## 1 – T—Policy

#### Interpretation: Affirmatives must defend a policy action

#### Violation—they don’t

#### Standards

#### [1] Textuality.

#### The resolution is an actionable statement, indicated by “resolved.” You’re not affirming if you don’t spec a plan or implementation.

Words and Phrases 64

Words and Phrases Permanent Edition. “Resolved”. 1964.

Definition of the word “resolve,” given by Webster is “to express an opinion or determination by resolution or vote; as ‘it was resolved by the legislature;” It is of similar force to the word “enact,” which is defined by Bouvier as meaning “to establish by law”.

#### Impacts are implied consequences of actions –No plan, no offense.

Larson 17

[Kenny Larson](https://www.quora.com/profile/Kenny-Larson-5), High school policy debater with national circuit experience. [Answered Apr 30, 2017](https://www.quora.com/In-high-school-debate-what-do-the-following-terms-mean-impact-link-perm-turn-appeal-role-of-the-ballot-DA-K-and-impact-calculus/answer/Kenny-Larson-5) · Author has 133 answers and 811k answer views <https://www.quora.com/In-high-school-debate-what-do-the-following-terms-mean-impact-link-perm-turn-appeal-role-of-the-ballot-DA-K-and-impact-calculus> -CAT

Impact: The consequence of something, usually framed in terms of an advantage or off-case position. Impacts are the last in a chain of events in a certain argument, and tell the judge why something is bad. For example, a team may argue that the affirmative team’s plan causes the President to lose key political capital, which means he cannot pass a certain policy in Congress (otherwise known as a politics disadvantage). The result of him not passing this policy is nuclear war, which is the impact of the disadvantage. Without the impact, there is no clear reason why the policy not passing is bad, and so no reason to vote the affirmative team down.

#### Semantics outweigh pragmatics

Nebel 19

Nebel, Jake. [PhD candidate in philosophy at New York University, executive director at the Victory Briefs Institute for Debate, professor of philosophy at the University of Southern California]. “Genericity on the Standardized Tests Resoulution,” Vbriefly, August 12, 2019 <https://www.vbriefly.com/2019/08/12/genericity-on-the-standardized-tests-resolution/>

