DATA ON CANNABIS ADVERSE REACTIONS: 2021 ANNUAL REPORT

Adverse reactions associated with cannabis reported to Health Canada between January 1, 2021 to December 31, 2021

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Canada

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KEY HIGHLIGHTS

In 2021, Health Canada received 260 reports of adverse reactions associated with cannabis as a suspected substance (including cases of polysubstance use). These reports include duplicates, such as multiple reporters of the same adverse reaction.

Out of the 260 reports, 174 were unique cases associated with legal cannabis products.

Of the cases involving legal cannabis products:

- 42% involved females and 30% involved males
- 56% involved cannabis used for medical purposes (self-reported)
- 57% involved ingestible cannabis liquid extracts (that is, ingestible cannabis oils and softgels)
- 43% were missing age-related information and 17% of cases involved adults aged 45 to 64 years
- 60% were reported as serious, with other (medically important condition) as the most frequently reported reason for seriousness

The most frequently reported adverse events across all cases involving legal cannabis products were:

- hallucinations (n=60)
- nausea (n=21)
- headache (n=17)
- dizziness (n=15)
- throat irritation (n=14)

In 2021, there were 2 suspected cases of vaping-associated lung injury reported involving legal cannabis products. However, neither were confirmed or probable cases according to the case definition established by the Public Health Agency of Canada.

Many findings have remained consistent from 2020 to 2021, however, some changes were observed, namely:

- a decrease in serious adverse reaction cases
- a decrease in the number of reports submitted from hospitals
- a shift in some of the reasons for seriousness being selected by reporters
- an increase in the total number of cases, including non-serious adverse reaction cases
- the types of adverse events reported, and, in some instances, the type of individuals involved in adverse reaction cases

However, further years of data are required to conduct proper trend analysis and to assess any long-term changes in findings.

Health Canada continues to monitor, assess and report on adverse reactions associated with cannabis, and findings continue to be used to inform evidence-based educational materials on health and safety risks with cannabis, including risk communications and educational resources.

INTRODUCTION

This report describes the findings of the domestic case reports of adverse reactions associated with cannabis submitted to Health Canada's Canada Vigilance database and analyzed by the Office of Cannabis Science and Surveillance of the Controlled Substances and Cannabis Branch in Health Canada. This work forms part of the Vigilance Framework for Cannabis that has been in place since the coming into force of the *Cannabis Act* and *Cannabis Regulations* (October 17, 2018).

This third annual data report presents a summary of all domestic case reports of adverse reactions submitted to Health Canada between January 1, 2021, and December 31, 2021, suspected of being associated with a cannabis product as defined under the *Cannabis Act* or its Regulations, intended for human consumption.

For the purposes of this report:

- A **legal cannabis product** means cannabis of 1 of the classes set out in Schedule 4 to the Act, or a cannabis accessory that contains such cannabis, after it has been packaged and labelled for sale to a consumer at the retail level. It does not include:
    - cannabis that is intended for an animal
    - health products containing cannabis or for use with cannabis
    - a cannabis accessory that contains cannabis that is intended for an animal
- An **adverse reaction** is a noxious and unintended response to a cannabis product that contains cannabis
- A **serious adverse reaction** is an adverse reactions that requires inpatient hospitalization or a prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death

Licence holders who sell or distribute a cannabis product must provide Health Canada with a detailed report within 15 days of becoming aware of a serious adverse reaction to the cannabis product. This report must contain all information in their possession associated with the use of the cannabis product by the individual who experienced the reaction.

The following groups may also submit adverse reaction reports on a voluntary basis:

- patients
- consumers
- medical cannabis clinics
- health care practitioners
- other reporters such as provincial and territorial authorized retailers

Reports may also be received from market authorization holders of licensed health products that submit adverse reaction reports for other suspect health products (such as prescription or non-prescription drugs or natural health products) in which cannabis is also identified as a co-suspect product.

Adverse reaction reports with cannabis may involve cannabis that is 1 of the following:

- from an illegal source
- a legal cannabis product

- cultivated[1] or produced[2] in the home for personal use
- undefined (cannabis as a substance not otherwise specified)

For the purposes of this report, case reports involving a legal cannabis product (that is, identifiable by product brand name or licence holder) are classified according to the intended use of the cannabis products as follows:

- **Cannabis use for non-medical purposes:** If there is no reported medical or therapeutic indication or reason for use provided in the adverse reaction report, minimal details or the intended use is for non-medical purposes, the case is classified as "non-medical use of cannabis".
- **Cannabis use for medical purposes:** This includes cases described as involving the cannabis being used pursuant to a medical authorization document provided by a health care practitioner; or cases that report the use of the cannabis for a medical or therapeutic purpose, without mention of a medical authorization document. This definition aligns with the definition of medical use within the Canadian Cannabis Survey. This is broader in scope than the definition of cannabis use for medical purposes under the *Cannabis Regulations*; which only includes cannabis being used pursuant to a medical authorization document from a health care practitioner.

Adverse reaction reports are collected and housed in the Canada Vigilance database. Most adverse reaction reports submitted to Health Canada with cannabis are reported spontaneously by consumers, patients, health care practitioners or by licence holders (referred to as market authorization holder in the Canada Vigilance database). However, reports may also originate from research studies, including:

- published case studies
- observational studies (non-interventional, real-world)
- interventional human studies involving cannabis that fall outside of the definition of a clinical trial
- other organized data collection systems (for example, patient registries)

While reports originating from clinical trials may be included in the broader Canada Vigilance dataset, these reports are excluded from this data report as they fall under the purview of the Clinical Trials Framework.

Health Canada conducts near-time monitoring, detection, assessment and associated activities for cases of adverse reactions involving cannabis products as part of the Vigilance Framework for Cannabis. Health Canada also monitors cases involving cannabis as a substance for broader issues of public health importance such as:

- vaping-associated lung illness
- cases involving pediatric populations
- other potential emerging safety issues

[1] Under the *Cannabis Act* and Regulations adults are allowed to legally grow up to a maximum of 4 cannabis plants for personal use. This is in addition to any plants that may be authorized for personal and designated production for medical purposes, which can vary across the provinces and territories. However, rules surrounding home growing for non-medical purposes may vary based on the rules and regulations of individual provinces or territories.
[2] Under the *Cannabis Act* and Regulations adults are allowed to make products at home for personal consumption using cannabis that they have grown legally or using cannabis that they obtained from other legal sources.

The purpose of this report is to provide a brief summary of adverse reaction reports involving cannabis, as well as a descriptive analysis of adverse reaction data associated with legal cannabis products, submitted to Health Canada between January 1, 2021 and December 31, 2021.

In addition to the descriptive analysis of cases from 2021, comparisons to the previous reporting period (January 1, 2020 to December 31, 2020) have been made, where appropriate. These comparisons are largely descriptive, and differences have not been tested for statistical significance in most cases due to the limited nature of the data. Therefore, caution should be taken with the interpretation of these changes in results over the 2 reporting periods.

Data for other reporting periods, including trends across periods, are also publicly available:

- Cannabis-related side effects: Key findings
- Data on cannabis adverse reactions: 2020 annual report
- Data on cannabis adverse reactions: 2018-2019 annual report

This report does not cover adverse reaction data associated with health products, including drugs containing cannabis, which are regulated under the *Food and Drugs Act* and its Regulations. A summary of adverse reactions associated with other health products received by Canada Vigilance in 2021 are described in Health Canada's InfoWatch Newsletter: Adverse reactions to health products - annual report 2021.

Considerations

Certain caveats should be considered when interpreting the adverse reaction data in this report.

Adverse reactions are generally spontaneously submitted to Health Canada and cannot be used to determine the incidence or prevalence of adverse reactions to cannabis in the general population.

Serious adverse reactions have a greater representation in this dataset as licence holders have a regulatory obligation to report these to Health Canada under section 248.1 of the *Cannabis Regulations*.

The submission of non-serious adverse reactions by licence holders to Health Canada as individual case reports is voluntary,[3] therefore, these cases are likely underreported and underrepresented in this dataset.

Reporting of adverse reactions for cannabis products is voluntary for:

- hospitals
- consumers
- medical cannabis clinics
- health care practitioners
- provincial and territorial retailers

Therefore, both serious and non-serious cases from these sources are likely underreported.

[3] As per paragraph 248.1(1)(b) of the *Cannabis Regulations*, all adverse reactions, including non-serious adverse reactions, must be maintained in an annual summary report by the licence holder, which can be requested by Health Canada.

Individuals experiencing serious outcomes or using cannabis products for medical purposes may be more motivated to report or seek out medical attention.

Several factors may influence the number and quality of case reports submitted to Health Canada such as:

- media coverage
- reason for cannabis use
- consumer or patient medical history
- length of time a product is on the market
- awareness, motivation and ability to report
- nature of reports (spontaneous reports versus studies or other organized data-collection systems)

This report includes information on cannabis for medical and non-medical purposes; however, the number of cases elsewhere may not directly align with what is presented in this current data report due to different dates of extraction from the Canada Vigilance database (for example, in the adverse reactions to health products - annual report 2021).

The inclusion of a particular report in the database does not necessarily mean that there is a causal relationship between the reported cannabis products and adverse events. Additional scientific investigations are required to establish a cause-and-effect relationship.

