recommendations (1–2 years)

Medium-term recommendations include collaborative predictive software purchases and the development of software sharing agreements where possible. The initiation of joint training ventures is also considered an important goal. In addition, the selection of case studies and their storage at a BEE (Q)SAR site is another medium-term recommendation that would provide very useful information for members of the HC community of risk assessors who are interested in applying (Q)SAR approaches (Table 5.2).

The desire to initiate collaborative software purchases and develop sharing agreements is driven by the extremely high cost of some commercial software packages. The development of sharing agreements could allow evaluators to gain access to useful software for the evaluation of substances. Collaborative purchases could enable better use of operating funds and allow access to programs that would otherwise not be available. HC groups that have similar program activities and the potential to use the same (Q)SAR approaches and tools could benefit from such initiatives. The high cost of commercial software was cited by many groups in the survey as a stumbling block to implementation of (Q)SAR, therefore collaborative purchases and sharing agreements may help to address this issue. It is recognized that setting up collaborative purchase agreements may take some dedicated efforts from staff and perhaps some negotiating with suppliers.

Joint training ventures could maximize the use of training funds and allow evaluators to be trained together. Such joint training could help to ensure consistency in the application of tools and in the interpretation of results. Joint training may also grant access to experts that may otherwise be difficult to obtain due to costs. Almost half of the respondents to the survey cited the need for training as one potential difficulty with implementing (Q)SAR tools and approaches. It is also felt that a seminar series on (Q)SAR tools would be very beneficial to the HC community.
Finally it is felt that the identification and development of case studies on the application of (Q)SAR tools in different programs could serve as examples of the use of such tools in different scenarios. These case studies could ultimately be posted on the BEE workspace (see short-term recommendations) for ease of access by various groups in Health Canada. Shared case studies could help improve understanding and promote consistent and defensible interpretation and application of (Q)SAR data.

Table 5.2  Medium-term Recommendations for Enhancing Communication and Information Sharing on (Q)SAR

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Software Purchases</td>
<td>• Different groups sharing costs, management of contract processes, etc.</td>
</tr>
<tr>
<td>Software Sharing Agreements</td>
<td>• MOUs, Intradepartmental Letters of Agreement, etc.</td>
</tr>
<tr>
<td></td>
<td>• Shared access to (Q)SAR models, databases, development tools, etc.</td>
</tr>
<tr>
<td>Joint Training Ventures</td>
<td>• Advertising upcoming (Q)SAR training courses and making spaces available to other groups in Health Canada and partner departments</td>
</tr>
<tr>
<td></td>
<td>• Joint efforts to design, share the costs, and the management of (Q)SAR training courses</td>
</tr>
<tr>
<td>Identification of Case Studies</td>
<td>• Identify case studies of the use of (Q)SAR from different programs in HC and house them in a BEE (Q)SAR workspace</td>
</tr>
<tr>
<td></td>
<td>• Case studies could be ‘templates’ or sources of guidance for groups with little experience in (Q)SAR</td>
</tr>
</tbody>
</table>

## 5.3  Long-term Recommendations (2–3 years)

(Q)SAR goals or projects that could be completed in the long-term are summarized in Table 5.3.

Long-term recommendations could include developing guidance documents on a variety of topics ranging from general applications and use of (Q)SAR tools to providing specific instructions to carry out analogue identification/read across. The guidance documents could be developed specific to individual tools and/or suited to specific program criteria and requirements.

In addition, in the longer term it could be possible to investigate and build chemical databases, including a range of information (e.g., physical–chemical, toxicity, structures, etc.) that follow a standard format so that these could be shared both nationally and internationally. Databases of this type would facilitate the development of a range of predictive tools (e.g., (Q)SAR models, chemical categories, etc.). This would likely involve establishing agreements between national and international agencies to share information.

As mentioned above, the development of new and improved (Q)SAR tools could be another long-term goal for Health Canada. These tools could be designed to be relevant to the specific types of chemicals, and predicted endpoints or properties that are relevant to the various programs at Health Canada.