Affirmatives tend to defend their (pseudo-)counterinterpretations on this issue by arguing that topicality should primarily be a matter of “pragmatic” rather than “semantic” considerations. (See my “Priority of Resolutional Semantics” for this distinction. Please note that these terms are being used in a debate-specific sense; the “semantic/pragmatic” distinction in linguistics and philosophy of language is completely different.) Semantic arguments are arguments about what the resolution means; pragmatic arguments are about what it would be better or worse to interpret the resolution as meaning. My view is that semantics function as a side constraint on resolutional interpretation, and that pragmatics can help us choose between different interpretations that are semantically eligible. If the resolution is genuinely ambiguous between two or more propositions—a claim that requires evidence of some form (e.g., explicit definitions or linguistic tests)—we can ask which of those propositions would be better to debate. But there are many propositions that the resolution just doesn’t mean; one, in the context of this resolution, is that some colleges and some universities ought not consider some tests in some admissions decisions. The alternative “pragmatics-first” view seems to hold that the pragmatic benefits of debating something can be sufficient to interpret the resolution as meaning that thing, even if the resolution doesn’t mean that thing. Now, even on the “pragmatics-first” view, it’s not at all clear that it would be better to interpret the resolution to mean that some colleges and some universities ought not consider some standardized tests in some undergraduate admissions decisions. After all, there are over five thousand colleges and universities in the United States. On the affirmative’s interpretation, there are vastly more topical affirmatives than there are atoms in the observable universe. (There at most 10^82 atoms in the observable universe. The number of non-singleton subsets of two or more items out of a set of five thousand is 2^5000 − 5001, or approximately 1.4 × 10^1505. For simplicity I’ve ignored the distinction between colleges and universities, since I don’t know the breakdown between them. It’s still an underestimate, though, because it doesn’t count affirmatives that specify different tests or decisions.) Against a generic interpretation of the topic, some complain that there is “only one aff.” That may be true, if you strangely insist on individuating affs only by their advocacy rather than their arguments or advantages (e.g., they think your Kant aff and my util aff are one and the same aff, which I find bizarre).4 But, however we count affs, it is much better for there to be only one—the generic generalization expressed by the resolution—than for there to be more than a googol. It’s impossible to adequately prepare specific answers to such a vast number of affs. That preparation burden leads to worse debates, since it leads negatives to have lower-quality answers to any particular aff; everyone knows this, so debaters are incentivized to quickly mine for surface-level arguments for obscure affs, so they can use the rest of their time finding the minimal viable quantity of barely responsive evidence against other people’s affs, or beefing up maximally generic arguments that are recycled from topic to topic. That is a worse outcome than everyone researching the very same proposition, knowing that everyone else will research that proposition, thereby creating an incentive for in-depth research, expertise, and innovation. Limits are not obstacles to creativity; they are essential to it. But even if our hypothetical affirmative’s interpretation would be better for debate, we should reject the “pragmatics-first” view that the pragmatic benefits of debating something can be sufficient to interpret the resolution as meaning something it doesn’t mean. This is because the pragmatically best proposition to debate could be something that has nothing to do with the topic or is straightforwardly inconsistent with the topic. So all the reasons to debate the resolution are reasons to reject the pragmatics-first view. Moreover, no one knows or could ever know which of all possible propositions would be best to debate, since there are infinitely many propositions that could be debated and no way of figuring out which of them would be best. So, on the “pragmatics-first” view, no one knows how the topic should be interpreted. That is an embarrassing result, because the purpose of having a resolution is to establish a commonly known basis for preparation. What’s more, it is incredibly unlikely that the proposition affirmed by the affirmative is the best possible proposition to debate, so the affirmative is incredibly unlikely to be topical even in its own terms. One reply to this argument is to say that we don’t have to consider all of the possible propositions that could be debated, but all and only those that are advanced via interpretations in any given debate. This doesn’t solve the problem. Suppose the negative interprets the current LD resolution to mean that the United States federal government should substantially reduce Direct Commercial Sales and/or Foreign Military Sales of arms from the United States. Since the affirmative defends no such reduction, they aren’t topical. This interpretation would be much better for clash, affirmative flexibility, limits, advocacy skills, and so on. Obviously it’s not what the resolution means, but that’s not what topicality is about—right? On the view we’re considering, pragmatic benefits can justify interpreting the resolution to mean something it doesn’t mean. As long as the negative can identify at least one proposition much better for debate than what the resolution actually means, the affirmative is not topical. Perhaps the view is the pragmatic benefits of an interpretation can justify it so long as it’s semantically good enough. I have no idea what it is for an interpretation to be semantically good enough, if it’s not just to be something the resolution might mean. And, as we have shown, the requisite interpretation for the affirmative is just not something the resolution could mean. There is no dialect of any language in which even one meaning of the resolution is that some colleges and some universities ought not consider some standardized tests in some undergraduate admissions decisions. If the resolution were genuinely ambiguous between the affirmative’s interpretation and others, or if we just couldn’t tell whether the resolution might mean what the affirmative wants it to mean, then perhaps its pragmatic benefits could justify it. But the resolution is not ambiguous along that dimension, for all the reasons we have already seen. It seems to me that, despite appearances encouraged by the format of topicality arguments, the “pragmatics-first” person isn’t really rejecting the second premise of my argument: that, even if some particular colleges and universities ought not consider particular tests in particular decisions, that doesn’t mean that that colleges and universities ought not consider standardized tests in undergraduate admissions decisions. They are instead rejecting the first premise of the argument: that, on this topic, the affirmative should have to argue that, in the United States, colleges and universities ought not consider standardized tests in undergraduate admissions decisions. They are, in other worse, rejecting the topicality rule, as I define it. So let’s now turn to that premise.