ADVERSE REACTIONS WITH CANNABIS

Adverse reactions associated with cannabis as a substance

Figure 1: Reports associated with cannabis as a substance

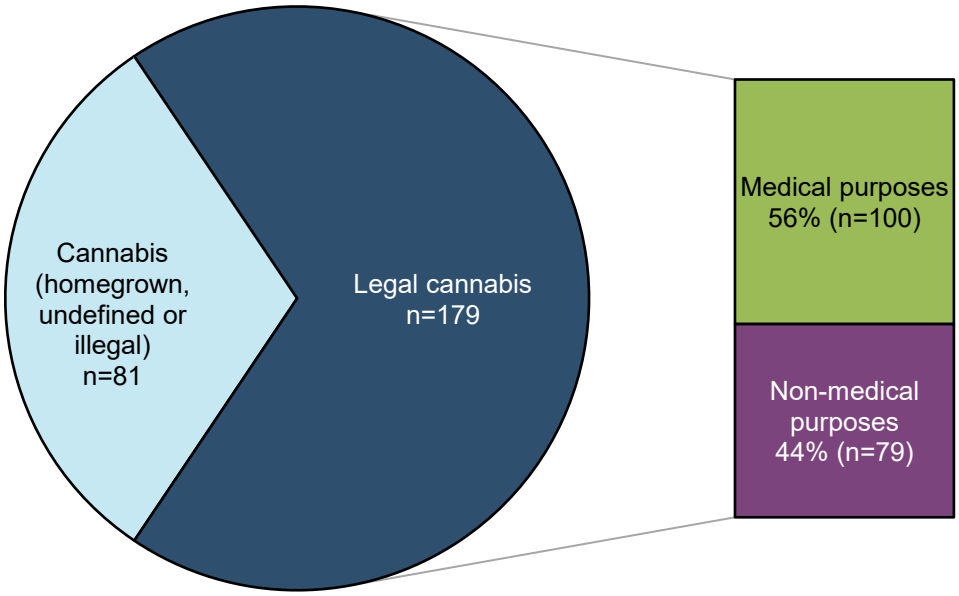

Figure 1 – Text description

	Number of reports	Proportion (%)
Cannabis (homegrown, undefined or illegal)	81	31
Legal cannabis products- Medical purposes	100	38
Legal cannabis products – Non-medical purposes	79	30
Total	**260**	**100**

Caveats:

- This figure represents all reports involving cannabis as a suspected substance that were submitted to Canada Vigilance database in 2021, including duplicate reports where the case details are the same, but reporters differ (n=33)
- Reports are classified for internal reporting purposes within Canada Vigilance depending on whether they report using legal cannabis products used for either for medical or non-medical purposes (1 classification per case); cases that do not involve cannabis products from legal sources are not assigned a classification and remain classified as cannabis as a substance only (undefined or illegal cannabis)
- Under the *Cannabis Act* and Regulations, adults are allowed to legally grow up to a maximum of 4 cannabis plants for personal use. However, this cannabis cannot legally be packaged and labeled for sale at the retail level. Therefore, adverse reaction reports involving homegrown cannabis are kept separate from reports involving legal cannabis products

A total of 260 reports (includes duplicates[4]) associated with cannabis as a suspect substance were submitted to Health Canada between January 1, 2021, and December 31, 2021. Most of these reports involved legal cannabis products (69%, n=179), of which most were self-reported as being used for medical purposes (56%, n=100). Of the reports involving unknown or illegal cannabis (31%, n=81) (for example, reports involving cannabis or marijuana without specific details), 28% (n=23) involved additional co-suspect substances or health products (for example, polysubstance or polypharmacy reports) in addition to cannabis. 1 report included the transformation of homegrown cannabis into edible cannabis.

Report of vaping-associated lung illness (VALI)

There were 2 suspected reports of VALI involving cannabis that were reported to the Canada Vigilance database in 2021. Both were suspected of involving multiple legal cannabis products. However, neither of these reports met the case definition of a confirmed or probable case of VALI as defined by the Public Health Agency of Canada.

More information is available at Vaping-associated lung illnesses.

Reports involving the pediatric population (under 18 years)

In 2021, there were 47 reports of adverse reactions to cannabis involving the pediatric population (aged under 18 years):

- 49% (n=23) of reports involving the pediatric population involved cannabis from an identifiable or suspected illegal source
- 49% (n=23) were from an unknown source

[4] Duplicate cases may exist if an adverse reaction report about the same adverse reaction event was received from different reporters (for example, from a health professional, consumer, hospital, or manufacturer).

- 1 report involved homegrown cannabis transformed into an edible format

In terms of route of administration:

- 77% (n=36) of these reports involved cannabis consumed orally, mostly in an edible format (n=33)
- 21% (n=10) involved inhalation as a route of administration, mostly smoking (n=7)
- route of administration was unknown in 1 report

Health Canada also monitors reports of accidental ingestion of cannabis in the pediatric population (under 18 years of age). 79% (n=37) of the reports involving the pediatric population involved accidental or unintentional exposure to cannabis, and all but 1 of these reports involved cannabis from an unknown or illegal source.

These case reports originate from multiple surveillance programs including the Canadian Surveillance System for Poison Information and the Canadian Paediatric Surveillance Program's study on non-medical cannabis use in children and youth: Serious and life-threatening events associated with non-medical (recreational) cannabis use in Canadian children and youth.

Health Canada continues to monitor pediatric exposures suspected to be associated with cannabis and will continue to take appropriate risk mitigation strategies as necessary. In August 2020, Health Canada issued a public advisory on accidental ingestion of edible cannabis by children. An updated public advisory was issued on May 10, 2023. These can be found at:

- Accidental ingestion of edible cannabis products causing serious harm to children (August 2020)
- Accidental ingestion of illegal "copycat" edible cannabis products causing serious harm to children (May 2023)

Case reports involving cannabis products for self-reported medical and non-medical purposes from the legal marketplace and regulated under the Cannabis Act and its Regulations form the basis for the remaining portions of this Annual Report.

Adverse reactions associated with legal cannabis products

Figure 2: Reports by reporting month and seriousness

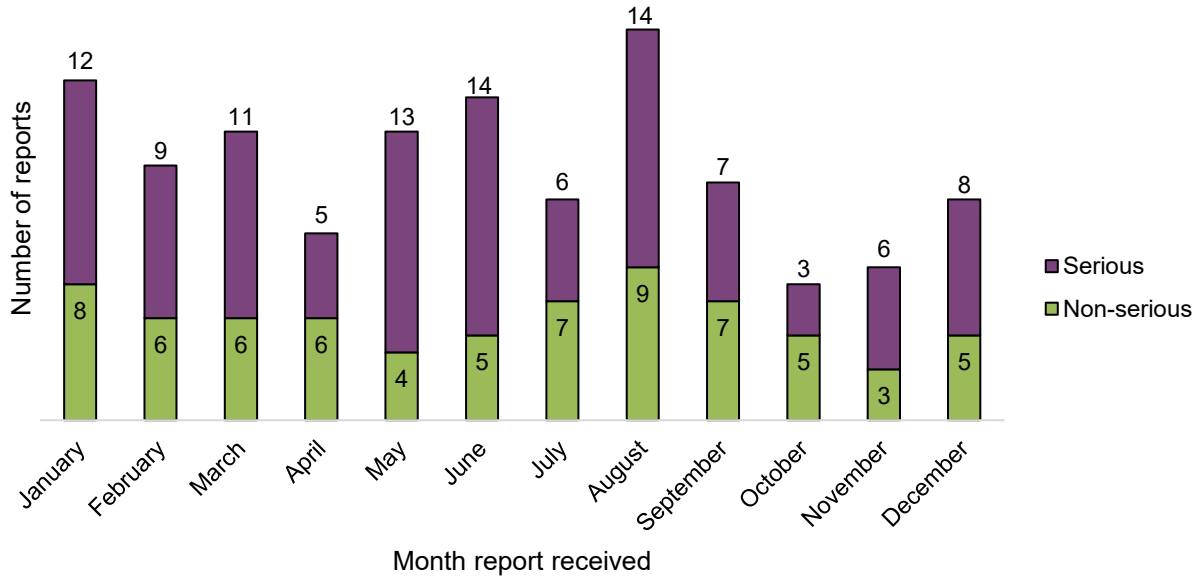

Figure 2 – Text description

Month report received	**Number of reports by seriousness**		
	Serious	Non-serious	Total
January	12	8	20
February	9	6	15
March	11	6	17
April	5	6	11
May	13	4	17
June	14	5	19
July	6	7	13
August	14	9	23
September	7	7	14
October	3	5	8
November	6	3	9
December	8	5	13
Total	**108**	**71**	**179**

Caveats:

- This figure includes duplicate reports where the case details are the same, but reporters differ (n=5)
- Seriousness is based on the initial report and may be subject to change if additional information is submitted to Health Canada
- Reports are presented according to the initial date of receipt by the Canada Vigilance database. The actual date of the adverse reaction may not align with the month that the report was received (lag time between event and reporting)

There were no clear temporal trends observed in the total number of adverse reaction reports involving legal cannabis products submitted to Health Canada in 2021. The average number of reports received by Health Canada per month during the reporting period was 14.5, ranging from 8 to 23 reports per month.

There were some descriptive trends observed in 2021 compared to 2020. The total number of reports overall (serious and non-serious) and the average number of serious and non-serious reports per month, increased in 2021 (total reports: from 161 to 179; average reports per month: from 13.4 to 14.5). However, the total number of serious reports submitted to Health Canada decreased from 123 reports in 2020 to 108 reports in 2021. In contrast, the total number of non-serious adverse reaction reports increased from 38 in 2020 to 71 in 2021.