The creation of a (Q)SAR expert advisory group could also be a long-term goal. This advisory group could either be a next step in the evolution of the (Q)SAR working group or be constituted on an ad hoc basis as required. The expert advisory group would include (Q)SAR users and developers with considerable experience who could provide advice on (Q)SAR issues encountered by individual groups and input to Health Canada management on policies related to the application of (Q)SAR tools to various risk assessment programs across the department. This type of advice would help to ensure consistency in the application and interpretation of (Q)SAR predictions. Experience gained and lessons learned by the expert advisory group could also be rolled into the development of guidance documents discussed previously. Finally this advisory group could also provide input into or help to influence international activities or initiatives on (Q)SAR.
Table 5.3  Long-term Recommendations for Enhancing Communication and Information Sharing on (Q)SAR

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Q)SAR Guidance Documents</td>
<td>• Guidance on general approaches to (Q)SAR for risk assessment, instructions for analog identification/read-across, information on specific tools</td>
</tr>
<tr>
<td>Investigating and Building Chemical Databases</td>
<td>• Databases of physical-chemical, toxicity data, and structures that could be shared locally and globally, and used for the development of predictive tools</td>
</tr>
<tr>
<td>Development of New and Improved Predictive Tools</td>
<td>• Tools relevant to the types of chemicals and endpoints or properties included in the mandates of various programs at HC</td>
</tr>
<tr>
<td>(Q)SAR Expert Advisory Group</td>
<td>• Provide advice on challenging (Q)SAR issues encountered by individual groups</td>
</tr>
<tr>
<td></td>
<td>• Provide input to HC management on policies on (Q)SAR application to risk assessment</td>
</tr>
<tr>
<td></td>
<td>• Ensure consistency in the application and interpretation of (Q)SAR</td>
</tr>
<tr>
<td></td>
<td>• Develop guidance documents on (Q)SAR applicable to multiple programs in HC</td>
</tr>
</tbody>
</table>

Resource Implications

The recommendations outlined above would require an investment of human and financial resources. Some activities would require only a small amount of time and effort by current staff in the short-term, such as the creation of inventories of current (Q)SAR tools and projects or establishment of a BEE workspace, although some continued effort would be required to maintain these information sources up to date over the longer term. Other recommendations would impact more on financial resources, such as the purchase or sharing of commercial models, understanding that some staff time and effort would be needed to research, acquire and maintain relevant models. While some recommendations related to training would require an extensive commitment of internal human resources, the value of such training activities could be enhanced significantly by engaging external experts or consultants. Likewise, the creation of an expert advisory group to develop a high level of expertise and establish and maintain Health Canada as a leader in the (Q)SAR field would require a significant commitment of employee time as well as financial support to attend relevant workshops and be involved in projects with other national and international agencies. Thus, it will be important to consider both human and financial resource requirements when addressing the recommendations from this survey.
6.0 REFERENCES


APPENDIX I:

The survey questionnaire distributed to various groups in Health Canada and Environment Canada in the fall of 2010 is included in the following pages.
SURVEY ON THE USE OF (QUANTITATIVE) STRUCTURE ACTIVITY TOOLS WITHIN HEALTH CANADA AND PARTNER DEPARTMENTS/AGENCIES

Introduction

Predictive tools based on (quantitative) structure activity relationships [(Q)SAR] are being applied in a range of academic and industrial settings, as well as in regulatory risk assessment programs around the world, including Health Canada. Over the past 10 years there has been an increasing interest from North American and European regulatory agencies in the application of predictive methods such as (Q)SAR both to lessen the reliance on conventional animal testing and to increase the efficiency of assessments, especially in light of mandates to address inventories of large numbers of data poor substances. At the same time, there have been ongoing developments in predictive technology, particularly in terms of increased access to large electronic databases of test results on which to base predictions. Consequently, it is very opportune at this time to survey the use of (Q)SAR tools and approaches in Health Canada. The purpose of this survey is to identify how predictive tools are currently being used in risk assessment activities under various mandates in the department, as well as in a number of Canadian partner departments/agencies.

The survey is being conducted through the identification of relevant risk assessment programs and the administration of a questionnaire. To gain an understanding of the breadth of use of predictive tools and opinions concerning their use in human health and environmental risk assessment, the questions included in the survey relate to which programs are currently using or planning to use (Q)SAR tools and approaches, which tools are being used in which applications, and feedback from government scientists with respect to the value and limitations of (Q)SAR tools and approaches in risk assessment.

The results of the survey should lead to enhanced communication and sharing of information on (Q)SAR tools and approaches across Health Canada and with a number of Canadian partner departments/agencies. An increased understanding of how (Q)SAR is applied should foster collaboration and potentially the development of common approaches for incorporation of (Q)SAR in risk assessment products within the department. The information gathered from this survey should also help with the identification of learning opportunities for Health Canada scientists and the sharing of (Q)SAR resources across various programs.