#### [2] Competitive equity—any alternative wrecks it—it’s impossible to negate alternative frameworks with the ground allocated to us by the parameters of the resolution—all 1AR defense to this claim will rely on concessionary ground which isn’t a stable basis for a year of debate.

#### They don’t get to weigh the aff – it’s just as likely that they’re winning it because we weren’t able to effectively prepare to defeat it.

#### [2] Switch Side Debate – read your stuff on the neg – WHICH YOU DO – that non-uniques your offense and is net better since a Kritik on the neg has to be tailored to the aff– otherwise your discussion starts and ends at the 1AC.

#### [3] Precision – not defending the text of the resolution justifies the affirmative doing away with random words in the resolution which

#### a] means they’re not within the topic which is a voter for jurisdiction since you can only vote affirmative on the resolution and this debate never should have happened,

#### b] they’re unpredictable and impossible to engage in so we always lose

#### [4] TVA – defend the aff through the state – it’s trivially easy to find topic lit on the how outer space interacts with queer folx; here you go

Anderson 20

Ruby Anderson, “Space is Gay and it Has an Important Lesson for Us” 6-30-2020 <https://www.thrillist.com/news/nation/space-is-gay-cosmos-model-of-inclusivity> -CAT

When my gay friends and I talk about a time “before we were gay,” we’re referring to the years before some beautiful queer disturbance fundamentally changed what we believed was, for us, written in the stars. It was a time when so much of our growth felt predetermined, when it seemed like the parts of life most unknown and worth exploring were mysteries like outer space, not our own sexualities. The irony behind the phrase “written in the stars” is that we’re using our largely ambiguous and ever-expanding universe to describe a predetermined path in life -- to describe fate -- which, for queer youth in the majority of American communities, is presumed to be heterosexuality. I remember a time in my early teens when, after a long day of grappling with my unidentifiable discomforts, I looked up and felt a kinship with the vast, equivocal darkness. Fate wasn’t what felt written in the stars -- it was something more like permission. In May of this year, queer online advice columnist John Paul Brammer answered the question “What is the unspoken bond that LGBTQ people have with space?” with “we queers tend to know a lot about the ordeal of being perceived and then being negotiated into rigid taxonomies that weren’t built with us in mind.” Inspired by his answer and my personal experiences, I set out to find queer people who had an intense love for space and ask them if they thought space was gay, and from everyone I spoke to, I received a resounding YES. But the follow-up answers informed not only how queer people have learned to relate to the world at large, but these folks are working to bring more cosmo-like diversity and harmony into their communities and relationships. Space is inherently counterculture Emily Hunt, a queer trans woman studying star clusters for her PhD, told me that she first became interested in the stars when she was around 7 years-old, after her parents showed her Venus transiting across the sun. She says she is humbled by space, and believes the universe is gay because it’s inadvertently “counterculture.” “It’s a completely unassuming space,” she said, laughing at the accidental pun. “It’s such a blank slate. I feel like that to me is a part of being queer. I see society as kind as very kind of on rails, and everything is kind of normative, and then you have queer people off on their own doing their own thing.” Counterculture’s mainstream debut in the mid-‘60s, when the norms of the ‘50s were largely rejected by youth, was fueled by a theory of social justice that scholars refer to now as “the politics of authenticity.” This theory holds that liberation requires being completely, unforgivingly yourself, which is certainly the ethos of both space and queerness. But Hunt wanted to make it clear that her whiteness has made her career much easier, a sentiment I often hear from queer people who pay close attention to Pride’s evolving culture, and are aware that all LGBTQ+ marginalization is not the same. Critics of our present-day, corporate-sponsored celebrations urge the community to honor Pride’s history and work towards being more inclusive. They often refer back to the 1969 Stonewall Uprising that sparked the queer liberation