Figure 3: Cases by reason for seriousness in serious cases

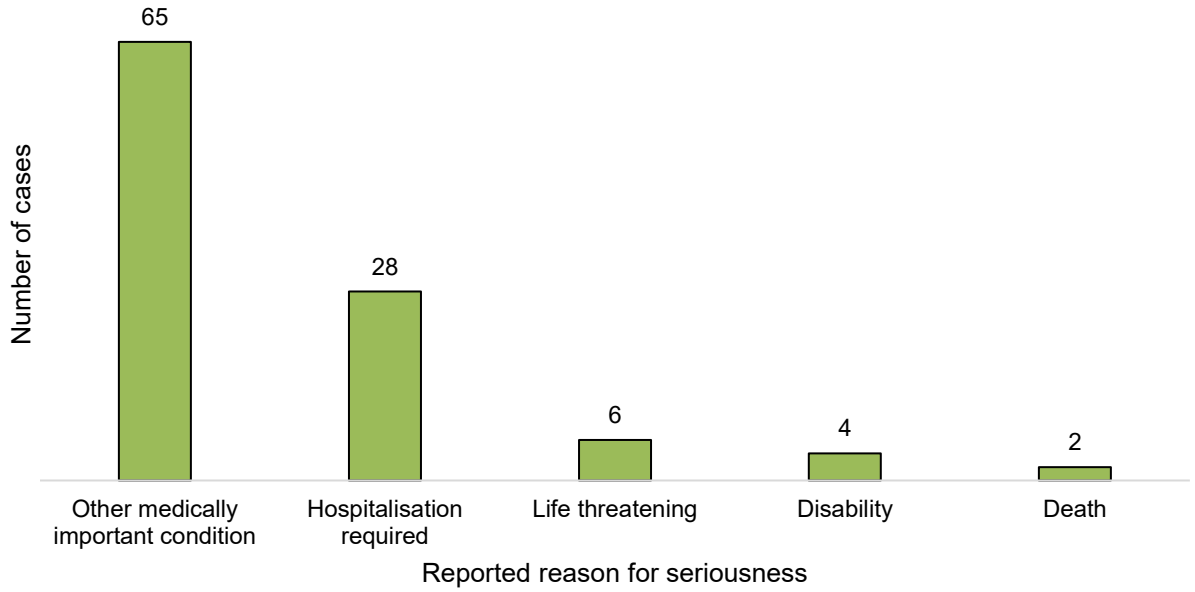

Figure 3 – Text description

Reason for seriousness	Number of cases
Other medically important condition	65
Hospitalisation required	28
Life threatening	6
Disability	4
Death	2
Total	**105**

Caveats:

- This figure includes unique cases where the reporter indicated that the adverse reaction was serious (n=105)
- Each serious case may have more than 1 reason for seriousness as the reporter may select multiple reasons

In 2021, all serious cases submitted to Health Canada involved 1 reason for seriousness, for a total of 105 responses for seriousness, spanning 5 categories selected by reporters (Figure 3). The most frequently selected category was “other medically important condition” (62%, n=65), followed by “hospitalization required” (27%, n=28). The category of “other medically important condition” includes events that are not immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require a medical intervention (for example, ambulatory services, emergency department visits, outpatient visits with an health care practitioner or at-home medical interventions) to prevent a serious outcome. In 2020, the most common reported reason for seriousness was also “other medically important condition” (71%, n=86).

2 cases associated with legal cannabis products involved fatal outcomes. More details regarding these 2 cases can be found below, in Fatal cases during the reporting period. Comparatively, no fatal outcomes were reported in 2020. 6 cases were reported as life threatening (an increase from 1 case in 2020) and 4 cases reported disability (an increase from 1 case in 2020).

Figure 4: Reports by initial reporter type and report source

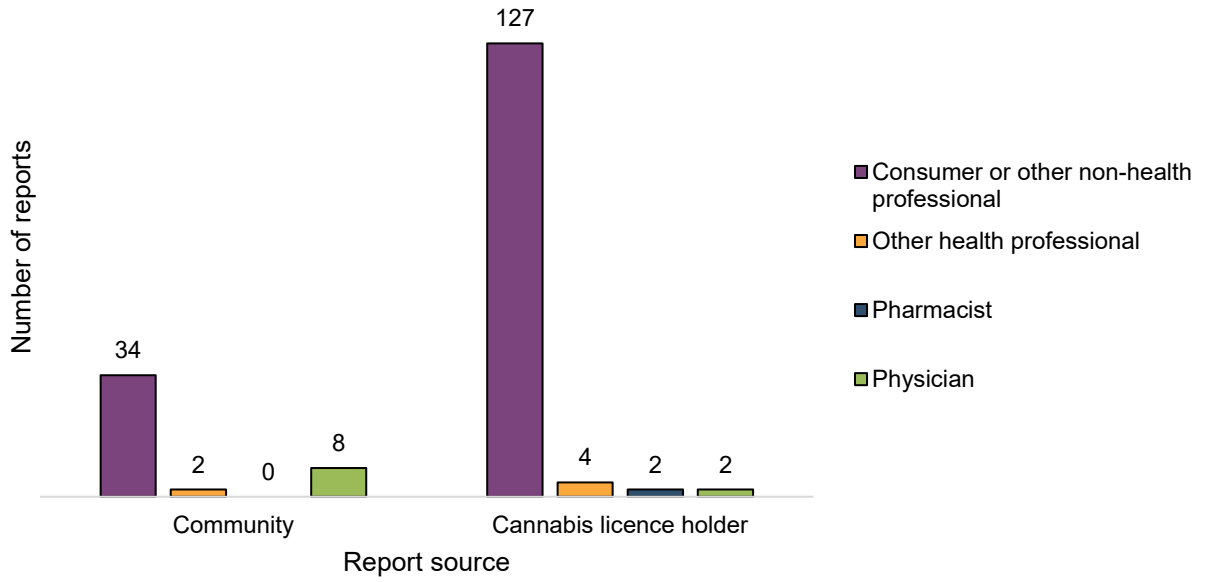

Figure 4 – Text description

Report source	Reporter type				
	Consumer or other non-health professional	Other health professional	Pharmacist	Physician	Total
Community	34	2	0	8	44
Cannabis licence holder	127	4	2	2	135
Total	**161**	**6**	**2**	**10**	**179**

Caveats:

- This figure includes duplicate reports where the case details are the same, but reporters differ (n=5)
- Reports from health care practitioners are considered medically confirmed as per international guidelines[5]; therefore, are distinct from consumer reports
- For purposes of this figure, each report source is further subdivided according to initial reporter type (consumer, health care practitioners [physician, pharmacist, other health professional])
- Report source is reflective from whom Health Canada received the report (community, hospital, or market authorization holder [for legal cannabis products, this would reflect and is labelled as a licence holder])

Most adverse reaction reports involving legal cannabis products were from cannabis licence holders (75%, n = 135), followed by voluntary community reporters (25%, n=44). Among cannabis licence holder reports, the main initial reporter type was a consumer (94%, n=127) followed by health care practitioners (6%, n=8). Consumers were also the main initial reporter type from the community (that is, reports submitted directly to Health Canada). These descriptive reporting trends are consistent with observations from 2020 in that consumers are more inclined to report adverse reactions directly to the licence holder who then submit to Health Canada as per their reporting obligations. Health care practitioners tend to report on behalf of their patients directly to Health Canada. However, compared to previous years, there has been a steady decrease in the number of serious and non-serious adverse reaction reports originating from health care practitioners (2018 to 2019: n=36; 2020: n=18; 2021: n=8). There were no reports of adverse reactions from hospitals that identified legal cannabis products in 2021, a decrease from 2020 (2%, n=3).

Under the *Protecting Canadians from Unsafe Drugs Act* (that is, Vanessa's Law), as of December 16, 2019, hospitals are required to submit all serious adverse reactions to Health Canada involving suspect drugs (including drugs containing cannabis) with or without other suspect products. Reports involving a co-suspect drug and co-suspect cannabis are also required to be submitted to Health Canada. However, under the *Cannabis Act* and its Regulations, hospitals may consider submitting, on a voluntary basis, any adverse reactions involving cannabis as the sole suspect product.

[5] World Health Organization (2012). Safety monitoring of medicinal products. Reporting system for the general public. Available from: https://www.who.int/publications/i/item/9789241503198.

Demographics

Figure 5: Cases by age group

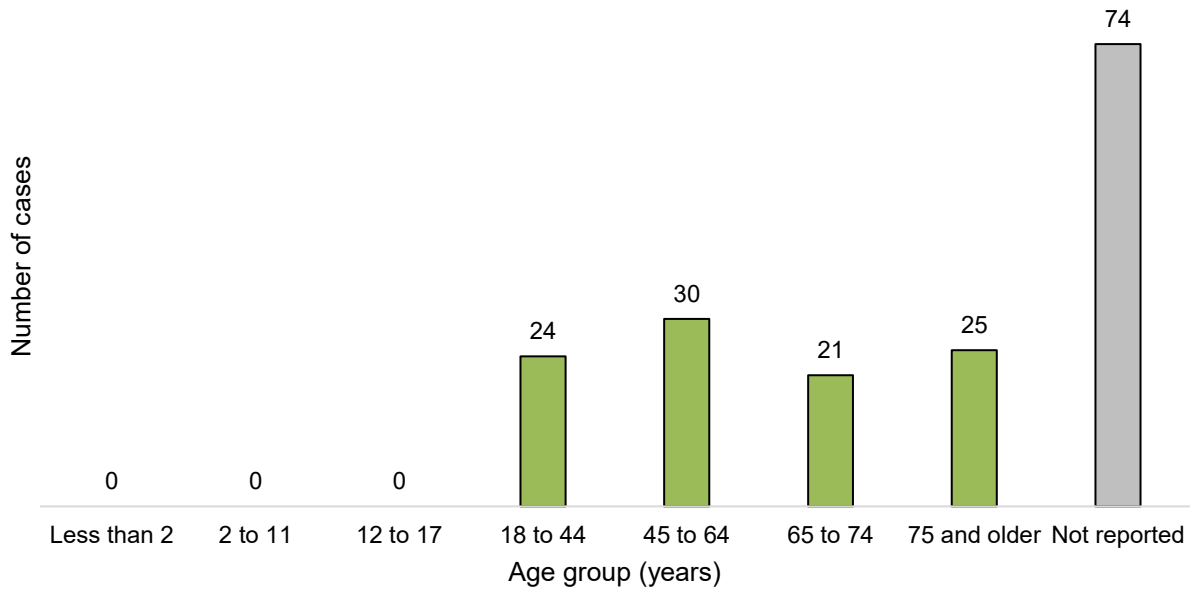

Figure 5 – Text description

Age group (years)	Number of cases
Less than 2	0
2 to 11	0
12 to 17	0
18 to 44	24
45 to 64	30
65 to 74	21
75 and older	25
Not reported	74
Total	**174**

Caveats:

- In cases where the year of birth and the date of reaction are listed in the report, then the age is calculated
- In cases where the year of birth is listed without a date of reaction, the date the report was submitted is used to calculate the age

The average age of individuals in cases involving adverse reactions to legal cannabis products in 2021 was approximately 59 years (95% CI: 55-63) with a range of 18 years to 99 years. This did not differ significantly from 2020 where the average age was 59 years (95% CI: 56-63) with a range of 5 months to 91 years.