(Q)SAR Tools and Approaches

(Quantitative) Structure-Activity Relationships [(Q)SAR] encompass a variety of techniques for predicting the biological activities, physical-chemical properties or other characteristics of untested chemicals based on structural similarity to chemicals with known activities or properties. The parentheses around the word, “Quantitative”, signify that these techniques can involve either qualitative approaches to extrapolating from
similar chemicals, also known as Structure-Activity Relationships (SAR), or estimates based on quantitative (statistical) methods which are referred to as QSAR. Examples of the types of activities and properties that can be predicted using (Q)SAR tools and approaches include toxicity endpoints (e.g., mutagenicity, carcinogenicity, etc.), ecotoxicity endpoints (e.g., LC50, NOAEC, etc.), other biological activities (e.g., metabolism/transformation products, efficacy, etc.), environmental properties (e.g., fate/partitioning, etc.), and physical-chemical properties (e.g., log P, solubility, vapour pressure, etc.).

(Q)SAR tools and approaches represent a continuum of methods that involve relating chemical structure to activity. These methods and tools range from simple extrapolations of the properties of a structural analog chemical to the chemical of interest; the identification of a group (category) of structurally similar chemicals and the interpolation/extrapolation of properties of the data rich group members to the data poor members (e.g., read-across, trend analysis); SAR models that predict activity based on libraries of structural alerts, decision trees and/or rules; and QSAR models that use databases of chemicals with known activities to develop statistical algorithms for predicting activities of untested chemicals.

This survey is intended to focus on (Q)SAR tools and approaches that directly relate the structure of a chemical to a particular activity or property. As such, predictive methods based on the analysis of the results of high throughput cellular and biochemical screening assays (HTS), toxicogenomic assays and other specialized in vitro assays are not included. Also, not included are (Quantitative) Activity-Activity Relationships [(Q)AAR] as their emphasis is on predicting the activity of a chemical based on available data on another activity of that same chemical without necessarily considering the structure of chemical (e.g., predicting long-term effects from short-term toxicity data).

Although the focus of this survey is on (Q)SAR tools and approaches, regulatory agencies including Health Canada are currently exploring methods for combining in vivo studies, (Q)SAR predictions, HTS assays, toxicogenomics, mechanistic studies, etc. in Integrated Approaches to Testing and Assessment (IATA). IATA may make it possible to refine, reduce or even replace selected in vivo/in vitro tests and focus more rapidly on specific hypotheses about chemicals while maintaining the scientific defensibility and human health and environmental protectiveness of chemical risk assessments. While the replacement of in vivo/in vitro tests with predictive methods such as (Q)SAR is a long-term goal of IATA, it is recognized that this would require a high degree of confidence in the predictive methods and a weight of evidence supported by a variety of different empirical and predictive data.

Structure and Format of Survey

The survey is structured to gather information from respondents concerning their affiliation, mandate and principal activities. There are questions about current use of (Q)SAR tools and approaches by respondents’ programs. Respondents who are currently not employing (Q)SAR tools are asked to indicate if they feel such tools might be of
assistance. Additional questions relate to soliciting interest in potential training and collaboration opportunities and general concerns regarding the use of (Q)SAR tools and approaches.

Survey Report

Once all survey results have been received, responses will be analyzed. A report will be prepared which will include an overview of the results obtained, as well as observations and conclusions of the survey team. The report will be presented to Health Canada’s Task Force on Risk Assessment (TFSRA) and made available to respondents. Depending upon the outcome, the results of the survey may lead to follow-up work such as investigation of options for training and/or collaboration.

Further Information

For further information or questions concerning this survey, please contact:

Titus Tao
Bioethics, Innovation and Policy Integration
Science Policy Directorate
Strategic Policy Branch, Health Canada
e-mail: titus.tao@hc-sc.gc.ca
HEALTH CANADA (Q)SAR SURVEY QUESTIONNAIRE

This survey aims to gain an understanding of the breadth of use of (Q)SAR tools and approaches, and opinions concerning their use in human health and environmental risk assessment, and related potential collaborations within Health Canada and its key Canadian partner departments and agencies.

Several of the survey questions require text to be supplied, while some require the respondent to choose among several options. Please feel free to elaborate on your response to any question in the additional spaces provided.

It is estimated that completion of the survey will take approximately 30 minutes.