movement and how the same people who facilitated the riots -- trans women of color -- are often forgotten during the largely cisgender, white-washed Pride parades of today. (The addition of a brown and black stripe to the Philadelphia rainbow flag three years ago is only one example of how public discourse is shifting.) Hunt said the same limitations are put on people of color within the astronomy field. To get a sense of queer history in astronomy, I talked to Tony Scupham-Bilton, an LGBTQ+ historian living in the United Kingdom, who grew up in a village with no light pollution and became fascinated by asteroids at a young age. “I remember copying out a list of asteroids from an encyclopedia when I was about 8 years-old,” he told me, and then leaped into a summary of astronomy’s rich queer history, from the BCs up to modern day. The queer community as a whole has made leaps and bounds within the last 100 years. Transgender astrophysicist Dr. Rebecca Oppenheimer discovered the first brown dwarf star, Dr. Sally Ride was the first American woman in space, transgender astrophysicist Dr. Jessica Mink discovered the rings around the planet Uranus, Dr. Nergis Mavalvala proved Einstein’s theory of gravitational waves, and Dr. James Pollack’s study of dust storms on Mars led to research into climate change on Earth, among others. But there’s still a lot of work to do in terms of inclusivity. “Many openly LGBT astronomers are involved in outreach work, popularizing astronomy, and working in public planetaria,” Scupham-Bilton said. “There is also an increasing number of openly LGBT students who are registering on LGBT science and university ‘out lists,’ and there are many LGBT astronomy professors.” The astronomy field could learn a thing or two from space, and the folks who study it PhD student KeShawn Ivory, who I contacted via the “Astro Twitter” network, is part of the welcoming committee for The Fisk-Vanderbilt Master's-to-PhD Bridge Program, the nation’s top producer of Black master's degrees in physics, and plans to become a planetarium director when he’s finished with his studies. Ivory says he became attracted to space after a lexicon activity wherein he was assigned the world “astronomy.” “I came home and looked it up like the assignment mandated and wrote down definition word for word… and it sounded kind of magical,” he said. “It was like ‘celestial bodies’ and planets and stars.” Ivory got back in touch with his initial passion for astronomy while planning his future; he wasn’t excited by the traditional academia path he saw laid out for him in the eyes of his professors. Ivory identifies as gay and aromantic, and tied his interests back to the thesis of my article to describe why he chose the planetarium path. “It’s funny that, you know, under the theme of ‘space is gay’... When I thought about what I really liked about [space], it came back to just imagery. I liked pictures. I like colors. I liked the image. And what’s the best way to present that image to the public and still get to use all of my specialized knowledge? Planetarium work.” I reached out to more astronomers via the “Astro Twitter” network, which Ivory says he stumbled into by accident, having initially made a Twitter account at age 13 to channel all of his Lady Gaga-loving energy. While his focus has shifted since then, he still talks openly about his personal life and opinions. When astronomers from school and conferences started following him, Ivory said he “wasn’t about to change his content.” In being unforgivingly Black and queer, Ivory is part of the astronomy counterculture working to change the narrative around who gets to study space. And he believes that, during the COVID-19 pandemic, astro Twitter is finally in a position to listen to criticism. We need to work harder to bring the queerness of space to our communities on Earth. Moiya McTier, a Black astrophysicist who identifies as bisexual and pansexual, said she didn’t have the typical “look up at the night sky” story, and only took an astronomy class in sophomore year because the professor promised free pizza each week. Then she was hooked. She told me about the American Astronomical Society, which comprises over 10,000 members and includes the Committee on the Status of Minorities in Astronomy, which she is a part of. She also has a podcast called “Exolor” wherein she talks to space experts about what life might be like on different kinds of alien planets. When I asked her to give me the gossip on “astro Twitter” right now, she echoed Ivory’s sentiments and said