When classified using the World Health Organization's Vigilyze database (Vigibase) age groupings, most cases involved persons aged 45 to 64 years (17%, n=30). This differs from 2020 where 65 to 74 years was the most common age group (23%, n=35). However, more than a quarter of cases in 2021 involved

older adults aged 65 years and older (26%, n=46), as a composite category. No pediatric cases (under 18 years of age) were reported as involving legal cannabis products in 2021.

Many cases in 2021 lacked age-related information (43%, n=74), which is a large increase from 2020 (23%, n=37).

Figure 6: Cases by sex

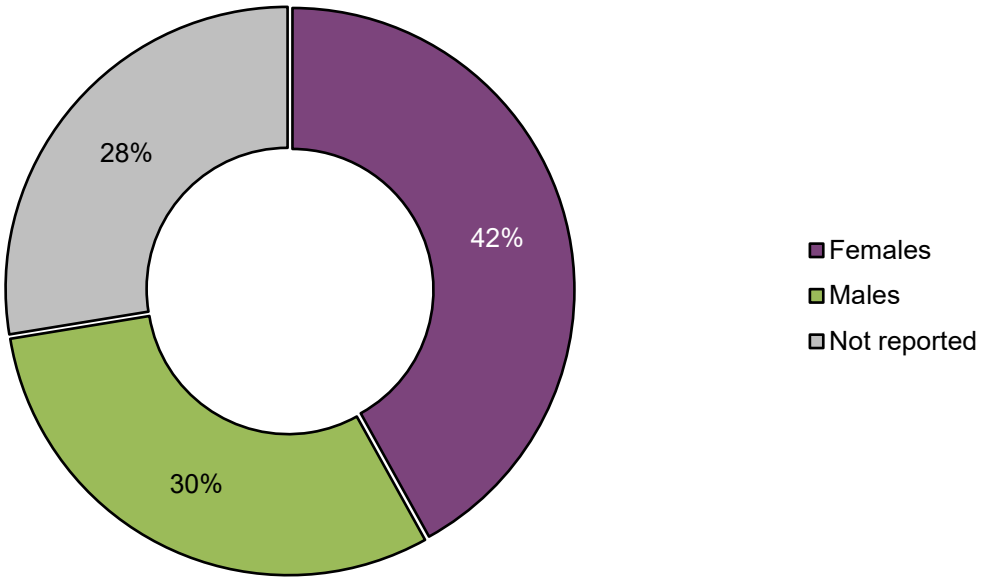

Figure 6 – Text description

Sex	Number of cases	Proportion (%)
Females	73	42
Males	53	30
Not reported	48	28
Total	**174**	**100**

Just under a half of the adverse reaction cases reported in 2021 involved females (42%, n=73), while about a third involved males (30%, n=53) and 28% (n=48) did not indicate the sex of the individual. The distribution of cases by sex was similar to 2020 in that female made up a greater proportion of the cases compared to males (females: 57%; males: 35%). The number of cases not reporting sex increased from 8% in 2020 to 28% in 2021.

Sex and age may not be reported for to several reasons, including consumers not wanting to disclose this information to licence holders or Health Canada, or cases originating from other reporting forms such as the Cannabis Reporting Form, which do not capture this type of demographic information.

Suspected cannabis products

Most adverse reaction cases reported tin 2021 were associated with legal cannabis products as the sole suspect product (94%, n=163), meaning that no other health products were reported as co-suspects. Health products may include:

- natural health products
- prescription or non-prescription drugs

- other types of health products regulated under the *Food and Drugs Act*

However, many cases (38%, n=66) included at least 1 concomitant product (that is, a product that is used at the time of the adverse reaction but not considered suspect by the reporter). Concomitant products may be:

- health products
- illegal substances
- other regulated substances (for example, alcohol, tobacco or other vaping products such as nicotine or flavours)

A small proportion of cases (13%, n=23) reported in 2021 had 2 or more suspect cannabis products reported, with a range of 2 to 4 cannabis products, similar to 2020 (17%, n=27). Of note, suspect products are based on the suspicion of the reporter and the involvement of other products, substances or factors cannot always be ruled out. These considerations form part of the clinical evaluation in the clinical summary portion of this report.

Figure 7: Cases by route of administration

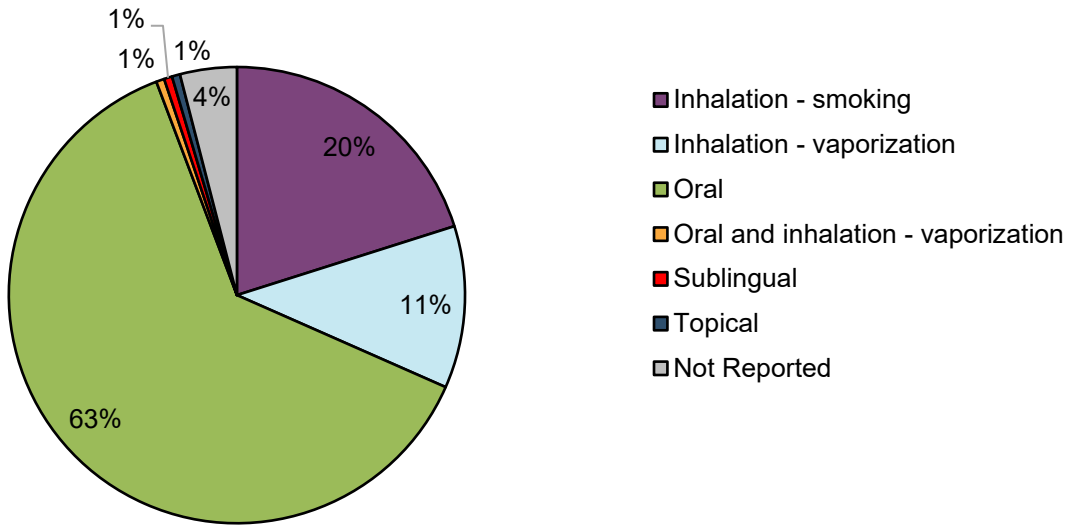

Figure 7 – Text description

Route of administration	Number of cases	Proportion (%)
Inhalation - smoking	35	20
Inhalation - vaporization	20	11
Oral	109	63
Oral and inhalation - vaporization	1	1
Sublingual	1	1
Topical	1	1
Not reported	4	4
Total	**174**	**100**

Caveats:

- This figure describes route of administration of suspect cannabis products in cases, which is coded separately from dosage form (that is, a cannabis oil product may be ingested or applied topically)
- Cases may involve more than 1 suspect cannabis product; therefore, multiple routes of administration may appear for a single case
- Inhalation refers to consuming cannabis through the respiratory tract and may involve smoking or vaporization, among others
- Oral administration refers to consuming cannabis by mouth and may involve, for example, ingestion, buccal administration or sublingual administration, meaning that absorption may occur at the level of the gastrointestinal tract as well directly into the bloodstream through oral mucosal tissue

Suspect cannabis products associated with adverse reaction cases were most frequently orally consumed cannabis extracts (63%, n=109) followed by inhalation via smoking (20%, n=35) and inhalation via vaporization (11%, n=20). All instances of vaporization included inhalation of vaporized cannabis extracts with no cases involving inhalation of vaporized dried cannabis. There were few instances of topical or sublingual administration (n=1 each) and 1 case involved multiple routes of administration.

These results are consistent with observations from 2020.

Figure 8: Cases by product class and reason for use

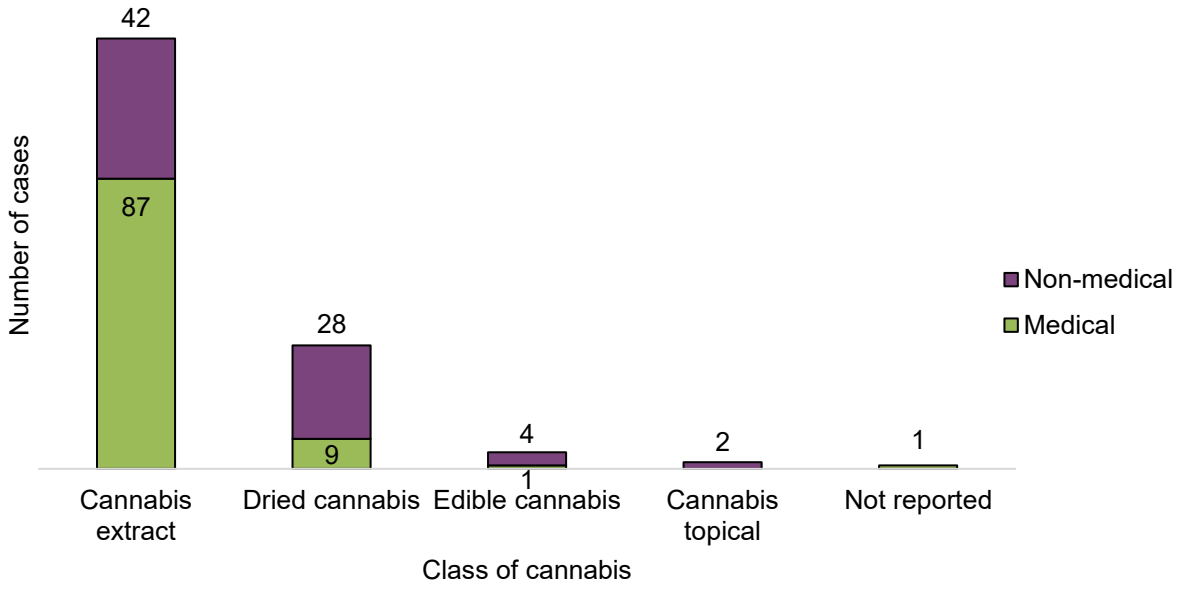

Figure 8 – Text description

Class of cannabis product	Reason for use		
	Medical	Non-medical	Total
Cannabis extract	87	42	129
Dried cannabis	9	28	37
Edible cannabis	1	4	5

Cannabis topical	0	2	2
Not reported	1	0	1
Total	**98**	**76**	**174**

More than half of adverse reaction cases reported in 2021 were associated with cannabis products used for medical purposes (56%, n=98), versus non-medical purposes (44%, n=76). The majority of the cases involving cannabis products for medical purposes were serious (81%, n=79). In contrast, most cases involving cannabis products for non-medical purposes were non-serious (66%, n=50).