This version of the survey can be completed electronically and sent to titus.tao@hc-sc.gc.ca or the survey questionnaire can be printed out, the questions answered in writing and the completed questionnaire faxed or mailed to:

Titus Tao
Bioethics, Innovation and Policy Integration
Science Policy Directorate
Science Policy Branch
Health Canada

COMPLETION AND RETURN OF THIS SURVEY IS KINDLY REQUESTED BY:

DECEMBER 17, 2010
(Q)SAR SURVEY QUESTIONS

Please note that if required, additional writing space is provided at the conclusion of the survey.

1. Please supply brief background information on your group:

   Organization Name (e.g., Section, Division, Bureau, Directorate, etc.)

   Mandate/Statutory Authority

   Main Activities

   Additional Information

2. Please fill in the table below with information on yourself and any other appropriate contact person/people in your group (i.e., section, division, directorate, etc) for (Q)SAR-related issues.

<table>
<thead>
<tr>
<th>Respondent</th>
<th>Contact 1</th>
<th>Contact 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-mail address</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Does your group currently use (Q)SAR tools and approaches?
   - Yes
   - No

4. If you are not currently using (Q)SAR tools and approaches are you planning on using them in the future?
   - Yes
   - No

5. If you are planning on using (Q)SAR tools and approaches in the future, approximately when do you plan on implementing them?

__________________________________________________________________

6. If your group does not currently use (Q)SAR tools and approaches, are there any tasks or projects within your program or related to your mandate where you think (Q)SAR tools could potentially be applicable?

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

__________________________________________________________________

7. If your group uses (Q)SAR tools and approaches, what types of applications do you use them for? (Please check all that apply)
   - Prioritization/screening
   - Identification of data requirements
   - Hazard assessment
   - Exposure assessment
   - Assessment of efficacy
   - Labelling requirements
   - Regulatory decisions
   - Grouping chemicals
   - Directing research
   - Other (Please elaborate)
8. If your group uses (Q)SAR tools and approaches, what biological activities and/or properties does your group use the (Q)SAR tools and approaches to predict? (Please check all that apply)

- Physical-chemical properties (e.g., Log P, solubility, vapour pressure)
- Toxicity (mammalian/human health (e.g., acute toxicity, mutagenicity)
- Ecotoxicity (e.g., LC₅₀, NOAEC)
- Environmental fate or exposure related parameters
- Therapeutic efficacy
- Metabolism
- Other properties of chemicals (Please elaborate)

9. If your group uses (Q)SAR tools and approaches, what types do you use? (Please check all that apply)

- Analog extrapolations
- Chemical categories
- Specific (Q)SAR models
- Other (Please elaborate)

10. If your group uses (Q)SAR tools and approaches, please fill in the table below with the names of the specific tools and the specific biological activities/properties predicted.

<table>
<thead>
<tr>
<th>Tool</th>
<th>Activity/Property Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. If your group uses (Q)SAR tools and approaches, please elaborate on how (Q)SAR is used by your group for each application (e.g., Predictions of acute toxicity from (Q)SAR models used as a basis for hazard ranking, labelling or other applications; Read-across predictions for genotoxicity from chemical categories used in combination with in vivo/vitro assay data in weight of evidence approaches for hazard assessment; etc.).

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__________________________________________________________________
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__________________________________________________________________

12. Is your group interested in learning more about (Q)SAR tools and approaches, and their applications?

☐ Yes
☐ No

13. If the answer to question 11 is "yes", please indicate what types of additional learning opportunities you would be interested in. (Check all that apply)

☐ Seminars
☐ Training courses
☐ Workshops
☐ Other (Please elaborate)

__________________________________________________________________
__________________________________________________________________
__________________________________________________________________
14. Is your group currently collaborating or interested in collaborating with other groups in Health Canada or other departments/agencies on the development and/or application of (Q)SAR tools and approaches?

☐ Yes
☐ No
15. If the answer to question 14 is “yes”, please elaborate on your current collaborations (i.e., types of collaboration and key contact(s) if possible) and/or the types of future collaborations you are interested in.

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16. Has your group encountered any difficulties with regards to obtaining and/or implementing (Q)SAR tools and approaches?

☐ Yes
☐ No

17. Do you foresee any potential difficulties for your group or for other parts of Health Canada in terms of obtaining access to or implementing (Q)SAR tools and approaches?