the focus has shifted. “A lot of the focus for me has been on racism in astronomy, which sort of bled into Pride Month as the focus has been ongoing.” Universal inclusion is a sentiment has been spreading among the white queer and ally communities since the Black Lives Matter protests began. Folks working towards a more inclusive Pride echo that there is simply no queer liberation without Black liberation. While the corporate Pride in my home city of New York was celebrated virtually due to COVID-19, the Dyke March and Queer Liberation March were altered to focus on the Black Lives Matter movement. And even though there were significantly less rainbow flags at this year’s Queer Liberation March, activists exuded the true queer, colorful, celestial spirit of the cosmos. Space has no orientation, literally McTier believes space is gay, because it has no technical orientation. “One of the most annoying things about working in space is that there’s no up and down,” she said. “Because there’s not a central gravity field, depending on where you are in space.” Most space “orientations” are chosen out of convenience. For example, because the galaxy has a center, astronomers created a coordinate system based on a “galactic north pole.” Human beings cannot possibly understand and make judgments about something without first putting it into systems they understand. Science, in that way, is inherently heterosexual, and space as it’s written plainly in the stars, is queer. I decided to include an astrologer in this story, not to lump the two into one interest, but to highlight the strengths of removing hard science from the space narrative. As a dyke immersed in astrology culture, I was largely reintroduced to the stars in my light-polluted city by fellow queer people who wanted to know about my sun, moon, and risings signs (Scorpio, Cancer, and Aquarius, honey). Before I go off about this, I want to make the distinction clear, and apologize if any astronomers take issue with the association. To some folks, associating astronomy and astrology is like comparing the chemical and biological mechanisms of an emotional experience with a poem about it, but to others -- and yes, to a great deal of the queer community -- astrology is the vast, mysterious darkness through which they can explore their inner worlds. I talked to Colin Bedell, a cosmopolitan astrologist and co-founder of the website queercosmos.com, to explore the question in the way I initially believed it was asked on Brammer’s advice column: “What is the unspoken bond that LGBTQ people have with space?” As in, why do people with little knowledge of astronomy, and from the same physical viewing point as non-queer people in space, tend to talk about the cosmos all the time at bars? Bedell said his fascination with astrology started when he was 11 or 12. “I was real curious,” he said. “I think this is very much like anybody born inside a majority culture. They start to lean on archetypal injury to help them make sense of their otherness.” He told me astrology hooked him, as it hooks a lot of queer youth, because it’s not “ascribed through traditional notions or presentations or behavior choices for sex, sexuality, and gender.” Bedell has been able to connect with a diverse range of queer folks through his work, and has picked up on some patterns within the community. But I believe that when queer kids notice that they're queer, they see their desire as a source of danger,” he said. “It's complicated, whereas the vast majority of heterosexual people -- but most importantly heterosexual men -- are encouraged to name their wanting without apology, invitation, remorse, or forgiveness.” His observation brought me back to the concept of permission -- how there’s a place in the vast unknown for everyone to live without apology, invitation, remorse or forgiveness, but that we need to work harder to bring the queerness of space to our communities on Earth. If space is so complicated that it is beyond human comprehension, and we on Earth are simply a product of space, then it is without question that our society can change in unimaginable ways. Ready to go stargayzing? If you're just getting started, check out our guide to astronomy for beginners. If you're lazy, stream the northern lights from home. If you want to be a queer astronomer, get inspired by folks on the astronomy and astrophysics "out" list, or check out student resources from the Committee for Sexual-Orientation & Gender Minorities in Astronomy and the Committee on the Status of Minorities in Astronomy.