Cases were associated with 4 main classes of legal cannabis products (Figure 8):

- cannabis extracts (n=129)
- dried cannabis (n=37)
- edible cannabis (n=5)
- cannabis topicals (n=2)

No cases in 2021 were associated with fresh cannabis. Most cases involving cannabis extract products were used for medical purposes (67%, n=87), unlike cases involving dried cannabis (24%, n=9). These descriptive observations are consistent with observations from 2020.

No cases involving transformation of legal cannabis products into homemade edible cannabis were reported in 2021.

Figure 9: Cases by suspect cannabis product sub-class and seriousness

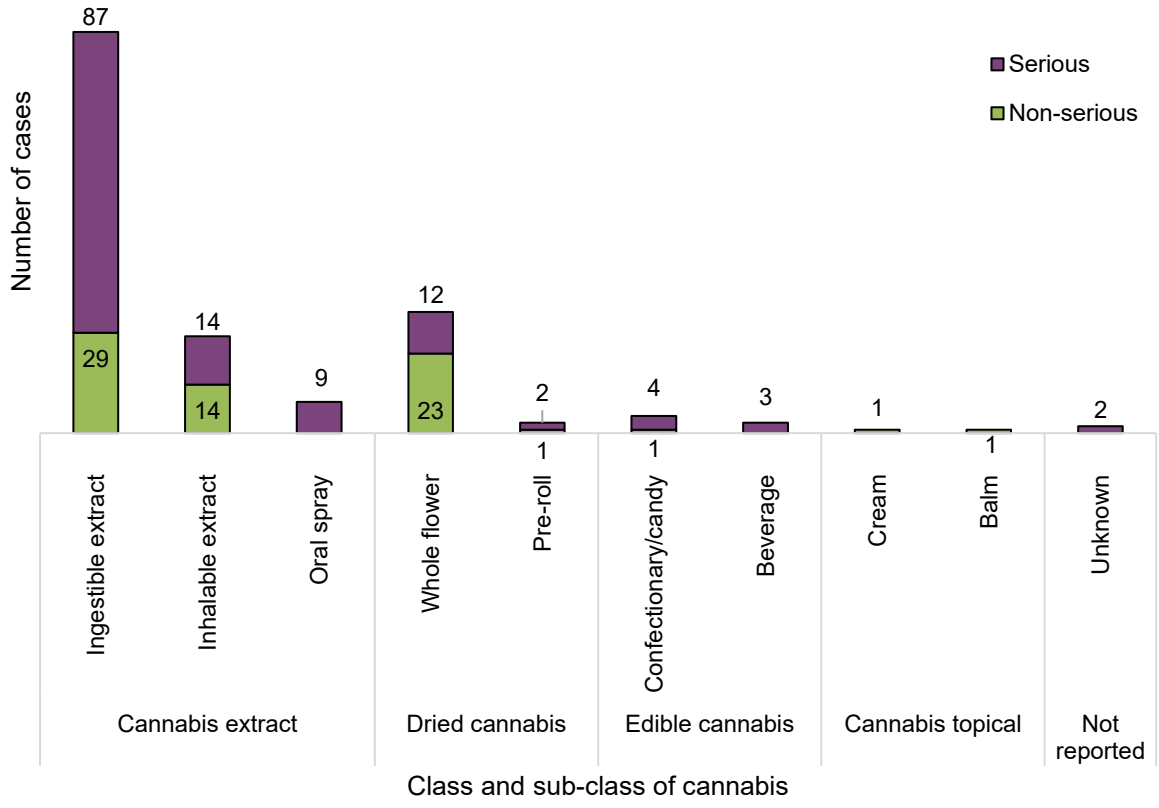

Figure 9 – Text description

Class of cannabis product	Sub-class of cannabis product	Total number of products by seriousness		
		Serious	Non-serious	Total
Cannabis extract	Ingestible extract	87	29	116
	Inhalable extract	14	14	28
	Oral spray	9	0	9
Dried cannabis	Whole flower	12	23	35
	Pre-roll	2	1	3
Edible cannabis	Confectionary/candy	4	1	5
	Beverage	3	0	3
Cannabis topical	Cream	0	1	1
	Balm	0	1	1
Not reported	Unknown	2	0	2
Total		**133**	**70**	**203**

Caveats:

- This figure was developed by Health Canada through manual categorization of cases according to their sub-class of suspect cannabis product(s)
- Cases may have multiple suspected cannabis product reported across different sub-classes of cannabis. For this reason, the total number reflected in the table according to count of suspect products by sub-classes and seriousness may exceed the number of unique cases
- Cannabis extracts as a class involves a diverse group of product forms including oral liquids or drops, softgels, capsules or tablets, sublingual sprays, dissolvable strips or highly concentrated extracts like shatter, wax, rosin, resin or vaping liquids. Dried cannabis includes whole dried flower, milled flower, and pre-rolls. Edibles includes food-like formats (chocolate, confectionary, mints) and beverages
- Oral sprays (ingestible) are noted separately from ingestible liquid extracts based to their intended sublingual or oro-mucosal use (that is, inside the mouth) that may absorb directly into the bloodstream

As noted above, cannabis extracts were the most frequently reported class of cannabis products among adverse reaction cases. Within the category of cannabis extracts, ingestible oils in liquid form (bottled oils with dropper) and in softgel capsules were most frequently involved, representing 56% (n=86) and 20% (n=30) of adverse reaction cases involving cannabis extracts. Inhalable liquid extracts (vaping liquids) represented 18% (n=28).

Consistent with 2020, all but 1 case involving older adults (65 years or older; where age was available) reported use of cannabis extracts, whereas cases involving younger adults reported use of both dried cannabis and cannabis extracts. When broken down by sub-class, young to middle aged adult groups (18 to 64 years) were more frequently involved in adverse reaction cases with vaping liquids and oral sprays, while older adults (65 years or older) were more frequently involved in adverse reaction cases with ingestible oils in liquid form and softgel capsules.

Some consumers or patients may preferentially select ingestible cannabis oil products for 1 or more reasons such as:

- for duration of effect
- to avoid inhaling cannabis
- for cannabinoid concentration
- for the ability to draw or titrate a specific measured dose
- other reasons

In addition, adults over 55 years of age may be more sensitive to cannabis and have a higher risk of experiencing adverse reactions. This is especially true when they have certain medical conditions or use other health products, which may increase the risk of possible interactions, thereby contributing to an increased risk of experiencing adverse reactions.

Types of individual events reported

Figure 10: Breakdown of individual events by system organ class (SOC)

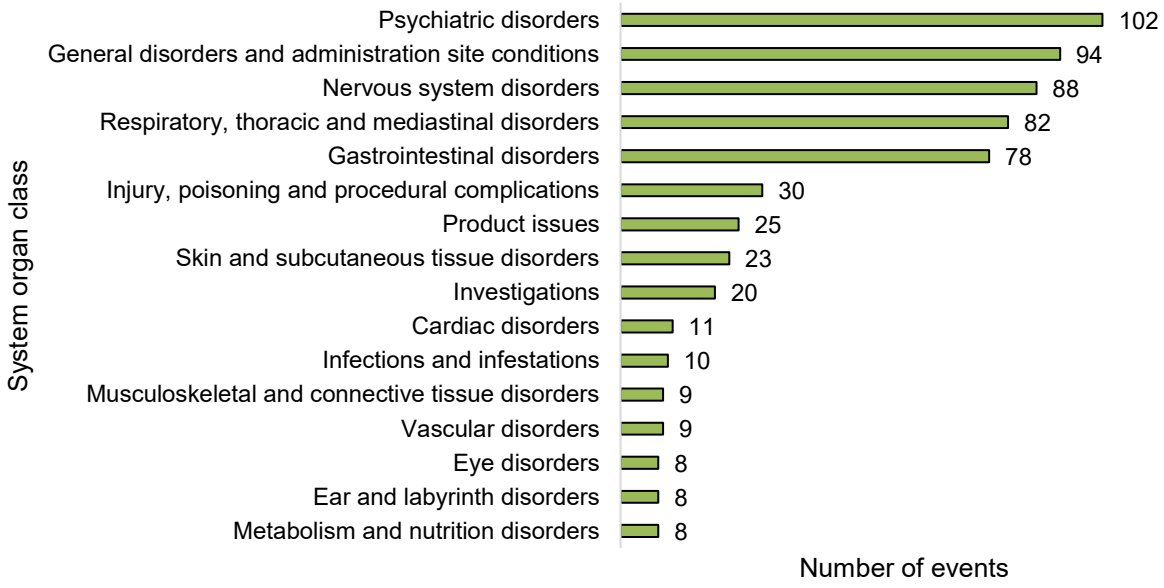

Figure 10 – Text description

System organ class	Number of events
Psychiatric disorders	102
General disorders and administration site conditions	94
Nervous system disorders	88
Respiratory, thoracic and mediastinal disorders	82
Gastrointestinal disorders	78
Injury, poisoning and procedural complications	30
Product issues	25
Skin and subcutaneous tissue disorders	23
Investigations	20
Cardiac disorders	11

Infections and infestations	10
Musculoskeletal and connective tissue disorders	9
Vascular disorders	9
Eye disorders	8
Ear and labyrinth disorders	8
Metabolism and nutrition disorders	8

Caveats:

- This figure focuses on the most frequently reported SOCs across all adverse reaction cases. Other SOCs reported less frequently do not appear in this figure
- Each case may describe 1 or more individual medical event reflective of signs, symptoms, diseases, diagnoses, investigations, and procedures
- Events are coded according to Medical Dictionary for Regulatory Activities (MedDRA), which provides standardized medical terminology in hierarchical groupings. The highest-level grouping is the SOC
- 1 adverse reaction case may be represented across multiple SOCs, and is influenced by how individual events (signs, symptoms, observations or diagnostics) are reported

Overall, 617 individual events (representing 269 unique types of event categories) were reported across the 174 cases in 2021. When grouped at the broadest grouping level (that is, SOC) the 5 most frequent categories were:

- psychiatric disorders (17%)
- general disorders and administration site conditions (15%);
- nervous system disorders (14%)
- respiratory, thoracic and mediastinal disorders (13%)
- gastrointestinal disorders (13%)

These top 5 SOCs for 2021 are consistent with the top 5 SOCs reported in 2020, but in varying order.