☐ Yes
☐ No
18. If the answer to question 15 or 16 is “yes”, please elaborate on the issue with respect to obtaining and implementing (Q)SAR tools and approaches.
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19. Do you have any concerns about the current or potential uses of (Q)SAR tools and approaches in your group or any concerns about their use in general?
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________________________________________________________________________

20. Are there any other (Q)SAR related issues you would like to comment on?
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
21. This survey was intended to be answered by relevant groups in Health Canada and a number of partner departments and agencies in Canada. Are you aware of any other groups in Canada with an interest or potential interest in (Q)SAR tools and approaches who you feel should also receive the survey?

**Health Canada:**

**HECSB**
- New Substances Assessment and Control Bureau
- Existing Substances Risk Assessment Bureau
- Water Quality and Science Division
- Air Quality Assessment Section
- Cosmetics Division
- Contaminated Sites Division
- Environmental Health Sciences Research Bureau

**PMRA**
- Health Evaluation Directorate
- Environmental Assessment Directorate

**HPFB**
- Bureau of Pharmaceutical Sciences
- Marketed Health Products Directorate
- Natural Health Products Directorate
- Veterinary Drugs Directorate
- Chemical Health Hazard Assessment Division
- Centre for Radiopharmaceuticals and Biotherapeutics
- Toxicology Research Division
- Office of Risk Management
- Bureau of Cardiology, Allergy and Neurological Sciences
- Bureau of Gastroenterology, Infection and Viral Diseases
- Bureau of Metabolism, Oncology and Reproductive Sciences
- Office of Clinical Trials
Please provide contact information for any other groups in Health Canada who should receive the survey


Other Canadian partner departments and agencies:

Hazardous Materials Information Review Commission:

Environment Canada:

Science and Technology Branch

- Ecological Assessment Division
- New Chemicals Evaluation Section

Please provide contact information for any other Canadian partner departments and agencies who should receive the survey


ADDITIONAL WRITING SPACE:
(Please refer to the question no. that you are elaborating on)
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THANK YOU FOR TAKING THE TIME TO COMPLETE THIS SURVEY
## APPENDIX II:

### Groups surveyed

The table below provides a complete list of the various groups who were contacted for the survey.

### Health Canada Groups Surveyed

<table>
<thead>
<tr>
<th>SECTION</th>
<th>DIVISION</th>
<th>BUREAU</th>
<th>DIRECTORATE</th>
<th>BRANCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Quality Assessment Section</td>
<td>Air Health Sciences Division</td>
<td>Water, Air and Climate Change Bureau</td>
<td>Safe Environments Directorate</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bureau of Cardiology, Allergy and Neurological Sciences</td>
<td>Therapeutic Products Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bureau of Gastroenterology, Infection and Viral Diseases</td>
<td>Therapeutic Products Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bureau of Metabolism, Oncology and Reproductive Sciences</td>
<td>Therapeutic Products Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bureau of Pharmaceutical Sciences</td>
<td>Therapeutic Products Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centre for Blood and Tissues Evaluation</td>
<td>Biologics and Genetic Therapies Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics</td>
<td>Biologics and Genetic Therapies Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centre for Vaccine Evaluation</td>
<td>Biologics and Genetic Therapies Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
</tr>
<tr>
<td>Food Contaminant Toxicology Assessment Section</td>
<td>Chemical Health Hazard Assessment Division</td>
<td>Bureau of Chemical Safety</td>
<td>Food Directorate</td>
<td>Health Products and Food Branch (HPFB)</td>
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<td></td>
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<td></td>
<td>Consumer Product Safety Directorate</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
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<td></td>
<td></td>
<td>Cosmetics Division</td>
<td></td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
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<td></td>
<td></td>
<td>Contaminated Sites Division</td>
<td>Environmental Health Bureau</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
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<td></td>
<td></td>
<td>Safe Environments Directorate</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
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<td></td>
<td></td>
<td></td>
<td>Controlled Substances and Tobacco Directorate</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
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<tr>
<td></td>
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<td></td>
<td>Environmental Assessment Directorate</td>
<td>Pest Management Regulatory Agency (PMRA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Environmental Health Sciences Bureau</td>
<td>Environmental and Radiation Health Sciences Directorate</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Existing Substances Risk Assessment Bureau</td>
<td>Safe Environments Directorate</td>
<td>Healthy Environments and Consumer Safety Branch (HECSB)</td>
</tr>
<tr>
<td>SECTION</td>
<td>DIVISION</td>
<td>BUREAU</td>
<td>DIRECTORATE</td>
<td>BRANCH</td>
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</tr>
<tr>
<td>Health Evaluation Directorate</td>
<td>Pest Management Regulatory Agency (PMRA)</td>
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**Environment Canada Groups Surveyed**

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