#### T isn’t violent –

#### A] I don’t have the power to impose a norm – only to convince you my side is better. T doesn’t ban you from the activity – the whole point is that norms should be contestable – I just say make a better arg next time.

#### B] Exclusion is inevitable – every role of the ballot excludes some arguments and even saying T bad excludes it – that means we should delineate ground along reciprocal lines, not abandon division altogether.

#### Reading T isn’t psychic violence – we use it preemptively to prevent aff shiftiness and make substance a viable option.

#### No silencing DA - T is just like a disad or critique we’ve said a certain practice the aff took was bad and it would’ve been better had they done it differently not that they are bad debaters – just like the cap k says the aff engaged in some practice that reinforced capitalism and it would’ve been better if they had emphasized Marxism – impositions in some form are inevitable because the negative has the burden of rejoinder and needs link arguments – every disad link says the aff did something wrong and theres an implicit version of the aff that wouldn’t have linked

#### Theory before the K – A] Prior question. My theory argument calls into question the ability to run the argument in the first place. They can’t say the same even if they criticize theory because theory makes rules of the game not just normative statements about what debaters should say.

#### B] Fair testing. Judge their arguments knowing I wasn’t given a fair shot to answer them. Prefer theory takes out K because they could answer my arguments, but I couldn’t answer theirs. Without testing their args, we don’t know if they’re valid, so you prefer fairness impacts on strength of link. Impact turns any critical education since a marketplace of ideas where we innovate, and test ideas presumes equal access.

#### No RVI’s or perf cons- illogical, baiting, if theory is bad and you vote on a turn to theory you are voting on theory

#### Reject aff pre empts – not clearly delineated, impossible to know implications

## 2

#### Analytic CP: A just government should (1) legalize 3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, (2) regulate ecstasy to insure pills aren’t contaminated with other substances, and (3) mandate warnings regarding ecstasy’s interactions with other substances

#### Net benefits versus 1AC “must experiment on your body”

#### 1] Uncontaminated ecstasy is relatively safe – but unregulated ecstasy often contains other substances that greatly increase lethality and toxicity

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TOXICOKINETICS AND METABOLISM The risky cocktail: what combination effects can we expect between ecstasy and other amphetamines? Diana Dias da Silva • Helena Carmo • Elisabete Silva Received: 14 June 2012 / Accepted: 27 August 2012 / Published online: 23 September 2012 Springer-Verlag 2012 Arch Toxicol (2013) 87:111–122 DOI 10.1007/s00204-012-0929-9 <https://www.researchgate.net/profile/Diana-Dias-Da-Silva-2/publication/257340580_The_risky_cocktail_What_combination_effects_can_we_expect_between_ecstasy_and_other_amphetamines/links/55644f8308ae6f4dcc98ea81/The-risky-cocktail-What-combination-effects-can-we-expect-between-ecstasy-and-other-amphetamines.pdf> -CAT