Figure 11: Frequency of individual events

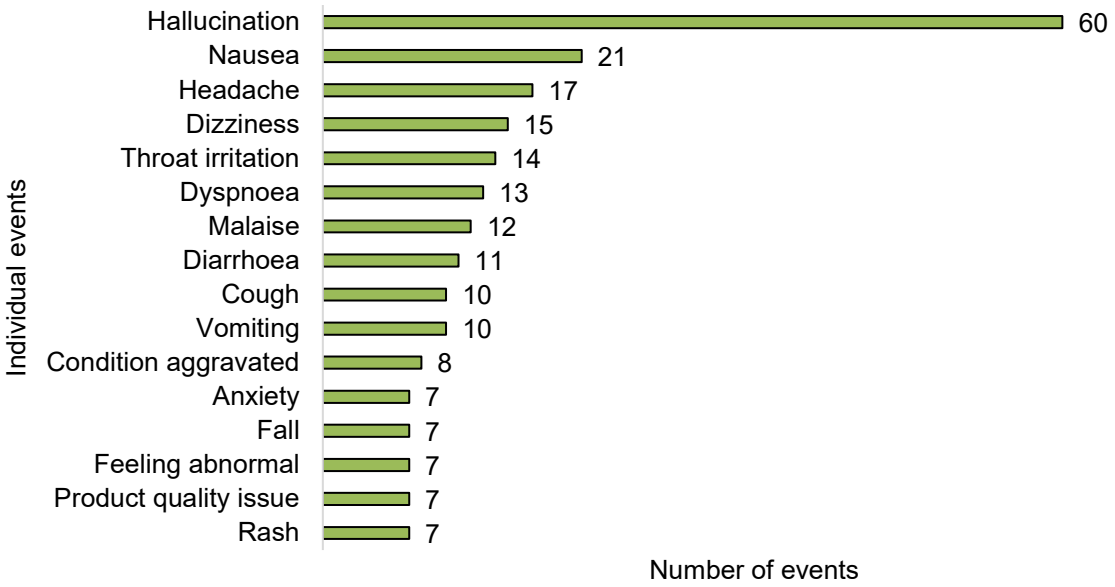

Figure 11 – Text description

Individual events	Number of events
Hallucination	60
Nausea	21
Headache	17
Dizziness	15
Throat irritation	14
Dyspnoea	13
Malaise	12
Diarrhoea	11
Cough	10
Vomiting	10
Condition aggravated	8
Anxiety	7
Fall	7
Feeling abnormal	7
Product quality issue	7
Rash	7

Caveats:

- This figure focuses on the most frequently reported across all adverse reaction cases. Other individual events reported less frequently do not appear in this figure
- Individual events are coded using MedDRA terminology based on the verbatim described in the case report

- Each case can have multiple individual events reported therefore the number of individual events exceeds the total number of cases
- The inclusion of a particular report in the database does not necessarily mean that the suspected product(s) caused it. Additional scientific investigations are required to establish a cause-and-effect relationship between a cannabis product and an adverse reaction
- Several types of hallucination were combined to create an all-inclusive hallucination category. These included auditory hallucination, visual hallucination, mixed hallucination, hypnagogic hallucination and pseudohallucination

As noted in Figure 11, the most frequently reported individual events in 2021 were:

- Hallucination (10%)
- Nausea (3%)
- Headache (3%)
- Dizziness (2%)
- Throat irritation (2%)

Other reported events of interest include suspected product issues (n=7), drug interactions (n=2) and hypoglycemia (n=1). Potential cannabis-drug interactions of interest that were identified during this period and risk of hypoglycemia are further described in Important potential risks during the reporting period.

In 2020, hallucination was also the most frequently reported individual medical event, followed by dizziness and nausea.

Figure 12: Frequency of individual events by cannabinoid ratio

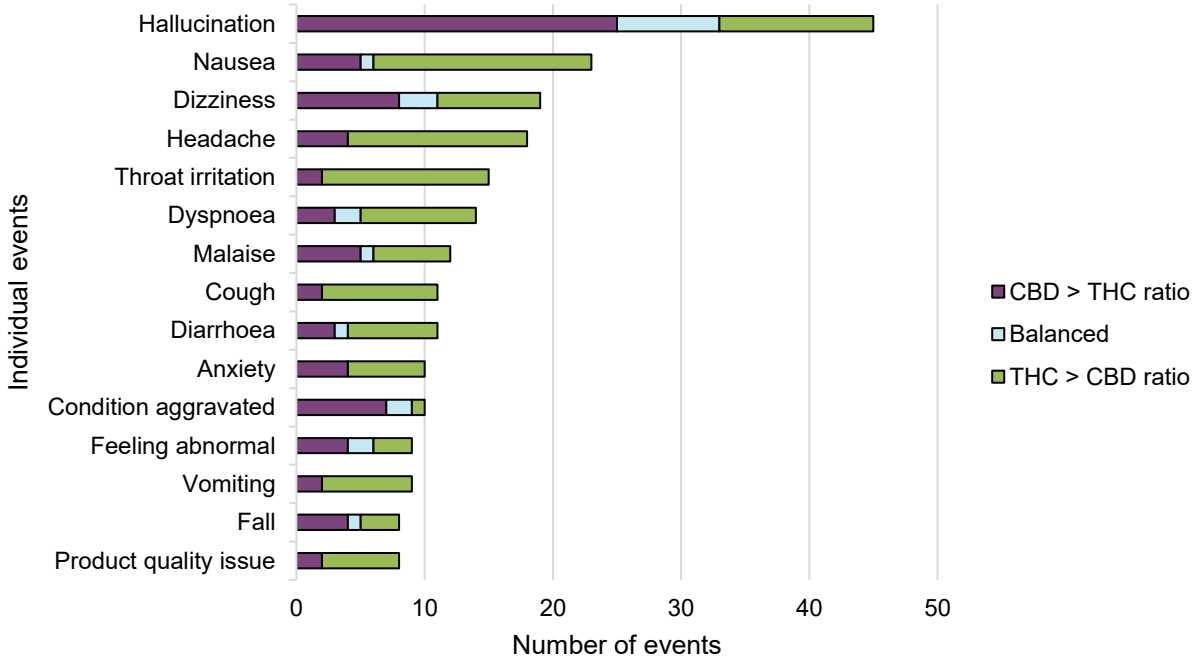

Figure 12 – Text description

Individual events	Cannabinoid dominance			
	CBD > THC ratio	Balanced	THC > CBD ratio	Total
Hallucination	25	8	12	45
Nausea	5	1	17	23
Dizziness	8	3	8	19
Headache	4	0	14	18
Throat irritation	2	0	13	15
Dyspnoea	3	2	9	14
Malaise	5	1	6	12
Cough	2	0	9	11
Diarrhoea	3	1	7	11
Anxiety	4	0	6	10
Condition aggravated	7	2	1	10
Feeling abnormal	4	2	3	9
Vomiting	2	0	7	9
Fall	4	1	3	8
Product quality issue	2	0	6	8

Caveats:

- This figure focuses on the most frequently reported individual events after stratification by cannabinoid ratio. This figure excludes cases without sufficient information for assignment of cannabinoid ratio (that is, unclassified), therefore, the events in this figure may differ from those observed in Figure 11. Other events were reported during the reporting period but do not appear in this figure
- This figure was manually created by Health Canada by classifying each suspect cannabis product to a cannabinoid ratio based on available product details and assigning all individual events within a case to all reported suspect cannabis products and their cannabinoid ratio (weighted equally for all events). Therefore, this may over-estimate the correlation between cannabinoid ratio and individual events and is not reflective of causality
- The category “balance” is considered a THC:CBD ratio between 1.2:1 and 1:1.2.

Overall, adverse reaction cases from 2021 more frequently involved products with a greater THC to CBD ratio (that is, a THC:CBD ratio greater than 1.2:1) compared to products containing a greater CBD to THC ratio (that is, a CBD:THC ratio greater than 1.2:1). As highlighted in Figure 12, certain individual medical events were more frequently reported with products containing a greater ratio of THC to CBD, whereas others were more frequently reported with products containing a greater ratio of CBD to THC.

For example, the following were more frequently reported with products containing a greater ratio of THC to CBD:

- cough
- nausea
- anxiety
- vomiting

- diarrhoea
- dyspnoea
- headache
- throat irritation

Whereas hallucinations and “condition aggravated” were more frequently reported with products containing a greater ration of CBD relative to THC.

These are reported events only and other factors may be contributing to these events, including:

- dosage
- route of administration
- knowledge or awareness of effects of cannabis and cannabinoids
- prior exposure to cannabis (for example, cannabis naïve consumers)
- reporting factors such as motivation to report, risk tolerance, awareness of reporting
- the age and health status of patients (including pre-existing health conditions and use of concomitant medications).

However, the ability to draw strong conclusions is limited due to the complex nature of the available data.