Amphetamine designer drugs are widely abused addictive psychostimulants. 3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, is the most popular analogue and its use has increased in all social settings, all over the world. As a result, ecstasy has often been associated with toxic episodes, including fulminant hyperthermia, disseminated intravascular coagulation, rhabdomyolysis and multi-organ failure (Walubo and Seger 1999). Reported drug abuse scenarios show that it is common practice among misusers to consume multiple substances concomitantly (Barrett et al. 2006; Wu et al. 2006; Mohamed et al. 2011). In addition to the deliberate intake of different types of drugs by the users, inadvertent consumption of multiple substances often occurs, as large number of other chemicals are regularly found in ecstasy party pills (Pavlic et al. 2010; Morefield et al. 2011), including lysergic acid diethylamide (LSD), dextroamphetamine (d-AMP), methamphetamine (METH), ketamine, mephedrone, cocaine and even the highly toxic 4-methylthioamphetamine (4-MTA), which has been linked to several fatalities (Elliott 2000; De Letter et al. 2001). In fact, polydrug abuse is one of the most pertinent confounding factors in predicting MDMA toxicity, since the combination with other chemicals can exacerbate the severity or widen the range of the toxic effects of this drug, resulting in potentially lethal intoxications (De Letter et al. 2006; Verschraagen et al. 2007). Nevertheless, when evaluating MDMA toxicity, most studies focus on MDMA alone rather than in combination with other substances. Moreover, the few combination studies reported so far between MDMA and other psychoactive drugs have been conducted without reference to the expected joint effects (Clemens et al. 2005; Pontes et al. 2008). Consequently, whilst the risk of interaction between MDMA and other stimulants has been widely acknowledged, there is still a lack of information regarding the toxicity and lethality of drugs in co-administration. To define the way in which amphetamine-like substances interact may represent an important improvement for understanding their toxicity mechanisms. Over the last decades, several studies on mixture toxicology have compared two well-established models for the calculation of expected additive mixture effects (Drescher and Boedeker 1995; Payne et al. 2000; Rajapakse et al. 2001; Silva et al. 2002; Pavlaki et al. 2011): concentration addition (CA), first defined by Loewe and Muchnik (1926), and independent action (IA) as described by Bliss (1939). The concept of CA is based on the assumption that the mixture constituents have similar modes of action, which means that any component can be replaced partially or totally with another without changing the overall mixture effect. This means that each individual component contributes to the global joint effect by acting in proportion to its concentration, even below concentrations producing no effect. This model has been used to assess combination effects of agents with a common site of action (Backhaus et al. 2000b; Silva et al. 2011a). Experimental evidence from some studies showed that combination effects of drugs with dissimilar mechanisms of action are better described using the alternative approach, that is, IA, which considers each agent interacting at differing sites of action (Backhaus et al. 2000a). The fractional response of one individual component is supposed to be independent from those induced by other components, presuming that mixture components present at zero effect concentrations will not contribute to the overall effect. The two models can produce very distinct expectations and, to our knowledge, have never been applied to amphetamine-like compounds. For this reason, the main aim of this study was to compare the applicability of CA and IA models in predicting the joint toxic effects of amphetaminic drugs in immortalized hepatoma Hep G2 cells, based on comprehensive information on the individual drugs. In addition to MDMA, the amphetamines d-AMP, METH and 4-MTA were selected for this study, due to their widespread presence in ecstasy pills. As amphetamine derivatives are often found as low-level contaminants in street drugs offered as ecstasy (Becker et al. 2003), we were also interested in investigating the potential for significant joint effects to occur, even when these individual components were combined at low concentrations, representative of real exposure scenarios. In order to address these questions, three specifically designed mixtures of the same four amphetamines, but combined at three different ratios, were tested. With these, we were able to compare the applicability of the described prediction models and evaluate amphetamine interactions in relevant exposure situations. Being able to accurately predict and study combination effects of amphetamines will improve the understanding of potential chemical interactions when simultaneous consumption occurs, as well as provide some potential insight into the reasons behind random occurrence of extreme toxicity and even fatalities after consumption of ecstasy pills, when this per se are not associated with high rates of mortality.

#### 2] Your alt locks me out of the choice – I’m extremely ADHD and take high levels of amphetamines to function – that’s super risky with ecstasy and other forms of self-intoxication

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Accordingly, we do not need to invoke synergistic combinations to prove that low levels of amphetamines present in illicitly consumed ‘rave pills’ can produce adverse effects, as significant mixture effects already occur in an additive fashion. Understanding this concept is crucial in the evaluation of mixture interactions, as studies frequently rely heavily on the search for synergisms to justify observed joint effects. A consequence of this approach is that often conclusions of synergisms are made, even in the absence of appropriate additive expectations. As mentioned earlier, besides MDMA, ecstasy pills often contain amphetamine-like products of uncontrolled and clandestine synthetic processes. Several previous publications highlighted the fact that many of the MDMA pills available in illicit markets contain a number of other substances, sometimes cheaper and easily obtained, like METH (Camilleri and Caldicott 2005), d-AMP (Sherlock et al. 1999; Teng et al. 2006), 4-MTA (Tanner-Smith 2006; Teng et al. 2006) and other related derivatives. In order to assess whether the prognostic value of CA expectations fitted to more realistic scenarios, we studied mixture C, where the influence of varying concentrations of a three-component mixture (4-MTA, METH and d-AMP) was combined with a constant concentration of MDMA. In a similar way to the observations made with mixtures A and B, our results demonstrated a good agreement with CA especially at low concentrations and joint effects were slightly lower than additivity for higher effect levels (above 40 %) indicating weak antagonisms. For the model of CA to be applicable, it relies on the assumption that all mixture components share the same toxicity mechanism and do not interact with, potentiate or antagonize each other. For this reason, this model does not take into account potential pharmacokinetic interactions between chemicals, such as the induction or inhibition of metabolic pathways. However, we know that amphetamine-related drugs have a close structural and functional relationship and use the same pharmacological and detoxification pathways (de la Torre et al. 2004). Therefore, it is plausible that all four amphetamines will compete and consequently interact with the metabolism and detoxification of each other in an unexpected manner. Ultimately, this could result in the deviations from additivity here reported. The effects caused by the consumption of amphetamines can be conditioned by a plethora of factors that converge in a certain individual, on a certain moment. The mechanisms involved in liver damage induced by amphetamines are complex and still not completely understood. A variety of hypotheses have been proposed including the increased efflux of neurotransmitters, the oxidation of biogenic amines, mitochondrial impairment and apoptosis, and a direct effect of amphetamines and/or reactive metabolites (Carvalho et al. 2012). In addition, genetic polymorphism of metabolizing enzymes (particularly CYP2D6), polydrug abuse, and environmental features accompanying illicit amphetamine use may increase the risk for liver complications (Carvalho et al. 2012). Hyperthermia is thought to greatly contribute to liver toxicity. However, in some cases, Arch Toxicol (2013) 87:111–122 119 123 liver damage appears unrelated to hyperpyrexia (Milroy et al. 1996; Jones and Simpson 1999). A well-known mechanism of toxicity in humans implies hepatic MDMA bioactivation into reactive species (de la Torre et al. 2004). The metabolism of MDMA is mainly regulated by cytochrome P450 (CYP450) enzymes and catechol-O-methyltransferase (COMT) in the liver. N-demethylation to MDA is a reaction mainly catalysed by CYP2B6. Both MDMA and MDA are then O-demethylated by CYP2D6, and to a lesser extent by CYP1A2, CYP2B6 and CYP3A4, to 3,4-dihydroxymethamphetamine (HHMA, N-methyl-a-methyldopamine, N-Me-a-MeDA) and 3,4-dihydroxyamphetamine (HHA, a-methyldopamine, a-MeDA), respectively. These catechol intermediates can undergo oxidation to the corresponding highly redox active orthoquinones, which can enter in redox cycling, originate semiquinone radicals and lead to the generation of ROS or RNS, which are highly toxic for the cell (de la Torre et al. 2004; Shenouda et al. 2009; Barbosa et al. 2012). In light of this, and because all chemicals tested herein share the same biotransformation pathways, we hypothesized that they would promote the saturation of specific enzymes involved in oxidative metabolism and, therefore, reduce the formation of reactive species and so, cytotoxicity. However, instead, we observed a statistically significant increase in the formation of MDA (\*\*p\0.01), an indication of increased metabolism. A possible explanation for this might be linked to the fact that in the mixture setting, the MDMA fraction bound to serum proteins or retained in the lipid bilayer membrane might decrease, as it is displaced from the binding sites by the remaining mixture components. This would increase the levels of free MDMA available for metabolism. Then, a preferential overexpression of CYP2B6, promoting N-demethylation with MDA formation, in detriment of O-demethylation, which would produce highly toxic reactive species, may play a role. As MDA has been shown to have slightly lower toxic effects than the parent compound MDMA in human proximal tubular cells (Carvalho et al. 2002), an increase in this metabolic product would justify the weak antagonisms observed. Nevertheless, the precise molecular interactions between amphetaminic drugs are still not fully understood, and it is possible that additional factors are involved in the deviations observed, requiring further biological and molecular investigation.