Figure 13: Primary reason for reporting (case level)

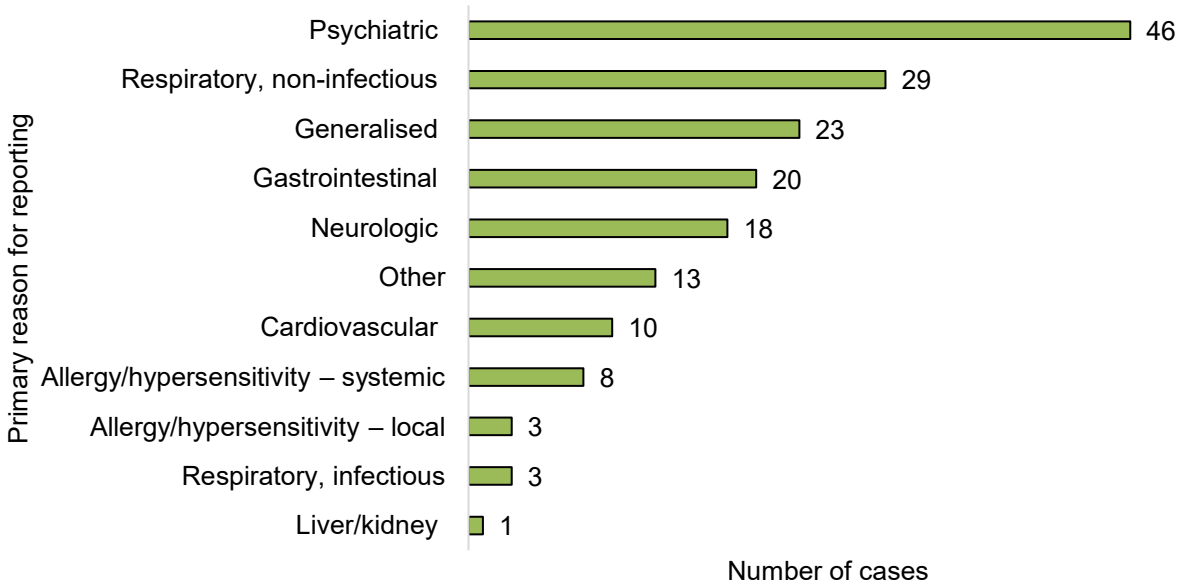

Figure 13 – Text description

Primary reason for reporting	Number of cases
Psychiatric	46
Respiratory - non-infectious	29
Generalised	23
Gastrointestinal	20

Neurologic	18
Other	13
Cardiovascular	10
Allergy/hypersensitivity – systemic	8
Allergy/hypersensitivity – local	3
Respiratory - infectious	3
Liver/kidney	1
Total	**174**

Caveats:

- This data was manually created by Health Canada by assigning 1 primary medical reason at the case level based on the overall details (including verbatim narrative), rather than by individual medical event level (frequency)
- If more than 1 reason existed, the event with greater severity was selected

As described above, the breakdown of individual events by SOC is useful for overall data presentation; however, it is not always sufficient to represent clinical conditions or events that may have multi-system involvement (that is, involve multiple SOCs or involve events that impact the same SOCs), which is important for ongoing monitoring and detection of new safety signals.

As such, Health Canada also conducts a manual review of case-level details to assign a primary reason for reporting to each case. If a primary reason is explicitly highlighted in a report, then this primary reason for reporting is used. This allows Health Canada to identify and highlight cases of clinical interest that may span across multiple SOCs[6], or that may fall under generalized SOC categories that lack specificity[7]. This aids in signal monitoring and case identification for further assessment.

Using this methodology, the following conditions were the most common primary reasons for reporting at the case level:

- psychiatric
- respiratory (non-infectious)
- generalized
- gastrointestinal
- neurologic

This is generally consistent with the SOC groupings according to frequency of individual events in Figure 11.

[6] For example, allergy or hypersensitivity reactions may span multiple SOCs, including SOC skin and subcutaneous disorders; SOC immune system disorders; and may involve others such as SOC cardiac disorders, SOC investigations, and SOC gastrointestinal disorders in instances of anaphylaxis.
[7] For example, drug interaction is classified under the SOC ‘General disorders and administration site conditions’.

SEX AND GENDER BASED ANALYSIS PLUS OF 2021 ADVERSE REACTION DATA

Figure 14 – SGBA plus: Cases by sex

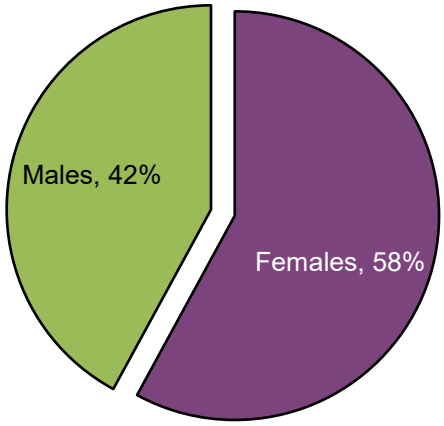

Figure 14 – Text description

Sex	Number of cases	Proportion (%) of total
Females	73	58
Males	53	42
Total	**126**	**100**

A total of 126 adverse reaction cases included a designation for sex in 2021. Of these cases 58% (n=73) involved females. Females were involved in 60% of all serious cases with a reported sex, and 81% of females and 64% of males used cannabis for medical purposes. Non-serious cases equally involved both females and males.

Females involved in adverse reaction cases associated with cannabis products were older than males. The average age of females was 61.6 years (95% CI: 56.4-66.7) and 55.7 years for males (95% CI: 48.9-62.5).

Under 65 years: Females, n=29; males, n=24

65 years and older: Females, n=30; males, n=15

Figure 15 – SGBA plus: Cases by age group (years)

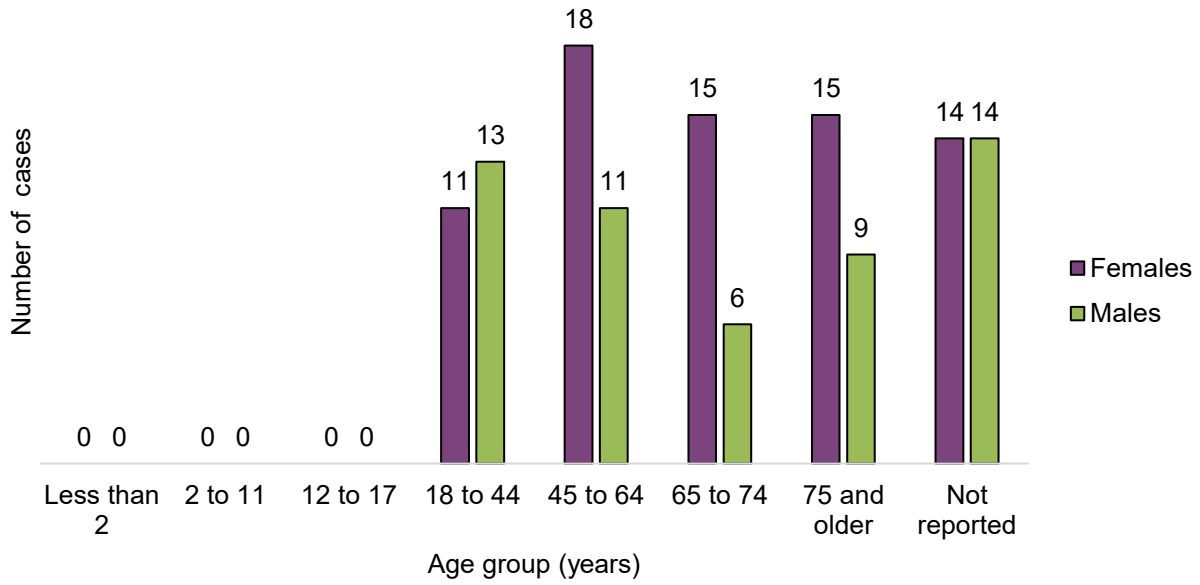

Figure 15 – Text description

Age group (years)	**Number of cases**	
	Females	Males
Less than 2	0	0
2 to 11	0	0
12 to 17	0	0
18 to 44	11	13
45 to 64	18	11
65 to 74	15	6
75 and older	15	9
Not reported	14	14
Total	**73**	**53**

Adverse reactions cases involving inhaled dried cannabis (whole flower) and edibles (beverages and confectionaries) more frequently involved males than females. Conversely, ingestible cannabis extracts in liquid format (bottled oils), inhalable liquid extracts (vapes) and oral sprays more frequently involved females than males.

Females were more frequently involved in adverse reaction cases where multiple suspect cannabis products were reported than males (12 vs. 10 cases with multiple products, respectively).

Table 1: Top individual events reported by sex	
Females	*Males*
Hallucination* (n=21)	Hallucination* (n=6)
Dizziness (n=12)	Dyspnoea (n=6)
Headache (n=8)	Vomiting (n=6)
Nausea (n=8)	

* including visual, auditory, mixed, hypnagogic and pseudohallucination.

CLINICAL EVALUATION OF SERIOUS AND MEDICALLY IMPORTANT CASES

Important identified risks during the reporting period

During this reporting period, no serious or medically important cases were classified as new important identified risks by Health Canada. An identified risk means that the association between a drug (for example, cannabis) and event has been proven, and that this risk could implications for public health.[8]

Most serious or medically important cases with "Probable" causality were considered to involve known identified risks (that is, the risk is has already been identified and characterised in Health Canada's Information for Health Care Professionals document; last updated: Spring 2018). These include:

- Psychiatric reactions (for example, panic, anxiety, hallucinations)
- Neurological reactions (for example, headache, light-headedness)
- Respiratory non-infectious reactions (for example, throat irritation)
- Cardiovascular reactions (for example, atrial fibrillation, palpitations, tachycardia)
- Hypersensitivity or allergic reactions (for example, systemic hypersensitivity reactions)

Important potential risks during the reporting period

3 important potential risks were observed in adverse reaction data with cannabis products during this reporting period.

A potential risk means that there is suspicion of association between a drug (for example, cannabis) and the event, which is yet to be proven, and that this risk could have implications for public health.[8]

Risk of hallucination with the use of CBD-dominant cannabis products

While hallucination is known to be associated with THC due to its psychotropic properties as described in Health Canada's Information for Healthcare Professionals document, hallucination following the use of

[8] European Medicines Agency. (2017). Guideline on good pharmacovigilance practices (GVP): Annex I - Definitions (Rev 4). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf

CBD-dominant[9] or CBD-leaning[10] products is considered a new and unexpected adverse reaction as CBD is not known to be psychotropic.

During this reporting period, there were 15 suspected cases of hallucination (auditory hallucination, visual hallucination, mixed hallucination, hypnagogic hallucination or pseudohallucination) involving CBD-dominant products. 17 cases of hallucination involving CBD-dominant cannabis products were reported during the 2020 reporting period.

It is important to note that although these products are defined as CBD-dominant, they do contain THC and dose and frequency of use may increase exposure to THC. Moreover, most of these cases occurred in adults aged 65 years and older with reported pre-existing conditions, and other risk factors may be involved in these cases.

As such, several factors may be playing a role in these adverse reactions. An in-depth assessment (signal assessment) was initiated by the Controlled Substances and Cannabis Branch, which included a review of domestic and foreign reports of hallucination as well as data from the published literature to determine whether CBD has the potential to cause hallucination in certain individuals.

Risk of hypoglycemia with the use of cannabis products

This signal was considered new and not previously well characterized; therefore, a review was initiated by the Controlled Substances and Cannabis Branch.

During this reporting period, there were 3 suspected cases in which a CBD-dominant or THC-dominant cannabis product was associated with the event of decreased blood glucose. No dose-response can be determined from the domestic cases, which lacked in important details (that is, concomitant medications and medical history).

At this time only a potential risk can be established and therefore, an in-depth assessment (case series) was initiated by the Controlled Substances and Cannabis Branch, which included a review of domestic and foreign reports of hypoglycemia as well as data from the published literature in order to determine whether or cannabis has the potential to cause hypoglycemia in humans.

Risk of cannabis-drug interaction

During this reporting period, there was 1 medically confirmed case involving a cannabis-drug interaction.

This case reported by a pharmacist involving CBD-dominant cannabis product and paroxetine, an antidepressant. This interaction was assessed as “Possible” due to an acceptable temporal relationship and pharmacological plausibility.

Interactions between CBD and anti-depressants are considered “known” and are described in the Information for Healthcare Professionals document.

Data from the scientific literature indicate that cannabinoids can modulate the activities of drug-metabolizing enzymes (for example, THC as a CYP1A2 inducer and CBD as a potent inhibitor of CYP3A4 and CYP2D6). Therefore, there is a possible risk of interaction between cannabinoids and certain medications that may vary in clinical significance depending on patient risk factors and on the cannabis

[9] THC:CBD ratio greater than 1:1.5
[10] THC:CBD ratio in between 1:1.2 and 1:1.5

product (for example, concentration of THC and CBD), dose, route of administration. Additionally, cannabinoids can have pharmacodynamic interactions with other drugs, as outlined in Health Canada's Information for Healthcare Professionals document (that is, central nervous system impairment from THC can be exacerbated with co-consumption of other central nervous system depressants).

As such, the signal of cannabis-drug interaction remains an important potential risk that Health Canada continues to monitor in the future.

Fatal cases during the reporting period

During this reporting period, Health Canada conducted a comprehensive assessment on 2 fatal cases involving cannabis products for medical purposes.

Case 1

1 fatal case involved a patient with multiple multi-system involvement and allergic events. In this reporting period, some cases, like those resulting in a fatal outcome, underwent a comprehensive causality assessment for each individual medical event reported, including the fatal outcome.

In this case, anaphylaxis associated with consumption of CBD-dominant cannabis product was assessed as "Certain" by Health Canada. There is biological plausibility given that cannabis is known to be associated with hypersensitivity or allergic type reactions in certain individuals, detailed in the Information for Healthcare Professionals document. Additionally, the fatal outcome in direct relation to the cannabis product in this case was assessed as "Unlikely" as the patient had many confounding factors and complex medical history.

Case 2

A second fatal case was received in 2021 and involved 2 cannabis vaping products with other concomitant medications in a patient with complex medical history and several risk factors who experienced seizures which led to hospital admission then death.

The outcome of death was determined to be from multi-organ failure and sepsis. The sepsis was most likely due to a staphylococcal infection, of which the source was the temporary hemodialysis line placed in the patient to address deteriorating kidney function.

The use of a cannabis vape product may have been a cause of the initial seizure but is less likely to be the cause of the patient's death. However, Health Canada cannot rule out the contribution of the vaping THC products to some of the underlying lung and kidney injury prior admission.

NOTE TO READERS

Adverse reaction reports with cannabis submitted to Health Canada are received and entered into the Canada Vigilance database. The Marketed Health Product Directorate of the Health Products and Food Branch collects, monitors and analyses adverse reactions submitted to the Canada Vigilance database, amongst other activities, and codes and houses adverse reaction reports for cannabis. The Controlled Substances and Cannabis Branch is responsible for the monitoring, detection, prioritization, evaluation and aggregate reporting of adverse reactions associated with cannabis (pharmacovigilance).

Voluntary reports from the public may be received via the online reporting form, through the toll-free number or through the printable form via electronic fax or mailing to Health Canada. Mandatory reports

are submitted by licence holders to meet their regulatory reporting obligations for serious adverse reactions under the *Cannabis Regulations* and are submitted through fax or mail, unless the company is registered to submit electronic reports directly to the Canada Vigilance database (specific format must be met). Cannabis complaints or product quality issues may also be referred via the Cannabis Reporting Form from Health Canada. Incidents involving cannabis accessories (for example, mechanical, physical or electrical issue or failure of a cannabis accessory and associated injuries) can be reported via the Consumer Product Incident Reporting Form from the Healthy Environment and Consumer Safety Branch.

All cannabis adverse reaction cases are coded in the following manner:

1. Case reports are translated into electronic data into the Canada Vigilance database. All individual events are coded using the MedDRA, which is developed, maintained and updated by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use as an international set of standardized medical terms for symptoms, signs, diseases, syndromes and diagnoses.
2. Case reports involving cannabis as a substance in a suspected role are coded as “cannabis sativa” at the active ingredient level, irrespective of the identity of the cannabis product (legal, illegal, unspecified, undetermined).
3. Case reports involving a legal cannabis product in a suspected role (identified either by product name or licence holder) are classified according to the intended use. This can be cannabis product used for medical purposes (medical cannabis) or for non-medical purposes (non-medical cannabis), based on the information in the report. Cannabis use for medical purposes includes reports described having a medical authorization document or a reported medical or therapeutic purpose or indication, without mention of a medical authorization document. If there is no reported reason for use provided in the report, minimal details or intended use for non-medical purposes, the report is classified as non-medical cannabis.
4. Case reports are coded as serious as reported if at least 1 criterion for seriousness is selected:
    - death
    - life-threatening
    - admitted to the hospital
    - lengthened hospital stay
    - disability
    - birth defect
    - other medically important condition may also be selected by the reporter
5. According to international pharmacovigilance guidelines (ICH guidelines[11]), medically important conditions may also be considered serious under certain circumstances and therefore are an option to select when reporting an adverse reaction to Health Canada, and any adverse reaction case identified as such are further reviewed. However, these cases technically fall outside of the regulatory definition of a serious adverse reaction under the *Cannabis Regulations*.

Health Canada conducts routine monitoring, detection, assessment and associated activities for all cannabis adverse reaction reports, which involves:

- Screening of all new cannabis case reports to ensure they are:
    - coded appropriately according to MedDRA
    - classified as either cannabis for medical or non-medical purposes (legal classes)

[11] European Medicines Agency (2004). ICH Topic E2D: Post Approval Safety Data Management Step 5. https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf

    - product names are accurate

- Case reports involving a suspected non-compliance (that is, presence of visual mould, metallic taste, unusual odour) are referred to the Compliance Directorate for verification
- Non-serious reports are screened by Health Canada and those deemed to be medically important events are included for further assessment (causality assessment)
- All serious and medically important case reports undergo further investigation and assessment, including:
    - conducting follow-up for additional information on product details or clinical details of cases to aid in assessment
    - conducting a cursory causality assessment to report on 1 causality per case
    - undergoing a comprehensive individual causality assessment[12] for all fatal and life-threatening cases, which are considered priority reports, including assessing causality for each individual medical event reported in the case
- Any cases involving new or unexpected adverse reactions of interest undergo preliminary assessment (signal prioritization) to determine if they should be further evaluated
- A case series evaluation (signal assessment) is conducted in the event of a cluster or related cases involving new adverse reactions of interest. These comprehensive assessments involve the determination of biological plausibility based on published literature, domestic as well as international adverse reaction data (for example, WHO Vigibase)

REPORTING AN ADVERSE REACTION INVOLVING A CANNABIS PRODUCT

Licence holders must submit serious adverse reaction reports, as defined by the *Cannabis Regulations*, involving a cannabis product. They are encouraged to voluntarily submit non-serious adverse reaction reports involving a cannabis product. More information can be found in the *Cannabis adverse reaction reporting guide for licence holders*.

Consumers and health care practitioners are encouraged to report any adverse reaction to a cannabis product directly to Health Canada. Consumers and health care practitioners may also send a report to the licence holder of the cannabis product.

Report an adverse reaction to Health Canada

CONTACT US

Any questions or comments on this report, including any requests for the data used to support this report, should be directed to cannabis_oss-cannabis_bss@hc-sc.gc.ca.

[12] Cases resulting in death undergo comprehensive causality assessment which involves the assessment of causality for each individual medical event reported, including the fatal outcome. Causality assessment is based primarily on the WHO-UMC system for standardised case causality assessment